TREATMENT FAILURE IN PATIENTS WITH EPILEPSY – EXPLORING CAUSES OF INEFFECTIVENESS AND ADVERSE EFFECTS

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GOMBERT-HANDOKO

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THERAPIEFALEN BIJ PATIËNTEN MET EPILEPSIE – OORZAKEN VAN INEFFECTIVITEIT EN BIJWERKINGEN

(met een samenvatting in het Nederlands)

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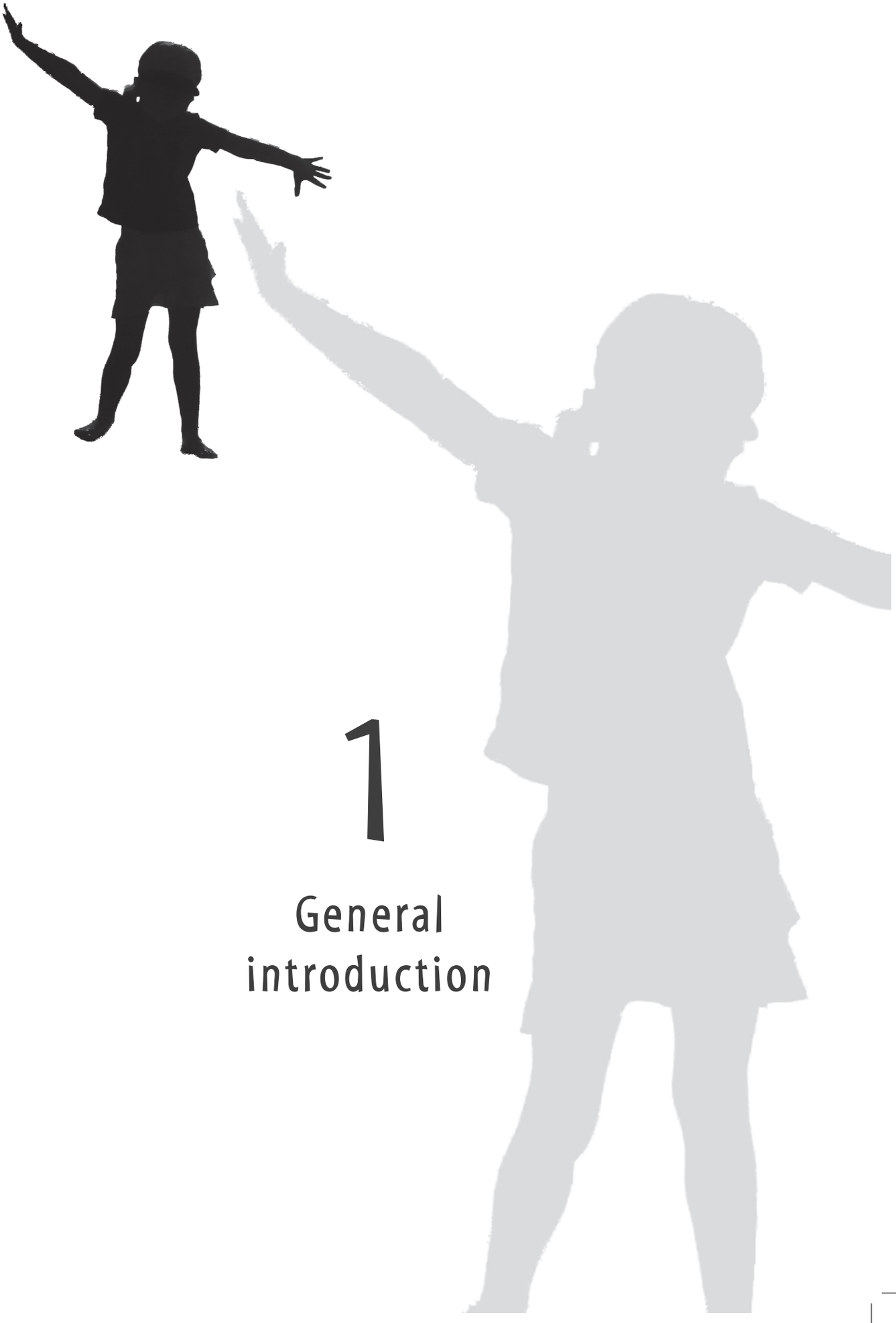
Life is like riding a bicycle.
To keep your balance you must keep moving.

Albert Einstein

CONTENTS



1

General introduction

OBJECTIVE OF THE THESIS

Epilepsy is a serious neurological disorder with seizures as its main symptom. For people with epilepsy, everyday issues like exercise, driving, education, and employment include special considerations. Epilepsy is mainly treated with antiepileptic drugs. If treatment fails, the impact on patients' life can be enormous. The aim of this thesis is to assess different determinants that could explain antiepileptic drug failure and to provide suggestions for interventions to improve successful drug treatment in patients with epilepsy.

Several observational studies were conducted to explore two important aspects of therapeutic failure of antiepileptic drugs:

1) antiepileptic drug failure due to ineffectiveness;
2) antiepileptic drug failure due to adverse effects.

This introductory chapter gives an overview on epilepsy in general, the treatment of epilepsy, and therapeutic failure in epilepsy (i.e. drug-resistant or refractory epilepsy). The chapter ends with the outline of this thesis.

EPILEPSY

The word epilepsy is derived from the Greek word 'epilambanein' which means 'to seize or to attack'. A seizure is an episodic disturbance of movement, feeling, or consciousness caused by sudden synchronous, inappropriate, and excessive electrical discharges in the cerebral cortex. It is estimated that up to 5% of the general population will experience a single seizure in some point in their lives. The diagnosis of epilepsy is reserved for those who have a history of at least one seizure and an enduring alteration in the brain that increases the likelihood of recurring seizures in the future.[1]

Worldwide, more than 50 million adults and children suffer from epilepsy. The prevalence is approximately 50-100 cases per 10 000 with an annual incidence of about 5-7 cases per 10 000 population. The two highest peaks of incidence are in children and in the elderly population (65 years of age or older).[2]

Seizures can be a consequence of structural and functional abnormalities in the brain and of a wide range of genetic and metabolic disorders. Two main categories of seizures can be distinguished: partial and generalised. Partial seizures have a focal onset and can be simple (meaning that no alteration of consciousness occurs) or complex (in which consciousness is impaired or lost). Generalised seizures, such as absences, myoclonic jerks, and tonic clonic events, have a deep bilateral onset and always result in a loss on consciousness.[1] Seizure types can be identified by

clinical characteristics and by EEG patterns during occurrence. Several factors such as emotional stress, sleep deprivation, the menstrual cycle, flickering lights, alcohol use, and illness can trigger the occurrence of seizures.[3,4]

In addition to the type of seizures epilepsy consists of a wide range of syndromes that can be divided into idiopathic (genetic), symptomatic (known structural abnormality) and cryptogenic (presumed anatomical abnormality) syndromes. Seizure type as well as epilepsy syndrome are classified according to the International League Against Epilepsy.[1] Identification of the epilepsy syndrome as well as the type of seizure provides important prognostic information and is essential for appropriate antiepileptic drug selection.[3,4]

TREATMENT OF EPILEPSY

Antiepileptic drugs

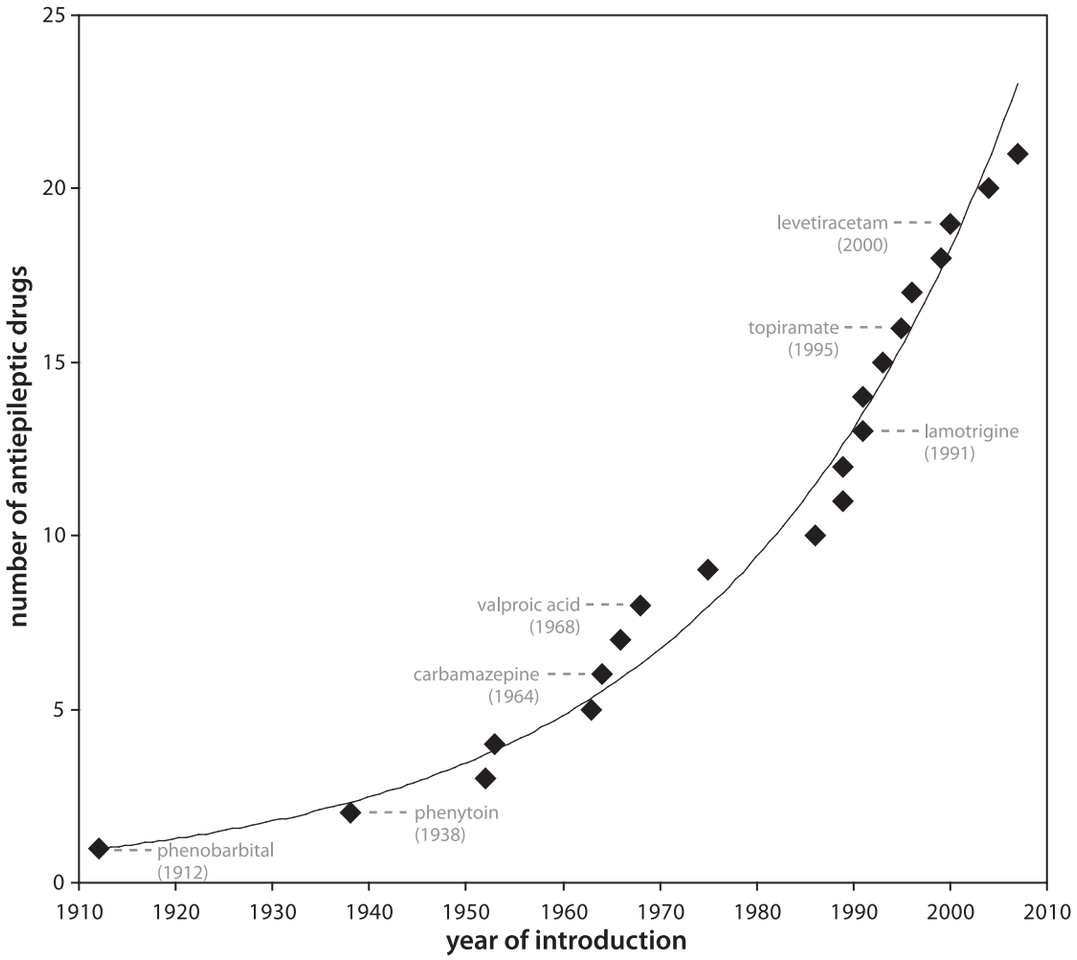
Antiepileptic drugs are the mainstay of treatment of epilepsy. The goal of treatment is the maintenance of a normal life style by complete seizure control with a minimum of drug-related adverse effects. In practice, only half of the newly diagnosed children and adults with epilepsy can be successfully treated (i.e. their seizures can be completely controlled for several years) with antiepileptic drugs.[5]

Phenobarbital was the first drug that was found to have a positive effect in antagonizing seizures. After phenobarbital, established antiepileptic agents such as phenytoin, carbamazepine and valproic acid were developed. Carbamazepine and valproic acid are still among the first choice drugs in the treatment of epilepsy. Currently, in total over twenty antiepileptic drugs have been licensed worldwide, from which ten agents have been developed in the last two decades (Figure 1).

The mechanisms of action are not fully understood and many antiepileptic drugs have multiple modes of actions. The principal mechanisms of the currently available antiepileptic drugs are thought to be inhibition of excitatory sodium channels (carbamazepine, oxcarbazepine, lamotrigine, and phenytoin), modification of calcium channels (ethosuximide, gabapentin, pregabalin, zonsamide) and enhancement of the inhibitory GABAergic system (benzodiazepines, phenobarbital, tiagabine, vigabatrin) (Table 1).[6,7]

Newly developed antiepileptic drugs have to be evaluated in add-on studies according to official registration guidelines. Studies with gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabaline and zonisamide showed that 20 to 40 percent of patients obtained a 50% or greater reduction in the frequency of seizures as compared to baseline. Very few patients became seizure free, which should be

Figure 1 Development of antiepileptic drugs in the past century



the ultimate goal.[8] Although some of the newer antiepileptic drugs may be better tolerated than established agents, overall, none of them has shown superiority in monotherapy.[9,10] In 2007 a large multicentre trial called SANAD with several years of follow up was published.[11,12] In this study patients with newly diagnosed epilepsy were randomised to several therapies. Although differences were small, they concluded that lamotrigine should be the first drug of choice for patients with partial epilepsy and valproic acid for generalised and unclassifiable epilepsy. With the enormous amount of available antiepileptic agents this answer was satisfying for the many physicians involved in the treatment of epilepsy. However, the effects measured in these studies may still turn out different in clinical practice.[13]

Table 1 The range of antiepileptic drugs in present use, their modes of action and main safety concerns [4,6]

Antiepileptic drug	Putative mode of action	Main safety issues or concerns
Carbamazepine	sodium-channel inhibition	idiosyncratic reactions; rarely Stevens-Johnson syndrome; aplastic anaemia; hepatotoxicity
Clobazam	GABA augmentation	rarely idiosyncratic rash
Clonazepam	GABA augmentation	rarely idiosyncratic rash; thrombocytopenia
Diazepam	GABA augmentation	respiratory depression
Ethosuximide	calcium-channel modification	rarely idiosyncratic rash; Stevens-Johnson syndrome; aplastic anaemia
Felbamate	glutamate reduction	hepatic failure; aplastic anaemia
Gabapentin	calcium-channel modulation	paradoxical increase in seizures
Lamotrigine	sodium-channel inhibition; glutamate reduction	idiosyncratic rashes; rarely Stevens-Johnson syndrome; Toxic Epidermal Necrolysis; liver failure; aplastic anaemia; multiorgan failure
Levetiracetam	synaptic vesicle protein modulation	behavioural problems
Phenobarbital	GABA augmentation	idiosyncratic rash; rarely toxic epidermal necrolysis; hepatotoxicity; osteomalacia
Phenytoin	sodium-channel inhibition	idiosyncratic rash; rarely pseudolymphoma; peripheral neuropathy; Stevens-Johnson syndrome; hepatotoxicity; osteomalacia
Pregabalin	calcium-channel modulation	weight gain; rarely increased seizures
Primidone	GABA augmentation	idiosyncratic rash; rarely agranulocytosis; thrombocytopenia; lupus-like syndrome
Oxcarbazepine	sodium-channel inhibition	idiosyncratic rash; hyponatraemia
Tiagabine	GABA augmentation	increased seizures; non-convulsive status
Topiramate	glutamate reduction; sodium-channel modulation; calcium-channel modification	weight loss; kidney stones; impaired cognition; word finding difficulties
Valproic acid	GABA augmentation	teratogenicity; rarely acute pancreatitis; hepatotoxicity; thrombocytopenia; encephalopathy; polycystic ovarian syndrome
Vigabatrin	GABA augmentation	visual field defects; increased seizures
Zonisamide	calcium channel inhibition	rash; rarely blood dyscrasias

Adverse effects of antiepileptic drugs

Antiepileptic drugs are known for their bothersome side effects: 70% of patients has general CNS related complaints (fatigue, slowing), 60% has cognition problems (memory, concentration or speech difficulties), 30% has gastrointestinal problems (nausea, diarrhae, weight gain) and 20% experience mood and behavioural effects (agitation, irritability).[14] It is estimated that about 25% of patients with epilepsy suffers from significant adverse effects as a result of using antiepileptic drugs. Some of the antiepileptic drugs can even aggravate seizures. The standard antiepileptic drugs share common dose-related (type A) side effects including headache, dizziness, diplopia, fatigue and ataxia. Other specific side effects include hyponatraemia and benign neutropenia with carbamazepine; gingival hyperplasia and hirsutism with phenytoin; weight gain and hair loss with valproic acid; hyperactivity, irritability and sedation with phenobarbital and primidone.[15] Furthermore, carbamazepine, phenytoin and phenobarbital have been associated with decreased bone mineral density and fractures.[16]

The unusual idiosyncratic (type B) adverse reactions are of greater concern; these can arise with any of the standard antiepileptic drugs. Carbamazepine, ethosuximide, phenytoin, and phenobarbital can all cause hypersensitivity reactions including rash, eosinophilia, lymphadenopathy, fever, or a full-blown Stevens-Johnson syndrome.[17,18] Blood dyscrasias and hepatic failure are less common consequences that can also be seen with use of valproic acid.[19]

Overall the newer antiepileptic drugs have less side effects than the established antiepileptic drugs, but do still produce dose-related nausea, headache, occasional tiredness, and skin reactions.[20] The majority of the adverse effects of the newer antiepileptic drugs are CNS-related.[21] Gabapentin causes movement disorders and psychiatric disturbances. Levetiracetam can cause behavioural changes. Topiramate frequently causes cognitive adverse reactions and also causes significant word-finding difficulties, renal calculi and bodyweight loss. Lamotrigine can cause behavioural side effects and serious hypersensitivity reactions. Vigabatrin-induced irreversible visual field constriction is one of the most worrying adverse affects.[22] The safety profile of oxcarbazepine is similar to that of carbamazepine, although rash seems to appear less often.

The gender-related issue is another important topic in epilepsy for the condition itself as well as the use of antiepileptic drugs affects sexual development, menstrual cycle, contraception, fertility and reproduction.[23] Especially pregnancy is an important topic since chances of birth defects are higher for woman with epilepsy.[24,25]

An overview of important safety issues of the individual antiepileptic drugs is given in Table 1.[20-22,26,27]

Interaction potential of antiepileptic drugs

Drug interactions are a major safety topic in patients using antiepileptic drugs. Multiple reasons for combining drugs are of importance. First of all, although monotherapy with antiepileptic drugs is preferred, often combinations of antiepileptic drugs are necessary for adequate seizure control. Secondly, Antiepileptic drugs are administered during prolonged periods of time, often there is a need for lifelong use, thus co prescription is inevitable. Also, many persons with epilepsy have comorbid conditions that are treated with concomitant medications.[28] Thus, chances for drug-drug interactions are high in this group of patients.

Pharmacokinetic drug interactions are the most prominent. Patients for whom first generation antiepileptic drugs (carbamazepine, phenytoin, phenobarbital and primidone) are prescribed have been shown to be at high risk for drug interactions with medications that involve the cytochrome P-450 (CYP) pathway. As a result these antiepileptic drugs drastically reduce the serum concentration of drugs which are substrates of the same CYP enzymes, including antipsychotics, contraceptives, tricyclic antidepressants, calcium channel blockers, and anticoagulants. Although valproic acid is not an enzyme inducer it may cause clinically relevant drug interactions by inhibiting the metabolism of selected substrates, most notably phenobarbital and lamotrigine.[29] Also many antiepileptic drugs, including oxcarbazepine, lamotrigine, felbamate and topiramate stimulate the metabolism of oral contraceptive steroids. Levetiracetam, gabapentin and pregabalin have not been reported to cause or be a target for clinically relevant pharmacokinetic drug interactions (Table 2).[29-31]

Pharmacodynamic drug interactions involving antiepileptic drugs are less well defined. An important reason may be that mechanisms of action of antiepileptic drugs are not fully understood. However, clinical observations suggest that these may be more common than previously thought.[32]

Therapeutic drug monitoring

Therapeutic drug monitoring is the measurement of drugs in serum in order to maintain a relatively constant concentration in the blood. Drugs that are monitored tend to have a narrow 'therapeutic range' – the quantity required to be effective is not far removed from the quantity that causes significant side effects and/or signs of toxicity. This is also the case for antiepileptic drugs, especially for phenytoin since this drug undergoes nonlinear saturation kinetics.[33] In addition, therapeutic drug monitoring in epilepsy is thought to be an important tool for several other reasons. First of all treatment is prophylactic and seizures occur at irregular intervals; thus, it may be difficult to find the optimal dose on clinical grounds alone. Furthermore,

Table 2	Common drugs with either increased or reduced clearance in the presence of antiepileptic drugs	
Type of medication	**increased clearance (and need for higher doses) with phenytoin, phenobarbital, carbamazepine**	**Decreased clearance (and need for lower doses) with valproic acid**
Cardiac	mexiletine, quinidine, amiodarone, propranolol, metoprolol, nifedipine, felodipine, nimodipine, digoxin, lovastatin, simvastatin, dicoumarol, warfarin	nimodipine
Psychiatric	amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, citalopram, paroxetine, buproprion, haloperidol, chlorpromazine, clozapine, olanzapine, risperidone, quetiapine	amitriptyline, nortriptyline, clomipramine, paroxetine
Antineoplastic	cyclophosphamide, busulfan, etoposide, methotrexate, teniposide, some vinca alkaloids	
Antiinfective	praziquantel, albendazole, doxycycline, nevirapine, efavirenz, delavirdine, indinavir, ritonavir, saquinavir	zidovudine, possibly others
Other	cyclosporine, tacrolimus, diazepam, alprazolam, prednisone, oral contraceptive pills, theophylline, methadone	lorazepam, diazepam

clinical symptoms and signs of toxicity can also be difficult to detect and interpret. Also, intermediate physiologic markers of clinical effects or toxicity of antiepileptic drugs are not available in epilepsy. However, guidelines no longer advise standard monitoring of antiepileptic drug plasma concentration levels.[34,35] TDM can still be valuable when drug regimens change, when insufficient seizure control is achieve and to evaluate the potential cause of antiepileptic drug toxicity or in pregnancy (since serum concentrations may be affected).[36,37]

REFRACTORY EPILEPSY

Defining refractory epilepsy

Approximately 50% of patients achieve complete abolishment of seizures with a single appropriately selected antiepileptic drug at a targeted dose. Another 20% needs two or more drugs. The choice of a second or a third antiepileptic drug depends on many individual patient characteristics and drug-related factors such as efficacy, adverse effects, interactions with other drugs and mode of action. The remaining 30% of patients with epilepsy remains to have seizures despite the use

of several antiepileptic drugs. This group of patients have refractory epilepsy or can be called therapy resistant.[38] Although refractory epilepsy has been extensively described and studied, in literature no official definitions exists. Devinsky formulated refractory epilepsy as: "when seizures are so frequent or severe that they limit the patient's ability to life fully according to his or her wishes or necessitate the use of medications that although effective produce adverse effects".[39]

Impact of refractory epilepsy

Refractory epilepsy can have devastating consequences. Uncontrolled seizures have an enormous impact on the physical health and emotional and social well-being of affected persons. Half of the patients with refractory epilepsy suffer from depression, from which almost 20% has a severe depression with suicidal thoughts. It is shown that, in general, the suicide rate among patients with epilepsy is 5-fold higher than that in the general population, while in temporal lobe epilepsy and complex partial seizures it is approximately 25-fold higher.[40,41] Many patients experience prolonged seizures or status epilepticus and, consequently, suffer from physical injuries requiring hospitalisation. Others have shortened life spans because they are confronted with sudden unexpected death that is associated with uncontrolled seizures.[28,42] Studies have shown that patients with refractory epilepsy have significant neuropsychological, psychiatric, and social impairments that limit employability, reduce marriage rates and decrease quality of life. [43,44]

Pharmacogenetics in refractory epilepsy

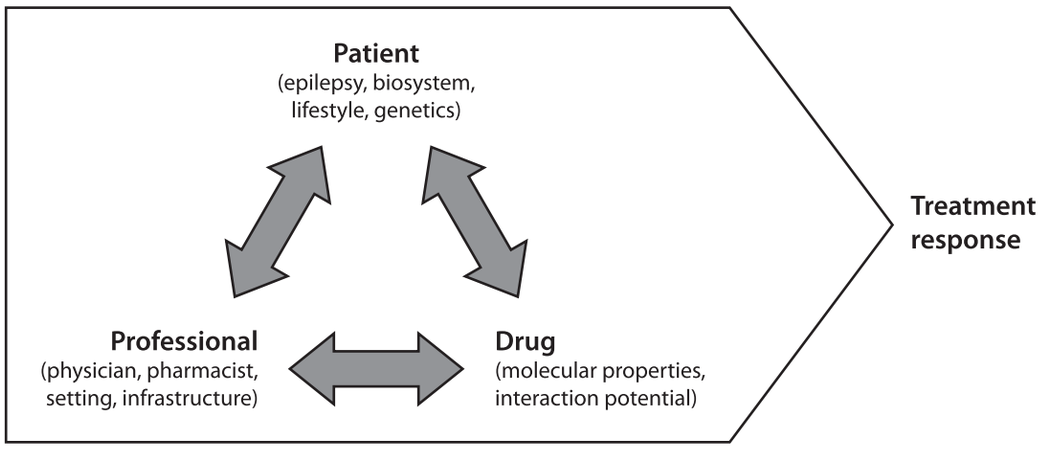
It is still unknown why and how certain patients with epilepsy become drug resistant while others with apparent identical seizure types or syndromes can achieve seizure control with medication. Thus, there is a pressing need to elucidate neurobiologic and clinical mechanisms underlying pharmacoresistance. In the last few years the role of pharmacogenetics has played a dominant role in epileptic literature. Two important theories have been proposed: the target hypothesis and the transporter hypothesis.[45] The foundation of the transporter hypothesis was laid in 1995 when a study was published in which an increased expression of the transporterprotein P-glycoprotein in the brain was found in patients with refractory epilepsy compared with normal people.[46] This suggested that the patients' lack of response to medication may be caused by inadequate antiepileptic drug levels in the brain due to overactivity of transporterproteins. In 2003 Siddiqui et al. were the first to find an association between a polymorphism in the ATP-binding cassette sub-family B member 1 (ABCB1, also known as MDR-1, encoding P-glycoprotein) and drug resistance in epilepsy.[47] Subsequent studies reported both negative and positive

associations.[48-51] The target hypothesis proposes that alteration in drug targets, such as modifications of the sodium channels, lead to poor response to drug treatment.[45] Although this hypothesis has been tested in animals, studies with humans are rare.[52] Also, other genes that may explain intractability in epilepsy have been explored. However, up until now no clear associations have been found.[53] If an association between certain genetic factors and refractory epilepsy could be confirmed, patients with epilepsy could be screened beforehand in order to optimize drug selection leading to improved seizure control.

THE ROLE OF PATIENT, PROFESSIONAL AND DRUG

Treatment response in general depends on the interaction between the patient (including his or her disease, views and expectations, biosystem, comorbidity, lifestyle, genetic profile) the drug (mechanism of action, molecular properties, interaction potential, tolerance, formulation, cost) and the health care professional (physicians, pharmacists, their knowledge and accordance to guidelines, setting, infrastructure, communication) (Figure 2). In epilepsy the balance between efficacy and safety is very delicate, requiring sufficient knowledge and effort of both patient and health care professional. Therefore in this thesis, the role of these key actors on treatment response in epilepsy will be enlightened.

Figure 2 Factors influencing treatment response in epilepsy



OUTLINE OF THIS THESIS

Patients with epilepsy in trials versus clinical practice

Since trials often include a highly selected population (e.g. no woman of childbearing age, no children or elderly patients) it is not surprising that efficacy of drugs studied in trials may differ from the effectiveness in clinical practice. [54] This has consequences for the interpretation of the results of the trial data. In our first study, we compared the clinical epilepsy population with the population selected for antiepileptic drug trials (*Chapter 2.1*).

Drug-treatment related causes for ineffectiveness

Chapter 3 gives an outline about the impact of various drug treatment-related factors, i.e. changes in medication regimes, compliance and serum drug concentrations that can lead to insufficient seizure control. In *Chapter 3.1*, we studied the impact of changes in antiepileptic and non-antiepileptic medication on epilepsy-related hospitalisation using a Dutch database in which pharmacy records are linked to hospital admissions. In *Chapter 3.2* patients with epilepsy in a clinical setting were assessed on the association of drug-treatment related factors and seizure control.

Gene-related causes for ineffectiveness

Chapter 4.1 and *4.2* concern the ROME study. ROME is the acronym for Response Of Medication in Epilepsy, a study that was set up in collaboration with Epilepsy centre Kempenhaeghe, a tertiary epilepsy clinic located in the south of the Netherlands. Patients who were drug resistant and patients who were responding well on antiepileptic drugs were invited to join this study. In these patients pharmacogenetic factors for therapy-resistance were examined. In *Chapter 4.1* the association between variations (haplotypes) in the ABCB1 gene and response to antiepileptic drug treatment was assessed (transporter hypothesis). In *Chapter 4.2* we studied the association between a polymorphism of the SCN1A gene and refractory epilepsy (target hypothesis).

Adverse effects of antiepileptic drugs

In **Chapter 5** we explore various adverse effects in users of antiepileptic drugs. Preventing and managing adverse effects is a major challenge in patients with epilepsy. Also, tolerability plays an important role with respect to the adherence of therapy. Therefore, adverse effects are an important factor that may lead to treatment failure in patients with epilepsy. In our first adverse-effects study (*Chapter 5.1*) we looked whether commonalities in chemical structures of antiepileptic drugs may explain hypersensitivity reactions, in other words: Is the drug responsible for the

adverse effects? In *Chapters 5.2* and *5.3* we studied the role of the patients using the drugs. *Chapter 5.2* describes the occurrence of metabolic syndrome in patients using valproic acid and lithium in the psychiatric setting. In *Chapter 5.3* the risk of aplastic anemia in patients using antiepileptic drugs is studied. Aplastic anemia is a rare, but feared idiosyncratic complication of drug treatment, often responsible for taking drugs from the market.

In **Chapter 6** the results presented in this thesis are discussed into a broader perspective. Also, clinical recommendations and directions for future research are provided.

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2

Patients with epilepsy in trials versus clinical practice

chapter 2.1

Highly selected subset of ambulatory patients with epilepsy qualifies for antiepileptic drug trials

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ABSTRACT

Objective

To assess the number of patients with epilepsy from clinical practice that would qualify for a standard antiepileptic drug (AED) trial.

Methods

A total of 432 outpatients with epilepsy represented the clinical practice cohort, 80 patients had recurrent partial seizures. Common in- and exclusion criteria used in clinical AED trials in epilepsy were applied to the clinical cohort and the subset of patients with recurrent partial seizures and the proportion of patients who would qualify for clinical trials was determined.

Results

Seven common exclusion criteria were found in 19 clinical trials between 2002 and 2007. Three-quarters (76%) of patients had a too low seizure frequency (<1 seizure per month) to be eligible for inclusion in a clinical trial. Half of the study population (51%) was evaluated as having clinically relevant comorbidity for exclusion from a clinical trial; 21% of patients had a neurological comorbidity, 19% had a psychiatric disorder and 23% suffered from relevant systemic illnesses, 23% of the patients used a combination of ≥3 AEDs. After application of all exclusion criteria, 9% of patients would be eligible for entering a clinical trial. After application of the in- and exclusion criteria to the subgroup of patients with recurrent partial seizures, 27.5% of patients would be able to enter a clinical trial.

Conclusion

This study shows that less than 10% of patients with epilepsy in our cohort and less than 30% of patients with recurrent partial seizures would qualify for clinical trials. Patients with specific clinical profile are studied in clinical trials and generalizability of clinical trial results to patients in clinical practice may therefore be limited.

INTRODUCTION

The efficacy of new antiepileptic drugs (AEDs) is studied before approval in randomized clinical trials (RCTs) as add-on therapy to one or more other AEDs in refractory, partial onset seizure patients. Monotherapy studies are only conducted after new AEDs have shown to be effective and safe in refractory patients with partial seizures. Although RCTs provide useful information about the efficacy and tolerability of a new AED, the external validity or generalizability of their results can be limited as they are usually conducted in protocol-restricted patient populations using fixed study designs and dosing schedules for short treatment periods.[1,2] This smaller degree of variability in patients and treatment schedules may therefore hamper the extrapolation of the information from RCTs to epilepsy patients in day-to-day clinical practice. It has for example been shown that the incidence of discontinuation of lamotrigine was higher in daily clinical practice in comparison with randomized clinical trials, which seemed at least partly attributable to differences in prognostic characteristics between RCTs and daily practice.[3]

This principle may apply to any therapeutic drug group, but the extent may vary. It has been demonstrated that about 90% of patients seeking clinical treatment of depression would not qualify for a clinical trial based on common exclusion criteria.[4,5] In clinical trials with cardiovascular drugs there was underrepresentation of elderly patients and patients with comorbidity.[6,7]

The aim of our study was to assess how many patients with epilepsy from clinical practice would qualify for a standard efficacy antiepileptic drug trial after application of common in- and exclusion criteria.

METHODS

Study population

Eligible patients were identified during 2005 through the medical records of two outpatient neurology clinics in the Czech Republic (the Clinic of Neurology of University Hospital Hradec Kralove and the Centre for Epileptology and Epileptosurgery of the University Thomayer's Hospital in Prague). Patients aged 17 years and older with a confirmed diagnosis of epilepsy and receiving antiepileptic therapy were included in the study. Ethical permission to conduct this study was obtained from the Ethics Committees of both participating hospitals.

