Monotherapy versus Polytherapy in Epilepsy

Experimental and Clinical Studies

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Monotherapy versus Polytherapy in Epilepsy

Experimental and Clinical Studies

Een wetenschappelijke proeve op het gebied
van de Medische Wetenschappen

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Preface

For the last twenty years, monotherapy with antiepileptic drugs (AEDs) has been promoted as the rational basis for the treatment of patients with epilepsy. This has partly been due to the unfavorable reputation of AED polytherapy. The disadvantages of polytherapy are deemed to be increased toxicity, drug interactions, failure to evaluate the effect of individual drugs and in some patients even seizure exacerbation (203). These conclusions were drawn from a number of open trials, in which patients on polytherapy were changed over to monotherapy. Many patients in these studies experienced a decrease in adverse effects and some even an improvement in seizure control.

However, apart from the fact that these trials were open and uncontrolled, the concept of drug load was neglected in their study design and analysis. One of the basic hypotheses of this thesis is that the drug loads of medication regimens should be equal before conclusions can be reached on differences of intrinsic efficacy and toxicity. Drug load is defined as the amount of drug exposure for a certain indication and a method to calculate drug load was developed and used by our group, the Nijmegen Epilepsy Research Group (NERG), in previous studies (133-135). In an earlier observational study our group in fact found that polytherapy is not associated with more toxicity than monotherapy when drug loads are equal (135). As polytherapy is often given at higher drug loads, this may very well be the most important reason for the increased toxicity associated with AED polytherapy.

This leads us to the main question of this thesis: do certain AED combinations offer advantages over their individual constituents ? This question may seem easy to answer, however there are a number of problems to consider. The first problem, in animal and in human studies, is the selection of adequate methods: which study design and statistical analysis should be used to study combination therapy; how should efficacy and toxicity be assessed; which neuropsychological tests should be used ? In chapter 1, the introduction, the history of the polytherapy controversy is examined and the different methodologies our group has employed in recent studies are briefly reviewed. In chapter 2, background information on these methodologies is given for the interested reader, and in chapter 3 our methods are put to the test: a literature review is performed to evaluate whether the number of drugs or drug load determines the number of adverse effects and another literature

review is carried out to assess the effect of different detection methods (i.e. spontaneous reporting and use of a clinimetric scale) on the frequencies of adverse effects.

The second problem our main question poses, is that it is unclear which pharmacodynamic combinations will lead to increased efficacy or reduced toxicity. In other words, which mechanisms of action should be combined to offer added value ? In recent years, some authors have claimed that drugs that act on the same ion channels or the same neurotransmitters should be combined whereas others believe that combinations should consist of drugs that do not share their targets. In chapter 4 the available polytherapy studies in animals and humans will be reviewed to evaluate this, but also to assess which designs and methodologies these studies used.

In chapter 5 and 6 our own studies on AED combinations are described. In chapter 5 polytherapy is evaluated in an animal model of absence epilepsy. The combination of sodium valproate (which will be referred to as valproate in this thesis) and ethosuximide is compared to its individual components with regards to efficacy and toxicity. In chapter 6, a randomized double-blind trial comparing monotherapy and combination therapy in patients with newly-diagnosed epilepsy is described. This is the first time a double-blind randomized trial has been carried out to evaluate the merits of combination therapy with AEDs.

Finally, in chapter 7 our findings and their relevance will be discussed and recommendations for future studies will be made.

In summary, the aims of this thesis are the following:

1. To investigate whether drug load, rather than the number of antiepileptic drugs, is responsible for adverse effects.
2. To evaluate whether polytherapy is a good alternative for monotherapy when prescribed at equal drug loads.
3. To assess the possibility of selecting AED combinations by mechanisms of action.
4. To determine the best methodologies to evaluate polytherapy with antiepileptic drugs.

Abbreviations and glossary

- additive — the sum of the drug fractions of the combination, needed for an effect equal to that of the individual drugs, equals 1
- AED — antiepileptic drug
- AHD — anxiolytic-hypnotic drug
- AMPA — α-amino-3-hydroxic-5-methylisoxazole-4-propionic acid
- ATL — average therapeutic level; average therapeutic serum level of a drug used in its main indication in adults
- AToxL — average toxic level
- BZD — benzodiazepine; group of drugs, which are used for epilepsy and other indications
- CBZ — carbamazepine; antiepileptic drug
- CI — confidence interval
- CII — Composite Index of Impairments; clinimetric epilepsy scale
- CNS — central nervous system
- clinimetrics — the domain concerned with indexes, ratings scales, and other expressions that are used to describe and measure symptoms, physical signs, and other distinct phenomena in clinical medicine
- DDD — Defined Daily Dose; average maintenance dose per day for a drug used in its main indication in adults
- drug load — the amount of drug exposure for a certain indication
- EEG — electro-encephalogram
- effectiveness — measure encompassing both efficacy and tolerability
- efficacy — level of seizure control
- ESM — ethosuximide; antiepileptic drug
- FBM — felbamate; antiepileptic drug
- FePsy — FerroPsychologist; computerized neuropsychological test battery developed at the SEIN, Heemstede
- GABA — γ-aminobutyric acid; neurotransmitter
- GABA-T — GABA-transaminase; enzyme drugs which converts GABA into succinic semialdehyde
- GAD — glutamic acid decarboxylase; enzyme which converts glutamate to GABA
- GBP — gabapentin; antiepileptic drug

- GHB γ-hydroxybutyrate; GABA-metabolite
- infra-additive the sum of the drug fractions of the combination, needed for an effect equal to that of the individual drugs, is greater than 1 (synonym: antagonistic)
- IS Index of Seizures, subscale of the Seizure Activity index
- LTCC low threshold calcium current; thought to be involved in absence epilepsy
- LTG lamotrigine; antiepileptic drug
- MES maximal electroshock; animal epilepsy model
- NERG Nijmegen Epilepsy Research Group
- NMDA *N*-methyl-D-aspartate; type of glutamate receptor
- NTX Neurotoxicity Index, subscale of the CII
- OSL observed serum level; serum level of a drug measured in a patient or average serum level measured in a group of patients
- OXC oxcarbazepine; antiepileptic drug
- PB phenobarbital; antiepileptic drug
- PDD Prescribed Daily Dose; the dose of a drug a patient uses per day or the average dose of a drug used daily in a group of patients
- PHT phenytoin; antiepileptic drug
- PRM primidone; antiepileptic drug
- Ptz pentylenetetrazole; drug which can induce seizures in animals and is used as epilepsy model
- SA Seizure Activity index, subscale of the CII
- STX Systemic Toxicity index, subscale of the CII
- supra-additive the sum of the drug fractions of the combination, needed for an effect equal to that of the individual drugs, is less than 1 (synonym: synergistic)
- SWD spike wave discharge
- TGB tiagabine; antiepileptic drug
- tolerability level of adverse effects
- TPM topiramate; antiepileptic drug
- VPA valproate; antiepileptic drug

Sources

Certain paragraphs in this thesis have been based on published papers, submitted papers and papers in preparation:

Paragraph 3.1 Deckers CLP, Hekster YA, Keyser A, Meinardi H, Renier WO. Reappraisal of polytherapy in epilepsy: a critical review of drug load and adverse effects. Epilepsia 1997;38:570-5.

Paragraph 3.2 Deckers CLP, Hekster YA, Keyser A, Meinardi H, Renier WO. Drug load in clinical trials: a neglected factor. Clin Pharmacol Ther 1997;62:592-5.

Paragraph 3.3 Deckers CLP, Hekster YA, Keyser A, Lammers MW, Meinardi H, Renier WO. Detection of adverse effects in epilepsy therapy: Wait and see or go for it ? Acta Neurol Scand 1997;95:248-52.

Paragraph 4.2 Deckers CLP, Czuczwar SJ, Hekster YA, Keyser A, Kubova H, Meinardi H, et al. Selection of antiepileptic drug polytherapy based on mechanisms of action: the evidence reviewed. Accepted for publication by Epilepsia.

Paragraph 5.1 Roks G, Deckers CLP, Meinardi H, Dirksen R, van Egmond J, van Rijn CM. Effects of monotherapy and polytherapy with antiepileptic drugs: an animal study. J Pharmacol Exp Ther 1999;288:472-7.

Paragraph 5.2 van Rijn CM, Deckers CLP, Zhen SM, Meinardi H. The combination of valproate and ethosuximide compared to its individual constituents in the WAG/Rij model of absence epilepsy. In preparation.

Paragraph 6.1 Deckers CLP, Hekster YA, Keyser A, van Lier HJJ, Meinardi H, Renier WO. Monotherapy versus polytherapy for epilepsy: the first multi-center double-blind randomized study. Submitted for publication.

Contents

Chapter 1 Introduction

1.1 The monotherapy versus polytherapy controversy

The rise and fall of polytherapy

Before 1960 the only drugs available for the treatment of epilepsy were bromides, barbiturates, phenytoin, tridiones and succinimides. These were all efficacious drugs, but their use was also associated with considerable side effects, most notably somnolence. It was believed that combining lower dosages of two of these drugs would be as efficacious but less toxic to patients than exposure to a full dose of one drug. Therefore it was customary, till around 1980, to start patients off on combinations of antiepileptic drugs (AEDs) (88). These compound preparations, which were often given in one capsule, would often also include substances known to counteract somnolence, such as caffeine, amphetamine, or atropine. In Italy for example Dintospina contained 100 mg of phenytoin, 60 mg of mephobarbital and 3 mg of amphetamine. In the Netherlands compound preparations were ready made by pharmacists.

An additional reason for the use of combination therapy according to Genton and Roger was that combination therapy was believed to be more efficacious (88). For example phenobarbital was considered to be especially efficacious against generalized tonic clonic seizures and phenytoin against both focal seizures and generalized tonic clonic seizures. The combination was supposed to increase protection against both seizure types, for example in partial epilepsy with secondary generalized seizures. Gram and Reynolds et al. however claim that it actually was a lack of agreement as to which drug was best for a certain seizure disorder and as to which drug to start first which had led to polytherapy (95, 203). All of these authors do agree that the absence of serum level measurements also contributed to the use of polytherapy, as some AEDs have unpredictable pharmacokinetics, e.g. phenytoin.

In the latter part of the seventies however, a number of reports by Reynolds and Shorvon led to the rise of monotherapy as the preferred treatment for epilepsy. In 1976, they found that only a small proportion of patients were truly resistant to phenytoin monotherapy when doses could be adjusted on the basis of serum levels (202). Of the 31 patients with generalized or focal epilepsy, only 3 needed a second drug during a mean follow-up period

of 15 months. In 1977, they reported that adding a second drug was only of benefit in about one third of the patients poorly controlled by monotherapy. When serum levels were measured in these patients, it was found that the improved control was significantly related to an optimum serum level of at least one of the drugs (228). They concluded that aiming for an optimum serum level may be of more benefit than adding a second drug. In 1978 Shorvon et al. reported that when carbamazepine or phenytoin was given to 51 newly referred untreated patients and blood levels were in the optimum range, a 98% reduction in 'grand mal' attacks and a 92-93% reduction in partial seizures was achieved (227). This was a much higher success rate than was achieved in previous studies and was attributed to drug-level monitoring, without which an estimated 60-70% of patients would have been treated with polytherapy. However, as Goldsmith et al. remark in their review, there were no patients with major neurological or psychiatric handicaps in that 1978 study, which may have been a major factor in its high success rate (91). In 1979 finally, Shorvon and Reynolds reported about a group of 40 patients in which they had tried to reduce the number of AEDs to one (229). They succeeded in doing so in 29 patients, and seizure control actually improved in 16 of these patients. Also, mental function improved in 16 of the 29 patients. Similar findings of improved seizure control in some patients and an overall decrease in toxicity after reduction of polytherapy to monotherapy were reported by a number of researchers (1, 16, 35, 78, 141, 218, 243, 245).

The advantages of monotherapy had become clear: better tolerability, fewer interactions, easier clinical monitoring and in some patients even better efficacy. Furthermore, two promising new drugs (carbamazepine and valproate) with less CNS (central nervous system) toxicity had become available and were proving to be useful in monotherapy. In 1981, after the publication of the revised international classification of epileptic seizures, studies were carried out in which the efficacy of different AEDs was evaluated per seizure type. Genton and Roger claim that the increased understanding of epilepsy and the fact that specific AEDs could now be recommended for specific seizure types were the most enduring reasons that monotherapy has become the gold standard for epilepsy treatment (88).

Effectiveness of monotherapy

Two of the best known comparative monotherapy trials were executed by the Veteran Affairs Epilepsy Cooperative Study Group (173, 174). In the first trial carbamazepine, phenobarbital, phenytoin and primidone were evaluated in partial and secondary generalized tonic-clonic seizures (total number of patients 622) . The results can be summarized as follows: there was no difference in efficacy for tonic-clonic seizures between the drugs; carbamazepine was more efficacious for partial seizures than primidone and phenobarbital; primidone and phenobarbital were discontinued more often than carbamazepine and phenytoin due to treatment failure or adverse effects.

In the second trial valproate and carbamazepine were compared in patients with complex partial and secondary generalized tonic-clonic seizures (total number of patients 480). These drugs were equally efficacious for generalized tonic-clonic seizures, but carbamazepine was more efficacious for complex partial seizures. It is remarkable that less than 50% of patients with either seizure type and treated with either drug remained seizure free in the first year of drug treatment. Mattson, one of the principal investigators of the VA Group, acknowledges that once an appropriately selected antiepileptic drug has been started, seizures still may occur during the period of adjustment. He stresses however that, if clinically acceptable, it may be appropriate to continue the initial medication (171). In the first VA trial, 58% of the patients experiencing seizures in the first 6 months of treatment were seizure free during the next 6 months while continuing to take the original drug (175). Some of these patients will have breakthrough seizures, but others will enter long-term remission. Overall, after one to two years 60% of patients have almost complete control of seizures (174). In the second VA trial approximately 75% of patients were still on their initial drug at 12 months (173). In the first VA trial approximately 60% of phenytoin and carbamazepine users stayed on their drug for more than two years (174).

In the British EPITEG-trial carbamazepine and valproate monotherapy were compared in adult onset epilepsy (total number of patients 281). Both drugs were associated with a high degree of seizure control, regardless of seizure type, and both had good long term tolerability. At the end of the 3 year trial period over 70% of the available patients were still on their randomized treatment or had recently stopped treatment after achieving full seizure control (204).

In patients whose first drug fails because of insufficient seizure control or adverse effects

an alternative monotherapy is often tried. In the first VA trial the alternative drug succeeded in 46% of patients (171). In a study by Schmidt et al. 31% of patients reached total seizure control or more than 75% seizure reduction with alternative monotherapy (total number of patients 59) (220). In a trial by Hakkarainen about half of the patients receiving carbamazepine or phenytoin were seizure-free at one year (total number of patients 100) (52). When the non-responders were switched to the alternative monotherapy, another 17% became seizure free.

In conclusion, as these data also indicate, it is generally accepted that 70% of epilepsy patients will have adequate seizure control with a single drug, either the initial drug or an alternative.

Effectiveness of combination therapy

When alternative monotherapy fails, the switch to polytherapy is made. According to Perucca, only a small group of the patients who were not effectively controlled with monotherapy, will benefit from a combination of two AEDs, often at the expense of adverse effects (194). In a trial by Schmidt et al., only 4 of 30 patients had more than 75% seizure reduction after the 2nd drug was added (217).

In the first VA trial however, it was found that approximately 40% of patients who had not benefitted from monotherapy, had improved control with two drug therapy, although only 10% achieved seizure remission. In another trial, Dean and Penry used valproate as add-on treatment in patients with inadequate seizure control on carbamazepine (total number of patients 100) (52). Marked improvement with at least 50% seizure reduction was achieved in 49% of patients, with 17% being seizure free after 1 year.

Especially partial epilepsy or symptomatic generalized epilepsy may turn out to be refractory to monotherapy. Krämer claims that in clinical practice, only 30% of patients with severe chronic epilepsy are satisfactorily controlled by monotherapy (127). He furthermore estimates that approximately 35% of patients with severe chronic epilepsy benefit from AED combinations. In a home for mentally retarded, Idzinga et al. reported that of 168 inhabitants with epilepsy, 24% were seizure free on monotherapy, and another 8% on two drugs (114). Using the criteria of Krämer for satisfactory control these numbers become 35% on one drug and an additional 27% on two or more. In a trial by Willmore et

al., patients were randomized to add-on valproate or add-on placebo after failing on phenytoin or carbamazepine monotherapy (total number of patients 137) (268). Forty-six percent of patients receiving add-on valproate experienced a greater than 50% reduction in seizure frequency compared to only 12% of patients who received add-on placebo. In a study by Walker and Koon 16 of 43 patients with refractory partial epilepsy responded to carbamazepine with a 50-100 % seizure reduction (258). Twenty-five of the non-responders were subsequently given valproate monotherapy, and 7 of them experienced a 50-100% seizure reduction. Finally, in 17 patients CBZ was then added to VPA, and 6 out of the 17 experienced complete control and 6 had ≥50% seizure reduction in seizure frequency compared to their best control on either monotherapy. The same combination of carbamazepine and valproate was also very successful in a study by Fröscher et al. involving patients with difficult-to-treat epilepsy: 28 of 37 patients with generalized tonic-clonic seizures experienced a 50-100% decrease in seizure frequency, whereas this was accomplished in 5 of 17 patients with complex partial seizures (84).

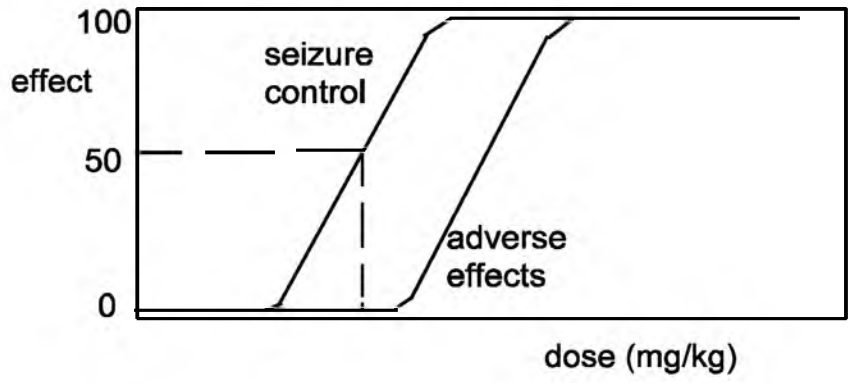
These are not the only trials in patients with refractory partial epilepsy. New antiepileptic drugs first have to prove their efficacy in add-on trials in patients with uncontrolled partial epilepsy before they are licensed. In these trials the new drug is added to baseline medication in patients with uncontrolled partial epilepsy. Many of the new drugs are found to achieve a greater than 50% seizure reduction in approximately 25 to 50% of these patients (82).

The aforementioned results strongly suggest that when needed and when properly selected, polytherapy with antiepileptic drugs can improve seizure control. The exacerbation of seizures due to polytherapy seen in the past, may have been due to intoxication or inappropriate AED selection (195).

Rational polytherapy

In the 1990s interest in combination therapy with AEDs has rekindled. There may be several reasons for this: 1. Clinical necessity because of the limitations of monotherapy. 2. An increased insight into the mechanisms underlying epilepsy and into the mechanisms of action of AEDs. 3. The introduction of several new AEDs, which are costly, but often have more predictable pharmacokinetics and less adverse effects than the established

AEDs.



In other fields of medicine, such as in the treatment of hypertension, cancer and infectious diseases, combination therapy has already proven to be of great value. The added value of polytherapy can be due to either increased efficacy or reduced toxicity or both. The theoretical basis for reduced toxicity of combination therapy can be derived from the log-linear dose-response curve, as Fagan has discussed in an editorial in the *Archives of Internal Medicine* (69). The dose-response curve for toxic effects of a drug generally lies to the right of the curve for the desired therapeutic curve of that drug. Therefore, if two drugs are combined at dosages with 50% effect, the toxicity of such a combination may be minimal, provided their effects result from different mechanisms of action.
Figure 1.1a illustrates this principle.

Figure 1.1a Theoretical therapeutic and toxic dose-response curve

The horizontal axis is a logarithmic scale with arbitrary dose units. The vertical axis is a linear scale showing percent of maximum possible response

It is important to realize however, that the summation of dose-independent adverse effects might prove disadvantageous when using combination therapy, as Fenickel and Lipicky point out in the same issue of the *Archives of Internal Medicine* (73). Nevertheless, except for the aforementioned open trials knowledge about the merits of polytherapy is scarce. Notably, there have been no double blind randomized clinical trials to evaluate AED monotherapy versus combination therapy. The Commission on Antiepileptic Drugs of the

International League Against Epilepsy (ILAE) recognizes "that there is urgent need to evaluate these different policies" (115). The reason that we have fallen behind other disciplines in this respect, may be due to the unfavorable reputation that AED polytherapy has acquired. The reason cannot be that the present monotherapy is considered sufficiently efficient, as even the most optimistic reports do not claim more than 80% success.

However, is the reputation of AED polytherapy really justified ? As mentioned, exacerbation of seizures may have been due to ignorance about specific effects of AEDs, e.g. worsening of absence seizures due to certain AEDs. As far as drug interactions are concerned, much more knowledge has been acquired about the interactions of the established AEDs. Finally, the new drugs generally have more predictable pharmacokinetics and less drug interactions, which makes them more suitable for combination therapy (28).

Perhaps the greatest concern about polytherapy has been the reputed risk of increased toxicity. When our group compared the drug loads of patients on monotherapy and patients on polytherapy, we found that on average patients on polytherapy received higher drug loads. When we subsequently compared groups of patients with equal drug loads of monotherapy and polytherapy, we found that under that condition polytherapy is not associated with more toxicity (135). This seems to take away one of the last objections to the evaluation of certain AED combinations. In fact, this observation led us to start a double-blind randomized clinical trial which will be presented in chapter 6.

1.2 Drug load

A structural problem in the comparison of multiple drug regimens is the neglect of differences in drug load. Drug load can be defined as the amount of drug exposure for a certain indication. What is seldom realized, is that differences in drug load may be responsible for differences in effects when drugs are combined. For example, when a patient who takes a 1000 mg carbamazepine per day is compared to a patient who takes a 1000 mg carbamazepine plus 300 mg phenytoin per day, differences in efficacy and toxicity may very well be found but do they prove that combination therapy is both more efficacious and toxic ? We claim that drug loads have to be equal for a valid comparison

of treatments.

Lammers et al. developed the Prescribed Daily Dose/Defined Daily Dose (PDD/DDD) ratio as an instrument to calculate drug loads (135). The Defined Daily Dose signifies the assumed average dose per day for the drug used in its main indication in adults. For each drug a DDD is assigned by the WHO Collaborating Center for Drug Statistics Methodology based on international textbooks, journals and documentation approved by drug control authorities (264, 265). The assigned DDD values for the AEDs are given in table 1.2.

Table 1.2a Defined Daily Dose values of antiepileptic drugs as assigned by the World Health Organization

Drug	Defined Daily Dose (mg)
Carbamazepine (CBZ)	1000
Phenytoin (PHT)	300
Valproate (VPA)	1500
Phenobarbitone (PB)	100
Ethosuximide (ESM)	1250
Primidone (PRM)	1250
Clonazepam (CLZP)	8
Oxcarbazepine (OXC)	1500
Vigabatrin (VGB)	2000
Lamotrigine (LTG)	300

For information on assigned Defined Daily Dose values, contact the WHO Collaborating Center for Drug Statistics Methodology, c/o Norsk Medisinaldepot AS, P.O. Box 100, Veitvet, N-0158 Oslo, Norway (tel: +47 22169810; fax: +47 22169818).

Pharmaco-epidemiologists use the term 'Prescribed Daily Dose' to express the average dose actually prescribed in a given patient population. The argument for this was that the DDD recommended by the WHO did not accurately reflect the drug exposure in selected populations and that the PDD is more accurate than the WHO-DDD because it is based on the actual dose prescribed by physicians for a new prescription, as obtained from databases referring to the groups studied.

Our group uses the PDD and DDD terminology in a slightly different fashion. First of all,

it is posited that drugs used for the same indication prescribed at a Defined Daily Dose are equipotent (132). Secondly, based on the severity of the disease different doses of a drug will be prescribed by physicians for individual patients. This is the Prescribed Daily Dose as used in our group and in this thesis. In order to compare the exposure of each individual patient, regardless of which AED they used, we employ the PDD/DDD ratio. The PDD/DDD ratio thus serves as a measure for the degree of drug exposure of each individual patient i.e. the drug load. To give an example of drug load calculation, the DDD of sodium valproate is 1500 mg and patient A using 1200 mg of valproate would have a drug load of 1200/1500 i.e. 0.8 PDD/DDD. The DDD of carbamazepine is 1000 mg and patient B using 800 mg of carbamazepine would have a drug load of 800/1000, which is also 0.8 PDD/DDD. When patients uses several drugs for the same indication the drug fractions can be added to each other, as the DDD's are the average maintenance dose and thus represent equally effective doses of these different compounds for that indication. Patient C using 600 mg of valproate and 400 mg of carbamazepine has a drug load of 600/1500 + 400/1000 = 0.8 PDD/DDD. Patients A, B and C all use equal drug loads, which makes them eligible for comparison.

In chapter 2 background information of the PDD and the DDD will be given and the accuracy of the current DDD's for AEDs will be evaluated. In chapter 3, the theoretical background and possible applications of the PDD/DDD method are discussed.

1.3 Outcome measures

In AED trials there has been a large variety of efficacy and toxicity measures, which has affected the comparability of these trials. Recently the Commissions on Outcome Measurement in Epilepsy and on Antiepileptic Drugs of the International League Against Epilepsy (ILAE) have published reports in which these issues are addressed and recommendations are made (115, 116).

The primary endpoint for many studies, and the most clinically relevant one, is considered to be effectiveness. Effectiveness is a measure encompassing both efficacy (i.e. seizure control) and tolerability (i.e. adverse effects) (115). It is best measured by the so-called retention time. This is the time to withdrawal from a study after randomization because of

inadequate efficacy and/or poor tolerability. Naturally, one also has to look at efficacy and tolerability when interpreting effectiveness, but their assessment is much more complicated.

Assessment of seizures

Efficacy is defined as a reduction in seizure frequency and/or severity directly attributable to treatment. Efficacy can be evaluated in several ways, depending on the seizure frequency before treatment: Time to first seizure, estimation of time to one year remission, change in seizure frequency, percentage seizure-free at a certain time are all measures based on seizure frequency.

These measures do not take seizure type and severity into account, which is an important flaw. When a drug changes a patient's usual four tonic-clonic seizures per month into four complex partial seizures per month, this effect will not be reflected in the seizure frequency. Usually complex partial seizures are less severe than generalized tonic-clonic seizures, and therefore the patient has benefitted from the treatment, without it being shown in the results. Furthermore, a 50% decrease in seizure frequency has a different impact in a patient who has 2 seizures per year than in a patient who has 10 seizures per year (123).

Even if seizure types are taken into consideration, a patient can benefit from a drug although he still has as many complex partial seizures as before, but the seizures are less severe and he or she recovers more quickly from them. Furthermore, clustering of seizures, the presence of an aura and the difference between nocturnal and diurnal seizures must be taken into account (123). Therefore, seizure severity should somehow be measured next to seizure frequency. Special clinimetric scales have been developed in order to measure seizure severity, which will be discussed later in this chapter.

Assessment of adverse effects

Tolerability is assessed by the incidence, severity and impact of drug-induced adverse effects. The most important measure of tolerability is deemed to be discontinuation of a drug due to intolerable or life-threatening adverse effects.

Adverse effects of AEDs can be very diverse, but may be classified into three major

categories: 1. dose-dependent neurotoxic effects (e.g. somnolence, cognitive impairment and cerebellar signs), 2. dose-dependent systemic effects (e.g. gastro-intestinal complaints, weight changes), and 3. idiosyncratic effects (e.g. hypersensitivity syndrome, liver failure and bone marrow suppression). For a detailed description of adverse effects per drug, the reader is referred to *Antiepileptic Drugs* (142).

In most clinical epilepsy studies, the detection of adverse effects has been flawed in two respects: adverse effects were only detected by self-reporting and the severity of adverse effects was not quantified. Self-reporting may result in an under-reporting of adverse effects, because of the patient's unfamiliarity with adverse effects and because the patient may attribute certain complaints to other causes (172). Use of a checklist will maximize reporting but may also produce complaints unrelated to the use of the drug or to epilepsy. In chapter 3 the frequency of adverse effects as measured by self-reporting and by use of a checklist will be compared.

Quantification of the severity of adverse effects is important, because AEDs may differ in the degree of adverse effects they cause. For example, are patients sleepy only after they return home from work or are they sleepy the whole day ? For all the adverse effects AEDs cause, such as ataxia, headache and hair loss, there is a need to know the severity for a more rational comparison.

The Commission on Antiepileptic Drugs considers the assessment of adverse effects to be the most in need of improvement, and therefore makes special recommendations for its assessment in clinical trials: Assessment should be clearly described in the protocol. Tolerability should be assessed preferably by checklists, if not by some form of standardized interview or examination. Incidence and prevalence of adverse effects should be measured at different time points, and preferably the severity of adverse effects should also be assessed. Specialized tests, such as laboratory tests and neuropsychological tests are considered to be of value and finally, post- marketing surveillance should be stimulated (115). Clinimetric scales have also been designed for the assessment of adverse effects and will be discussed in section 1.4.

In its report,, the Commission on Antiepileptic Drugs also acknowledges that it is often hard to demonstrate differences in efficacy, as has been shown in the large comparative monotherapy trials of the established AEDs (107, 173, 174, 204). It is easier to find

differences in adverse effects or in withdrawal rates due to adverse effects, as has been shown in the aforementioned trials by differences in retention time.

Assessment of Quality of Life (QoL)

Quality of life has become an important outcome measure for patients with chronic illnesses requiring long-term therapy. Some even claim it is the ultimate outcome measure. Many QoL scales have been developed, however generic QoL scales leave many important disease-specific topics uncovered. Therefore the number of disease-specific quality of life instruments has also increased dramatically, especially concerning cancer, renal disease and diabetes (13). Seizure activity and AED-adverse effects are obviously important epilepsy-specific issues, but psycho-social factors may have an even larger effect on the lives of patients. Furthermore, even when seizure frequency is low, these problems, such as seizure worry and unemployment, may continue to exist. Psycho-social issues to be considered are shown in table 1.3 (60).

Table 1.3 Psychosocial issues in epilepsy

General issues Self-esteem, dependence, driving, cognitive and behavioral problems, fear and embarrassment of seizures, stigma (real or perceived) and discrimination	*Recreation* Sports, hobbies, alcohol consumption, reproductive behavior
Education Learning problems and social interactions	*Home* Family relationships and social activities
Work Discrimination, unemployment, underemployment, ability to perform	*Insurance* Health, life, handicaps

As is clear in this table, QoL scales are dearly needed in a field where traditionally seizure frequency was the all-important outcome. Therefore tools to measure quality of life of epilepsy patients have been developed or are being developed. The sensitivity of these tools, especially for efficacy and tolerability is currently uncertain. There is some suggestion that QoL outcomes are still too dependent on seizure freedom to add valuable extra information (117). One of these scales, the Quality Of Life In Epilepsy (QOLIE) scale, will be discussed in paragraph 1.4.

1.4 Clinimetric epilepsy scales

In everyday practice physicians are used to work with so-called 'soft' data, such as the medical history of the patient and findings on physical examination, and 'hard' data, such as the results of laboratory or microbiology investigations, or of imaging techniques. What makes laboratory data 'hard' data, is that international laboratory standards have been defined and thus the results of a test are scientifically trustworthy. No such standard procedures have been developed for the appraisal of clinical data, such as the magnitude of symptoms or disability. When comparing treatments for angina pectoris for example, a patient can have less complaints of chest pain and his functional status can be improved but we do not know exactly how much he has improved. Similarly, for many findings on physical examination large inter-rater variabilities have been found. Because these important clinical data are usually not quantified, statistical comparison between therapies is difficult (71).

An example in epilepsy treatment which has already been mentioned is the evaluation of adverse effects. Lammers et al. found that often only the incidence of adverse effects is reported in anti-epileptic drug trials, which may render misleading data (136). For example treatment A and B can be found to result in sleepiness in 20% of patients. Theoretically treatment A could have resulted in a light feeling of drowsiness in the evening in 20% of patients, whereas the same proportion of patients using treatment B could have been near-comatose, without this difference being reflected in the results of the trial.

Obviously, methods for the classification or quantification of clinical data need to be developed. The science for the measurement of clinical data has appropriately been called clinimetrics and has been extensively discussed by Feinstein in his classic book of the same name (71). The subject of clinimetrics and the construction of clinimetrics is briefly discussed in chapter 2.

In the last 20 years a number of scales have been developed for the clinimetric evaluation of epilepsy. Four scales have been developed specifically to quantify seizure severity: the Veterans Affairs (VA) Seizure Frequency and Severity Rating Scale (45), the Liverpool Seizure Severity Scale (14, 15), the National Hospital Seizure Severity Scale (189) (a modification of the Chalfont Seizure Severity Scale (65)) and the Occupational Hazard Scale (118). These scales have been compared by Cramer et al. and by Lammers (43, 132). The VA Seizure Frequency and Severity Rating Scale is the only scale which takes seizure

type (i.e. simple partial, complex partial or generalized tonic clonic), seizure frequency and seizure severity all into account. Another three scales have been developed to evaluate antiepileptic drug adverse effects: the Veterans Affairs (VA) Neurotoxicity and Systemic Toxicity ratings (45), Liverpool Adverse Events Profile (89) and the Neurotoxicity Scale (5, 6).

The VA Seizure Frequency and Severity Rating Scale and Neurotoxicity and Systemic Toxicity ratings can be added to produce a composite score that reflects the total effect of seizures and of AEDs on the quality of life of the patient (45). These scales were used in the two VA monotherapy trials that were discussed in paragraph 1.1. In these trials all toxicity was compared to pre-entry values for each patient, thus only increased problems resulting from AED therapy would be scored. The composite score was considered a sensitive measure of change, demonstrating differences between drugs (173, 174).

As the composite format enables the evaluation of both efficacy and toxicity, the NERG chose the VA Ratings as the method to be used to in its studies (266). In our slightly adapted scale, named the Composite Index of Impairments (CII), serum levels were left out as a modifying factor and other modifying factors were somewhat differently defined. The other items of the VA Ratings were left unchanged. However, as some of the items of the VA Ratings were changed by its authors based on the experiences after the first VA trail, these changes have been adopted in the CII (43, 172).

The CII consists of three subscales: the Seizure Activity Index, the Neurotoxicity Rating, and the Systemic Toxicity Rating. The outcomes of all three subscales are dimensionless units, enabling the addition of the results to a single composite score. In the usual outpatient epilepsy population the CII score will vary between 0 and 50. A score of zero is the ultimate goal: no seizures and no adverse effects. A score reduction of $\geq$ 10 points signifies a clinically relevant change. A score above 50 is indicative of an unacceptable amount of seizures, severe adverse effects, or a combination of high seizure activity and high toxicity. If a patient is using AEDs and has a score $\geq$ 50, a medication change (dose adjustment, drug substitution, adding another drug) is in order. Table 1.4a illustrates this.

Table 1.4a Clinical relevance of CII scores

CII	Impairments
0	none
1-10	mild
11-49	moderate
≥50	severe

The range of scores from 0 to 50 is designed to reflect the usual outpatient population. The SA index will render higher scores than 50 in patients with frequent seizures, such as in some people with severe brain damage. The subscales will be reviewed in detail in chapter 2, and the CII is shown in full detail in appendix A. The CII is used in the trial described in chapter 6.

Quality of life

As was described in paragraph 1.3, the QOLIE-89 was developed to assess health-related quality of life in a general epilepsy population (61). Health-related QoL (HRQL) refers to the way in which individuals function and to their perceived well-being in physical, mental and social domains of life. The WHO defines health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity".

The QOLIE-89 includes the RAND 36-Item Health Survey 1.0 as a generic score coupled with epilepsy-specific items grouped into four domains: epilepsy-targeted, cognitive, mental health, and physical health. Generic measures evaluate global functioning and well-being and allow comparisons with patients with different diseases or the general population. Disease-targeted measures focus on issues relevant to the disease and allow more detailed and sensitive comparison among epilepsy patients. Item selection was based on patient and physician input and on a literature review, thus maximizing content validity (61). In a study of 304 adult epilepsy patients reliability and construct validity of the QOLIE-89 were supported.

