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REVIEW ARTICLE

Pharmacotherapy of epilepsy: state of the art and developments

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SUMMARY

***Purpose*: A discussion of modern day practice and new developments in antiepileptic drug treatment.**
***Contents*: Important principles of antiepileptic therapy are addressed—starting with antiepileptic drug therapy, pharmacokinetics and pharmacodynamics, therapeutic drug monitoring, drug-induced adverse effects and the withdrawal of antiepileptic drugs. Furthermore, the pathophysiology of focal and generalized epilepsies and the mechanism of action of several antiepileptic drugs are briefly reviewed. Modern treatment algorithms for different types of epileptic seizures are presented.**

A significant development is the introduction of new antiepileptic drugs and particularly of those drugs that have been developed according to the latest insights into pathophysiology. Also of interest is the increased focus on adverse effects and on quality of life. Partly due to these developments, combining antiepileptic drugs has received renewed attention in an attempt to maintain effective seizure control but with a reduction of adverse effects.

INTRODUCTION

Epilepsy is a common disorder, with an estimated prevalence of 6·8–10·3 per 1000 residents (1, 2). Correspondingly, a recent survey revealed that 0·89% of the population uses antiepileptic drugs (AEDs). The drugs most frequently prescribed now are carbamazepine, valproate and phenytoin (3). Although AEDs are also prescribed for other indications, unpublished data show that this proportion does not surmount 30%.

Epileptic seizures can be caused by any disease that brings about damage to the brain, such as a brain tumour, head trauma or cerebrovascular accident. Epilepsy, however, is not necessarily a symptom of another disorder, it may also be idiopathic or genetically determined. The relative contributions of various causes of epilepsy have been estimated in the Rochester Epidemiology Project, for example 68% of epilepsy cases are presumed to be idiopathic and 55% of newly diagnosed cases in patients over 65 years of age are attributed to cerebrovascular disease (4). Because of the variety in aetiologies and epilepsy syndromes, three diagnostic levels have been delineated: (i) aetiological diagnosis, (ii) seizure diagnosis and (iii) epilepsy syndrome diagnosis. The first level provides guidance as to whether therapeutic action should be taken against an underlying cause, and if so what kind of action. The second level (i.e. seizure classification) is essential for choosing the correct antiepileptic drug. The last level provides insight into prognosis and duration of therapy.

The aim of AED therapy is to achieve remission of seizures without the occurrence of (unacceptable) adverse effects. In other words, an antiepileptic drug has to combine good efficacy with a large therapeutic window. The adverse effects caused by AEDs are receiving more attention in epilepsy treatment research, especially the cognitive effects. The extent of these cognitive impairments was only fully recognized after methods for the detection of neuropsychological effects had improved. In addition, as in other areas of modern medicine, quality of life (QoL) has become a major issue. Some of the new AEDs, such as lamotrigin, have been found to have a positive effect on QoL (5).

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In this article the pathophysiology of focal and generalized epilepsies and the mechanisms of action of frequently prescribed AEDs will be briefly reviewed. The indications for these different drugs and important principles of the treatment of epilepsy patients will be discussed and modern treatment algorithms for AED selection presented.

PATHOPHYSIOLOGY

Epilepsy is not a separate disease entity but an umbrella term for a group of syndromes, as is shown by the international classification of epilepsies and epilepsy syndromes (Table 1) (6). Although basic mechanisms do not play a role in the definition of these syndromes, in recent years research has revealed considerable differences in their pathophysiologies (7).

Key to all epilepsies, however, are the periods of hypersynchronous neuronal activity in one or more parts of the brain. In the 'focal epilepsies' neurones in a certain brain area spontaneously develop so-called 'bursts' or series of action potentials. In these cells, a short depolarization can open up calcium channels, which leads to a long and large depolarization period and a series of action potentials, i.e. a burst. Intrinsic bursts especially arise in layers IV and V of the neocortex and in the hippocampus. Bursts increase the probability that the postsynaptic neurone will discharge, because the numerous presynaptic action potentials increase the excitatory (depolarizing) postsynaptic potential (EPSP). Thus a giant EPSP or a paroxysmal depolarization shift (PDS) can develop in the 'epileptic neurone'. However, one burst in a single neurone does not result in an epileptic discharge. Through a network of interneuronal connections bursts can cause hypersynchronization, in which a large group of neurones discharge simultaneously. This leads to a functional impairment: the focal epileptic seizure.

Several physiological mechanisms prevent continuous discharges and the development of hypersynchronuous discharges in brain areas. Interneurones, for example, release the neurotransmitter γ-aminobutyric-acid (GABA). Attachment of GABA to the postsynaptic receptor causes an inhibitory (i.e. hyperpolarizing) postsynaptic potential ('IPSP'), which counteracts the development of postsynaptic action potentials. Hyperpolarization also inhibits the occurrence of bursts and PDS. Glutamate, an excitatory neurotransmitter, conversely, activates receptors to increase the production of bursts by neurones.

The origin of seizures in primary generalized epilepsy differs from the aforementioned focal epilepsy. In absence epilepsy, for example, a generalized cortical synchronization of spike-wave complexes appears on the electroencephalogram (EEG) with a typical frequency of 3 Hz. Thalamic neurones normally discharge to cortical neurones continuously. This regularity results from a balance between GABAergic inhibition and a voltage dependent, low-threshold calcium current, through the T-type calcium channel. In absence epilepsy the latter current is increased and acts as a pacemaker for the 3 Hz rhythmic spike-wave pattern. Drugs which block this type of calcium channel, such as ethosuximide, valproate and trimethadione can be prescribed to patients with absences.

MECHANISM OF ACTION OF ANTIEPILEPTIC DRUGS

Knowledge of the mechanism of action of the available AEDs could point the way to the development of more effective and less toxic drugs. Regrettably the information is fragmentary. In the past attention was centred on the effects on cell metabolism and neuronal membrane changes. Now the focus is on two other aspects:

(i) important neurotransmitters, such as the inhibition of glutamate-mediated excitation, or amplifying GABA-mediated inhibition, and
(ii) direct electrochemical transport by ion-channels.

Obviously these are not independent processes. Lamotrigin, for example, inhibits glutamate release by its influence on voltage dependent sodium channels. The sodium, calcium and potassium channels play an important role in the spread of action potentials and are often interdependent and voltage dependent. The voltage dependent T-type calcium channel mentioned earlier is an important factor for the rhythmic activity of the relay neurones in the thalamus.

The chloride channel determines the passage of chloride into the cell and thus influences the polarization of the neurone. The state of this channel is adjusted through receptors for GABA, benzodiazepines, phenobarbital and convulsants such as bicucullin. Phenobarbital and benzodiazepines facilitate the effects of GABA by opening the channel longer and more frequently, respectively.