Randomised controlled trials

We searched PubMed using the following terms: 'efficacy' and 'clinical trial' and 'epilepsy' and 'antiepileptic drug'. Additionally, we performed a search in the Cochrane database of randomized clinical trials. Efficacy studies with antiepileptic drugs published in English in the period from 2002 to May 2007 were considered for analysis. Studies limited to children, people with mental retardation or restricted to any specific subtype of epileptic seizures or syndrome (like myoclonic epilepsy, Lennox-Gastaut syndrome, status epilepticus) were excluded. Studies on patients with newly diagnosed epilepsy were not evaluated since our study population represented patients from referral centres treated with antiepileptic drugs that are not comparable with newly diagnosed patients. The quality of the resulting 25 RCTs was assessed using the method described by Jadad.[8] Studies with insufficient quality according to this scale (less than 2 points, n=6) were not included. The remaining 19 clinical trials were reviewed for exclusion and inclusion criteria.[9-27]

Table 1 The most frequently used exclusion criteria in antiepileptic drug clinical trials

Exclusion criteria	Clinical trials where the criterion was used n (%)
1. Pregnancy or breastfeeding	19 (100.0%)
2. Insufficient seizure frequency (< 1 seizure per month)	16 (84.2%)
3. Clinically relevant systemic illness (heart, renal, hepatic or other diseases)	16 (84.2%)
4. Concomitant use of more than three antiepileptic drugs	15 (78.9%)
5. Progressive neurological or cerebral disease, neoplasia, structural lesion	14 (73.7%)
6. Presence of psychiatric disorder	10 (52.6%)
7. Alcohol or drug abuse	10 (52.6%)
8. Medication to interfere, CNS influencing drug, use of other investigational drug within preceding month	10 (52.6%)

CNS = central nervous system

Data analysis

From the 19 included RCTs a set of the most frequently used in- and exclusion criteria was made (Table 1). Criteria used in at least 50% (i.e. ten or more) of the studies were applied for further assessment. The necessary information was retrieved from the medical records of the patients. The nature of the epilepsy was

classified according to the International League Against Epilepsy.[28] We could not evaluate non antiepileptic co-medication of the patients since this information was not standard recorded by the neurologists. Also pregnancy and especially breastfeeding could not be evaluated. Hence features two till seven were examined in our population of patients with epilepsy. First, we examined these criteria in the whole group of patients. Finally, we selected subgroup of patients with recurrent partial seizures (with or without secondary generalization) and demonstrated the percentage of patients from this subgroup remaining after sequential application of in- and exclusion criteria.

RESULTS

A total of 432 outpatients were evaluated (Table 2) with an age ranging from 17 to 88 years (mean 40.7, standard deviation [sd] 15.5). In this study population, 172 (39.8%) patients were prescribed an AED in monotherapy, 162 (37.5%) needed two AEDs. Combination of three AEDs was used in 81 (18.8%) patients, four AEDs in 17 patients (3.9%).

Three-quarters (75.5%) of patients had lower seizure frequency (less than one seizure per month) than that required for inclusion in clinical trial. Approximately half of the study population (51%) was evaluated as having clinically relevant comorbidity for exclusion from the clinical trial and these comorbidities were distinguished according to the exclusion criteria (Table 2). Fifteen patients (3.5%) would have been excluded because of history of alcohol abuse. Many patients met multiple exclusion criteria.

Figure 1 illustrates the impact of sequential application of the exclusion criteria. Exclusion of patients with lower seizure frequency, concomitant neurological, psychiatric or other medical illnesses left only 45 eligible patients (10.4%). If patients with more than 3 concomitant AEDs were also excluded, then 394 (91.2%) subjects would have been excluded from an efficacy study.

Finally, we applied the exclusion criteria to the subgroup of patients with recurrent partial seizures (n=80). Presence of concomitant neurological, psychiatric and other medical illnesses led to exclusion of 65% of patients. If patients with more than three concomitant AEDs were also excluded, then 72.5% of subjects would have been excluded (Figure 2).

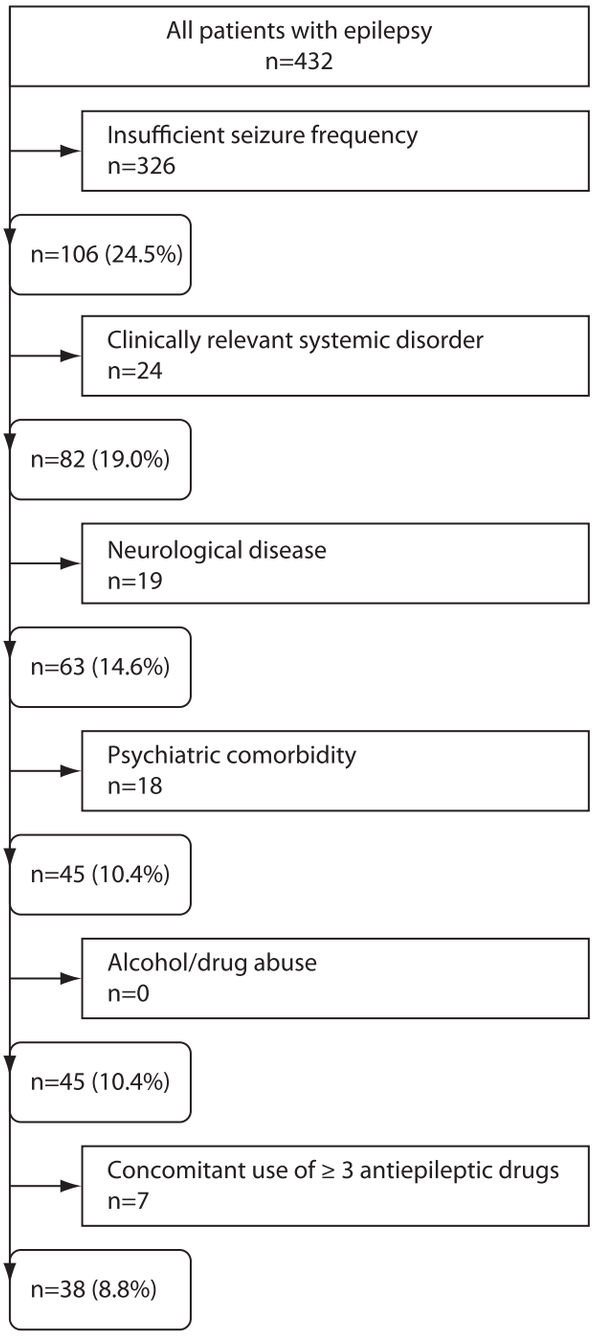
Table 2 Demographics and clinical characteristics of the study population	
Characteristic	**Number of patients n=432 (100%)**
Gender	
male	183 (42.4%)
ILAE Classification	
partial seizures	305 (70.6%)
generalized seizures	107 (24.8%)
unclassified seizures	20 (4.6%)
Seizure frequency	
≥ 2 years without seizures	152 (35.2%)
1 year without seizures	59 (13.7%)
< 12 seizures per year	97 (22.5%)
>12 seizures per year	106 (24.5%)
re-occurrence of seizures	13 (3.0%)
newly diagnosed	5 (1.2%)
Comorbidities	
patients with no comorbidity	212 (49.1%)
any relevant medical comorbidity	220 (50.9%)
neurological disease	92 (21.3%)
psychiatric disorder	83 (19.2%)
medical (systemic) illnesses	99 (22.9%)
- cardiovascular	31 (7.2%)
- respiratory	13 (3.0%)
- renal	8 (1.9%)
- other	55 (12.7%)

DISCUSSION

In the present study we determined the proportion of patients who would qualify for participation in a clinical trial in epilepsy. When we applied the exclusion criteria to the whole group of patients, more than 90% of patients would have been excluded. After application of the most frequently used exclusion criteria to patients with recurrent partial seizures, only 27.5% of this group could be included in a standard clinical trial. Our findings support apprehensions that efficacy trials in epilepsy tend to evaluate only a small subset of patients with a specific clinical profile that are not representative for patients treated in day-to-day clinical practice.[2,29]

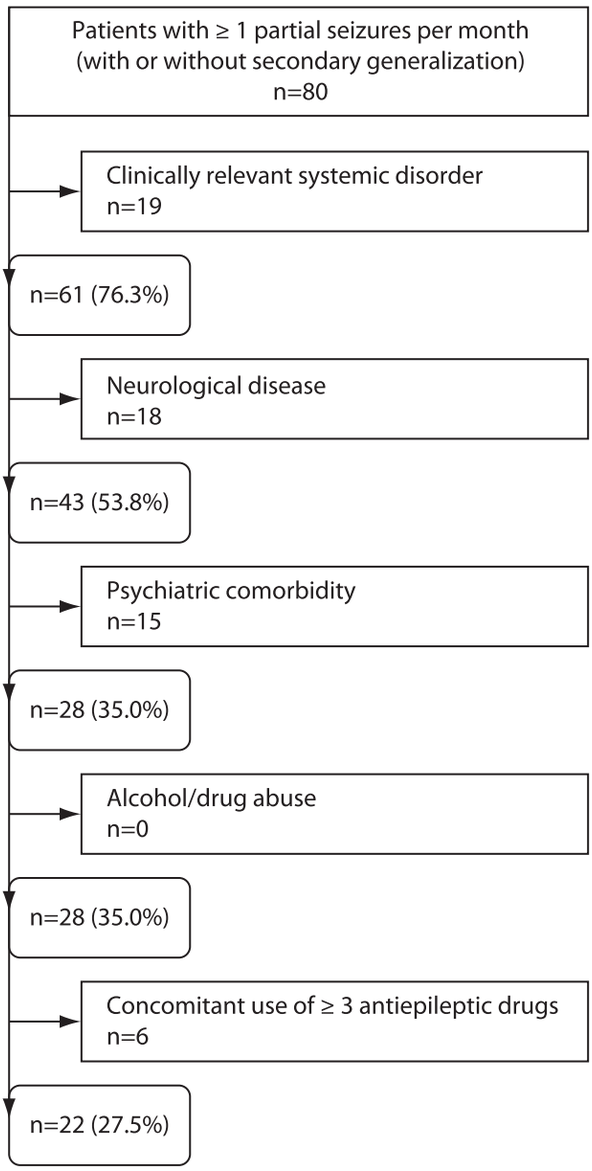
More than half of the patients in our study would be excluded because of history or presence of comorbidities. Furthermore, this criterion would exclude 65%

Figure 1 Sequential application of exclusion criteria to the whole group of patients



Many patients met multiple criteria. Numbers and percentages represent patients remaining after application of each preceding criterion.

Figure 2 **Sequential application of exclusion criteria to the subgroup of patients with ≥ 1 partial seizures per month**



Many patients met multiple criteria. Numbers and percentages represent patients remaining after application of each preceding criterion.

of patients with recurrent partial seizures. It has been demonstrated that both psychiatric and somatic diseases are more frequent in patients with epilepsy.[30-35] Since the prevalence ratio of many common psychiatric and somatic conditions is increased in adults with epilepsy, the extrapolation of the results of clinical trials

to the real-world clinical practice after exclusion of patients due to other medical illnesses is largely limited.

The seizure frequency required for inclusion in 10 out of the 19 clinical trials was at least three or four seizures per month. For understandable reasons patients with well-controlled seizures are not included in clinical trials. However, efficacy trials tend to include patients with high seizure frequency who are more likely to demonstrate drug-placebo differences. This fact provides further limitation to extrapolate the data from clinical trials to the entire population of patients with epilepsy that are going to be treated with these new AEDs after market authorization.

The effectiveness found in clinical trials on patients with a specific clinical profile may differ from effectiveness in daily clinical practice. A retrospective population-based study on lamotrigine effectiveness showed that several characteristics including baseline seizure frequency and drug load were significantly associated with effectiveness of lamotrigine.[36]

There are several possible limitations of our study. First, if co-medication, pregnancy and lactation could have been evaluated, probably more patients would have been excluded. Additionally, the frequency of various comorbidities in our study could be underestimated since the information was retrieved from medical records. Nevertheless, the prevalence of various comorbidities in our study corresponds to previous findings where half of patients suffered from a systemic comorbidity, psychiatric comorbidity or both.[37] It is obvious that the number of patients who are excluded due to medical comorbidities will differ according to the rigorousness of diagnostic evaluations conducted in clinical trials.

In conclusion, this study provides evidence that only a subset of patients with epilepsy are studied in efficacy clinical trials where rigid exclusion and inclusion criteria are used for the entry of patients. Some criteria may be judged more useful or ethically important than others. For example, pregnant or lactating women are routinely excluded from AED trials. In addition, it is not reasonable to change medication in patients with well-controlled seizures. Questionable criteria include history or presence of psychiatric disorders or other medical conditions. Differences in patients' characteristics may cause discrepancies in effectiveness seen in clinical trials in comparison with daily clinical practice. Development of guidelines for uniform collection and reporting of comorbidity data in clinical trials would be useful, as well as further utilization of data. The information gleaned from clinical trials provides only partial information on the effectiveness of AEDs in the real clinical practice and observational research within the setting of daily clinical practice is necessary for completing the results of clinical trials.

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3

Drug-treatment related causes of ineffectiveness

chapter 3.1

Changes in medication associated with epilepsy-related hospitalisation: A case-crossover study

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ABSTRACT

Objective

To assess the association between changes in medication and epilepsy-related hospitalisation.

Methods

Data were obtained from the PHARMO Record Linkage System (Jan 1998 to Dec 2002). We conducted a case-crossover study among patients with a first epilepsy-related hospital admission who had continuously used at least one antiepileptic drug (AED) during a 28-week period before admission. For each patient, changes in medication in a 28-day window before hospitalisation were compared with changes in four earlier 28-day windows. Evaluated changes were: changes in AEDs (pattern and dosage), changes in interacting co-medication and changes in non-interacting co-medication (i.e. introduction of non-interacting drugs). The strength of the association between changes in medication and epilepsy-related hospitalisation was estimated using conditional logistic regression analysis and expressed as odds ratios (ORs) with 95% confidence intervals (CI).

Results

Out of 1185 patients with a first epilepsy-related hospitalisation, 217 patients met the inclusion criteria. Of the changes in antiepileptic therapy, discontinuation showed a trend towards an increased risk of hospitalisation (OR 2.57, 95% CI 0.81-8.17). Drug interactions influencing antiepileptic therapy rarely occurred. Introduction of three or more non-interacting drugs was significantly associated with epilepsy-related hospitalisation (OR 4.80; 95% CI 2.12-10.87). Of individual drugs, addition of antimicrobial agents was significantly associated with epilepsy-related hospitalisation (OR 1.99; 95% CI 1.06-3.75).

Conclusion

Changes in AED therapy were not significantly associated with epilepsy-related hospitalisation and few drug interactions influencing antiepileptic therapy occurred. However, patients starting three or more new non-AEDs had a nearly five times increased risk of epilepsy-related hospital admission.

INTRODUCTION

Epilepsy is one of the most common neurological disorders. The age-adjusted incidence in developed countries is around 50 per 100 000 persons per year (range 24-70 per 100 000 persons per year) and the prevalence is between 4 and 10 per 1000 persons.[1] Antiepileptic drugs (AEDs) are the mainstay of treatment. The ultimate aim of AED treatment and seizure control is the maintenance of the patients' normal lifestyle and the reduction of epilepsy-related morbidity and mortality. Optimal AED therapy can abolish seizures in 60 to 70% of patients with epilepsy, but in the remaining patients remission is elusive.[2,3]

Antiepileptic drugs are selected first and foremost according to clinical efficacy, then tolerability, drug interaction profile and ease of use.[4] Although monotherapy is mostly aimed for, in up to 50% of patients, combination therapy is necessary.[5] Once the optimal treatment for the individual patient has been found, it is important to maintain the policy chosen.

However, changes in AED treatment such as dose adjustment, add-on, switch, or discontinuation may be needed or are worth trying when adverse effects are present or optimum seizure control is not yet achieved.[6] Therefore, changes in treatment may be needed to finally obtain the ideal, though delicate, balance in AED treatment. Also, changes in concomitant medication can lead to a disturbance of the balance in AED treatment. It is known that AEDs are susceptible to pharmacodynamic and pharmacokinetic drug interactions.[7,8] Most AEDs have a narrow therapeutic index, meaning that simultaneous administration of interacting drugs may result in a change in AED plasma concentration and an increased risk for adverse drug events or reduced efficacy.[9] This applies particularly to established AEDs (phenytoin, phenobarbital and carbamazepine) that are metabolized by the cytochrome P450 enzyme system. Drug interaction compendia such as 'Drug Interactions: Analysis and Management'[10] and the 'MICROMEDEX (DRUG-REAX) system'[11] mention over 600 drug interactions involving AEDs. Many of these drug interactions can be potentially hazardous and are often noted as 'combination should be avoided if possible'.[10] From a pharmacodynamic point of view many drugs are known to influence the seizure thresholds.[12] Also, concomitant drugs can deregulate epileptic treatment, for instance by disturbing the metabolic balance. It is known that metabolic disorders such as hypoglycaemia can induce epileptic seizures.[13] Therefore, we were also interested in starting of new medication. Thus, changes in AEDs as well as in non-AEDs may disturb the delicate balance of AED treatment, which may lead to a reduced seizure control and a higher seizure rate possibly resulting in epilepsy-related hospitalisation.[14]

Each year approximately 7000 patients in the Netherlands are admitted to hospital because of epilepsy.[15] Until now, studies on the cause of epilepsy related hospital admissions are scarce and often the reason for admission is unclear.[16] No studies were found on the impact of changes in medication on epilepsy-related hospital admissions. To investigate this subject we explored the association between changes in medication and epilepsy-related hospitalisation.

METHODS

Setting

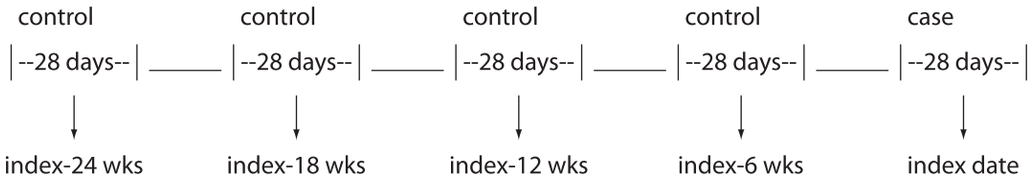
The setting of the study was the PHARMO Record Linkage System (RLS). The PHARMO RLS includes pharmacy dispensing records from community pharmacies linked to hospital discharge records of all 950 000 community-dwelling residents of 25 population-defined areas in the Netherlands from 1985 onwards.[17] Since virtually all patients in the Netherlands are registered with a single community pharmacy, independent of prescriber, pharmacy records are virtually complete with regard to prescription drugs. The computerised drug dispensing histories contain information concerning the dispensed drug, dispensing date, prescriber, amount dispensed and prescribed dosage regimen. The duration of use of each dispensed drug is estimated by dividing the number of dispensed units by the prescribed number of units to be used per day. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification. The hospital discharge records are obtained from PRISMANT, previously known as the Dutch Centre for Healthcare Information (LMR database), an institute that collects nationwide all hospital discharge records in the Netherlands since the 1960s in a standardised format. These records include detailed information concerning the primary and secondary discharge diagnoses, diagnostic, surgical and treatment procedures, type and frequency of consultations with medical specialists and dates of hospital admission and discharge. All diagnoses are coded according to the International Classification of Diseases, 9th edition (ICD-9-CM). Each patient is registered with an anonymous unique patient identification code that allows for the observation of patient medication in time. The database does not provide information concerning the indications for use of medicines. Our data covered the period from January 1998 to December 2002.

Study design and study population

A case-crossover study was conducted. In this design each case serves as its own control, that is each case contributes one case window and one or more control windows.[18] The case window is defined as the 'at risk period' preceding the event (hospital admission in our study).

The study population comprised all patients aged 18 years and older with a first primary hospital admission for epileptic seizures (ICD-9 codes 345.0 to 345.5, 345.7 to 345.9 and 780.3). Patients were eligible for inclusion when continuously exposed (80% of time) to at least one AED for a period of 28 weeks preceding the date of hospitalisation. AEDs were defined as drugs that are prescribed for epilepsy and approved for use in The Netherlands. The date of hospital admission was termed the index date. For each patient, four control moments were defined at 6, 12, 18 and 24 weeks prior to the index date. Per patient changes in medication were studied during the 28-day window prior to the index date as well as during the 28-day windows prior to the control moments (Figure 1).

Figure 1 Case-crossover design

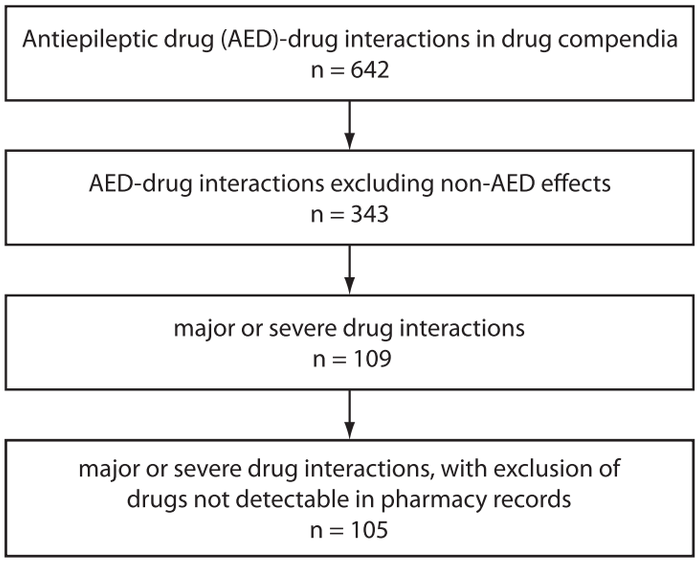


Determinants

Three types of changes in medication were defined. First, we studied changes in AED therapy; this consisted of changes in pattern (add-on, discontinuation, switch) and changes in AED dose. AED patterns were divided into four mutually exclusive groups: 1) no change in AED use, 2) add-on of another AED, 3) discontinuation of an AED, and 4) switch of AEDs. Add-on was defined as a start with a new AED in combination with the AED(s) the patient was already using. Discontinuation was defined if no follow up dispensing was recorded for at least 90 days after the theoretical end date of the last AED supply. We defined a switch of an AED if an AED was started and another AED was discontinued within the 28-day time window. Dose changes of AED were divided into three groups: 1) no change in AED dose, 2) higher dose of AED, 3) lower dose of AED.

Second, we investigated changes in interacting drugs. For this, we examined introduction and discontinuation of drugs that can either lead to changes in AED plasma concentration levels or affect the seizure threshold. Interacting drugs include both AEDs and non-AEDs. To identify the relevant drug interactions the following process was undertaken (Figure 2): drug interactions were selected and cross-referenced from three commonly used drug interaction compendia namely Drug Interactions: Analysis and Management,[10] MICROMEDEX (DRUG-REAX) system,[11] and the Dutch Z-index.[19] AED drug interactions were selected if they were listed as 'major' or 'severe' drug interactions. From 642 drug interactions involving AEDs, 343 affected the AED efficacy or the seizure threshold and 109 of them were marked as major or severe. Drug interactions were excluded when the drug was not routinely dispensed in a community pharmacy setting (e.g.

Figure 2 Selection of relevant drug interactions [10,11,19]



pancuronium) or when the interaction involved a product not likely to be captured by a computerized database, such as non-prescription medications (e.g. St John's Wort). After application of these criteria 105 drug interactions remained (Table 1). Use of co-prescribed interacting drugs were categorized into four mutually exclusive groups: 1) no use of an interacting drug, 2) continued use of an interacting drug (i.e. the drug was started before the four weeks of observation), 3) start of an

Table 1 Relevant interactions with AEDs and convulsion thresholds [10,11,19]

Potential drug interaction	Interacting drugs
Lowering convulsive thresholds	antipsychotics, selective serotonine reuptake inhibitors, tricyclic antidepressants, maprotiline, mefloquine
Carbamazepine toxicity	acetazolamide, cimetidine, clarithromycine, danazol, diltiazem, erythromycine, fluconazole, fluoxetine, fluvoxamine, isoniazide, ketoconazole, nefazodone, propoxyphene, rifampicine, rifabutine, verapamil, vigabatrin
Primidone toxicity	valproic acid
Ethosuximide toxicity	isoniazide, phenytoin
Phenytoin toxicity	amiodarone, azapropazone, capecitabine, chloramphenicol, cimetidine, diltiazem, disulfiram, esomeprazole, ethosuximide, fluconazole, fluoxetine, fluvoxamine, isoniazide, miconazole, omeprazole, phenylbutazone, pyrimethamine, theophylline, topiramate, trimethoprim, voriconazole
Reduced phenytoin efficacy	methotrexate, rifampicine, sucralfate
Lamotrigine toxicity	valproic acid
Reduced lamotrigine efficacy	carbamazepine, methsuximide, oxcarbazepine, phenobarbital, phenytoin, primidone, rifampicine
Valproic acid toxicity	cimetidine, primidone

interacting drug, 4) discontinued use of an interacting drug. Start of an interacting drug was defined if a new prescription (i.e. no prior use of at least 90 days for this prescription) for this drug was started. Discontinued use of an interacting drug was defined if a patient had no new prescription for this drug 90 days after the theoretical end date. We were particularly interested in starting and discontinuing of interacting drugs, given our objective to examine the influence of changes in therapy.

Third, we examined changes in non-interacting concomitant medication, that is introduction of new drugs, which were defined as no prior prescription for the same drug for at least 180 days before the dispensing date.

Potential confounding factors

As each patient served as its own control, confounding due to fixed characteristics such as genetic factors, personality, education, lifestyle, and chronic diseases was eliminated by the study design. In case-crossover studies known potential confounders are usually time related. Recent hospitalisation with potential seizure

related events such as stroke, head trauma etc. was considered as a potential confounding factor. Therefore, hospital admissions for cerebrovascular diseases (ICD codes 430 to 438), neurological diseases (ICD-9 codes 320 to 359) and trauma (ICD-9 codes 800-999) were compared for case and control moments.

Data analysis

Data were analysed by use of a case-crossover design. Each subject represented a matched set of data for case and control exposures. Thus, for each subject, the odds of a recent change (within 28 days) in medication before the date of hospital admission (index date) was compared with the odds of a recent change in medication before a control date. The strength of the association between changes in medication and the risk of hospitalisation was estimated using conditional logistic regression and expressed as odds ratios (ORs) with 95% confidence intervals (95% CI). Covariates were included in the regression model if they were either independently significantly associated with the outcome, or induced a 10% change or more in the crude OR for the exposure of interest on the risk of hospitalisation.

RESULTS

Of 1185 patients in our cohort with a first epilepsy-related hospital admission, 352 patients had used at least one AED prescription in the year before hospital admission. Out of this group, 217 patients met our criteria for continuous AED use. The characteristics of the study population are displayed in Table 2. Of the population 51.6% were men. The median age was 49 years. The majority of patients (57.1%) were admitted for unspecified epilepsy, followed by grand mal status epilepsy (13.4%) and generalized convulsive epilepsy (9.2%). Monotherapy was the most common AED treatment (56.2%) in our study population. The most frequently used AEDs were valproic acid, carbamazepine, and phenytoin. The frequency of hospital admissions for cerebrovascular diseases, neurological diseases or trauma was low and was not different between case and control moments. This did not lead to a significant difference between case and control moments and therefore we did not adjust for this factor.

Add-on tended to be associated with a reduced risk of epilepsy-related hospitalisation, although the confidence interval was wide (OR 0.46; 95% CI 0.14-1.54). We observed a non-significant increased risk of epilepsy-related hospitalisation after discontinuation of AEDs (OR 2.57; 95% CI 0.81-8.17). No association was found

Table 2 Characteristics of the study population	
Characteristic	**Study population n=217 (100%)**
Demographics	
male gender	112 (51.6%)
age (years)	
18-34	49 (22.6%)
35-49	60 (27.6%)
50-64	49 (22.6%)
≥ 65	59 (27.2%)
International Classification of Diseases (ICD)-9	
epilepsy, unspecified	124 (57.1%)
grand mal status epilepsy	29 (13.4%)
generalized convulsive epilepsy	20 (9.2%)
partial epilepsy, no impaired consciousness	15 (6.9%)
other	29 (13.4%)
Number of antiepileptic drugs[a]	
0	3 (1.4%)
1	122 (56.2%)
2	73 (33.6%)
≥ 3	19 (8.7%)
Antiepileptic drug[a]	
valproic acid	96 (44.2%)
carbamazepine	84 (38.7%)
phenytoin	61 (28.1%)
lamotrigine	22 (10.1%)
oxcarbazepine	21 (9.8%)
vigabatrine	15 (7.0%)
phenobarbital	11 (5.1%)
other antiepileptic drugs	17 (7.8%)

a) Use four weeks before hospitalisation.

between both increased and reduced AED dosage and epilepsy-related hospital admissions (OR 0.73; 95% CI 0.35-1.50 and OR 0.71; 95% CI 0.26-1.95) (Table 3). In 25.3% (55/217) of our study population we identified the co-prescribing of predefined interacting drugs, half of them (26/217) involving AED-AED interactions. Relevant drug interactions for our research objective by the introduction or discontinuation of interacting drugs occurred in 11% of patients (24/217). Two interactions leading to potential loss of AED efficacy occurred in case moments compared to eleven changes in control moments (OR 0.72; 95%CI

Table 3 Changes in medication among case and control moments			
Exposure	**Case n=217 (100%)**	**Control n=868 (100%)**	**OR (95% CI)**
Changes in AEDs			
Changes in AED patterns			
continuous use/no change	209 (96.3%)	832 (95.9%)	1.00 (ref)
switch	0 (0.0%)	2 (0.2%)	NE
add-on	3 (1.4%)	26 (3.0%)	0.46 (0.14-1.54)
stop	5 (2.3%)	8 (0.9%)	2.57 (0.81-8.17)
Changes in AED dosage			
no dose change	202 (93.1%)	795 (91.6%)	1.00 (ref)
higher dose	10	53	0.73 (0.35-1.50)
lower dose	5	27	0.71 (0.26-1.95)
Interactions that can affect AED efficacy/toxicity			
No interaction or no change in interaction	214	847	1.00 (ref)
Interaction leading to AED toxicity	1	10	0.40 (0.05-3.10)
Interaction leading to reduced AED efficacy	2	11	0.72 (0.16-3.24)
Introduction of new non-interacting drugs			
Number of new started drugs	154	682	1.00 (ref)
none			
1	42	145	1.33 (0.90-1.97)
2	8	28	1.40 (0.60-3.27)
≥ 3	13	13	4.80 (2.12-10.87)
Group of new drugs			
antibiotics	15	31	1.99 (1.06-3.75)
benzodiazepines	7	25	1.12 (0.48-2.59)
antiinflammatory and antirheumatic drugs	7	18	1.61 (0.65-4.00)
antithrombotics	2	11	0.72 (0.16-3.32)

AED = antiepileptic drug; ref = reference; NE = not estimable

0.16-3.24). One interaction leading to a potential AED toxicity in the case moments versus ten in the control moments was found (OR 0.40; 95% CI 0.05-3.10).
Exploring the introduction of new non-interacting drugs a significant association was observed when three or more drugs were started (OR 4.80; 95% CI 2.12-10.87) (Table 3). Drugs that were newly started in our study population were antimicrobial agents (13%), benzodiazepines 9%), antiinflammatory and antirheumatic drugs (7%) and antithrombotic agents (4%). For antibiotics and epilepsy-related hospitalisation the association was statistically significant (OR 1.99; 95% CI 1.06-3.75).

DISCUSSION

The main findings of this study are that 1) changes in AED therapy were not significantly associated with epilepsy-related hospital admissions, although discontinuation of AED therapy tended to be associated with an increased risk of epilepsy-related hospital admissions, 2) no significant association in changes of interacting drug by means of start or discontinuation of interacting drugs was found, and 3) addition of three or more non-interacting drugs in patients with epilepsy was statistically significantly associated with epilepsy-related hospital admissions.

Discontinuation of AEDs has been and still is a field of discussion.[20] When epilepsy is in remission, it may be in the patients' best interest to discontinue medication to avoid side effects, drug interactions, and teratogenicity. On the other hand, one should assess the risk of recurrent seizures. Based on a meta-analysis, the risk of relapse after AED withdrawal was 25% after one year and 29% at two years.[21] Specchio et al.[22] found that the risk of seizure relapse after discontinuing treatment was 2.9 times that of patients continuing treatment. Our study supports the evidence of the difficulties that are associated with discontinuing AEDs.

In response to increasing cost pressures, healthcare systems are encouraging the use of and the switch to generic medicines. Both physicians and patients are concerned that the generic substitute would not be clinically equivalent with the brand name formulation.[23] This kind of change was not a topic in our current study and as such these switches are not included in our definition of changes in medication. Separately, we found that within our database only three patients switched from brand to generic AED. This small number did not allow us to further investigate this topic.