Two abbreviated instruments were derived from this scale (QOLIE-31 and QOLIE-10) (44). The QOLIE-10 questionnaire was extracted from the QOLIE-89 to provide a brief screening instrument to be used in daily practice. This instrument was selected for the trial described in chapter 6, to have an indicator for possible differences in QoL without entering the question why and in what respect such differences would occur. The QOLIE-10 will be described in detail in chapter 2.

1.5 Neuropsychological effects of antiepileptic drugs

In the last twenty years, it has become clear that AED treatment may have a much greater impact on cognitive function than previously had been expected. However, the evaluation of these effects is not straightforward, as pre-existing brain damage, interictal discharges, seizure activity and the epileptogenic focus may affect cognitive functioning as well (and even more !) (3, 249). The type of pre-existing neuro-psychological impairment is largely dependent on the site of the brain lesion or brain dysfunction. A relationship has been reported to exist between memory impairment and temporal lobe epilepsy, but also between impaired attention and high frequency tonic-clonic seizures and between impaired mental speed and use of high dose AED or AED polytherapy (3). Transitory cognitive

impairment can occur during interictal discharges (also discharges < 3 seconds or focal discharges) and absence seizures.

The literature is not clear on the effects AEDs have on cognitive functioning. Vermeulen and Aldenkamp reviewed over 90 reports in which the cognitive effects of AEDs were studied (253). Many of these studies failed to meet the basic standards for methodology, design and analysis. Therefore no evidence-based answer could be given to the most important question, i.e. whether AEDs in therapeutic dosages do have negative cognitive effects in a significant proportion of patients. However, there is some consensus that newer AEDs such as lamotrigine and gabapentin (GBP) may have less effect on cognition than the established AEDs.

The neuropsychological department of the SEIN (Stichting Epilepsie Instellingen Nederland: an Epilepsy Center based in Heemstede and Zwolle in the Netherlands), has developed a computerized program for neuropsychological assessment (7). This test battery, called FePsy, was designed for the detection of drug-induced effects and for pre-surgical evaluation. The battery covers a broad spectrum of neuro-psychological functions such as memory, attention, problem solving, visuo-motor performance, language and cerebral dominance (3). The investigator can make a selection of tests he or she wishes to administer, depending on the research questions. Three tests from the FePsy battery are described in detail in chapter 2 and have been used in the clinical trial described in chapter 6.

Chapter 2 Methodology

In this chapter background information is given on the methods used in our studies. These methods include the PDD/DDD ratio, the clinimetric epilepsy outcome scales and the neuropsychological tests. Furthermore, a method to calculate drug loads from serum levels, which was used in an earlier study, is re-introduced (133). In chapter 3 the drug load concept will be used to compare monotherapy and polytherapy in a number of trials by other researchers and the theoretical background and possible applications for its use are discussed. Readers familiar with our methodologies may want to continue with chapter 3.

2.1 Drug load

Studies on the use of drugs have become a major issue in recent years. Comparisons have shown large differences in drug utilization for similar indications between countries. An internationally accepted methodology allowing these comparisons is the Defined Daily Dose method, which was introduced by the WHO Drug Utilization Research Group as a tool to convert drug consumption data from different sources into comparable units (19). The WHO Group determines and assigns the average maintenance dose of a drug for its main indication, i.e. the Defined Daily Dose (DDD), for each individual drug by analyzing literature and drug registration data. The WHO has thus assigned DDDs to all widely used drugs for their main indication; the list is available from the WHO. The DDD of the antiepileptic drug carbamazepine for example is 1000 mg (263).

Although the DDD is considered to be the average maintenance dose, it is meant to be used as a technical unit of measurement and comparison rather than as a target dose (20). Analyzing the DDDs sold per 1000 inhabitants in a population for different drugs creates insight into prescription patterns and allows comparison with other regions, other time periods, other drugs etc..

The analysis of DDD prescription rates may also be used as a "therapeutic audit to follow and influence therapeutic habits of health personnel" (20). Analysis of the use of anxiolytic-hypnotic drugs (AHD) between different cities and counties in Sweden and differences in suicide rates, revealed that the city of Malmö had both the highest AHD prescription rate and the highest suicide frequency in 1978 (178). Prescription surveillance and an information campaign in Malmö were accompanied by a 4-year decrease in AHD-prescribing (12%), in AHD-abuse (40%), in barbiturate prescribing (45%) and in barbiturate suicides (70%). In Göteborg, where no surveillance or information campaign were undertaken, barbiturate suicides decreased by 45%, but there was an increase in overall AHD (± 12%) and benzodiazepine (± 24%) prescribing, surpassing Malmö after five years.

In hospitals, the total DDD per 100 bed days can be analyzed per drug to give an indication of the number of patients treated with a particular drug in different hospitals (18, 106). Such an analysis showed that the introduction of new guidelines for the use of antibiotics for prophylaxis and treatments in the surgical departments of the Nijmegen University Medical Center had resulted in a decrease of prophylactic drug consumption per operation

and a higher quality of both prophylaxis and infection therapy (101).

The DDD does not however reflect the actual prescribed dose in all situations. Therefore the Prescribed Daily Dose (PDD) as the average prescribed dose in a population was introduced. Several authors have studied differences between PDD and DDD in large populations using a particular drug. Wessling and Böethius, for example, compared sales figures (DDD data) with actual prescription data (individuals for which a prescription had been dispensed) for 8 different drugs (260). For antibiotics (phenoxymethyl-penicillin, erythromycin) the number of users based on the DDD figure ranged from 4% below to 28% above the manifest use, which means that the DDD was set below the actual PDD. For naproxen the DDD-derived figure was 80% below the apparent use, which means that the DDD was set much too high relative to the PDD. Digoxin had the closest correlation between the DDD figure and the apparent use. The PDD appears to approximate the DDD value better when it concerns drugs which are prescribed chronically instead of for one or two short periods, and when drugs are used for only one indication. Defined Daily Doses are based on cross-sectional data and PDDs can deviate from DDDs according to the population studied. Friesen et al. for example showed that the PDDs for NSAIDs differ between populations visiting outpatient clinics and patients admitted to the hospital (80). For the PDD/DDD ratio to be an accurate indicator of drug load in polytherapy, it is required that the DDDs approximate the average therapeutic dose for the drugs concerned (i.e. their average PDDs). As the DDD data for certain AEDs did not seem correct at inspection, prescription data of AEDs were collected to determine possible differences in PDDs and DDDs. The PHARMO database of the university of Utrecht which contains all prescription data from 6 representative Dutch towns in 1992 (total population ± 300.000), was used to determine the average PDDs for AEDs in a community-based population (108). For data from a secondary center records of the neurology department of the Nijmegen University Hospital were studied. The SEIN in Heemstede supplied figures of the average dosages of antiepileptic drugs prescribed at a tertiary center. The average dosages of AEDs in monotherapy and the average dosages in polytherapy are shown as PDD data in table 2.1. To allow comparison, the DDDs for these AEDs as assigned by the World Health Organization are also given in these tables (263).

Table 2.1 PDD data for monotherapy and polytherapy

Drug	DDD (mg/day)	Mono PHARMO (n=1995)	Mono Nijmegen (n=280)	Mono Heemstede (n=840)	Poly PHARMO (n=435)	Poly Nijmegen (n=102)	Poly Heemstede (n=2361)
CBZ	1000	0.50 (n=909)	0.68 (n=131)	0.81 (n=412)	0.77 (n=260)	0.81 (n=76)	1.05 (n=1678)
VPA	1500	0.66 (n=321)	0.68 (n=94)	0.71 (n=236)	0.83 (n=214)	1.04 (n=48)	1.01 (n=1279)
PHT	300	0.86 (n=389)	1.01 (n=38)	1.00 (n=80)	0.84 (n=218)	0.96 (n=38)	1.04 (n=847)
PB	100	0.96 (n=167)	1.21 (n=10)	1.17 (n=18)	1.03 (n=124)	1.34 (n=20)	1.05 (n=335)
VGB	2000	0.71 (n=6)	-	0.83 (n=10)	0.73 (n=66)	0.92 (n=26)	0.84 (n=287)
OXC	1500	0.90 (n=2)	0.60 (n=1)	1.2 (n=74)	1.40 (n=3)	-	1.62 (n=235)
ESM	1250	0.46 (n=11)	-	0.8 (n=2)	0.57 (n=18)	-	0.62 (n=116)
CLZP	8	0.30 (n=169)	0.38 (n=5)	0.39 (n=6)	0.34 (n=46)	0.3 (n=8)	0.4 (n=80)
PRM	1250	0.44 (n=21)	0.48 (n=1)	0.25 (n=2)	0.45 (n=22)	0.55 (n=2)	0.42 (n=81)

Data from the PHARMO database, the University Hospital Nijmegen and the SEIN in Heemstede, the Netherlands. The DDD as assigned by the WHO are listed. The PDD/DDD ratio for each drug is given per database and per monotherapy ("mono") or polytherapy ("poly"), and the number of patients the drug is given in brackets. In Heemstede, in addition to the given data, 434 patients used an average 222 mg lamotrigine daily (DDD=300 mg) and 470 patients used an average 17 mg clobazam daily (no DDD assigned).

The PDDs of phenytoin, phenobarbital and vigabatrin when given as monotherapy corresponded reasonably well with their official DDDs. The PDDs of ethosuximide, clonazepam and primidone monotherapy were considerably lower than their assigned DDDs, although patient numbers were very small. It is important to note however that the DDDs of the two most widely used AEDs, carbamazepine and valproate, also appeared to be incorrect. Their PDDs for epilepsy patients visiting a university hospital and an epilepsy clinic were only approximately 0.6 to 0.8 of their assigned DDDs. The even lower PDD value for carbamazepine in the PHARMO database may have been influenced by the prescription of the drug for other indications in the community-based population (e.g. neuralgia, headache), although only prescriptions which had been maintained for over six months were admitted to the PHARMO database. Furthermore individual drug exposure is of course influenced by a variety of factors, such as socio-economic status, disease severity, co-morbidity, compliance etc. (108). However, the PDDs of carbamazepine in large monotherapy trials published from 1991 to 1995 were also only between 450 and 722

mg (33, 55, 173, 204, 252). The PDDs of valproate in large monotherapy trials of the past five years were between 688 and 1082 (42, 70, 204, 252), with the exception of the trial by Mattson et al., where the PDD was 2099 mg (173). Giuliani et al. found very low PDDs of anti-epileptic drugs in an Italian community: carbamazepine 442 mg, valproate 389 mg, phenytoin 103 mg and primidone 239 mg (90). In this group 61,5 % of the AED users had active epilepsy; the remaining 38,6 % of patients had experienced a single convulsion (12,5%) or a febrile convulsion (11%) or used AEDs for other indications. In view of all this evidence, it seems unlikely that the deviation of our PDD figures from the DDD values is limited to the Netherlands. We have therefore recommended to the WHO Collaborating Center for Drug Methodology to adjust the DDD figures for carbamazepine and valproate.
Another noticeable phenomenon is that antiepileptic drugs are given in higher dosages when given in a multiple drug regimen. A possible explanation is that a dichotomy exists in the epilepsy population: a large group of patients that respond well to low dosages of one antiepileptic drug and a second, smaller group of patients that need a high total drug load of AEDs. In the literature similar findings have been reported (90, 171). Thus the PDD/DDD ratio may also be used as a parameter indicating average severity of the disorder in the population concerned.
Meinardi and Meijer have shown that in a special center for epilepsy the average amount of antiepileptic drug, expressed in DDDs, used per patient in 1972, was almost the same as in 1985 notwithstanding a substantial change in the choice of drugs prescribed (167). This supports the rationale of adding up different PDD/DDD ratio's.

Serum levels

An analogous ratio was developed for the serum levels of AEDs, the Observed Serum Level (OSL)/ Average Therapeutic Level (ATL) ratio (132). The OSL is the serum level found for each AED prescribed for the patient. The ATL was assessed, by analyzing literature data (83, 98, 124, 137, 177, 197, 223). As is possible with PDD/DDD ratio's, the OSL/ATL ratio's of individual drugs can be added up calculate the total drug load of a patient using polytherapy. The ATLs of the standard AEDs can be found in paragraph 3.1.

2.2 Clinimetrics and the Composite Index of Impairments

Clinimetrics

Feinstein defines clinimetrics as the domain concerned with indexes, ratings scales, and other expressions that are used to describe and measure symptoms, physical signs, and other distinctly clinical phenomena in clinical medicine (71). Clinimetric indexes or rating scales will enable clinical data to be described quantitatively, and for them to used as determinants of prognosis, for evaluation of therapy and for clinical decision making. Classic examples of clinimetric indexes are the Apgar score and the Glasgow Coma Scale, which are both used to follow clinical condition and prognosis.

Feinstein's book gives a manual for the development of a clinimetric scale, such as the choice of variables and the organization of the scale, but also for their evaluation (validation). There are three goals an index should fulfill: sensibility, consistency and accuracy. The sensibility of a scale is often judged by its face and content validity. Face validity for a clinical instrument has been defined as the application of enlightened common sense, which is a mixture of ordinary common sense plus a reasonable knowledge of pathophysiology and clinical reality (71). In assessing content validity, the component parts are evaluated more thoroughly for omissions, inappropriate inclusions, weighting of components and the use of an appropriate scale.

A consistent or reliable clinimetric scale yields consistent results when measurement is repeated. Input, instrument and inter- and intra-observer variability may threaten the consistency of a scale. When the instructions are clear and the scale is easy to use, it will often have good consistency.

Accuracy is usually assessed by comparing the observed measurement and the result obtained with a standard reference system. Evaluating whether a scale is accurate, may be difficult in absence of a definite standard (e.g. what is the gold standard of anxiety or pain ??). When a gold standard exists, measurements can be compared to it, which is called evaluation of criterion-related validity. When there is no gold standard, the so-called construct validity is tested which means that the effectivity of the index in describing an actual construct or condition is tested.

Feinstein has also discussed what a clinimetric scale for epilepsy should measure: frequency and severity of ictal and interictal events, i.e. seizures and adverse effects (72). Furthermore, he suggests that consistency may be difficult to test because of the paroxysmal character of the disorder, which makes it necessary to assemble different

patients and different clinicians at the same time and place. Regarding accuracy, there is no gold standard for the measurement of epilepsy.

Feinstein urges to concentrate mainly on the sensibility of an epilepsy index. However, there is quite a difference of opinion between experts which attributes to include in such an index and how to weigh them. This may differ between patients as well, so patients should be offered the opportunity to rate the importance of each attribute. An alternative approach might be to let the patient give one global rating of improvement, for example on a visual analogue scale, which corresponds to a quantification of the old-fashioned 'how are you'-question. After this rating extra questions may be added to determine what has improved or deteriorated. This seemingly simple 'how are you'-rating may bewilder people, especially coming from Feinstein, the pioneer of clinimetrics. He argues however that this has often been found to be the most powerful index of effectiveness and that it has often been used as a gold standard.

Composite Index of Impairments

The Composite Index of Impairments (CII) consists of three subscales: the Seizure Activity Index (SA), the Neurotoxicity scale (NTX) and the Systemic Toxicity scale (STX). The outcomes of all three subscales are dimensionless units, enabling addition of the results to a single composite score. The subscales are described here and the CII is shown in full detail in Appendix A.

Index of Seizures

The Seizure Activity index (SA) can be calculated by deducting points from the Index of Seizures (IS) when certain modifying factors are present. The IS is a score which expresses seizure frequency in relationship to the seizure type. In the IS, as in the VA Seizure Frequency and Severity Rating, only the most frequently occurring seizure types are rated, i.e. generalized tonic-clonic seizures and complex and simple partial seizures. If a patient has more than one seizure type, the scores of these seizure types are added up to arrive at the IS. The method of scoring the Index of Seizures for each of these three different seizure types is shown in tables 2.2a -2.2c The number of seizures are counted since the last visit (for partial seizures) or since starting the drug (for tonic-clonic seizures).

Table 2.2a Scoring method for generalized tonic-clonic seizures

Generalized Tonic-Clonic Seizure	IS Score
- Three or more seizures/12 months	20/seizure
- Two seizures/first 3 months	50
- Two seizures/6 months	45
- One seizure/first 3 months	40
- One seizure/6 months	40
- Two seizures/6-12 months	30
- One seizure/6-12 months	20
- Two seizures/12-24 months	20
- One seizure/12-24 months	10
- Seizure free >24 months	0

By looking at the scores given in table 2.2a, one can see what is deemed acceptable. Based on the severity of tonic-clonic seizures, one or two seizures in 6 months is considered almost unacceptable (40-45 points), except in the presence of modifying factors (see next page). One or two seizures in more than a year however, represents reasonable seizure control.

Table 2.2b Scoring method for complex partial seizures

Complex Partial Seizure	IS score
Equal to or greater than 4 seizures/month	50 (+ 10 per extra seizure)
Three seizures/month	40
Two seizures/month	30
One seizure/month	20
One seizure in 1-3 months	15
Less than one seizure in 3 months	10
Seizure free	0

Table 2.2b shows that four complex partial seizures per month, in the absence of modifying factors, will render a score of 50 points. As partial seizures are difficult to control, less than a seizure per month represents fairly good seizure control (15 points). As is shown in table 2.2c on the next page, it takes over 12 simple partial seizures per month to reach a score of 50. Again, less than one seizure per month represents fairly good seizure control (13 points).

Table 2.2c Scoring method for simple partial seizures

Simple Partial Seizure	IS score
Equal to or greater than 7/month	33 (+3 per extra seizure)
Six seizures/month	30
Five seizures/month	28
Four seizures/month	25
Three seizures/month	23
Two seizures/month	20
One seizure/month	15
One seizure in 1-3 months	13
Less than one seizure in 3 months	10
Seizure free > 1 year	0

Seizure Activity index (SA)

This index is a modification of the Index of Seizures. The modifiers are used per seizure type and the modified scores per seizure type are added up to produce the Seizure Activity score.

The modifiers are:

1. Presence of an aura, in the case of a generalized tonic-clonic or complex partial seizure. The patient is aware of the fact that a seizure is about to occur, in which case he can take precautions to prevent self-harm. When an aura is present, the seizure score is reduced by 20 percent.*
2. Precipitating factors provoking a seizure, which are avoidable, such as lack of sleep, use of alcohol, reduce the seizure score by 50 percent.
3. Restriction of seizures to the period of sleep or of awakening, reduces the seizure score by 40 percent.
4. Restriction of interference with function to less than 15 minutes reduces the seizure score by 50 percent **.
5. Clustering of seizures reduces the seizure score by 50 percent **.

* Only to be used with complex partial seizures and generalized tonic clonic seizures.

** Only to be used with partial seizures.

Neurotoxicity Index (NTX)

The NTX scores the incidence and severity of neurological adverse effects due to the anti-

epileptic medication. When an adverse effect is present, the score of that effect is above zero and the severity is scored 'relative to the importance of stopping the drug causing the problem' (45). This means that the physician assesses which of the given descriptions of severity applies to the patient which leads to a given score. For example, sleepiness only in the evenings scores 5 points while sleepiness during the day scores 10. In table 2.2d the range of possible scores when an adverse effects listed in the NTX is present, is shown.

Table 2.2d Range of Neurotoxicity scores per symptom

Neurotoxicity	Scoring range
Diplopia	15-30
Nystagmus	5-10
Dysarthria	5-30
Ataxia/gait disturbance	5-50
Problems with rapid alternating movements	15
Tremor	10-50
Sedation	5-50
Affect and mood disturbances	5-50
Cognitive impairments	5-50
Dizziness	3-50
Headache	3-50

Systemic Toxicity Index (STX)

The STX scores the incidence and severity of the systemic adverse effects, as the NTX does for neurotoxicity. In table 2.2e the range of scores of the STX is present.

Table 2.2e Range of Systemic Toxicity scores per symptom

Systemic toxicity	Scoring range
Drug-related gastrointestinal problems	3-50
Hematopoietic system problems	50
Dermatologic problems	20-50
Loss of libido/ impotence	20-50
Hyponatremia	50
Elevated liver function tests	25-50
Weight gain	3-20
Changes in hair/hair loss	5-50

The planning committee of the VA scales, on which the CII is based, considered the appropriate weighting of severity for each factor relative to the need to alter therapy. The point system was reviewed by a dozen neurologists who specialize in epilepsy (45). A difference of approximately 10 points in the composite score indicates a clinically important difference. A composite score $\geq$ 50 denotes an unacceptable epilepsy control or

serious adverse effects, or a combination of seizures and adverse effects sufficiently serious to discontinue the causative drug (see table 1.3) (45).

The reproducibility of the CII was assessed for both individual scores of patients as for inter-rater agreement for the four ranges (266). The individual CII scores made of 24 patients by the investigator and by the treating clinician correlated well ($r=0.90$). No systematic difference was seen between the scores obtained by both evaluators. The inter-rater agreement for the four ranges of the CII was moderate ($\kappa=0.52$), but the agreement on whether the epilepsy control was acceptable or unacceptable was good ($\kappa=0.63$).

To assess the suitability of the index the hypothesis was tested whether an increased chance existed that the time until the next consultation for patients with a CII score ≤ 50 (acceptable epilepsy control) would be > 3 months and that this time would be < 3 months for patients with a CII score ≥ 50 (unacceptable epilepsy control). The relation between the length of time until the next consultation and the CII score was significant (Wilcoxon rank sum test $p<0.01$) and inverse ($r=-0.66$), and showed the suitability of the Composite Index of Impairments as an indicator of clinical severity of epilepsy.

2.3 *QOLIE-10*

The QOLIE-10 questionnaire was extracted from the QOLIE-89. The ten-item questionnaire covers general and epilepsy-specific domains, grouped into three factors: epilepsy effects (memory, physical and mental effects of medication), mental health (energy, depression, overall quality of life), and role functioning (seizure worry, work, driving, social limits) (44). The QOLIE-10 is completed by the patient, for example in the waiting room. For each of the 10 questions the patient can choose between five answers, ranging from very negative to very positive. The three QOLIE-10 subscales correlated well with their QOLIE-89 counterparts. Concerning construct validity, the QOLIE-10 responses correlated well with the POMS (Profile Of Mood States) which is used to assess tension, anger, depression, vigor, fatigue and confusion. Correlations of systemic and neurotoxicity scores with the QOLIE-10 subscales were not high. Low seizure frequency patients had better scores on the QOLIE-10 role functioning-subscale. The scale had good consistency/reliability and is shown in table 2.3a (44).

Table 2.3a The QOLIE-10 Questionnaire

How much of the time during the past 4 weeks .....

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
1. Have you had a lot of energy ?	1	2	3	4	5
	None of the time	A little of the time	Some of the time	Most of the time	All of the time
2. Have you felt down-hearted and blue ?	1	2	3	4	5
	Not at all	A little	Somewhat	A lot	A great deal
3. Has your epilepsy or antiepileptic medication caused trouble with driving?	1	2	3	4	5

During the past 4 weeks, how much of the time have you been bothered by .....

	Not at all bothersome	A little	Somewhat	A lot	Extremely bothered
1. Memory difficulties ?	1	2	3	4	5
2. Work limitations ?	1	2	3	4	5
3. Social limitations ?	1	2	3	4	5
4. Physical effects of antiepileptic medication ?	1	2	3	4	5
5. Mental effects of antiepileptic medication ?	1	2	3	4	5

	Not at all fearful	Mildly fearful	Moderately fearful	Very fearful	Extremely fearful
9. How fearful are you of having a seizure during the next month ?	1	2	3	4	5
	Very well; could hardly be better	Pretty good	Good and parts about equal	Pretty bad	Very bad; could hardly be worse
10. How has the quality of your life been during the past 4 weeks ? That is, how have things been going for you ?	1	2	3	4	5

The QOLIE-10 may provide a useful screen for epilepsy-related QoL problems, with which

patients can alert their physicians and the physician-patient interaction can be facilitated. The developers state that it is not a research tool, but that it can be a value-adding aspect to clinical practice (44).

2.4 Neuropsychological outcome measures

FePsy

The FePsy is a computer program which contains a range of computer-aided tests for neuropsychological assessment. Three of these tests were used in our comparative study of mono- and polytherapy described in chapter 6: the tapping task, the binary choice task and the computerized visual searching task (CVST):

- Tapping task: This task is an adaptation of the similar task in the Halstead-Reitan battery. The test person is instructed to tap the space bar with the index finger as fast as he or she can during 10 seconds. Tapping speed is measured for both hands. It provides a measure of motor speed.
- Binary choice task: In this task there are two stimuli: a red square on the left or a green square on the right of the screen which appear on the screen in random order. The patient is instructed to press a specific key with the left hand when the red square appears and to press another specific key with the right hand when the green stimulus appears. The patient is instructed to react as quickly as possible, but to make no mistakes. This is a measure of the reaction time that includes a decision component.
- Computerized Visual Searching Task (CVST): This task is an adaptation of Goldstein's visual searching task. A centered grid pattern has to be compared to 24 surrounding patterns, only one of which is identical. The test consists of 24 trials (the 24 patterns change after 12 trials). The task deals with visual information processing.

Retesting usually leads to a learning or practice effect (7). For tests in which every item has the same difficulty level, a pool of items is used and there is a random selection of items each test. The learning effect does not occur through learning the sequence of items. In tasks such as the CVST, the profile time of each item is important. Here fixed retests must be made.

In the tapping task epilepsy patients achieve less taps than controls, and the difference between the dominant and the non-dominant hand is greater. In healthy controls the 18

year-olds perform twice as fast 8 year-olds. In the binary choice task the test scores are not different from normal controls. The reaction times do become lower as people become adults.. In epilepsy patients the decrease in average CVST-time is much less from 11 years on. There is no difference between controls and patients in errors made. Probably the same problem-solving strategy is used and differences depend on slower mental speed (7).

Chapter 3 Drug load and evaluation of adverse effects

Introduction

In the first two chapters it became clear that patients on AED polytherapy usually have higher drug loads than patients on AED monotherapy. It is quite conceivable that these drug load differences may be (partly) responsible for the reported differences in effects between mono- and polytherapy. In paragraph 3.1 a literature study is described in which this hypothesis is put to the test with respect to adverse effects. In paragraph 3.2 the broad relevance of drug load in clinical studies is discussed and theoretical arguments are given for the PDD/DDD method.

As was discussed in chapter 1, clinimetric evaluation has been introduced to measure the severity of adverse effects in AED trials. However, the danger of using these scales is that false-positive results may be introduced. To evaluate this, adverse effect data yielded by self-reporting and by clinimetric scales are compared in paragraph 3.3.

3.1 Polytherapy in epilepsy: a review of drug load and adverse effects

Introduction

One of the main arguments against the use of AED polytherapy is that it is supposed to lead to more adverse effects (203). However, Lammers et al. found that the drug load may be more important than the number of drugs in determining the number of adverse effects (135). Drug load, i.e. the amount of drug exposure for a certain indication, can be expressed for dosages and serum levels, by the Prescribed Daily Dose/Defined Daily Dose (PDD/DDD) ratio and the Observed Serum Level/Average Therapeutic Level (OSL/ATL) ratio respectively (see chapters 1 & 2). In the present study a survey of the literature was performed using these ratio's to evaluate the reporting of adverse effects in relationship to antiepileptic drug load. Only papers in which polytherapy was used in at least one of the treatment groups were selected.

Methods

The Medline program was used to screen the literature from 1974-1994, using the search commands: [epilepsy] AND [adverse OR side effects OR cognitive OR toxicity] AND [combination therapy OR add-on OR discontinuation]. Next, a further selection was made using the following requirements:

1. A multiple drug regimen in one of the treatment groups of a trial.
2. Mention of the dose or serum level of every prescribed antiepileptic drug per patient or mean dose respectively serum level and number of patients using each antiepileptic drug per treatment group.
3. Mention of incidence and specification of adverse effects per patient or treatment group.

Defined Daily Doses and Average Therapeutic Levels

For this study not the ATL but the average toxic level (AToxL) was used as this study focuses on adverse effects. The average toxic levels of the different AEDs were assessed from literature data (67, 142, 177, 197). The Defined Daily Doses, Average Therapeutic and Average Toxic Levels found are listed in table 3.1a.

Table 3.1a Defined Daily Dose (DDD), Average Therapeutic Level (ATL) and Average Toxic Level (AToxL) values for individual drugs

	DDD (mg) [1])	ATL (mg/l) [2])	AToxL(mg/l) [2])
Carbamazepine	1000	7	12
Phenytoin	300	15	20
Valproate	1500	70	120
Phenobarbital	100	30	40
Primidone	1250	12	15
Ethosuximide	1250	70	120
Clonazepam	8	-	-
Clobazam	20	-	-
Progabide	1800 [2])	-	-
Vigabatrin	2000	-	-
Flunarizine	30 [2])	-	-
Felbamate	2700 [2])	40	80
Clorazepate	-	1 [3])	5 [3])

[1]) Assigned by the WHO; [2]) Assigned according to literature data; [3]) Nordiazepam level

Statistical analysis was performed using Pearson's correlation coefficient and the z-transformation to test correlations between parameters. Dice were thrown to randomly select one observation per patient for statistical analysis in studies where drug load could be evaluated per patient.

Results

Screening of the literature

Through the Medline-search 661 papers were retrieved, of which 118 were trial reports with a multiple drug regimen in at least one of the treatment groups. Next, the above-mentioned requirements were applied to select papers suitable for analysis. The bulk of papers was rejected for two reasons:

1. Eighty studies in which new drugs, multiple drug regimens or a reduction in the number of antiepileptic drugs in these regimens were evaluated, were rejected

because the authors did not provide data on doses or serum levels of each individual drug or about the number of patients taking the drug; a few representative examples are cited in the reference list (8, 103, 131, 160, 170, 206).

2. Twenty papers were rejected because adverse effects were not or inadequately mentioned (one fourth of the papers mentioned sub 1 suffered from the same deficiency). Seizure control was the only outcome measure in these cases; again just a few examples are cited (1, 131, 217).

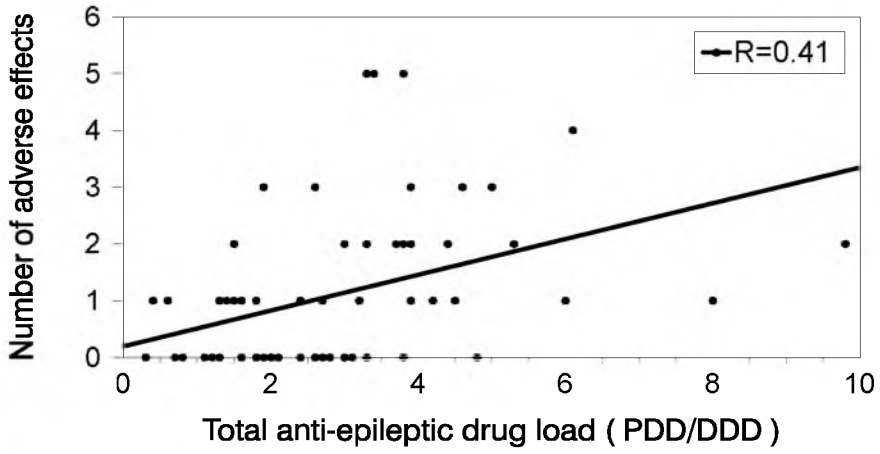
Two papers were not suitable as differences in frequency of administration were compared, e.g. a daily dose versus three doses per week; a third study was unsuitable as it concerned a new drug of which no information about the average effective dose was available. Fifteen papers met the three requirements listed in the methods section. In these, drug toxicity was evaluated by listing subjective complaints, repeated neurological examinations and/or neuropsychological testing. No systematic comments were made in these papers regarding the severity of the adverse effects. We pooled the selected papers into three groups: A, B and C.

Pool A *Adverse effects and dose/serum levels reported per individual patient*

In five papers the number and dose of all anti-epileptic drugs (but not serum levels) and adverse effects were reported per patient (153, 183, 219, 248, 256).

The total antiepileptic drug-load in relation to the number of adverse effects in individual patients is shown in figure 3.1a. Although the correlation coefficients vary between the trials, a weak positive association between these parameters does exist for the total group (correlation coefficient=0.41).

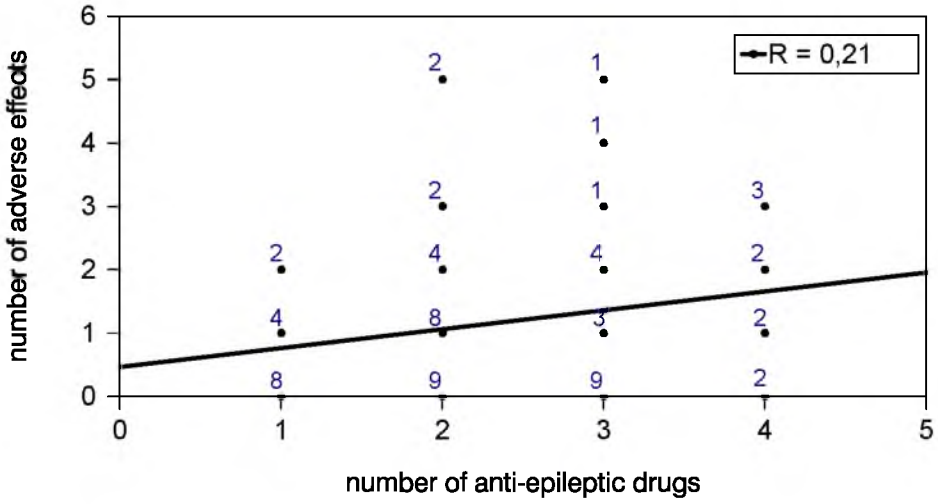
Figure 3.1a *Total drug load in relation to the number of adverse effects*



Combined data from five studies (153, 183, 219, 248, 256).

From the published data one measurement per patient was taken at random. The number of AEDs in relation to the number of adverse effects is shown in figure 3.1b. The correlation coefficient was 0.21 for these two parameters.

Figure 3.1b Number of antiepileptic drugs in relation to the number of adverse effects



Combined data from studies as in figure 3.1a. From the published data the same measurement per patient was taken as in figure 3.1a. Numbers next to data-points indicate number of patients; for example, of the patients using 2 drugs, two were bothered by 3 adverse effects.

Pool B Adverse effects and dose/serum levels reported per treatment group

In seven papers two treatments were compared and the number of adverse effects and the average dose or serum level of every AED were stated per treatment group (139, 154, 156, 213, 218, 240, 267).

The mean total antiepileptic drug-loads (expressed in PDD/DDD or OSL/AToxL ratio) with the respective number of adverse effects reported per treatment group are shown in table 3.1b. All of these studies used a cross-over design, except Schmidt (218). In all papers the number of adverse effects was higher in the treatment group with a higher total antiepileptic drug-load and a higher number of AEDs (table 3.1b), except for the trial of Wilensky et al. where the number of AEDs was two in both treatment groups (267).

Table 3.1b Trials where number of adverse events were reported per treatment group

	Treatment groups	**PDD/DDD [1])**	**No. of side effects**
Loiseau et al. (n = 23)	Vigabatrin versus placebo add-on	3.6 versus 2.1	18 versus 11
Loiseau et al. (n = 23)	Lamotrigine versus placebo add-on	3.1 versus 2.2	50 versus 20
Tartara et al. (n = 21)	Vigabatrin versus placebo add-on	3.5 versus 2.3	26 versus 9
Sander et al. (n = 18)	Lamotrigine versus placebo add-on	3.3 versus 2.6	20 versus 14
	Treatment groups	**OSL/AToxL [1])**	**No. of side effects**
Leppik et al. (n = 56)	Felbamate versus placebo add-on	1.7 versus 1.4	133 versus 16
Wilensky et al. (n = 42)	Phenobarbital versus clorazepate both added to phenytoin	1.7 versus 1.5	22 versus 16
Schmidt (n = 36)	Two-drug versus monotherapy	1.4 versus 0.9	41 versus 31

[1]) The mean total antiepileptic drug-load (PDD/DDD) or OSL/AToxL per treatment group is listed.

Pool C *Drug toxicity evaluated by neuropsychological testing*

In four papers neuropsychological testing had been used to detect drug-related changes in cognitive functioning and doses or serum levels had been adequately reported (66, 176, 246, 267). The trial of Wilensky et al. is also used in group B (267). Different neuropsychological tests were applied by the various authors, which complicated a detailed comparison.