Table 1. International classification of epilepsies and epileptic syndromes

1.	Localization related (focal, local, partial) epilepsies and syndromes
1.1.	Idiopathic (with age-related onset)
	Benign childhood epilepsy with centro-temporal spike
	Childhood epilepsy with occipital paroxysms
	Primary reading epilepsy
1.2.	Symptomatic
	Chronic epilepsia partialis continua (Kojewnikow's syndrome)
	Syndromes characterized by seizures with specific modes of precipitation (for example visual)
	Temporal lobe epilepsies, frontal lobe epilepsies, occipital lobe epilepsies, parietal lobe epilepsies
1.3.	Cryptogenic
	Presumed to be symptomatic, however, the aetiology is unknown
2.	Generalized epilepsies and syndromes
2.1.	Idiopathic (with age-related onset; listed in order of age)
	Benign neonatal familial convulsions
	Benign neonatal convulsions
	Benign myoclonic epilepsy in infancy
	Childhood absence epilepsy (pyknolepsy)
	Juvenile absence epilepsy
	Juvenile myoclonic epilepsy (impulsive petit-mal)
	Epilepsy with generalized tonic-clonic seizures (GTCS) on awakening
	Epilepsies with seizures precipitated by specific modes of activation (for example visual)
2.2.	Cryptogenic or symptomatic
	West syndrome (infantile spasms, Blitz-Nick-Salaam-Krämpfen)
	Lennox–Gastaut syndrome
	Epilepsy with myoclonic-astatic seizures
	Epilepsy met myoclonic absences
2.3.	Symptomatic
	2.3.1. Non-specific aetiology
	Early myoclonic encephalopathy
	Early infantile epileptic encephalopathy with suppression burst
	Other symptomatic generalized epilepsies not defined above
	2.3.2. Specific syndromes
	Diseases in which seizures are a presenting or predominant feature
3.	Epilepsies and syndromes undetermined whether focal or generalized
3.1.	With both generalized and focal seizures
	Neonatal seizures
	Severe myoclonic epilepsy in infancy
	Epilepsy with continuous spike waves during slow wave sleep
	Acquired epileptic aphasia (Landau–Kleffner syndrome)
	Other undetermined epilepsies not defined above
3.2.	With unequivocal generalized or focal features
	All cases with GTCS in which clinical and EEG findings do not permit as clearly generalized or localization related.
4.	Special syndromes
4.1.	Situation-related seizures (Gelegenheitsanfälle)
	Febrile convulsions
	Isolated seizures or status epilepticus
	Seizures occurring only when there is an acute metabolic or toxic event due to factors such as alcohol, drugs, eclampsia, non-ketotic hyperglycaemia

The pharmaceuticals in use as AEDs can have several mechanisms of action. Valproate, like carbamazepine and phenytoin, blocks sodium channels, but it also inhibits GABA metabolization and may have an effect on T-type calcium channels as well.

It is beyond the scope of this article to discuss the current vision on the mechanisms of all AEDs. Interested readers are referred to the chapter on this subject by Macdonald and Meldrum in the fourth edition of *Antiepileptic Drugs* (8).

STARTING ANTIEPILEPTIC DRUGS

Prior to starting AED treatment, it is essential for the physician to discriminate between epileptic and non-epileptic attacks. Non-epileptic attacks may be organic, for example through a cardiac cause, or psychogenic. The latter attacks are sometimes, rather negatively, called 'pseudo-seizures' (9). A correct diagnosis will prevent the patient from being wrongly treated for epilepsy; a diagnosis and treatment with serious medical and social consequences.

After a first seizure one would normally not prescribe AEDs, as it is very well possible that no other seizures will follow. The typical risk of seizure recurrence after a single unprovoked seizure is 40% (10). Starting AEDs after a first unprovoked seizure, irrespective of EEG or CT abnormalities, reduces the risk of a second seizure by half, but does not appear to alter the prognosis of epilepsy (10, 11). Furthermore, starting AEDs has a great impact on people's lives, such as the prospect of having to take medication for at least 2 years and the possibility of adverse effects.

Hence it is necessary to determine the risk of a second seizure for each individual patient and weigh this risk against the disadvantages of AED treatment. The EEG and the CT-scan play an important role in determining the risk of seizure recurrence. In a recent study a routine-EEG, and when necessary a sleep deprivation EEG, were made in 157 patients after a first idiopathic seizure (12). After 1–2 years, seizures had occurred in 83% of the patients who had epileptiform discharges on the EEGs, 41% in patients with nonepileptic abnormalities and 12% in patients with two normal EEGs. This does offer support for a decisive role for the EEG in whether or not to start AEDs after a first idiopathic seizure. In the Netherlands many physicians start drug treatment when epileptiform discharges are found on the EEG after a first unprovoked seizure, however, this is not common practice in all European countries. Furthermore, it is also important to note that the absence of abnormalities on several EEGs does not rule out epilepsy or the recurrence of seizures.

The existence of certain abnormalities on the CT-scan offers further support to a decision to start AEDs. The probability of a second seizure is increased, for example, in case of brain tumours (13). New advanced radiographic techniques such as the MRI- and the PET-scan are more sensitive in detecting an epileptogenic focus from which seizures arise. These techniques are particularly of use in decisions about whether surgical treatment will be of benefit.

CLASSIFICATION AND CHOICE OF DRUG

As mentioned in the introduction, seizure type will generally determine which drug to prescribe. Nevertheless, classification of the epilepsy syndrome is also important. The treatment of generalized tonic-clonic seizures with carbamazepine in idiopathic generalized epilepsy instead of in partial epilepsy, for example, does carry the risk of provoking absence seizures to occur. The international classification of epileptic seizures is shown in Table 2 (14). Depending on the individual patient, treatment policy is determined step by step, as shown in Figure 1. Different treatment algorithms apply to partial seizures, generalized seizures and absence seizures. Furthermore, antiepileptic drug selection depends on toxicity profile, pharmacokinetic properties, special patient characteristics, drug interactions and cost of treatment. For example, valproate is not given to pregnant women because of the increased risk of spina bifida. Because of its risk of causing hyponatremia, carbamazepine may be inappropriate for use in patients who use drugs that also may lead to hyponatremia (lithium, diuretics, etc.) (15).

Since the end of the 1970s it has been customary to start treatment of epilepsy with one drug (monotherapy) (16). The dose of this drug is gradually increased until adequate seizure suppression is established. When this fails due to lack of effect or to the occurrence of adverse effects, a second drug is given as monotherapy. Because the first drug should not be withdrawn abruptly for fear of withdrawal seizures, the second drug should initially be given as add-on therapy, after which the first drug is gradually phased out. The expected advantage of monotherapy should

Table 2. The International Classification of Epileptic Seizures (14)

I.	Partial (focal, local) seizures (local onset; consciousness impaired or not?)
	(a) Simple partial seizures (consciousness not impaired; local contralateral discharge)
	(b) Complex partial (consciousness impaired; may start as simple partial seizure; frequently bilateral discharge)
	(c) Partial seizures evolving to secondary generalized seizures (above discharges become generalized)
*II.	Generalized seizures (bilateral and without local onset; consciousness may be impaired)
	(a) Absence seizures (3 Hz spike and slow wave ictal EEG pattern)
	(b) Myoclonic seizures (polyspike and wave ictal and interictal EEG pattern)
	(c) Clonic seizures (ictal EEG: fast activity and waves)
	(d) Tonic seizures (ictal EEG: fast activity or fast rhythm)
	(e) Tonic-clonic seizures (tonic phase: fast rhythm; clonic phase: slow waves)
	(f) Atonic seizures (ictal EEG: polyspike and wave or flattening or low-voltage fast activity)
III.	Unclassified seizures (seizures that cannot be classified because of incomplete data or because they defy classification in hitherto described categories)

*Combinations may occur: for example b and f.