We were not able to detect important interacting drugs that could lead to epilepsy-related hospital admissions. The incidence of start or discontinuation of interacting drugs was low, despite the many drug interactions mentioned in compendia involving AEDs. We found that almost 50% of the drug interactions affected the non-AED (due to enzyme inducing properties) and not the AED effect itself. Furthermore, another 30% of interactions was not marked as severe or major. Nonetheless, 105 drug interactions remained (Figure 2). Novak et al.[24] reported an incidence of 3% of co-prescribed potentially harmful interacting non-AEDs in children on chronic AEDs. In our adult population we found a higher prevalence of interactions affecting only the AED effect, 13%. This may be because of a more frequent use of antidepressants, SSRIs and antipsychotics in an adult population. Most drug interactions are based on pharmacokinetic studies or case reports. As stated by Aronson[25] there are two classes of susceptibility, interactions to which

all patients are equally susceptible and interactions that affect only a subset of individuals. By selecting only major or severe drug interactions we did not account for most of the interactions in the latter category.

Addition of three or more non-AEDs was associated with a higher risk of epilepsy-related hospitalisation. Since patients with epilepsy are at higher risk of having concomitant diseases, such as disorders affecting the nervous system or ear–nose–throat disorders, co-prescription of other drugs may often occur.[26] An existing or new disease that requires intervention with multiple drugs may be the underlying problem for epilepsy-related hospitalisation. In addition, this may also lead to an increase of physical stress, which is known as a trigger for seizures. Since a substantial number (13%) of the introduced noninteracting drugs were antibiotics, the occurrence of infections and subsequent triggering of an epileptic event can also explain the observed association.[27]

The results of this study should be interpreted in the light of its limitations. Our small sample size was one of our main limitations. In a case-crossover design there is no confounding by conditions that do not vary over time. However, irregular use of alcohol, drugs, or stress may confound the relations we observed.[28,29] Moreover, underlying focal brain abnormalities such as brain tumors and systemic metabolic derangements including hypoxia or electrolyte imbalance are also important predictive factors for seizure occurrence that could not be taken into account due to the limited clinical information provided.[29,30]

Our hypothesis was that changes in drug treatment in patients with epilepsy can trigger an epileptic seizure. However, patients with seizures do not all end-up in the hospital. With our study design we were only able to observe the 'tip of the iceberg'. It is unknown what proportion of the total number of seizures was not detected. It would have been interesting to know the development in total seizure frequencies of the study population, not only the ones leading to hospitalisation. Also, additional information would be helpful in asserting the reason for prescribing new drugs or changes in AED treatment.

Changes in medication were studied within a 28-day time window. This period of time was chosen for several reasons. It ensures that drugs of which intake is started or discontinued during the time window had enough time to reach steady state concentrations and it allows interactions through the cytochrome P450 system to develop. However, it is possible that this period of 28 days may have been too short for these interactions to result in clinical effects, and thus, our results may have been diluted.

Although risk factors for seizures have been studied, to our knowledge this is the first study approaching the problem from the perspective of epilepsy-related

hospital admissions. In our opinion, outcome studies such as ours can broaden our view of the clinical significance of different changes in drug treatment in patients with epilepsy. Further studies are needed to explain and/or confirm our findings. In addition, studies in epileptic centres where patients are stimulated to keep seizure diaries could give more information on the change of seizure frequency that may be caused by changes in medication. We are currently setting up a clinical study to explore this subject.

In conclusion, this study showed that changes in AED therapy were not significantly associated with epilepsy-related hospitalisation and that only few drug interactions occurred. In patients with epilepsy start of antibiotics or start with multiple non-AEDs (not known interact with AEDs) is associated with an increased risk for epilepsy-related hospitalisation. In clinical practice, health care practitioners should be aware that starting antibiotics or starting three or more new non-AEDs may be a proxy for a disturbance of the delicate balance in treatment that may exist in many patients with epilepsy.

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chapter 3.2

Drug treatment-related factors of inadequate seizure control

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ABSTRACT

Objective

To optimize seizure control it is important to identify modifiable factors.

Methods

We conducted a case-control study to explore to what extent drug treatment-related factors are associated with seizures.

Results

Eighty-six patients with epilepsy were evaluated: 45 cases (recently experienced a seizure) and 41 controls (seizure free for at least two months). There was a significant association for low antiepileptic drug (AED) serum concentration and seizures (odds ratio [OR] 8.9; 95% confidence interval [CI] 1.7-47.8), compliance was not associated with seizures (OR 0.9; 95% CI 0.2-4.0), and changes in medication (mainly non-AEDs) were more frequently observed in the case group than in the control group (OR 4.1; 95% CI 0.9-18.3).

Conclusion

These findings indicate that patients with low AED serum levels have a nine times higher risk of seizures compared with patients with therapeutic AED levels and that changes within medication regimes in patients with epilepsy should be made with care.

INTRODUCTION

Approximately 50% of all patients with epilepsy report having seizures of varying frequency and severity despite antiepileptic drug (AED) treatment.[1,2] Evidently, the aim of AED treatment is to keep the number, as well as the severity, of seizures to a minimum, as seizures can have significant negative impact on work, family and social life.[3,4] It is therefore important to identify the various modifiable factors that may affect seizure control once patients are taking AEDs.

Seizures can be triggered by environmental factors such as emotional stress, sleep deprivation, infections or various drug treatment-related factors.[5,6] One of these drug treatment-related factors is AED serum concentration. Although epileptic guidelines no longer recommend standard drug monitoring,[7,8] it is known that serum concentrations of AEDs are in fact related to clinical effects.[9,10] This implies that low AED levels may result in deterioration of seizure control and that therapeutic drug monitoring (TDM) may still be required. Also, poor compliance is probably a major contributor to suboptimal control of epileptic seizures.[11] In the literature, the proportion of poorly-compliant patients with epilepsy varies from 30 to 50%.[12-14] Finally, changes in medication (AEDs as well as non-AEDs) may influence seizure control, as it is known that AEDs are susceptible to drug-drug interactions.[15] The metabolism of many older AEDs is easily influenced by other AEDs and non-AEDs (pharmacokinetic interactions). In addition, non-AEDs may lower seizure thresholds or be epileptogenic, leading to higher seizure rates (pharmacodynamic interactions).[16-18]

In the study described here, our aim was to investigate to what extent drug treatment-related factors, that is, AED serum concentrations, compliance, and changes in medication, are associated with the occurrence of seizures.

METHODS

Setting and study population

From November 2004 to May 2007 a case-control study was conducted in the Neurology Department of Jeroen Bosch hospital, a major 770-bed teaching hospital located in the south of The Netherlands. Ethical permission to conduct this study was obtained from the ethics committee of the hospital. Patients were aged 18 years or older and diagnosed with epilepsy, for which they had been treated with AEDs for at least one year. Cases were patients who were admitted to the emergency department or visited their neurologist as a consequence of a recent seizure (≤14 days before the visit). Control patients were patients who had been seizure-free

at least two months and visited their neurologist for a regular checkup. Besides pregnancy, no other exclusion criteria were defined. Informed consent was obtained from each patient.

Determinants

Serum concentrations of cases and controls on the day of admission or (control) visit were determined in the laboratory using standard techniques. Target AED serum concentrations were defined according to the TDM laboratory reference values of the hospital (Table 1). These are in accordance with commonly accepted therapeutic ranges for the various AEDs.[19,20] Subsequently, patients were classified into four categories: high, therapeutic, subtherapeutic, and low AED concentrations. High concentrations were defined as concentrations above the therapeutic range; serum concentrations below the therapeutic range but above 50% of the lowest therapeutic level were labeled subtherapeutic; low concentrations were defined as

Table 1 Classification of serum concentrations of antiepileptic drugs (AEDs)[19,20]

AED	Concentration (µg/ml)			
	Low	Subtherapeutic	Therapeutic	High
carbamazepine	< 2	2–4	4–12	> 12
ethosuximide	< 20	20–40	40–100	> 100
lamotrigine	< 1.25	1.25–2.5	2.5–15	> 15
levetiracetam	< 4	4–8	8–26	> 26
oxcarbazepine	< 6	6–12	12–35	> 35
phenobarbital	< 7.5	7.5–15	15–40	> 40
phenytoin	< 4	4–8	8–20	> 20
topiramate	< 2.5	2.5–5	5–20	> 20
valproate	< 25	25–50	50–100	> 100

concentrations >50% below the lowest therapeutic level. Patients who used multiple AEDs were classified in the lowest category applicable.

To study AED compliance, drug-dispensing histories were requested from the patients' pharmacies with written permission of the patients. Compliance for the year preceding the index date was calculated by dividing the sum of the durations of the individual AED prescriptions in the year prior to the index date by the total number of days between the start date of the first prescription and the start date of

the prescription directly after the index date. A patient with compliance below 80% was categorized as poorly compliant.[21,22]
Changes in medication included both changes in AEDs and changes in co-medications (interacting and non-interacting agents). Changes were defined as dose adjustment, initiation, or discontinuation of medication in the 28-day window before the seizure or the control visit. All patients were asked to complete a questionnaire on seizure frequency, seizure-free period, drugs being taken, and recent changes in medication (start, stop or changes in dose 28 days before the index date). Information on recent medication changes was obtained from the questionnaires and from the drug-dispensing histories.
Medical records were consulted to obtain additional clinical patient characteristics such as type of epilepsy and possible cause of the seizure (cases).

Data analysis

Cases and controls were compared with respect to baseline parameters by using χ^2 test for frequency data and Student's t-test for comparison of means. A p-value <0.05 was considered statistically significant. The strength of the association between drug treatment-related factors and seizures was estimated using conditional logistic regression analysis and expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Covariates were included in the regression model if they were independently significantly associated with the outcome (at a $p<0.2$ level).

RESULTS

In total 86 patients, 45 cases and 41 controls were included in this study. The majority of cases (77.8%) were recruited from the emergency department. Cases and controls were comparable with respect to age, gender and type of epilepsy. Cases had a significant higher seizure frequency than controls. Also, although the majority in both groups were on monotherapy, cases more often were taking three or more AEDs than controls (15.5% versus 2.4%). We therefore adjusted our analysis for seizure frequency and number of AEDs (Table 2).
With respect to AED concentrations, approximately one-third (37.2%) of cases had therapeutic concentrations compared with more than half (58.5%) of controls. The prevalence of low serum concentrations in the case group was 27.9% versus 7.3% in the control group. A significant association was noted between low AED concentrations and seizures (adjusted OR 8.9; 95% CI 1.7-47.8). Poor compliance was comparable in cases and controls (15.8% vs 15.0%; adjusted OR 0.9; 95% CI

Table 2 Patient demographics and characteristics

	Cases (n=45)	Controls (n=41)	p-value
	n (%)	n (%)	
Age (years)			0.88 [a]
range	20-80	19-84	
mean	49.2	48.7	
Sex (male)	27 (60.0%)	22 (53.7%)	0.55 [b]
Type of epilepsy			0.52 [b]
localization-related	25 (55.6%)	21 (51.2%)	
generalized epilepsy	16 (35.6%)	13 (31.7%)	
undetermined epilepsy	4 (8.9%)	7 (17.1%)	
Seizure frequency [c]			0.04 [b]
≤ 1 per year	9 (23.7%)	21 (52.5%)	
1 per 3-12 months	9 (23.7%)	8 (20.0%)	
1 per 1-3 months	10 (26.3%)	6 (15.0%)	
> 1 per month	10 (26.3%)	5 (12.5%)	
Number of antiepileptic drugs			0.08 [b]
1	25 (55.6%)	30 (73.2%)	
2	13 (28.9%)	10 (24.4%)	
≥ 3	7 (15.6%)	1 (2.4%)	
Antiepileptic drug use			
carbamazepine	12 (26.7%)	11 (26.8%)	
lamotrigine	11 (24.4%)	1 (2.4%)	
levetiracetam	5 (11.1%)	6 (14.6%)	
oxcarbazepine	6 (13.3%)	3 (7.3%)	
phenytoin	10 (22.2%)	7 (17.1%)	
valproic acid	21 (46.7%)	20 (48.8%)	
other	7 (15.6%)	5 (12.2%)	

a) Students t-test.
b) χ^2 test.
c) Numbers do not add up to the total number of cases and controls because of missing data; calculated percentages are with respect to respectively 38 (cases) and 40 (controls).

0.2-4.0). Recent changes in medication were observed more often in cases than in controls (22.5% vs 7.5%, adjusted OR 4.1; 95% CI 0.9-18.3) (Table 3). Changes in medication in both groups consisted mainly of changes in non-AEDs. None of these changes were known to influence either AED serum concentrations or seizure thresholds (i.e., pharmacokinetic or pharmacodynamic drug interactions). Examples of changes in medication were dose adjustment of an antidepressant (1x) and initiation of analgesics (2x).

Table 3 Drug-treatment related factors in cases and controls

	Cases (n=45)	Controls (n=41)	Crude	Adjusted[a]
	n (%)	n (%)	OR (95% CI)	OR (95% CI)
Antiepileptic drug concentration[b]	*n=43 (100%)*	*n=41 (100%)*		
therapeutic	16 (37.2%)	24 (58.5%)	1.0 (ref)	1.0 (ref)
subtherapeutic	14 (32.6%)	12 (29.3%)	1.8 (0.7-4.7)	0.9 (0.3-3.2)
low	12 (27.9%)	3 (7.3%)	6.0 (1.5-24.7)	8.9 (1.7-47.8)
high	1 (2.3%)	2 (4.9%)	0.8 (0.1-9.0)	1.5 (0.1-25.5)
Antiepileptic drug compliance[b]	*n=38 (100%)*	*n=40 (100%)*		
> 80%	32 (84.2%)	34 (85.0%)	1.0 (ref)	1.0 (ref)
< 80%	6 (15.8%)	6 (15.0%)	1.1 (0.3-3.6)	0.9 (0.2-4.0)
Changes in medication[b]	*n=40 (100%)*	*n=40 (100%)*		
no changes	31 (77.5%)	37 (92.5%)	1.0 (ref)	1.0 (ref)
any change	9 (22.5%)	3 (7.5%)	3.6 (0.9-14.4)	4.1 (0.9-18.3)
- changes in AEDs	2 (5.0%)	1 (2.5%)	2.4 (0.2-27.6)	2.8 (0.2-42.5)
- changes in non-AEDs	7 (17.5%)	2 (5.0%)	4.2 (0.8-21.6)	4.7 (0.8-26.8)

ref = reference; AED = antiepileptic drug

a) Adjusted for the number of AEDs and seizure frequency.

b) Numbers do not add up to the total number of cases and/or controls because of missing data, see numbers in italic.

All cases were asked to report the possible causes of their seizure. In 22 of 45 cases, no reason was given for the hospital-indicated seizure. In the remaining cases, the suspected seizure trigger was: infection (4x), failure to remember to take AED(s) (4x), tensions/stress (2x), head trauma (1x), cerebrovascular accident (1x), loss of sleep (1x), and premenstrual seizure (1x). Three of the four patients who reported forgetting to take their medication, did indeed have low serum concentrations.

DISCUSSION

This study demonstrated the existence of a clear association between low antiepileptic serum concentrations and the occurrence of seizures. A trend was observed between recent changes in medication, mainly non-AEDs, and the occurrence of seizures. Poor compliance in the year prior to the seizure was not associated with seizures in our study.

The role of TDM in patients with epilepsy remains a topic of ongoing discussion. In accordance with both Dutch neurology guidelines and the NICE epilepsy clinical guideline, AED serum concentrations are not routinely measured in our hospital.[7,8]

The concept of TDM is based on the assumption that clinical effects of AEDs, especially of the older-generation AEDs, corresponds better to drug concentration than to dose.[23] Believers advocate that TDM is valuable given the marked and unpredictable pharmacokinetics of AEDs, especially phenytoin. Furthermore, they state that it can be a useful tool in evaluating the potential cause of lack of efficacy.[24-26] Nonbelievers advocate that it is possible to improve overall therapeutic outcome on purely clinical grounds.[27,28] Only one multicentre randomized controlled trial on TDM has been conducted.[29] In this study, early implementation of serum AED level monitoring did not improve overall clinical outcome. However, this may be due to the fact that strict therapeutic ranges were used. Also, much discussion arises on the subject of therapeutic ranges, especially with respect to the newer AEDs. It is clear that the optimal serum concentration varies with the individual. Furthermore, it is generally agreed that if a well-stabilized patient has a subtherapeutic drug level, dose adjustment is unnecessary.[30] In our study, two levels of serum concentrations below the therapeutic window were distinguished: subtherapeutic and low. Subtherapeutic levels were not associated with seizures, but patients with low AED concentrations had a nine times higher chance of seizures compared with patients with therapeutic drug concentrations. This result suggests that routine measurement of AED serum concentrations, in addition to clinical observations, may be an important tool in optimizing seizure control.

In addition to dose and metabolizing factors, poor compliance can be one of the explanations of low serum concentrations. However, we found no correlation between poor compliance and AED blood levels (Pearson's r=0.1). Furthermore, poor compliance was not associated with seizures in this study. This failure to find an association may be due to our approach of measuring refill compliance using pharmacy records over the 1-year period before the seizure. One of the limitations in measuring drug compliance by refill is that this is not necessarily a good marker of consumption of the medication. Ideally the information needed is the compliance in the week or the 24-hours preceding the seizure. Unfortunately we did not have this information, except for the four cases who reported their forgetting to take medication may have triggered the seizure they experienced. Also, one could argue about the threshold of 80%. However, sensitivity analyses varying the percentage from 50% to 90% did not alter our findings.

In a previous study, we reported a significant association between initiation of three or more new drugs and epilepsy-related hospital admissions.[15] Again, in the present study we found a clear indication that changes in medications are associated with a higher chance of seizures. Even non-AEDs that are not necessarily known to interact with AEDs or seizure thresholds seem to be associated with a higher incidence of

seizures. This implies that patients with epilepsy have a delicate balance that may easily be disturbed.

In addition to the issues mentioned above, sample size was another limitation of this study. The wide margins of the odds ratios are probably related to the small number of patients. Also, because of this, we were not able to analyze the influence of the different types of changes in medication. However, despite the small sample size, we found a clear and statistically significant association between low drug concentrations and seizures.

Overall, even taking into account these limitations, the findings herein suggest that drug treatment-related factors such as AED serum concentrations and changes in medication regimens can be optimized to obtain better seizure control in patients with epilepsy.

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4

Gene-related causes of ineffectiveness

chapter 4.1

Lack of association between genetic variations in ABCB1 and drug-resistant epilepsy

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ABSTRACT

Objective

Association studies between polymorphisms in ABCB1 (encoding drug transporter P-glycoprotein) and antiepileptic drug (AED) response have produced inconsistent results. This may be due to the fact that only a few single nucleotide polymorphisms (SNPs) or small haplotype blocks have been studied. In this study, we extensively explored the association between all known variations (high resolution haplotypes) of the ABCB1 gene and drug-resistant epilepsy.

Methods

A case-control study was conducted in a main tertiary epilepsy centre in the Netherlands. Patients were eligible for inclusion if they were 18 years or older and treated with AEDs for at least one year at this centre. Cases were AED resistant patients and controls were patients who were responsive to AED treatment. The frequency of 18 SNPs and the consequently 32 haplotypes of ABCB1 were compared and tested with $\chi 2$ test and logistic regression analysis.

Results

287 Patients were included and genotyped in this study: 128 AED resistant patients and 159 AED responding patients with epilepsy. No association was found for individual SNPs and drug-resistant epilepsy. Almost 90% of all patients was represented by 9 haplotypes of ABCB1. No association was found for haplotypes of ABCB1 and drug-resistant epilepsy.

Conclusion

In this study, assessing all known variations in the ABCB1 gene, we found no association between ABCB1 and drug-resistant epilepsy.

INTRODUCTION

Epilepsy is the most common serious neurological disorder affecting an estimated 50 million people worldwide. Although the majority of patients is well under control with antiepileptic drugs (AEDs), about 30% of patients continues to experience debilitating seizures despite AED treatment.[1] Patients with drug resistant or refractory epilepsy endure a devastating disease with significant neuropsychological, psychiatric, and social impairments that greatly influences their quality of life.[2,3]

The reason for therapeutic failure is still unknown. Several hypotheses, have been proposed, one of which is the transporter hypothesis. This hypothesis proposes that AEDs do not reach significant concentrations in the brain as a result of active efflux mediated by over expressed drug transporter proteins.[4,5] Since patients who failed their first drugs of choice are less likely to gain seizure control with each successive AED, irrespective of which AED, this theory seems plausible.[6]

The transporter theory has been studied in patients with epilepsy, comparing genetic variations (single nucleotide polymorphisms, SNPs) in the ABCB1 gene (encoding drug transporter P-glycoprotein) of patients responding to AEDs with drug resistant patients. Although the first study published showed promising results – a clear association was found between the CC genotype of ABCB1 3435C>T and drug resistance [7] – a replication study failed to confirm this association.[8] Also, other research groups have looked at associations between various other SNPs in ABCB1 and drug resistance in epilepsy.[9-12] So far, results have not been consistent. One of the drawbacks from studies published until now is that these have mainly looked at associations between individual SNPs and drug resistance. However, association tests based on high-resolution haplotypes (combinations of multiple SNPs) may provide more information than tests based on limited numbers of underlying SNPs. We therefore set up a study extensively exploring genotypes as well as high-resolution haplotypes of ABCB1 and comparing the prevalence in a group of drug-resistant patients with epilepsy versus a group of drug-responding patients.

METHODS

Patients

This study was approved by the ethics committee of Epilepsy Centre Kempenhaeghe in Heeze, one of the two tertiary centres for epilepsy in the Netherlands. Patients were eligible for inclusion if they were 18 years and older, had an established diagnosis for epilepsy (classified according to the International League Against Epilepsy Classification (ILAE), 1981)[13] and were treated with AEDs for at least one

year at this centre. Exclusion criteria were: patients with non-epileptic psychogenic seizures, progressive neurologic diseases, comorbidity or lifestyle (e.g. use of alcohol or drugs) that may affect seizure frequency, unreliable drug adherence, and incapacity of keeping track of seizure frequency.
A case-control study was performed, cases were drug-resistant patients and controls were drug-responsive patients. Patient demographics and characteristics such as epilepsy classification, seizure frequency, medication history and current use of AEDs were obtained from the patient's medical record and by patient interview. Blood collection of all patients took place for genetic analysis. All participants gave written informed consent to participate in this study.

Definition of drug response and drug resistance

Drug response was defined as seizure freedom or a 50% or more reduction in seizure frequency compared with start of AED therapy in the year prior to the date of inclusion.[12,14,15] By looking at the response on AED treatment at one year before inclusion, data are most likely to be sufficiently reliable. Drug-resistance was defined as less than 30% reduction in seizure frequency in the year prior to the date of inclusion compared with start of AED therapy, in patients who were treated with at least three established AEDs at the maximally tolerated doses. We chose for this definition to emphasize the effect of AEDs, rather than the absolute number of seizures that could also be associated with the epilepsy diagnosis. In order to contrast cases and controls the distinction between <30% and >50% was made.

Genotyping

To study ABCB1 haplotypes, Single Nucleotide Polymorphisms (SNPs) with a variation of >0.5% in Caucasian population were selected from a study by Kroetz et al., who sequenced the entire ABCB1 gene.[16] These haplotypes together with the accompanying SNPs (with rs numbers) are shown in Table 1. Rs 9282564 is also known as 61A>G, rs2229109 as 1199G>A, rs1128503 as 1236C>T, rs9282563 as 2650C>T, rs2032582 as 2677G>T/A, and rs1045642 as 3435C>T.
DNA was isolated from 80 µl patient's blood using the Generation capture column kit (Qiagen Benelux, Venlo, the Netherlands) according to manufacturer's instructions. The DNA eluate (200 µl) was diluted 1:5 in Ultrapure Water (Invitrogen, Fisher-Emergo B.V., Landsmeer, The Netherlands) The 18 SNPs were analysed with real time PCR assays employing TaqMan MGB probes (Applied Biosystems, Nieuwerkerk aan den IJssel, The Netherlands). Rs28381801, rs28381802, rs2235033, rs2032582GA and rs2032582GT were Custom Genotyping Assays, rs28381916 and rs2235063 were Predesigned Assays, rs1045642 and rs9282564 were Validated Assays, and all

Table 1 ABCB1 haplotypes in Caucasians and accompanying SNPs [16]

Exon	1		2		5	10	11	12		13	14	15	18	20	21		26	
	1.8	1.10	2.2	2.3	5.1	10.1	11.2	12.2	12.5	13.1	14.2	15.1	18.1	20.2	21.2	21.3	26.3	
Haplotype	rs3213619	rs28381802	rs2214102	rs9282564	rs2235015	rs10276036	rs2229109	rs1128503	rs2032588	rs2235033	rs2235013	rs28381916	rs2235063	rs2235040	rs9282563	rs2032582	rs1045642	Frequency Caucasian[16]
*1	T	C	G	A	G	A	G	C	C	C	A	G	A	G	C	G	C	0.15
*13						G		T		T	G					T	T	0.32
*13C								T		T	G					T	T	?
*26					T									A				0.09
*14				G		G		T		T	G					T	T	0.075
*2A			A														T	0.07
*2																	T	0.05
*3	C																	0.045
*21					T				T	T	G							0.035
*15						G		T		T	G					T		0.025
*24																A		0.02
*26A					T									A				0.015
*30							A											0.01
*29			A															0.01
*2B																A	T	0.01
*26C					T									A		T		0.01
*11						G		T		T	G							0.01
*16						G		T		T	G		G			T	T	0.01
*17A										T	G					T	T	0.01
*4A	C	A														A		0.005
*25														A				0.005
*21D					T				T	T	G					T		0.005
*20									T	T	G							0.005
*9										T	G							0.005
*12						G		T		T	G						T	0.005
*14A				G		G		T		T	G	A			T	T	T	0.005

*1 denotes reference sequence; the squares represent respectively the following SNPs:

- intron
- non-coding
- synonymous
- non-synonymous

other Real Time PCR assay's were Drug Metabolising Enzyme Assays (DME assays) The Real Time PCR reaction (20 µl) contained 20mM Tris-HCl pH 8.4, 50mM KCl, 3mM $MgCl_2$, (prepared from 10xPCR buffer and 50mM $MgCl_2$ solution delivered with Platinum Taq polymerase), 0.75U Platinum Taq Polymerase (Invitrogen), 4% glycerol (molecular biology grade; CalBiochem, VWR International, Amsterdam, The Netherlands), 200 mM of each dNTP (Invitrogen), 0.5 µl Rox Reference Dye (Invitrogen), 450nM primers and 100nM probes (Applied Biosystems) and 15-50 ng target DNA. However, genotyping of rs1128503 and rs2032582GA was performed in Taqman universal mastermix (Applied biosystems) using the same

Table 2 Patient characteristics

Characteristic	Non-responders n=128 (100%)	Responders n=159 (100%)	p-value
Age in years			
mean (sd)	41.7 (13.5)	43.4 (14.7)	0.315[a]
range	18-71	18-79	
Male	63 (49.2%)	93 (58.5%)	0.117[b]
Diagnosis			0.011[b]
focal epilepsy			
- idiopatic	0	3 (1.9%)	
- symptomatic	43 (33.6%)	37 (23.3%)	
- cryptogenic	77 (60.2%)	92 (57.9%)	
generalised epilepsy			
- idiopatic	0	8 (5.0%)	
- cryptogenic	1 (0.8%)	1 (0.6%)	
undefined	7 (5.5%)	18 (11.3%)	
Current number of antiepileptic drugs			<0.01[b]
1	30 (23.4%)	76 (47.8%)	
2	40 (31.3%)	57 (35.8%)	
≥ 3	58 (45.3%)	26 (16.4%)	
Current antiepileptic drug use			
carbamazepine	55 (43.0%)	68 (42.8%)	0.927[b]
levetiracetam	42 (32.8%)	18 (11.3%)	<0.01[b]
lamotrigine	54 (42.2%)	48 (30.2%)	0.031[b]
oxcarbazepine	18 (14.1%)	20 (12.6%)	0.674[b]
phenytoin	23 (18.0%)	23 (14.5%)	0.404[b]
valproic acid	19 (14.8%)	40 (25.2%)	0.034[b]

a) Student's t-test
b) Chi-square test

volume and primer/probe concentration as described above. ABI Prism sequence detection systems 7000/7500 Fast (Applied Biosystems) were used for amplification and detection (2' 50°C, 10' 95°C, 45 cycles of 15" 95°C, 1' 60°C in 9600 emulation mode) Genotypes were determined by analyses of component plots.

Data analysis

Responders and nonresponders were compared with respect to baseline parameters by using the χ^2 tests for frequency data and Student's t-test for comparison of means. A p-value <0.05 was considered statistically significant. Also, χ^2 tests were performed to assess the significance of genotypic and allelic contingency (Hardy Weinberg equilibrium). Allele frequencies of individual SNPs in responders and nonresponders were analyzed with the χ^2 test. If an association was found, we corrected for multiple testing by performing the false discovery rate test.[17] The program Phase 2.1 was used to construct haplotypes.[18] Associations between haplotypes and drug resistance were estimated using logistic regression analysis and expressed as odds ratios (ORs) with 95% confidence interval (95% CI). Potential confounding factors, such as age, gender, diagnosis, and AED use, were included in the regression model.

RESULTS

We included 287 patients (131 women, 156 men, mean age 43 years), 159 patients were drug responders and 128 were nonresponders for AED therapy. A total of 110 patients were seizure free for at least one year. All patients were Caucasian and no significant differences were found with respect to age or gender. Focal epilepsy was more frequently diagnosed in the nonresponders than in the responder group (93.8% versus 83.0%). Nonresponders more often were using three or more drugs at the same time than responders (45.7% versus 16.4%). Furthermore, nonresponding patients more often were taking newer AEDs such as lamotrigin (45.7% versus 16.4%) and levetiracetam (33.1% versus 11.3%) (Table 2).

We obtained complete genotypic data on the 18 polymorphisms (SNPs) of all patients. All allele frequencies followed the Hardy Weinberg equilibrium (χ^2 <3.40 and p>0.05). No significant association of the original SNP C3435T with drug resistant epilepsy was noted (p=0.84) (Table 3). In addition, none of the other allele frequencies in the nonresponding and responding groups show significant differences across the 18 ABCB1 polymorphisms studied (smallest p-value=0.15) (Table 4).

Table 3 Single SNP analysis in AED nonresponders and AED responders				
SNP	**Allele ratios (ww/wv/vv)**		**χ^2**	**p-value**
	nonresponders (n=128)	**responders (n=159)**		
rs3213619	112/16/0	141/18/0	0.094	0.759
rs28381802	128/0/0	159/0/0	NE	NE
rs2214102	112/16/0	126/32/1	3.853	0.146
rs9282564	101/26/1	128/30/1	0.122	0.941
rs2235015	87/37/3	103/52/5	0.589	0.745
rs10276036	57/59/12	76/66/17	0.627	0.731
rs2229109	109/18/0	141/19/0	0.333	0.564
rs1128503 (1236C>T)	34/71/23	50/79/30	1.063	0.588
rs2032588	113/15/0	137/22/0	0.283	0.595
rs2235033	24/72/32	36/79/44	1.286	0.526
rs2235013	24/72/32	36/79/44	1.286	0.526
rs28381916	126/2/0	156/3/0	0.044	0.835
rs2235063	127/1/0	155/4/0	1.246	0.264
rs2235040	101/27/0	122/35/1	0.873	0.646
rs9282563	126/2/0	156/3/0	0.044	0.835
rs2032582 (2677G>T/A)	34/66/24/3/1^	47/76/30/4/2^	0.592	0.964
rs1045642 (3435C>T)	21/68/39	30/84/45	0.357	0.837

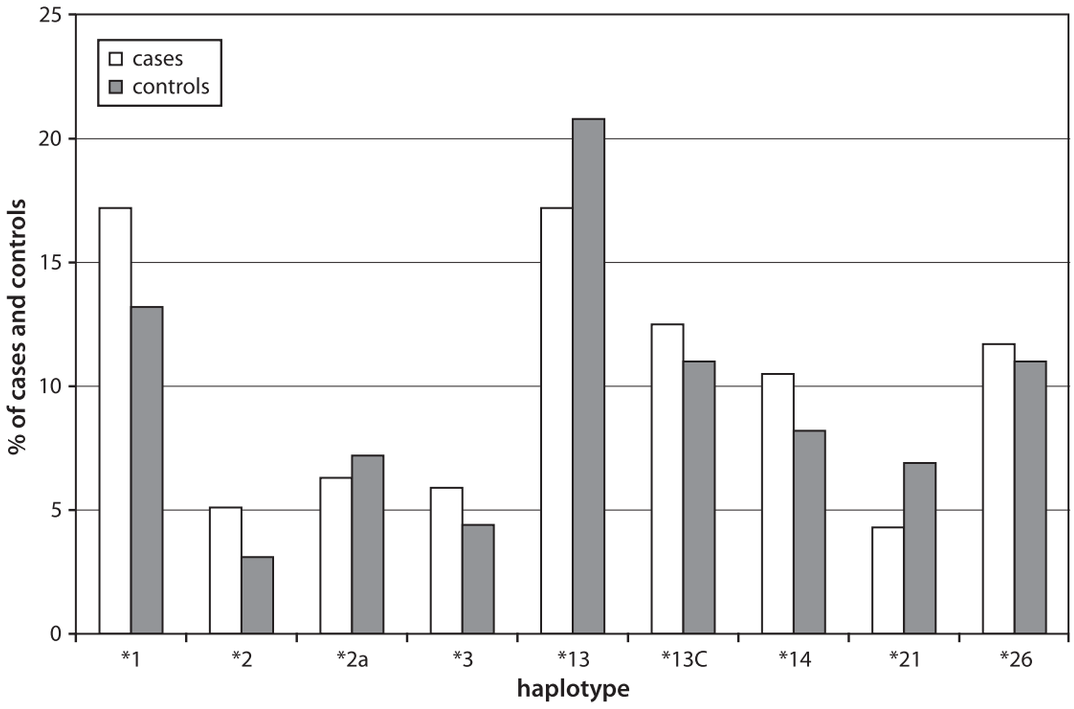
SNP = single nucleotide polymorphism; AED = antiepileptic drug; w = wildtype; v = variant; NE = not estimable
^ for 2677G>T/A: GG/GT/GA/TT/AA.