The mean total antiepileptic drug-load or OSL/AToxL ratio was calculated per treatment group (table 3.1c). The tests used have been categorized according to cognitive functions and the results of the various trials. Thus for example, decision making and visual scanning are categorized as components of mental speed. Intellectual achievement was tested by arithmetic in three trials.

Overall, patients in treatment groups with higher drug loads or higher OSL/AToxL ratio's performed as well as, or worse, but not better, on neuropsychological tests than patients in treatment groups with a lower drug-load.

Table 3.1c Trials where drug-related effects on cognitive functioning were measured. Trial designs, total drug-loads and conclusions on cognitive changes are shown. The changes of the cognitive functions are those after switching from the first named treatment to the second (e.g. vigabatrin versus placebo - the condition while on placebo)

	Treatment groups [1])	**PDD/DDD [2])**	Mental speed	Short term memory	Attention/ concentr.	Visuo-motor response	Intellect. level	Motor speed
McGuire et al. (n = 30)	Vigabatrin versus placebo add-on	3.0 versus 2.4	=	-	=	=	↓ =	=
	Treatment groups 1)	**OSL/AToxL [2])**						
Duncan et al. (n=23)	Before versus after removal of phenytoin from a multiple drug regimen	1.2 versus 0.9	=	=	↑	-	=	↑
Duncan et al. (n=24)	Before versus after removal of carbamazepine from a multiple drug regimen	0.9 versus 0.4	=	=	=	-	=	↑
Duncan et al. (n=25)	Before versus after removal of valproate from a multiple drug regimen	0.9 versus 0.6	=	=	=	-	=	↑
Wilensky et al. (n = 42)	Phenobarbital versus clorazepate in combination with phenytoin	1.7 versus 1.5	-	↓	↑	-	=	=
Thompson and Trimble (n = 28)	High level versus low level multiple drug regimens	0.95 versus 0.63	↑	↑	-	↑	-	=

1) Characterization of groups: In trials by Wilensky et al. (267), Duncan et al. (66) and Thompson and Trimble (246) a cross-over design was used. In the trial by McGuire et al. (176) a parallel design was applied

[2]) Total antiepileptic drug-load (in PDD/DDD) or OSL/AToxL is listed per treatment group

Discussion

Critique of the literature

Methodology to assess adverse effects and in particular methods of reporting about the incidence leave much to be desired. Very few of the papers collected in this literature search satisfied the requirements for inclusion. Lack of information about the exact dosages or serum levels of individual AEDS, or about the frequency of adverse effects, or both, was particularly frequent.

The small number of papers selected would have been reduced even further if adequate quantification of the severity of adverse effects had been a requirement.

Relation between number of drugs, total drug-load and adverse effects

Only group A allowed comparison of toxicity in individual patients and could therefore be used to estimate the correlation coefficient between toxicity and drug-load respectively number of drugs. The comparison of the papers presented in group A points to a weak relationship between adverse effects and total antiepileptic drug-load. An inherent weakness of our analysis is that Defined Daily Doses are established only for the main indication of a drug, i.e. seizure control, and not for toxicity. While correlations between serum levels and toxicity have been published, unfortunately few papers retrieved in this study contained information about serum levels. This is also to be regretted because the PDD/DDD ratio does not account for possible pharmacokinetic interactions. In group B and C it was not possible to disentangle the cause of higher toxicity, which might just as well be due to the higher drug-load as to the use of multiple drugs or both.

The results from group A do show that the correlation between incidence of adverse effects and drug load is slightly stronger than between adverse effects and number of antiepileptic drugs taken, although both are weak and thus cannot be taken as proof. The information presented does not as yet permit any conclusions, however it does remove one of the objections to study relative efficacy of mono- and polytherapy. That polytherapy may have its own merits also has been advocated in hypertension and oncology therapy (63, 73, 81).

Not all results were in accordance with the hypothesis of an association between total drug-load and number of adverse effects. One study in group C showed that the elimination of phenytoin did have a beneficial effect on attention and concentration, whereas withdrawing valproate or carbamazepine did not (66). This is in agreement with reports that different

anti-epileptic drugs often have different effects on cognitive functioning (4, 155). Phenytoin for example is reported to have a greater impact on motor speed and mental speed than carbamazepine (4).

The advantages of using methods to calculate total antiepileptic drug-load are illustrated by the paper by McGuire et al. (176). Here total drug loads in the vigabatrin add-on group and placebo control group were high. Adding vigabatrin only changed the drug load by 20%. This means that, given the premises of this method, the patients in the placebo group were exposed to an only slightly less toxic total of drugs than the add-on group, from which the effect of vigabatrin on cognitive function had to be evaluated. This emphasizes the importance of reporting doses or serum levels of concomitant drugs, particularly in parallel studies.

3.2 Theoretical background of the drug load concept

Introduction

Nowadays combining drugs on pharmacological grounds is increasingly being used for other disorders than epilepsy, for example in hypertension treatment and cancer chemotherapy, etc. (81, 182, 192). The goal of using two or more drugs instead of one is to achieve greater efficacy with the same or less adverse effects or equal efficacy with less adverse effects (69, 74). In pharmacological terms this would signify supra-additive efficacy with additive or infra-additive toxicity and additive efficacy with infra-additive toxicity respectively. Consequently, numerous clinical trials are being undertaken to compare combination regimens with their individual constituents.

However the total drug load, i.e. the amount of drug exposure for a certain indication, is a neglected factor in many of these trials. When differences in effects are found in these trials, these are attributed to the pharmacodynamic properties of the therapeutic regimens, instead of to a possible difference in drug load between the groups. The drug loads of two regimens should however be equal before conclusions can be reached on differences of intrinsic efficacy or toxicity.

Many examples of neglecting drug load can be found in the literature. McKay et al. evaluated the effects of losartan 50 mg alone, hydrochlorothiazide 12,5 mg alone, a combination of losartan 50 mg and hydrochlorothiazide 6,25 mg and a combination of losartan 50 mg and hydrochlorothiazide 12,5 mg for essential hypertension, and concluded that the combination of losartan 50 mg and hydrochlorothiazide 12,5 mg produced an additive and safe reduction (165). However, for a clinically relevant evaluation they should have included a high-dose hydrochlorothiazide group and a high-dose losartan group, or should have used lower dosages of both drugs in the combination regimen, in order to compare regimens with a more equal drug load. This would have challenged the merits of the combination of losartan and hydrochlorothiazide. Similarly, studies by Faarvang et al. and by Nelson et al. on the possible advantages of combining anti-rheumatic drugs and of combining antidepressive drugs respectively, also did not include high dose monotherapy groups or lower dosages for the combinations (68, 188).

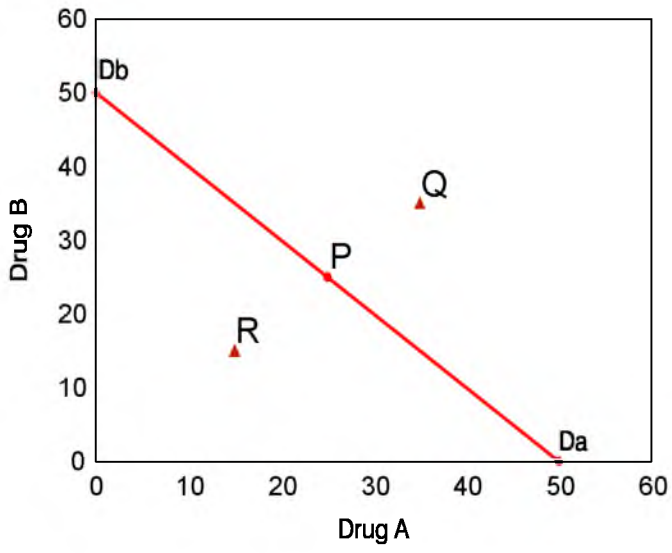
Another frequently encountered manner in which drug load is neglected, is the habit of not taking baseline medication into account. Onghena and Van Houdenhove reviewed 39

placebo-controlled trials on antidepressant-induced analgesia for chronic non-malignant pain, and found that in these trials the use of other analgesics, ergotamine or anti-rheumatic drugs was permitted (190). For example in one of the reviewed papers, a study by Loldrup et al., patients were allowed to have up to 30 mg oxazepam and up to 3 g of paracetamol in addition to the study medication, without taking in-between group differences of oxazepam and paracetamol into account (157). Similarly, but in an anti-hypertension drug trial research, Avanzini et al. compared the effects of 4 different drug regimens, but started off one regimen with a considerably higher drug load than the others (11).

This problem is also of importance in add-on studies of antiepileptic drugs. The first trials to establish efficacy of a new antiepileptic drug are conducted by adding the new drug in comparison to adding placebo to existing insufficiently effective medication. This is necessary as it is unethical to give new antiepileptic drugs or placebo to newly diagnosed epilepsy patients, and thus the effects of the new compound are evaluated as if only this drug is given. However, as was shown in paragraph 3.1, total drug loads of baseline medication of the active and the placebo group sometimes differ, and therefore it is unclear whether observed differences in toxicity are really due to the new antiepileptic drug or are drug load-related (54).

Although the concept of drug load is intuitively obvious, little has been published about a methodology to evaluate drug load in polytherapy. Such a methodology should be helpful in the planning and analysis of clinical trials and enable to determine the role of drug load as a prognostic factor. In experimental settings, fractions of drug exposure are already used in the isobologram method. This is the preferred method to detect synergy, zero interaction or antagonism (17). The dosages of a drug combination (d_a, d_b) are determined, which have the same effect as certain dosages of the drugs alone (D_a and D_b). The equation for the zero interaction line for two agents is: $d_a/D_a + d_b/D_b = 1$ (17, 238). When the sum is less than one or more than one, the combination is judged to be supra-additive or infra-additive respectively. The interaction can thus be evaluated for the dosages used, irrespective of the nature of the dose-response curves of the individual drugs. This is illustrated in figure 3.2a.

Figure 3.2 Isobologram method



Poi nts D_a and D_b represented on the axes of drug A and B respectively to reach an effect of certain magnitude. Next the two drugs are combined in order to reach that same effect. When (d_a,d_b) is on the zero interaction line (point P) the drugs are considered additive for that dose pair. Point Q represents infra-additivity and point R supra-additivity

We have developed a method to assess drug load, analogous to the isobologram method.

Methodology

The Prescribed Daily Dose/Defined Daily Dose (PDD/DDD) ratio can be used to calculate

the drug load in treatment groups, when one uses the Prescribed Daily Dose as the average dose of a drug taken in a certain treatment group. The method assumes that, thus normalized, the drug loads of several drugs in one regimen can be added up. For example, the DDD of sodium valproate is 1500 mg (265) and patients in group A using 900 mg would have a drug load of 900/1500 i.e. 0.6 PDD/DDD. The DDD of carbamazepine is 1000 mg (265) and patients in group B using 600 mg carbamazepine would have a drug load of 600/1000, which is also 0.6 PDD/DDD. Patients in group C using 450 mg of valproate and 300 mg of carbamazepine thus have an equal total drug load of 0.6 PDD/DDD, which makes them eligible for comparison with patients of group A and B. So instead of comparing iso-effective drug fractions as is done in the isobologram method, we compare the effects of equal drug fractions.

Results in epilepsy research

In paragraph 3.1 we have applied the described method of measuring drug loads in a retrospective analysis of antiepileptic drug trials where multiple drug regimens were used. In this review, toxicity was weakly but significantly correlated with drug load and not with the number of antiepileptic drugs (54).

The PDD/DDD ratio can also be used to start both treatment groups of a clinical trial off with equal drug loads, as was done in the trial described in chapter 6. This prevents bias, for example when one treatment group would start with a lower drug load it may take longer to get these patients into remission, although the drugs may be equally effective. Alternatively, in a treatment group which starts off with a higher drug load, more patients may drop out because of adverse effects, while in fact the two regimens may be equally toxic when equal drug loads are used. The PDD/DDD ratio furthermore allows physicians participating in this trial to adjust the dose in terms of PDD/DDD, thus keeping physicians, patient and investigator blinded.

Also, predicting outcome of drug withdrawal after a reasonable symptom-free period may benefit from the concept of drug load. Until now, the number of antiepileptic drugs has been deemed an important factor in determining the risk of seizure recurrence (185). The total drug load of the antiepileptic drug regimen may very well prove to be of more relevance in this respect.

Discussion

The DDD-methodology was originally developed to convert available volume data from sales statistics or pharmacy inventory data into medically meaningful units, and the PDD was introduced as the DDD did not accurately reflect the drug exposure in selected populations. So, one may ask whether it is justified to use the PDD/DDD methodology for our purpose and if so, under what conditions ?

For example, does the use of PDD/DDD ratio's assume that the dose-effect curves are linear for the dose range under consideration ? It has been established that the isobologram method can be used irrespective of the nature of the dose-effect curves of the individual drugs (17). In judging a combination, one is only interested in how the added drug fractions of a combination needed to reach a certain effect compare with the full amount of the individual drugs needed to reach that same effect. It is actually because the same effect is used to compare the drugs with their combination, that the dose-effect curves become irrelevant. The PDD/DDD ratio actually turns the isobologram method around, as it is based on equal drug loads/fractions and then looks at differences in effects. Nevertheless, the PDD/DDD ratio does not rely on the nature of the dose-effect curves either. One important point to realize is that the isobologram method and the PDD/DDD method is that they only give information about the effect or drug load under evaluation, and that the nature of the interaction may change when one looks at different magnitudes of effect or drug load respectively. Also, the nature of the interaction may change when the proportion of the two drugs in the combination is changed. However, when a combination is found to be infra-additive for a certain effect, this will usually still be the case when the drugs are given in different proportions (17).

In the isobologram method the doses of the individual drugs used in monotherapy are equipotent. It is important that the DDDs of the different drugs under evaluation are also equipotent when using the PDD/DDD ratio, which might not always be the case. Drugs may also have several indications, e.g. CBZ and VPA being used as antidepressants. Furthermore, as is shown in chapter 2, the DDD's assigned by Oslo may differ from the usual dosages, e.g. in the Netherlands. This may be due to different dosages used for same indication, which can vary between countries but even between experts in the same hospital. DDD values seem to approximate the average prescribed dose better when it concerns drugs which are prescribed chronically instead of for one or two short periods

(260).

Nevertheless, it seems safe to conclude that failing to evaluate drug load may complicate the evaluation of drug efficacy and toxicity, especially where combination therapy or fixed dosages are concerned. Not only should drug loads be determined in the retrospective analysis of clinical trials, but also should they be used to ensure equal drug loads at the start of treatment. In our field, antiepileptic drug treatment, neglecting drug load obscures the evaluation of new antiepileptic drugs and may have also been responsible for unfavorable reports about polytherapy, which now seem unjustified.

3.3 Monitoring adverse effects in antiepileptic drug therapy: Wait and see or go for it?

Introduction

Consensus on a detection strategy for AEs of antiepileptic drugs is lacking; clearly neurologists often follow different strategies (39). Unfortunately, these differences are reflected in the variability of reports about efficacy and tolerability of antiepileptic drugs. For example, in a large multi centre survey the frequency of AEs reported varied widely between centres from 6% to 79% of patients (39).

In the literature, a dichotomy can be found between papers in which the authors actively looked for AEs or only took notice of AEs if the patient proffers them.

Examples of rigorous assessment of AEs are papers of the Veteran Affairs group (173,174) and our own group which adopted the same technique (135). This method was developed by neurologists to be used in drug trials. The outcome was expressed in neurotoxicity and systemic toxicity scales (45). Comparing studies which made use of active inquiry about AEs, including our own database, and those which did not, we discovered that apparently the difference in approach does not equally affect the detection of all types of AEs.

To identify the effects of these different approaches more precisely, we only used papers that discussed either carbamazepine or valproate monotherapy .

Methods

The literature

A Medline search for papers from 1991-1995 on carbamazepine and valproate monotherapy trials was performed. Data of the seven papers identified (33,42,55,70,173,204,252), if necessary, were translated to the V.A.-neurotoxicity and systemic toxicity scales in order to enhance comparability with the data of the trial by Mattson et al. (173) and of the Nijmegen database. For example, reports of "somnolence" were interpreted as "sedation" whereas "fatigue" and "depression" were classified in the "affect and mood disturbances" category.

The database

Frequency of AEs associated with carbamazepine or valproate monotherapy were extracted from the database of epilepsy patients of the out-patient department of a University neurology clinic, maintained by the Nijmegen Epilepsy Research group. The Neurotoxicity and the Systemic toxicity scales were used for detection of AEs (45).

Results

The literature

The occurrence rates of AEs during carbamazepine or valproate monotherapy are listed per trial in tables 3.3a and 3.3b. (33,42,55,70,173,204,252). Certain rates vary considerably among trials, which is exemplified by sedation in 42% of the patients in both carbamazepine and valproate groups in the trial by Mattson et al. (173), respectively in 41% for carbamazepine and 36% for valproate in the Nijmegen Database as opposed to 11% to 22% in the carbamazepine group and 3% to 8% in the valproate group in the other trials.

Table 3.3a *Percentages of patients in selected papers with drug-induced adverse effects while on carbamazepine monotherapy*

Publication # refers to reference list N between ()	204 (178)	252 (130)	33 (131)	55 (139)	173 (231)	NDB (196)
Method*	a + c	a + c	a	c + d	e + f	e
Carbamazepine Mean Dose mg/day	516	450	600 median	?	722	762
Follow up (months)	36	36	± 11	12	12-60	12-???
Diplopia	-	4%	-	+	10%	7%
Nystagmus	-	-	-	-	30%	9%
Dysarthria	-	-	-	-	-	5%
Gait	2%	4%	9%	-	25%	6%
Rapid alternating movements	-	-	-	-		-
Tremor	2%	-	-	+	22%	11%
Sedation	11%	19%	22%	32%	42%	41%
Affect and mood disturbances	12%	17%	9%	24%	24%	6%
Cognitive impairments	2%	2%	3%	-	18%	29%
Dizziness	7%	6%	17%	16%	29%	8%
Headache	6%	7%	25%	33%	20%	7%
Other neurotoxicity	2%	-	-	-	-	-
Gastro-intestinal complaints	8%	4%	19%	+	29%	3%
Haematopoietic disturbances	-	-	-	-	-	-
Dermatological reactions	10%	6%	19%	-	11%	1%
Impotence	-	-	-	-	7%	-
Hyponatremia	-	-	-	-	-	-
Abnormal liver function tests	2%	-	-	-	4%	-
Weight change	1%	6%	-	-	32%	8%
Hair loss/hirsutism	1%	2%	-	-	6%	11%
Other systemic toxicity	23%	24%	28%	-	-	-

* Methods of detection of AEs: a = self-reporting; b = physical examination; c = laboratory investigations; d = adverse effect checklist; e = specific toxicity scales; f = neuropsychological testing. Use of 'e' (specific toxicity scales) includes a,b,c and d. The "+" sign denotes "present", but no percentages given. NDB denotes the Nijmegen Epilepsy Research Group database.

Table 3.3b *Percentages of patients in selected papers with drug-induced adverse effects while on valproate monotherapy*

Publication # refers to reference list N between ()	204 (174)	252 (130)	70 (39)	42 (17)	173 (240)	NDB (145)
Method*	a + c	a + c	a+b+c	d + f	e+f	e
Valproate Mean Dose mg/day	924	700	1082	688	2099	1127
Follow up (months)	36	36	± 4	12	12-60	12-???
Diplopia	-	-	5%	-	6%	4%
Nystagmus	-	-	-	-	26%	1%
Dysarthria	-	-	-	-	-	5%
Gait	-	-	-	12%	23%	6%
Rapid alternating movements	-	-	-	-	-	3%
Tremor	5%	-	3%	29%	45%	30%
Sedation	7%	8%	3%	18%	42%	36%
Affect and mood disturbances	11%	8%	15%	18%	25%	2%
Cognitive impairments	3%	5%	-	-	18%	28%
Dizziness	3%	1%	5%	-	23%	11%
Headache	3%	5%	23%	-	15%	10%
Other neurotoxicity	1%	-	-	-	-	-
Gastro-intestinal complaints	7%	5%	10%	-	33%	12%
Haematopoietic disturbances	-	-	-	-	-	-
Dermatological reactions	2%	3%	-	-	1%	1%
Impotence	-	-	-	-	10%	-
Hyponatremia	-	-	-	-	-	-
Abnormal liver function tests	1%	-	-	-	3%	-
Weight change	12%	13%	-	12%	43%	20%
Hair loss/hirsutism	3%	4%	-	12%	12%	19%
Other systemic toxicity	25%	23%	5%	-	-	-

* Methods of detection of AEs: a = self-reporting; b = physical examination; c = laboratory investigations; d = adverse effect checklist; e = specific toxicity scale; f = neuropsychological testing. Use of 'e' (specific toxicity scales) includes a,b,c and d. The "+" sign denotes "present", but no percentages given. NDB denotes the Nijmegen Epilepsy Research Group database.

Cognitive impairments, sexual dysfunction, hair changes, weight changes, nystagmus, gait

disturbances, and tremor were also found more often when an active approach was employed.

Discussion

Differences in detection strategy

The considerable methodological variability between trials results in large differences in the frequency of certain AEs. This leaves the practising neurologist with uncertainty as it limits the information about AEs needed for assessing risks and benefits of treatment.

To minimize false positive reports when actively looking for AEs necessitates a baseline measurement, as is required when using the V.A. scales (45). It is also important to determine what the exact complaint of the patient is, e.g. drowsiness or fatigue and to take into account comments from family and other staff.

Nevertheless, differences found between active and passive approach might be partially explained by a number of false-positive reports due to the explicit nature of the scales. Complaints unrelated to either the antiepileptic drug use or to epilepsy may get included (172).

However, self-reporting may not always result in a correct representation of AEs either. Höppener et al. reported that AEs due to carbamazepine use were not mentioned spontaneously, but had to be asked for especially in order to track them (111). Patients did not complain about their sleepiness, as they believed that it was related to their work or their epilepsy. After adjusting the dosage scheme all AEs disappeared. Salinsky et al. compared the results of patients taking AED's and several control groups on a patient-based sleepiness scale and an EEG-based wakefulness measure (212). They found that the subjective complaints of AED users did not sufficiently reflect the considerable objective differences in drowsiness found.

Self-reporting of cognitive functioning may be influenced by personality and mood factors. Patients with negative personality or mood complain more of poor memory. The use of neuropsychological tests has furthermore revealed a much greater impact of antiepileptic drug treatment on cognitive functioning than had been expected previously (249). These reports suggest that especially sedation and cognitive impairments may indeed be underdetected by self reporting, and that an active approach or an objective measurement is necessary here.

The lack of a standard physical examination also causes an under representation of certain AEs, such as nystagmus, gait disturbances, tremor, hair and weight changes. Correspondingly, in a large multi centre study of 509 patients at least 36% of AEs were not self-reported but were found only on examination (39).

Laboratory monitoring

Contrary to neurotoxicity monitoring, for systemic toxicity screening it is a tradition in medical practice to perform laboratory tests of all patients receiving antiepileptic drugs. However, many clinically non-significant abnormalities are detected (which lead to retesting) whereas life-threatening events may still occur the day after testing or even go undetected by testing. A more cost-effectieve approach would be to let patients who are not at risk contact the physician when certain symptoms occur and to do routine monitoring only in high-risk patients.

Dose dependency

The relationship of dose or serum level with AEs is a source of conflicting reports in the literature. Therapeutic ranges have been set for various antiepileptic drugs, however, AEs may also occur at supposedly subtoxic levels (133). This is an unresolved problem This also true in the field of neuropsychology (253). Therefore it seems important to be equally as attentive for AEs at serum levels in the therapeutic range as at levels in the toxic range. In tables 3.3a and 3.3b it is shown that the researchers who did not actively probe for AEs used lower average doses of carbamazepine and valproate than the authors who used clinimetric scales. However, taking the lack of interindividual correlation between dose and AEs into account, it is reasonable to assume that the observed disparity in frequency of AEs reported is at least partly due to methodological differences in assessing AEs, and not solely to dosage.

Conclusions

Different approaches in detection strategies for AEs result in differences in the numbers found of certain AEs. We are of the opinion that baseline measurements and active checking are advisable for sedation, cognitive impairments, sexual dysfunction, hair changes, weight changes, nystagmus, tremor and gait. Routine laboratory monitoring is of

doubtful value in patients who are not known to be at risk of idiosyncratic reactions.

Chapter 4 Rational polytherapy: can combinations be based on mechanisms of action ?

Monotherapy has been the gold standard in epilepsy treatment for the last twenty years. However, seizure control is not achieved in up to one third of patients at maximally tolerated dosages of AED monotherapy, at which point polytherapy comes into the picture (171). In recent years, criteria have been proposed to aid in the selection of AED combinations for these difficult-to-treat patients (such as lack of pharmacokinetic interactions and relative lack of toxicity of individual drugs) (74). However, there is some controversy as well about one of the criteria for this 'rational polytherapy': should two drugs that work on the same neurotransmitter system or ion channel be combined, or should the drugs have totally different "targets" ? Both views have their supporters (74, 91, 102, 126).

There have also been experts that claim that mechanistic polytherapy (i.e. polytherapy based on mechanisms of action) is not possible as we know too little about the chain of events leading to seizures and about mechanisms of action of AEDs and of their relative importance per drug (148, 163). In this chapter we will review the available polytherapy studies and try to discover whether, and if so how, AEDs may be combined based on their mechanisms of action.

4.1 Pathophysiology of seizures and mechanisms of action of antiepileptic drugs

Before we assess the feasibility of 'mechanistic polytherapy', the pathophysiology of seizures is summarized and the mechanisms of action of the current AEDs and the relevance of these mechanisms for their antiepileptic spectrum are briefly described.

Mechanisms underlying focal epilepsy

The current view on the mechanism of focal seizures will be summarized here. It should be noted that much is still unclear and that other mechanisms are involved in the development of intractable seizures (105, 147).

Cells in layers IV and V of the neocortex and pyramidal cells in the CA2 and CA3 regions of the hippocampus have the intrinsic potential to develop "bursts" (164). These bursts consist of a calcium-dependent membrane depolarization that evokes a train of sodium-dependent action potentials. In case of abnormal excitability, due to injury or an impaired balance between glutamate-mediated excitation and GABA-mediated inhibition, burst firing can be evoked and can synchronize. This means that a large group of neurons synchronously depolarizes, which is represented by an interictal spike in the EEG. This so-called paroxysmal depolarizing shift (PDS) and accompanying train of action potentials is normally followed by a large prolonged hyperpolarization, which is the correlate of the slow wave that usually follows EEG spike discharges (158). The spike wave discharge (SWD) in the EEG is the electrical correlate of this process of consecutive depolarization and hyperpolarization. The 'epileptic' neuron thus alternates between excitation and inhibition.

The excitatory PDS or giant excitatory post-synaptic potential (EPSP) appears to be generated by a combination of synaptic currents (mediated by glutamate) and voltage-dependent depolarizing currents, especially calcium and sodium currents (62). The inhibitory hyperpolarization or inhibitory post-synaptic potential (IPSP) that follows the PDS is also generated by synaptic events (GABA acting at both the $GABA_A$ and $GABA_B$ receptor) and intrinsic membrane currents (voltage- and calcium-dependent potassium currents, possibly chloride currents) (62).

The transition into a seizure is probably mediated by repetitive firing, in other words by

repetition of interictal discharges. Inhibitory synapses become less effective when repetitively activated and in contrast, excitatory synapses often show increased efficacy in those circumstances. Each PDS is then followed by a prolonged depolarization, until the neuron is tonically depolarized and fires synchronously with its neighbors to produce a seizure (62). This seizure activity may be propagated by specific anatomical routes, to result in a complex partial seizure or a secondary generalized seizure (150).

The cellular mechanisms discussed here are all potential targets for antiepileptic drugs against partial epilepsy. For example, drugs that block either glutamate receptors or drugs that block voltage-dependent sodium or calcium channels may decrease sustained repetitive firing. Similarly, drugs that enhance inhibition, especially γ-aminobutyric acid (GABA)-mediated and potassium-mediated inhibition, can be effective in limiting burst firing and arrest of the discharge (62, 164).

Antiepileptic drugs designed to limit seizure propagation through the common propagation pathways may have a broader anticonvulsant spectrum than therapies that only target the site involved in seizure initiation (150). The amygdala and piriform cortex may form a gate for forebrain recruitment and partial generalization of kindled seizures, while the substantia nigra may be responsible for brainstem gating recruitment and thus full generalization (via the superior colliculus) (150).

Mechanisms underlying generalized seizures

The origin of seizures in primary generalized epilepsy differs from focal epilepsy. Neurons within the nucleus reticularis thalami (NRT) and thalamocortical relay cells are believed to be responsible for the mechanism underlying generalized absence epilepsy. The NRT is composed of GABAergic cells that project heavily to one another and to almost all thalamocortical relay nuclei (232). Thalamocortical relay cells normally discharge to cortical neurons continuously (so-called tonic firing). These neurons may produce low threshold calcium currents (LTCC), through the T-type calcium channel, however at resting membrane potential this channel is inactivated (159). The LTCC represents a key membrane property in burst firing excitation and is associated with the oscillatory activity in relay cells during synchronized sleep and during absence seizures (232). It is triggered by a late $GABA_B$-mediated IPSP (i.e. hyperpolarization) from the NRT, which gives rise to a rebound burst of action potentials (158, 232). $GABA_A$-mediated inhibition in the NRT

diminishes its GABAergic output to thalamocortical relay cells.

In absence epilepsy a generalized cortical synchronization of SWDs appears on the electroencephalogram (EEG) with the typical 3 Hz-frequency. Drugs which block the T-type of calcium channel, such as ESM and trimethadione are prescribed to patients with absences. Drugs that enhance $GABA_A$ inhibition in the nucleus reticularis thalami and/or reduce $GABA_B$-mediated inhibitory input into thalamocortical relay neurons, may also be efficacious in absence epilepsy.

Mechanism of action of AEDs

The present knowledge about the mechanisms of action of antiepileptic drugs is incomplete. Not only are the mechanisms of action of the antiepileptic effect not completely known, there is even less knowledge about the mechanism of action of the adverse effects. However, there are two major target categories for AEDs:

- Altered intrinsic membrane properties: these usually include abnormal ionic conductances (calcium, sodium, potassium).
- Altered synaptic function: manifested as an increase in excitatory transmission or insufficient inhibitory transmission.

The current knowledge about the effects of the presently available AEDs on these processes is summarized here.

Sodium channels

The voltage-gated sodium channel is involved in generation and propagation of sodium-dependent action potentials, and delaying its reactivation significantly reduces the frequency of sustained repetitive firing (75). Phenytoin (PHT) and carbamazepine (CBZ) are believed to bind to the sodium channel in its inactive state after a depolarization and to slow its recovery from inactivation (224, 269). These drugs do not reduce the amplitude or duration of single action potentials, but reduce the ability of neurons to fire 'trains' of action potentials at high frequency (163). The effect of CBZ and PHT on sustained repetitive firing has three properties: 1) voltage dependency: it increases after depolarization and decreases after hyperpolarization; 2) use-dependency: the first action potential in the 'train' is unaffected, but with successive action potentials the heights of these potentials are reduced until there is failure of firing; 3) time-dependency: the

reduction in action potential properties lasts several hundreds of milliseconds after the first action potential train (162). The use dependency of these effects ensures that normal physiological action remains undisturbed.

The significance of valproate's (VPA) effects on sodium channels is uncertain: the spontaneous firing of neurons is usually inhibited only by high doses or concentrations of VPA, but in the substantia nigra pars reticulata (SNR) of rats a reduction in the firing rate was already found at low dosages. This inhibitory effect on SNR neurons might however also be due to the selective increase in GABA turnover induced by VPA in the substantia nigra of rats (149). In cultured hippocampal neurons VPA did slow the recovery from inactivation, but in the rat hippocampal slice VPA had no effects on the bursting behavior of neurons (2, 149). There are other experts that claim that VPA's sodium channel blocking is it main mechanism of action (163, 179).

Barbiturates and benzodiazepines (BZDs) do reduce sustained repetitive firing by blocking sodium channels, but only at high drug concentrations, which may explain part of their efficacy in status epilepticus (261). Blocking sodium channels (directly or indirectly) is deemed to be relevant for the efficacy of several of the new AEDs: felbamate (FBM), gabapentin (GBP; only after prolonged administration), lamotrigine (LTG), oxcarbazepine (OXC) and topiramate (TPM).

The drugs that limit sustained repetitive firing through effects on sodium channels do not share efficacy for all seizure types and often have different adverse effects. This may be caused by other mechanisms of action that these drugs have (see below), but another possibility is that the drugs vary in their selectivity for the various α subunits at Na+ channels; preferential actions on particular subunit types could produce markedly different effects on seizures as well as unique adverse effects (179). Furthermore, AEDs could affect the slow or the fast inactivation of sodium channels and differences may exist in voltage, use and/or time dependency.

Calcium channels

Many of the available antiepileptic drugs have effects on voltage-dependent calcium channels. The best characterized calcium channels are the L-type, T-type, N-type and P-type channels. Depolarization of a neuron causes Ca^{2+} to enter the cell through these pre-synaptic calcium channels (207). This causes a release of excitatory neurotransmitters,

which results in a further Ca^{2+} influx through excitatory amino acid-operated and voltage-dependent post-synaptic channels. This large Ca^{2+} influx is thought to trigger burst firing (207). The calcium channels have different voltage ranges for, and rates of, activation and inactivation (159, 164). P-type channels appear most significant for glutamate release; N- and P-type channels control monoamine release (179). Contrastingly, T-type calcium currents are activated by hyperpolarization.

Phenytoin, barbiturates and BZDs all have been demonstrated to inhibit calcium influx during depolarization and to block presynaptic release of neurotransmitter, but only at supratherapeutic concentrations (164). Ethosuximide (ESM) and trimethadione (TRM) reduce T-type currents in thalamic relay neurons at therapeutic concentrations, whereas VPA did not (41). The efficacy against absence seizures of ESM and TRM is often explained by this mechanism. VPA does block T-type currents in afferent neurons (120) CBZ blocks veratrine-stimulated calcium-flux, which is in agreement with its sodium channel blocking properties (162). Of the new antiepileptic drugs, LTG, OXC and FBM all reduce high-threshold voltage-sensitive calcium currents, but the clinical relevance of these effects are uncertain (262). GBP binds with high affinity to a novel $\alpha_2\delta$ regulatory subunit of a voltage-sensitive calcium channel. It has been suggested that GBP may modify monoamine neurotransmitter release through its interaction with this subunit (262).

So far, non-T-type calcium channel blockers such as flunarizine and nifedipine have not proven to be very effective antiepileptic drugs in clinical practice. In the future, calcium channel blockers may possibly be employed as anti-epileptogenic or neuroprotective agents, considering their role in glutamate release and second-messenger systems (234).

Glutamate

Excitation in the nervous system is produced primarily by glutamate and possibly also by aspartate. Glutamate binds to three different ligand-gated ion channel (ionotropic) receptors: the *N*-methyl-D-aspartate (NMDA), the α-amino-3-hydroxic-5-methylisoxazole-4-propionic acid (AMPA) and the kainate receptor (99). When glutamate is released into the synaptic cleft and interacts with these postsynaptic receptors, this causes membrane depolarization and increases the chance that the postsynaptic cell will initiate an action potential (99).

Activation of AMPA receptors appears to mediate most of the excitatory neurotransmission in the CNS (99). The giant EPSP, which is represented by the interictal spike in the EEG, is normally also only AMPA-mediated. However when the depolarizations are of sufficient amplitude and duration (such as during the onset of a seizure) NMDA receptors are activated (158). These then reinforce the persistent envelope of depolarization that underlies a tonic-clonic discharge. Thus glutamate-mediated synaptic transmission accounts for the synchronization of epileptiform activity.

The NMDA receptor is also involved in the hippocampus, where epileptiform bursts can produce long-lasting hyperexcitability. The induction of these plastic changes requires NMDA-receptor activation which then enhances NMDA and non-NMDA receptor mechanisms (222). NMDA receptor density and utilization is increased in temporal lobe epilepsy (271).

Much work has been done on glutamate receptor antagonists. Theoretically, NMDA receptor antagonists are more interesting than AMPA receptor antagonists, as AMPA is constantly involved in normal brain function (158). NMDA receptor antagonists initially looked very promising in animal epilepsy models. However, clinical trials and recent animal data demonstrated problems with NMDA-antagonists. No efficacy could be found for partial seizures and there were marked adverse effects. This was surprising as tolerability in healthy volunteers was fine, although perhaps cognitive adverse effects were to be expected as NMDA is also involved in synaptic plasticity and learning (32). Furthermore, it has been shown in experiments that limbic epileptogenesis enhances the adverse effects of NMDA receptor antagonists, leading to motor impairment, proconvulsant effects and psychotomimetic effects (110). Perhaps NMDA-antagonists in low dosages in combination therapy can be of use (46). AMPA or kainate antagonists are in the process of evaluation.