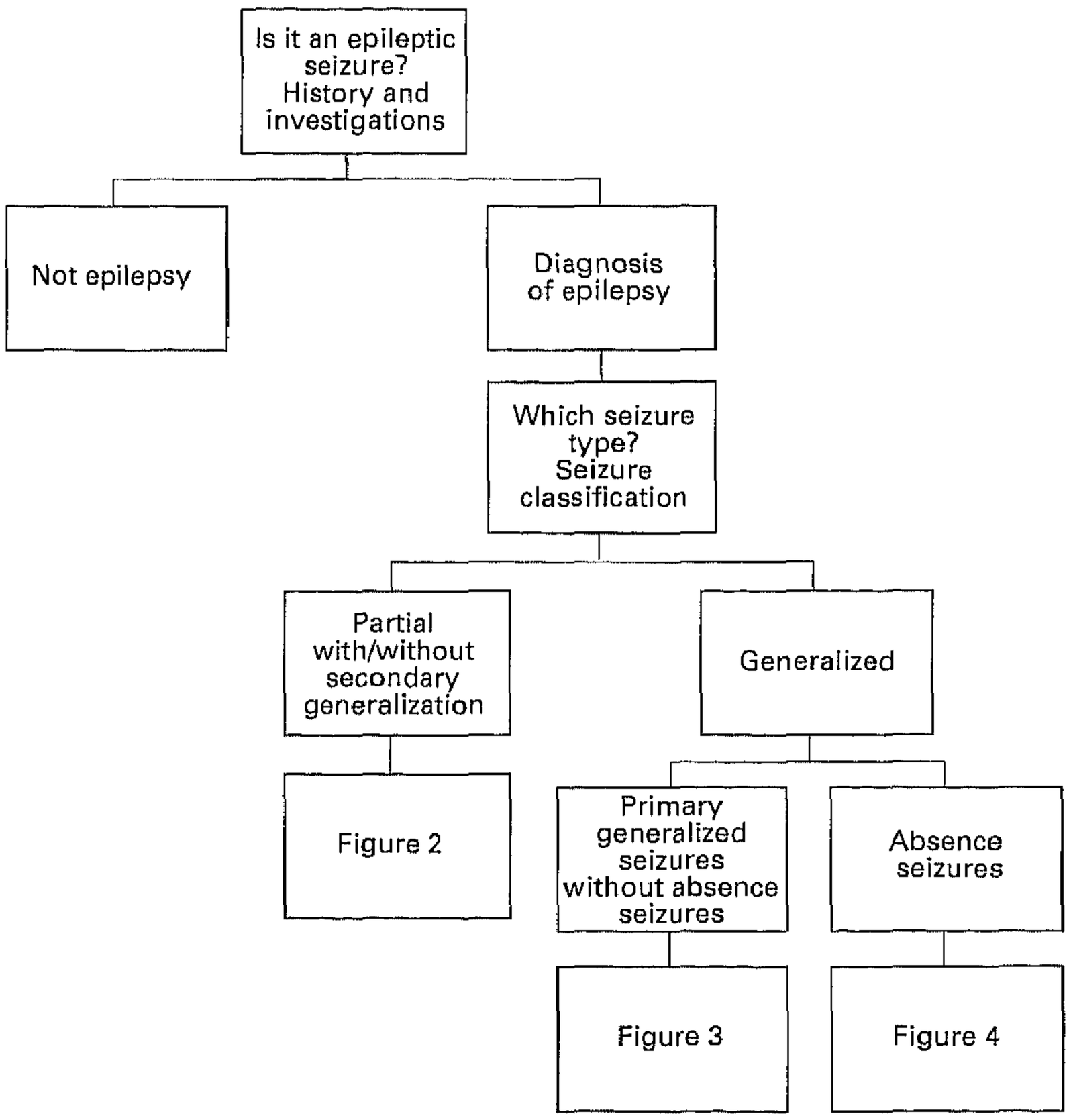

Fig. 1. Diagnosis and classification of epileptic seizures.

be carefully explained to the patient, otherwise if seizure freedom is reached somewhere en route of withdrawing the old and introducing the new drug the patient may wish to stop further changes and continue with the combination.

If the results accomplished with the second monotherapy regimen are again unsatisfactory, duotherapy is the next option. The original first drug may be added, however, usually another AED will be chosen. When AED treatment is not successful, it is advisable

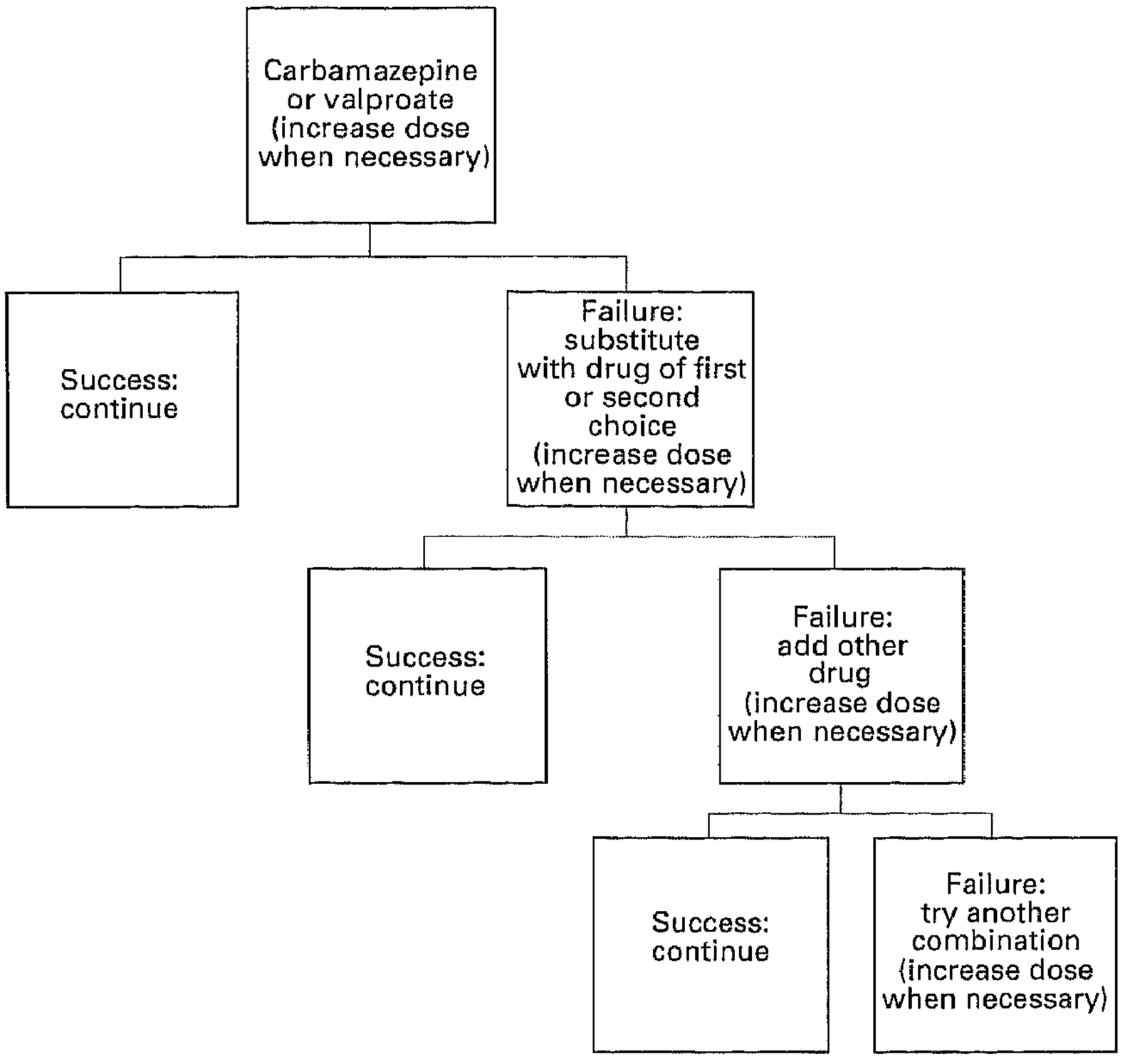

Fig. 2. Partial seizures with or without secondary generalization.

to check the diagnosis (at all three delineated levels) at some point.