Table 4 ABCB1 haplotype analysis in AED nonresponders and AED responders				
Haplotype	**Nonresponders**	**Responders**	**OR_{cru} (95% CI)**	**OR_{adj} [a] (95% CI)**
	n=256 (100%)	**n=318 (100%)**		
*1	44 (17.2%)	42 (13.2%)	1.00 (ref)	1.00 (ref)
*2	13 (5.1%)	10 (3.1%)	1.24 (0.49-3.13)	1.92 (0.54-6.86)
*2a	16 (6.3%)	23 (7.2%)	0.66 (0.31-1.43)	0.38 (0.06-2.42)
*3	15 (5.9%)	14 (4.4%)	1.02 (0.44-2.37)	0.72 (0.33-1.57)
*13	44 (17.2%)	66 (20.8%	0.64 (0.36-1.13)	1.23 (0.27-5.71)
*13c	32 (12.5%)	35 (11.0%)	0.87 (0.46-1.65)	0.98 (0.57-1.69)
*14	27 (10.5%)	26 (8.2%)	0.99 0.50-1.97)	0.74 (0.06-9.45)
*21	11 (4.3%)	22 (6.9%)	0.48 (0.21-1.10)	0.58 (0.20-1.65)
*26	30 (11.7%)	35 (11.0%)	0.82 (0.43-1.56)	0.95 (0.35-2.58)

AED = antiepileptic drug; OR_{cru} = crude odds ratio; OR_{adj} = adjusted odds ratio; ref = reference
a) Adjusted for age, gender, epilepsy diagnosis, current number of AEDs and current AED use.

The combination of 18 SNPs revealed 32 haplotypes of ABCB1, from which nine haplotypes (*1, *2, *2a, *3, *13, *13c, *14, *21, *26, nomenclature according to Kroetz et al.[16]) represented 88% of our population. Frequencies of these haplotypes were similar in cases and controls, thus no significant association was found between one of the haplotypes of ABCB1 and drug-resistant epilepsy (Figure 1). Also, no significant association of the haplotype analysis, based on three often reported SNPs 1236C>T, 2677G>T/A and 3435C>T and drug-resistant epilepsy was found. ($OR_{TTT\ vs\ CGG}$ 0.99; 95% CI 0.68-1.42 and $OR_{CGT\ vs\ CGG}$ 1.11; 95% CI 0.65-1.90).

Figure 1 Prevalence of ABCB1 haplotypes among cases and controls



No statistically significant results were found.

DISCUSSION

In this study, no association was found between ABCB1 gene variants and drug-resistant epilepsy. This is in agreement with some previous studies that have looked at associations between a limited number of polymorphisms or low resolution

haplotypes (maximum of three SNPs) and drug resistance in epilepsy,[8,10-12] but not with others.[7,9,19] These inconsistencies may be due to several factors.

First, the responder and non-responder phenotypes were defined differently among the studies. Our definition of drug resistance (less than 30% reduction in seizure frequency in the year prior to the date of inclusion, in patients who were treated with more than two established AEDs at the maximally tolerated doses) versus drug response (seizure freedom or a 50% or more reduction in seizure frequency in the year prior to the date of inclusion) may not be distinctive enough. Former studies have used definitions for drug resistance in epilepsy varying from one or more to at least ten seizures per year.[10,19] We choose this definition since we wanted to express the effect of the AED treatment and look at seizure reduction as a result of AEDs instead of the absolute number of seizures. A limitation of looking at the absolute number of seizures is that beside studying the effect of the AEDs, the severity of the underlying disease is studied. For comparison, we did perform an analysis comparing drug-resistant patients with patients who were seizure free for at least one year before inclusion. The results of this analysis did not show an association between ABCB1 and drug-resistant epilepsy as well. In order to be able to compare studies, an international consensus on the definition of drug resistant epilepsy is needed. This process is currently being undertaken by the ILAE.

Second, it is not entirely clear which AEDs are a substrate for P-glycoprotein and which are not. Only animal studies have shown that carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, and topiramate are substrates for P-glycoprotein and that valproic acid, gabapentin, and levetiracetam are not.[20-23] However, in humans no direct evidence exists that AEDs are substrates for P-glycoprotein or any other human efflux transporter. Indirect evidence is provided by a few case studies in patients that show that the addition of verapamil, an important P-glycoprotein inhibitor, may enhance AED response.[24,25] However, these findings have not been confirmed in a randomized controlled trial.

Studies so far have explored polymorphisms in DNA while other factors, such as methylation of ABCB1, the amount of messenger RNA (mRNA) or the presence of micro RNA, that can all influence P-glycoprotein expression are not yet evaluated. However, this is difficult to study, as these analyses require brain tissue. Recently Mosyagin et al. presented a study in which ABCB1 3435C>T and 2677G>T mRNA in brain tissue of refractory patients with epilepsy was studied, they also did not find an association.[26]

ABCB1 is just one of the drug transporters present in human tissue. More research is needed to evaluate the role of other transporters such as ABCB2, MRP1, MRP2 and their eventual redundancy. Although overexpression of drug transporter proteins

is observed in drug-resistant patients with epilepsy[27,28] (but not in responding patients with epilepsy), this may be an epiphenomenon of recurrent seizures or the underlying pathology.

Finally, we have to consider the role of the drug targets in drug resistance in epilepsy. The target hypothesis suggests that seizures may induce a decreased sensitivity in the subunits of voltage-gated ion channels, causing a lessened response to certain AEDs. Further studies should therefore aim at enhancing our understanding of the relative importance of transporter and target mechanisms in the development of resistance to AEDs. To link specific genetic variants in drug target and transporter genes to clinical responsiveness in epilepsy patients, nowadays genome wide screens might be the best approach.

The strength of this study is that we assessed all variations of ABCB1 in a large population of patients with drug-resistant and drug-responsive epilepsy. A limitation of this study is the possibility of selection bias, since our controls are also patients from a tertiary centre. Thus, the controls may have a comparable genetic profile as the cases. However, we also performed a study in a secondary centre (Jeroen Bosch Hospital, 's-Hertogenbosch, The Netherlands) and these patients were comparable with the patients in this control group.[29] We, therefore think that selection bias may be minor.

In conclusion, we found that variations in ABCB1 do not explain drug resistance in epilepsy. Future studies to unravel the mechanism behind drug resistant epilepsy should focus on other genes or a combination of genes including ABCB1.

Acknowledgement: We thank the neurologists from the Epilepsy Centre Kempenhaeghe for including patients in this study. Also, we thank Ad Schellekens, Jacques Hulsman, Kim Breure, and Jean Conemans for their effort on the blood collection and the bio-analysis.

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chapter 4.2

Exploring the association between a functional polymorphism in the SCN1A gene and patients with drug-resistant epilepsy

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ABSTRACT

Objective

Many antiepileptic drugs (AEDs) act by binding to the α-subunits of voltage-gated sodium channels in neurons. One of the genes encoding these subunits is SCN1A. Earlier research has shown that a polymorphism in the SCN1A gene was associated with use of higher maximum doses of carbamazepine and phenytoin. We investigated whether the AA genotype of the SCN1A IVS5-91 polymorphism, which is associated with lower sensitivity in the a subunit sodium channels, influences the response to AED treatment.

Methods

A case-control study was conducted in a main tertiary epilepsy centre. 287 Patients with epilepsy were included: 128 were classified as refractory or drug-resistant (cases) and 159 as drug-responsive (controls). SCN1A IVS5-91 was genotyped in all patients and allele frequencies in cases and controls were compared. Also, the height of the maintenance doses of carbamazepine, phenytoin, and cumulative AED load were compared for the different genotypes in cases and controls.

Results

The frequency of the SCN1A IVS5-91 AA (32.0% versus 28.9%), the GA (51.6% versus 55.3%) or the GG genotypes (16.4% versus 15.7%) did not differ significantly between the cases and controls (χ^2=0.435; p=0.805). No association with SCN1A genotype and carbamazepine, phenytoin maintenance dose or cumulative AED load was found.

Conclusion

In this study no association was found between SCN1A IVS5-91 G>A polymorphism and drug-resistant epilepsy.

INTRODUCTION

Although the majority of patients with epilepsy is reasonably well under control with antiepileptic drugs (AEDs), about 30% continues to experience debilitating seizures despite AED treatment.[1] The reason for therapeutic AED failure is still unknown. Most first-line AEDs (e.g. carbamazepine, lamotrigine, valproate, phenytoin) act on voltage-gated sodium channels, which are essential for the initiation and propagation of action potentials in neurons. It has been postulated that a decreased sensitivity in the subunits of voltage-gated ion channels may cause a decreased response to AEDs.[2] Therefore, genes encoding for these channels are important targets when exploring pharmacogenetic determinants for drug-resistant epilepsy.

Of the nine mammalian genes encoding α-subunits of active channels, four (SCN1A, SCN2A, SCN3A and SCN8A) are expressed in the central nervous system.[3] Most mutations associated with epilepsy described so far are in SCN1A, encoding the neuronal α-subunit of the sodium channel ($Na_v1.1$).[3,4] Tate et al. assessed whether variation in *SCN1A* in patients with epilepsy was associated with the clinical use of carbamazepine and phenytoin.[5] They found that patients with AA genotype of one SNP, namely rs3812718 or SCN1A IVS5-91, more frequently received higher maximum doses of both carbamazepine and phenytoin.

The IVS5–91 G>A polymorphism is located in the 5' splice donor site of a highly conserved, alternatively spliced exon (5N). The major allele (A) disrupts the consensus sequence of the fetal exon (5N), possibly reducing the expression of this exon relative to the adult exon (5A). In fact, Tate et al. showed that the SCN1A IVS5-91 significantly affects proportions of 5N in total SCN1A in individuals with a history of epilepsy.[5,6]

Since the need for higher AED dosages implicates a worsened reaction on AEDs, we investigated whether patients carrying the SCN1A IVS5–91 AA genotype have a higher risk for drug-resistant epilepsy. Furthermore, we explored whether an association exists between patients carrying the SCN1A IVS5–91 AA genotype and higher carbamazepine, phenytoin maintenance dose and cumulative AED load.

METHODS

Patients

This study was approved by the ethics committee of Epilepsy Centre Kempenhaeghe in Heeze, one of the two tertiary centres for epilepsy in the Netherlands. Patients were eligible for inclusion if they were 18 years and older, had an established

diagnosis for epilepsy (classified according to the International League Against Epilepsy Classification [ILAE], 1981) and were treated with AEDs for at least one year. Exclusion criteria were: patients with non-epileptic psychogenic seizures, progressive neurologic diseases, comorbidity or lifestyle (e.g. use of alcohol or drugs) that may affect seizure frequency, unreliable drug adherence, and incapacity of keeping track of seizure frequency.
A case-control study was performed, cases were drug-resistant patients and controls were drug-responsive patients. Patient demographics and characteristics such as epilepsy classification (according to ILAE), seizure frequency, medication history and current use of AEDs were obtained from the patient's medical record and by patient interview. Blood collection of all patients took place for genetic analysis. All participants gave written informed consent to participate in this study.

Definition of drug response and drug resistance

Drug response was defined as seizure freedom or a 50% or more reduction in seizure frequency compared with start of AED therapy in the year prior to the date of inclusion.[7-9] By looking at the response on AED treatment only one year before inclusion data are most likely to be sufficiently reliable. Drug-resistance was defined as less than 30% reduction in seizure frequency in the year prior to the date of inclusion compared with start of AED therapy, in patients who were treated with more than two established AEDs at the maximally tolerated doses. We choose for this definition to emphasize the effect of AEDs, rather than the absolute number of seizures that could also be associated with the epilepsy diagnosis. In order to contrast cases and controls the distinction between <30% and >50% was made.

AED dose

To compare our results with those of Tate et al., carbamazepine and phenytoin maintenance doses were studied in relation to SCN1A IVS5-91 genotype.[5] Maintenance dose was defined as the dose on which a patient was treated during at least two consecutive visits to the neurologist. In all patients treated within this centre serum concentrations were monitored on regular basis and dosages were changed based on clinical parameters and serum concentration. However, these drugs are not the only AEDs acting on voltage-gated sodium channels, in fact the majority of AEDs (carbamazepine, lamotrigine, oxcarbazepine, phenytoin, phenobarbital, primidone, topiramate, valproate) act on these sodium channels. Therefore, the cumulative AED load between patients receiving monotherapy and polytherapy was compared. For this, the AED load per AED was determined by dividing the prescribed daily dose (PDD) of each AED by the defined daily

dose (DDD).[10] The DDD is based on the assumed average daily dose in its main indication in adults and is assigned by the World Health Organization (WHO) for each drug. In Table 1 the DDD values per individual AED are shown.[11] The result (PDD/DDD) is the ratio of the actual dose divided by the average therapeutic dose. The cumulative drug load in polytherapy patients was calculated by summing the PDD/DDDs of the individual drugs per patient.

Table 1 DDD of antiepileptic drugs according to WHO guidelines[11]

Antiepileptic drug	DDD (mg)	Antiepileptic drug	DDD (mg)
Acetazolamide	750	Phenobarbital	100
Carbamazepine	1000	Phenytoin	300
Clobazam	20	Pregabaline	300
Clonazepam	8	Primidon	1250
Ethosuximide	1250	Primidone	1250
Felbamate	2400	Topiramaat	300
Gabapentine	1800	Trimethadion	1500
Lamotrigine	300	Valproate	1500
Levetiracetam	1500	Vigabatrin	2000
Oxcarbazepine	1000		

DDD = defined daily dose; WHO = World Health Organization

Genotyping

DNA was isolated from 80 µl patient's blood using the Generation capture column kit (Qiagen Benelux, Venlo, the Netherlands) according to manufacturer's instructions. The DNA eluate (200 µl) was diluted 1:5 in Ultrapure Water (Invitrogen, Fisher-Emergo B.V., Landsmeer, The Netherlands). Rs3812718 was analysed with a Custom Genotyping Assay (functionally tested assay) with MGB probes (Applied Biosystems, Nieuwerkerk a/d IJssel, The Netherlands). The Real Time PCR reaction (20 µl) contained 20mM Tris-HCl pH 8.4, 50mM KCl, 3mM $MgCl_2$, (prepared from 10xPCR buffer and 50mM $MgCl_2$ solution delivered with Platinum Taq polymerase), 0.75U Platinum Taq Polymerase (Invitrogen), 4% glycerol (molecular biology grade; CalBiochem, VWR International, Amsterdam, The Netherlands), 200 mM of each dNTP (Invitrogen), 0.5 µl Rox Reference Dye (Invitrogen), 450nM primers and 100nM probes (Applied Biosystems) and 15-50 ng target DNA. ABI Prism sequence detection system 7500 Fast (Applied Biosystems)

was used for amplification and detection (10' 95°C, 45 cycles of 3" 95°C, 30" 60°C in 7500 Fast mode). Genotype was determined by analyses of component plots.

Data analysis

Equality between cases and controls was tested with χ^2 tests. Standard χ^2 analyses were performed to test allelic contingency (Hardy-Weinberg equilibrium) and to compare genotype frequencies between case and control patients. The association between the SCN1A polymorphism and drug resistance was estimated using logistic regression analysis and expressed as odds ratios (ORs) with 95% confidence interval (CI). Potential confounding factors, such as age, gender, diagnosis, and AED use, were included in the regression model. Student's t-tests were used to compare carbamazepine and phenytoin maintenance dose as well as cumulative AED load in cases and controls.

RESULTS

In this study, 287 patients (131 women, 156 men, mean age 43 years) were included: 121 cases and 159 controls. All patients were Caucasian and no significant differences were found with respect to age or gender. Focal epilepsy was more frequently diagnosed in the nonresponders than in the responder group (93.8% versus 83.0%). The cumulative AED load was significantly higher in the cases than in the controls (2.75 versus 1.67; $p<0.01$). The amount of patients treated with carbamazepine (n=55; 43.3%) in the case group was comparable with those in the control group (n=68; 42.8%) (Table 2).

The SCN1A IVS5-91 G>A polymorphism is in Hardy-Weinberg equilibrium. The frequency of the AA (32.0% versus 28.9%), the GA (51.6% versus 55.3%) or the GG genotypes (16.4% versus 15.7%) did not differ significantly between the cases and controls ($\chi^2=0.435$; $p=0.805$) (Figure 1). Thus, no association between the different genotypes and drug-resistancy was found (adjusted OR for AA versus GG genotype 0.75; 95% CI 0.36-1.56).

Maintenance doses of carbamazepine averaged 910 mg, 1012 mg, 991 mg respectively for AA, AG and GG individuals within the cases and 735 mg, 846 mg, 767 mg respectively for AA, AG and GG individuals within the controls. Thus, SCN1A IVS5-91 G>A polymorphism was not associated with the maintenance dose of carbamazepine in our study ($p_{AA\ vs\ GG} = 0.48$, cases), ($p_{AA\ vs\ GG} = 0.82$, controls). Only few patients in both groups were treated with phenytoin, 22 cases (18.2%) and 23 controls (14.5%). No association was found between dosing of phenytoin

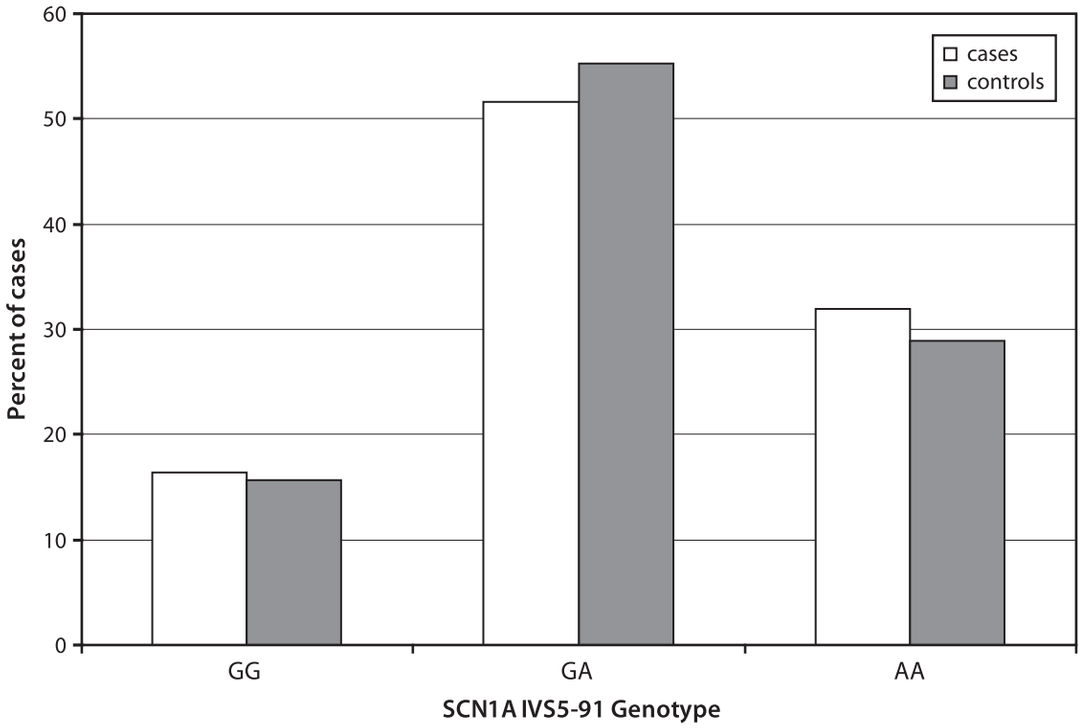
Table 2 Characteristics of cases and controls			
Characteristic	**Cases n=128 (100%)**	**Controls n=159 (100%)**	**p-value**
Age in years			
mean	41.7	43.4	0.315[a]
range	18-71	18-79	
Male	63 (49.2%)	93 (58.5%)	0.117[b]
Diagnosis			0.011[b]
focal epilepsy			
- idiopatic	0 (0.0%)	3 (1.9%)	
- symptomatic	43 (33.6%)	37 (23.3%)	
- cryptogenic	77 (60.2%)	92 (57.9%)	
generalised epilepsy			
- idiopatic	0 (0.0%)	8 (5.0%)	
- cryptogenic	1 (0.8%)	1 (0.6%)	
undefined	7 (5.5%)	18 (11.3%)	
Antiepileptic drugs			<0.01[b]
1	30 (23.4%)	76 (47.8%)	
2	40 (31.3%)	57 (35.8%)	
≥ 3	58 (45.3%)	26 (16.4%)	
Cumulative antiepileptic drug load (PDD/DDD); mean (sd)	2.75 (1.51)	1.67 (1.17)	<0.01[a]
Antiepileptic drug			
carbamazepine	55 (43.0%)	68 (42.8%)	0.927[b]
levetiracetam	42 (32.8%)	18 (11.3%)	<0.01[b]
lamotrigine	54 (42.2%)	48 (30.2%)	0.031[b]
oxcarbazepine	18 (14.1%)	20 (12.6%)	0.674[b]
phenytoin	23 (18.0%)	23 (14.5%)	0.404[b]
valproic acid	19 (14.8%)	40 (25.2%)	0.034[b]

PDD = prescribed daily dose; DDD = defined daily dose
a) Student's t-test.
b) Chi-square test.

and SCN1A IVS5-91 G>A genotype 311 mg versus 300 mg ($p_{AA\ vs\ GG} = 0.86$) in cases and 318 vs 367 mg ($p_{AA\ vs\ GG} = 0.55$) in controls.

The mean cumulative AED load was lower in patients with AA genotype (2.26) than the GG genotype (3.20) in the cases group (Figure 2), however this was not significant (p=0.09). For the controls we saw the opposite, AA genotype (1.62) had higher cumulative AED load than GG genotype (1.22) (p=0.19).

Figure 1 Distribution of SCN1A-IVS5-91 genotypes of cases (drug-resistant patients) and controls (drug-responders)



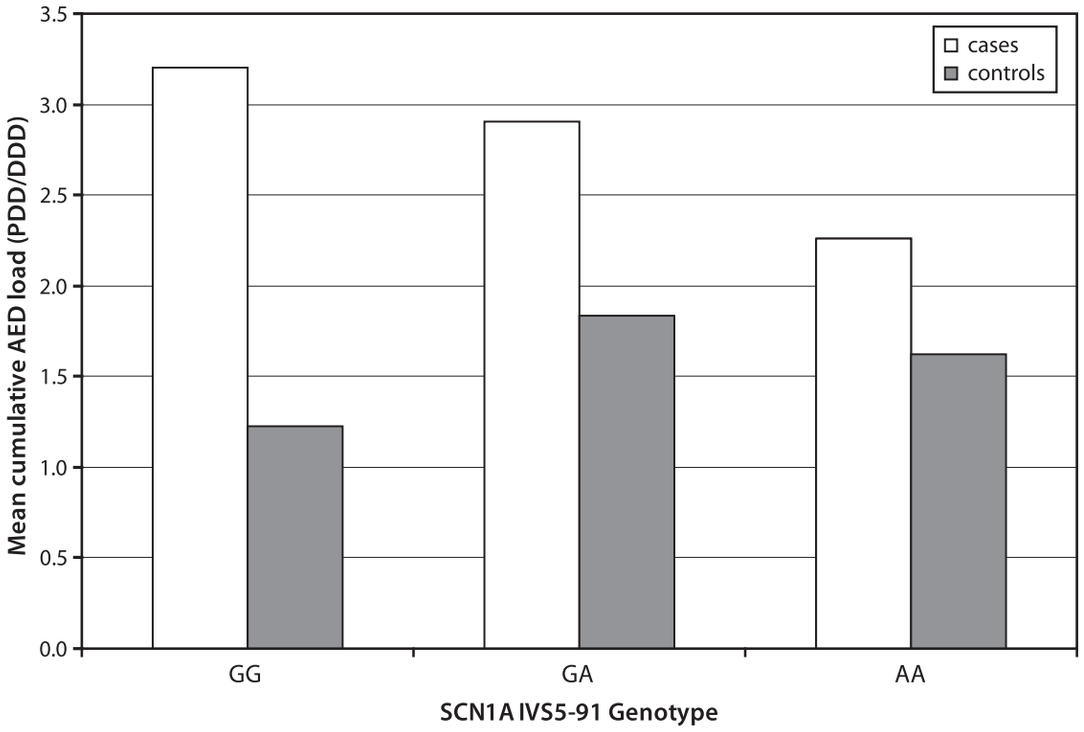
DISCUSSION

In this study no association was found between SCN1A IVS5-91 A>G and therapy resistance in patients with epilepsy. Also, we were not able to replicate the finding of Tate et al, namely an association between the SCN1A IVS5-91 AA genotype and higher carbamazepine and phenytoin doses.[5]

A number of reasons can be given for not finding an association. First, initial positive published studies tend to overestimate effect size and findings can often not be replicated.[12] The same conflicting findings have been shown in relation to the ABCB1 gene and drug-resistant epilepsy.[13,14] In addition, the low sample size might be the reason for non-significant results. However, although their study was performed with a larger sample size (n=425), we did not even detect a trend in this direction.

Second, patients included in the study of Tate et al.[5] also used other AEDs than carbamazepine and phenytoin targeting voltage-gated sodium channels. This may have influenced results. Therefore, we searched for a formula to correct for use

Figure 2 Mean cumulative antiepileptic drugload (PDD/DDD) for cases (drug-resistant patients) and controls (drug-responders) per SCN1A genotype



PDD = prescribed daily dose; DDD = defined daily dose

of multiple AEDs and chose the cumulative PDD/DDD ratio for this purpose.[10] The drawback of our method is that drugs not necessarily acting on voltage-gated sodium channels are also included. However since the majority of AEDs act on voltage-gated sodium channels this method is probably more precise than not taking into account other antiepileptic agents used.

Furthermore, there are some important differences in our study compared with the study of Tate et al.[5] One important difference is that we excluded patients under the age of 18. By doing this, patients with severe myoclonic epilepsy in infancy, an intractable epilepsy also known as syndrome of Dravet and possibly other types of epilepsy that are known to be associated with mutations with sodium channel diseases and difficult-to-treat epilepsy, were not included in our study population.[15] This is one of the strengths in our study, since the results may be a better reflection of the actual drug-response compared with the intractability associated with the epilepsy form itself.

In the study by Tate et al.[5] maximum doses were studied, which was also noted as a possible limitation. Therefore, a second study was set up in a different population (Chinese origin) studying maintenance dose of phenytoin in relation to SCN1A IVS5-91 polymorphism.[16] In this second study performed with 168 patients, no association was found between the SCN1A polymorphisms and phenytoin maintenance dose. Recently, the SCN1A IVS5-91 polymorphism was tested in Austrian patients with focal epilepsy, again SCN1A polymorphism was not associated with carbamazepine doses.[17] Our study, also using maintenance doses, is in agreement with these findings.

In the current study, a distinction was made between responders and nonresponders of AED therapy. Our hypothesis was that patients with epilepsy who responded well on their medication needed lower AED doses. This was confirmed in our study, responders had lower PDD/DDD ratios than drug-resistant patients. Our hypothesis was that if drug-resistant patients would more often had the AA genotype, which was associated with higher maximum doses, this would have explained and strengthened the earlier findings. However, this was not the case.

Recently Abe et al. found a significant association between the SCN1A IVS5-91 AA genotype and carbamazepine-resistant epilepsy, but not with overall drug-resistant epilepsy in a Japanese population.[18] However, dosing strategy differed largely from Tate et al.[5] or this study. Abe et al.[18] detected relatively low maximum carbamazepine doses (mean maximum dose carbamazepine of 500 mg) after which a switch was made to another AED compared with carbamazepine maintenance doses of 800-1000 mg in our study and maximum doses 1000-1400 mg (median) in the study of Tate et al.[5]

One could argue about the definition for drug-response. In former studies, absolute numbers of seizures were used to define responders versus nonresponders. Also, in earlier studies responders were often seizure-free patients.[19] When we redefined our responder group and analyzed only the patients who were seizure free for at least one year (110 out of 159 controls) also no association with drug-resistance was found (adjusted OR for AA versus GG genotype 0.79; 95% CI 0.34-1.84). However, should a patient who because of AEDs had his seizures reduced from thirty to one seizure a month indeed be classified as non-responding?

Only one polymorphism of the SCN1A gene was studied. Tate et al. showed that only one of the four studied SCN1A tag SNPs, that together represent 94% of SCN1A haplotype diversity, namely SCN1A IVS 5-91 G>A (rs3812718) was associated with higher maximum phenytoin and carbamazepine doses.[5] Therefore, we decided to analyze only this polymorphism.

Drug-resistance is most likely a multifactorial problem and there is only a small chance that there would be only one gene responsible. Future studies should therefore include multiple polymorphisms of multiple genes, including other brain-expressed voltage-gated sodium channels such as SCN2A, 3A and 8A,[3,20] and ABCB1, BCRP, MRP1 and MRP2 that have previously been associated with drug response in epilepsy.[21,22]

In summary, our study showed no association between a functional polymorphism of SCN1A and drug-resistant epilepsy. In addition, we were not able to confirm previous findings in which an association was found between higher doses of carbamazepine and phenytoin and SCN1A genotype.

Acknowledgement: The authors thank the neurologists from the Epilepsy Centre Kempenhaeghe for their patient recruitment, and Jeroen Poodt, Kim Breure, Jean Conemans, Ad Schellekens, and Jacques Hulsman for their effort on the blood collection.

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5

Adverse effects of antiepileptic drugs

chapter 5.1

Influence of chemical structure on hypersensitivity reactions induced by antiepileptic drugs: The role of the aromatic ring

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Drug Safety 2008;31:695-702

ABSTRACT

Objective

Antiepileptic drugs (AEDs) can cause various 'idiosyncratic' hypersensitivity reactions, i.e. the mechanism by which AEDs induce hypersensitivity is unknown. The aim of this study was to assess whether the presence of an aromatic ring as a commonality in chemical structures of AEDs can explain symptoms of hypersensitivity.

Methods

Between January 1985 and January 2007, all adverse drug reactions (ADRs) reported to the Netherlands Pharmacovigilance Centre Lareb related to AEDs as suspected drug were included in this study. ADRs were analysed using a case/non-case design. Cases were defined as those patients with ADRs involving symptoms of hypersensitivity. Non-cases were patients with all other ADR reports. Symptoms of hypersensitivity were classified according to the Gell and Coombs classification (type I-IV) and the organ involved (e.g. cutaneous, hepatic). AEDs were classified as aromatic anticonvulsant if their chemical structure contained at least one aromatic ring. All other AEDs were classified as non-aromatic. We assessed the strength of the association between aromatic AEDs versus non-aromatic AEDs and reported hypersensitivity reactions with logistic regression and expressed these as reporting odds ratios (RORs).