Another potential indication of glutamate receptor antagonists is as neuroprotective/anti-epileptogenic agents. Although NMDA receptor antagonists had no efficacy in fully kindled rats (and can even have seizure exacerbating effects), activation of NMDA receptors is a prerequisite for epileptogenesis in the kindling model (150). Administration of (the NMDA receptor-associated) glycine site antagonists and administration of AMPA antagonists does increase the focal seizure threshold in kindled rats (150).

A drug such as LTG which reduces glutamate release by blockade of sodium channels is

very different from receptor antagonists and is not associated with 'NMDA-tolerability problems'. Part of the antiepileptic effect of LTG has been attributed to inhibition of glutamate release. However, other sodium channel blocking drugs such as CBZ and OXC also have this effect, and it is questionable whether the magnitude of inhibited glutamate release by any of these drugs is clinically significant (257).

Felbamate modulates glutamate receptor function through its action on glycine (a co-agonist with glutamate at the NMDA-receptor) and its anticonvulsant action is reversed by glycine agonists (262). The binding of FBM has been reported to have a striking resemblance to the binding of AMPA, however it does not modulate AMPA-dependent action potentials (215). Topiramate reduces kainate-evoked inward currents, and thus decreases neuronal excitability (261). Some work is now also being done on metabotropic glutamate receptors and epilepsy (32).

GABA

GABA is synthesized in GABAergic nerve terminals through decarboxylation of glutamate by glutamic acid decarboxylase (GAD) and is degraded to succinic semialdehyde by GABA-transaminase (GABA-T) in nerve terminals and glial cells. Succinic semialdehyde can either be oxidated to succinate or reduced to gamma-hydroxybutyrate (GHB).

It is a fallacy that in most brain regions, augmentation of GABA will be anti-convulsant (85). GABA does appear to constrain the seizure activity of the amygdala, an area which is believed to believed to be critical for the initial propagation of focal seizure activity (150). Another region where stimulation of GABA receptors and elevation of GABA seems to be anticonvulsant against a broad spectrum of seizures, is the SNR (85). The SNR appears to indirectly control various distinct epileptogenic circuits via the superior colliculus, including those circuits responsible for generating limbic seizures, thalamocortical seizures and brain stem-generated tonic convulsions (58, 85). In the kindling model, GABA synthesis and receptor density were decreased only in the amygdala and the substantia nigra (150). It is important to note that nerve terminal GABA levels, and not so much the GABA in metabolic pools, are clinically relevant (85, 150).

$GABA_A$

The $GABA_A$ receptor forms a gated postsynaptic Cl^- channel, which is activated by binding

at least two molecules of GABA. Compounds that potentiate chloride influx through the $GABA_A$-receptor, have long been known to have anticonvulsant effects. Barbiturates and BZDs both have their own allosterically coupled $GABA_A$ binding sites. Barbiturates cause the chloride channel to stay open longer, whereas BZDs cause the chloride channel to open more frequently (164).

Recent studies on the $GABA_A$ receptor subunits have established that receptors formed from $\alpha 1\beta 1$ subunits are sensitive only to barbiturates, whereas the transient expression of $\gamma 2$, $\alpha 2$ and $\beta 1$ subunits results in both BZD and barbiturate sensitivity (261). The genes coding for these different subunits are differentially expressed in various regions of the brain, suggesting that the receptor may vary from region to region, possibly introducing functional variations in synaptic inhibition and drug action. CBZ and PHT also potentiate the GABA-mediated current when the $\alpha 2\beta 1\gamma 2$ receptor subtype is expressed, but the potentiation is smaller than the potentiation by barbiturates and benzodiazepines (97). However, the concentrations of PHT and CBZ needed to reach this effect are far below the normal brain concentrations of CBZ and PHT, so the authors of this last paper consider it likely that the interaction of these drugs with certain $GABA_A$ receptors contributes to their antiepileptic activity.

The effects of VPA seem more complex. Animal and human experiments have produced evidence that CNS GABA levels increase significantly at commonly used VPA dosages and especially in the clinically important nerve terminals (85, 149). Regional brain studies in VPA-treated rats have shown marked differences in increased GABA levels. For example, GABA levels are increased more in the substantia nigra, which is thought to have a critical role in seizure propagation. The onset of VPA's effect on presynaptic GABA levels in brain regions (notably the SNR) is very rapid, and the time course of anticonvulsive and antinociceptive activity correlated with that of the nerve terminal alterations in SNR GABA levels (149). Valproate probably inhibits GABA-transaminase in nerve terminals and increases GABA synthesis by activating glutamic acid decarboxylase (GAD), the latter especially in the substantia nigra (149). This results in increased GABA release into the synaptic cleft. Toxic doses of VPA decrease GAD activity, resulting in decreased synaptic GABA release (149). The special effects of VPA in the SNR could be explained by the uneven distribution and regional heterogeneity of enzymes involved in GABA synthesis and degradation (150). VPA does not exert effects

at the postsynaptic $GABA_A$ receptor complex. However, in vivo VPA has been shown to increase BZD-binding, which is probably due to increased GABA levels. Benzodiazepine-antagonists do not reduce the anticonvulsant potency of VPA, but there is some evidence of cross-tolerance (87).

Vigabatrin (VGB) binds to GABA-T and irreversibly inactivates it, thereby increasing brain GABA levels (261). Tiagabine (TGB) blocks the re-uptake in the presynaptic nerve terminal and thus increases synaptic GABA levels. Felbamate only enhances GABA-evoked chloride currents at supratherapeutic concentrations. Gabapentin has been shown to increase GABA levels in some brain regions and a potentiation of GABA-mediated inhibitory currents has been observed in cultured hippocampal neurons (179, 261). Topiramate increases the opening and bursting frequency of the $GABA_A$ receptor channel, similar to the effect of the BZDs, but probably via a novel binding site. Interestingly, VGB, GBP and TGB differ considerably in their efficacy in several epilepsy models, which has yet to be explained (51).

There is some evidence that $GABA_A$ is also involved in generalized absence epilepsy (113). Activation of $GABA_A$ receptors in the NRT appears to suppress the generation of absence seizures in the lethargic (*lh/lh*) mouse absence model. Vigabatrin injected into thalamocortical relay nuclei resulted in an exacerbation of absence seizures while injection of VGB into the NRT resulted in inhibition of SWDs (232). Therefore, if NRT neurons are inhibited, SWDs decrease and if NRT inhibitory input into thalamocortical relay nuclei is increased, SWDs increase (232). Benzodiazepines have been shown to enhance $GABA_A$ mediated inhibition within the NRT and thereby suppress $GABA_B$-mediated inhibition in relay neurons (232). In the pentylenetetrazole model (Ptz-model: an animal model used for myoclonic and/or absence seizures), mice who had developed tolerance to BZDs were also tolerant to VPA (87). Barbiturates, PHT, CBZ, VGB and TGB exacerbate absence seizures in humans (148).

$GABA_B$

$GABA_B$ receptors are often located presynaptically on axon terminals and one major function of these receptors is believed to be inhibition of neurotransmitter release (24). $GABA_B$ receptor antagonists may affect the release of GABA and glutamate, but some may just inhibit the release of one of the two. This suggests that the $GABA_B$ receptors mediating

GABA and those mediating glutamate release are probably pharmacologically distinct (24).

One of the defining features of generalized absence epilepsy is their potentiation by increased GABAergic brain activity. Baclofen, a $GABA_B$ agonist is much more effective than the $GABA_A$ agonists in potentiating the synchronous rhythmic SWDs in experimental absence seizures (233). The role of $GABA_B$ is further supported by the finding that $GABA_B$ antagonists significantly reduce or block rhythmic SWD.

Other mechanisms of action

There are also other mechanisms of action which have been associated with the effects of certain AEDs. Valproate inhibits formation of γ-hydroxybutyrate (GHB) by inhibiting aldehyde reductase, which is the enzyme that enhances the transformation of succinic semialdehyde into GHB. This effect of VPA may be important because GHB produces absence-like episodes in animals and is used as an absence epilepsy model (149).
L-dopamine and *d.l.*-amphetamine have been shown to potentiate the efficacy of PHT and PB in the MES, while apomorphine had no effect (125). There is some evidence suggesting that release of dopamine in the striatum leads to inhibition of SNR neurons, which may lead to seizure control (for example in absence epilepsy) (58). This mechanism may contribute to the anticonvulsant mechanisms of some of the present AEDs.
Topiramate inhibits certain carbonic anhydrase isoforms (261). This effect probably does not contribute to the efficacy of TPM, but may be responsible for some of the adverse effects.

Does mechanism of action predict anticonvulsant spectrum ?

The clinically relevant mechanisms of action of the currently available drugs are summarized in table 4.1a.

Table 4.1a Mechanisms of action of presently licensed antiepileptic drugs

AED	Na+ channel blockade	T-type Ca^{2+} channel blockade	non-T-type Ca^{2+} channel blockade	GABA mimetic drugs	anti-glutamate action
PHT	+++		+	+	
PB/PRM *	++		+	++	++

AED	Na+ channel blockade	T-type Ca^{2+} channel blockade	non-T-type Ca^{2+} channel blockade	GABA mimetic drugs	anti-glutamate action
CBZ	+++			+	+
OXC	+++		+		+
VPA	++	+		++	+
ESM		+++			
CLZP **	+		+	+++	
LTG	+++				+
VGB				+++	
TGB				+++	
GBP	+			++	+
FBM	+		+	+	++
TPM	++			++	++

Adapted from (149, 163, 179, 232, 262).
* PB is the major active metabolite of PRM. It is uncertain to which extent primidone itself contributes to efficacy and to toxicity.
** representative of 1-4 benzodiazepines.
+++: well-documented action believed to account for a major part of the drug's anticonvulsant effect.
++: effect probably of clinical significance
+: effect only tentatively characterized or seen only at supratherapeutic concentrations

As can be seen in table 4.1a, almost all AEDs have multiple mechanisms of action, which complicates classifying them according to their mechanism of action and anticonvulsant spectrum. It must be emphasized that it is still controversial as to how much each separate mechanism of action contributes to the overall anticonvulsant effects of these different drugs. This is true not only for the newer AEDs, but also for some of the older drugs, such as valproate. Furthermore, it is important to highlight that most of the drugs shown in table 1 have additional pharmacological actions, but these are presently not considered to be essential for anticonvulsant activity. Nevertheless, a possible classification of mechanisms of action to explain anticonvulsant spectra of the various AEDs is:

1) Drugs that decrease sustained repetitive firing:

these drugs may be efficacious against partial and generalized tonic-clonic seizures. Many of the conventional AEDs do this by delaying the recovery from inactivation of sodium channels. Sustained repetitive firing may also be decreased by glutamate receptor

antagonists (blocking either the α-amino-3-hydroxic-5-methylisoxazole-4-propionic acid (AMPA) or the *N*-methyl-D-aspartate (NMDA) subtype of the glutamate receptor) and by drugs that block voltage-dependent calcium channels.

2) Drugs that increase GABAergic neurotransmission:

these drugs may be efficacious against all seizure types, dependent on their site of action and on whether they target $GABA_A$ or $GABA_B$ receptors. As was mentioned before, it is a fallacy that in most brain regions augmentation of GABA will be anticonvulsant (85) A fine example is absence epilepsy, in which $GABA_A$ mediated inhibition in the nucleus reticularis thalami (NRT) blocks seizures, whereas $GABA_A$ mediated inhibition in thalamocortical relay neurons enhances seizures (232). Thus it seems that the anticonvulsant spectrum of a drug that enhances GABA-mediated inhibition is determined by the regions in which it has this effect and by the receptors ($GABA_A$ or $GABA_B$) on which it acts;

3) Drugs which block the T-type calcium channel in thalamocortical relay cells:

these are efficacious against generalized absence seizures.

Although being quite useful, this classification still has some unresolved issues: For example, LTG is reported to block absence seizures but it does not enhance GABAergic neurotransmission nor does it block the T-type calcium channel (21). Another example are the main mechanisms of action of carbamazepine (CBZ) and phenytoin (PHT) which are often thought to be the same (i.e. slowing the recovery of the sodium channel from its inactive state). However, patients not responding to CBZ may benefit from PHT and vice versa (102). Also, in the amygdala kindling model, animals not responding to PHT may respond to CBZ (147). Experimental data suggest that PHT produces a more frequency-dependent block than CBZ (224). It is also possible that they bind to different types of the α-subunit of the sodium channel or to different sites of the $GABA_A$/BZD receptor, which may have different regional distributions, and consequently lead to differences in efficacy and tolerability (163). Furthermore, it is quite possible that a combination of the mechanisms of action of a drug, in some critical proportion, might be what determines the antiepileptic potency of a drug (199).

4.2 Animal and human polytherapy studies: the evidence reviewed

Now that we have briefly covered the pathophysiology of epileptic seizures and the mechanisms of action of the presently available AEDs, we can proceed with our literature review. In this review the available studies on AED polytherapy are reviewed to determine whether drugs can be selected for combination therapy based on their mechanisms of action and if so, which combinations lead to increased effectiveness. Consequently we also needed to evaluate the merits of the various designs and methods of analysis used in these studies.

Methods

The PubMed program of the National Library of Medicine was used to screen the literature for every combination of the drugs listed in table 1, using the search command: [combination] AND [seizures] AND [name drug 1] AND [name drug 2]. Additional papers reporting on AED combinations were identified by checking the cited references of review papers and the cited references of the retrieved research papers. Only those papers reporting on combinations of two drugs were eligible for inclusion in this study.

Results

Animal data

Twenty-one papers satisfied the criteria described above, of which 13 were retrieved by Medline search. Of the drugs listed in table 1, 30 different two-drug combinations have been evaluated in animals. However, it is difficult to compare these data because of the various epilepsy models employed and because the methods to evaluate drug interaction were often different. The most important animal models will be briefly discussed now:

The maximal electroshock model (MES): a 50 or 60 Hz alternating current is administered for 0.2 sec through corneal or auricular electrodes. Abolition of the hind-limb tonic extensor component following stimulation is taken as the endpoint for this test, signifying the ability to prevent spreading of seizure activity through neural tissue. This model was thought to represent partial seizures and generalized tonic-clonic seizures, but because of the lack of efficacy of VGB in this model it is now only acknowledged as a model for generalized tonic-clonic seizures (GTCS).

The pentylenetetrazol test (Ptz): Ptz impairs GABAergic neurotransmission. A convulsive dose of Ptz is injected subcutaneously and the animals are then watched for 30 minutes for the presence of an episode of clonic spasm persisting for at least 5 seconds. Absence of such an episode is suggestive of raising seizure threshold. This model is used for myoclonic and/or absence seizures. A problem is that phenobarbital (PB) is efficacious in this model, although it is not efficacious against absence seizures (261).

Amygdala-kindling: repeated electrical stimulations in the amygdala induce the progressive development of seizures, evolving through well-defined stages. Once the enhanced sensitivity has developed, as evidenced by seizures resembling secondary generalized seizures, the animal is said to be fully kindled. If kindling stimulations are continued thereafter, spontaneous seizures may develop, demonstrating that kindling has resulted in epileptogenesis (149). This model is used to test the efficacy of a drug in limiting focal seizures from the amygdala and is considered useful as a model for complex partial seizures. If the electrical stimulations are continued during AED treatment, the seizures may become refractory to all anticonvulsants, resembling the development of intractable temporal lobe epilepsy (147).

Some of the papers found were not eligible as they were not in English, French, German or Dutch. The collected animal data are summarized in table 4.2a (29, 37, 48, 50, 56, 140, 168, 184, 196, 221, 237, 259),

(30, 93, 94, 187, 208, 214, 215, 225, 235). The term 'non-protective dose' signifies that the drug in question is efficacious in the model studied, but is administered at a dose which does not offer full protection. The term 'non-efficacious' means that the drug is not efficacious in the animal model studied at maximally tolerated dosages. In almost all of the studies listed, the ED_{50} and TD_{50} were defined as the dose at which 50% of the animals had reached the desired endpoint or had reached a certain level of toxicity respectively (in some studies the EC_{50} and TC_{50} were determined; i.e. the plasma or brain concentrations at 50% of the animals had reached the desired endpoint or had reached a certain level of toxicity respectively).

Table 4.2a Polytherapy studies in animal models of epilepsy

AEDs	first author (ref. nr.)	animal	model	experimental design	method of analysis	efficacy	toxicity
PHT/PB	Weaver (259)	mice	MES[1]	ED_x PB + (ED_{50} - ED_x) PHT *	estimated and observed ED_{50} compared	supra-additive	additive
	Leppik (140)	rats	MES	ED_x drug PB + (ED_{50} - ED_x) PHT	estimated and observed ED_{50} compared	additive	no info
	Masuda (168)	mice + rabbits	MES	doses given alone and together	isobologram method	supra-additive	no info
	Picker (196)	rats	effects on behavior	low doses added together	estimated and observed effects compared	no info	effect combi = drugs alone
	Bourgeois (29)	mice	MES	drugs tested alone and together	FEC method **	additive	infra-additive
	Stringer (237)	rats	MDA[2]	non-efficacious PHT added to PB	MDA duration and time to onset	effect PB ↑	no info
PHT/CBZ	Schmutz (221)	mice + rats	MES	drugs tested alone and together	summation of effects method	effect combi >drugs alone	effect combi = drugs alone
	Morris (184)	mice	MES	drugs tested alone and together	FEC method	additive	additive
PHT/VPA	Chez (37)	mice	MES	drugs tested alone and together	FEC method	supra-additive	additive
	D. Paschoa (56)	rats	CS[3]	non-protective VPA added to PHT	stimulus is increased until response occurs	efficacy PHT ↑	no info
PHT/CZP	Czuczwar (50)	mice	Ptz[4]/ bicuc[5]	non-efficacious PHT added to CZP	re-evaluation of the effects of CZP	ED_{50} CZP ↓	no info
	Czuczwar (48)	mice	MES	drugs tested alone and together	visual comparison of data	effect combi >drugs alone	no info
PB/PRM	Bourgeois (29)	mice	MES	drugs tested alone and together	FEC method	supra-additive	infra-additive
PB/VPA	Picker (196)	rats	effects on behaviour	low doses added together	estimated and observed effects compared	no info	effect combi = drugs alone
	Bourgeois (29)	mice	MES	drugs tested alone and together	FEC method	additive	additive
CBZ/VPA	Schmutz (221)	mice + rats	MES	drugs tested alone and together	summation of effects method	effect combi >drugs alone	effect combi = drugs alone
	Bourgeois (29)	mice	MES	drugs tested alone and together	FEC method	additive	infra-additive
VPA/ESM	Bourgeois (29)	mice	Ptz	drugs tested alone and together	FEC method	additive	infra-additive
	Musolino (187)	rats	Ptz	low-dose drug added to the other	comparison of regression lines	effect combi >drugs alone	no info
	Roks (208)	rats	no epilepsy	drugs tested alone and together	isobologram method	no info	infra-additive

* ED_x PB + (ED_{50} - ED_x) PHT; for example: ED_{20} PB + (ED_{50} - ED_{20}) PHT; ** FEC method: fractional effective concentration method; 1) MES: maximal electroshock seizures; model for generalized tonic-clonic seizures; 2) MDA: maximal dentate activation; model for complex partial seizures; 3) CS: cortical stimulation: model for partial seizures; 4) Ptz: pentylenetetrazol; model for myoclonic and/or absence seizures; 5) bicuculline: $GABA_A$ receptor antagonist; model used for partial seizures. For AED abbreviations see table 4.1a.

Table 4.2a Polytherapy studies in animal models of epilepsy (continued)

AEDs	first author (ref. nr.)	animal	model	experimental design	method of analysis	efficacy	toxicity
VPA/CZP	Bourgeois (30)	mice	Ptz	low dose CZP added to VPA	re-evaluation of VPA's ED_{50} and TD_{50}	ED_{50} VPA ↓	TD_{50} VPA ↓
ESM/CZP	Bourgeois (30)	mice	Ptz	low dose CZP added to ESM	re-evaluation of ESM's ED_{50} and TD_{50}	ED_{50} ESM ↓	TD_{50} ESM ↓
LTG/PHT	De Sarro (214)	mice	DBA[6]	non-protective dose of LTG added to PHT	re-evaluation of PHT's ED_{50} and TD_{50}	ED_{50} PHT ↓	TD_{50} PHT ↓
LTG/PB	De Sarro (214)	mice	DBA	non-protective dose of LTG added to PB	re-evaluation of PB's ED_{50} and TD_{50}	ED_{50} PB ↓	TD_{50} PB ↓
LTG/CBZ	De Sarro (214)	mice	DBA	non-protective dose of LTG added to CBZ	re-evaluation CBZ's ED_{50} and TD_{50}	ED_{50} CBZ ↓	TD_{50} CBZ ↓
LTG/VPA	De Sarro (214)	mice	DBA	non-protective dose of LTG added to VPA	re-evaluation of VPA's ED_{50} and TD_{50}	ED_{50} VPA ↓	TD_{50} VPA ↓
LTG/DZP	De Sarro (214)	mice	DBA	non-protective dose of LTG added to DZP	re-evaluation of DZP's ED_{50} and TD_{50}	ED_{50} DZP ↓	TD_{50} DZP ↓
LTG/TPM	Stephen (235)	mice	Ptz	non-efficacious drugs given together	evaluation of seizure control	efficacious combination	no info
GBP/PHT	De Sarro (215)	mice	DBA	non-protective dose of GBP added to PHT	re-evaluation of PHT's ED_{50} and TD_{50}	ED_{50} PHT ↓	TD_{50} PHT ↓
GBP/PB	De Sarro (215)	mice	DBA	non-protective dose of GBP added to PB	re-evaluation of PB's ED_{50} and TD_{50}	ED_{50} PB ↓	TD_{50} PB ↓
GBP/CBZ	De Sarro (215)	mice	DBA	non-protective dose of GBP added to CBZ	re-evaluation of CBZ's ED_{50} and TD_{50}	ED_{50} CBZ ↓	TD_{50} CBZ ↓
GBP/VPA	De Sarro (215)	mice	DBA	non-protective dose of GBP added to VPA	re-evaluation of VPA's ED_{50} and TD_{50}	ED_{50} VPA ↓	TD_{50} VPA ↓
GBP/DZP	De Sarro (215)	mice	DBA	non-protective dose of GBP added to DZP	re-evaluation of DZP's ED_{50} and TD_{50}	ED_{50} DZP ↓	TD_{50} DZP ↓
GBP/FBM	De Sarro (215)	mice	DBA	non-protective dose of GBP added to FBM	re-evaluation of FBM's ED_{50} and TD_{50}	ED_{50} FBM ↓	TD_{50} FBM ↓
GBP/LTG	De Sarro (215)	mice	DBA	non-protective dose of GBP added to LTG	re-evaluation of LTG's ED_{50} and TD_{50}	ED_{50} LTG ↓	TD_{50} LTG ↓
FBM/PB	Gordon (94)	mice	MES	non-protective dose of PB added to FBM	re-evaluation of FBM's ED_{50} and TD_{50}	ED_{50} FBM ↓	TD_{50} FBM ↓
FBM/CBZ	Gordon (94)	mice	MES	non-protective dose of CBZ added to FBM	re-evaluation of FBM's ED_{50} and TD_{50}	ED_{50} FBM ↓	TD_{50} FBM =
FBM/VPA	Gordon (94)	mice	MES	non-protective dose of VPA added to FBM	re-evaluation of FBM's ED_{50} and TD_{50}	ED_{50} FBM ↓	TD_{50} FBM ↓
FBM/DZP	Gordon (93)	mice	MES/ Ptz	non-protective dose of FBM added to DZP	re-evaluation of DZP's ED_{50}	ED_{50} FBM ↓	no info
TPM/PHT	Shank (225)	mice	MES	drugs tested alone and together	isobologram method	additive	no info
TPM/PB	Shank (225)	mice	MES	drugs tested alone and together	isobologram method	supra-additive ***	no info
TPM/CBZ	Shank (225)	mice	MES	drugs tested alone and together	isobologram method	supra-additive ***	no info

*** Some of the ratio's of this combination were synergistic. 6) DBA/2 mice: genetically epilepsy prone rats.

Comments

A few conflicting results between the studies are immediately apparent from table 4.2a. For example, the PB/PHT combination which was reported to be synergistic for efficacy in three papers, whereas it was reported to have additive efficacy in two other papers.

Furthermore, not all of the methods used to evaluate interactions have the same merit. In fact, most studies did not employ the isobologram method, which is considered to be the optimal method to detect supra-additivity (synergy), additivity (zero interaction) or infra-additivity (antagonism) (17, 238). The method used by Weaver et al and Leppik et al. and the Fractional Effective Concentration (FEC) method as used in most of Bourgeois' experiments and in some other studies are quantitative methods similar to the isobologram method (29, 37, 140, 184, 259). Recently, a sound statistical basis for the isobologram method was published by Roks et al. (208). Thus in table 4.2a, the results of studies using isobologram or similar methods are defined in terms of infra-additivity, additivity and supra-additivity (these terms are reserved for these methods). A combination may offer advantages when the balance between efficacy and toxicity, i.e. the therapeutic index (the TC_{50}/EC_{50}; T.I.) is improved. This was the case for the combinations PHT/PB (29, 259), PHT/VPA (37), PB/PRM (29), CBZ/VPA (29) and VPA/ESM (29). However, due to the low T.I. of PB, combinations with this drug still had a lower T.I. than the other constituents of these combinations (i.e. PHT and PRM). A number of other studies using the isobologram method only studied either efficacy or toxicity, and therefore the T.I.'s of these combinations could not be determined (140, 168, 208, 225).

There is another study design which, although not using the isobologram method, is also informative: the study of Stephen et al. showed that two drugs (i.e. LTG and TPM) which have no efficacy in the Ptz test at maximal dosages, protected against Ptz-induced seizures when they were given in combination (235). However, no information was given concerning the toxicity of the combination.

In the bulk of the studies listed in table 4.2a a different design was used, in which both drugs are efficacious in the employed animal model. In this design drug B is titrated to its ED_{50} in the presence of a non-protective dose of drug A, and potentiation of anticonvulsant effect is claimed when the ED_{50} of drug B proves to be reduced compared to its ED_{50} in monotherapy. If, however, we use the 'sham combination test' of Berenbaum (in which drug A and B are the same drug) for this study design, the addition of a non-protective dose

of drug A will lead to a reduced ED_{50} of drug B and to the conclusion that drug A potentiates the anticonvulsant effect of drug B. This is impossible, as drug A and B are the same drug (17). Furthermore, if one examines the therapeutic index, it will also be elevated in the sham combination test, which is equally impossible. Demonstrating that there is no interaction between two anticonvulsants is indeed possible by using this method as was shown by Borowicz et al. (26).

One study used response surface modeling to evaluate interactions between CBZ, FBM and PHT (86). This study is not listed in table 4.2a, because of the complexity of the data presented. In his review, Berenbaum also discusses this model (17).

Human data

Of the drugs listed in table 1, 12 different two-drug combinations have been evaluated in epilepsy patients. In most of these studies, patients were diagnosed to have difficult-to-treat epilepsy and had already tried many AEDs, in monotherapy and in combination therapy (10, 34, 36, 52, 84, 100, 102, 104, 112, 186, 191, 211, 239, 241, 258), (181, 209, 230, 235). Of these 19 papers, 12 were retrieved by the Medline search. The main outcome measure in the selected studies was seizure frequency. The studies had open, uncontrolled and non-randomized designs and some were (partly) retrospective. The effects on tolerability were mostly described very briefly or not reported on at all. The data of these studies are summarized in table 4.2b. Dosages and serum levels are listed when available, as these may have some relevance for estimating intractability. Serum levels are not included in Table 4.2a, as intractability was not considered an issue in animal studies.

Case reports about a certain combination are not listed if there are larger studies reporting about that combination. Interesting studies on combinations of VPA+LTG, VPA+VGB, LTG+VGB, LTG+TPM and TGB+VGB were not eligible for inclusion because patients in those studies also took other drugs in addition to the combination (9, 76, 77, 128, 138, 198, 216, 236, 251).

Table 4.2b. Polytherapy studies in epilepsy patients

Drugs	first author (ref. nr.)	number of patients	seizure type	study design	efficacy	adverse effects
PHT/PB	Gruber (100)	24	generalized tonic-clonic and partial seizures	patients were given placebo, 50 mg PB monotherapy, 50 mg PHT monotherapy or 25 mg PB + 25 mg PHT in a crossover design	the combination was equally efficacious as the two drugs alone	no info
	Painter (191)	59	neonatal seizures	29 patients not completely controlled by one of the two drugs at serum levels in the therapeutic range were given PB + PHT	9 of 29 (31%) had complete control of seizures	no overt clinical toxicity
	Cereghino (36)	41	generalized tonic-clonic and partial seizures	patients were given PHT 300 mg dd, PB 300 mg dd and CBZ 1200 mg dd in the following combinations: PHT+PB; PHT+CBZ; PB+CBZ; PHT+PB+CBZ in a cross-over study	of the three 2-drug combinations, PB + PHT was most efficacious	PB+PHT: no patients withdrew
PHT/CBZ	Hakkarainen (102)	100	adult-onset seizures	33 patients not controlled by either drug were given PHT/ CBZ	5/33 seizure free with PHT/CBZ	no info
	Cereghino (36)	41	generalized tonic-clonic and partial seizures	patients were given PHT 300 mg dd, PB 300 mg dd and CBZ 1200 mg dd in the following combinations: PHT+PB; PHT+CBZ; PB+CBZ; PHT+PB+CBZ in a cross-over study	of the three 2-drug combinations, CBZ + PHT was least efficacious	CBZ+PHT: 3 patients withdrew
PHT/LTG	Brodie (34)	92	all seizure types	patients were not controlled by PHT were given PHT + LTG (average add-on dose 359 mg dd)	38% of patients > 50% seizure reduction; 13 of 16 pts. completed LTG monotherapy phase	13% withdrew due to toxicity
CBZ/VPA	Armour (10)	18	generalized tonic-clonic and partial seizures	intractable patients not controlled by maximal VPA monotherapy were given VPA+CBZ	12 improved with CBZ/VPA combination	no info
	Dean (52)	100	partial seizures (+/- secondary generalization)	patients were not controlled by maximal CBZ monotherapy were given VPA + CBZ	17% of patients were seizure-free; another 39% had a > 50% reduction	no info
	Fröscher (84)	54	generalized tonic-clonic and partial seizures	difficult-to-treat patients were given VPA+CBZ at therapeutic serum levels	GTCS*: 76% > 50% reduction; partial seiz.: 29% > 50% reduction	adverse effects in 50%
	Harden (104)	18	partial seizures (+/- secondary generalization)	patients not controlled by maximal CBZ monotherapy were given VPA + CBZ	3 patients > 50% seizure reduction	some toxicity
	Walker (258)	43	complex partial seizures + secondary generalization	patients were first given VPA monotherapy; if not controlled CBZ monotherapy; still not controlled CBZ+VPA	17 patients not controlled by either drug alone: 12> 50% reduction (6 seizure free) on VPA + CBZ	no new or additive toxicity

Efficacy mostly described by average percentage seizure reduction and/or by percentage seizure free patients; pts.= patients; GTCS = generalized tonic-clonic seizures

Table 4.2b. Polytherapy studies in epilepsy patients (continued)

Drugs	first author (ref. nr.)	number of patients	seizure type	study design	effi
CBZ/CLZP	Tatzer (241)	34	West (24) or Lennox Gastaut Syndrome (10)	patients were given CBZ + either CLZP or nitrazepam (NZP) all at their usual dose range	IS: 14 > 50% seizure re free);myoclonic-astatic
	Hosada (112)	28	partial seizures	children with seizures refractory to maximal CBZ monotherapy were given CBZ + CLZP	23 of 28 patients st 12 months after th
CBZ/LTG	Brodie (34)	129	all seizure types	patients not controlled by CBZ were given CBZ + LTG (average add-on dose 347 mg dd)	41% of patients > 50% s pts. completed LTG
CBZ/VGB	Murri (186)	40	partial seizures (+/- secondary generalization)	patients not controlled by maximal CBZ monotherapy were given CBZ + VGB (average add-on dose 2,75 g dd)	overall 70% se 7 patients
	Tanganelli (239)	14	partial seizures (+/- secondary generalization)	patients not controlled by maximal CBZ monotherapy nor by maximal VGB monotherapy were given CBZ + VGB	8 of 14 > 75% seizur 5 were se
VPA/ESM	Rowan (211)	5	absence seizures	all patients refractory to maximal VPA and two also to ESM; all were given VPA + ESM	all five becam
VPA/CZP	Mireles (181)	55	mixed	retrospective review of patients with intractable epilepsy who had received VPA (average serum level 56.6 mg/l) + CZP (average serum level 22.6 ng/l) combination	seizure control improv absences, 8/9 with myoc CPS: 3/14 with prim. GT and in 3/14 with
	Rosenberry (209)	12	absence and/or myoclonic seizures	patients were not controlled by either VPA or CZP alone and were given combination	6 of 8 patients remai experienced a mark
VPA/LTG	Brodie (34)	115	all seizure types	patients not controlled by VPA were given VPA + LTG (average add-on dose 96 mg dd)	64% of patients > 50% s pts. completed LTG
VPA/FBM	Siegel (230)	13	Lennox-Gastaut Syndrome	Patients on VPA alone at therapeutic serum levels received add-on FBM or placebo in a cross-over study	40% fewer drop attack seizures on FBM (VP
LTG/TPM	Stephen (235)	2	mixed seizure types (partial/generalized)	Patients receiving maximal LTG monotherapy were given TPM as add-on medication	Both patient

IS = infantile spasms; pts. = patients; CPS = complex partial seizures; GTCS = generalized tonic-clonic seizures

Comments

There is no straightforward methodology for the investigation of AED pharmacodynamic interactions in the clinical setting (200). In humans the isobologram method cannot be used, as it is impossible to titrate to exactly the same effect in all treatment groups. Gruber et al. used an approach somewhat similar to the isobologram method by giving patients either 50 mg of PHT, 50 mg PB or a combination of 25 mg of PHT plus 25 mg of PB (100). All three regimens were found to have equal efficacy in this study, however it is somewhat surprising that 50 mg of PHT was as efficacious as 50 mg of PB.

A study design similar to that in the animal experiment of Stephen et al. (235) has been used by various investigators. In these studies patients, who did not respond to drug A given alone nor to drug B given alone at maximal dosages, were given the combination of drug A and B (often adding the first drug to the drug the patient was taking at the time). When the combination of A and B resulted in improved seizure control in a considerable number of these patients and pharmacokinetic interactions have been ruled out, this was considered to be suggestive of either improved efficacy or improved tolerability. Using this design, Hakkarainen, Walker et al. and Tanganelli et al. respectively observed that the combinations of CBZ/VPA and CBZ/VGB had added value, whereas CBZ/PHT did not (102, 239, 258). Other studies, in which patients had received only one of the drugs prior to receiving the combination (similar to add-on drug trials for new AEDs), offer less convincing evidence regarding effectiveness of combination therapy. Using this design one cannot exclude the possibility that the added drug is solely responsible for the improved effectiveness.

Another approach which does have merit, is the one used by Brodie et al. and by Cereghino et al. (34, 36). In these studies the investigational AED was used in several two-drug combinations. If seizure control brought about by one combination exceeded the control brought about by any other combination and pharmacokinetic interactions had been ruled out, this was considered to be suggestive of a positive pharmacodynamic interaction. Indeed, this was observed to be the case for the combinations PB/PHT and VPA/LTG.

Discussion

Based on those animal and human studies that had one of the preferred designs (i.e. studies that used isobolographic analysis or similar methods, studies in which both of the drugs combined were non-efficacious in the animal model or patients studied and studies in which

combinations were compared to other combinations), a number of combinations appear to be associated with increased effectiveness. These potentially advantageous combinations are listed in table 4.2c (29, 34, 36, 37, 48, 168, 225, 235, 239, 258, 259). The clinically significant mechanisms (marked with three or two asterisks in table 4.1a) of the drugs involved are also shown.