When a second drug is added this increases the total drug load, just as a dose increase in monotherapy would do. A method to calculate drug load is the prescribed daily dose/defined daily dose (PDD/DDD) ratio. This a ratio of the actual dose taken and the average therapeutic dose. Thus normalized, the drug loads of constituent drugs in a polytherapy regimen can be added up to determine the total drug load of that regimen. A patient receiving 2000 mg of carbamazepine and a patient receiving 800 mg of carbamazepine plus 1800 mg of valproate both have a total drug load of 2 PDD/DDD (17).

Partial epilepsy

For all syndromes with local-onset seizures, whether they are signs of a symptomatic, cryptogenic or (rare) idiopathic epilepsy, the drugs of first choice are carbamazepine or valproate (Fig. 2). Whether valproate is as effective as carbamazepine for complex partial seizures is an ongoing debate. Mattson *et al.* found carbamazepine to be superior to valproate for complex partial seizures, but they did not study only newly diagnosed patients and used much higher dosages of the two drugs than usual (18). In several European studies no difference in efficacy was found for complex partial seizures, however, these studies used only one efficacy parameter and had smaller patient numbers (19, 20). The trials do agree on equal effectiveness for secondary generalized seizures. Phenytoin is as effective as carbamazepine and possibly valproate in treatment of seizures, but has a more unfavourable toxicity profile (21, 22). Oxcarbazepine is a good alternative for carbamazepine, certainly in cases of carbamazepine hypersensitivity or when very high dosages are needed (23).

If a first monotherapy regimen fails, one can choose the other drug of first choice or a drug of second choice, depending on the individual patient. Drugs of second choice are vigabatrin, oxcarbazepine, lamotrigin, phenytoin and acetazolamide, although the latter is rarely used in monotherapy (16). Today phenobarbital is very seldomly used in the Netherlands for the management of newly diagnosed patients due to its sedative effects, slow metabolization and chance of withdrawal seizures. The same disadvantages apply to primidone, of which the active metabolite phenobarbital, and not

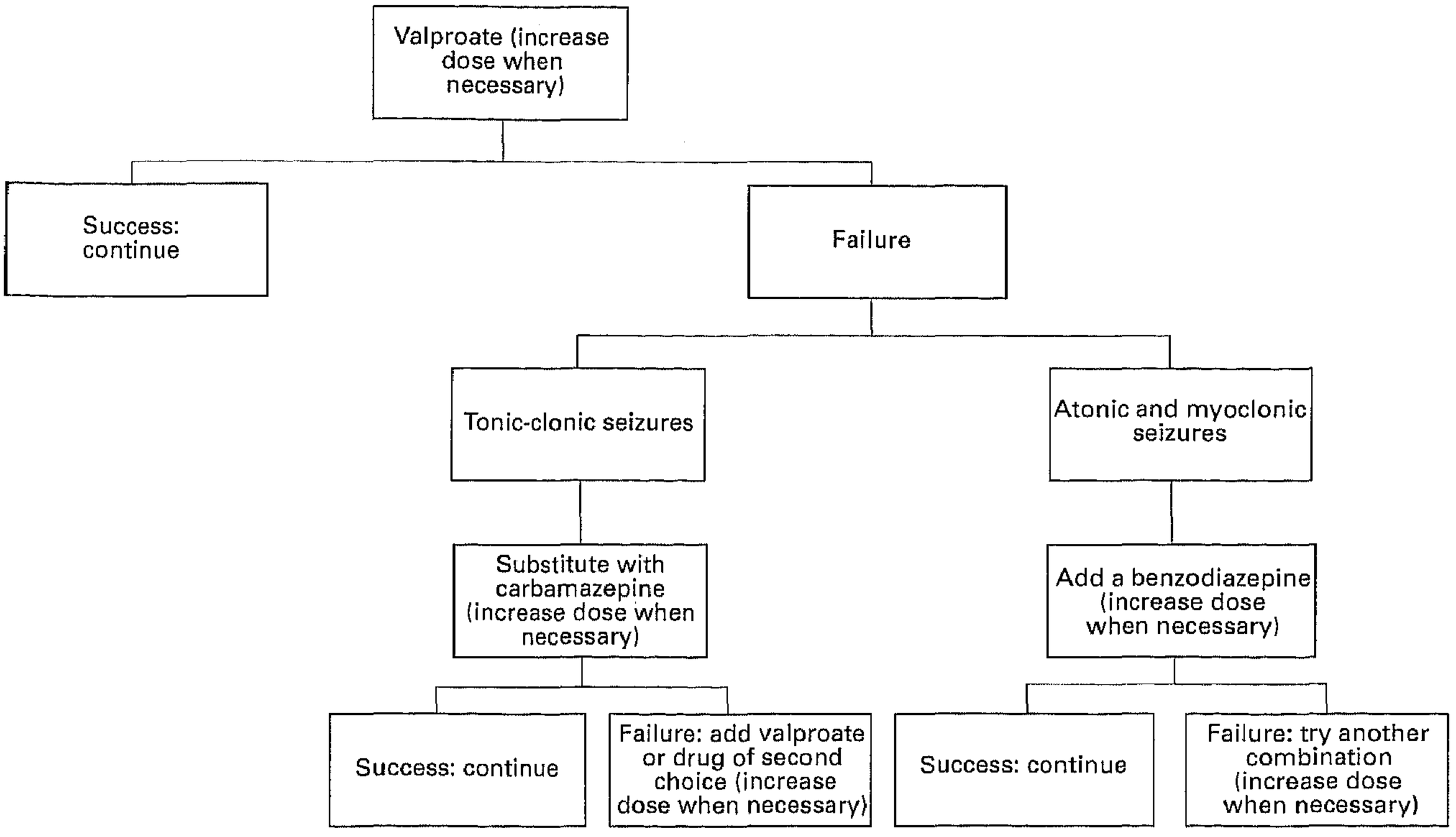

Fig. 3. Generalized seizures (not absence seizures).

phenylethyl-malonimide (PEMA), is probably mainly responsible for its seizure suppression.