Results

In total 303 cases of hypersensitivity associated with the use of AEDs were reported. Aromatic AEDs were suspected in 64.4% of these reports versus in 41.3% (574/1389) of the non-hypersensitivity reports. A significant ROR of 2.15 (95% confidence interval [CI] 1.63-2.82) was found for aromatic AEDs and all hypersensitivity reactions. Aromatic AEDs were significantly associated with immunoglobulin E-mediated type I hypersensitivity reactions (ROR 2.15; 95% CI 1.23-3.78) and T cell-mediated type IV reactions (ROR 6.06; 95% CI 3.41-10.75). Type II and III reactions did not show an association. Cutaneous symptoms represented 39.9% of the hypersensitivity-related ADRs. Aromatic AEDs were significantly associated with cutaneous hypersensitivity reactions (ROR 5.81; 95% CI 3.38-9.99).

Conclusion

This study confirms that the presence of an aromatic ring as a commonality in chemical structures of AEDs partly explains apparent 'idiosyncratic' hypersensitivity reactions. Symptoms of hypersensitivity were reported two times as frequent with

aromatic AEDs than with non-aromatic AEDs. Strong associations for aromatic AEDs versus non-aromatic AEDs were found for T-cell-mediated (type IV) reactions, as well as for cutaneous reactions.

INTRODUCTION

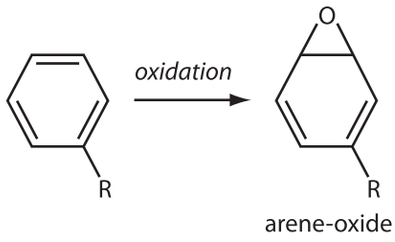
It is well known that the use of antiepileptic drugs (AEDs) may cause hypersensitivity reactions in susceptible patients with a varying clinical presentation such as skin involvement, eosinophilia and/or systemic symptoms like hepatitis. Hypersensitivity reactions also differ in severity ranging from mild urticarial eruptions to potentially life-threatening events.[1-3] The most feared AED-related adverse reactions are 'Stevens-Johnson syndrome (SJS)', 'toxic epidermal necrolysis (TEN)' and 'anticonvulsant hypersensitivity syndrome'. The estimated incidence of these events ranges from 1 per 1000 to 1 per 10 000 users of AEDs.[4] Clinical symptoms appear usually two to eight weeks after initiation of therapy and typically start with fever, rash, and lymphadenopathy, followed by involvement of various internal organs leading to hepatitis, eosinophilia, blood dyscrasias and nephritis. In case of SJS and TEN rash with extensive mucosal blistering or erosions is characteristic.[5-7] Rash alone is a much more common hypersensitivity reaction with an average rate of approximately 3 per 100 AED users.[8]

Hypersensitivity reactions are often typed as idiosyncratic ('type B') adverse effects as they cannot be explained on the basis of known pharmacological mechanisms and occur mostly unpredictably in susceptible patients only, irrespective of dosage.[9] Since the serious nature of most idiosyncratic reactions, extensive research to unravel the mechanism explaining these effects has been carried out.[9,10] One of the most widely proposed theories of hypersensitivy reactions in general is based on the hapten hypothesis of immune recognition of drugs by specific antibodies or T cells.[11-13] Evidence shows that drugs associated with a high incidence of hypersensitivity are converted to protein-reactive intermediates in the normal processes of drug metabolism. The drug-protein complex may then act as an immunogenic complex and elicit the production of specific antibodies (humoral response) and/or the generation of specific T lymphocytes (cellular response), thus being responsible for the allergic effects.[14]

Various reports have shown that specific AEDs such as carbamazepine, phenytoin, phenobarbital, and lamotrigine were connected with hypersensitivity.[3-5] The mechanism by which these AEDs induce hypersensitivity is unknown. One of the main hypotheses is that AEDs containing an aromatic ring in their chemical structure can form an arene-oxide intermediate (Figure 1).[6] This chemically reactive product may become immunogenic through interactions with proteins or cellular macromolecules in accordance with the hapten hypothesis suggesting that this structural commonality between AEDs may be responsible for hypersensitivity reactions.[15] This hypothesis is based on incidental case reports and in vitro experiments. So far, no in vivo experimental or observational studies have been

published supporting this theory. Therefore, we conducted this study to investigate the association between the presence of an aromatic ring as a structural commonality in AEDs and hypersensitivity reactions using the spontaneous reporting database of our national pharmacovigilance centre.

Figure 1 **Possible metabolic pathway for production of toxic metabolites of aromatic antiepileptic drugs**



OBJECTIVE

The aim of this study was to assess whether an aromatic ring as a commonality in chemical structures of AEDs is associated with the occurrence of symptoms of hypersensitivity.

METHODS

Setting

The Netherlands Pharmacovigilance Centre Lareb maintains the spontaneous adverse drug reaction (ADR) reporting system in the Netherlands on behalf of the Dutch Medicines Evaluation Board. Its objective is to detect, record and analyse ADRs and by doing so, to contribute the safe and rational use of drugs.[16] ADRs are reported by healthcare professionals and patients on a voluntary basis and include relevant clinical information about the patient (age and sex), the suspected ADR, medication used at time of the event ('suspected' and 'concomitant'), source (physician, pharmacist, marketing authorisation holder or patient) and year of reporting. Each report is evaluated by a qualified assessor (physician or pharmacist) and is coded according to the Medical Dictionary for Regulatory

Activities (MedDRA).[17] For this study all suspected ADRs on AEDs reported to the Netherlands Pharmacovigilance Centre were taken into account.

Selection and stratification of cases and non-cases

All ADRs related with AEDs as the suspected drug reported between January 1985 and January 2007 were included in this study and categorized into hypersensitivity or non-hypersensitivity reports. The reported hypersensitivity reactions were stratified according to the Gell and Coombs classification (Table 1).[18-20] This

Table 1 **Included hypersensitivity symptoms based on reported suspected ADRs classified by Gell and Coombs (MedDRA terms)[18-20]**

Type	Reaction
I	Anaphylactic reaction, Anaphylactic shock, Angioneurotic oedema, Eye swelling, Eyelid oedema, Face oedema, Oedema mouth, Periorbital oedema, Pharyngeal oedema, Shock, Urticaria
II	Agranulocytosis, Increased alanine aminotransferase, Anaemia, Increased aspartate aminotransferase, Increased hepatic enzymes, Hepatic failure, Abnormal hepatic function, (Cholestatic) hepatitis, Toxic hepatitis, Hepatocellular damage, Leukopenia, Abnormal liver function test, Rhabdomyolysis, Thrombocytopenia
III	Arthralgia, Arthritis, Arthropathy, Lymphadenopathy, Myalgia, Nephritis interstitial, Pleural effusion, Pleurisy, Pneumonia, Pneumonitis
IV	Dermatitis (allergic, bullous), Drug rash with eosinophilia and systemic symptoms, Erythema multiforme, Rash (erythematous, maculo-papular, papular, pustular), Skin exfoliation Stevens-Johnson syndrome, Toxic Epidermal Necrolysis

MedDRA = Medical Dictionary for Regulatory Activities

procedure was executed by two of the authors (Annemarie Bijl and Eugène van Puijenbroek) independently of each other. Differences were discussed until consensus was reached (Table 1). Furthermore, since hypersensitivity reactions are often clustered in literature by the involved organ, these were also distinguished if applicable as cutaneous, hepatic, haematologic and pulmonary hypersensitivity reactions (Table 2).[6,8,20] ADRs were analysed using a case/non-case design. A case was defined as a patient with a report of hypersensitivity related to a suspected AED. All patients with non-hypersensitivity ADRs related to AEDs, namely reports without any of the included MedDRA terms mentioned in Tables 1 or 2, were defined as non-cases. If more than one AED was suspected in the report, than these were included as separate cases. As such, the number of cases and non-cases may exceed the number of reports, and thus the number of patients, since one report could contain more than one suspected AED.

Table 2	Classification of hypersensitivity symptoms on organ involvement based on reported ADRs (MedDRA terms)
Type	**Reaction**
Cutaneous	Dermatitis (allergic, bullous), Drug rash with eosinophilia and systemic symptoms, Erythema multiforme, Rash (erythematous, maculo-papular, papular, pustular), Skin exfoliation, Stevens-Johnson syndrome, Toxic Epidermal Necrolysis, Urticaria
Hepatic	Increased alanine aminotransferase, Increased aspartate aminotransferase, Increased hepatic enzymes, Hepatic failure, Abnormal hepatic function, (Cholestatic) hepatitis, Toxic hepatitis, Hepatocellular damage, Abnormal liver function test
Haematologic	Agranulocytosis, Anaemia, Leukopenia, Thrombocytopenia
Pulmonal	Pleural effusion, Pleurisy, Pneumonia, Pneumonitis

MedDRA = Medical Dictionary for Regulatory Activities

Exposure definitions

AEDs were classified as aromatic anticonvulsants if their chemical structure contained at least one aromatic ring (carbamazepine, felbamate, lamotrigine, oxcarbazepine, phenytoin, phenobarbital, primidone and zonisamide). All other AEDs were classified as non-aromatic (Figure 2).

Data analysis

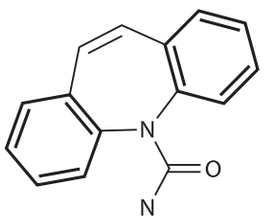
The Chi-squared test, Student's t-test or Mann-Whitney test were used to compare cases and non-cases as appropriate. The strength of the association between the different types of hypersensitivity reactions and the aromatic AEDs in comparison with non-aromatic AEDs was calculated using the ADR reporting odds ratio (ROR) as a measure of disproportionality.[21] The calculation of a ROR is comparable to the calculation of an odds ratio from a case-control study. RORs, adjusted for age, sex, year of reporting, and the source of reports (health professional or patient) were calculated by means of logistic regression analysis and expressed as point estimates with corresponding 95% confidence intervals (CIs).

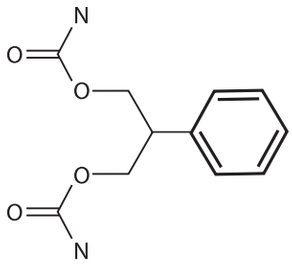
RESULTS

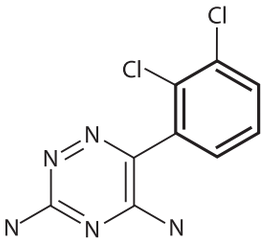
A total of 1692 cases and non-cases of ADRs with AEDs as suspected medication involving 1593 patients were included. There were no significant differences in patients with or without hypersensitivity reactions in terms of age, sex, or reporting source ($p>0.05$). A significant difference in the year of reporting was detected (Table 3).

Figure 2 Aromatic and non-aromatic antiepileptic drugs (AEDs)

Aromatic antiepileptic drugs


carbamazepine


felbamate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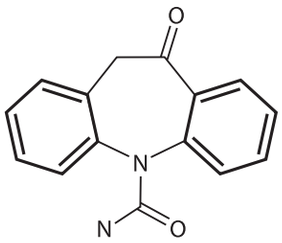
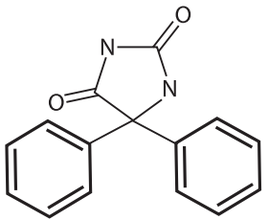
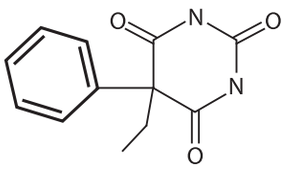
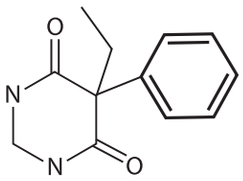

oxcarbazepine


phenytoin


phenobarbital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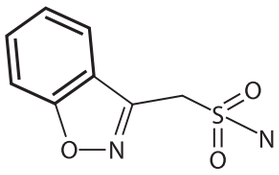
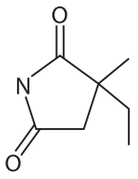

zonisamide

Non-aromatic antiepileptic drugs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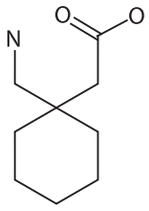
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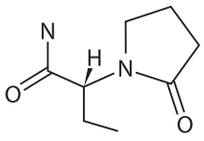
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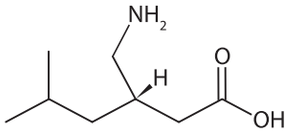
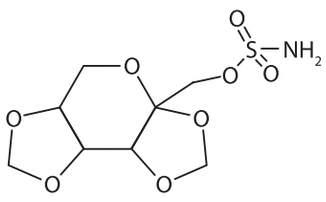

pregabalin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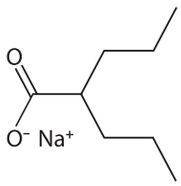
valproate

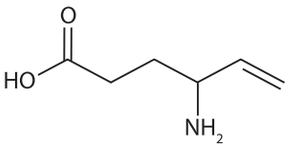
vigabatrin

Table 3 Main patient characteristics			
Patient characteristics	**Patients with hypersensitivity**	**Patients without hypersensitivity**	**p-value**
	n=293 (100%)	**n=1300 (100%)**	
Sex: female	180 (61.4%)	779 (59.9%)	0.663[a]
Mean age (years) ± sd	44.4 ± 22.1	46.1 ± 21.1	0.228[b]
Source:			0.074[a]
healthcare professional	281 (95.9%)	1210 (93.1%)	
patient	12 (4.1%)	90 (6.9%)	
Reporting year:			
range	1986 – 2006	1987 – 2006	
mean ± sd	2000 ± 4.7	2002 ± 4.0	<0.001[c]

a) Pearson χ^2.
b) Student's t-test.
c) Mann-Whitney test.

In total, 303 cases of hypersensitivity were reported. Aromatic AEDs were suspected in 64.4% (195/303) of cases versus 41.3% (574/1389) of non-cases. The presence of an aromatic ring in the chemical structure was associated with a significant increased risk of hypersensitivity reactions (adjusted ROR 2.15; 95% CI 1.63-2.82). Among the aromatic AEDs, hypersensitivity was significantly associated with carbamazepine (adjusted ROR 2.04; 95% CI 1.46-2.85), lamotrigine (adjusted ROR 2.89; 95% CI 1.98-4.23) and phenytoin (adjusted ROR 1.88; 95% CI 1.12-3.15) (Table 4).

Of 303 cases of hypersensitivity, 62 (20.5%) represented immunoglobulin E (IgE)-mediated response reactions (type I), 94 (31.0%) corresponded with immunoglobulin mediated cytotoxic reactions (type II), 36 (11.9%) were suggestive for immune complex deposition reactions (type V), and 111 (36.6%) for T-cell-mediated hypersensitivity reactions (type IV). Type I reactions were significantly associated with aromatic AEDs (adjusted ROR 2.15; 95% CI 1.23-3.78). Furthermore, a high adjusted ROR of 6.06 (95% CI 3.41-10.75) was found for aromatic AEDs and type IV reactions. The use of aromatic AEDs was not associated with type II (adjusted ROR 0.93; 95% CI 0.61-1.45) and type III reactions (adjusted ROR 1.17; 95% CI 0.58-2.36) (Table 5).

Cutaneous symptoms represented 39.9% (121/303) of cases. Rash (erythematous, maculo-papular, papular, pustular or unspecified) was the most frequently reported hypersensitivity symptom 79/303 (26.3%). Of all cases 51/303 (16.8%) were hepatic, 41/303 (13.5%) were haematological, and 7/303 (2.3%) were pulmonary. Aromatic

AEDs were significantly associated with cutaneous hypersensitivity reactions, adjusted ROR 5.81 (95% CI 3.38-9.99), but not with hepatic, haematologic, or pulmonary hypersensitivity reactions.

Table 4 Use of aromatic and non-aromatic AEDs in cases and non-cases

AED	Cases	Non-cases	Reporting Odds Ratio	
	n=303 (100%)	n=1389 (100%)	crude (95% CI)	adjusted[a] (95% CI)
Non-aromatic AEDs	108 (35.6%)	815 (58.7%)	1.00 (ref)	1.00 (ref)
Aromatic AEDs	195 (64.4%)	574 (41.3%)	2.56 (1.98-3.32)	2.15 (1.63-2.82)
Carbamazepine	97 (32.0%)	275 (19.8%)	2.66 (1.96-3.62)	2.04 (1.46-2.85)
Felbamate	3 (1.0%)	0 (0.0%)	NE	NE
Lamotrigine	55 (18.2%)	135 (9.7%)	3.07 (2.12-4.46)	2.89 (1.98-4.23)
Oxcarbazepine	12 (4.0%)	56 (4.0%)	1.62 (0.84-3.11)	1.45 (0.75-2.79)
Phenobarbital	4 (1.3%)	21 (1.5%)	1.44 (0.48-4.27)	1.23 (0.41-3.71)
Phenytoin	24 (7.9%)	77 (5.5%)	2.35 (1.43-3.88)	1.88 (1.12-3.15)
Primidon	0 (0.0%)	10 (0.7%)	NE	NE

AED = antiepilectic drugs; ref= reference; NE = not estimable
a) Adjusted for age, gender, source, and year of reporting.

Table 5 Association of aromatic vs non-aromatic AEDs and type of hypersensitivity reaction

Hypersensitivity reaction	Aromatic	Non-aromatic	Reporting Odds Ratio	
	n (%)	n (%)	crude (95% CI)	adjusted[a] (95% CI)
All	195 (100%)	108 (100%)	2.56 (1.98-3.32)	2.15 (1.63-2.82)
Allergic reactions: Gell and Coombs classification				
Type I	40 (20.5%)	22 (20.3%)	2.45 (1.32-3.82)	2.15 (1.23-3.78)
Type II	42 (21.5%)	52 (48.1%)	0.97 (0.64-1.47)	0.93 (0.61-1.45)
Type III	17 (8.7%)	19 (17.6%)	1.08 (0.56-2.08)	1.17 (0.58-2.36)
Type IV	96 (49.2%)	15 (13.9%)	8.64 (4.97-15.01)	6.06 (3.41-10.75)
Allergic reactions: Organ classification				
Cutaneous	104 (53.3%)	17 (15.7%)	8.34 (4.94-14.05)	5.81 (3.38-9.99)
Hepatic	23 (11.8%)	28 (25.9%)	0.96 (0.56-1.73)	0.96 (0.53-1.74)
Haematologic	18 (9.2%)	23 (21.3%)	0.94 (0.50-1.75)	0.86 (0.45-1.66)
Pulmonal	2 (10.3%)	5 (4.6%)	0.48 (0.09-2.48)	0.56 (0.10-3.24)

AED = antiepilectic drugs
a) Adjusted for age, gender, source, and year of reporting.

DISCUSSION

This study shows that a commonality in chemical structures of AEDs partly explains specific types of hypersensitivity reactions. We found that symptoms of hypersensitivity were reported twice as frequent with aromatic AEDs as with non-aromatic AEDs. The association was strongest for T-cell-mediated (type IV) reactions. Also, IgE-mediated response reactions (type I) reactions showed a significant ROR for the relation with aromatic AEDs. Furthermore, a strong association was found for aromatic AEDs and cutaneous hypersensitivity reactions.

In general, it is assumed that small molecules with molecular weights less than 1 kDalton cannot directly induce an immune response. AEDs, as well as the majority of other drugs, fall into this category. Therefore, it is assumed that they must covalently bind to components of the immune system in order to cause hypersensitivity reactions. This principle forms the basis of the hapten hypothesis, which proposes that drugs or reactive metabolites of drugs act as haptens and bind to proteins or other endogenous macromolecules. Covalently modified macromolecules are immunogenic and elicit an immune response.[22] In 1974, Jerina and Daly [23] described the metabolic formation of arene-oxides. According to them, arene-oxides were responsible for many toxic and carcinogenic properties of aromatic hydrocarbons. Although the involvement of alternative reactive metabolites of AEDs have been proposed in experimental systems, the formation of arene-oxides is believed to be the most likely mechanism of hypersensitivity reactions.[24] Another argument supporting this theory is the cross sensitivity that has been reported among patients using aromatic AEDs.[25] This phenomenon has also been studied in vivo and in vitro in patients that showed clinical hypersensitivity reactions to phenytoin, phenobarbital and carbamazepine. A rechallenge with a possible cross-reactive AED resulted in hypersensitivity reactions in up to 87% of patients.

Apart from the hapten formation hypothesis, another immune mechanism might be involved. In this hypothesis there is direct, non-covalent binding of the drug to the T-cell receptor of specific T-cell clones. Drug-specific T cells have been identified in lamotrigine and carbamazepine.[19,27] Our findings of the strong association for T-cell-mediated (type IV) hypersensitivity reactions in these aromatic AEDs might support this hypothesis.

Arif et al.[8] recently studied predictors of rash associated with AEDs. They found higher rash rates in patients treated with phenytoin, lamotrigine and carbamazepine (all aromatic AEDs) and lower rates with levetiracetam, gabapentin and valproate (all non-aromatic AEDs). When we reanalysed their data, we found an OR of 2.18

(95%CI 1.80-2.56) for the association between aromatic AEDs vs. non aromatic AEDs and rash. These findings are in accordance with our data.

Recently, a study was published in which an association was found between HLA-B*1502 allele and AED-induced cutaneous reactions in a small sample size of Han Chinese.[28] If confirmed in larger studies and other ethnic cohorts, identification of genetic polymorphisms predisposing AED-induced hypersensitivity and subsequent avoidance of aromatic AED treatment could help preventing life-threatening hypersensitivity events.

Not all reactions included in this study are necessarily based on hypersensitivity. Some reactions are more likely to have an allergic basis (i.e. urticaria or pneumonitis) whereas in other reactions, such as rash or hepatic reactions, immunopathology is less certain This might have led to a relative overestimation of the proportion of allergic reactions and subsequent overestimation of the point-estimates involved.

Spontaneous reporting, the major system used by national pharmacovigilance centres, has been found to be especially effective in detecting idiosyncratic adverse events. One of the limitations of this system as a source of collecting data on suspected ADRs is that it is known to represent only a fraction of the drug-related adverse events; therefore no relative incidence can be obtained from our data.[29] It is recognized that less than 10% of all serious and 2 to 4% of non-serious adverse reactions are reported.[30] Thus, this may have led to both over- and underestimation of the RORs. In this study, an underestimation is expected, as it is well accepted by potential reporters that some of the aromatic AEDs lead to hypersensitivity.

The approach outlined in this study should be replicated with other study designs such as prescription event monitoring, case control surveillance or record linkage by use of large automated databases.[31] Unravelling the association between a commonality in chemical structures of AEDs and hypersensitivity reactions with these methods could provide additional evidence for the association we found.

CONCLUSION

In conclusion, this study shows that apparent 'idiosyncratic' hypersensitivity reactions can partly be explained by a commonality in chemical structures of AEDs. A significant association was found for aromatic versus non-aromatic AEDs and hypersensitivity reactions. When stratifying for different types of hypersensitivity, the association was strongest for T cell-mediated (type IV) reactions and cutaneous reactions.

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chapter 5.2

Changes in metabolic syndrome parameters in patients starting with valproate or lithium as a mood stabilizer: An interim analysis

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ABSTRACT

Objective

To study the changes in metabolic syndrome (MetS) parameters in patients starting lithium or valproate as a mood stabilizing agent.

Methods

A prospective, open label, multicentre, cohort study was conducted with patients starting with lithium or valproate as a mood-stabilizer. MetS parameters (waist circumference, blood pressure, fasting plasma glucose, triglycerides, high-density lipoprotein [HDL] cholesterol) and weight were measured at the start of treatment and three, six, and twelve months after start with lithium or valproate.

Results

This interim analysis concerns 23 patients, who had at least been measured at baseline and after three months of follow-up. Twenty patients started with lithium and three patients started with valproate. Significant changes in weight (mean increase 4.9 kg; p=0.047) and waist circumference (mean increase 5.3 cm; p=0.035) were found 12 months after start of lithium. A non-significant increase in systolic blood pressure (mean increase 11.3 mmHg; p=0.09) was seen after start of lithium. In patients who started with valproate non-significant increases in weight (mean increase 7.0 kg; p=0.18), waist circumference (mean increase 8.5 cm; p=0.18) and fasting glucose (mean increase 1.0 mmol/L; p=0.34) were seen six months after start.

Conclusion

In this interim analysis, significant associations between use of lithium and increasing weight and waist circumference were found. Only three patients with valproate were included at the time of analysis, therefore no conclusions can be drawn yet regarding changes in MetS parameters associated with use of valproate.

INTRODUCTION

While the concept of the metabolic syndrome (MetS) has existed for at least 80 years, it was not until 1998 that the first internationally recognized definition was developed.[1] Currently at least three definitions exist, one of the World Health Organization (WHO, 1999),[2] one of the National Cholesterol Education Program's - Adult Treatment Panel III (NCEP: ATP III, 2001),[3] and the latest from the International Diabetes Federation (IDF, renewed in 2005).[4] These definitions all agree on the essential components -glucose intolerance, central obesity, dyslipidaemia, and hypertension- all well-documented risk factors for cardiovascular disease.[5] Although, there is debate about whether the apparent clinical value of MetS represents anything more than the cardiovascular risk associated with its individual components, studies have shown a clear association between MetS and increased all-cause-mortality and between MetS and cardiovascular death.[6-9] The last two decades, the number of people with obesity, diabetes and MetS has reached the level of a global epidemic.[10] Therefore, urgency exists for the development of strategies to prevent and treat MetS.

There is growing attention and concern about the association between use of medication and the development of MetS, obesity and diabetes, especially in psychiatric patients.[11] Several studies have shown that treatment with atypical antipsychotic drugs (e.g. olanzapine, clozapine) is significantly associated with weight gain, diabetes and a worsening lipid profile.[12,13] Since this effect is considerable, a consensus statement was developed concerning the monitoring of patients treated with atypical antipsychotics.[14]

Mood stabilizers such as lithium and valproate are also known to cause weight gain.[15,16] Furthermore, reports suggest an association with valproate and changes in lipid levels.[17,18] Also, the prevalence of cardiovascular risk factors in patients with bipolar disorder was found to be higher than in the general population, but comparable with schizophrenic patients.[19] It is unknown whether an association exists between the use of mood stabilizers and the development of MetS or whether this may be associated with the underlying disease or both.[20,21] Currently, it is unknown whether monitoring for MetS should also be done in patients initiating valproate or lithium treatment. Therefore, we set up a prospective study to explore the association between the use of mood stabilizers (lithium and valproate) and the development of parameters of the MetS (waist circumference, blood pressure, fasting plasma glucose, triglycerides, and high-density lipoprotein [HDL] cholesterol).

METHODS

Study design, setting and patient population

A prospective, multicentre, open-label, cohort study was conducted. Inclusion of patients took place in seven psychiatric centres in the Netherlands. Patients were eligible for inclusion if they were 18 years or older, diagnosed with bipolar disorder, schizoaffective disorder, or depression (DSM-IV criteria), started with lithium or valproate as a mood stabilizer, and had not used this same drug in the two years before. Patients were excluded if they were already diagnosed with MetS at the start of treatment or if they were currently treated with a combination of antidiabetic drugs, lipid-lowering drugs and antihypertensive drugs. Inclusion took place within four weeks of the start of lithium or valproate. All patients gave written informed consent. The ethics committee of the collaborating psychiatric centres in the Netherlands ('METIGG') approved the study protocol. We aimed to include 90 patients, of which 60 patients starting lithium therapy and 30 patients starting valproate as a mood stabilizer.

Table 1 Metabolic syndrome according to International Diabetes Federation, 2005 [4]

Obligatory criterion:	
• Central obesity	Waist circumference ≥ 80 cm (female) ≥ 94 cm (male)
Plus two of the following four factors:	
• raised triglyceride level	>1.7 mmol/L (150 mg/dL); or specific treatment for this lipid abnormality
• reduced HDL cholesterol	< 0.9 mmol/L (40 mg/dL) (male); < 1.1 mmol/L (50 mg/dL) (female); or specific treatment for this lipid abnormality
• raised blood pressure	≥ 130/85 mmHg; or treatment of previously diagnosed hypertension
• raised fasting plasma glucose	≥ 5.6 mmol/L (100 mg/dL); or treatment of previously diagnosed type 2 diabetes

Metabolic syndrome parameters

Parameters of MetS, i.e. waist circumference, blood pressure, fasting glucose, HDL and triglycerides, and weight were measured at the start of the treatment with the mood stabilizer (t=0), and three, six and twelve months thereafter. Changes of these parameters were compared to baseline (t=0). In addition, the number of

patients that developed MetS was determined. MetS was diagnosed in patients who fulfilled three or more of the following five criteria: waist circumference of 80 cm or more in women and 94 cm or more in men (obligatory criterion); fasting blood glucose level of 5.6 mmol/L (100 mg/dL) or more; serum triglyceride level of more than 1.7 mmol/L (150 mg/dL); HDL of less than 0.9 mmol/L (40 mg/dL) in men and less than 1.1 mmol/L (50 mg/dL) in women; and an arterial blood pressure of 130/85 or more (IDF, 2005) (Table 1).[4] Current treatment with antihypertensives was categorized as raised blood pressure. Treatment with lipid-lowering drugs was scored as reduced HDL and raised triglycerides. A diagnosis of diabetes mellitus and/or use of antidiabetic drugs fulfilled the raised fasting plasma glucose criterion.[4]

Statistical analysis

Chi-square tests and student's t-tests were used to compare demographic variables, comedication and clinical variables in patients treated with lithium or valproate. The paired student's t-test was used for comparing the changes in the individual parameters of MetS and weight gain per patient over time.

RESULTS

A total of 23 patients were evaluated in this interim analysis, three patients started with valproate and twenty patients started with lithium as a mood stabilizer. The majority of patients (91%) were diagnosed with bipolar disorder. None of the patients used conventional antipsychotics, eleven patients used atypical antipsychotics (olanzapine (4), quetiapine (6), risperidone (1)) and nine patients used antidepressants (Table 2). The median duration of follow up for the lithium group was 208 days and this was 161 days for the valproate group.