Table 4.2c Potentially advantageous AED combinations and clinically relevant mechanisms of action of the drugs involved

Combinations	Mechanisms of action	Seizure type	Animal studies	Human studies
PHT/PB	Na^+/GABA, Na^+, glutamate	generalized tonic-clonic and partial seizures	96, 168, 201, 259	36
PHT/VPA	Na^+/GABA, Na^+	generalized tonic-clonic seizures	37	
CBZ/VPA	Na^+/GABA, Na^+	generalized tonic-clonic and partial seizures	29	258
CBZ/VGB	Na^+/GABA	partial seizures (+/- secondary generalization)		239
VPA/ESM	GABA, Na^+/ T-type calcium channel	absence seizures	29	
VPA/LTG	GABA, Na^+/Na^+	generalized tonic-clonic and partial seizures		34

Only mechanisms of action with three or two "+" in Table 1 are shown. Some of the combinations listed only had increased effectiveness in animal experiments; some only in clinical studies and some in both. Slashes divide the two drugs in column 1 and the mechanisms of action of the respective drugs in column 2.

Other interesting combinations are PHT/CZP, PB/TPM, CBZ/TPM, LTG/TPM, although toxicity was not reported in the studies of these combinations (48, 225, 235). Table 4.2c shows combinations with improved effectiveness, whether this was accomplished by actual synergy between drugs or increased tolerability. It is unknown whether the mechanisms responsible for the anti-convulsant effects of these drugs also cause their adverse effects. As is shown in table 2, Bourgeois did observe additivity for efficacy and infra-additivity for toxicity for several combinations, which suggests that increased effectiveness is often due to improved tolerability (29).

Further insight on this may be forthcoming from experimental animal studies involving candidate AEDs. Czuczwar et al. reported that AMPA/kainate antagonists and NMDA-antagonists reduced each other's ED_{50} in an electroconvulsion model (47). However, in some of these combinations adverse effects were also potentiated. The same group also

reported that some NMDA-antagonists and some non-competitive AMPA/kainate antagonists reduced the ED_{50}'s of CBZ, PHT and VPA in the maximal electroshock-induced convulsions without exacerbating adverse effects (46). Löscher et al. found that NMDA antagonists, which only exhibited weak efficacy in kindled rats, potentiated the efficacy of the competitive AMPA-antagonist 2,3-dihydroxy-6-nitro-sulfamoylbenzo(F)quinoxaline (NBQX) without potentiating its toxicity (151).

Klitgaard et al. reported that combining a glutamate-receptor antagonist (AMPA or NMDA) and a drug that enhances GABAergic inhibition did not result in a supra-additive effect against audiogenic seizures in DBA/2 mice, whereas combining two glutamate antagonists or combining two GABAergic drugs did (126). Increased efficacy of two GABAergic drugs has also been found in vitro (205); these authors constructed a molecular model that could describe and explain the synergy between two GABAergic drugs at a molecular level, giving a rational for the observed synergy in the in vivo setting. Löscher's group also found that NMDA receptor antagonists combined with GABA-enhancing drugs did not result in increasing effectiveness in kindled rats (150). However, Czuczwar's group did find increased effectiveness for these combinations in the electroconvulsive threshold test and also reported that LY 300164, an AMPA/kainate receptor antagonist, interacts with clonazepam in the MES and in amygdala-kindled rats (25, 49).

The latter group has also reported that some calcium channel blockers may decrease the ED_{50} of some of the standard AEDs against electroconvulsions and in the Ptz model (46). Although these data have been corroborated by other groups (207), clinical add-on trials of calcium channel blockers have not been very successful.

Based on the data described and on our present knowledge of AED mechanisms of action, the following mechanistic combinations may be useful in patients with generalized tonic-clonic seizures and partial seizures:

1. combining a sodium channel blocker with a drug enhancing GABAergic inhibition 2. combining two drugs that both enhance GABAergic inhibition

3. combining an AMPA antagonist with a NMDA antagonist

The case of combining two sodium channel blockers seems less promising: CBZ and PHT do not act synergistically, and LTG interacts more efficaciously with VPA than with CBZ or PHT. It may be argued, however, that the success of combining VPA with LTG, or for that matter PB with PHT, is based on the fact that these drugs all possess sodium channel

blocking properties. On the other hand, questions have been raised whether sodium channel blocking really contributes to VPA's or PB's clinical efficacy (149, 262).

Furthermore it is important to keep in mind that improved effectiveness, i.e. an improved balance between efficacy and tolerability, is the goal of combination therapy. For example, combinations of drugs that enhance GABAergic inhibition may enhance efficacy, but some of them also produce supra-additive hypnotic effects (57, 109). Also, idiosyncratic reactions may increase simply because two drugs are used instead of one, but also because of metabolic interactions.

Instead of looking at cellular mechanisms, AEDs have also been categorized according to their ability to increase seizure threshold (as evidenced by efficacy in the Ptz model) and to prevent seizure spread (as evidenced by efficacy in the MES test) (151). It is uncertain whether one should combine two drugs that raise seizure threshold, two drugs that inhibit seizure spreading or that one should combine one of each category (158). Given the efficacy of the AEDs in these two models (148), the combinations listed in table 4 do not help in distinguishing these options.

It is also interesting to consider the regional effects of AEDs. Increasing GABAergic neurotransmission in the substantia nigra pars reticulata (SNR) for example, is a remarkably effective means of suppressing seizure propagation in a wide range of convulsive and non-convulsive animal epilepsy models (85, 150). Benzodiazepines, VPA and PB have been shown to inhibit firing in the SNR, whereas PHT and CBZ were ineffective in this respect (150). Perhaps this could be another area worth exploring for rational polytherapy.

It is very apparent that our knowledge of the mechanisms of action of the presently licensed AEDs is far from complete, and consequently we cannot fully explain their anticonvulsant spectra. Furthermore, Macdonald concludes that until the basic mechanisms of seizures are fully understood, there will only be a theoretical basis for rational polypharmacy (163). This will be discussed further in chapter 7.

Chapter 5 AED combination therapy in animals

As was discussed in chapter 4, there are a number of animal models for epilepsy. In Nijmegen, the Department of Comparative and Physiological Psychology of the Catholic University has worked extensively with the WAG/Rij rat as a model for human absence epilepsy. The WAG/Rij rat shares behavioral, electro-encephalographic and anticonvulsant profiles with human absence epilepsy (161, 193).

In this chapter the research which was done in collaboration with the Department of Comparative and Physiological Psychology (Dr. C.M. van Rijn) is described. The first paragraph concerns a study which was focused on the neurotoxic effects of valproate (VPA) and ethosuximide (ESM), alone and in combination, in Wistar rats and on the design and analysis of polytherapy studies in animals. In the second study, described in paragraph 5.2, the effect of VPA and ESM, alone and in combination, on the number of spike-wave discharges in WAG/Rij rats was assessed.

5.1 Neurotoxicity of the combination of valproate and ethosuximide in Wistar rats

Introduction

Bourgeois has studied the possible advantages of many antiepileptic drug combinations in mice (29). Anti-convulsant effect was studied by observing whether clonic seizures elicited by maximal electroshock or pentylenetetrazole (depending on the drugs to be studied) were suppressed and neurotoxicity was evaluated by use of the rotarod test (absence of neurotoxicity being defined as the ability to stay on a rotating horizontal rod for at least 10 minutes). Results were presented as a therapeutic index, which in these studies was a ratio of the TC_{50} (concentration with toxic action in 50% of the animals) and the EC_{50} (concentration with therapeutic action in 50% of the animals). As was discussed in chapter four, Bourgeois found two drug pairings to have advantages when used in combination: valproate plus carbamazepine and valproate plus ethosuximide. In both cases the anti-convulsant effect was purely additive but due to an infra-additive neurotoxicity the combination had a better efficacy versus toxicity ratio than the single drugs. However, neurotoxicity was only evaluated by use of the rotarod test, measuring motor coordination and praxis, while for example, sedative effects were not assessed.

In the present study we will focus on the combination of valproate and ethosuximide and on a more extensive evaluation of neurotoxic effects; the grip strength meter, the accelerod (an accelerating version of the rotarod), and video observation were used to assess neurotoxicity. Dose-effect curves of valproate and ethosuximide in mono- and polytherapy were determined in order to assess drug interaction with respect to strength, ataxia, and sedation. Also, a novel approach for the statistical analysis of drug interactions is presented.

Methods

Animals

Male adult Wistar rats, weighing between 224 and 320 grams, were used for this experiment. They were housed in identical plastic cages and had free access to food and water except during the motor experiments. They were kept on a reversed light dark cycle (dark between 9.00 en 21.00 hours).

Drugs

Valproate (Albic Inc. Maassluis, The Netherlands) and ethosuximide (Sigma chemical co., The Netherlands), dissolved in 0.9% sodium chloride, were administered intraperitoneally alternating left and right to prevent adhesions.

Experiment

The animals were divided in four groups of eight rats, one group receiving valproate, one group receiving ethosuximide, one group receiving the drug combination and one saline control group. Every rat received six dosages including a zero dosage of the drug it was randomly assigned to, with an interval of 7 days. This interval was chosen on basis of the half-life of elimination of valproate (146) and ethosuximide (12), being respectively 4.6 and 22 hours. The sequence of the six different doses was assigned to an individual rat according to an adapted Latin square. This design was chosen to correct for follow up effects. All injections were blinded for the investigator. The dose of valproate ranged from zero to 560 mg/kg and of ethosuximide from zero to 360 mg/kg, based on pilot experiments. For the drug combination a fixed weight ratio of 2/3 valproate with 1/3 ethosuximide was given, the doses ranged from zero to 360 mg/kg valproate with 180 mg/kg ethosuximide. The ratio of valproate and ethosuximide were based on their TD_{50} (in this case the amount of drug causing 50% of the maximum effect) found in the aforementioned pilot experiments. After weighing and injection, the rats were evaluated using the three aforementioned tests in a fixed sequence.

First, the grip strength of the fore-paws was determined (130). The grip strength apparatus consists of a push-pull strain gauge attached to a T-bar. To measure the grip strength the animal is placed with its fore-paws on the T-bar and is than gently pulled backwards until its grip is broken. The strength is measured in grams. Before the experiment the animals

were trained for three days. The grip strength test took place between 40 and 60 minutes after injection. The average of three trials was taken in the further analysis of the data.
Next, the animals were placed on an accelerating rotarod (119). The rod started at 15% of maximum speed (50 rev/min) and accelerated 0.2% per second. The time a rat managed to stay on the rod was scored and the longer one of two runs was taken for further analysis. Before the experiment, the animals were trained for three days and had to be able to stay on the accelerod for at least one minute to participate in the experiment. Each test day, before injection, the animals were tested on the accelerod and grip strength. These test results were used to correct for possible time effects. The test took place between 80 and 100 minutes after injection.
The third test was a behavioral analysis. The animals were observed for 25 minutes by video camera between 100 and 125 minutes after injection. The animals were in observation cages of 30 by 30 by 50 cm and a minimum of light was used to keep them in an active state. The videotapes were observed with help of "The Observer" computer program (Noldus Information Technology Inc. Wageningen The Netherlands). The behavior was categorized into four classes, namely: 1. active behavior being all movements automatic behavior not included, thus locomotion, sniffing and rearing; 2. passive behavior being the absence of any movement; 3. grooming and 4. automatic behavior, being eating and drinking.

Data analysis

The data of all three tests were analyzed by non-linear regression analysis using the program Graphpad Prism 2.0.
The data were fitted to the sigmoid Emax model:

equation 1:

$$E_{drug} = E_{\min} + \frac{E_{\max} - E_{\min}}{1 + \left[\frac{dose}{TD_{50}}\right]^{Hill}}$$

E_{drug} is the measured effect of the drug at a certain dose. E_{drug} starts at E_{min} and goes to E_{max} with a sigmoid shape. The TD_{50} and Hill factor (Hill) were calculated for the three drugs (VPA, ESM, and VPA+ESM according to its total weight).

Next the theoretical additive curve was generated for the drug combination using the sigmoid Emax model for a mix of two compounds according to equation 2*:

$$E_{combination} = E_{\min} + \frac{E_{\max} - E_{\min}}{1 + \left[\frac{(A) * dose}{TD_{50,\ valproate}} + \frac{(1-A) * dose}{TD_{50,\ ethosux}}\right]^{Hill_{combination}}}$$

with equation 3:

$$Hill_{combination} = \frac{\frac{(A)}{TD_{50,\ valproate}} * Hill_{valproate} + \frac{(1-A)}{TD_{50,\ ethosux}} * Hill_{ethosux}}{\frac{(A)}{TD_{50,\ valproate}} + \frac{(1-A)}{TD_{50,\ ethosux}}}$$

$E_{combination}$ is the calculated additive effect of the combination of drug at a certain dose. $E_{combination}$ starts at E_{min} and goes to E_{max} with a sigmoid shape. A is the fraction of valproate in the combination. The $Hill_{combination}$ is the weighted mean of the Hills of the single compounds. Next, the sigmoid Emax model of equation 1 was fitted to the generated additive data yielding an expected additive TD_{50} and an expected additive Hill. Confidence intervals (CI's) of the expected additive parameters are calculated from the CI's of the measured single compound curves using

* After publication of the paper, we found out that equation 2 is correct for calculating the theoretical additive TD_{50}, but only approaches the rest of the curve. The correct equation will be used when the paper in paragraph 5.2 is submitted. equation 4:

Expected CI= [(A x % $_{CIvalproate}$ + (1-A) x % $CI_{ethosuximide}$) x expected TD_{50}]

The experimental parameter estimates of the drug combination were compared to the theoretical additive parameter estimates using the 95% confidence intervals. The curves of valproate and of ethosuximide were normalized using their TD_{50}s. The curve of the experimental combination was normalized using the TD_{50} of the theoretical additive combination.

The TD_{50} parameter estimates obtained by the sigmoid Emax model were plotted in an isobologram to visualize the type of interaction (17, 238).

Results:

Baseline measurements

To obtain baseline values and to correct for time effects, the grip strength and the accelerod performance were measured each test day before injection. A group x day analysis of variance was performed on these data. A group difference was present ($F(3,144) = 6.51$, $P < 0.001$ for the grip strength and $F(3,144) = 7.11$, $P < 0.001$ for the accelerod). A day difference was present for the grip strength only ($F(5,144) = 2.39$, $P< 0.05$). No group x time interaction was present, indicating that the changes over time are the same for all groups.

For the grip strength the group means varied from 970 grams (S.E.M. 30 g) in the drug combination group to 1160 g (S.E.M. 30 g) in the saline control group. For the accelerod performance the group means varied from 110 seconds (S.E.M. 11 s) in the ethosuximide group to 171 s (S.E.M. 6 s) in the valproate group. An increase of grip strength was found over the test days, from 980 g (S.E.M. 30 g) on test day 1 to 1130 g (S.E.M. 50 g) on test day 6. Because of this time effect, we used the percentage post-injection performance of pre-injection performance as the measure for drug effects for the grip strength and the accelerod performance. In this way, every rat functioned as its own control.

Grip strength

The overall mean pre-injection grip strength was 1060 g (S.E.M. 20 g). Both compounds as well as the combination negatively influenced grip strength performance in a dose-dependent fashion. Equation 1, the sigmoid Emax model, was fitted to the data, yielding the

TC_{50} and the Hill. With these parameter values of the single drugs the theoretical additive curve for the drug combination was calculated using equation 2. The grip strength data (table 5.1a) show that the experimental dose needed to get 50% toxicity in the combination experiment is lower than the theoretical additive dose, suggesting supra-additivity in toxicity.

Table 5.1a. Side effects quantified by grip strength

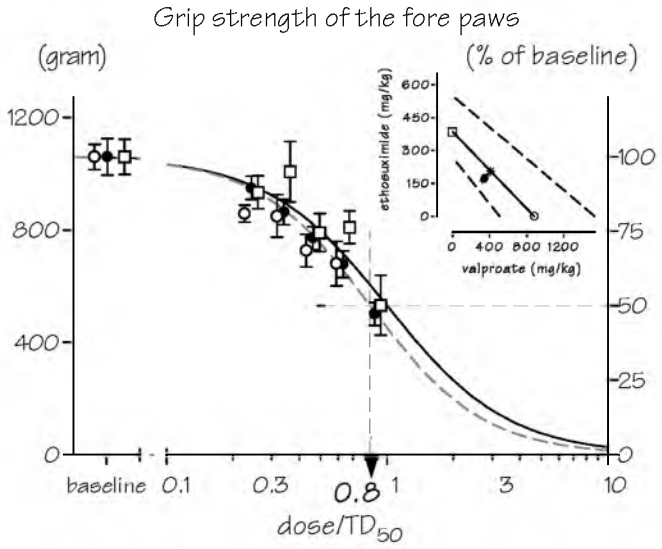
	VPA	**ESM**	**VPA/ESM**	**Theoretical TD_{50}**
TD_{50} (mg/kg)	883	385	345/173	411/206
95 % CI	509 - 1534	270 - 550	323/161 - 370/185	254/127 - 672/336
PDD/TD_{50}	1	1	0.39/0.45	0.47/0.53
Norm. TD_{50}	1	1	0.84	1
Hill	-1.1	-2.1	-1.7	
95% CI	-1.7 - -0.4	-3.6 - -0.6	-1.9 - -1.4	

Parameter estimates of fitting the sigmoid Emax curve to the data. The TD_{50} is the dose at which 50% toxic effect is achieved. All weight values are normalized using the TD_{50} values. The experimental combination uses the TD_{50} of the individual drugs as norm. A normalized TD_{50} of the experimentally determined combination below 1 points to supra-additivity whereas more than 1 indicates infra-additivity. If the 95% confidence intervals of the normalized TD_{50} of the experimental combination do not overlap with the intervals of the theoretical additive ones than the interaction is assumed to be statistically significant. Hill is a measure for the steepness of the curve.

However, the 95% confidence intervals of the experimental TD_{50} and the theoretical TD_{50} overlap to a great extent, as is shown in the inset of figure 5.1a.

Therefore, the finding of supra-additivity proved not to be statistically significant (table 5.1a).

Figure 5.1a Normalized dose-response curves and isobologram for the effect on grip strength performance



Dose response graphs for the change in grip strength performance in rats following injection of valproate (open circles), ethosuximide (open squares) or of the combination of both (closed circles), after fitting the sigmoid Emax model to the data. All weight values are normalized using the TD_{50} values. The experimental combination value uses TD_{50}s of the individual drugs as norm. The normalized drug doses (dose/ED_{50}) are plotted on the abscissas and the grip strength data on the ordinate. The solid lines show the theoretical additive dose response curves as derived from equation 2, and the broken lines show the experimentally measured dose response curves. While fitting the curves to the data, the tops of the curves were fixed at 100 % and the bottoms were fixed at 0 %. The inset shows the TD_{50}s plotted in an isobologram with the TD_{50} of valproate on the abscissa, and the TD_{50} of ethosuximide on the ordinate. The straight line that connects the two plotted TD_{50}s of the pure single drugs is the "zero interaction line" (131), with the dotted lines marking their 95% confidence intervals (CI's). Indicated with an * is the theoretical additive TD_{50} which would be obtained with the used ration. The closed circles indicate the experimental TD_{50}s with their 95 % CI's. If experimentally determined data points lie on the zero interaction line then the drug effects are additive (no interaction). If the points lie below this line then there is supra-additivity and if they lie above this line then there is infra-additivity. If the 95% CI of the experimentally determined combination do not overlap with the intervals of the zero interaction line than the interaction is assumed to be statistically significant.

Accelerod performance

The pre-experiment training required that every animal could stay on the accelerod for 60 seconds. The overall mean pre-injection accelerod performance was 140 s (S.E.M. 5 s). Both compounds as well as the combination negatively influenced accelerod performance in a dose dependent way. Equation 1, the sigmoid Emax model, was fitted to the data, yielding the TD_{50} and the Hill. With these parameter values of the single drugs the theoretical additive curve for the drug combination was calculated using equation 2. The accelerod data (table 5.1b) show that the experimental dose needed to get 50% toxicity in

the combination experiment is higher than the theoretical additive TD_{50}, suggesting infra-additivity in toxicity.

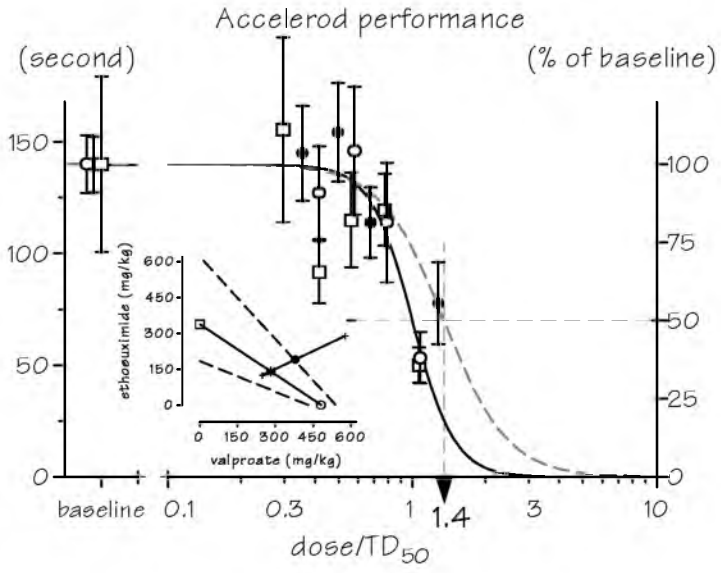
Table 5.1b. Adverse effects quantified by the accelerod

	VPA	ESM	VPA/ESM	Theoretical TD_{50}
TD_{50} (mg/kg)	482	338	379/190	281/141
95% CI	431 - 540	184 - 620	249/125 - 579/289	219/109 - 382/191
PDD/TD_{50}	1	1	0.79/0.56	0.58/0.42
Norm. TD_{50}	1	1	1.35	1
Hill	-6.8	-2.7	-3.3	
95% CI	-12.0 - -1.5	-7.5 - 2.1	-8.7 - 2.1	

For details, see legend to table 5.1a.

However, the 95% confidence intervals of the experimental TD_{50} and the theoretical TD_{50} do overlap, as is shown in the inset of figure 5.1b. Therefore, the finding of infra-additivity is not statistically significant (table 5.1b).

Figure 5.1b Normalized dose-response curves and isobologram for the effect on accelerod performance



Valproate (open circles), ethosuximide (open squares) or the combination (closed sqaures), after fitting the sigmoid Emax model to the data. While fitting the curves to the data, the tops of the curves were fixed at 100 % and the bottoms were fixed at 0 %. For additional details, see legend to figure 5.1a.

Observation of behavior

Both compounds caused, in a dose-dependent way, the animals to be less active and more passive than the control animals. Grooming and automatic behavior was not influenced in a dose-dependent way and no further inference was performed on these data. Equation 1, the sigmoid Emax model, was fitted to the data, yielding the TD_{50} and the Hill. With these parameter values of the single drugs the theoretical additive curve for the drug combination was calculated using equation 2. The experimental TD_{50}s of the drug combination are higher than the theoretical additive ones for both the passive behavior and the active behavior (tables 5.1c and 5.1d).

Table 5.1c. Adverse effects quantified by observation of active behavior

	VPA	**ESM**	**VPA/ESM**	**Theoretical TD_{50}**
TD_{50} (mg/kg)	493	346	471/235	288/144
95% CI	376 - 648	261 - 459	415/208 - 534/267	219/109 - 379/190
PDD/TD_{50}	1	1	0.95/0.68	0.58/0.42
Norm. TD_{50}	1	1	1.63	1
Hill	-2.8	-1.8	-2.4	
95% CI	-5.1 - -0.4	-2.8 - -0.8	-2.9 - -1.8	

For details, see legend to table 5.1a.

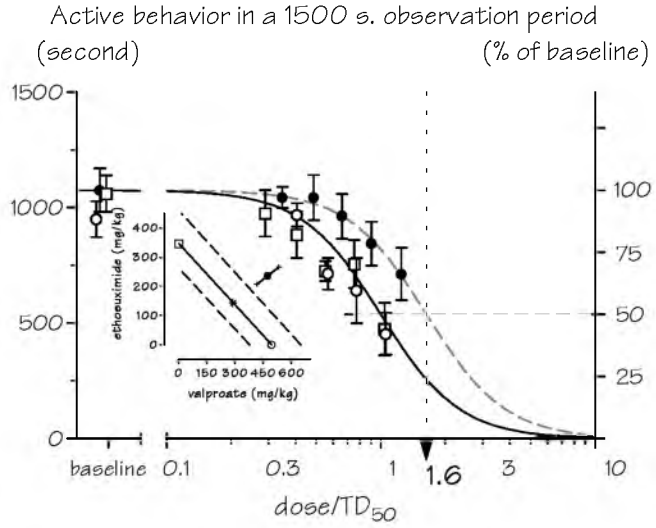
Table 5.1d. Adverse effects quantified by observation of passive behavior

	VPA	**ESM**	**VPA/ESM**	**Theoretical TD_{50}**
TD_{50} (mg/kg)	418	300	451/226	247/123
95% CI	356 - 490	254 - 353	373/187 - 545/273	210/105 - 289/145
PDD/TD_{50}	1	1	1.08/0.75	0.59/0.41
Norm. TD_{50}	1	1	1.83	1
Hill	3.1	2	2.1	
95% CI	1.3 - 4.9	1.2 - 2.7	1.4 - 2.8	

For details, see legend to table 5.1a.

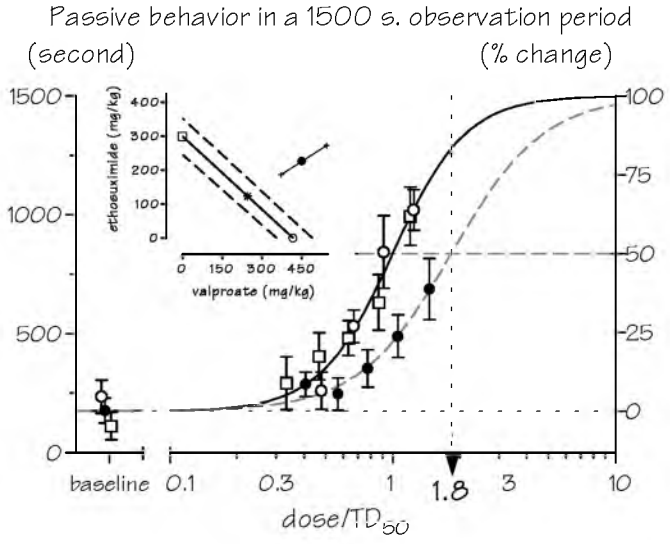
In both cases the 95% confidence intervals of the experimentally measured TD_{50} and the theoretical TD_{50} do not overlap, as the insets of figures 5.1c and 5.1d show.

Figure 5.1c Normalized dose-response curves and isobologram for the effect on b ehavior



While fitting the curves to the data, the tops of the curves were fixed at specific baseline values of active behavior: for valproate 950 s (SEM 31 s), for ethosuximide 1061 s (SEM 30 s) and for the combination 1076 s (SEM 36 s). The bottoms of the curve were fixed at 0 s. For additional details, see legend to figure 5.1a.

Figure 5.1d Normalized dose-response curves and isobologram for the effect on passive behavior



While fitting the curves to the data, the bottoms of the curves were fixed at specific baseline values of passive behavior: for valproate 238 s (SEM 28 s), for ethosuximide 112 s (SEM 22s) and for the combination 177 s (SEM 19 s). The tops were fixed at 1500 s. For additional details, see legend to figure 5.1a.

Thus, statistically significant infra-additivity was found for these effects of combination

therapy.

Discussion

Various methods have been used for the analysis of drug interactions. In an extensive review Berenbaum lists the most commonly used approaches, such as the isobologram method, the summation of effects-method, the multiplication of surviving fractions-method, the method of calculating the effect of a zero-interactive combination from the law of mass action and the very popular "no method approach" (i.e. authors claiming to have demonstrated supra-additivity or synergy without specifying their methods) (17). In his review, Berenbaum argues that the isobologram method, which was created by Fraser (79) and further developed by Loewe (152), is the most valid method. He claims that the greatest advantage of this method compared to others, is that interactions can be analyzed "irrespective of their mechanism of action or of the nature of their dose-response relationships" (17).

In this experiment we used the isobologram method to evaluate the interaction of valproate and ethosuximide on adverse effects. Loss of strength, as measured by the grip strength meter, and loss of coordination, as measured by the accelerod, combined in an additive way. However, accelerod performance only became significantly affected at the maximal dose permitted (in contrast to the other adverse tests).

Observation of behavior shows significantly more active and less passive behavior in polytherapy compared to monotherapy, indicating infra-additivity. These two measurements are not totally complementary, because grooming and automatic behavior were other behavioral variables (the latter two were not included in the analysis). The fact that the behavioral studies show significant infra-additivity in toxicity is an important finding when translated to humans, as sedation is the most frequently reported side effect of antiepileptic drug therapy (39). Furthermore, our experiments may reflect clinical experience that adverse effects become apparent earlier in spontaneous behavior than in elicited behavior, as is also exemplified by the accelerod results.

How these results may be explained is uncertain. The mechanisms behind most adverse effects of antiepileptic drugs are unknown. Löscher et al. have shown that functional tolerance for VPA's adverse effects develops relatively fast in kindled rats, whereas VPA is efficacious during chronic treatment of these animals (247). In that study VPA levels

were higher in the substantia nigra and the striatum than in other regions, and remained high throughout the study duration of 6 weeks (247). One may suggest that, as tolerance develops for VPA's adverse effects but not for its anticonvulsant effect, these effects must be mediated by different mechanisms or at different locations. A study by Liljequist and Engel in Sprague-Dawley rats suggests that VPA 's effects may be mediated through differentiated mechanisms at the GABA-BZD-complex (248). The anti-conflict effects of VPA were blocked by the benzodiazepine receptor antagonist Ro 15-1788 and by picrotoxin, but not by another benzodiazepine receptor antagonist, Ro 5-3663, nor by bicuculline. Valproate's effects on locomotor activity were blocked only by a small dose of Ro 15-1788 and its effect on rotarod performance were only blocked by Ro 5-3663. The doses needed to produce impairment of locomotor activity and rotarod performance were equal to the doses used to produce toxicity in our study, and higher than needed for VPA's anticonvulsant effects (239).

As for the adverse effects of ESM, Lin-Michell et al. showed that administration of a high dose of ESM significantly increased neurotoxicity and brain GABA levels in mice (145). As GABA levels decreased during chronic administration of this toxic dose, tolerance for the neurotoxic effects developed. Thus ESM's adverse effects may be GABA-mediated. Lin-Michell et al. furthermore showed that co-administration of ethosuximide with progabide, a $GABA_A$ agonist led to additive neurotoxic effects, as measured by the rotarod (145).

The infra-additivity of sedation in our experiment suggests that the two drugs cause sedation by different mechanisms. Therefore, although both VPA's and ESM's adverse effects may be GABA-mediated, it is quite possible that the exact mechanisms by which they influence spontaneous behavior do differ, which would explain our finding.

A criticism may be that we did not measure serum levels, let alone brain levels, during this experiment. However, the rats were used repeatedly and the schedule of the experiment did not permit time for drawing of blood and recovery to allow serum level sampling. As this combination is used relatively often in clinical practice, there have been some studies on pharmacokinetic interactions between the two drugs. Bourgeois et al. reported that ESM brain levels were higher when VPA was co-administered, and they suggested that this was due to enzyme inhibition (27). However, the overall evidence does not suggest major pharmacokinetic changes when the two drugs are given in combination (22).

Both Berenbaum and Tallarida advise to analyze drug interactions with the isobologram method (17, 238). The problem with this method is that it only visualizes the interaction and that no statistical inference is given. Bourgeois used a method to quantify the difference between mono- and polytherapy, namely the fractional effective concentration (FEC). The FEC is the ratio between the concentration of a drug in combination with another drug and the concentration at which the drug alone achieves the same effect. When the two FEC values of the two drugs are added the FEC index is obtained. An additive interaction exists if the FEC index is between 0.7 and 1.3. If the FEC index is below 0.7, there is supra-additivity, and an FEC index over 1.3 indicates infra-additivity. This method quantifies the isobologram method but still does not use statistics to prove interaction because the border values are arbitrary and do not take into account the variance of the measurements.

The expected regression curve of the combination therapy is calculated by entering the TD_{50} of both compounds and the ratio which was applied in the experiment into equation 2. Thus we create points with variance that can be compared to actually measured points using statistical evidence by 95% CI which is analogous to statistical testing with a p value of 0.05. Woolverton and Balster used linear regression by using only the linear portions of the dose-effect curves and they also determined 95% confidence intervals (270). In our study non-linear regression was used, which enables us not only possible to say something about the middle of the curve, but also about the extremes of the curve, where for example the TD_{10} is located. In future experiments therapeutic effects will also be measured, and this might enable us to calculate the TD_{10}/ED_{90} ratio. The TD_{50}/ED_{50} ratio and the TD_{10}/ED_{90} ratio are not necessarily equal and the latter ratio may be of more relevance as it approaches the goals set in clinical practice better.

5.2 Monotherapy versus polytherapy in the WAG/Rij model of epilepsy

Introduction

The methodology described in paragraph 5.1 provides a statistical basis for the isobologram method (208). Furthermore, three tests for neurotoxicity were evaluated. In the present study efficacy and toxicity of the same therapeutic regimens as used in paragraph 5.1 will be evaluated in the WAG/Rij rats, a model of human absence epilepsy. The WAG/Rij strain is an inbred genetic rat strain that spontaneously develops spike-wave discharges (SWDs) in the first 12 months of its life, which can be visualized by EEG. The SWDs resemble the spike-wave discharges seen in human absence epilepsy (161). During drug efficacy studies in these rats the number of SWDs, and not the clinical phenomena that accompany the SWDs, are taken as outcome measure. The WAG/Rij rat also shares its pharmacological profile with human absence epilepsy (193).

Methods

Animals

Male adult WAG/Rij rats, approximately 9 months of age and weighing between 300 and 342 grams, were used for this experiment. They were housed in identical plastic cages and had free access to food and water during the experiments. They were kept on a reversed light dark cycle (dark between 9.00 en 21.00 hours).

A tripolar EEG-electrode (Plastic Products Company, The Netherlands) was placed on the surface of the cortex: one in the frontal region (coordinates with skull surface flat and bregma zero-zero: A2.0 L3.5) and a second one in the parietal region (A6.0 L4.0). The ground electrode was placed over the cerebellum. Following surgery, subjects were allowed to recover for at least two weeks before the start of the experiment.

Drugs

Valproate (Albic Inc. Maassluis, The Netherlands) and ethosuximide (Sigma chemical co., The Netherlands), dissolved in 0.9% sodium chloride, were administered intraperitoneally alternating left and right to prevent adhesions.

Experiment

The 16 animals were divided in four groups of four rats, which received every therapeutic regimen for one week during the 8 week experiment. Groups 1 and 2 were used in weeks 1, 3, 5 and 7. Groups 3 and 4 were used during weeks 2,4, 6 and 8. The experiment schedule is shown in table 5.2a.

Table 5.2a Week schedule of the experiment

	Group 1	Group 2	Group 3	Group 4
Week 1	VPA	ESM		
Week 2			VPA + ESM	control
Week 3	ESM	VPA + ESM		
Week 4			control	VPA
Week 5	VPA + ESM	control		
Week 6			VPA	ESM
Week 7	control	VPA		
Week 8			ESM	VPA + ESM

During treatment weeks each rat received their assigned treatment in ascending dosages. For example, during the valproate week the rats received the zero-dose the first day, 100 mg/kg the second day, 140 mg/kg the third day, 200 mg/kg the fourth day and 280 mg/kg the fifth day. In the ethosuximide week the dosages given were 0 mg/kg, 14.3 mg/kg, 20 mg/kg, 28.6 mg/kg and 40 mg/kg. In the polytherapy group the dosages of VPA/ESM were 0/0 mg/kg, 50/7.14 mg/kg, 70/10 mg/kg, 100/14.3 mg/kg and 140/20 mg/kg respectively. During the control week the animals received a saline injection each day. The ratio of valproate and ethosuximide were based on their ED_{50} (in this case the amount of drug causing 50% of maximum effect) found in a pilot experiment.

On each test day, the animals were placed in observation cages of 30 by 30 by 50 cm and a minimum of light was used to keep them in an active state. Baseline EEG was recorded for two hours. After drug injection, another four hours of EEG were recorded.