To what extent lamotrigin will play a role in the Netherlands is uncertain, however it is used frequently in other countries. Due to its lack of teratogenicity in animals, it is often prescribed in the U.K. for women who want to become pregnant. Felbamate (phenylpropanediol-carbamate, a substance related to the tranquillizer meprobamate) is a new antiepileptic drug that has proven to be reasonably effective in the treatment of partial seizures. Regrettably, idiosyncratic reactions due to felbamate use are reported relatively frequently (aplastic anaemia, hepatotoxicity), leading to its use being restricted to emergency situations such as intractable cases of Lennox–Gastaut syndrome (although this is a symptomatic generalized epilepsy, strictly speaking, it is probable that many patients in fact have a multifocal partial epilepsy). New AEDs may be tried as monotherapy in patients in which they are successful as add-on medication.

Idiopathic generalized epilepsy

For idiopathic generalized epilepsy the drug of first choice is valproate, as is shown in Figure 3. When valproate fails, clobazam or possibly phenobarbital may be tried for atonic and myoclonic seizures. In cases of generalized tonic-clonic seizures carbamazepine or possibly phenytoin may also be chosen, although one should be aware of the danger of provoking absence seizures with these two drugs. In absence epilepsies (Fig. 4) one should start with either valproate or ethosuximide (24). When ethosuximide monotherapy is given the absences are often adequately suppressed, but generalized tonic-clonic seizures are not suppressed and may even be provoked.

Symptomatic or cryptogenic generalized epilepsy

In general, corticosteroids or ACTH are given as first treatment to patients with cryptogenic West syndrome (see Table 1), although high-dose valproate is another possibility and is recommended for symptomatic cases (25). Vigabatrin has also been shown to be effective in certain cases, especially when West syndrome develops in children with tuberous sclerosis (this is an inherited disorder located on chromosome 9, which expresses itself through epilepsy, mental retardation, cutaneous adenomata sebacea and tubers of

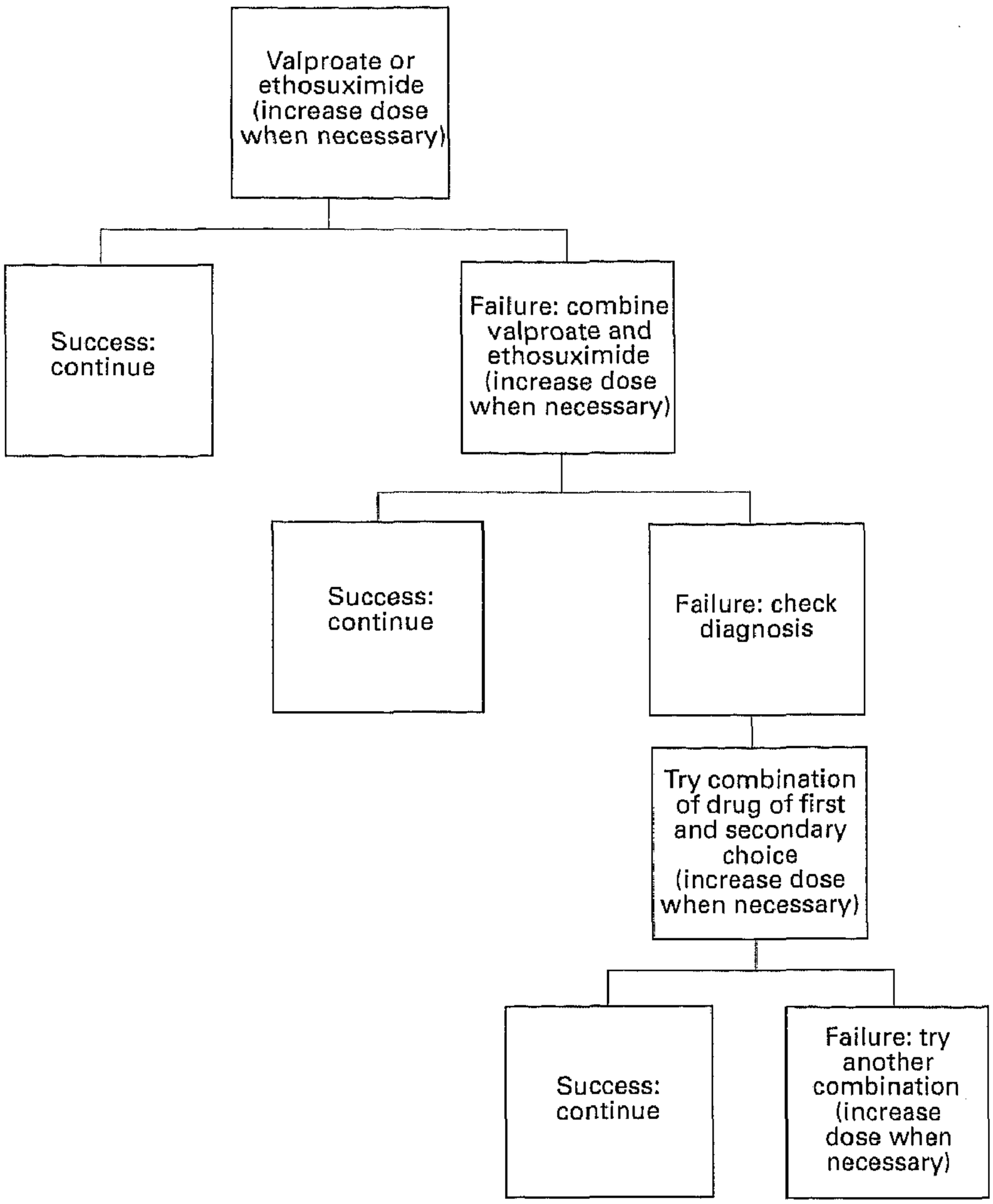

Fig. 4. Absence seizures.

swollen neurones and astroglia in cerebro. Synonym: M. Bourneville). Nitrazepam is also used for this syndrome, however, as with all benzodiazepines functional (dynamic) tolerance may develop.

For all other cryptogenic or symptomatic syndromes the therapeutic regimen is much more complicated. As mentioned before, Lennox–Gastaut syndrome often presents itself with a mixture of different types of generalized and partial seizures. Valproate has the broadest spectrum of action, hence may be given as a first drug. When partial and generalized tonic-clonic seizures predominate, carbamazepine and phenytoin are other options. In cases of myoclonic and absence seizures benzodiazepines should be part of the regimen, again with the risk of developing tolerance. Recently, favourable reports have appeared about the use of lamotrigin (26). An additional advantage of this drug is the positive effect of this drug on mood (5), however, a systematic study of its effectiveness in this syndrome has yet to appear. In many patients satisfactory seizure control can only be established with a combination of AEDs (27).

STATUS EPILEPTICUS

Status epilepticus is a series of continuing epileptic seizures lasting at least 30 min, which may even be the first manifestation of epilepsy. Every type of seizure may develop into a status epilepticus. Although the type of seizure may be used to characterize the status, usually only convulsive and non-convulsive status epilepticus are discriminated. Especially the convulsive status epilepticus carries the risk of mortality and serious remaining morbidity. First action to be taken, when a status is suspected, is the administration of a diazepam rectiole, aiming at a dose of 0·3 mg/kg.

When the status is not terminated 10 min after the rectiole has been administered or when the cause of the status so determines, the patient needs to be transported to a hospital. Dependent on the expected duration and type of transport a second rectiole may be given.