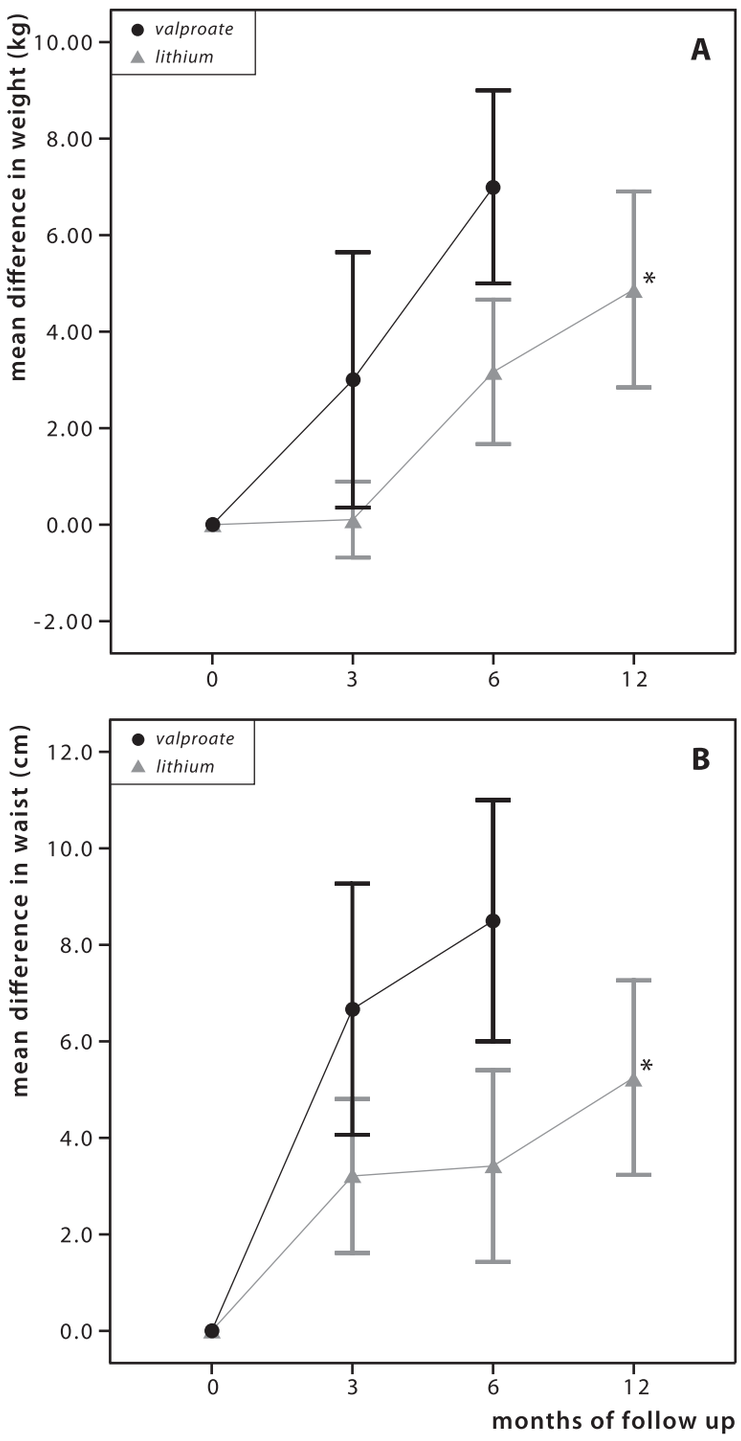
Changes in weight and MetS parameters are shown in Figures 1A-G. Data are presented as line plots with mean changes ± 1 standard error of the mean (SEM). Twelve months after initiation of lithium therapy, increases in weight (mean increase 4.9 kg; p=0.047) and waist (mean increase 5.3 cm; p=0.035) were statistically significant. In patients who started with valproate non-significant increases in weight (mean increase 7.0 kg; p=0.18) and waist circumference (mean increase 8.5 cm; p=0.18) were seen six months after start. Also, an increase in systolic blood pressure (mean increase 11.3 mm Hg) was seen after start of lithium, although this was not significant (p=0.09). An increasing fasting plasma glucose level was seen after initiation of valproate (mean increase 1.0 mmol/L; p=0.34), but not lithium

Table 2 Patient characteristics at baseline		
Characteristic	**Valproate n=3 (100%)**	**Lithium n=20 (100%)**
Gender, male	1 (33%)	6 (30%)
Age in years; mean (range)	33.1 (32-34)	44.9 (23-78)
Diagnosis		
bipolar I disorder	3 (100%)	8 (40%)
bipolar II disorder	0 (0%)	10 (50%)
depression	0 (0%)	2 (10%)
Disease phase		
depression	1 (33%)	11 (55%)
euthymia	1 (33%)	3 (15%)
mixed state	1 (33%)	0 (0%)
hypomania	0 (0%)	5 (25%)
mania	0 (0%)	1 (5%)
Concomitant use of psychotropics		
conventional antipsychotics	0 (0%)	0 (0%)
atypical antipsychotics	0 (0%)	11 (55%)
antidepressants	2 (67%)	7 (35%)
benzodiazepines	1 (33%)	8 (40%)
other mood stabilizers	0 (0%)	1 (5%)
Body weight in kg; mean (sd)	79.0 (18.2)	72.0 (13.4)
BMI in kg/m^2; mean (sd)	25.3 (2.27)	23.9 (3.8)
Waist in cm; mean (sd)	91 (10.5)	88.1 (12.1)
male	92	93.5 (11.2)
female	86 (8.5)	85.8 (12.0)
Bloodpressure (mm Hg); mean (sd)	117/70	124/77
Glucose (mmol/L); mean (sd)	4.20 (0.79	4.79 (0.47)
HDL (mmol/L); mean (sd)	1.20 (0.17)	1.50 (0.39)
male	1.10	1.20 (0.28)
female	1.25 (0.21)	1.63 (0.36)
Triglycerides (mmol/L); mean (sd)	1.00 (0.26)	0.97 (0.38)
male	1.20	1.03 (0.48)
female	0.90 (0.28)	0.94 (0.34)

BMI = body mass index; HDL = high-density lipoprotein

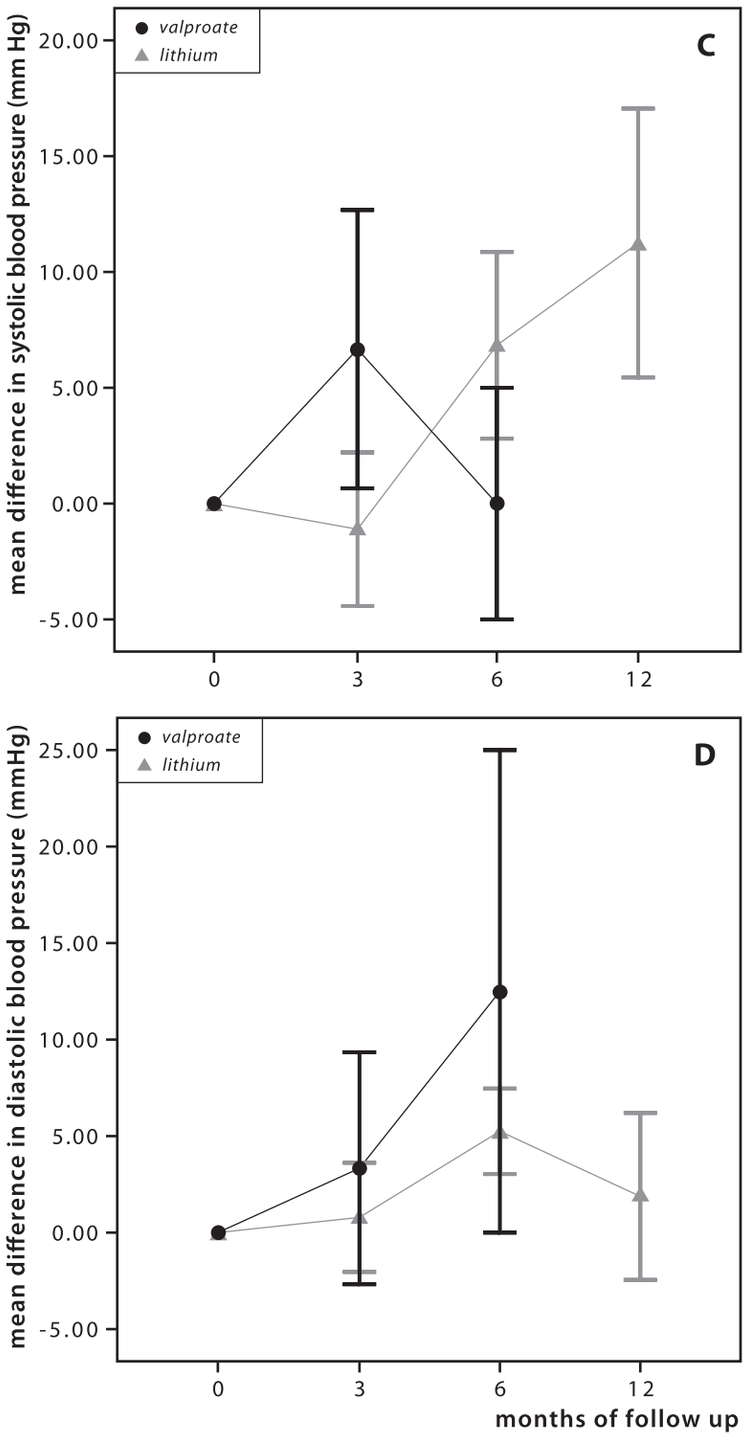
(mean increase 0.1 mmol/L; p=0.40). However, since only three patients with valproate were included in this interim analysis, these results should be interpreted with care. No clear changes in plasma HDL and triglycerides and start of the two

Figure 1 A+B Changes in body weight (A) and waist circumference (B) 3, 6, and 12 months after start of valproate or lithium (* statistically significant)



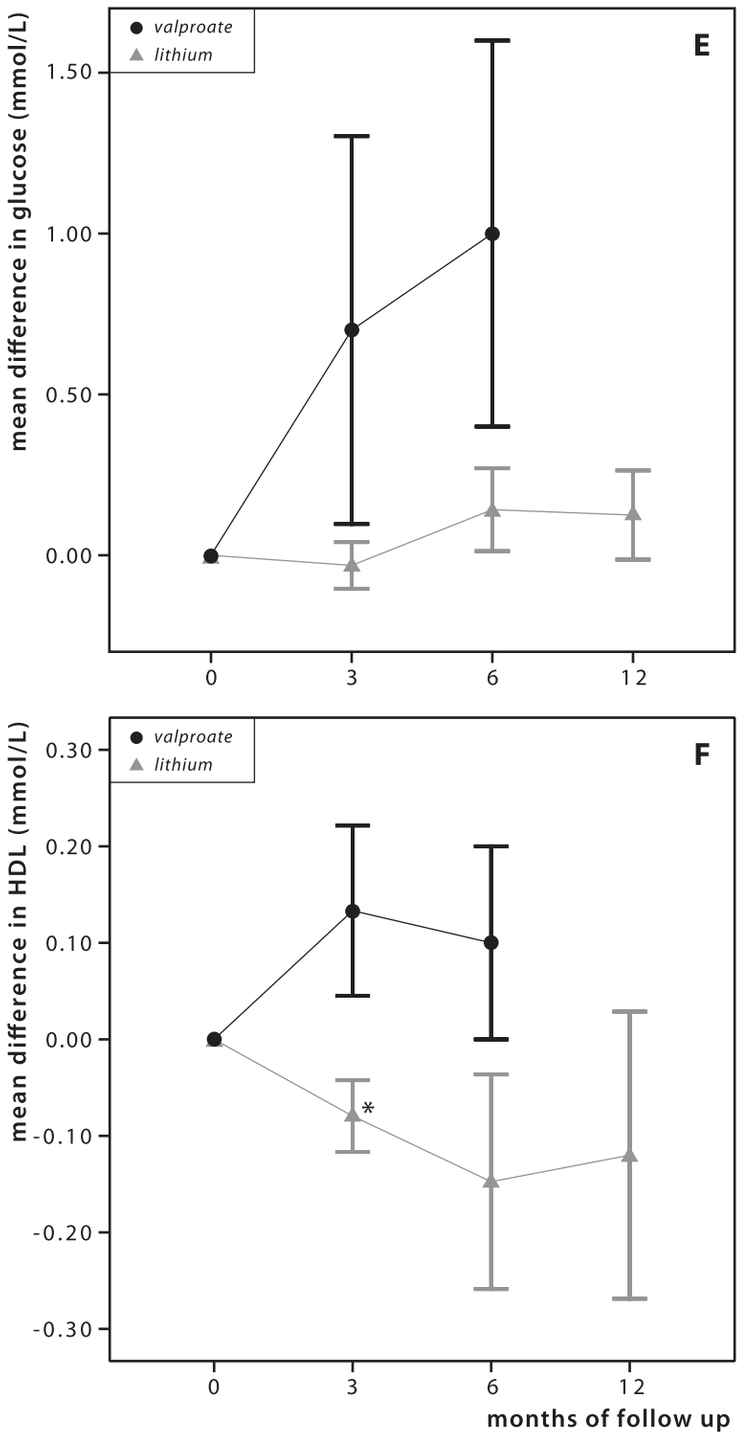
Evaluable patients (n)				
valproate	3	3	2	-
lithium	19	19	12	8

Figure 1 C+D Changes in systolic blood pressure (C) and diastolic blood pressure (D) 3, 6, and 12 months after start of valproate or lithium



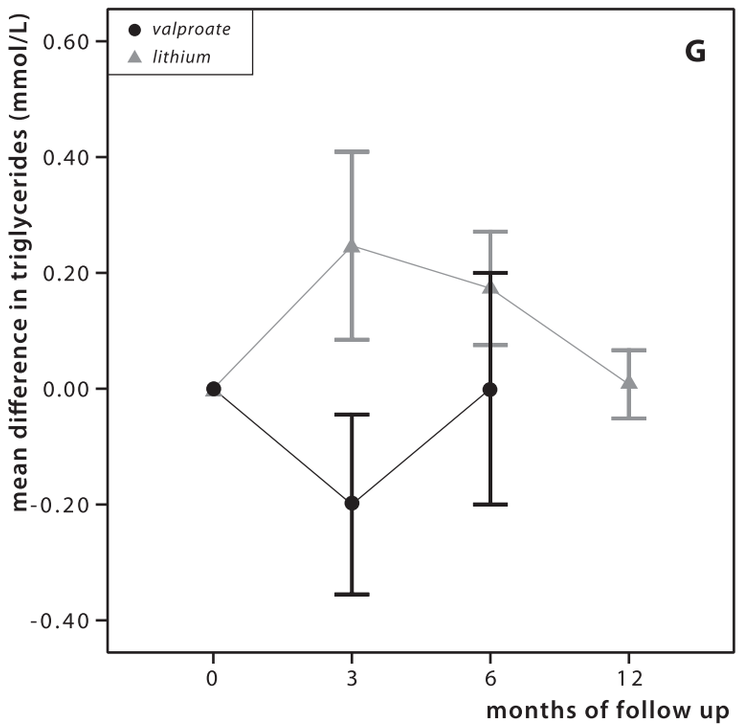
Evaluable patients (n)				
valproate	3	3	2	-
lithium	19	19	12	8

Figure 1 E+F Changes in glucose (E) and HDL (F) 3, 6, and 12 months after start of valproate or lithium (* statistically significant)



Evaluable patients (n)				
valproate	3	3	2	-
lithium	19	19	12	8

Figure 1 G Changes in triglycerides (G) 3, 6, and 12 months after start of valproate or lithium



Evaluable patients (n)				
valproate	3	3	2	-
lithium	19	19	12	8

mood stabilizers could be detected. Since the influence of atypical antipsychotics (AA) in MetS parameters is well established we compared parameters of patients using AA (n=11) with patients not using these drugs (n=9) in patients on lithium. No significant differences were seen regarding to weight gain, in patients without AA versus with AA (p=0.211) or waist circumference (p=0.303).

In the lithium group, 13 (65%) patients fulfilled the criteria for waist circumference and nine (45%) fulfilled the criteria for raised blood pressure before start of therapy. After a median follow up of 208 days of lithium treatment, 16 (80%) patients fulfilled the criteria for increase in waist circumference, 14 (70%) for blood pressure, three (15%) for fasting glucose and one (5%) for triglycerides. A total of 3 patients, (one male and two female) who started with lithium, developed MetS after six months of treatment. Details are shown in Table 3. Unfortunately, numbers so far were too small to allow for a proper statistical analysis. In the valproate group no changes with respect to fulfilling MetS criteria occurred after start of treatment.

DISCUSSION

In this interim analysis, a significant increase in body weight and waist circumference was seen with initiation of lithium therapy. Since only three patients starting with valproate could be included at the time of this analysis no firm conclusions can be drawn for changes in metabolic parameters in patients after initiating valproate treatment.

Our findings are comparable with previous findings in which an increase of weight was detected with use of lithium and valproate.[22,23] The mean weight gain of 4.9 kg after start of lithium found in this study was higher than a previous study by Sachs et al.[24] who found a 4.0 kg increase after one year of lithium treatment in a group of 24 patients, but lower than a study by Chengappa et al.[25] who found a mean change in bodyweight of 6.3 kg in 70 patients after a mean duration of 131 days of lithium. Bowden et al.[26] reported that weight gain associated with lithium was essentially limited to patients with pre-existing obesity (BMI>30 kg/m^2). In our study only two patients had a BMI>30 kg/m^2 at the start of treatment. Excluding these patients from our analysis did not influence our results, i.e. the association between lithium use and weight and waist circumference were still significant. No previous research was found in which a change in waist circumference was explored as a result of lithium therapy. Other researchers did find an association with respect to glucose intolerance and lipid profile and use of lithium or valproate.[17,27,28] In this interim analysis we were not able to confirm these previous findings.

Yumru et al. reported a cross-sectional study in which no significant difference was found in MetS rates prevalence between bipolar patients taking mood stabilizers only (MetS rate 23.7%) or the combination of mood stabilizers and AA (MetS rate 24.2%).13 Also, in our study no significant differences were seen regarding to weight gain in patients without AA versus with AA (p=0.211) or waist circumference (p=0.303). However, the influence of AA should not be underestimated and future analyses should be stratified or corrected for use of AA.

Several mechanisms for both lithium and valproate-induced weight gain have been proposed, such as carbohydrate craving, defective sympathetic nervous system, leptin-resistancy, modulation of islet cell insulin secretion.[11,23,29] Furthermore, lithium may have a direct effect on the hypothalamus to stimulate appetite.[30] In addition, an important side effect of lithium therapy is thirst. If thirst is relieved by taking high calorie drinks, this may lead to weight gain.[31]

Unfortunately at the time of this analysis only 25% of the amount of patients that was aimed for could be evaluated, therefore one of the important limitations of this exploration is the small sample size. Another limitation is that the effect may be underestimated. Since patients were informed about the possibility of developing

MetS they may have changed their diet or habits to influence these parameters and therefore the so-called healthy user bias may have played a role. The conditions of this study were not designed to distinguish whether the drug or the disease leads to changes in MetS parameters. To study this, a group treated with placebo should also be included. Since this is not ethically defendable, no placebo-controlled group was set-up.

In summary, an association was found between start of lithium and central obesity, which is measured as an increase in waist circumference. No recommendations on the screening of MetS parameters can be given yet, for this we will have to wait until enough patients are included allowing for a proper final analysis.

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chapter 5.3

Risk of aplastic anemia in patients using antiepileptic drugs

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ABSTRACT

Objective

To assess the association between exposure to antiepileptic drugs (AEDs) and the occurrence of aplastic anemia.

Methods

A retrospective case-control study was conducted using data from the UK General Practitioners Research Database (GPRD). Cases were defined as patients diagnosed with aplastic anemia. For each case, up to three control patients were matched on age, sex, and medical practice. Cases and controls were compared with respect to AED use. The effect of duration of AED use were assessed. Characteristics of individual cases with AED use were reviewed.

Results

The study population comprised 173 cases and 497 controls. AED use was more prevalent among cases (9.2%) than among controls (0.8%). After adjustment for confounders, the use of AEDs was significantly associated with aplastic anemia (adjusted odds ratio (OR) 9.5; 95% confidence interval (CI) 3.0-39.7). The most frequently used AEDs were carbamazepine, valproic acid and phenytoin. The 16 exposed cases were heterogeneous with respect to patient and exposure characteristics: the age of these patients varied from 1 to 92 years and the duration of AED use varied from 17 days to 6.8 years.

Conclusion

This study indicates that use of AEDs, in particular carbamazepine and valproic acid, is associated with a ninefold increased risk of aplastic anemia. Physicians should be alert to the possibility of AED-associated aplastic anemia.

INTRODUCTION

Aplastic anemia is a hematopoietic stem-cell disorder characterized by pancytopenia of the peripheral blood and hypocellular bone marrow. In its most severe form, aplastic anemia requires intensive therapy with either bone marrow transplantation or immunosuppression. Case fatality rate is approximately 10%.[1]

Although aplastic anemia has an incidence of a few cases per million per year, it is one of the most feared idiosyncratic complications of drug treatment. In addition to causing patient harm, aplastic anemia may also harm the drug: when evidence emerges that a drug is associated with aplastic anemia, regulatory agencies are reluctant to seek approval in case of a new drug, as well as imposed to withdraw an already approved drug from the market.[2,3]

The association between antiepileptic drug (AED) use and aplastic anemia has been described in several case reports.[4-7] The International Agranulocytosis and Aplastic Anemia Study (IAAAS) was conducted to identify various drugs that were associated with an increased risk of agranulocytosis or aplastic anemia.[8] Although carbamazepine and phenytoin were suspected to be associated with aplastic anemia, the authors acknowledged they had insufficient data to evaluate this specific association with AEDs with adequate control for confounding. Blackburn et al.[9] investigated the frequency of serious blood dyscrasias, including aplastic anemia, in a cohort study among 29 357 patients taking AEDs. They found only one case of aplastic anemia and could not draw specific conclusions with respect to the association between use of antiepileptic agents and aplastic anemia.

To our knowledge, no studies have specifically investigated the relation between AEDs and aplastic anemia. Therefore the aim of our study was to assess the strength of the association between AED use and the risk of aplastic anemia.

METHODS

We conducted a case-control study using data from the UK-based General Practice Research Database (GPRD). The GPRD contains the computerized medical records of 686 general practices in the UK. Clinical data are stored and retrieved by means of Oxford Medical Information Systems (OXMIS) and Read codes for diseases or causes of morbidity and mortality that are cross-referenced to the International Classification of Diseases (ICD-9). The GPRD has shown to be a useful and valid source for several observational studies, including research on the frequency of blood dyscrasias among patients taking AEDs[9] as well as a study on the risk of

agranulocytosis and neutropenia associated with current drug use.[10] Our study was approved by the Scientific and Ethical Advisory Group of the GPRD.

We identified all patients with a first diagnosis of aplastic anemia (ICD-9 code 284) recorded during the period of time from the enrolment date of their practice in GPRD up to the end of data collection (1987-2002). Cases were eligible for inclusion if they had at least one year of history in the GPRD. Given our interest in idiosyncratic disease, patients with a history of use of chemotherapy, immunosuppressive drugs or hormone antagonists prior to the index date were excluded. Control patients did not have a diagnosis of aplastic anemia at any time. The same inclusion and exclusion criteria were applied to controls and case patients. We matched up to three controls to each case on age (within one year), sex, and medical practice. The index date of each control patient was that of the matched case.

The determinant of interest in this study was exposure to AEDs. Exposure status was based on the prescription information prior to the index date. Because aplastic anemia may develop over several months after exposure to the suspected agent and can have a lag time before definitive diagnosis,[11] we defined exposure to AEDs as a prescription for an AED within the time window of one year before the index date. A medical history of malignancy (i.e. without chemotherapy), systemic lupus erythematosus, myelodysplasia, megaloblastic anemia, mycobacterial infections, viral infections or allergies were in line with available evidence considered as potential confounders.[8,12,13] In addition, exposure to nonantiepileptic agents that have been implicated with aplastic anemia in the medical literature,[8,12,13] or of which five or more case reports in relation to aplastic anemia were reported to the WHO Collaborating Centre for International Drug Monitoring[14] were also considered as potential confounding factors (Appendix 1). Furthermore, characteristics of individual cases with AED use, as available in the GPRD database, were reviewed.

The strength of the association between use of AEDs and aplastic anemia was estimated by using exact conditional logistic regression analysis and expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Potential confounders were studied both in univariate models and in a multivariate model. They were included in the multivariate model if they induced a 10% change or more in the crude OR for the exposure of interest.

RESULTS

Of 265 patients with a first diagnosis of aplastic anemia, 92 patients did not meet our inclusion criteria (88% because of a history in GPRD of less than one year).

The study population comprised 173 cases with aplastic anemia and 479 matched controls. The characteristics of cases and controls are displayed in Table 1. History of malignancy, viral infection and allergy were more frequently reported in the case group than in the control group, as were current use of betalactam antibiotics, antidepressants, and nonsteroidal antiinflammatory drugs (NSAIDs). Other

Table 1 Characteristics of case patients with aplastic anemia and matched controls

Characteristic	Case n=173 (100%)	Control n=479 (100%)	OR (95% CI)	p-value
Sex[a]				
male	73 (42.2%)	205 (42.8%)	NE	
female	100 (57.8%)	274 (57.2%)		
Age[a] *(years)*				
< 20	22 (12.7%)	61 (12.7%)	NE	
20-39	19 (11.0%)	49 (10.2%)		
40-59	35 (20.2%)	99 (20.7%)		
60-79	64 (37.0%)	178 (37.2%)		
≥ 80	33 (19.1%)	92 (19.2%)		
Comorbidity				
malignancy	23 (13.3%)	20 (4.2%)	3.6 (1.8− 7.4)	<0.001
viral infection	17 (9.8%)	15 (3.1%)	3.5 (1.6− 8.2)	0.002
allergy	9 (5.2%)	3 (0.6%)	7.7 (1.9−44.3)	0.002
myelodysplasia	8 (4.6%)	1 (0.2%)	21.2 (2.8−946)	<0.001
Comedication				
betalactam antibiotics	26 (15.0%)	38 (7.9%)	2.4 (1.3− 4.6)	0.006
antidepressants	14 (8.1%)	17 (3.5%)	2.4 (1.0− 5.3)	0.041
NSAIDs	24 (13.9%)	33 (6.9%)	2.2 (1.2− 4.1)	0.014

NE = not estimable; NSAIDs = nonsteroidal antiinflammatory drugs
a) Matching variables not applicable.

determinants were not significantly associated with aplastic anemia (data not shown).

Overall, exposure to AEDs was more prevalent among cases (9.2%) than among controls (0.8%), yielding a crude OR of 10.9 (95% CI 3.5-45.1). After adjustment for confounders the OR was lower, but still clearly increased (adjusted OR 9.5; 95% CI 3.0-39.7). Polytherapy with AEDs was more strongly associated with aplastic anemia than monotherapy (Table 2).

Table 2	Association between use of AEDs and risk of aplastic anemia					
	Case	Control	Crude		Adjusted [a]	
	n=173 (100%)	n=479 (100%)	OR (95% CI)	p-value	OR (95% CI)	p-value
AED use						
no use	157 (90.8%)	475 (99.2%)	1.0 (ref)		1.0 (ref)	
AED user	16 (9.2%)	4 (0.8%)	10.9 (3.5-45.1)	<0.001	9.5 (3.0-39.7)	<0.001
AED mono- versus polytherapy						
no AEDs	157 (90.8%)	475 (99.2%)	1.0 (ref)		1.0 (ref)	
AED mono-therapy	11 (6.3%)	4 (0.8%)	7.9 (2.1-31.6)	<0.001	7.3 (2.1-31.6)	<0.001
AED poly-therapy	5 (2.9%)	0 (0.0%)	16.1 (2.2-∞)	0.005	11.2 (1.3-∞)	0.025
Specific AED use						
no use	157 (90.8%)	475 (99.2%)	1.0 (ref)		1.0 (ref)	
any CBZ	8 (4.6%)	2 (0.4%)	11.2 (2.2-108)	0.001	10.3 (2.0-101)	0.003
any PHT	4 (2.3%)	2 (0.4%)	5.3 (0.8-58.7)	0.107	3.5 (0.4-44.4)	0.346
any VPA	6 (3.5%)	0 (0.0%)	21.7 (3.1-∞)	<0.001	18.2 (2.5-∞)	0.002

AED = antiepileptic drug; CBZ = carbamazepine; PHT = phenytoin; VPA = valproic acid
a) Adjusted for allergy.

Of the sixteen patients that were users of AEDs (Table 3), eight used carbamazepine (OR 10.3; 95% CI 2.0-101), six used valproic acid (OR 18.2; 95% CI 2.5-∞) and four used phenytoin (OR 3.5; 95% CI 0.4-44.4) during the year before the index date. The cases were rather heterogeous with respect to age (range 1 to 92 years) and duration of AED exposure (range 17 days to 6.8 years). For the latter we chose the duration of the last AED regimen. After aplastic anemia was recorded, four patients continued their AED therapy, two patients switched to other AEDs and eight patients discontinued AED therapy.

DISCUSSION

In this study, we found that exposure to AEDs was associated with a ninefold increased risk of aplastic anemia.

Several case reports described a possible association between AED use and aplastic anemia, felbamate being the most frequently reported AED involved. In our study population, none of the cases and the controls used felbamate, which could be explained by the study period (up to 2002). Use of carbamazepine and valproic acid was significantly associated with aplastic anemia in our study. After aplastic

Table 3 Individual features of sixteen AED users among cases with aplastic anemia

Case	Age (yrs)	Sex	AED in year before index date	Duration of last AED regimen (days)	AED after index date	Potential confounders
1	1	F	carbamazepine	26	Continue carbamazepine	-
2	8	M	vigabatrine and phenytoin	69	Stop vigabatrin and phenytoin; switch to clonazepam, gabapentine, topiramate, ethosuximide	-
3	20	F	carbamazepine	174	Stop carbamazepine; no AEDs	Use of betalactam antibiotics and antidepressants
4	33	M	lamotrigine, valproic acid and primidone	927	Stop valproic acid; continue lamotrigine and primidone	-
5	39	F	phenytoin and carbamazepine	299	Stop carbamazepine and phenytoin; switch to gabapentine	Recorded urticaria, allergic rash
6	40	M	carbamazepine	129	Stop carbamazepine; no AEDs	-
7	43	M	valproic acid	1106	Stop valproic acid; start phenytoin, vigabatrin, lamotrigin, carbamazepine	-
8	50	F	valproic acid and carbamazepine	107	Stop carbamazepine and valproic acid; no AEDs	Use of betalactam antibiotics and antidepressants
9	61	F	valproic acid	1205	Continue valproic acid	-
10	68	F	carbamazepine	1291	Stop carbamazepine; no AEDs	-
11	70	F	phenytoin	235	Continue phenytoin	-
12	71	M	carbamazepine	57	Stop carbamazepine; no AEDs	-
13	73	M	carbamazepine	113	Stop carbamazepine; no AEDs	Use of betalactam antibiotics and antidepressants
14	75	F	valproic acid	638	Continue valproic acid	-
15	81	F	phenytoin and phenobarbital	2872	Stop phenytoin and phenobarbital; no AEDs	-
16	92	F	valproic acid	2492	Stop valproic acid; no AEDs	-

AED = antiepileptic drug; F = female; M = male

anemia had been diagnosed, the AED regimen was changed in most patients, presumably indicating that physicians suspected the AED to be responsible for aplastic anemia.

The pathophysiology of acquired aplastic anaemia is thought to be immune mediated. Since Palace and Lang[15] hypothesized that autoimmune mechanisms might have an etiological role in patients with epilepsy, one could argue that our results could be explained by the underlying disease instead of the AED. However, evidence supporting this hypothesis is not yet available in the literature.

This study should be seen in the light of its limitations. AEDs have been associated with several blood dyscrasias.[8,9] Therefore, diagnostic suspicion bias could be a problem with aplastic anemia since clinicians often make the diagnosis based on the drug-exposure history. This could lead to an absolute risk overestimation. It is possible that patients with aplastic anemia died before being diagnosed. This would have resulted in an underestimation of the true risk estimate. Furthermore, the coding of the outcome event may have been inaccurate. We did not perform a validation of cases. Van Staa et al.[10] validated cases of neutropenia and agranulocytosis in the GPRD by sending questionnaires to the general practitioners: the diagnosis was confirmed in 94.6% and 97.1% of cases, respectively. Aplastic anemia is a laboratory-based diagnosis as well, but requires additional bone marrow examination. We cannot exclude the possibility of some misclassification, but it seems unlikely that this can explain the large effect we observed.

To our knowledge this study is one of the few epidemiological studies on aplastic anemia and AED exposure. Most of what is known or suspected about this association is based on case reports. We used data up to 2002, while the last epidemiological study on antiepileptic drugs and blood dyscrasias used data up until 1994.[9] We adjusted for confounding by taking into account comorbidities associated with aplastic anemia and other potentially causal drugs, including the latest registrations in the WHO database.

Carbamazepine and valproic acid are the most widely prescribed AEDs. However, the relative risk for aplastic anemia in other AEDs may be comparable. Thus, further research is needed to study whether use of newer AEDs (besides felbamate) such as topiramate, levetiracetam, and gabapentin, is associated with the occurrence of aplastic anemia. It would be interesting to study whether use of AEDs is associated with other immune-modulated hematologic adverse events, such as pure red cell aplasia.

In conclusion, our study adds to the limited evidence on the association between exposure to AEDs and aplastic anemia. Thus, physicians should be alert to the possibility of AED-associated aplastic anemia.