For each rat, the number and mean duration of spike-wave discharges before and after injection were measured on all its test days, according to criteria reported elsewhere (161). Briefly, trains of spike-waves with a spike (peak) amplitude of at least twice the background EEG and a duration of at least 1 second were assigned as spike-wave discharges.

Serum levels

To control for pharmacokinetic interactions, a separate experiment was carried out. Animals in group I received 28.6 mg/kg ESM and animals in group II received 200 mg/kg VPA. Blood was collected from the tail of animals 40 minutes after drug administration and serum levels were determined by gas chromatography.

One week later all animals received both 28.6 mg/kg ESM and 200 mg/kg VPA. Blood was collected from the tail of animals 40 minutes after drug administration; in group I ESM serum levels were analyzed and group II VPA serum levels were analyzed.

Data analysis:

EEG data were analyzed by non-linear regression analysis using the program Graphpad Prism 2.0. The data were fitted to the sigmoid Emax model and the ED_{50}'s and Hill's with their respective confidence intervals calculated for the different treatment regimens. The theoretical additive curve was generated for the drug combination using the sigmoid Emax model for a mix of two compounds according to the equations used in paragraph 5.1 (208). The experimental parameter estimates of the drug combination were compared to the theoretical additive parameter estimates using the 95% confidence intervals. The curves of valproate and of ethosuximide were normalized using their ED_{50}s. The curve of the experimental combination was normalized using the ED_{50} of the theoretical additive combination and the ED_{50} parameter estimates obtained by the sigmoid Emax model were plotted in an isobologram to visualize the type of interaction (17, 238).

Results

All rats showed spontaneously occurring spike-wave discharges in their cortical EEG and were used throughout the experiment. Every test day the EEG was recorded two hours pre-injection and a group x day analysis of variance was performed on these data: there were no significant group or day effects.

The pre-injection number of spike wave discharges per hour averaged at 18, with a standard deviation of 8. In the first 15 minutes post-injection the number of spike waves was very variable: it averaged at 17 SWD/hour and the standard deviation was also 17. As efficacy seemed to decline after 75 minutes at lower dosages it was decided to take the 15 to 75

minute post-injection interval as the time frame to assess efficacy from. As the baseline number of SWDs per hour varied, the number of SWD/hour post-injection was divided the number of SWD/hour pre-injection and thus the animals served as their own controls. These percentage data were used for further analysis.

Efficacy

Both compounds as well as the combination reduced the number of SWDs in a dose dependent way. The sigmoid Emax model, was fitted to the data, yielding the ED_{50} and the Hill of the various regimens (table 5.2b). With these parameter values of the single drugs the theoretical ED_{50} for the drug combination was calculated using the isobologram method. The experimental dose needed to get 50% efficacy in the combination experiment is higher than the theoretical additive ED_{50}, suggesting infra-additivity for efficacy. As the confidence intervals overlap, this finding is not statistically significant.

Table 5.2b Efficacy of valproate and ethosuximide, alone and in combination.

	VPA	**ESM**	**VPA/ESM**	**theoretical additive ED_{50}**
ED_{50} (mg/kg)	174.5	23.2	114.1/16.3	84.3/12.0
95% CI	136.6 - 223.0	20.44 - 26.34	100.2/14.3 -130.0/18.6	74.0/10.5 - 100.9/14.4
dose/ED_{50}	1	1	0.65/0.70	0.48/0.52
Norm. ED_{50}	1	1	1.35	1
Hill	-3.4	-2.4	-3.7	
95 % CI	-6.4 - -0,4	-3.4 - -1.5	-5.5 - -1.8	

Parameter estimates of fitting the sigmoid Emax curve to the data. The ED_{50} is the dose at which the number of SWDs per hour is reduced by 50%. All weight values are normalized using the ED_{50} values. The experimental combination value uses the theoretical additive ED_{50} as norm. A normalized ED_{50} (Norm. ED_{50}) of the experimentally determined combination below 1 points to supra-additivity whereas more than 1 indicates infra-additivity. If the 95% confidence intervals of the normalized ED_{50} of the experimental combination do not overlap with the intervals of the theoretical additive ones than the interaction is assumed to be statistically significant. Hill is a measure for the steepness of the curve.

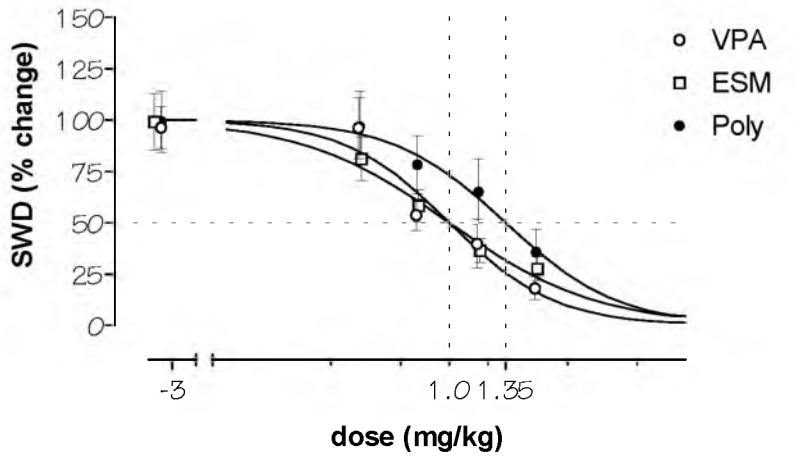
The normalized dose response curves of the drugs are shown in figure 5.2.a.

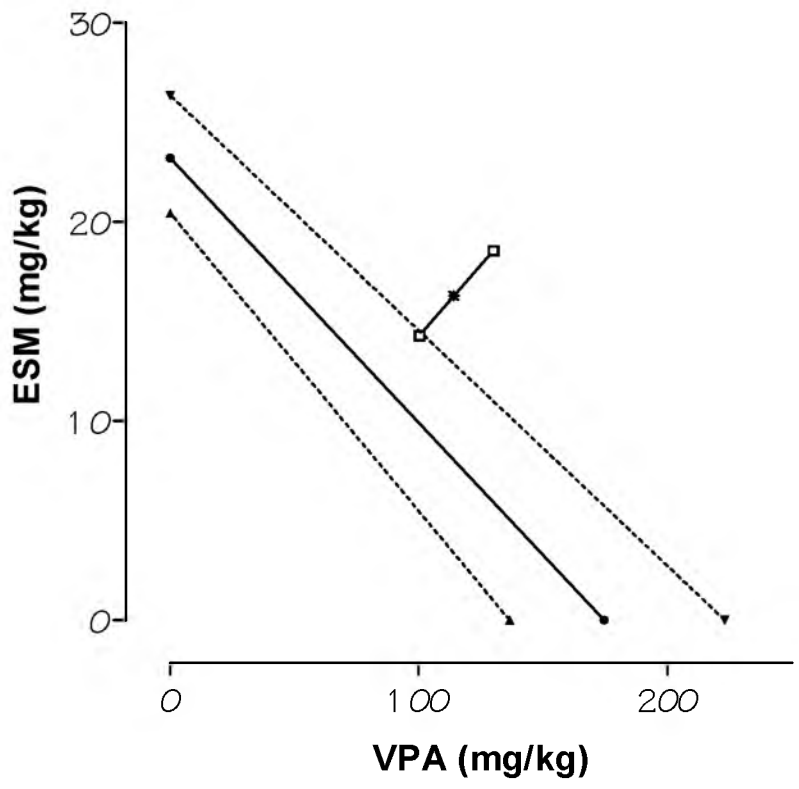
Figure 5.2a Normalized dose-response curves for ethosuximide, valproate and their combination

Dose response graphs for the change of spike wave discharges (SWD)in rats following injection of valproate (open circles), ethosuximide (open squares) or of the combination of both (closed circles), after fitting the sigmoid Emax model to the data. All weight values are normalized using the ED_{50} values. The experimental combination value uses the ED_{50}s of the individual drugs as norm. The normalized drug doses (dose/ED_{50}) are plotted on the abscissas and the SWD data on the ordinate. ED_{50} values (table 5.2b) were obtained by fitting the sigmoid Emax model (equation 1) to the data.

The isobologram visualizes that the confidence intervals of the theoretical additive ED_{50} and the experimental ED_{50} of the combination, do overlap, as is shown in figure 5.2b

Figure 5.2b Isobologram for a 50% reduction in spike wave discharges of WAG/Rij rats by a combination of ethosuximide and valproate





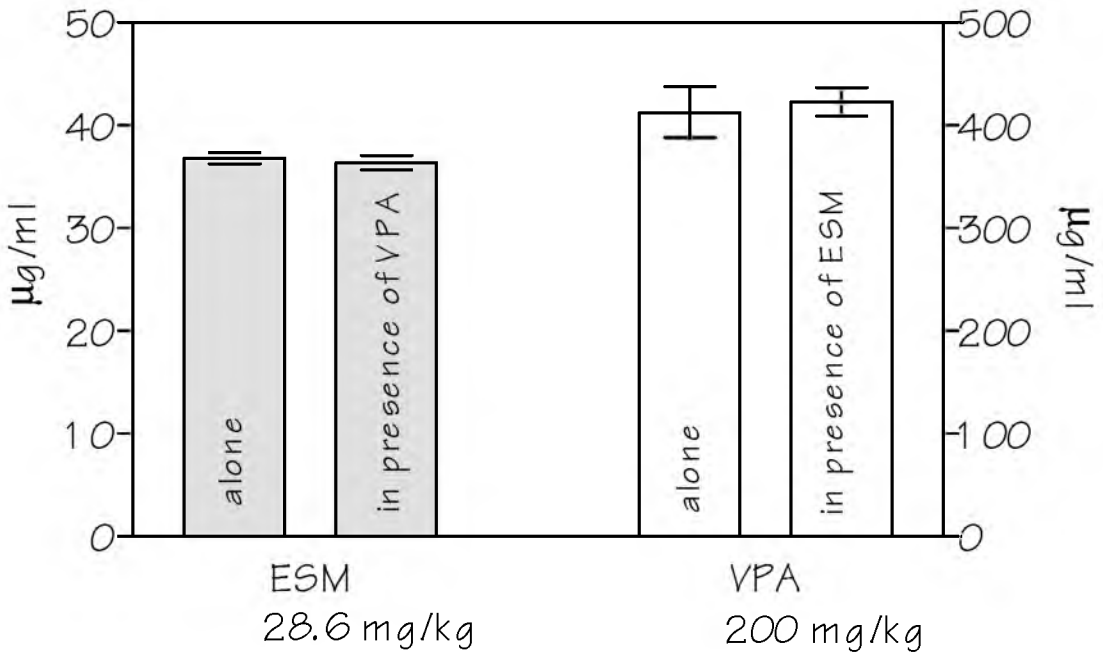
For additional details, see legend to figure 5.1a.

Serum levels

The result of the test for pharmacokinetic interaction between ESM and VPA is shown in figure 5.2c.

Figure 5.2c Serum levels of ESM and VPA alone and in each other's presence

Analysis of variance did not show any significant differences in serum levels of ESM or



VPA in the presence of the other drug.

Discussion

Our results indicate that the efficacy of the VPA/ESM combination tended to be infra-additive, although this did not reach statistical significance. In two previous studies the efficacy of this combination was studied in the pentylenetetrazole (Ptz) model, a model which represents absence and myoclonic seizures (197, 250). Bourgeois et al. found the combination to have an additive "anti-Ptz" effect, while Musolino et al. found a supra-additive interaction. The isobologram method was used in the former study, but not in the

latter one. Rowan et. al. described five patients with refractory absence seizures who became seizure-free only after receiving this combination (217).

A first explanation for the differences in results may be offered by the differences in animal model and species. Although the WAG/Rij rat and the Ptz model are both considered to be models for human absence epilepsy, the models do differ in doses needed for their effects and there are some differences in their pharmacological profiles (145, 239). There are also pharmacokinetic issues to consider: during treatment weeks animals were used for five consecutive days and some drug accumulation may be suspected. However, no day effects were found. We can not shed more light on these differences either by looking at the mechanism of action of the two drugs, as it is uncertain by which mechanism VPA blocks absence seizures. Coulter et al. have shown that ESM reduces the low-threshold (T-type) calcium current of thalamic neurons at clinically relevant concentrations and this mechanism is generally accepted to be responsible for ESM's anti-absence effect (162). Valproate was shown not to have this effect, but it does block T-type calcium currents in afferent neurons (162, 163). Löscher has contended that VPA's effect of enhancing nerve terminal GABA in the substantia nigra may explain its efficacy in a variety of epilepsy types, including absence epilepsy (157). Another explanation for VPA's anti-absence effect could be its inhibition of the formation of γ-hydroxybutyrate, a GABA-metabolite which has been shown to produce absence-like effects in several species (157).

However, when the results of the studies of both our studies are taken together, they are quite similar to the findings of other researchers. Bourgeois et al. found that efficacy was additive in Ptz-treated mice, but that toxicity was infra-additive (250). Rowan et al. were not able to control absence seizures with VPA at maximal dosages, and the addition of ESM to VPA resulted in seizure freedom in five patients (217). The VPA dosage was not reduced in these patients, bit apparently it was possible to add ethosuximide without producing unacceptable adverse effects (in one patient the VPA dose was reduced, but this had to be reversed because of renewed seizures). In accordance with these data additivity for efficacy was found in the present study (although marginal), and infra-additivity for toxicity in the study described in paragraph 5.1. When toxicity is reduced without reducing efficacy, it enables the physician to use higher drug loads than was possible in monotherapy, in an attempt to increase seizure control. In conclusion, the studies described in this chapter do suggest possible advantages of the use of the valproate-ethosuximide combination.

Chapter 6 Combination therapy in epilepsy patients

In this chapter a clinical trial is described, in which the combination of carbamazepine and valproate was compared to carbamazepine monotherapy. As this trial was aimed at evaluating the effectiveness of polytherapy for adult patients with newly diagnosed epilepsy, a different combination of AEDs was used than the one in the previous chapter. The majority of patients with adult-onset epilepsy have symptomatic or cryptogenic partial epilepsy, and they are usually prescribed either carbamazepine or valproate in the Netherlands.

6.1 Double-blind randomized trial comparing carbamazepine plus valproate against an equal drug load of carbamazepine in untreated adult epilepsy patients

Introduction

Reynolds and Shorvon showed in 1979 that when the number of antiepileptic drugs (AEDs) was reduced to one in selected patients using polytherapy, these patients had fewer adverse effects and sometimes even better seizure control (229). This finding was confirmed by other researchers; a few representative examples are cited in the reference list (1, 218, 245). In 1995 however, Devinsky suggested that these studies had not been optimally designed: small groups of patients who were doing poorly with polytherapy were switched to monotherapy; selection was not randomized and factors such as changes in blood levels were often not controlled (59). He claimed that if a small group of patients doing poorly on monotherapy were converted to low-dose polytherapy, the outcome of such a study would likely support polytherapy over monotherapy. Indeed, such a study was published two years later: a selected group of patients did much better after the switch from monotherapy to low-dose polytherapy (23).

The aim of the present study is to compare monotherapy to combination therapy in a multi-center double-blind clinical trial of adult-onset epilepsy patients, with patients starting off on equal drug loads. The combination of carbamazepine (CBZ) and valproate (VPA) was selected because this combination was found to be effective in patients who had an unsatisfactory response to monotherapy in a number of open non-randomized studies (10, 52, 84, 104, 258). The planned time frame and expected inclusion rate in the present trial did not allow for two monotherapy groups. Choosing between CBZ and VPA for monotherapy, CBZ was selected based on the largest trial comparing CBZ and VPA to date, in which CBZ was more efficacious against complex partial seizures than VPA whilst being equally efficacious against generalized tonic-clonic seizures, and in which the incidence of sedation (42% each), change in affect or mood (24% CBZ vs 25% VPA) and cognitive disturbance (18% each) were similar (173). Our main hypothesis is that the combination of low doses of CBZ and VPA will have less neurotoxic adverse effects than CBZ monotherapy, as measured with the Composite Index of Impairments (CII).

Methods

Population: The trial was initiated in July 1995. The inclusion criteria were: adult patients with untreated generalized tonic-clonic, complex partial and/or simple partial seizures; an accurate history including adequate neuro-physiological data for a firm diagnosis; well-defined types of seizures according to the International Classification of Epileptic Seizures (40); age 18 years and older. Criteria for exclusion were: not satisfying the inclusion criteria; inability to give informed consent (e.g. language or cultural barrier); absence seizures; juvenile myoclonic epilepsy; acute or progressive neurological disorders; alcohol or other substance abuse; psychiatric diseases; mental retardation.

Procedure of the trial: Neurologists of 17 hospitals in the vicinity of Nijmegen and of the Nijmegen University Hospital, identified eligible patients who needed AED treatment. When the patient had given written consent, after being adequately informed, the clinician alerted the principal investigator (C.L.P.D.). The principal investigator then interviewed and tested patients in their own hospital, using the clinimetric and neuropsychological methods described below. Subsequently patients started with their trial medication. There was general agreement between the participating neurologists that patients would start on a maintenance dose of 0.4 PDD/DDD; neurologists were allowed to deviate from this in individual cases. The dose was titrated from 0.1 PDD/DDD in the first week and 0.2 PDD/DDD in the second week to 0.4 PDD/DDD (table 6.1a).

Table 6.1a Dosage titration schedule for monotherapy and polytherapy groups

		Morning	Evening
Monotherapy	1st week 0.1 PDD/DDD	-	1 CBZ 100 mg verum
	2nd week 0.2 PDD/DDD	1 CBZ 100 mg verum 1 VPA 150 mg placebo	1 CBZ 100 mg verum 1 VPA 150 mg placebo
	from 3rd week onwards 0.4 PDD/DDD	2 CBZ 100 mg verum 1 VPA 150 mg placebo	2 CBZ 100 mg verum 1 VPA 150 mg placebo
Polytherapy	1st week 0.1 PDD/DDD	-	1 CBZ 100 mg verum
	2nd week 0.2 PDD/DDD	1 CBZ 100 mg verum 1 VPA 150 mg placebo	1 CBZ 100 mg placebo 1 VPA 150 mg verum
	from 3rd week onwards 0.4 PDD/DDD	1 CBZ 100 mg verum 1 CBZ 100 mg placebo 1 VPA 150 mg verum	1 CBZ 100 mg verum 1 CBZ 100 mg placebo 1 VPA 150 mg verum

DDD carbamazepine 1000mg; DDD valproate 1500 mg

During the trial the neurologist could change the dosage, in terms of PDD/DDD fractions, when clinically necessary. Patients participating in the trial had scheduled evaluation points after 2 and after 12 months. Between these scheduled evaluation points patients were interviewed and examined by the principal investigator at irregular intervals, depending on seizure frequency and AED toxicity. During the year of their participation in the study the patients were seen at least four times by the principal investigator. The procedures followed were in accordance with the ethical standards of the medical ethical committees of all the hospitals involved and with the Helsinki Declaration of 1975.

Assignment and Blinding procedure: Random numbers were linked to monotherapy or polytherapy by an unblinded observer at the SEIN (Stichting Epilepsie Instellingen Nederland), an epilepsy center in Heemstede, the Netherlands. Each patient included received the next available number from one onwards. The principal investigator, treating neurologists and patients were blinded to the randomization code. An envelope containing the code was kept in the patient's medical file for emergencies. Sanofi (Paris, France)

supplied enteric-coated VPA and placebo-VPA 150 mg tablets. Katwijk Farma (Katwijk, the Netherlands) supplied CBZ and placebo CBZ 100 mg tablets. The drugs were packaged in strips of plastic dispensed by an Automatic Tablet Counter (Baxter) at the SEIN and were placed in randomly numbered paper bags; the paper bags and plastic strips were marked with the dose in PDD/DDD fractions but not whether the dose contained one or two active drugs. The principal investigator was told by the unblinded observer which numbered paper bag to dispense to which patient.

Outcome measures: the following outcome measures were used: seizure diaries, the Composite Index of Impairments (CII), QOLIE-10 and FePsy (7, 44, 266). These methods have been discussed in detail in chapters one and two.

Therapeutic drug monitoring: Serum levels were collected at the first control visit and after each change in drug load. Samples were analyzed by the laboratory of the SEIN using high pressure liquid chromatography (carbamazepine) and gas chromatography (valproate). The results were reported to the physician and the principal investigator in terms of the observed serum level divided by the average therapeutic level (OSL/ATL ratio) (thus leaving the blinding procedure intact) (133). Laboratory tests such as liver function and hematological tests were done at the first control visit and after every dose change.

Statistics: Sample size calculation was based on the NTX scores, as differences between the two treatments were expected especially in neurotoxic effects. With 55 patients in each treatment group, the study had a power of 80% and a significance level of 0.05 to show a difference of 10 points in NTX-score between treatments.

Wilcoxon tests and paired t-tests were used to compare outcome measures. Three analyses were performed: an analysis of patients completing the trial; a 'per protocol' analysis of trial completers and treatment failures; an 'intention-to-treat' analysis of all patients that had completed one follow-up visit. The Kaplan-Meier method was used to compare retention time between treatments in the 'per protocol' and the 'intention-to-treat' groups. Analysis of variance was used to analyze changes in the FePsy test results.

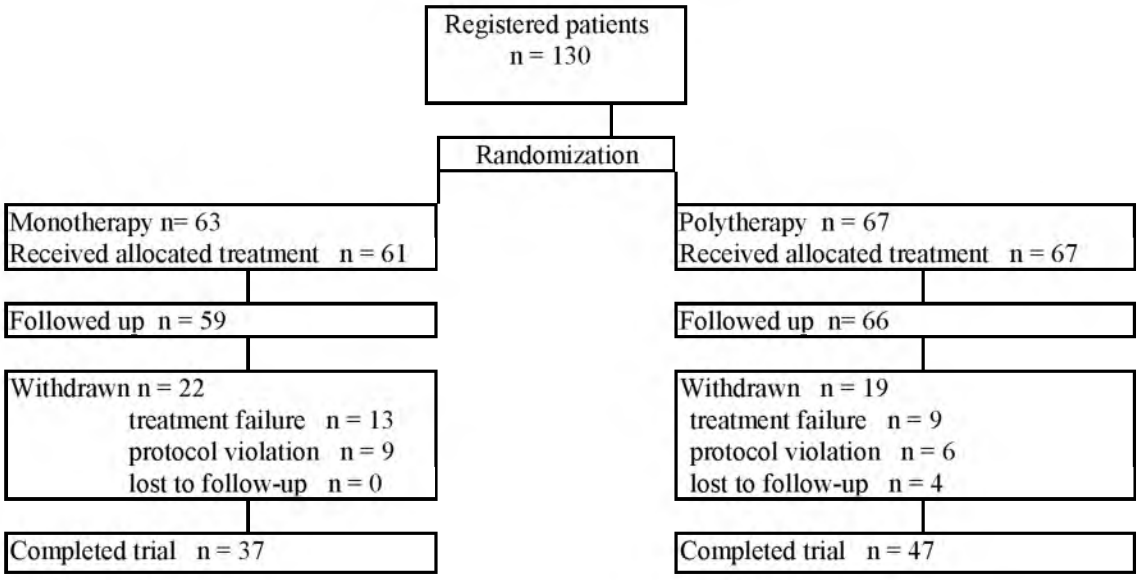
Results

Descriptions of the study groups

The 130 enrolled patients were either patients with newly-diagnosed epilepsy or known epilepsy patients not on AEDs for the past two years, who had suffered a relapse. Of these

130, five patients were excluded from the analysis: in the monotherapy group two patients elected not to participate after the baseline visit. Another two patients did start their allocated treatment, but their neurologists were forced to break the code due to pre-existing cardiologic conditions before the first follow-up visit. In the polytherapy group one patient died of brain metastasis before the first follow-up visit and should not have been randomized. Thus, 125 patients were included in the intention-to-treat analysis; figure 6.1a is a flow diagram presenting the progress of the trial through its various stages.

Figure 6.1a Flow diagram of the progress of the trial



Reasons for not receiving treatment, treatment failure or protocol violation are given in the text.

In the monotherapy group there were nine protocol violators: three non-compliant patients; two patients with juvenile myoclonic epilepsy; two patients with alcohol abuse; two patients that left the trial for other medical conditions (hepatitis B infection and meningeoma). Of the non-compliant patients, one was later lost to follow-up, one restarted carbamazepine treatment after seizure recurrence and one was started on valproate monotherapy after seizure recurrence.

In the polytherapy group there were six protocol violators: two patients got pregnant (did not use oral contraceptives or other birth control despite warnings about possible teratogenic effects; both have delivered healthy babies); one patient with atypical absence seizures; one patient with dizzy spells who turned out to have obstructive sleep-apnea syndrome; one patient with brief episodes of altered consciousness who later was found not to have epilepsy; one patient who was transferred to a nursing home and was given carbamazepine

monotherapy by the resident physician. Four polytherapy patients were lost to follow-up; one of these patients died of a lung carcinoma. The demographic characteristics of the 125 patients included in the analysis are summarized in table 6.1b.

Table 6.1b Baseline characteristics of study participants

	Monotherapy	Polytherapy
Total	59	66
Sex: - male - female	35 (59%) 24 (41%)	40 (61%) 26 (39%)
Age at onset of epilepsy: - mean - median	41 37	38 35
Previous brain injury	28 (47%)	30 (45%)
Lesions on brain imaging	16 (27%)	21 (32%)
Education: - Elementary/Prevocational - Junior general secondary/ Senior secondary vocational - Senior general secondary/ Higher professional - Pre-university/University	27 (46%) 20 (34%) 9 (15%) 3 (5%)	39 (59%) 15 (23%) 9 (14%) 3 (4%)
Seizure types: - generalized tonic clonic seizures - complex partial seizures - simple partial seizures	50 (85%) 11 (19%) 6 (10%)	47 (71%) 20 (30%) 8 (12%)

There were no statistical differences in the demographic characteristics between the treatment groups. In the monotherapy and polytherapy groups respectively 6 and 4 patients had taken AEDs in the past.

Clinimetric scores

The seizure activity (SA), neurotoxicity (NTX), systemic toxicity (STX), Composite Index of Impairments (CII) and QOLIE-10 scores did not show significant differences between the two treatment groups after two or twelve months of treatment in any of the three analyses. The polytherapy group did have a higher baseline CII, but the CII scores of the study groups were almost equal after twelve months. The SA, NTX, STX, CII and QOLIE-10 scores at baseline, 2 and 12 months are shown in table 6.1c for patients that completed the trial.

Table 6.1c Average clinimetric scores per treatment group of patients that completed the trial (in parentheses data the median data are shown)

	Monotherapy (n=37)	Polytherapy (n=47)		Monotherapy (n=37)	Polytherapy (n=47)
baseline SA	43.6 (40)	54.7 (40)	baseline CII	56.1 (53)	65.7 (54)
2 month SA	1.9 (0)	3.1 (0)	2 month CII	22.4 (20)	22.4 (20)
12 month SA	0.8 (0)	4.0 (0)	12 month CII	13.4 (10)	13.6 (10)
baseline NTX	11.5 (10)	10.3 (10)	baseline QOLIE	17.2 (17)	16.9 (17)
2 month NTX	18.2 (15)	15.0 (13)	2 month QOLIE	17.9 (17)	18.1 (17)
12 month NTX	9.2 (5)	6.8 (5)	12 month QOLIE	15.8 (15)	15.9 (15)
baseline STX	0.9 (0)	0.7 (0)			
2 month STX	2.4 (0)	4.5 (0)			
12 month STX	3.4 (0)	4.3 ()			

The average median clinimetric score are given in parenthesis

The changes compared to baseline of the overall QOLIE-10 score did not show significant differences between treatment arms. At baseline the answer to Question-1 of the QOLIE ('Have you had a lot of energy ?') differed significantly in favor of the monotherapy group, but this was not the case at follow-up visits. The answer to Question-10 ('How has the quality of your life been during the past 4 weeks; that is, how have things been going for you ?') was also more favorable for the monotherapy group at baseline, but this did not reach significance. When the 2 month-measurement for this question was compared to the baseline visit, there was an improvement which was significantly greater in the polytherapy group, the scores now being about equal in both groups. There were no other significant differences in the individual QOLIE-10 questions or overall QOLIE-10 score between the mono- and polytherapy groups in any of the analyses.

Efficacy

In both treatment arms seizure frequencies were reduced successfully, without statistical differences between the two treatments in any of the three analyses (analysis of patients that completed the trial, 'per protocol' analysis and intention-to-treat analysis). In both treatment groups the percentage of seizure free patients was much higher in patients with generalized tonic-clonic seizures than in patients with partial seizures. In table 6.1d the seizure frequencies and numbers of seizure free patients are shown per seizure type for the group which completed the study (n= 84). Seizure free patients are patients who did not have any

seizures for at least three months on the dose they were using at the end of the trial.

In the polytherapy group there was one patient in which the dose was elevated to 1.6 PDD/DDD (= 800 mg carbamazepine plus 1200 mg of valproate). At this dose the patient still had 2 complex partial seizures per month (baseline frequency 12/month). The highest drug load given in the monotherapy group was 0.8 PDD/DDD (800 mg/day), which was used by two patients. Both patients became seizure free at this drug load.

Table 6.1d Seizure frequency and percentage of responders (patients that completed the trial)

Group (number of patients)	Baseline seizure frequency (per month)	12 months seizure frequency (per month)	% seizure free at 12 months
Mono GTCS (33)	0.4	0.003	94%
Poly GTCS (34)	1.6	0.01	85%
Mono CPS (5)	4.6	0.01	80%
Poly CPS (14)	6.2	0.47	50%
Mono SPS (5)	5.4	0.02	40%
Poly SPS (4)	13.4	0.58	50%
Mono overall (37)	1.7	0.02	86%
Poly overall (47)	3.9	0.21	74%

Seizure frequencies per month. GTCS: generalized tonic-clonic seizures; CPS: complex partial seizures; SPS: simple partial seizures

Table 6.1e shows the distribution of dosages in PDD/DDD ratio's for both treatment groups at the end of the trial.

Table 6.1e Distribution of dosages of patients that completed the trial

Group (number of patients)	0,4 PDD/DDD	0,6 PDD/DDD	0,8 PDD/DDD	1,2 PDD/DDD	1,6 PDD/DDD
Monotherapy (n=37)	28	8	1	-	-
Polytherapy (n=47)	37	5	3	1	1

Adverse effects

Individual adverse effects were actively sought after by use of the NTX and STX scales. In table 6.1f the frequency and clinimetric score of each adverse effect at baseline and at two months are shown for patients that completed the trial.

Table 6.1f Frequency of adverse effects at baseline, two months and 12 months for the two treatment arms

Adverse effect	Mono baseline % (n=37)	Mono 2 mth toxicity % (n=37)	Mono 12 mth toxicity % (n=37)	Poly baseline % (n=47)	Poly 2 mth toxicity % (n=47)	Poly 12 mth toxicity % (n=47)
Diplopia	0%	3%	0%	2%	2%	0%
Nystagmus	0%	0%	0%	0%	0%	0%
Dysarthria	8%	5%	3%	6%	2%	0%
Gait	8%	22%	0%	11%	11%	2%
Rapid alternating movements	3%	3%	0%	0%	0%	0%
Tremor	0%	0%	0%	2%	2%	2%
Sedation	16%	57%	41%*	21%	53%	15%*
Affect and mood disturbances	35%	43%	38%	32%	45%	16%
Cognitive impairments	46%	51%	32%	32%	43%	26%
Dizziness	8%	24%	5%	19%	21%	2%
Headache	30%	14%*	11%	30%	32%*	2%
Other neurotoxicity	0%	3%	0%	0%	0%	1%
Gastro-intestinal complaints	14%	11%	13%	6%	15%	5%
Hematopoietic disturbances	0%	0%	0%	0%	0%	0%
Skin reactions	0%	5%	0%	0%	4%	0%
Impotence	0%	0%	3%	0%	2%	0%
Hyponatremia	0%	0%	0%	0%	0%	0%
Abnormal liver function tests	0%	0%	0%	0%	0%	0%
Weight change	0%	3%	0%*	0%	11%	10%*
Hair loss/ hirsutism	0%	11%	11%	4%	2%	8%
Other systemic toxicity	0%	5%	0%	0%	6%	3%

The frequencies per adverse effect, at baseline, 2 months and 12 months as measured with the Composite Index of Impairments. Frequencies that differ significantly are marked with asterisks

In all three analyses statistically significant differences were found in frequency or average severity of separate adverse effects (not corrected for multiple comparisons): in the monotherapy group the proportion of sedated patients and the clinimetric score for sedation (absolute score and score relative to baseline) were significantly higher after 12 months. In

the polytherapy group the number of patients with headache was higher at two months but this difference had disappeared at twelve months (the headache severity score did not differ between treatments at any time). After twelve months the frequency and the severity score of weight change were significantly higher in the polytherapy group.

In the monotherapy and polytherapy groups 13 and 9 patients respectively withdrew because of adverse effects. In table 6.1g the adverse effects leading to withdrawal are shown. Most treatment failures were due to two or more adverse effects and therefore there are more than 22 adverse effects shown.

Table 6.1g Adverse effects leading to treatment failure

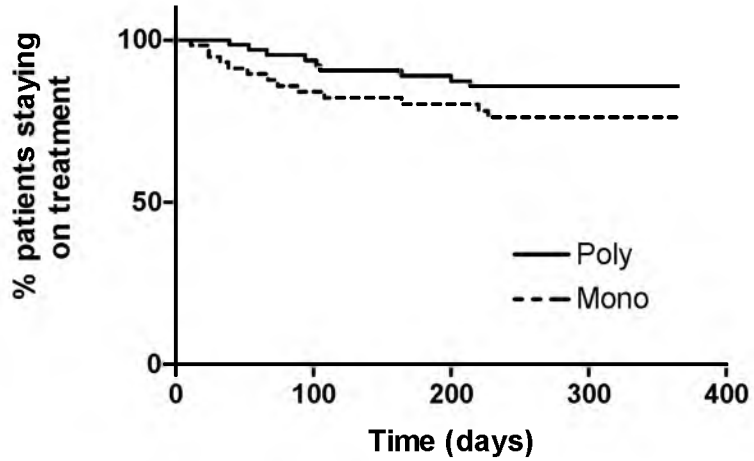
	ataxia	sedation	affect/ mood disturbance	memory impairmt	dizziness	headache	gastro-intestinal complaints	rash	weight gain
Monotherapy (13 patients)	2	5	5	5	2	1	2	4	0
Polytherapy (9 patients)	1	4	6	4	0	2	2	1	1

There was a higher number of rash-related treatment failures in the monotherapy group, although this did not reach statistical significance. The overall higher frequency of rash observed in the monotherapy group is not reflected in table 6.1e, which only concerns patients who completed the trial.

Retention time

The Kaplan-Meier graph of the time to withdrawal (figure 6.1b) suggests that patients on monotherapy were more likely to withdraw before patients on polytherapy, especially in the first two months. However, this did not reach statistical significance (Mantel-Haenszel test p=0.16). The hazard ratio was 1.83 and its 95% confidence intervals was 0.79-4.26.

Figure 6.1b Survival curve for patients staying on treatment



Neuropsychological assessment

Patients often had better performances on the tests after the baseline visit, as is shown in table 6.1h. The repeated measures analysis of variance of the test results did not show significant differences between the treatment groups in any of the three analyses. There were a few individual patients that performed worse after treatment start, but this was without significant difference between treatments.

Table 6.1h FePsy data for the intention-to-treat group

	BASELINE	2 MONTHS	12 MONTHS
Monotherapy tapping dominant hand	63	62	62
Monotherapy tapping non-dominant hand	57	56	59
Monotherapy BCH reaction time	533	485	458
Monotherapy CVST	12	11.8	10.7
Polytherapy tapping dominant hand	60	61	59
Polytherapy tapping non-dominant hand	56	57	54
Polytherapy BCH	487	464	433
Polytherapy CVST	13.8	13.1	11.1

Dosages/serum levels

The average serum levels and drug loads (expressed in PDD/DDD and OSL/ATL) at two

months, twelve months and at time of treatment failure are shown in table 6.1i.