PHARMACOKINETICS AND DYNAMICS

Knowledge of the pharmacokinetic properties of AEDs is important for several reasons (28). It is necessary for the determination of dosage intervals, timing of drug monitoring, the use of co-medication and for acute interventions, such as the treatment of a status epilepticus. Important information of frequently used AEDs is listed in Table 3 (8, 16, 29, 30). Although a linear relationship exists between dose and serum level for some AEDs, this relationship is often complicated by interindividual differences in absorption and metabolism. Other AEDs do not have clear dose–serum level relationships; the metabolism of phenytoin for example is saturable, hence above a certain concentration only a limited amount of the drug can be metabolized (31). This is relevant when the dose needs to be adjusted, because it requires monitoring of the serum level.

Active metabolites are formed in the transformation of several AEDs, especially of carbamazepine and primidone (32). These metabolites contribute to seizure control, but may lead to (possibly hazardous) adverse effects.

When an AED is combined with other drugs, also with other AEDs, the metabolism of these drugs may be changed. Phenytoin, phenobarbital and carbamazepine for example induce hepatic enzymes and thus, indirectly, decrease the serum levels of oral anticoagulants, oestrogens and progestagens (cave anticonception!), vitamin D, as well as their own serum level and the serum level of other AEDs (33). Valproate inhibits hydroxylases and thus delays the elimination of all sorts of pharmaceuticals, including other AEDs.

With regard to pharmacodynamics one has to keep in mind that some AEDs have a narrow therapeutic window. This means that for a patient whose seizures are poorly controlled, there is not much room for dosage increase of that AED. The variation in epilepsy severity between patients and syndromes also contributes to the non-transparent relationship between dose or serum level on the one hand and seizure control on the other. Unexplained phenomena remain, such as the fact that the effect of valproate lasts longer than serum levels would suggest and that, although the elimination half-life suggests otherwise, once-daily dosing is feasible and effective (16).

DRUG MONITORING

Use of drug monitoring is somewhat controversial, but is useful when rationally employed. Drug monitoring is used because serum levels often cannot be predicted from drug dosages. However, serum levels appear to be only of relative use, because the effect of a certain serum level (like the dose) can differ greatly from person to person.

Hence it is not justified to increase drug dose based on a sub-therapeutic serum level when the patient's seizures are controlled. In case of an 'easy to control' epilepsy a low serum level may be sufficient. When seizures are not suppressed despite high dosages, some authors argue to increase dosages until adequate control is achieved or adverse effects arise (34). However, the *primum nil nocere* (i.e. most important is not to cause harm) applies here. A high serum level in the toxic range is a warning signal that adverse effects are likely to develop. Certainly when the toxic range is reached with a first AED, it is wise to change medication before adverse effects arise, otherwise the patient may become reluctant to use AEDs.

When patients use several drugs, whether or not they use several AEDs, drug monitoring can reveal pharmacokinetic interactions. Serum levels are also employed to confirm compliance, when the seizure frequency remains elevated despite dose increases. Drug monitoring, furthermore, is useful in special circumstances such as pregnancy and co-morbidity, and when pharmacokinetic conditions are changed due to polypharmacy, fever, organ function impairments, nephrodialysis, diarrhoea or hypoalbuminaemia.

In summary, principal indications for drug monitoring are: prevention of toxicity at onset of therapy, the absence of an effect despite a considerable dosage (compliance, pharmacokinetics or pharmacodynamics?), in cases of polytherapy and to detect interactions.

ADVERSE EFFECTS

In epilepsy treatment adverse effects have always played, and will continue to play, an important role. This is inherent to the paroxysmal character of

Table 3. Pharmacokinetic properties of established antiepileptic drugs

Drug	Dose (mg/day)	Therapeutic range (μg/ml)	Clinical value serum levels	Protein binding	Elimination	Half-life (adults)	Comments
Carbamazepine	400–1800 in 2–4 doses	4–12	++	75%	Liver (active metabolite)	10–30 h	Enzyme and autoinduction
Valproate	500–3000 in 1–3 doses	50–100	+ (mediocre relationship with effect)	± 90% concentration-dependent	Liver (active metabolites)	9–21 h	Enzyme inhibition
Phenytoin	15–600 in 1–2 doses	10–20	+++ (zero order kinetics)	85–90%	Liver (saturable metabolism)	9–140 h saturation kinetics	Enzyme induction
Vigabatrin	2000–4000 in 1–2 doses	No relationship with effect	−	nil	Kidney (70% unchanged in urine)	5–7 h	Few interactions; binds irreversibly to GABA-T
Phenobarbital	30–240 in 1–2 doses	10–40	+ (mediocre relationship with effect; tolerance)	45%	Liver (25% unchanged in urine)	50–160 h	Enzyme induction; sedative effect; tolerance
Ethosuximide	50–1500 in 1–2 doses	40–100	+ (safe drug)	negligible	Liver (20% unchanged in urine)	40–70 h	Fast excretion in children; no protein binding
Clonazepam	1–10 in 2–3 doses	0·002–0·006	+ (relationship with effect? tolerance)	85%	Liver (inactive metabolites)	20–40	Sedative effect; tolerance; rebound effect
Lamotrigin	50–400 in 1–2 doses	?	− (relationship with effect unclear)	55%	Liver (inactive metabolites)	8–90 h (very dependent on enzyme induction/ inhibition	In polytherapy dose adjustment needed
Oxcarbazepine	600–1800	10–35	++ (in case of polytherapy)	40%	Liver (active MHD metabolite)	8–12 for MHD metabolite	

the disease, in which the dose needed for seizure control may give rise to chronic toxicity. Antiepileptic drugs associated with many adverse effects (e.g. bromides) have become obsolete and new AEDs which involve unacceptable risks are kept out. This does not imply that the most popular AEDs, such as carbamazepine and sodium valproate are free of toxicity.

Adverse effects can be roughly divided into dose-related and non-dose-related effects. Dose-related adverse effects are mostly neurotoxic reactions, of which sedation and co-ordination problems are the most disturbing to patients. Recently, cognitive impairments are receiving growing attention—they sometimes can only be detected by psychological testing (35). Systemic toxicity is mostly not dose-related and may be very serious, such as bone marrow depression, hepatic toxicity, glomerulonephritis and dermatitis bullosa. These serious idiosyncratic effects, however, occur very infrequently, for example, 1 in 700 000 carbamazepine users will develop agranulocytosis (36). A detailed account per AED can be found in *Antiepileptic Drugs* (8).

When AEDs are started, the dose is increased gradually, because patients often experience drowsiness, sedation or gastrointestinal complaints in the first weeks of drug therapy. Some AEDs induce the action of hepatic enzymes, which leads to an increased rate of their metabolism and thus to lower serum levels and lower efficacy. The resulting elimination half-life also is important for determining dosage intervals. Because it is usually not practical to take drugs at optimal intervals, AEDs are often taken with meals. This can lead to fluctuating serum levels, regularly reaching the toxic or subtherapeutic range. This has been reported for carbamazepine by Höppener *et al.* (37). A solution is the use of sustained-release preparations.

Haemoglobin, haematocrit, thrombocytes and liver and kidney function tests are performed prior to AED therapy, to identify patients at risk for systemic adverse effects. Systematic monitoring of these values during AED therapy is controversial, because it does not predict severe idiosyncratic reactions efficiently (36, 38). Some adverse effects occur, especially in patients at risk, such as pregnant women or infants, therefore it is wise to withhold certain drugs from these patients. The risk of spina bifida and the risk of hepatotoxicity in infants are reasons not to prescribe valproate. In patients with a psychiatric history one should not prescribe vigabatrin for fear of eliciting a psychosis.