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Appendix 1 Potential confounders [8,12-14]

Diseases	Prescription drugs	
- cancer	- ACE inhibitors	- disease modifying antirheumatic drugs
- leukemia	- allopurinol	- H_2 antagonists
- Lupus Erythematodus	- amphotericin B	- macrolide antibiotics
- lymphoma	- antidepressive drugs	- mebendazole
- megaloblastic anemia	- antipsychotics	- nitrofurantoin
- mycobacterial infections	- antithyroid medication	- NSAIDs
- myelodysplasia	- azoles	- oral antidiabetics
- viral infections	- betablockers	- protonpompinhibitors
	- betalactam antibiotics	- quinolones
	- calcium antagonists	- statins
	- carboanhydrase inhibitors	- sulfasalazine
	- chloramphenicol	- thiazides
Other	- clopidrogel	- trimethoprim/sulfamethoxazole
- allergies	- clozapine	- vaccins
- pesticides	- digoxin	

ACE = angiotensin I converting enzyme; NSAIDs = nonsteroidal antiinflammatory drugs

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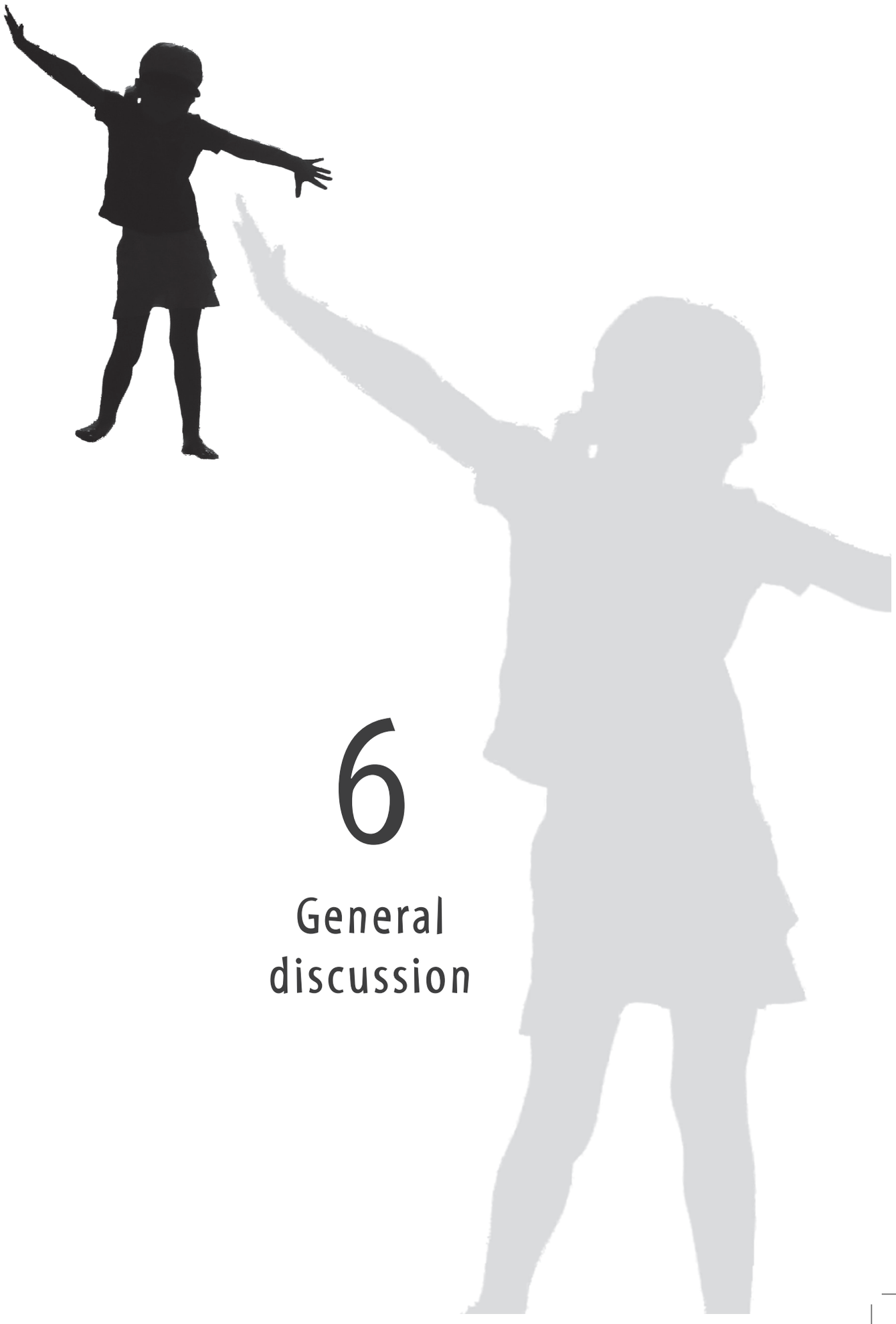


6

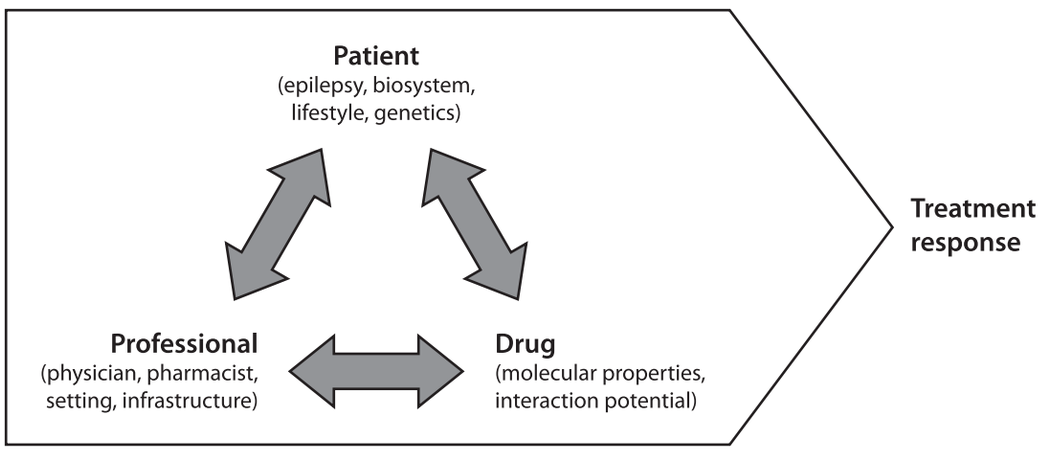
General discussion

INTRODUCTION

For patients with epilepsy the ultimate goal of antiepileptic drug treatment is to maintain a normal life style, with complete seizure control and absence of adverse effects. However, in practice this is difficult to accomplish. Therefore, for each individual patient a balance has to be found between effectiveness and safety of antiepileptic drug treatment. In case this balance in treatment is not achieved and the patient is still unable to live a normal life, this can be considered as treatment failure.

Treatment failure in epilepsy can be divided into two main and interconnected components: *ineffectiveness* and *adverse effects* (responsible for tolerability and safety). The aim of this thesis is to assess and evaluate different determinants that could explain antiepileptic drug failure and to provide suggestions for interventions in order to improve treatment response in patients with epilepsy. In our general introduction (**Chapter 1**) we introduced three actors that constitute major determinants of the response of the individual patient to antiepileptic drug treatment: the patient, the healthcare professional and the drug (Figure 1). In this

Figure 1 Factors influencing treatment response in epilepsy



final chapter, the role of these three key actors –patient, professional and drug– as important modulators for achieving treatment success in epilepsy will be explored by discussing six themes that have come up during our studies and that go beyond the discussion of the individual studies included in this thesis:

1. Patient adherence to drug treatment
2. Drug-drug interactions
3. Monitoring
4. Structure-activity relations
5. Tertiary centres in epilepsy
6. Pharmacogenetics

In addition, we will provide recommendations for clinical practice and directions for future research.

FROM TREATMENT FAILURE TO TREATMENT SUCCESS IN EPILEPSY

Patient adherence to drug treatment

An important modifiable factor for successful treatment response is the appropriate use of antiepileptic drugs by the patient, i.e treatment adherence. Urquhart et al. proposed that drug adherence can be divided into three phases: 1) acceptance by the patient of the treatment plan, leading to 2) execution of the drug regimen, and eventually 3) discontinuation.[1] In patients with epilepsy, execution of the treatment plan is often the most complex part. Jones et al. found a negative correlation between adherence and seizure frequency, i.e. in non-adherent patients seizures occurred more frequently.[2]

One of the difficulties in antiepileptic drug treatment execution is the dosing frequency; it has been shown that once daily dosing is associated with higher compliance rates than regimens with two or more doses a day.[3] Unfortunately, the majority of antiepileptic drugs have a relatively short elimination half-life and therefore these drugs have to be administered several times a day. Although pharmaceutical companies have been developing slow release formulations, until now only few antiepileptic drugs can be taken once daily.

In our study (*Chapter 3.2*), no differences were seen in adherence rates between patients with epilepsy-related hospitalizations and patients who were well under control. Adherence in this study was measured by refill in pharmacy records. However, when we asked the patients themselves for possible reasons for the occurrence of seizures, dose omission was the most frequent answer. Also during the patient interviews for the Response On Medication in Epilepsy (ROME) study –where we studied pharmacogenetic explanations for antiepileptic drug treatment failure (*Chapters 4.1* and *4.2*)– difficulties with dose regimens and preventing dose omission was one of the important topics that came up underlining the importance

of 'easy' dosing regimens that help patients in successful treatment execution. Cramer et al. reported similar findings in their study on the association between poor medication compliance and seizure occurrence.[4] Out of 661 respondents 71% reported dose omissions, from which 45% of patients reported a seizure after a missed dose. It is well known that adherence estimates based upon pharmacy dispensing records are especially suitable to detect long-term non-adherence and are not sensitive for the detection of occasional dose omissions. Patient interviews, patient diaries and electronic compliance measurement devices provide better insight in such execution patterns.

In order to improve treatment adherence, physicians should -in consultation with the patient- consider prescribing the simplest regimen with the fewest daily doses and tablets possible since this will improve chances on treatment adherence and also reduces the burden of pill-taking in daily life. However, if it is not possible to provide simple drug regimens, healthcare professionals can support patients by offering them tools to make adherence to medication easier. Different tools have been developed for improving or supporting patients to adhere to their medication regime. An example is the supply of medication in medication boxes or bags sorted by day or by administration time.[5,6] Sorting of medication may also help to stimulate the awareness of doses that have been missed. Furthermore, keeping seizure diaries or continuous EEG monitoring with help of portable wireless devices may also help patients and healthcare professionals gain insight in seizure patterns and their association with medication intake.[7] Recently, researchers in the field of HIV and diabetes care have studied the effect of mobile phone or short message service (SMS) to improve adherence and better treatment outcome was measured as a result of these services.[8,9]

To summarize, the regular evaluation of treatment adherence is exceedingly important especially in patients with unstable epilepsy.

Drug-drug interactions

Antiepileptic drugs are well known for their drug-drug interaction potential. Therefore, our hypothesis was that these interactions would play a major role in epilepsy-related hospital admissions. However, in two of our studies (*Chapters 3.1* and *3.2*) pharmacokinetic as well as pharmacodynamic drug-drug interactions hardly contributed to epilepsy-related hospitalisations. Several reasons can be given for not finding a prominent role for drug-drug interactions. First, the effects of pharmacokinetic drug-drug interactions do occur, but do not result in substantial alteration of plasma levels to be of clinical importance. Second, since this is a known topic, physicians and pharmacists adequately manage drug-drug interactions and

therefore they do not lead to clinically relevant effects. In general, prescribers prefer the newer antiepileptic drugs since they appear to have better safety profiles.[10,11] In addition, drug-drug interaction problems are less prominent since the majority of the newer antiepileptic drugs are not metabolized via cytochrome-P450 enzymes.[12,13] In an unpublished study in the GIP reimbursement database –which held prescription data of all patients who received at least one antiepileptic drug in the Netherlands (98 043 patients)– we found that the overall frequency of drug-drug interactions was low indeed. This finding strengthens our explanation that the overall occurrence of drug-drug interactions is relatively low. Recently, a large study in an American Medicaid database showed that approximately 45% of patients receiving monotherapy with an older antiepileptic drug had a potential drug-drug interaction, compared with 3.9% receiving a newer antiepileptic drug. An average of 0.08 potential drug-drug interactions per year of exposure occurred in the newer antiepileptic drug monotherapy cohort compared to 1.18 potential drug-drug interactions per year in the older antiepileptic drug monotherapy cohort.[14] The most common potential interaction was a decreased concentration of non-antiepileptic drug co-medication. This underlines the lower drug-drug interaction potential of newer drugs. Also, it shows that the drug-drug interactions do not usually affect the antiepileptic drug therapy but the other drugs involved. Thus, with the current antiepileptic drug treatment options drug-drug interactions are of minor importance with regards to treatment failure.

Instead of focusing on the known drug-drug interactions that might be responsible for epileptic seizures, it might for medication surveillance be more important to look at overall changes in the medication regimen. We detected that changes in the patient's medication regimen, namely start, switch, discontinuation of antiepileptic drugs and non-antiepileptic drugs, and in particular the start of three or more drugs, were associated with a five-fold increase in epilepsy-related hospital admissions (Odds Ratio (OR) 4.8; 95% CI 2.1-10.9) (*Chapter 3.1*). Start of antibiotics was associated with a two-fold increase in epilepsy-related hospitalizations (OR 2.0; 95% CI 1.1-3.8) (*Chapter 3.1*). Antibiotics are not known for their alterations in antiepileptic drug levels or lowering the seizure threshold (except for betalactam and fluorquinolone antibiotics given in very high doses).[15] Wilting et al. performed a study on drug-drug interactions with lithium and also concluded that initiation of antibiotics, although not known for their interaction with lithium, was the most important contributor for elevated lithium levels.[16] Initiation of antibiotics can be seen as a proxy for an infection, and therefore as a proxy for a destabilization of the patient's general condition. Thus, the interaction between the drug and the disease may be responsible for a loss of seizure control. This is supported by the

findings that seizures are common in metabolic (e.g., uraemia, hypoglycaemia, hyperglycaemia, and hepatic failure), toxic (e.g., drug overdose or withdrawal), and infectious (e.g., meningitis and encephalitis) conditions.[17] Likewise, starting of three or more concomitant drugs can also be seen as a proxy for a destabilization of the patient's condition.

It is important that healthcare professionals (physicians and pharmacists) are alert when changes in medication occur, as these are intra-individual indicators of an increased susceptibility for the occurrence of seizures. Since changes in the medication regimen, especially starting new drugs, usually go hand in hand with a visit to the pharmacist, the pharmacist would be the designated professional to give out a warning to the patient and the physician to be alert for signs that may announce seizures. Warning should be given especially when physicians not involved in the antiepileptic drug treatment make changes in drug regimens. More specifically, we would advise to give a warning in case of start of antibiotics or start of three or more drugs (*Chapter 3.1*). In future, larger population studies should be undertaken to more specifically detect which changes in medication can lead to an increased susceptibility for seizures and how this risk can adequately be managed.

Monitoring

Once antiepileptic drug treatment is initiated, regular monitoring of the patient is necessary. Monitoring entails aspects such as tracking the severity, the duration, and the frequency of the seizures. In case seizures still regularly occur, keeping seizure diaries is recommended. On the other hand monitoring entails also the occurrence of adverse effects (in behaviour or physical). For both, measuring antiepileptic drug serum concentrations and biomarkers can be of help.

In *Chapter 3.2* we studied the role of therapeutic drug monitoring in seizure occurrence and found that patients with low antiepileptic drug serum levels had a nine times higher risk of seizures compared with patients with therapeutic levels. (OR 8.9; 95% CI 1.7-47.8). Although therapeutic drug monitoring is not recommended as routine,[18,19] we advise at least an annual test for two reasons. First, if the serum level is low and seizures still occur an alteration in drug regimen is indicated. Second, if serum levels are near zero and seizures have not occurred for at least two years withdrawing antiepileptic drug therapy should be considered.[20]

Biomarkers such as a full blood count, electrolytes, renal function, liver enzymes, total cholesterol, vitamin D levels and other tests for bone metabolism are not routine in patients using antiepileptic drugs. However, it is known that antiepileptic drugs can cause liver damage (valproate),[21] hyponatremia (carbamazepine, oxcarbazepine),[22] decreased thyroid hormone levels (all enzyme inducing antiepileptic drugs),[23] low

bone density [24] that may lead to fractures [25] (all antiepileptic drugs), and blood dyscrasias (*Chapter 5.3*). Also, a decreased renal function may lead to unwanted higher serum levels. In *Chapter 5.2* we found clues that valproate may be associated with the development of metabolic syndrome. This association has to be further explored, especially since it is already known that valproate but also carbamazepine, gabapentin, vigabatrin, and pregabalin can cause a significant weight gain.[23,26,27] Since weight gain is associated with an increased risk for metabolic syndrome, and thus diabetes and cardiovascular morbidity and mortality,[28] it should be further investigated whether routine tests on metabolic syndrome parameters (blood pressure, glucose, HDL, triglycerides, waist circumference) are necessary. Patients using antiepileptic drugs also have a ninefold increased risk of aplastic anaemia compared with non- antiepileptic drug users as we found in *Chapter 5.3*. Although aplastic anaemia has a low absolute incidence, the severity of the disease is such (10% mortality)[29] that a routine laboratory test on full blood count could lead to adequate and timely interventions.

In summary, therapeutic drug monitoring and biomarker monitoring are important tools in optimizing antiepileptic drug treatment response. Future studies should investigate the cost-effectiveness of performing routine laboratory tests in order to increase successful antiepileptic drug treatment response, especially by lowering the risk of or the early detection and management of adverse reactions. However, we will always have to treat the patient and not the numbers, therefore laboratory data should never be the lead but the supporting tool in treating patients with epilepsy.

Structure-activity relations

An important safety issue in the treatment with antiepileptic drugs is the possibility of the development of hypersensitivity reactions, occurring in >3% of patients treated with antiepileptic drugs.[30] Hypersensitivity reactions vary from relatively mild urticarial eruptions to potentially lethal Stevens-Johnson syndromes.[31,32] Hypersensitivity reactions have always been considered as type B adverse effects, namely effects that cannot typically be explained on the basis of known pharmacological mechanisms and occur mostly unpredictable in susceptible patients only.[33]

Currently, over twenty antiepileptic drugs are available and major differences exist between these drugs. At the molecular level there are evident structural distinctions but commonalities as well.[34] In *Chapter 5.1* we have shown that a structural similarity within the group of antiepileptic drugs -namely the presence of an aromatic ring- is associated with hypersensitivity reactions. Symptoms of hypersensitivity were reported two times as frequent with aromatic antiepileptic drugs as with non-

aromatic antiepileptic drugs. Strong associations for aromatic antiepileptic drugs versus non-aromatic antiepileptic drugs were found for T cell-mediated (type IV) reactions (Reporting Odds Ratio (ROR) 6.06; 95% CI 3.41-10.75) as well as for cutaneous reactions (ROR 5.81; 95% CI 3.38-9.99). This evidence contributes to the explanation for the occurrence of hypersensitivity. An important lesson to be learned from this study is that cross-reactivity may also play an important role in choosing the antiepileptic drug for the individual patient. It is well known that drugs containing a sulfonamide structure can provoke allergic reactions, and that healthcare professionals should be alert for cross-reactivity between for example a sulfonamide antibiotic and certain oral antidiabetic drugs.[35,36] Our study added the evidence for an explanation that once a hypersensitivity reaction has occurred on antiepileptic drug treatment with an aromatic ring, caution for giving other antiepileptic drugs and possibly even other drugs with aromatic rings is appropriate. With respect to the latter, more research should be undertaken to explore adverse drug reactions by using chemical structure instead of therapeutic drug classes to classify exposure.

Knowledge of chemical structures of drugs is typically a clinical pharmacists or pharmacologists territory. In future, these health care professionals could also monitor their patients on drug reactions and outcome, by analyzing adverse effects (especially hypersensitivity) related on their chemical structure and reporting these to the pharmacovigilance centres. By doing this, recurrent allergic reactions might be prevented in future and treatment response can be improved. In order to accomplish this implementation of this knowledge in the automated medication surveillance systems of health care professionals can be of help.

Tertiary centres in epilepsy

The majority of general practitioners refer patients with suspected epilepsy to a general neurologist. When the diagnosis epilepsy is set, usually treatment with an antiepileptic drug is started. National and international guidelines support neurologists in making the appropriate choice, and monitoring and evaluation of treatment with an antiepileptic drug. Almost half of the patients are well under control with the antiepileptic agent prescribed and do not suffer from bothersome side effects.[37] However, often they or their families have additional questions on epilepsy and work, education, driving ability or other social problems that may come up for which the general neurologist may have insufficient expertise and time to provide the required specialized care.[38,39] Recently, in the Netherlands epilepsy consultants were introduced in some of the general hospitals. These specialized nurses can assist patients and their families who have recently been diagnosed with

epilepsy. Besides their knowledge about epilepsy they can also provide information on the specialized healthcare that is available.

Treatment guidelines on epilepsy provide information on the diagnosis and management of epilepsy in adults and children in primary and secondary care. It involves recommendations on investigations, tests, treatment, and referral to tertiary centres.[18] However, guidelines are not always followed. During the interviews for the ROME study (*Chapter 4.1* and *4.2*) we learned that it could take up to seven years before patients with uncontrolled epilepsy are referred to specialized centres. Some of these patients were still on unconventional antiepileptic drugs. In our opinion, a late referral in these patients is a delay of adequate treatment, since these patients are also not provided by the appropriate care. Nowadays patients are more informed by patient associations, the internet, and other sources of information. Still, it is important that healthcare settings provide accurate information and that patients are referred to tertiary centres in time. More research is needed to study the actual adherence of healthcare professionals to guidelines in epilepsy. Not only in neurology, but also in other medical fields, such as cardiology and diabetology, adherence to guidelines is highly variable. Therefore, several programs have been initiated to increase guideline adherence.[40,41] If adherence to guidelines in epilepsy is indeed suboptimal, adherence programs should be set up in order to increase the number of patients with therapeutic success.

Patients should be referred to specialized epilepsy centres in case of diagnostic doubt (up to 20% of patients might have been misdiagnosed),[42] if epilepsy is not controlled with medication within a certain amount of time (2 years), if the patients are of young age (<2 years) or if unacceptable side effects occur.[18] In these patients more individualized therapy is required and guidelines no longer apply.[43] As shown in *Chapter 2.1* patients included in antiepileptic drug clinical trials are not representative for the majority of ambulant patients with epilepsy. In this study we showed that less than 10% of patients would be eligible to enter a clinical trial and that less than 30% of patients with recurrent partial seizures would qualify. Therefore, generalization of clinical trial results to patients in clinical practice may be limited. In practice treatment has to be fine-tuned for the individual patient in order to improve satisfactory treatment response. Comparable with rare and difficult surgery procedures that are only performed in selected centres, patients with difficult-to-treat epilepsy should ideally be treated in specialized tertiary centres because they are more experienced in treating these patients.

In tertiary epilepsy centres a multidisciplinary team that consists of epileptologists, specialized nurses, neurophysiologists, paediatricians, psychologists, and social workers who can support to improve quality of life by advising or assisting on

education, work, and social functioning. In addition, the majority of these centres are supported by trained clinical pharmacist who can advise on or prepare special drug formulations. Moreover, in tertiary centres extensive infrastructure is also present. For example, electronic patient dossiers in which medical history is documented, EEG and lab are stored, reports of every involved healthcare professional are recorded, seizures are accurately described, videos –if available– are included, and current medication or medication history is kept. We experienced during our studies (*Chapter 2.1*, *4.1* and *4.2*) that the availability of these data is also of great help for research purposes.

In summary, the concentration of health care professionals specialised in the treatment of epilepsy –such as present in tertiary epilepsy centres– is vital for patients with treatment failure. The majority of patients that are referred to these centres experience better seizure control, less bothersome side effects, and are supported with living their life in general.[44]

Pharmacogenetics

One of the main goals for this thesis was to explore genes that may explain therapeutic drug failure. If detected, the genetic make-up of individual patients can be used to predict the effectiveness and the occurrence of adverse effects. In practice, patients could be screened before start of antiepileptic drug treatment in order to establish the optimal antiepileptic drug therapy in the optimal dose. Also, in patients with genetic high-risk refractory profiles alternative treatment such as vagus nerve stimulation or surgery could be started at an earlier stage.

In cooperation with Kempenhaeghe, a tertiary epilepsy centre, we set up the Response On Medication in Epilepsy (ROME) study. With this study we wanted to explore both theories that have been proposed by Remy and Beck: the transporter theory and the target theory.[45] To test the transporter theory we investigated the multidrug resistant gene (MDR1 or ABCB1), a gene that encodes for an important transporter P-glycoprotein. We did not find an association between high-resolution haplotypes of ABCB1 and drug-resistant epilepsy (*Chapter 4.1*). For the target hypothesis we chose to study SCN1A. Again, no association between a functional polymorphism in SCN1A and drug-resistant epilepsy was found. (*Chapter 4.2*) Although we could not detect an association, it is important that the search for pharmacogenetic associations continues.[46]

In this thesis we chose the candidate gene approach to study the association with drug-resistant epilepsy. In this approach, target genes are chosen based on the potential pharmacological mechanism. However, in the last few years genome wide scans –that allow studying hundreds of thousands of SNPs across the entire

genome– have become more common and affordable to perform.[47] One of the downsides of genome wide scans is the potential for false-positive and false-negative results. On the other hand genome wide association studies propose new candidate genes but may also interrogate traditional candidates.[48] This approach will provide new opportunities in coming closer to the truth. Likewise, further progression in the science of the regulation of the expression of genes, will help to unravel the contribution of the genetic make-up in the response of the individual epilepsy patient to antiepileptic drugs. As Tan et al. stated: "The truth is out there!"[49]

CONCLUSION

In conclusion, this thesis provides different determinants that could explain antiepileptic drug failure. Three key actors –patient, drug and healthcare professional– are major determinants for antiepileptic drug treatment response. We have shown the role of modifiable factors such as patient-adherence, drug prescribing and making changes in drug regimens. The role of patient monitoring, such as therapeutic drug monitoring and monitoring of adverse effects was illustrated. Also the role of non-modifiable factors such as gene-related causes of drug-resistant epilepsy were explored. Considering these factors, we provided suggestions for interventions in clinical practice in order to improve treatment response in patients with epilepsy.

Recommendations for clinical practice

- To improve antiepileptic drug adherence, physicians should consider prescribing the simplest regimen with the fewest daily doses and tablets possible.
- Patients with adherence difficulties should be supported by handing out awareness or remembrance tools.
- If substantial changes in medication take place, a warning for a lower seizure threshold should be given to the patient and involved healthcare professionals.
- Therapeutic drug monitoring and laboratory testing on full blood count, electrolytes, thyroid function, vitamin D, hepatic enzymes, and renal function should regularly be performed in patients with epilepsy.
- Prescribing aromatic antiepileptic drugs to patients who developed hypersensitivity reactions on previous aromatic antiepileptic drugs should be avoided.
- Patients should be referred to tertiary centres within a limited period of time in case of treatment failure.

Directions for future studies

- Development of new drug formulations with lower dosing frequencies should be continued.
- Large population studies should be set up to more specifically detect which modifiable factors can lead to a disbalance in seizure control (for example recorded with seizure diaries or portable wireless EEG monitoring devices) and how to avoid or control this.
- Cost-effectiveness studies on therapeutic drug monitoring and biomarker monitoring in patients with antiepileptic drug treatment should be performed.
- Research should be done to explore adverse drug reactions by using chemical structure instead of therapeutic drug classes to classify exposure.
- Guideline adherence in epilepsy in relation to treatment outcome should be studied.
- Future studies in exploring genetic associations in drug-resistant epilepsy should study combination of genes instead of single genes.
- Inclusion criteria for clinical trials should be broadened in order to be able to value the outcome of these studies for daily practice.

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summary

INTRODUCTION

Epilepsy is a neurological disorder that leads to seizures affecting a variety of mental and physical functions. The age-adjusted incidence in developed countries is around 50 per 100 000 persons per year and the prevalence is between 4 and 10 per 1000 persons. Unfortunately there is no cure for epilepsy yet. Antiepileptic drugs (AEDs) are the mainstay of treatment. Although the name suggests otherwise, AEDs cannot cure epilepsy in the same sense that antibiotics can cure an infection. The ultimate goal of treatment in epilepsy is to prevent further seizures, avoid side effects and to make it possible to live a normal life style.

A significant number of people continue to have seizures regularly despite taking medication. Also, AEDs are notorious for their side effects that may vary from gastrointestinal complaints, to problems in cognition, mood and behaviour or severe hypersensitivity reactions. It is estimated that in fact in one third of patients the treatment goal as described above cannot be achieved: patients keep getting seizures or experience bothersome side effects. Treatment failure in patients with epilepsy can have devastating consequences: these people are limited in their job opportunities; they are not able to drive or even to use public transportation; and they experience difficulties to have a relationship or a family. It is therefore important that research on the causes of treatment failure is carried out.

In this thesis the two components of treatment failure in epilepsy are studied:
1) Ineffectiveness: the burden that seizures cannot be controlled with medication, and 2) Adverse effects: the unwanted symptoms of AEDs. We state that treatment response –independent of the disease or the syndrome– relies on three key actors: the patient, the drug, and the health care professional. In this thesis we wanted to clarify the interaction and the different roles of these important modulators on treatment response in epilepsy.

CHAPTER 1

In **Chapter 1** the scope and objective of this thesis are described. This introductory chapter gives an overview on epilepsy in general, treatment with AEDs, and drug-resistant epilepsy. Also, the three key actors (patient, drug and health care professional) in treatment response are introduced.

CHAPTER 2

Chapter 2 of this thesis is entitled **'Patients with epilepsy in trials versus clinical practice'**. Trials often include a highly selected population (i.e. no woman of childbearing age, no children or elderly patients) and it is therefore not surprising that the efficacy of drugs in trials differs from the effectiveness in clinical practice.

In *Chapter 2.1* we focused on the differences between the populations of patients with epilepsy in the clinical trial setting versus clinical practice. The purpose of this study was to assess the number of patients with epilepsy from clinical practice that would qualify for a standard AED trial. A total of 432 outpatients with epilepsy represented the clinical practice cohort, 80 patients had recurrent partial seizures. Common in- and exclusion criteria used in clinical AED trials in epilepsy were applied to the clinical cohort and the subset of patients with recurrent partial seizures and the proportion of patients that would qualify for a standard clinical AED trial was determined. Seven common exclusion criteria were found in 19 clinical trials between 2002 and 2007. Three-quarters (76%) of patients had a too low seizure frequency (<1 seizure per month) to be eligible for inclusion in a clinical trial. Half of the study population (51%) was evaluated as having clinically relevant comorbidity for exclusion from a clinical trial; 21% of patients had a neurological comorbidity, 19% had a psychiatric disorder and 23% suffered from relevant systemic illnesses, 23% of the patients used a combination of ≥3 AEDs. After application of all exclusion criteria, 9% of patients would be eligible for entering a clinical trial. After application of the in- and exclusion criteria to the subgroup of patients with recurrent partial seizures, 27.5% of patients would be able to enter a clinical trial. In conclusion, this study showed that less than 10% of patients with epilepsy in our cohort and less than 30% of patients with recurrent partial seizures would qualify for clinical trials. Thus, patients with specific clinical profiles are studied in clinical trials and generalization of clinical trial results to patients in clinical practice may therefore be limited.

CHAPTER 3

To optimize treatment response it is important to identify modifiable factors. In **Chapter 3** we focused on **drug-treatment related causes of ineffectiveness**. Ineffectiveness was defined here as epilepsy-related hospital admission (Chapter 3.1) or an emergency hospital visit as a result of a seizure (Chapter 3.2). We illustrated that health care professional-related factors such as changes in medication regimes,

and patient-related factors such as omitting medication can lead to insufficient seizure control. Also the role of patient monitoring was enlightened.

In *Chapter 3.1* we explored the association between changes in medication and epilepsy-related hospitalisation. Data were obtained from the PHARMO Record Linkage System (Jan 1998 to Dec 2002). We conducted a case-crossover study among patients with a first epilepsy-related hospital admission who had continuously used at least one AED during a 28-week period before admission. For each patient, changes in medication in a 28-day window before hospitalisation were compared with changes in four earlier 28-day windows. Out of 1185 patients with a first epilepsy-related hospitalisation, 217 patients met the inclusion criteria. Of the evaluated changes in antiepileptic therapy, discontinuation showed a trend towards an increased risk of hospitalisation (odds ratio [OR] 2.57; 95% confidence interval [95% CI] 0.81-8.17). Drug interactions influencing antiepileptic therapy rarely occurred. Introduction of three or more drugs was significantly associated with epilepsy-related hospitalisation (OR 4.80; 95% CI 2.12-10.87). Of individual drugs, addition of antimicrobial agents was significantly associated with epilepsy-related hospitalisation (OR 1.99; 95% CI 1.06-3.75).

In *Chapter 3.2* a case-control study in the clinical setting of the Jeroen Bosch Hospital, 's-Hertogenbosch, was conducted to explore to what extent drug treatment-related factors are associated with seizures. Eighty-six patients with epilepsy were evaluated: 45 cases (recently experienced a seizure) and 41 controls (seizure free for at least two months). A significant association was found between low AED serum concentration and seizures (OR 8.9; 95% CI 1.7-47.8) and changes in medication (mainly non-AEDs) were more frequently observed in the case group than in the control group (OR 4.1; 95% CI 0.9-18.3). Poor compliance (measured by refill of pharmacy records) was not associated with seizures (OR 0.9; 95% CI 0.2-4.0). However, 10% of cases admitted a dose omission that may have lead to the seizure. These findings indicate that patients with low AED serum levels have a nine times higher risk of seizures compared with patients with therapeutic AED levels and that changes within medication regimes in patients with epilepsy should be made with care.

CHAPTER 4

The last decade several hypotheses have been proposed for **gene-related causes of drug-resistant epilepsy**. This is an interesting phenomenon since if an association

between certain genetic factors and refractory epilepsy could be confirmed, patients with epilepsy could be screened beforehand in order to optimize drug selection leading to improved seizure-control. To study pharmacogenetic associations collaboration with epilepsy centre Kempenhaeghe, Heeze, one of the main tertiary epilepsy clinics in the Netherlands was sought. Together we set up the ROME study, ROME being the acronym for Response On Medication in Epilepsy. In this study 287 patients with epilepsy were included: 128 were classified as refractory or drug-resistant (cases) and 159 as drug-responsive (controls). In **Chapter 4** the results of the two genetic case-control association studies performed with the ROME population are presented. Thus, the focus was put on the patient-related factors of treatment failure.