Table 6.1i Average serum levels and drug loads

Group	Mono 2 months (n=47)	Poly 2 months (n=61)	Mono 12 months (n=37)	Poly 12 months (n=47)	Mono treatment failures (n=7*)	Poly treatment failures (n=8*)
PDD/DDD	0.4	0.4	0.45	0.49	0.4	0.44
CBZ (mg/l)	5.4	3.4	5.5	3.4	5.8	3.7
CBZ-E (mg/l)	0.57	0.33	0.49	0.33	0.69	0.33
VPA (mg/l)	-	20	-	21	-	20
OSL/ATL	0.77	0.77	0.79	0.79	0.83	0.81

CBZ-E = carbamazepine epoxide; * = in some cases of treatment failure, no serum level sampling was performed

Serum level sampling times depended on the appointments between the principal investigator and patients, and thus were not standardized. The average sampling times were 4.08 hours ± 2.27 and 4.10 hours ± 2.27 for mono- and polytherapy respectively.

Discussion

We did not find a clinically significant difference in NTX scores between monotherapy and polytherapy, which the study was powered to do. It is important to note that the study was not designed to show differences in efficacy, and differences in efficacy were not expected to be found as they are almost never found in clinical trials of newly-diagosed epilepsy patients. One can however also look at effectiveness, which is a measure expressing both efficacy and toxicity. The Commission on Antiepileptic Drugs of the International League Against Epilepsy considers retention time to be the most clinically relevant endpoint of AED trials, as it is a measure for effectiveness (115). In our study the difference in retention time did not reach statistical significance, but chances of withdrawal from treatment tended to be lower for the polytherapy group. The results of this trial suggest that low doses of two drugs may be as efficacious but less toxic than a full dose of a single drug (i.e. at equal drug loads). This is remarkable, as polytherapy has been reputed to cause increased toxicity. The pharmacological explanation for the lesser toxicity of polytherapy may be that dose-related adverse effects of both drugs are not caused by the same

mechanism of action, and thus may be milder because of the lower dosages and serum levels of the individual drugs (69).

It is unknown whether the mechanisms of action held responsible for the anticonvulsant effects of these AEDs, are also the mechanisms by which their adverse effects are caused. For VPA, there is even uncertainty which is its main anti-convulsant mechanism of action: its GABA effects or its sodium channel blocking properties (2, 149, 179, 261). A study by Liljequist and Engel suggests that VPA 's adverse effects are mediated through differentiated mechanisms at the GABA-benzodiazepine-ionophore complex, as was already discussed in chapter 5 (144). The anticonvulsant effects of CBZ are thought to be mediated mainly through its sodium channel-blocking properties, but CBZ has also been shown to have GABAergic and anti-glutamatergic effects (97, 257). The mechanism behind CBZ's adverse effects is unknown. Thus it is reasonably clear that CBZ and VPA's anti-convulsant mechanisms of action have some differences, but also some overlap. As for their adverse effects, the results of our clinical trial suggest that there is a sufficient difference in the mechanisms of the two drugs to result in infra-additive toxicity.

Actually, in most open trials of specific AED combination therapy high doses of two drugs are added together to achieve increased efficacy where one drug is not sufficient at maximally tolerated dosages. The increased efficacy of the combinations in these studies is usually accomplished because of a higher total drug load, which indicates that the adverse effects of these combinations are infra-additive (i.e. actually less than when the adverse effects were the result of the same drug load of a single drug).

In this context it is interesting that the efficacy measures did not show any statistical differences between the monotherapy and the polytherapy regimens. Unfortunately, the number of patients with complex partial seizures and the seizure frequencies these patients had differed between the two tretament groups. There were a few patients in the polytherapy group who proved difficult to treat, and although continuing treatment at twelve months, still had frequent seizures. The reason that these patients did continue their treatment is that the treatment did have some success, and particularly after dose changes. If the proportion of patients with complex partial seizures had been higher in both groups, it would have been possible to get a better impression about possible diiferences in efficacy for this seizure type.

Nevertheless, despite higher baseline seizure frequencies, polytherapy reduced seizure

frequency successfully for all seizure types, which is remarkable at a drug load of about 0.50. One could argue however that the actual drug loads are higher because the the DDDs for CBZ and VPA are rather high, being set at 1000 and 1500 mg respectively. This is corroborated by the fact that the OSL/ATL data indicate that the overall drug load expressed in serum levels is 0.8 instead of 0.5. In terms of serum levels, the relative proportion of CBZ in polytherapy was higher than VPA's, which may be explained by CBZ's induction of VPA's metabolism (143). Moreover, valproate has been shown to inhibit CBZ metabolism, thus prolonging its elimination half life (166). Either way, one has to assume that for most polytherapy patients a low drug load of one of the drugs was sufficient or that the two drugs both contributed to the efficacy of the combination. The latter would be in agreement with animal experiments in which some AED combinations, such as the combination of valproate and carbamazepine, were shown to have additive efficacy (but infra-additive adverse effects) compared to the individual drugs (29).

Although there were no differences in overall NTX scores, significant differences were found for individual adverse effects. At the last visit significantly more monotherapy patients complained of sedation, one of the most important adverse effects of AEDs (39). More polytherapy patients appear to have developed tolerance for this adverse effect. Unfortunately, mechanisms of tolerance are still ill-understood. Significant differences were also found for weight gain (after twelve months) and for headache (only after two months). Weight gain is a well-known adverse effect of valproate, which has been associated with impaired oxidation of fatty acids (64).

Regarding systemic toxicity, the overall clinimetric score (STX) did not show significant differences between the groups. Valproate inhibits the epoxide hydrolase enzyme, and thus moderately increases the epoxide-to-CBZ ratio which probably does not enhance adverse effects in general, but may increase the chance of hypersensitivity reactions (226, 242, 247). However, in this trial the number of patients with serious skin reactions and the absolute epoxide were higher in the monotherapy group (table 6.1h), and thus low-dose polytherapy may actually reduce the frequency of idiosyncratic drug reactions. It is also possible that the higher CBZ titration rate in the monotherapy group is partly responsible for the higher number of rashes. As far as hepatotoxicity is concerned, only one patient in the polytherapy group developed both a rash and elevated liver enzymes. No significant differences were found using the quality of life scale.

Using three tests of the FePsy battery, we were not able to find significant differences in neuropsychological functioning. Most patients did better when they were medication than at the baseline visit, which should be interpreted as training effects (W. Alpherts, personal communication). Most of the patients could be rendered seizure free easily, and therefore one may deem them to have "light" forms of epilepsy. Consequently, the dosages they took were low and this may all be responsible for the lack of deterioration in the tests results.

Due to the unfavorable reputation that polytherapy has, which now seems unjustified, epileptology is lagging behind other disciplines in their knowledge of the merits of drug combinations. When two drugs or three drugs have failed as monotherapy, neurologists have no information as to which combinations they should prescribe. The only available data come from open trials in which some potentially advantageous combinations have been identified (34, 239, 258). More double-blind trials like the present one are needed to make an evidence-based choice when a monotherapy drug fails (even a first monotherapy drug).

Using the concept of drug load could give some insight whether the increased effectiveness of a combination is due to an improvement in efficacy or tolerability: in case of improved efficacy, drug loads will be more or less equal between groups; in case of improved tolerability, it will be possible to increase the drug load in that treatment group more than in other treatment groups and thus achieve better efficacy.

In conclusion, the results of this study do not provide evidence that monotherapy is superior to polytherapy with antiepileptic drugs. In the case of carbamazepine and valproate, as shown by this study, improved effectiveness may be attained through improved tolerability. Both pharmacological and clinical studies of AED combinations are needed to develop evidence-based treatment algorithms.

The following neurologists contributed patients for inclusion in the trial: Rijnstate Ziekenhuis Arnhem: dr. H.F.H Tacken

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Chapter 7 Discussion

In the preface the aims of this thesis were defined. These were:

1. To investigate whether drug load, rather than the number of antiepileptic drugs, is responsible for adverse effects.
2. To evaluate whether polytherapy is a good alternative for monotherapy when prescribed at equal drug loads.
3. To assess the possibility of selecting AED combinations by mechanisms of action.
4. To determine the best methodologies to evaluate polytherapy with antiepileptic drugs.

In this chapter we examine whether these aims have been achieved and if not, what remains to be done. In the last paragraph the clinical relevance of the findings of this thesis is discussed.

7.1 Is drug load, rather than the number of antiepileptic drugs, responsible for adverse effects ?

One should not expect that either drug load or the number of AEDs will explain all the differences in adverse effects between patients using polytherapy and patients using monotherapy. There are well-recognized differences in mechanisms of actions and in adverse effect profiles between the standard AEDs. For example, GABAergic drugs such as benzodiazepines and barbiturates are well-known for their sedative effects and sodium channel blockers such as PHT and CBZ are known to cause ataxia when given in high dosages (122, 250). Furthermore, as Hönack and Löscher have shown that kindled rats are more susceptible to motor impairment induced by AEDs than non-kindled rats, the susceptibility of patients for AED-induced adverse effects may vary because of differences in the type and severity of their epilepsy (110). As patients that use polytherapy will generally have a more severe epilepsy, they may be more susceptible to the deleterious effects of AEDs. Nevertheless, polytherapy with AEDs is thought to be one of the factors that may increase adverse effects (203).

As was discussed in the preface and chapter 1, the Nijmegen Epilepsy Research Group had already performed a couple of studies on the relationship between adverse effects and drug load in epilepsy patients prior to this thesis (133, 135). The first study showed that polytherapy does not lead to more toxicity than monotherapy, when patients with equal total drug loads are compared (135). However, when the correlation between adverse effects and drug load (expressed by the PDD/DDD ratio and the OSL/ATL ratio) was evaluated in the second study, it was only marginal in both monotherapy and polytherapy patients (133). These studies did have the drawbacks that baseline values were not available and that most of the patients studied had been epilepsy patients for many years, and thus already had been using AEDs for a very long period. Nevertheless, another interesting result of these studies was that polytherapy patients had much higher average drug loads than monotherapy patients (133, 135). This was to be expected, as polytherapy is mostly used in difficult-to-treat patients, but it does support the assumption that drug load may just as well be the cause of higher toxicity in polytherapy patients.

In paragraph 3.1 published research papers were analyzed to evaluate whether drug load or the number of drugs determines toxicity in AED polytherapy. In those studies in which

medication was specified for each individual patient, the number of adverse effects was correlated more strongly with drug load than with number of AEDs. However, the correlation between number of adverse effects and drug load again only amounted to 0.41, which explains about 17% of the variance in number of adverse effects. In the other papers studied, where medication use could only be compared per group, drug load was consistently higher in patient groups which had more adverse effects.

In the animal experiment described in paragraph 5.1, both valproate and ethosuximide influenced the toxicity measures (grip-strength, accelerod and behavior) in a dose-dependent fashion. When these drugs were administered together toxicity as measured by the rotarod and the grip strength meter combined in an additive manner, whilst the negative effects on spontaneous behavior were infra-additive. Thus two AEDs produced less, instead of more, sedation than one AED.

In the double-blind clinical trial described in chapter 6, the PDD/DDD method was used to start patients off on the same drug load. This ensured us that drug load was not a factor in possible differences in efficacy and toxicity between the treatment groups at the start of the trial. However, the aim of that study was not to determine possible relationships between PDD/DDD, OSL/ATL and adverse effects, but to compare efficacy and adverse effects between mono- and polytherapy with AEDs. This meant that the drug load could be changed whenever clinically necessary, but that most patients remained at their initial daily drug load of 0.4.

As was shown in chapter 6, overall neurotoxicity and systemic toxicity did not differ between mono- and polytherapy. Only a few specific adverse effects did differ significantly, such as sedation, headache and rash, at selected points in time. It was in fact again polytherapy that tended to be tolerated better as less patients withdrew due to adverse effects, although this did not reach statistical significance.

Polytherapy has also been implicated in the occurrence of idiosyncratic drug reactions, such as serious skin reactions and hepatotoxicity. Regarding the CBZ-VPA combination, VPA has been found to increase CBZ epoxide levels, and these epoxides may be involved in the pathophysiology of rashes and the other dermatologic reactions (121, 226). However, epoxide levels in the polytherapy group stayed well below the epoxide levels in the monotherapy group (where the CBZ dose was twice as high) and a higher high number of serious skin reactions was found in the monotherapy group. Thus drug load (and/or a higher

CBZ titration rate) proved to be more important than the number of drugs.

Generally speaking, it is more difficult to establish a relationship between drug load and adverse effects in humans than in animals, as the relationship between dose and effect varies considerably between individuals. For example, most patients that completed the trial still used the starting maintenance dose of 0.4 PDD/DDD, but the majority of patients who were withdrawn from treatment because of adverse effects, were also on that drug load. In animals, especially when using one genetic strain of animals, dose-effect studies can be readily constructed as these animals share (roughly) the same susceptibility for efficacy and adverse effects. Furthermore, animals in these studies receive the whole range of dosages, whereas in patients dosages are adjusted only when this is considered to be safe and clinically necessary.

Although we have not been able to answer question number 1 unequivocally, the studies described in paragraph 3.1 and in chapters 5 and 6 did show that drug load may be an important factor in determining the toxicity of an AED regimen. Moreover, these studies demonstrated the importance of taking drug load into account in the design and analysis of clinical trials. This will be commented upon further in paragraph 7.4.

7.2 Is low-dose polytherapy a good alternative for monotherapy ?

In the studies described in chapters 5 and 6 this question was evaluated for two AED combinations (VPA-ESM in rats and VPA-CBZ for epilepsy patients). The results were quite similar for these two combinations, but there were some differences as well. The valproate-ethosuximide combination appeared to be infra-additive for efficacy, but this did not reach statistical significance. Combining two drugs with different mechanisms of action apparently is no guarantee for additive anticonvulsant effects. As for adverse effects, the combination proved to be infra-additive for sedation and additive for grip-strength and rotarod performance (although it is important to note that the VPA:ESM proportion given in the polytherapy experiments differed between the two studies in chapter five). In the clinical trial, the combination of CBZ and VPA did look slightly less efficacious than carbamazepine monotherapy, but there was a strong suggestion that the effectiveness of the combination may actually be higher because of less adverse effect-related treatment failures. Can some sense be made out of these results when one looks at the theoretical dose response curve of a single drug ? In the simplest circumstance, agonist occupancy of the receptor obeys the law of mass action, and the relationship between agonist concentration and response is reflected by a rectangular hyperbola (31, 210). At low doses the effect of the drug increases proportionally with the dose, but at higher doses the incremental response diminishes. This may be explained by receptor binding: as the number of unoccupied receptors decreases the drug concentration needed to occupy a "free" receptor increases. In the physiological situation there are thought to be "spare" receptors, i.e. not all the receptors have to be occupied for the maximal effect to take place. This is more efficient as a lower drug concentration is needed for a maximal effect. Also, addition of an irreversible antagonist will not automatically diminish the maximal effect. The maximal effect is not only dependent on occupancy of receptors, as later steps in the receptor-effect pathway can become the limiting factor.

This illustrates what to expect from combination therapy tin theory: when two drugs are combined that act at the same receptor, it is improbable that this can really improve the effect (partly because these drugs will compete for receptor binding (163)). When drug B is added to drug A which acts at a different receptor of the same molecular target, drug B might change the receptor affinity for drug A (e.g. barbiturates enhance benzodiazepine receptor affinity by an allosteric mechanism) or enhance its post-receptor effects, and thus

the combination may be supra-additive. If two drugs are combined which modify the same neurobiological process, but act at different molecular targets (e.g. "presynaptic" vigabatrin and "postsynaptic" phenobarbital), this might either lead to increased GABAergic inhibition and/or the possibility to administer each drug at non-toxic dosages, provided that the adverse effects do not share the final common pathway (163).

Finally, when we combine two drugs which act on different neurobiological processes and act at different molecular targets, one might expect that low doses of the two drugs will produce a supra-additive effect. However, this does not seem to apply to the combinations tested in our studies (assuming that they really have different mechanisms of action), which might be explained by a limiting final common pathway. It could also be that the two processes are not suited for combination. For example, GABA-mediated membrane hyperpolarization theoretically could decrease the actions of sodium channel blockers, as actions of the latter drugs are voltage dependent (163). Nevertheless, Fagan's theoretical argument for combination therapy, which was discussed in paragraph 1.1, seems to hold true (69). If two drugs are combined at dosages with 50% effect, the toxicity of such a combination may be minimal. In other words, the therapeutic window of the combination may be enhanced.

7.3 Assessing the possibility of selection of AED combinations based on mechanisms of action

Many experts in the field of AED therapy have suggested that selected AED combinations may improve effectiveness, i.e. increase efficacy and/or increase tolerability. Ferrendelli has defined criteria to assist the clinician in the rational selection of AED polypharmacy, which are listed in table 7.3a (74).

Table 7.3a Principles of rational AED combinations

Selection criteria for rational AED combinations
1. Drugs with different mechanisms of action
2. Drugs with good efficacy
3. Drugs with low potential for toxicity (including idiosyncratic toxicity)
4. Drugs with low potential for drug interactions
5. Drugs with high therapeutic indexes

Ferrendelli obviously belongs to the experts that claim that efficacy can be increased by combining two drugs that have different mechanisms of action (criterion one) (74, 102). Other expert epileptologists recommend combining drugs which act at the same target to increase efficacy (91, 126). As was discussed in the previous paragraph, theoretically both strategies could work. However, most of the presently available AEDs have multiple mechanisms of action and the relative contributions of single mechanisms of action to the efficacy of the AEDs are not known. Almost all of the available AEDs block voltage-dependent sodium channels or increase GABAergic neurotransmission, and many of them do both. In paragraph 4.2 it was found that it is difficult to apply either strategy, but that advantageous combinations may seemingly consist out of two drugs acting at the same target but also out of two drugs acting at different targets. When the adverse effects of two AEDs are not additive, this will enable the clinician to administer two drugs at high, but non-toxic dosages. In other words, it may be possible to give higher drug loads in combination therapy than in monotherapy. As was argued in chapter 4, this strategy is probably responsible for the increased effectiveness of most of the combinations which proved to be useful in the clinical studies described in that chapter. As it is not known whether the mechanisms of action responsible for anticonvulsant efficacy are also involved

in the pathophysiology of adverse effects, drugs acting at the same target for their anticonvulsant effect may also be combined in an attempt to achieve increased tolerability. The studies discussed in chapter 4, do not provide more insight concerning this aspect: for example, the PHT/PB combination (Na^+/GABA, Na^+, glutamate) was infra-additive for toxicity in mice, but the PHT/CBZ combination (Na^+/Na^+) and the CBZ/PB (Na^+/GABA, Na^+, glutamate) were both additive (29).

Contrary to criterion one, criteria two to five can be evaluated quite easily for each of the currently marketed AEDs. When we for take criterion four for example, it has become possible to determine a drug's metabolic pathways and its enzyme-inducing or inhibiting effects of cytochrome P450 isoforms (169). This will allow researchers and clinicians to predict interactions and anticipate the necessity of dose adjustments (169). Enzyme-inducing or inhibiting effects may be beneficial, when a toxic metabolite is metabolized faster or when its formation is reduced respectively. When stiripentol is given to patients using CBZ, this inhibits the transformation of the CBZ parent drug into its metabolites, and these patients tolerate higher carbamazepine levels (169). Likewise, danazol inhibits the formation of CBZ-epoxide, which makes CBZ levels exceeding 20 mg/l tolerable (82). In chapter 4, it was described that drug interactions may also increase the incidence of idiosyncratic reactions. In this respect pharmacovigilance is very important, which could lead to dosing recommendations for certain combinations.

With regard to therapeutic indexes (criterion five), the combination of PB + PHT did display infra-additive toxicity in animals, but because of the low therapeutic index of phenobarbital the combination still had a lower therapeutic index (TC_{50}/EC_{50}) than phenytoin alone (29). This confirms the point made by Ferrendelli, that drugs with high therapeutic indexes generally are more suitable for combination therapy (74).

The criteria listed in table 7.3a do offer some assistance in selecting AED combinations, but they do not identify the combinations which are really advantageous in clinical practice. It may be that two drugs, although both block the sodium channel and both have an average therapeutic index, may interact differently with other drugs (e.g. CBZ and PHT). Therefore we still need a thorough testing procedure of AED combinations.

7.4 Which are the best methodologies to evaluate polytherapy with antiepileptic

drugs ?

Now that we have established that selected AED combinations may offer some advantages over their individual constituents, the question arises which way we should proceed ? This question raises many issues to consider:

A. Which combinations should be tested ?

B. Which study subjects should be chosen (i.e which animal models and which patients) ?

C. Which outcome measures should be used ?

D. What are the best study designs to evaluate AED combination therapy ?

In this last paragraph of this chapter, an attempt will be made to address these issues.

B. Which combinations ?

As was discussed in paragraphs 4.2 and 7.3 mechanisms of action and the criteria defined by Ferrendelli may be of some assistance to select possible combinations. However, the most appropriate selection criterion seems to be clinical practicality or necessity. For example, in absence epilepsy combinations between valproate, ethosuximide and lamotrigine are of interest. Patients with juvenile myoclonic epilepsy may benefit from a combination of VPA with drugs such as PB, LTG and TPM (74). For symptomatic generalized epilepsies combinations of VPA, LTG, TPM and a benzodiazepine may be evaluated. In patients with partial epilepsy, combinations of a conventional AED with either LTG, TPM, levetiracetam (LEV) or TGB or combinations of these new drugs should be investigated. Case reports of successful combinations can be helpful in selecting these combinations.

C. Which study subjects ?

Löscher has underlined the importance of selecting appropriate models for testing of theoretically promising combinations (150). A problem of current animal studies is that most concentrate on the MES model, and some on the Ptz model. Polytherapy is usually only used in refractory epilepsy and it is questionable whether these models really predict efficacy in such patients (147). Therefore, Löscher urges to use other models, such as the amygdala kindling model in which the 'epilepsy' really becomes intractable (147). He has

proposed a two step model: combinations would first be tested in acute seizure models (MES, Ptz) and in case of success in more labor-intensive models such as the amygdala-kindling model.

If combinations come through this animal testing successfully, they should be formally tested in humans. The patients probably most suited for polytherapy are the patients that need polytherapy in clinical practice i.e. patients with intractable epilepsy. In patients with newly diagnosed epilepsy, differences in efficacy are harder to demonstrate. The epilepsy syndromes which are most difficult to treat, such as the malignant childhood epilepsies and temporal lobe epilepsy, are obviously in need of high-quality polytherapy studies.

D. Which outcome measures

Animals

Animal epilepsy models may differ in having either quantal or graded efficacy measures: the MES and Ptz have quantal measures, i.e. how much drug is needed to suppress a seizure (component) in 50% of the animals. Log probit analysis is used to analyze the data and to estimate ED_{50}, TD_{50} and confidence intervals (92). In the WAG/Rij model a graded response is used, i.e. how much drug is needed on average to reduce the number of spike-wave discharges per animal with 50%. The ED_{50}, TD_{50} and confidence intervals can be estimated by non-linear regression. It is important to keep this distinction in mind, but in both cases it is possible to make dose-response curves, to use the isobologram method and to use them for clinical decision making (31).

As for adverse effects, the behaviors which can be tested in animals are obviously different from those which can be measured in epilepsy patients (129). In animals the distinction between active and passive behavior, coordination and hypotonia may be evaluated, whereas in man coordination tests and very extensive neuropsychological testing are available (129). Three adverse effect "detection methods" were used in the study described in paragraph 5.1: grip-strength, rotarod and active/passive behavior. These methods have already been discussed by Kulig and Lammers (130).

The grip-strength and accelerod data showed large 95% confidence intervals, which may make them less suitable for future experiments. In contrast, the active/passive behavior data had small confidence intervals. However, a cautionary remark is in place. It has not been ascertained whether this finding holds true for all AEDs: Kulig et al. showed that PHT, PB,

CBZ and VPA have different effects on rotarod performance and spontaneous behavior (129). Whereas PHT had no effect on rotarod performance at dosages up to 40 mg/kg, the other three drugs did have a negative influence at high dosages. Phenytoin, PB and CBZ impaired spontaneous behavior at serum levels which are in the therapeutic range in man, but valproate only did so at toxic levels. In more elaborate psychological tests, the effects of these drugs showed even larger differences (129). It is important to use such data in the selection of tests per experiment.

Furthermore, pharmacokinetic interactions, and possibly even brain concentrations, should be measured in these experiments. In two studies synergy was found when the authors looked at serum levels, whereas the brain concentrations in the same animals showed that there only was additive interaction (140, 184).

Humans

Clinimetric scales

In recent years, many papers have been published on outcome measurement in epilepsy. Two fine examples are reports by commissions of the International League Against Epilepsy (115, 116). In these reports recommendations are made for the evaluation of efficacy and toxicity. Although the methods used in our clinical trial, i.e. Composite Index of Impairments, QOLIE and FePsy, are all included in these recommendations, some remarks will be made regarding their use.

As was discussed in chapter 1, several clinimetric scales have been developed to measure seizure severity and adverse effects. These scales have been compared by Cramer and Mattson (43, 172). The VA scales and the Composite Index of Impairments have three important features that make them powerful research instruments: the scales express both seizure frequency and seizure severity, they are physician-based and the effect of treatment can be summarized in one composite score. The VA scale and the CII give a score for seizure frequency for each seizure type and points can be deducted per seizure type if modifying factors are present. Other seizure severity scales only express severity so that there is another variable next to seizure frequency to consider.

As was mentioned, patient-based as well as physician-based have been developed: the relative importance attributed to seizure severity and to adverse effects differs between patients and doctors. Regarding seizure severity, doctors tend to concentrate on loss of

consciousness, generalization of seizures, falls and length of the ictal period, whereas for patients duration of unconsciousness, slow post-ictal recovery, unpredictability of seizures and circumstances in which they occur are more important (255). Regarding adverse effects, there are considerable differences between patients in the amount of adverse effects they accept and in which adverse effects they find unacceptable (e.g. ataxia, weight gain, sexual disturbances). Some patients find seizure control most important and are willing to accept adverse effects whereas others accept almost no toxicity. Although these are important issues for individual patient care and although patient-based scales are very helpful as screening instruments, for research purposes an "objective" doctor-based scale with a rigid scoring system may be preferable. Moreover, the physician may be more objective and experienced in scoring the severity of seizures and adverse effects.

The great advantage of having one composite score is that it expresses the overall impairments the disease and its treatment have for patients. However, Cramer and Mattson suggest that it is also important to look at the individual items of their toxicity scales (43). In the second VA trial VPA had a less favorable neurotoxicity score, and this could lead a reader to conclude that all aspects of neurotoxicity were involved, although only one measure (tremor) was more frequent with VPA than with CBZ (173).

The high percentage of adverse effects yielded with the CII in our trial does bring the question that was posed in paragraph 3.3 up again: is using clinimetric scales producing false-positive adverse effects ? The criticism one could have of the review article on which paragraph 3.3 is based, is that the dosages were higher in the trials which used clinimetric scales to detect adverse effects (53). However, in our double-blind trial a low-dose CBZ monotherapy group was studied, so the adverse effects in this group can now be compared with the literature data on CBZ monotherapy from paragraph 3.3. We will only show those adverse effects that were found more often in table 3.3a when an active approach was used. As in paragraph 3.3 it seems that the active approach does reveal a higher incidence of certain adverse effects: sedation, cognitive impairments, gait disturbances, and hair changes. However diplopia, nystagmus, tremor, sexual dysfunction and weight changes were not found to be more frequent in our trial compared to studies which used self reporting of adverse effects. These effects might have been due to the higher dosages used by Mattson et al. in their trials (173, 174). One may conclude that the data from our trial confirm that some of the differences in toxicity rates between self-reporting and clinimetric evaluation

of adverse effects were due to methodology and not due to dosages. This could of

Table 7.4a *Percentages of patients in selected papers with drug-induced adverse effects while on carbamazepine monotherapy*

Publication # refers to reference list N between ()	204 (178)	252 (130)	33 (131)	55 (139)	173 (231)	NDB (196)	Mono-poly (53)
Method*	a + c	a + c	a	c + d	d + e	e	e
Carbamazepine Mean Dose mg/day	516	450	600 median	?	722	762	450
Follow up (months)	36	36	± 11	12	12-60	> 12	12
Gait disturbances	2%	4%	9%	-	25%	6%	13%
Tremor	2%	-	-	+	22%	11%	2%
Sedation	11%	19%	22%	32%	42%	41%	47%
Cognitive impairments	2%	2%	3%	-	18%	29%	23%
Gastro-intestinal complaints	8%	4%	19%	+	29%	3%	11%
Impotence	-	-	-	-	7%	0%	0%
Hyponatremia	-	-	-	-	-	0%	0%
Weight change	1%	6%	-	-	32%	8%	4%
Hair loss/hirsutism	1%	2%	-	-	6%	11%	11%

The papers concerned can be found in the reference list: (33, 70, 173, 204, 252). * Methods of detection of adverse effects: a = self-reporting; b = physical examination; c = laboratory investigations; d = adverse effect checklist; e = specific toxicity scale. The "+" sign denotes "present", but no percentages given. The "-"sign denotes not mentioned in the paper. NDB = Nijmegen DataBase. Monopoly = trial reported in chapter 6.

course mean that using the self-reporting technique may result in under-reporting of adverse effects, which was also the experience of some other researchers (111, 212).

The QOLIE-10 was chosen as QoL scale, partly because of its brevity. The originators of the QOLIE-10 see this scale as a questionnaire which the patient can fill out in for example the doctor's waiting room (44). One criticism of the scale may be that only one question is seizure-related, and although a patient can be very satisfied with a drug because of the seizure control, his or her QoL as measured by the QOLIE-10 may be worse because of adverse effects or circumstances not related to having epilepsy. Nevertheless, the scale was not designed to express AED effectiveness, and it may alert physicians to certain aspects which may otherwise remain unmentioned (44). For research purposes a more elaborate version of the QOLIE, such as the QOLIE-31 may be preferable.

Neuropsychological testing

Common problems with the clinical assessment of the cognitive impairments due to AEDs are that these impairments are often subtle at onset and that diminished learning and decreased speed of intellectual performance are hard to document (250). Moreover, directed action increases the level of attention, thereby overcoming sedation, and thus the doctor or the neuropsychologist may be deceived by the temporary alertness of the patient (250). It is a common observation that patients mostly do not complain of drowsiness at work, but of drowsiness at home (i.e. where they are challenged less, although pharmacokinetics may also play a role (111)). Another problem with many neuropsychological tests is that they have motor components, which complicates the recognition of cognitive changes, as AEDs may also have motor effects.

There does not appear to be international agreement on how to tackle these problems and on which standard tests should be used during AED trials. Cochrane et al. found that a 'plethora' of tests is being used and that most of them were non-epilepsy specific (38). They recommend that first of all a battery of tests should be used that has proven reliability and validity and has been designed and standardized to assess people with epilepsy. Only these will have sufficient sensitivity to detect the cognitive changes induced by AED treatment. A minimum of measures would include assessment of motor speed, attention and concentration, learning, memory and higher executive functioning (38). The FePsy battery does meet the requirements set by Cochrane et al. .

As for the individual tests used in our trial, the tapping test was not found to be very sensitive in the first VA trial (231). The Discriminative Reaction Time test (a test which is somewhat similar to the Binary Choice task) on the other hand was very sensitive in discriminating between epilepsy patients and healthy controls. The Computerized Visual Searching Task is also thought to be a sensitive task: generally one could say that the more highly timed a test is, the likelier finding a significant drug effect is (38).

It should be noted that a high degree of sedation, as found in our trial, may result in decreased attention and subjective memory impairments. Furthermore, Vermeulen et al. claim that patient memory complaints do not accurately reflect disturbances that can be measured on standard neuropsychological tests. For this neuroticism and psycho-social factors may be held responsible, not the epilepsy itself or drug-related factors (254). Thompson et al. however, reported that patients tend to underestimate rather than

overestimate the extent of these problems and that the nature of these impairments does not seem to be adequately detected by traditional memory tests (244).

For all of these outcome measures it is important to look at the scores of individual patients. In epilepsy treatment the majority of patients can be treated satisfactorily, and thus the minority which is not doing well may not be reflected well in group averages.

It might even be advisable to compare the number of patients doing poorly between groups, next to comparing group averages.

E. Which study designs

Animals

Based on the papers reviewed in paragraph 4.2 and the experiments described in chapter 5, the following recommendations can be made for animal experiments on AED combinations:

- the determination of dose-response curves for both individual drugs and for the combination.
- the recording of baseline data for all animals (to normalize the experimental data in case of variability in baseline data between groups).
- use of the isobologram method to evaluate interactions between the drugs. When the dose-effect curve is determined for several weight ratio's of a combination, the interaction can be visualized by reponse surface modelling, which is a model which is alo based on the isobologram method (180).
- when animals are used repeatedly: use of a Latin-square, baseline recordings on each test day and sufficiently long intervals to eliminate carry-over effects.
- assessment of pharmacokinetic interactions (by measurement of serum levels) and possibly even measure brain concentrations in these experiments. The importance of this is particularly emphasized by two studies in which synergy was concluded when the authors looked at serum levels, whereas the brain concentrations in the same animals showed that there only was an additive interaction (140, 184).

Humans

The human study designs that have rendered the most definite results are the method in which patients who did not respond to drug A nor to drug B when given separately, are

given the combination of A and B and the method used by Brodie et al. amongst others, where the addition of the investigational AED to different single conventional AEDs is compared (34). The concept of drug load could give insight into whether the increased effectiveness of a combination is due to an improvement in efficacy or tolerability: in case of improved efficacy, drug loads will be more or less equal between groups; in case of improved tolerability, it will be possible to increase the drug load in that treatment group more than in other treatment groups

7.5 Relevance for clinical practice

What is the direct relevance of our findings for clinical practice:

- adverse effects are related to several factors, and drug load, rather than the number of drugs, appears to be one of them.
- some adverse effects, such as sedation, may be under-reported if not routinely asked for.
- The selection of AED combinations needs empirical testing as it is not possible to make recommendations on theoretical grounds.
- when monotherapy with antiepileptic drugs fails, combination therapy may offer advantages because of a larger therapeutic window, i.e. higher drug loads may be used before adverse effects become unacceptable. However, this may not hold true for all AED combinations. The trial described in chapter 6 is the only clinical study to date in which this has been proven for an AED combination, i.e. the combination of carbamazepine and valproate.

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Chapter 8 English and Dutch summary

8.1 English summary

Epilepsy is a generic term for the large variety of epilepsy syndromes that exist: each syndrome has its own characteristic spectrum of seizures, its own typical abnormalities on the EEG, its own degree of response to drug therapy etc.. Over the whole population of patients with epilepsy, it is estimated that with the use of antiepileptic drugs it is possible to control approximately 75% of patients. Drug trials in which several drugs were compared to each other demonstrated that ±70% of patients can be adequately controlled with a single drug (i.e. monotherapy). Thus combination therapy will result in adequate control in only an extra 5%. Moreover, polytherapy has been reputed to lead to increased toxicity, and thus at the present polytherapy is being avoided whenever possible.
In a 1995 study the Nijmegen Epilepsy Research Group (NERG) found however that, when monotherapy patients and polytherapy patients were compared that were being treated with equal total drug loads, there was no difference in adverse effects between these groups. Drug load is defined as the amount of drug exposure for a certain indication. In that study, the NERG used a clinimetric index to check for the presence of a range of adverse effects and, when present, to score severity of those adverse effects. The surprising finding that polytherapy was not per se more toxic than monotherapy, led to the research that is described in this thesis.

In chapter one the history of the monotherapy-polytherapy debate is discussed and the concepts of drug load and of clinimetric epilepsy scales are re-introduced. In chapter two background information is given on the methods used in this thesis (drug load, the clinimetric epilepsy scales adopted by the NERG, neuropsychological tests) for the interested reader.

Chapter three contains a number of papers in which these aforementioned methods are tested and re-examined. Paragraph 3.1 describes a literature study in which drug load was calculated for a number of published studies, and which showed that higher drug load is usually associated with increased toxicity. In paragraph 3.2 the theoretical basis for the drug load concept is discussed. The method our group has developed to calculate drug

loads, shows analogies to the isobologram method, which is the preferred method to analyze the effects of combining drugs in animals. In paragraph 3.3 the results of studies in which adverse studies were detected by clinimetric scales are compared to the results of studies which relied upon self-reporting for the detection of adverse effects. Active inquiry about specific adverse effects (i.e. the clinimetric approach) does increase the frequency with which certain adverse effects are found. This is in accordance with several reports in the literature that suggest that an active approach is needed for an accurate detection of certain complaints and symptoms. However, routine laboratory monitoring does not appear to be necessary for all patients using antiepileptic drugs.