Sometimes seizure control is only reached at the cost of some adverse effects. The decision whether the balance between the reduction in seizure frequency and the occurrence of adverse effects is acceptable has to be reached by repeated consultation between physician and patient.

THE WITHDRAWAL OF ANTIEPILEPTIC DRUGS

The decision to withdraw AEDs is a difficult one, because of the chance that the seizures will return. It is possible to withdraw AEDs without seizure recurrence in 30–60% of patients (39–41). A gradual withdrawal is necessary, because an abrupt method can lead to so-called withdrawal seizures.

Unfavourable factors for the prognosis of AED withdrawal are: abnormalities during neurological examination, long period before seizure control was reached, epileptiform phenomena on the EEG and presence of tonic-clonic or myoclonic seizures before the withdrawal (42, 43). Juvenile myoclonic epilepsy is a syndrome characterized by its tendency to relapse if medication is withdrawn. Two recent randomized trials in children have demonstrated that the length of the seizure-free period does not affect the probability of remaining in remission (44, 45). Nevertheless, a seizure-free period of approximately 2 years before stopping AED treatment is customary in adults. The rate of withdrawal is also dependent on the individual drug. Phenobarbital and the benzodiazepines, for example, are notorious for withdrawal seizures, hence these drugs should be phased out very gradually.

In cases of polytherapy only one drug should be withdrawn per period, preferably starting with the least effective or most toxic drug. The period needed to reach a new steady state, which will take five times the elimination half-life, is also of importance. It is advisable to schedule a control visit after each period.

Failure of the withdrawal of AEDs is a heavy emotional strain for patients. Therefore close counselling of this process is 'good clinical practice'. The speed of AED withdrawal may thus also depend on the ability of the patient to visit the physician.

NEW DEVELOPMENTS

Not until very recently have AEDs been developed from a rational perspective. The first effective AEDs,

bromide and phenobarbital, were sedatives which were accidentally found to have an effect on seizures. The drugs which are in wide use now were also introduced without knowledge of their mechanisms of action.

Increased insight into the pathophysiologies of the epilepsies opens up new possibilities for the rational development of AEDs. Until now only a few of these AEDs have been registered (e.g. vigabatrin). This drug blocks the enzyme that converts GABA, a compound that inhibits neurones, into the inactive succinic-acid.

The effectiveness of new AEDs is always first evaluated as add-on drugs in the treatment of difficult to treat epilepsies. It would be unethical to prescribe new drugs without proven effectiveness to patients with newly diagnosed epilepsy. In these add-on trials novel drugs such as vigabatrin, lamotrigin and topiramate have proven to be effective and relatively safe (46–48). A recent meta-analysis showed that, based on the available data no significant differences in efficacy or tolerability are found between the new AEDs (49). This study was, however, based on findings in intractable epilepsy, in which seizure control is not easily obtained. It is conceivable that differences between these drugs will be found when they are studied in less refractory epilepsy.

Furthermore, the same percentage of success does not exclude the possibility that patients successfully treated with drug 1 are not identical to the patients successfully treated with drug 2. Therefore, it may well be that some of these new AEDs supplement each other. Severe idiosyncratic reactions are, because of their relative rarity, very likely to remain undiscovered until the post-registration phase, as happened with felbamate.

At this time it is still under investigation whether certain epilepsy syndromes are more responsive to GABAergic medication and others to sodium channel blockade. If this is the case, one would not only adjust monotherapy preferences, such knowledge could also help to determine which combinations of AED should be given to an individual patient. It is very conceivable that the combination of two drugs which have different mechanisms of action, may have a greater effect than the individual constituents. Ferrendelli has suggested criteria to select combinations of AEDs (50). The use of such 'rational polytherapy' is now receiving growing attention. It is necessary to heed the total drug load in polytherapy in order to avoid toxicity (16).

CONCLUSION

It is of great importance to give due attention to the diagnosis and classification of epileptic seizures in individual patients. Today, in addition to a more extensive repertoire of AEDs, more means are available to determine the type of epilepsy. For different epilepsy syndromes some specificity appears to exist with respect to choice of AED. The modern physician is further aided in this choice by the improved insights concerning pharmacokinetics and pharmacodynamics.

Based on increased knowledge of the pathophysiologies of the epilepsies, new AEDs have been developed, the merits of which will only be known after extensive use. These developments, together with the increased attention on cognitive adverse effects and the use of rational polytherapy, show that the pharmacotherapy of epilepsy is still in full motion.

REFERENCES

1. Hauser WA, Annegers JF, Rocca WA. (1996) Descriptive epidemiology of epilepsy: contributions of population-based studies from Rochester, Minnesota. *Mayo Clinic Proceedings*, **71**, 576–586.
2. Sander JWAS, Shorvon SD. (1996) Epidemiology of the epilepsies. *Journal of Neurology, Neurosurgery and Psychiatry*, **61**, 433–443.
3. Lammers MW, Hekster YA, Keyser A, Meinardi H, Renier WO, Herings RMC. (1996) Use of anti-epileptic drugs in a community-dwelling population. *Neurology*, **46**, 62–67.
4. Annegers JF, Rocca WA, Hauser WA. (1996) Causes of epilepsy. Contributions of the Rochester Epidemiology Project. *Mayo Clinic Proceedings*, **71**, 570–575.
5. Smith D, Chadwick D, Baker G, Davis G, Dewey M. (1993) Seizure severity and the quality of life. *Epilepsia*, **34** (Suppl. 5), 31–35.
6. Commission on Classification and Terminology of the International League Against Epilepsy. (1989) Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia*, **30**, 389–399.
7. Jefferys JGR. (1993) The pathophysiology of epilepsies. In: Laidlaw A, Richens A, Chadwick D, eds. *A Textbook of Epilepsy*, 4th edn. London: Churchill Livingstone, 241–276.
8. Levy RH, Mattson RH, Meldrum BS. (eds) (1995) *Antiepileptic Drugs*. 4th edn. New York: Raven Press.
9. Betts T. (1990) Pseudoseizures: seizures that are not epilepsy. *Lancet*, **336**, 163–164.
10. Berg AT, Shinnar S. (1991) The risk of seizure recurrence after a single unprovoked seizure: a quantitative review. *Neurology*, **41**, 965–972.