The main hypothesis on gene-related causes for drug-resistant epilepsy is the transporter hypothesis. This hypothesis proposes that AEDs do not reach significant concentrations in the brain as a result of active efflux mediated by overexpressed drug transporter proteins. One of the most important drug transporters is P-glycoprotein that is encoded by the ABCB1 gene. In *Chapter 4.1*, we extensively explored the association between all known variations (high resolution haplotypes) of the ABCB1 gene and drug-resistant epilepsy. So far, association studies between polymorphisms in ABCB1 and AED response have produced inconsistent results. This may be due to the fact that only a few single nucleotide polymorphisms (SNPs) or small haplotype blocks have been studied. Therefore, in this study the frequency of 18 SNPs and the consequently 32 haplotypes of ABCB1 were compared between the drug-resistant and the drug-responsive patients of the ROME population. No association was found for individual SNPs and drug-resistant epilepsy. Almost 90% of all patients were represented by 9 haplotypes of ABCB1. No association was found for haplotypes of ABCB1 and drug-resistant epilepsy. In this study, assessing all known variations in the ABCB1 gene, we found no association between ABCB1 and drug-resistant epilepsy.

In *Chapter 4.2* we investigated whether the AA genotype of the SCN1A IVS5-91 polymorphism, which is associated with lower sensitivity in the α-subunit sodium channels, influences the response to AED treatment. It is known that many AEDs act by binding to the α-subunits of voltage-gated sodium channels in neurons. One of the genes encoding these subunits is SCN1A. Earlier research has shown that a polymorphism in the SCN1A gene was associated with use of higher maximum doses of carbamazepine and phenytoin. In this study, SCN1A IVS5-91 was genotyped in all patients included in the ROME study and allele frequencies

in cases and controls were compared. Also, the height of the maintenance doses of carbamazepine, phenytoin, and cumulative AED load were compared for the different genotypes in cases and controls. The frequency of the SCN1A IVS5-91 AA (32.0% versus 28.9%), the GA (51.6% versus 55.3%) or the GG genotypes (16.4% versus 15.7%) did not differ significantly between the cases and controls (χ^2=0.435; p=0.805). No association with SCN1A genotype and carbamazepine, phenytoin maintenance dose or cumulative AED load was found. In this study, no association was found between SCN1A IVS5-91 G>A polymorphism and drug-resistant epilepsy.

CHAPTER 5

Adverse effects of AEDs are studied in **Chapter 5**. It is known that AEDs can cause a variety of adverse effects. For this thesis we made a selection of those that we thought were clinically relevant and often leading to therapeutic failure.

In *Chapter 5.1* we studied 'idiosyncratic' drug-related hypersensitivity reactions. Idiosyncratic suggests that in these reactions the mechanism by which AEDs induce hypersensitivity is unknown. We aimed to assess whether the presence of an aromatic ring as a commonality in chemical structures of AEDs can explain symptoms of hypersensitivity. Between January 1985 and January 2007, all adverse drug reactions reported to the Netherlands Pharmacovigilance Centre Lareb that were related to AEDs as suspected drug were included in this study. Adverse drug reactions were analysed using a case/non-case design. In total 303 cases of hypersensitivity associated with the use of AEDs were reported. Aromatic AEDs were suspected in 64.4% of these reports versus in 41.3% (574/1389) of the non-hypersensitivity reports. A significant reporting odds ratio (ROR) of 2.15 (95% CI 1.63-2.82) was found for aromatic AEDs and all hypersensitivity reactions. Aromatic AEDs were significantly associated with immunoglobulin E-mediated type I hypersensitivity reactions (ROR 2.15; 95% CI 1.23-3.78) and T cell-mediated type IV reactions (ROR 6.06; 95% CI 3.41-10.75). Type II and type III reactions did not show an association. Cutaneous symptoms represented 39.9% of the hypersensitivity-related reactions. Aromatic AEDs were significantly associated with cutaneous hypersensitivity reactions (ROR 5.81; 95% CI 3.38-9.99). This study confirms that the presence of an aromatic ring as a commonality in chemical structures of AEDs partly explains apparent 'idiosyncratic' hypersensitivity reactions.

Metabolic syndrome (MetS) is in fact not known to be an adverse effect of AEDs. However, substantial weight gain and changes in glucose and cholesterol levels (all factors belonging to MetS) have been associated with several AEDs. In *Chapter 5.2* we studied the changes in MetS parameters in patients starting lithium or valproate as a mood-stabilizing agent. A prospective, open label, multicentre, cohort study was conducted. MetS parameters (waist circumference, blood pressure, fasting plasma glucose, triglycerides, HDL cholesterol) and weight were measured at the start of treatment and three, six, and twelve months after start with lithium or valproate. The interim analysis concerned 23 patients, who had at least been measured at baseline and after three months of follow-up. Twenty patients started with lithium and three patients started with valproate. Significant changes in weight (mean increase 4.9 kg; p=0.047) and waist circumference (mean increase 5.3 cm; p=0.035) were found 12 months after start of lithium. A non-significant increase in systolic blood pressure (mean increase 11.3 mmHg; p=0.09) was seen after start of lithium. In patients who started with valproate non-significant increases in weight (mean increase 7.0 kg; p=0.18), waist circumference (mean increase 8.5 cm; p=0.18) and fasting glucose (mean increase 1.0 mmol/L; p=0.34) were seen six months after start. In this interim analysis, significant associations between use of lithium and increasing weight and waist circumference were found. Only three patients with valproate were included at the time of analysis, therefore no conclusions can be drawn yet regarding changes in MetS parameters associated with use of valproate.

In *Chapter 5.3* we wanted to assess the association between exposure to AEDs and the occurrence of aplastic anemia. Aplastic anemia is a rare, but feared idiosyncratic adverse effect of drug treatment often responsible for taking drugs from the market. A retrospective case-control study was conducted using data from the UK General Practitioners Research Database (GPRD). Cases were defined as patients diagnosed with aplastic anemia. For each case, up to three control patients were matched for age, sex, and medical practice. The study population comprised 173 cases and 497 controls. AED use was more prevalent among cases (9.2%) than among controls (0.8%). After adjustment for confounders, the use of AEDs was significantly associated with aplastic anemia (adjusted OR 9.5; 95% CI 3.0-39.7). The most frequently used AEDs were carbamazepine, valproic acid and phenytoin. The 16 exposed cases were heterogeneous with respect to patient and exposure characteristics: the age of these patients varied from 1 to 92 years and the duration of AED use varied from 17 days to 6.8 years. This study indicates that use of AEDs, in particular carbamazepine and valproic acid, is associated with a ninefold increased

risk of aplastic anemia. Therefore, health care professionals should be alert to the possibility of AED-associated aplastic anemia.

CHAPTER 6

In **Chapter 6** the results presented in this thesis are discussed in a broader context. In this final chapter, the role of these three key actors –patient, professional and drug– as important modulators for achieving treatment success in epilepsy are explored by discussing six themes that have come up during our studies and that go beyond the discussion of the individual studies included in this thesis: 1) Patient adherence to drug treatment; 2) Interactions; 3) Monitoring; 4) Structure-activity relations; 5) Tertiary centres in epilepsy; and 6) Pharmacogenetics. We conclude with recommendations both for clinical practice and directions for future research.

In conclusion, treatment failure in epilepsy has an enormous impact on daily life. In this thesis we studied causes of ineffectiveness and adverse events of AED treatment and provided suggestions for interventions in order to improve treatment response in patients with epilepsy.

samenvatting

EPILEPSIE

Epilepsie is een tijdelijke functiestoornis in de hersenen, waarbij zich plotseling en ongecontroleerd, hersencellen ontladen. Er ontstaat een soort 'kortsluiting' in de hersenen. Meestal is dit zichtbaar: iemand krijgt een aanval. Deze aanvallen variëren van heel onschuldige korte wegrakingen tot ernstige wegrakingen met ademnood en bewustzijnsverlies. Wereldwijd zijn er zo'n 50 miljoen mensen met epilepsie. In Nederland zijn dit er ongeveer 120.000.

Oorzaken epilepsie

Bij meer dan de helft van de patiënten is de oorzaak van de epilepsie onbekend.

Een aantal bekende oorzaken van epilepsie zijn de volgende:

- zuurstoftekort in de hersenen voor of tijdens de geboorte of bij een ongeval
- afwijking van hersenweefsel, van het weefsel dat de hersencellen ondersteunt, van de bloedvaten in de hersenen
- stofwisselingsstoornis in de hersenen of van het gehele lichaam
- infecties (waaronder hersen- of hersenvliesontsteking)
- hersenabces, hersentumor, beroerte
- overmatig alcohol- of druggebruik
- toxische stoffen en medicijnen (psychofarmaca)
- littekenweefsel als gevolg van bovenstaande factoren (zuurstoftekort, infectie, abces, tumoroperatie)
- aangeboren afwijkingen (verstandelijke handicap, spasticiteit, autisme)
- (erfelijke) aanleg

LEVEN MET EPILEPSIE

De impact van epilepsie kan heel groot zijn. Leven met epilepsie betekent dat iemand zich regelmatig moet afvragen of hij of zij er goed mee om gaat. Vaak komen mensen voor een keuze te staan die met epilepsie te maken heeft. Kan ik deze opleiding gaan volgen? Is het verstandig om op vakantie te gaan? Kan ik een nieuwe baan aan? Kan ik deze sport uitoefenen? Zou ik zwanger kunnen worden en wat zijn de risico's? Zal ik andere medicijnen proberen? Zou ik mijn medicijnen kunnen afbouwen of stoppen? Dit soort vragen zullen steeds weer opnieuw beantwoord moeten worden. Daarnaast zijn veel activiteiten (zwemmen, autorijden) niet toegestaan voor epilepsiepatiënten aangezien ze zichzelf en anderen bij een aanval ernstig letsel zouden kunnen toebrengen. Auto- of brommerrijden mag bijvoorbeeld pas na een medische keuring waarvoor onder andere een aanvalsvrije periode van een jaar is vereist.

BEHANDELING VAN EPILEPSIE

Tot nu toe heeft men nog geen behandeling voor epilepsie gevonden die ervoor kan zorgen dat de patiënt ook daadwerkelijk geneest van zijn epilepsie, zoals antibiotica een bacteriële infectie kunnen genezen. Wel bestaan er de zogenaamde anti-epileptica, geneesmiddelen die ervoor kunnen zorgen dat de aanvallen onderdrukt worden. Anti-epileptica worden langdurig gebruikt en soms zelfs levenslang. Het doel van de behandeling van epilepsie is om aanvallen te voorkomen en daarbij de bijwerkingen tot een minimum te beperken zodat het mogelijk is een normaal leven te kunnen leiden. Er zijn ook andere behandelingsmogelijkheden zoals Nervus Vagus stimulatie (een soort pacemaker die kleine stroomstootjes geeft die tot doel heeft de aanvallen in aantal te doen verminderen of deze sneller te laten verlopen), het ketogeen dieet of het chirurgisch verwijderen van hersenweefsel. Deze opties zijn echter maar voor een beperkt aantal patiënten mogelijk en behoeven meestal nog steeds aanvullende medicatie.

Anti-epileptica

Anti-epileptica zijn geneesmiddelen tegen epilepsie. Ze kunnen ook vanwege andere aandoeningen (o.a. bipolaire stoornis, zenuwpijn, migraine, angststoornis) worden gebruikt.

De volgende middelen vallen onder de anti-epileptica:
carbamazepine (Carbymal®, Tegretol®), clobazam (Frisium®), clonazepam (Rivotril®), diazepam (Diazemuls®, Stesolid®, Valium®), ethosuximide (Ethymal®, Zarontin®), felbamaat (Taloxa®), fenobarbital, fenytoïne (Diphantoïne®, Epanutin®), gabapentine (Neurontin®), lamotrigine (Lamictal®), levetiracetam (Keppra®), nitrazepam (Mogadon®), oxcarbazepine (Trileptal®), pregabaline (Lyrica®), primidon (Mysoline®), stiripentol (Diacomit®), topiramaat (Topamax®), valproïnezuur (Convulex®, Depakine®, Orfiril®, Propymal®), vigabatrine (Sabril®), zonisamide (Zonegran®)

THERAPIEFALEN

Een groot aantal mensen met epilepsie heeft regelmatig aanvallen ondanks het gebruik van anti-epileptica. Zij reageren dus onvoldoende op de behandeling. Daarnaast zijn anti-epileptica berucht om hun bijwerkingen die variëren van maagdarmproblemen (misselijkheid, braken), cognitieve stoornissen (vertraagd denken, taalproblemen), stemmings- en gedragsveranderingen (depressie, agressie) en (ernstige) allergische reacties. Bij ongeveer 30% van de epilepsiepatiënten wordt het beoogde doel van de behandeling niet behaald en is er dus sprake van

therapiefalen. Deze patiënten blijven aanvallen houden of ondervinden teveel last van de bijwerkingen van de anti-epileptica.
Therapiefalen kan ernstige gevolgen hebben in het dagelijkse leven: mensen zijn niet in staat om zich maatschappelijk te handhaven, zijn gelimiteerd in hun carrièreperspectieven, mogen niet autorijden, zijn beperkt in het gebruik van openbaar vervoer en ondervinden relatieproblemen of problemen binnen het gezin. Het is daarom van groot belang dat er onderzoek wordt gedaan om de behandeling van patiënten met epilepsie, en in het bijzonder bij therapiefalen, te verbeteren.

Epidemiologie

Epidemiologie is het wetenschappelijk onderzoek dat zich bezig houdt met het vóórkomen en de verspreiding van ziekten onder de bevolking. Hierin wordt gezocht naar verbanden tussen het voorkomen van ziekten en de factoren (determinanten) die hier invloed op kunnen uitoefenen. De term epidemiologie slaat zowel op een samenhangend geheel van methoden en technieken als op de resultaten van de toepassing hiervan. In dit proefschrift wordt gebruik gemaakt van diverse epidemiologische technieken (o.a. follow-up, case controle (ook wel patiënt controle onderzoeken genoemd), case cross-over en case non-case design) om factoren van therapiefalen bij epilepsie te onderzoeken.

DIT PROEFSCHRIFT

In dit proefschrift worden de twee belangrijke componenten van therapiefalen bij behandeling van epilepsie bestudeerd:

1. **ineffectiviteit**, en daarmee het probleem dat de aanvallen niet voldoende onder controle zijn, en
2. **bijwerkingen**, de ongewenste en soms onverdraagbare neveneffecten die de anti-epileptica veroorzaken.

Het doel van dit proefschrift was om verschillende factoren te bestuderen die therapiefalen zouden kunnen verklaren en suggesties aan te dragen die kunnen leiden tot een verbetering van de behandeling van epilepsie.

Hoofdstuk 1 is een **algemene inleiding** waar wordt ingegaan op het ziektebeeld epilepsie en de behandeling hiervan. Ook worden de drie partijen die van groot belang zijn bij de behandeling van epilepsie geïntroduceerd: de patiënt, het geneesmiddel en de gezondheidszorg. In dit proefschrift wilden we ook ingaan

op de interactie en de verschillende rollen die deze drie partijen hebben op het therapiefalen bij patiënten met epilepsie.

Hoofdstuk 2 van dit proefschrift is getiteld **'Patiënten met epilepsie in geneesmiddelonderzoek versus de dagelijkse praktijk'**. Geneesmiddelen moeten voordat ze op de markt komen uitgebreid worden onderzocht op o.a. effectiviteit en veiligheid: eerst in het laboratorium, dan in gezonde vrijwilligers en vervolgens in onderzoeksverband in patiënten (klinisch trial). Het probleem is dat de patiënten die deelnemen aan deze onderzoeken vaak niet overeenkomen met de patiënten die het daarna in de praktijk gaan gebruiken.

In *hoofdstuk 2.1* bestudeerden we de verschillen tussen de epilepsiepatiënten die deelnamen aan een geneesmiddelonderzoek versus de epilepsiepatiënten in de dagelijkse praktijk. Het doel van deze studie was het percentage patiënten te berekenen dat voor een standaard anti-epileptica onderzoek (bedoeld voor de registratie van het anti-epilepticum) in aanmerking zou komen. Uit 19 klinische trials die werden uitgevoerd tussen 2002 en 2007 werden acht gemeenschappelijke uitsluitingscriteria gevonden. Deze waren: 1) borstvoeding of zwangerschap; 2) een onvoldoende hoge aanvalsfrequentie (<1 aanval per maand); 3) een klinisch relevant systemische comorbiditeit (het tegelijkertijd hebben van andere ziekten naast epilepsie); 4) gebruik van drie of meer anti-epileptica; 5) progressieve neurologische of cerebrale aandoeningen; 6) psychiatrische comorbiditeit; 7) alcoholmisbruik of drugsgebruik; 8) gebruik van andere medicijnen die kunnen interfereren met het te onderzoeken studiegeneesmiddel. Vervolgens bekeken we in een groep van 432 epilepsiepatiënten of deze criteria op hen van toepassing waren. Driekwart (76%) van de klinische patiënten hadden een te lage aanvalsfrequentie (<1 aanval per maand) om aan een trial deel te mogen nemen. De helft van de patiënten (51%) hadden een comorbiditeit waardoor zij niet aan een trial zouden mogen deelnemen en een kwart van de patiënten (23%) gebruikten een combinatie van drie of meer anti-epileptica waardoor ook zij niet zouden mogen deelnemen. Uiteindelijk zou slechts 9% van de klinische populatie toegelaten worden tot een standaard epilepsie onderzoek. Hieruit kan geconcludeerd worden dat patiënten in de praktijk tegelijkertijd meer andere ziekten hebben dan patiënten in de geneesmiddelonderzoeken. Ook hebben de patiënten in de praktijk minder aanvallen of gebruiken zij meer anti-epileptica. Dit betekent dat we daarom voorzichtig moeten zijn om de effecten die gemeten worden bij geneesmiddelonderzoeken te vertalen naar de dagelijkse praktijk.

In **Hoofdstuk 3** bestudeerden we **therapiegerelateerde oorzaken van ineffectiviteit**. Ineffectiviteit werd hier gedefinieerd als een epilepsiegerelateerde ziekenhuisopname (3.1) of een aanval die leidde tot een versnelde afspraak bij de behandeld neuroloog of opname in het ziekenhuis (3.2).

In *hoofdstuk 3.1* onderzochten we de associatie tussen veranderingen in medicatie en epilepsiegerelateerde opnamen in een grote Nederlandse database, de PHARMO database. Deze database bestaat uit aflevergegevens van openbare apotheken waar ziekenhuisopnames aan gekoppeld zijn. We bestudeerden het starten, stoppen en switchen van anti-epileptica en overige medicatie die de patiënten gebruikten. Anti-epileptica zijn berucht om de wisselwerking die zij hebben met andere medicatie. Sommige geneesmiddelen kunnen de werking van anti-epileptica verminderen of zelfs tegengaan. Er werd gekeken of het starten met geneesmiddelen zou resulteren in aanvallen waarvoor de patiënt naar het ziekenhuis moest. We bestudeerden een groep van 1185 patiënten met epilepsiegerelateerde ziekenhuisopnames, waarvan 217 patiënten voldeden aan de inclusiecriteria. Er werd gekozen voor een zogenaamd 'case-cross over' onderzoeksopzet. Dit is een methode waarbij elke patiënt (case) ook zijn eigen controle is. De veranderingen in medicatie vier weken voor de epilepsiegerelateerde opname ('case' moment) werd vergeleken met vier controle periodes van eveneens vier weken van deze zelfde patiënt. De belangrijkste bevindingen waren dat het starten met drie of meer geneesmiddelen (die geen anti-epileptica waren) significant geassocieerd was met epilepsiegerelateerde ziekenhuisopnames (odds ratio [OR] 4,8; 95% betrouwbaarheidsinterval [BI] 2,12-10,87) en dat het starten met antibiotica significant geassocieerd was (OR 1,99; 95% BI 1,06-3,75). Veranderingen in het gebruik van anti-epileptica gaven geen significante associaties.

In *hoofdstuk 3.2* beschreven we de resultaten van een case controle onderzoek opgezet in het Jeroen Bosch Ziekenhuis te 's-Hertogenbosch. Doel van dit onderzoek was te bestuderen in hoeverre behandelingsgerelateerde factoren (concentraties van anti-epileptica in het bloed, therapietrouw en veranderingen in medicatie) geassocieerd waren met het optreden van ernstige aanvallen. In totaal werden 86 patiënten geïncludeerd, 45 cases (recente aanval) en 41 controles (minimaal twee maanden aanvalsvrij). We vonden dat patiënten met lage anti-epileptica concentraties een negen keer verhoogde kans hadden op aanvallen (OR 8,9; 95% BI 1,7-47,8) en dat veranderingen in medicatie vaker gezien werden bij de cases vergeleken met de controles (OR 4,1; 95% BI 0,9-18,3). Er werd geen

associatie gezien met therapietrouw, gemeten over een jaar voor het optreden van de aanval of het controlemoment, desondanks gaf 10% van de cases aan dat het vergeten in te nemen van de anti-epileptica waarschijnlijk de reden van de aanval was geweest.

In het laatste decennium zijn er diverse hypotheses opgesteld voor **genetische oorzaken van therapieresistente epilepsie**. Dit is interessant omdat dit zou impliceren dat patiënten voorafgaand aan hun behandeling gescreend zouden kunnen worden met als doel op grond van hun genetisch profiel te bepalen welke anti-epileptica voor hen het beste zouden werken. Om farmacogenetische aspecten (zie kader) te bestuderen hebben wij in samenwerking met epilepsiecentrum Kempenhaeghe te Heeze een case controle onderzoek opgezet. Het onderzoek kreeg het acroniem ROME: Respons Op Medicatie bij Epilepsiepatiënten. Er werden in totaal 287 patiënten geïncludeerd: 128 therapieresistente patiënten (cases) en 159 therapieresponders (controles). Met deze patiënten werden de onderzoeken uitgevoerd die in **Hoofdstuk 4** worden beschreven.

Farmacogenetica

Onderzoek naar genetische verschillen die de werking en veiligheid van een geneesmiddel kunnen voorspellen: dat is het terrein van de farmacogenetica. Er zijn op dit moment nog niet veel voorspellende genetische tests, maar de verwachting is dat dit wel eens snel zou kunnen veranderen.

In *hoofdstuk 4.1* bestudeerden we de transporterhypothese. Deze hypothese stelt dat anti-epileptica bij therapieresistentie onvoldoende hoge concentraties in de hersenen bereiken doordat transportereiwitten actief het antiepilepticum uit de hersenen terug de bloedbaan in transporteert. Een van de belangrijkste transporteiwitten voor geneesmiddelen is het P-glycoproteïne, welke wordt gecodeerd door het ABCB1-gen. Mutaties (polymorfismen) van dit gen zijn in eerdere onderzoeken geassocieerd met geneesmiddelresistente epilepsie, echter andere onderzoeken vonden deze associatie niet. De oorzaak hiervan ligt mogelijk in het feit dat telkens slechts een beperkt aantal polymorfismen bekeken zijn. In dit onderzoek werden zowel genvariaties (haplotypen, ofwel: combinaties van polymorfismen) van het ABCB1-gen bekeken in plaats van naar een gering aantal polymorfismen. Met het analyseren van 18 polymorfismen konden we alle relevante haplotypes bestuderen. In het ROME onderzoek vonden

we 32 haplotypes van het ABCB1-gen. Negen haplotypes kwamen het meeste voor, namelijk bij 90% van het totale aantal patiënten. Er werd gekeken of de therapieresistente patiënten vaker een bepaald polymorfisme of haplotype hadden dan de therapieresponders. Dit was niet het geval, er werden geen significante associaties gevonden tussen haplotypes van het ABCB1 gen en therapieresistente epilepsie.

Een tweede hypothese die veel genoemd wordt is de targethypothese. Bij deze hypothese wordt gesteld dat het aangrijpingspunt van het antiepilepticum bij therapieresistente patiënten een verandering heeft ondergaan waardoor het antiepilepticum niet meer goed kan aangrijpen en daardoor minder tot geen effect heeft. Deze hypothese is nog maar weinig getest. We onderzochten in dit kader het SCN1A gen, het onderzoek dat beschreven is in *hoofdstuk 4.2*. Recent onderzoek heeft uitgewezen dat een polymorfisme in dit gen geassocieerd is met een lagere gevoeligheid in een belangrijke gedeelte van de natriumkanalen en dat patiënten die dit polymorfisme hadden een hogere dosis van het antiepilepticum (carbamazepine of fenytoine) nodig hadden. Veel anti-epileptica grijpen aan op de natriumkanalen in de hersenen en ook daarom was het interessant om dit gen te onderzoeken. Wij vonden geen verschillen in het voorkomen van dit polymorfisme tussen de therapieresistente groep en de therapieresponders. Ook vonden wij niet dat patiënten die dit polymorfisme hadden hogere doseringen anti-epileptica voor hun behandeling nodig hadden.

Bijwerkingen van anti-epileptica werden bestudeerd in **Hoofdstuk 5** van dit proefschrift. Het is bekend dat anti-epileptica veel bijwerkingen kunnen geven. In dit proefschrift gaven we aandacht aan een aantal belangrijke bijwerkingen die vaak aanleiding zijn tot therapiefalen.

In *hoofdstuk 5.1* onderzochten we geneesmiddelgerelateerde overgevoeligheids-reacties. Een bekend voorbeeld van een ernstige overgevoeligheidsreactie door het gebruik van anti-epileptica is het Syndroom van Stevens-Johnson. Dit syndroom wordt gekenmerkt door hoge koorts en ernstige blaren aan mondslijmvliezen, lippen, ogen en genitaliën. Anti-epileptica zijn geneesmiddelen met heel verschillende chemische structuren, maar er zijn ook een aantal gelijkenissen. In dit onderzoek bekeken we of overeenkomsten in de chemische structuur van anti-epileptica symptomen van overgevoeligheid zouden kunnen verklaren. Onze hypothese was dat de aanwezigheid van een aromatische ring die bij een aantal anti-epileptica aanwezig is hiervoor wellicht verantwoordelijk is. Dit onderzoek

werd uitgevoerd in samenwerking van het Nederlands bijwerkingencentrum LAREB. Dit centrum verzamelt alle meldingen van mogelijke bijwerkingen op geneesmiddelen. We bekeken de meldingen tussen 1985 en 2007 die gerelateerd waren aan het gebruik van anti-epileptica. Er werden in totaal 1692 meldingen van bijwerkingen tijdens gebruik van anti-epileptica gerapporteerd, waarvan 303 overgevoeligheidsreacties. Anti-epileptica met een bepaalde chemische structuur, namelijk een aromatische ring, waren verdacht in 64,4% van de overgevoeligheidsreacties, de niet-aromatische anti-epileptica in 41,3% van de gevallen. Er werd een significante associatie gevonden tussen aromatische anti-epileptica en overgevoeligheidsreacties (reporting odds ratio [ROR] 2,15; 95% BI 1,63-2,82). Ook waren aromatische anti-epileptica bijna zes keer vaker geassocieerd met overgevoeligheidsreacties van de huid (ROR 5,81; 95% BI 3,38-9,99). Uit dit onderzoek kan geconcludeerd worden dat een aromatische ring in de structuur van een anti-epilepticum een goede verklaring kan geven voor de overgevoeligheidsreacties.

Het metabool syndroom is een combinatie van overgewicht, hypertensie, laag HDL, hoog triglyceriden en een hoog nuchter plasma glucose. Indien dit syndroom zich voordoet neemt de kans op suikerziekte en hart- en vaatziekten toe. Het is bekend dat een aantal geneesmiddelen (zoals een aantal psychofarmaca) dit syndroom kunnen veroorzaken. Tot nu toe is het nog niet vastgesteld of anti-epileptica hier ook toe kan leiden. Toch zijn verschijnselen zoals gewichtstoename, hypertensie en een verhoogd glucose in het bloed wel in verband gebracht met het gebruik van anti-epileptica. In *hoofdstuk 5.2* werden de veranderingen in parameters van het metabool syndroom gemeten bij patiënten die starten met lithium of valproïnezuur (= een antiepilepticum) als een stemmingsstabilisator. Er werd een follow-up onderzoek uitgevoerd waar acht verschillende Nederlandse centra aan deelnamen. De metabool syndroom parameters werden gemeten bij starten en drie, zes en twaalf maanden na het starten van lithium of valproïnezuur. In het proefschrift hebben we een interimanalyse opgenomen waarin 20 patiënten lithium gebruikten en drie patiënten valproïnezuur. Er werd een significante associatie gevonden tussen het gebruik van lithium en een toename in gewicht (+4,9 kg; p=0,047) en buikomvang (+5,3 cm; p=0,035). Daarnaast werd een trend gezien in het toenemen van de systolische bloeddruk (bovendruk) na starten van lithium. Ook bij valproïnezuur zagen we een trend van toename in gewicht, buikomvang en nuchter glucose zes maanden na starten. Dit onderzoek loopt nog op het moment van het drukken van dit proefschrift.

Aplastische anemie is een vorm van bloedarmoede die gekenmerkt wordt door een tekort aan alle soorten bloedcellen, zowel aan witte en rode bloedcellen als aan bloedplaatjes. Het is een zeldzame maar ernstige levensbedreigende aandoening met een hoge mortaliteit, naar schatting 10% van de patiënten met deze aandoening overlijdt hieraan. In het verleden zijn er geneesmiddelen van de markt gehaald omdat er te veel gevallen van aplastische anemie werden gezien bij het gebruik van het middel. In *hoofdstuk 5.3* bekeken we in hoeverre het gebruik van anti-epileptica geassocieerd was met het optreden van aplastische anemie. Er werd een retrospectief case controle onderzoek opgezet waarbij data werden gebruikt van de Britse huisartsendatabase, de UK-General Practitioners Research Database (GPRD). Cases waren gedefinieerd als patiënten die gediagnosticeerd waren met plastische anemie. Voor elke case werden drie vergelijkbare patiënten gezocht, dus met dezelfde leeftijd, geslacht en huisartsenpraktijk. De onderzoekspopulatie bestond uit 173 patiënten (cases) en 497 controles. Zestien cases werden gevonden waarvan de aplastische anemie geassocieerd was het gebruik van anti-epileptica. Deze patiënten bleken heterogeen voor wat betreft leeftijd, geslacht of duur van het gebruik van anti-epileptica. Anti-epileptica gebruik bleek geassocieerd met een negen keer verhoogde kans op aplastische anemie (OR 9,5; 95% BI 3,0-39,7).

Tot slot worden in **Hoofdstuk 6** de onderzoeken en de resultaten daarvan, gepresenteerd in dit proefschrift, in een bredere context geplaatst. De rollen van de patiënt, het antiepilepticum en de gezondheidszorg en de interactie daartussen wordt nader toegelicht. Het gaat hierbij om zes thema's die in dit proefschrift naar boven kwamen als belangrijke modulatoren bij het optimaliseren van therapierespons. Deze thema's waren: 1) Therapietrouw; 2) Interacties; 3) Monitoring; 4) Structuuractiviteitsrelaties; 5) Tertiaire epilepsiecentra; en 6) Farmacogenetica. Dit hoofdstuk wordt afgesloten met aanbevelingen voor de klinische praktijk en toekomstig onderzoek.

Concluderend kan gesteld worden dat therapiefalen bij epilepsie een enorme impact heeft op het dagelijks leven van deze patiënten en hun omgeving. In dit proefschrift onderzochten we oorzaken van ineffectiviteit en bijwerkingen, twee belangrijke componenten van therapiefalen. Tevens worden suggesties gegeven hoe de therapierespons in deze patiëntengroep verbeterd zou kunnen worden en waar toekomstig onderzoek zich op zou moeten richten.

dankwoord

DANKWOORD

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list of publications

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Kim Gombert-Handoko was born on 2 September 1975 in Delft, The Netherlands. She grew up in Uithoorn and completed secondary school (VWO) at the 'Alkwin Kollege' in Uithoorn in 1993. Subsequently, she started her studies in Pharmacy at Utrecht University. During her studies she completed a research traineeship at the Saint Joseph's Hospital, one of the teaching hospitals of the University of Western Ontario, London, Canada. In 1998, she obtained her Master's degree in Pharmacy at Utrecht University, followed by her Pharmacist degree in 2001.

Thereafter she worked as a pharmacist at the Medical Centre 'Haaglanden', The Hague. In 2002 she started her training to become a hospital pharmacist at the 'Jeroen Bosch' Hospital, 's-Hertogenbosch and combined this training with PhD research at the Department of Clinical Pharmacy of the University Medical Centre Utrecht in affiliation with the Department of Pharmacoepidemiology & Pharmacotherapy of the Utrecht Institute for Pharmaceutical Sciences of Utrecht University. During this period she obtained a Master of Science degree in Epidemiology at the EMGO Institute of the VU University Medical Centre in Amsterdam.

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