In paragraph 4.1 the current knowledge about the mechanisms underlying seizures and about the mechanisms of action of the presently licensed antiepileptic drugs is summarized. There has been increasing attention in the last decade for "rational polytherapy", i.e. the selection of AED combinations based on their pharmacological properties. However, uncertainty exists as to whether drugs with the same mechanism of action or drugs with different mechanisms of action should be combined.
The available polytherapy studies in animals and in epilepsy patients were reviewed in paragraph 4.2 to determine whether it is possible to combine AEDs based on mechanisms of action, and if so, which combinations may lead to increased effectiveness. It proved to be quite difficult to evaluate the results of the studies, animal studies as well as clinical studies, because of the diversity of methods used to analyze drug interactions. The results of only a limited number of studies were used to address the issue, because their designs were deemed to be of better quality than the others. Using this limited set of data, it was found that although there may be some promising "mechanistic" combinations, the knowledge concerning mechanisms of action and pathophysiology is still too incomplete to make definite recommendations.

The animal studies done as part of this thesis are described in chapter five. In the first study (paragraph 5.1) ethosuximide and valproate were administered to Wistar rats (i.e. a rat strain without epilepsy), alone and in combination. Possible adverse effects were evaluated by the use of three different methods, measuring strength, coordination and level of spontaneous activity. The isobologram method showed that the combination produced less

passive behavior (which could be interpreted as sedation) than the drugs given alone. There were no significant differences in strength or coordination. This result suggests that giving two drugs at low dosages, may have advantages over giving either drug alone at higher dosages. In the second study (paragraph 5.2) the efficacy of the ESM-VPA combination in WAG/Rij rats (i.e. a rat strain which shares behavioral, electro-encephalographic and anti-convulsant profiles with human absence epilepsy) was compared to the efficacy of ESM alone and VPA alone. Although it did not reach statistical significance, the data suggested that the combination was less efficacious than the individual drugs. This may compromise the positive findings of the study described in paragraph 5.1.

The first double-blind clinical trial comparing monotherapy and polytherapy with AEDs is described in chapter six. A 125 patients were randomized to either carbamazepine monotherapy or a combination of carbamazepine and valproate, starting off on equal drug loads. The primary outcome measure (which is also used to calculate how many patients should be included in the trial) was neurotoxicity. Patients were interviewed and tested regularly during the trial to have a reliable record of seizure frequency, possible adverse effects and their quality of life. Patients were followed for up to a year, but could drop out because of insufficient seizure control despite dose increases or because of an unacceptable level of adverse effects. At the end of the trial, there were no significant differences in clinimetric scores for seizure frequency, neurotoxic adverse effects or systemic adverse effects. More patients on monotherapy were still bothered by sedation at the end of the trial, but more polytherapy patients had gained weight. More patients on monotherapy dropped out because of adverse effects, however this did not reach statistical significance.

In chapter 7, the findings of this thesis were discussed and can be summarized into four main points:

1. It was not demonstrated that drug load is more important than the number of drugs in producing adverse effects, but drug load is an important aspect to take into account when planning or analyzing (multi-)drug trails.
2. Some polytherapy combinations may offer advantages over their individual constituents, and, in the case of the combinations studied in this thesis, this was due to infra-additive toxicity.

3. It may be that certain “mechanistic” AED combinations offer more advantages than others, however the present knowledge concerning mechanisms of action of AEDs does not allow us to pursue these. Therefore, a large range of combinations should be tested.
4. Recommendations are made concerning future polytherapy studies: specifically concerning possible AED combinations, study subjects to be studied, outcome measures and study designs.

8.2 Samenvatting

Epilepsie is een verzamelnaam voor het grote aantal vormen van epilepsie die voorkomen: vormen met elk een eigen spectrum aan eigen aanvalsuitingen, eigen afwijkingen op het EEG ("hersenfilmpje"), een eigen mate van reageren op therapie etc.. Over de hele groep genomen, kan men zeggen dat ongeveer 75% van de epilepsie-patiënten met succes behandeld kan worden met medicijnen die de aanvallen onderdrukken, de zogeheten. Uit geneesmiddelenonderzoek is gebleken dat de aanvallen van ±70% van de patiënten voldoende kunnen worden onderdrukt wanneer zij één middel (oftewel monotherapie) gebruiken. Het inzetten van combinaties van anti-epileptica levert dus maar bij een verdere 5% succes op. Bovendien wordt gedacht dat het geven van meerdere anti-epileptica tegelijk (oftewel polytherapie) kan leiden tot meer bijwerkingen, and daarom wordt polytherapie tegenwoordig zoveel mogelijk vermeden.

In een onderzoek in 1995 vond de Nijmeegse Epilepsie Research Groep (NERG) echter dat, wanneer patiënten met monotherapie en patiënten met polytherapie eenzelfde drug load gebruikten werden vergeleken, er geen verschil in bijwerkingen bestond. Drug load wordt gedefinieerd als de hoeveelheid geneesmiddelen waar de patiënt aan wordt blootgesteld voor een bepaalde aandoening. In datzelfde onderzoek, gebruikte de NERG een zogenaamde klinimetrische schaal waarmee specifiek naar de aanwezigheid van bepaalde bijwerkingen wordt gevraagd en, indien een bijwerking aanwezig is, de ernst van bijwerkingen wordt gescoord. De verrassende bevinding dat polytherapie niet per se met meer bijwerkingen gepaard gaat, was de directe aanleiding voor het onderzoek wat in dit proefschrift wordt beschreven.

In hoofdstuk 1 wordt de geschiedenis van de controverse over monotherapie en polytherapie verteld en worden de concepten van drug load en klinimetrische epilepsie-schalen opnieuw ten tonele gevoerd. In hoofdstuk 2 wordt achtergrondinformatie gegeven over de methodologieën die in het onderzoek zijn gebruikt (drug load, klinimetrische epilepsie-schalen, neuropsychologische tests) voor de geïnteresseerde lezer.

Hoofdstuk 3 bevat een aantal studies waarin deze methoden opnieuw worden hun waarde

moesten bewijzen. In paragraaf 3.1 wordt een literatuur-onderzoek beschreven waarbij de drug load werd berekend voor een aantal reeds gepubliceerde studies; hieruit blijkt dat in elk van deze studies een hogere drug load geassocieerd was met meer bijwerkingen. Vervolgens wordt in paragraaf 3.2 de theoretische basis voor het drug load concept besproken; dit betreft diens gelijkenis met de isobologram-methode, één van de beste methodes om bij dier-experimenten de effecten van het combineren van middelen te analyseren. In paragraaf 3.3 worden de resultaten van studies waarbij bijwerkingen werden gedetecteerd met klinimetrische schalen vergeleken met de resultaten van studies waarbij men vertrouwde op zelf-rapportage van bijwerkingen. Actief navragen van specifieke bijwerkingen (i.e. de klinimetrische benadering) blijkt hogere frequenties voor bepaalde bijwerkingen op te leveren. Ook andere onderzoekers hebben gerapporteerd dat een actieve detectie-methode nodig is voor een nauwkeurig opsporen van bepaalde bijwerkingen. Het lijkt echter niet noodzakelijk om bij alle patiënten die antiepileptica gebruiken routinematig bloed-onderzoek (naar leverfunctie-afwijkingen etc.) te verrichten.

In paragraaf 4.1 wordt de huidige kennis samengevat over de mechanismen in de hersenen die tot een epileptische aanval leiden en over de werkingsmechanismen van anti-epileptica. In de laatste 10 jaar is er aandacht ontstaan voor "rationele polytherapie", d.w.z. de selectie van combinaties van anti-epileptica op basis van hun farmacologische eigenschappen. Er bestaat echter onzekerheid of juist medicijnen met dezelfde werkingsmechanismen of middelen met verschillende werkingsmechanismen moeten worden gecombineerd.
Eerder verrichte onderzoeken naar verschillende combinaties van antiepileptica in diermodellen van epilepsie en bij epilepsie-patiënten worden in paragraaf 4.2 op een rij gezet. Dit om te bepalen of het mogelijk is om combinaties op basis van werkingsmechanismen te combineren (gezien het feit dat de meeste anti-epileptica meerdere werkingsmechanismen hebben) en zo ja, welke combinaties dan tot meer effectiviteit leiden. Het bleek echter vrij moeilijk te zijn de verschillende studies te vergelijken door de grote variëteit aan methodes die werden gebruikt om de effecten van het combineren te interpreteren. Alleen de resultaten van een beperkt aantal studies, met een studie-opzet die als kwalitatief hoogstaand werd beoordeeld, werden gebruikt om de genoemde vragen te beantwoorden. Met deze set van gegevens werd gevonden dat alhoewel er wellicht bepaalde veelbelovende combinaties zijn, de kennis omtrent de

onderliggende mechanismen van aanvallen en omtrent de werkingsmechanismen van de antiepileptica nog te incompleet is om harde aanbevelingen te doen.

De dier-experimenten worden beschreven in hoofdstuk 5. In het eerste onderzoek (paragraaf 5.1) werden de antiepileptica ethosuximide en valproaat toegediend aan Wistar ratten (dit is een rattenstam die niet spontaan epilepsie ontwikkelt), alleen en in combinatie. Mogelijke bijwerkingen werden geëvalueerd door het meten van spierkracht, coördinatie en spontaan actief gedrag. Middels de isobologram methode werd aangetoond dat de combinatie tot minder passief gedrag leidde dan de afzonderlijke middelen, en dat er wat betreft kracht en coördinatie geen significante verschillen waren. De resultaten van deze studie suggereren dat het geven van twee middelen in lage doseringen voordelen kan hebben t.o.v. het geven van de afzonderlijke middelen in hogere doseringen.
In het tweede onderzoek (paragraaf 5.2) werd de werkzaamheid van de ethosuximide-valproaat combinatie in WAG/Rij ratten (een rattenstam die wel spontaan epilepsie ontwikkelt) vergeleken met de werkzaamheid van de middelen alleen in dit model. Het leek dat de combinatie minder werkzaam was in dit diermodel dan de afzonderlijke middelen, alhoewel dit statistisch significant werd. Dit resultaat van het werk beschreven in paragraaf 5.2 kan de mogelijke voordelen die ten aanzien van de combinatie werden gevonden in paragraaf 5.1, (deels) teniet doen.

In hoofdstuk zes wordt een dubbelblind onderzoek (d.w.z. zowel de betrokken arts als de patiënt wisten niet welke medicatie de patiënt gebruikte; deze code werd bewaard in het SEIN in Heemstede) beschreven. In totaal 125 patiënten kregen hetzij carbamazepine monotherapie of een combinatie van carbamazepine en valproaat, waarbij in beide groepen met een gelijke drug load werd gestart. Omdat de meeste verschillen werden verwacht in de neurotoxische bijwerkingen (zoals slaperigheid, hoofdpijn of evenwichtsproblemen), werden deze genomen als zogenaamde primaire uitkomstmaat (deze maat wordt gebruikt om uit te rekenen hoeveel patiënten er in een onderzoek moeten worden opgenomen om na afloop van het onderzoek met enige zekerheid conclusies te kunnen trekken). De patiënten werden in het jaar van deelname regelmatig gezien op de poliklinieken om een goed beeld te hebben over mogelijke aanvallen en bijwerkingen. Zoals werd verwacht vielen er ook patiënten uit voordat ze de medicatie een jaar hadden

gebruikt en dit gebeurde met name ten gevolge van bijwerkingen. De meerderheid van de patiënten nam wel een heel jaar deel, en bij hen werden er geen verschillen gevonden wat betreft aanvalscontrole of bijwerkingen in het algemeen. Wel hadden na 12 maanden meer monotherapie-patiënten nog last van slaperigheid en meer polytherapie-patiënten waren in gewicht aangekomen. Het leek zo te zijn dat er relatief meer monotherapie-patiënten gedurende het onderzoek uit waren gevallen vanwege bijwerkingen, maar dit was niet statistisch significant verschil.

In hoofdstuk 7 word het totaal van de bevindingen van het promotie-onderzoek besproken en worden deze samengevat in vier punten:

1. Het werd niet aangetoond dat drug load meer invloed heeft op het aantal bijwerkingen of de ernst van bijwerkingen, dan het aantal anti-epileptica heeft. Wel werd duidelijk dat drug load een belangrijk aspect is bij het opzetten of analyseren van geneesmiddelen-onderzoek (zeker wanneer combinaties van geneesmiddelen worden onderzocht).
2. Sommige combinaties van antiepileptica kunnen voordelen bieden t.o.v. van hun afzonderlijke bestanddelen. In het geval van de studies die in dit onderzoek werden bestudeerd was dit dankzij het minder hebben van bijwerkingen. Dit is opvallend, omdat men juist altijd beweert dat polytherapie met meer bijwerkingen gepaard gaat.
3. Het kan zo zijn dat bepaalde combinaties van types anti-epileptica (lees: werkingsmechanismen) effectiever zijn dan andere. De huidige kennis van werkingsmechanismen staat echter niet toe dit met zekerheid te zeggen en daarom zou men wat dit betreft een groot scala van combinaties moeten testen. 4. Aanbevelingen worden gedaan voor toekomstig onderzoek naar polytherapie: welke combinaties moeten testen worden, welke diermodellen en welk type patiënten moeten worden bestudeerd, welke uitkomsten en studie-opzetten moeten worden gebruikt.

Appendix A

COMPOSITE INDEX OF IMPAIRMENTS

SEIZURE ACTIVITY INDEX

Section A: Complete this section if patient has either primary or secondary gegeneralized tonic-clonic seizures.

1. Total number of seizures since last visit: _____
2. Total number of seizures since start drug: _____

   Select the seizure frequency that applies to this patient and enter number of points on score line

   a. Three or more seizures/12 months = 20 p. each seizure
   b. Two seizures/first 3 months = 50
   c. One seizure/first 3 months = 40
   d. Two seizures/6 months = 45
   e. One seizure/6 months = 40
   f. Two seizures/6-12 months = 30
   g. One seizure/6-12 months = 20
   h. Two seizures/12-24 months = 20
   i. One seizure/12-24 months = 10
   j. No seizures/ last 24 months = 0

   Score _____

3. Was seizure modified by an aura ? Yes O No O
   If yes: reduce I.S. score with 20 %. Score _____
4. Was seizure(s) precipitated by unusual, remedial factors
   (e.g. lack of sleep, alcohol, illness)? Yes O No O
   If yes: reduce I.S. score with 50%. Score _____
5. Are seizures modified by known cyclic or diurnal pattern
   (e.g. nocturnal or early a.m.)
   If yes: reduce I.S. score with 40%. Score _____

Score A _____

Section B: Complete this section if patient has complex partial seizures (with altered consciousness) that do not generalize.

1. Total number of seizures since last visit: _____
2. Did seizures occur as a cluster (more than 2 seizures within 24 hours) ?
   If yes: count only half of the seizures in that cluster.
3. Select the seizure frequency that applies to this patient and enter number of points on score line

   a. Four or more seizures/month = 50 p. (+ 10 per extra seizure)
   b. Three seizures/month = 40
   c. Two seizures/month = 30
   d. One seizure/month = 20
   e. One seizure/1-3 months = 15
   f. Less than one seizure/3 months = 10
   g. No seizures in last 12 months = 0

   Score _____

4. Was seizure modified by an aura ? Yes O No O
   If yes: reduce I.S. score with 20 %. Score _____
5. Was seizure(s) precipitated by unusual, remedial factors
   (e.g. lack of sleep, alcohol, illness)? Yes O No O
   If yes: reduce I.S.score with 50%. Score _____
6. Are seizures modified by known cyclic or diurnal pattern
   (e.g. nocturnal or early a.m.) ?
   If yes: reduce I.S. score with 40%. Score _____
7. Was patient able to resume daily activities within 15 minutes
   If yes: reduce I.S. score with 50%. Score _____

Score B _____

Section C: Complete this section if patient has simple partial seizures (without loss of consciousness).

1. Total number of seizures since last visit: _____
2. Did seizures occur as a cluster (more than 2 seizures within 24 hours) ?
   If yes: count one half of the seizures in that cluster.
3. Select the seizure frequency that applies to this patient and enter number of points on score line
   a. Seven or more seizures/month = 33 p. (+ 3/extra seizure)
   b. Six seizures/month = 30
   c. Five seizures/month = 28
   d. Four seizures/month = 25
   e. Three seizures/month = 23
   f. Two seizures/month = 20
   g. One seizures/month = 15
   h. One seizure/1-3 months = 13
   i. Less than one seizure/3 months = 10
   j. No seizures in last 12 months = 0

   Score _____
4. Was seizure(s) precipitated by unusual, remedial factors
   (e.g. lack of sleep, alcohol, illness)? Yes O No O
   If yes: reduce I.S.score with 50%. Score _____
5. Are seizures modified by known cyclic or diurnal pattern
   (e.g. nocturnal or early a.m.) ?
   If yes: reduce I.S. score with 40%. Score _____
6. Was patient able to resume daily activities within 15 minutes
   If yes: reduce I.S. score with 50%. Score _____

Score C _____

Score A + score B + score C = S.A. score

Neurotoxicity rating scale

Instructions: all toxicity is scored relative to normal for this patient before starting this medication. Do not change the drug when toxicity occurs with high serum level; reduce the drug dosage. Circle all scores that apply and record on score line. Enter zero when no toxicity is present.

	Score			
1. Diplopia				
a. Intermittent			15	
b. Constant			30	_____
2. Nystagmus (not end point):				
a. Horizontal			5	
b. Vertical			10	_____
3.Dysarthria				
a. Mild (intermittent slurring)			5	
b. Moderate (constant slurring, no difficulty communicating)			10	
c. Severe (understanding of speech difficult if topic unknown to listener)		30	_____	
4. Gait, normal walking				
a. Slight ataxia (slowness or unsteady turning)		5		
b. Mild ataxia (veer from side to side, difficulty with tandem gait)		15		
c. Moderate ataxia (quite unsteady, walks with wide-based gait; tendency to fall toward one side or other)			25	
d. Severe gait disturbance (can walk only with assistance; unsteady sitting)		50	_____	
5. Rapid alternating movements (hand on knee; flip side to side; grossly clumsy)		15		_____
6. Intention tremor (finger to nose, long reach; eyes open/ eyes closed)				
a. Mild (large tremor seen as finger approaches nose; fingers misses nose)		10		
b. Moderate (finger misses nose most of the time)			25	
c. Moderately Severe (frequent or constant tremor, compromises to some degree: writing, fine motor movement, etc.)		35		
d. Severe (disturbs everyday functioning: eating, writing, working)		50	_____	
Enter total for items 1-6 (if more than 1 score, multiply by 50%)			_____	
7. Sedation (level of consciousness)				
a. Lethargic in early AM or PM			5	
b. Occasionally sleepy during day			10	
c. Often difficult staying awake			25	
d. Stuporous			50	_____
8. Affect and mood (depression; tension/agitation; anger/hostility; vigor/excitability; fatigue/apathy; confusion/thought disorder)				
a. Mild (disturbance recognized by patient, but not interfering with usual life)		5		
b. Moderate (mood disturbance results in reduced abilities)		15		
c. Severe ((nearly) continuous mood disturbances interfering with normal life)		50	_____	
9. Cognitive function (attention and concentration)				
a. Mild (symptoms recognizable, but no interference with usual life)		5		
b. Moderate (interference with some daily activities)			10	
c. Severe (interference with all daily activities)		50	_____	

10. Dizzy/lightheaded (enter zero if categories do not apply)	Occass. after med.	Often after med.	Often during day	
a. Mild (symptoms recognizable, but no interference with usual life)	3	5	10	
b. Moderate (interference with some daily activities)		5	10	25
c. Severe (interference with all daily activities)	10	25	50	

11. Drug-related Headaches (enter zero if categories do not apply)	Occass. after med.	Often after med.	Often during day	
a. Mild (symptoms recognizable, but no interference with usual life)	3	5	10	
b. Moderate (interference with some daily activities)		5	10	25
c. Severe (interference with all daily activities)	10	25	50	

12. Other neurotoxicity (describe):_____				_____
Neurotoxicity Score (sum 7 to 13)			**Total score**	_____

Systemic Toxicity Rating

Instructions: all toxicity is scored relative to normal for this patient before starting this medication. Do not change the drug when toxicity occurs with high serum level; reduce the drug dosage. Circle all scores that apply and record on score line. Record the '0' value when no toxicity is present.

					Score
1. Does the patient have any drug-related gastro-intestinal problems ? (enter highest applicable score on score line; enter zero if categories do not apply)	Distress	Nausea	Vomiting	Other	
a. Transient or occasionally after medication	3	5	10	___	
b. Often after medication	5 10	25		___	
c. Often during the day	10	25	50	___	
					_____
2. Does patient have hematopoietic system problems ? (enter a score for each of the following; enter zero if category does not apply)					
a. Reduced platelet count < 75,000 (score 25 if under observation; score 50 if drug discontinued)					
b. Reduced WBC < 2,000 (score 25 if under observation; score 50 if drug discontinued)					
c. Other hematologic problems: _____					_____
3. Does patient have dermatological problems ?					
a. Transient general maculopapular rash (stopped with treatment)			15		
b. Severe general maculopapular rash (did not stop with treatment)				50	
c. Acne noticeable on face, trunk, limbs				10	
d. Severe acne, excessive and bothersome to the patient			30		_____
4. Does patient have problems with impotence (libido or potency) related to drug use ?					
a. Transient, occasional or tolerable			20		
b. Continuous or intolerable				50	_____
5. Does patient have hyponatremia with serum sodium < 120 mol./l ?					
If yes, score 50					_____
6. Does patient have drug-related liver disease with abnormal liver function tests (ASAT, ALAT) ?					
a. Yes, under observation			25		
b. Yes, drug discontinued			50		_____
7. Has patient gained weight because of a drug-related increased appetite ?					
Weight gain: small (4-6 lbs)				3	
moderate (7-12 lbs)				10	
large (>13 lbs)				20	_____
8. Does patient have any changes in hair quantity or texture since starting drug ?					
a. Hair loss: mild (hair in comb)				5	
moderate (visible thinning of hair or hair loss in clumps)			20		
severe (visible alopecia or exceedingly bothersome to the patient)			50		
b. Hair texture change (becoming coarse, fine, curly)			5		
c. Hirsutism: moderate (noticeable on face, trunk or limb)			20		
severe (excessive and bothersome to the patient)			50		_____
9. Other systemic toxicity (describe): _____					
					_____
Systemic Toxicity score			**Total score**		_____

Composite Index of Impairments schaal

Patiënt:_____ Patiëntnr.:_____

Formulier ingevuld door:_____ Datum:_____

SEIZURE ACTIVITY SCHAAL

Sectie A: Vul dit onderdeel in indien de patiënt een primaire dan wel een secundaire gegeneraliseerde tonisch-clonische aanval heeft gehad.

1. Aantal aanvallen sinds laatste bezoek: _____
   Aantal aanvallen sinds start anti-epilepticum: _____
2. Selecteer de juiste aanvalsfrequentie:
   a. Drie of meer aanvallen/12 maanden = 20 p. elke aanval
   b. Twee aanvallen/eerste 3 maanden = 50
   c. Eén aanval/eerste 3 maanden = 40
   d. Twee aanvallen/6 maanden = 45
   e. Eén aanval/6 maanden = 40
   f. Twee aanvallen/6-12 maanden = 30
   g. Eén aanval/6-12 maanden = 20
   h. Twee aanvallen/12-24 maanden = 20
   i. Eén aanval/12-24 maanden = 10
   j. Aanvalsvrij meer 24 maanden = 0

   Score _____
3. Is er sprake van een aura? Ja O Neen O
   Indien ja: reduceer de IS score met 20%. Score _____
4. Worden de aanvallen door niet-alledaagse, vermijdbare factoren geprovoceerd (slaapgebrek, alcohol, ziekte, vermoeidheid, etc.)? Ja O Neen O
   Indien ja, reduceer de IS met 50%. Score _____
5. Vinden de aanvallen plaats in een cyclisch of diurnaal ritme?
   Dus alleen s'nachts of vroeg in ochtend ? Ja O Neen O Score _____
   Indien ja, reduceer de IS met 40%.

   Score A _____

Sectie B: Vul deze sectie in indien de patiënt een complex partiële aanval heeft gehad die niet tot een gegeneraliseerde aanval leidde.

1. Aantal aanvallen sinds laatste bezoek: _____
   Aantal aanvallen sinds start anti-epilepticum: _____
2. Kwamen de aanvallen in cluster (= meer dan 2 binnen 24 uur)? Ja O Neen O
   Zo ja, hoeveel aanvallen in het cluster: _____ Tel bij ≥3 aanvallen, slechts de helft van de aanvallen.
3. Selecteer de juiste aanvalsfrequentie:
   a. 4 of meer aanvallen/maand = 50 (+10 per extra aanval)
   b. Drie aanvallen/maand = 40
   c. Twee aanvallen/maand = 30
   d. Eén aanval/maand = 20
   e. Eén aanval in 1-3 maanden = 15
   f. Minder dan 1 aanval in 3 maanden = 10
   g. Aanvalsvrij = 0 Score _____
4. Is er sprake van een aura? Ja O Neen O
   Indien ja: reduceer de IS score met 20%. Score _____
5. Worden de aanvallen door niet-alledaagse, vermijdbare factoren geprovoceerd (slaapgebrek, alcohol, ziekte, vermoeidheid, etc.)? Ja O Neen O
   Indien ja, reduceer de IS met 50%. Score _____
6. Vinden de aanvallen plaats in een cyclisch of diurnaal ritme?
   Dus alleen s'nachts of vroeg in ochtend ? Ja O Neen O
   Indien ja, reduceer de IS met 40%. Score _____
7. Kan de patiënt binnen 15 minuten na de aanval weer op het oude niveau functioneren ?
   Ja O Neen O Indien ja, reduceer de IS met 50 % Score _____

Score B _____

Sectie C: Vul deze sectie in indien de patiënt een elementaire (simpel) partiële aanval heeft gehad.

1. Aantal aanvallen sinds laatste bezoek: _____
   Aantal aanvallen sinds start anti-epilepticum: _____
2. Kwamen de aanvallen in cluster (= 2 binnen 24 uur)? Ja O Neen O
   Zo ja, hoeveel aanvallen in het cluster: _____ Tel bij >3 aanvallen, slechts de helft van de aanvallen.
3. Selecteer de juiste aanvalsfrequentie:
   a. 7 of meer aanvallen/maand = 33 (+ 3 p. voor elke extra aanval)
   b. 6 aanvallen/maand = 30
   c. 5 aanvallen/maand = 28
   d. 4 aanvallen/maand = 25
   e. 3 aanvallen/maand = 23
   f. 2 aanvallen/maand = 20
   g. 1 aanval/maand = 15
   h. Eén aanval in 1-3 maanden = 13
   i. Minder dan 1 aanval in 3 maanden = 10
   j. Aanvalsvrij = 0

   Score _____
4. Worden de aanvallen door niet-alledaagse, vermijdbare factoren geprovoceerd (slaapgebrek, alcohol, ziekte, vermoeidheid, etc.)? Ja O Neen O
   Indien ja, reduceer de IS met 50%. Score _____
5. Vinden de aanvallen plaats in een cyclisch of diurnaal ritme?
   Dus alleen s'nachts of vroeg in ochtend ? Ja O Neen O
   Indien ja, reduceer de IS met 40%. Score _____
6. Kan de patiënt binnen 15 minuten na de aanval weer op het oude niveau functioneren ?
   Ja O Neen O Indien ja, reduceer de IS met 50 % Score _____

Score C _____

Score A + score B + score C = SA score

Neurotoxiciteits schaal

Instructies: alle toxiciteit wordt gescoord in verhouding met wat normaal was voor deze patiënt voor de start van deze medicatie. Wijzig de medicatie niet wanneer er toxiciteit optreedt bij hoge serumspiegels, maar reduceer de dosis. Omcirkel die scores die van toepassing zijn op deze patiënt en vul deze in op de scorelijn. Vul nul-waarde in wanneer betreffende toxiciteit niet aanwezig is.

		Score	
1. Diplopie:	a. Intermitterend	15	
	b. Constant	30	____
2. Nystagmus (niet eindpunt):	a. Horizontaal	5	
	b. Verticaal	10	____
3. Dysartrie: a. Mild (intermitterend slurring):		5	
b. Matig (constant slurring, geen moeilijkheden met communicatie)		10	
c. Ernstig (moeilijk te verstaan indien onderwerp onbekend)		30	____
4. Looppatroon, normaal lopen: a. Lichte ataxie (traagheid of onstabiel draaien)		5	
b. Milde ataxie (loopt schommelend, moeite met lopen)		15	
c. Redelijke mate van ataxie (redelijk onstabiel, loopt breed-basisch; neiging naar een of andere kant te vallen)		25	
d. Ernstige loopstoornis (kan alleen met assistentie lopen; onstabiel zitten)		50	____
5. Snelle alternerende bewegingen (hand op knie; beurtelings aanraken; slordig)		15	____
6. Intentie-tremor (vinger-neus-proef met ogen open/dicht)			
a. Mild (tremor; vingers missen de neus soms)		10	
b. Redelijk (grote tremor; vingers missen neus meestal)		25	
c. Redelijk ernstig (frequente of constante tremor)		35	
d. Ernstig (verstoort dagelijks functioneren: eten, schrijven, werk)		50	____
Vul totaal in voor items 1-6 (indien > 1 score, dan delen door 2)			____
7. Sedatie (bewustzijnsniveau)			
a. Lethargisch in vroege AM of PM		5	
b. Af en toe slaperig overdag		10	
c. Vaak moeilijkheden wakker te blijven		25	
d. Stuporeus		50	____
8. Affect en stemming (depressie; gespannen/agitatie; woede/hostiliteit; energierijk/ prikkelbaarheid; moeheid/apathie; verwardheid/gedachtestoornis)			
a. Mild (stoornis herkend door patiënt, maar interfereert niet met gewone leven)		5	
b. Redelijk ernstig (stemmingstoornis resulteert in verminderd presteren)		15	
c. Ernstig (continue of bijna continue stemmingsstoornis interfererend met normale leven)		50	____
9. Cognitief functioneren (attentie en concentratie)			
a. Mild (stoornis herkend door patiënt, maar interfereert niet met gewone leven)		5	
b. Redelijk ernstig (stoornis resulteert in verminderd presteren)		10	
c. Ernstig (continue of bijna continue stoornis interfererend met normale leven)		50	____

10. Duizeligheid/licht in het hoofd (vul '0' in als absent)		Soms na med.	Vaak na med.	Vaak over-dag
a. Mild (symptomen herkenbaar, maar beïnvloedt niet normale leven)	3	5	10	
b. Redelijk ernstig (resulteert in verminderd presteren)	5	10	25	
c. Ernstig (interfereert met alle dagelijkse activiteiten)	10	25	50___	

11. Hoofdpijn (vul '0' in als absent)		Soms na med.	Vaak na med.	Vaak over-dag
a. Mild (symptomen herkenbaar, maar beïnvloedt niet normale leven)	3	5	10	
b. Redelijk ernstig (resulteert in verminderd presteren)	5	10	25	
c. Ernstig (interfereert met alle dagelijkse activiteiten)	10	25	50___	

12. Andere neurotoxiciteit (beschrijf):_____ ____

Neurotoxiciteits Score (som 7 to 13) **Totaal score** ____

Systemische Toxiciteits Schaal

Instructies: alle toxiciteit wordt gescoord in verhouding met wat normaal was voor deze patiënt voor de start van deze medicatie. Wijzig de medicatie niet wanneer er toxiciteit optreedt bij hoge serumspiegels, maar reduceer de dosis. Omcirkel die scores die van toepassing zijn op deze patiënt en vul deze in op de scorelijn. Vul nul-waarde in wanneer betreffende toxiciteit niet aanwezig is.

	Score				
1. Heeft de patiënt medicijn-gerelateerde gastro-intestinale problemen ? (Vul de hoogste toepasselijke score in; vul '0' in als categorieën niet van toepassing zijn)		Ongemak	Nausea	Braken	Ander
a. Voorbijgaand of soms na medicatie		3	5	10	___
b. Vaak na medicatie		5	10	25	___
c. Vaak overdag	10	25	50	___	
					____
2. Heeft de patiënt problemen van het hematopoietische systeem ? (Vul score in bij elke categorie; vul '0' in als categorieën niet van toepassing zijn)					
a. Verlaagd trombocyten getal < 75,000 (scoor 25; scoor 50 als medicatie gestaakt)					____
a. Verlaagd leukocyten getal < 2,000 (scoor 25; scoor 50 als medicatie gestaakt)					____
c. Andere hematologische problemen: _____					____
					____
3. Heeft de patiënt dermatologische problemen t.g.v. de medicatie ?					
a. Voorbijgaande gegeneraliseerde maculopapulaire uitslag (reagerend op behandeling)	15				
b. Ernstige gegeneraliseerde maculopapulaire uitslag (niet reagerend op behandeling)	50				
c. Acne op gelaat, romp en extremiteiten				10	
d. Ernstige acne, excessief en lastig voor de patiënt				30	____
4. Heeft de patiënt potentie of libido problemen t.g.v. de medicatie ?					
a. Voorbijgaand, soms en tolerabel	20				
b. Continu of intolerabel	50				____
5. Heeft de patiënt een hyponatriëmie met serum natrium < 120 mmol/l ? Zo ja, scoor 50					____
6. Heeft de patiënt gestoorde lever-waarden (ASAT, ALAT) t.g.v. de medicatie?					
a. Ja, onder observatie				25	
b. Ja, medicijn gestaakt				50	____
7. Is het gewicht van de patiënt toegenomen door verhoogde eetlust t.g.v. de medicatie ?					
Gewichtstoename: gering (2-3 kg)				3	
redelijk (3-6 kg)				10	
groot (> 6 kg)				20	
					____
8. Heeft de patiënt veranderingen bemerkt n de hoeveelheid en toestand van het haar ?					
a. Haarverlies: mild (haar in kam)				5	
redelijk ernstig (zichtbaar dunner of stukken haar in kam)	20				
ernstig (zichtbare alopecia of zeer lastig voor de patiënt)	50				
b. Verandering in toestand van het haar (grof, sluik, gekruld)	5				
c. Hirsutisme: redelijk ernstig (op gelaat, romp en extremiteiten)				20	
ernstig (excessief en lastig voor de patiënt)	50				____
9. Andere systemische toxiciteit (beschrijf): _____					____
Systemische Toxiciteits score				**Totaal score**	__

Dankwoord

Allereerst wil ik de werkgroep epilepsie, tegenwoordig omgedoopt in Nijmegen Epilepsy Research Group, bedanken dat ze mij als net afgestudeerde arts hebben binnengehaald in Nijmegen en mij met grote inzet en kunde hebben begeleid. Deze groep bestond bij mijn komst uit vier heren (een epileptoloog, een apotheker, een neuroloog en een kinderneuroloog) en deze diversiteit was zeer vruchtbaar.

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Curriculum vitae

Charles Deckers was born in Eindhoven, the Netherlands, on January 22, 1968. He graduated from the van Maerlantlyceum (high school) in 1986 and started studying medicine at the University of Leiden in that same year.

In 1990 he participated in research projects of the Department of Anaesthesiology of the University of Utah Medical Centre in Salt Lake City (professor Th. Stanley, M.D.) for six months. During that period, he was particularly involved in human drug studies and in studies on drug administration via the buccal mucosa. During the last four months of 1990 he did a laboratory project in the Department of Immunohematology of the Leiden University Medical Centre (prof. F.J. Claes), trying to find certain mismatches that had caused patients to reject their kidney-transplants.

For his graduation project he worked in the Department of Immunobiology of the University of Edinburgh Scotland (A.H. Maddy) from September 1991-July 1992, studying the morphological and biochemical changes murine thymus cells underwent during the process of apoptosis. In December 1994 he graduated form medical school.

From April till June 1995 he worked as a resident in the department of Neurology of the Nijmegen University Medical Centre (prof. G.W.A.M. Padberg, M.D.), where after he started his doctoral research project titled "Comparison of the value of monotherapy and polytherapy with AEDs" (promotor: prof. Meinardi, M.D.). This was a project of the Nijmegen Epilepsy Workgroup (which has now been re-named Nijmegen Epilepsy Research Group or NERG), funded by the Dutch National Epilepsy Fund (NEF).

As from September 1, he is partly employed as a resident by the Heemstaete epilepsy clinic in Zwolle (which is part of the Stichting Epilepsie Instellingen Nederland) and partly employed as a research fellow of the Department of Clinical Pharmacy of the Nijmegen University Medical Centre (prof. Y.A. Hekster), working on NERG-projects.

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