11. First Seizure Trial Group. (1993) Randomized clinical trial on the efficacy of antiepileptic drugs in reducing the risk of relapse after a first unprovoked tonic-clonic seizure. *Neurology*, **43**, 478–483.
12. van-Donselaar CA, Schimsheimer RJ, Geerts AT, DeClerck AC. (1992) Value of the electroencephalogram in adult patients with untreated idiopathic first seizures. *Archives of Neurology*, **49**, 231–237.
13. Hopkins A, Garman A, Clarke C. (1988) The first seizure in adult life. *Lancet*, **1**, 721–726.
14. Commission on Classification and Terminology of the International League Against Epilepsy. (1981) Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia*, **22**, 489–501.
15. Britton JW, So EL. (1996) Selection of antiepileptic drugs: a practical approach. *Mayo Clinic Proceedings*, **71**, 778–786.
16. Richens A, Perucca E. (1993) Clinical pharmacology and medical treatment. In: Laidlaw J, Richens A, Chadwick D, eds. *A Textbook of Epilepsy*. 4th edn. London: Churchill Livingstone, 495–559.
17. Lammers MW. (1984) *Clinimetrics in Epileptology* [thesis]. Institute of Neurology, University Hospital Nijmegen, the Netherlands.
18. Mattson RH, Cramer JA, Collins JFA. (1992) Comparison of valproate with carbamazepine for the treatment of complex partial seizures and secondarily generalized tonic-clonic seizures in adults. The Department of Veterans Affairs Epilepsy Cooperative Study no. 264 Group. *New England Journal of Medicine*, **327**, 765–71.
19. Richens A, Davidson DL, Cartlidge NE, Easter DJA. (1994) A multicentre comparative trial of sodium valproate and carbamazepine in adult onset epilepsy. Adult EPITEG Collaborative Group. *Journal of Neurology, Neurosurgery and Psychiatry*, **57**, 682–687.
20. Heller AJ, Chesterman P, Elwes RD, *et al.* (1995) Phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed adult epilepsy: a randomised comparative monotherapy trial. *Journal of Neurology, Neurosurgery and Psychiatry*, **58**, 44–50.
21. Mattson RH, Cramer JA, Collins JF, *et al.* (1985) Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. *New England Journal of Medicine*, **313**, 145–151.
22. Callaghan N, Kenny RA, O'Neill B, Crowley M, Goggin TA. (1985) A prospective study between carbamazepine, phenytoin and sodium valproate as monotherapy in previously untreated and recently diagnosed patients with epilepsy. *Journal of Neurology, Neurosurgery and Psychiatry*, **48**, 639–644.
23. van-Parijs JAP, Meinardi H. (1994) Survey of 260 epileptic patients treated with oxcarbazepine (trileptal) on a named-patient basis. *Epilepsy Research*, **19**, 79–85.
24. Sato S, White BG, Penry JK. (1982) Valproic acid vs. ethosuximide in the treatment of absence seizures. *Neurology*, **32**, 157–163.
25. Jeavons PM, Livet MO. (1992) West syndrome: infantile spasms. In: Roger J, Bureau M, Dravet C, Dreifuss FE, Perret A, Wolf P, eds. *Epileptic Syndromes in Infancy, Childhood and Adolescence*. 2nd edn. London: John Libbey, 53–67.
26. Fitton A, Goa KL. (1995) Lamotrigine. An update of its pharmacology and therapeutic use in epilepsy. *Drugs*, **50**, 691–713.
27. Beaumanoir A, Dravet C. (1992) The Lennox–Gastaut syndrome. In: Roger J, Bureau M, Dravet C, Dreifuss FE, Perret A, Wolf P, eds. *Epileptic Syndromes in Infancy, Childhood and Adolescence*. 2nd edn. London: John Libbey, 115–134.
28. Meijer JWA. (1991) Knowledge, attitude and practice in antiepileptic drug monitoring. *Acta Neurologica and Scandinavica*, **83** (Suppl. 134), 1–128.
29. Brodie MJ. (1986) Therapeutic drug monitoring. *The Practitioner*, **230**, 1003–1009.
30. Kilpatrick ES, Forrest G, Brodie MJ. (1996) Concentration-effect and concentration toxicity relations with lamotrigine: a prospective study. *Epilepsia*, **37**, 534–538.
31. Richens A, Dunlop A. (1975) Serum phenytoin levels in the management of epilepsy. *Lancet*, **2**, 247–248.
32. Bertilsson L, Tomson T. (1986) Clinical pharmacokinetics and pharmacological effects of carbamazepine and carbamazepine 10,11-epoxide: an update. *Clinical Pharmacokinetics*, **11**, 177–198.
33. Perucca E. (1987) Clinical consequences of microsomal enzyme induction by anti-epileptic drugs. *Pharmacology and Therapeutics*, **33**, 139–144.
34. Lesser RP, Pippenger CE, Luders H, Dinner DS. (1984) High-dose monotherapy in treatment of intractable seizures. *Neurology*, **34**, 707–711.
35. Alpherts WC, Aldenkamp AP. (1990) Computerized neuropsychological assessment of cognitive functioning in children with epilepsy. *Epilepsia*, **31** (Suppl. 4), 35–40.
36. Pellock JM, Willmore LJ. (1991) A rational guide to routine blood monitoring in patients receiving antiepileptic drugs [editorial]. *Neurology*, **41**, 961–964.
37. Höppener RJ, Kuyer A, Meijer JW, Hulsman J. (1980) Correlation between daily fluctuations of carbamazepine serum levels and intermittent side effects. *Epilepsia*, **21**, 341–350.
38. Camfield C, Camfield P, Smith E, Tibbles JAR. (1986) Asymptomatic children with epilepsy: little benefit

from screening for anticonvulsant-induced liver, blood, or renal damage. *Neurology*, **36**, 838–841.
39. Hauser WA, Hesdorffer DH. (1990) *Facts About Epilepsy*. New York: Demos Publications.
40. Overweg J. (1985) Withdrawal of antiepileptic drugs in seizure-free adult patients: prediction of outcome [Dissertation]. University of Amsterdam, Amsterdam, p. 194.
41. Chadwick D. (1990) Epilepsy Octet: Diagnosis of epilepsy. *Lancet*, **336**, 291–295.
42. Medical Research Council Antiepileptic Drug Withdrawal Study Group. (1991) A randomized study of antiepileptic drug withdrawal in patients in remission of epilepsy. *New England Journal of Medicine*, **337**, 1175–1180.
43. Callaghan N, Garrett A, Goggin T. (1988) Withdrawal of antiepileptic drugs in patients free of seizures for two years. A prospective study. *New England Journal of Medicine*, **318**, 942–946.
44. Braathen G, Theorell K. (1995) Is one year treatment enough in uncomplicated epilepsy? *Epilepsia*, **36** (Suppl. 3), 163–164.
45. Peters ACB, Brouwer van-Donselaar CA, Geerts AT, Stroink H, Arts WFM. (1995) The Dutch study of epilepsy in children: early discontinuation. *Epilepsia*, **36** (Suppl. 3), 29.
46. Mumford JP, Dam M. (1989) Meta-analysis of european placebo controlled studies of vigabatrin in drug resistant epilepsy. *British Journal of Clinical Pharmacology*, **27**, 101–107.
47. Matsuo F, Bergen D, Faught E, *et al.* (1993) Placebo-controlled study of the efficacy and safety of lamotrigine in patients with partial seizures. US Lamotrigine Protocology and 0.5 Clinical Trial Group. *Neurology*, **43**, 2284–2291.
48. Ben-Menachem E, Henriksen O, Dam M, *et al.* (1996) Double-blind placebo-controlled trial of topiramate as add-on therapy in patients with refractory partial seizures. *Epilepsia*, **37**, 539–543.
49. Marson AG, Kadir ZA, Chadwick DW. (1996) New antiepilepic drugs: a systematic review of their efficacy and tolerability. *British Medical Journal* 313, 1169–1174.
50. Ferrendelli JA. (1995) Relating pharmacology to clinical practice: the pharmacologic basis of rational polypharmacy. *Neurology*, **45** (Suppl. 2), 12–16.