Trick or treat?

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TRICK or TREAT?

Cognitive side-effects of antiepileptic treatment

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TRICK or TREAT?

Cognitive side-effects of antiepileptic treatment

PROEFSCHRIFT

Ter verkrijging van de graad van doctor aan de Universiteit Maastricht,
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in het openbaar te verdedigen op
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Voor mijn ouders

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Chapter 1

General introduction

Introduction

Epilepsy is a neurological disorder characterized by the occurrence of unprovoked epileptic seizures that may differ in their manifestation. Worldwide, about 70 million people are estimated to have epilepsy.^{1,2} The highest incidence is found in children³ and the prevalence of epilepsy among people with intellectual disabilities is much higher than in the general population,⁴ where one in five will have epilepsy (22%).

Seizures can be divided into generalized seizures occurring in both hemispheres (bilaterally) such as tonic-clonic seizures or absences or focal, partial seizures which are limited to one hemisphere.⁵ Classification of type of epilepsy based on etiology has recently been replaced from idiopathic (no underlying cause, presumed genetic), symptomatic (known or suspected disorder of the central nervous system) and cryptogenic (no underlying etiology identified, unknown cause) to genetic, structural-metabolic, and unknown.⁵

Cognitive impairment is a common comorbidity in patients with epilepsy.⁶ Different factors contribute to the development of cognitive impairment in people with epilepsy, such as age at onset, underlying etiology or the frequency and severity of seizures. Furthermore, treatment can adversely affect cognition.

In the majority of the patients, epilepsy is treated with antiepileptic drugs (AEDs) which have as primary goal to control seizures without causing any side-effects. The accurate balance between efficacy of the drug in controlling the seizures and the tolerability (the avoidance of side-effects) is important for optimal treatment effects and compliance. Many AEDs are available and during the last 20 years, the list of new AEDs that have been developed, shows a steep increase (see Figure 1.1). Monotherapy is always preferred but after failure of one or more AEDs, a combination therapy is usually considered.

In literature, several synonyms are used for refractory of epilepsy such as intractability, drug-resistant or pharmaco-resistant which indicates that two AEDs have failed to achieve sustained seizure freedom.⁷ About one third of patients suffer from refractory epilepsy, both in children⁸ and in adults.⁹ These patients mostly have frequent seizures, are at risk for status epilepticus and often use high dosing polytherapy which will last for years. For these patients also alternative nonpharmacological treatment options are available, such as epilepsy surgery, vagus nerve stimulation and the ketogenic diet. Of all patients with epilepsy in the Netherlands, about 25% of the epilepsy patients is referred to a specialized (tertiary referral) center for further treatment considerations or uncertainty about the diagnosis.

One of the complications of AED treatment is the occurrence of side-effects. There seems to be agreement that polytherapy and high-dose treatment can produce cognitive side-effects.^{10,11} However, even in patients who are well-controlled and on monotherapy,¹² cognitive side-effects are among the most commonly reported complaints in patients.^{13,14} Children are potentially more susceptible to the adverse

effects of AEDs than adults because of the potential effects of AEDs on brain maturation and hence on neurodevelopment. Furthermore, children have a higher risk of learning disabilities and poor academic performance.¹⁵ Effective and timely control of the development of side-effects are therefore an important aspect of establishing overall treatment effectiveness.

Figure 1.1 Adapted from Brodie & Sills (2011).¹⁶

Aim and outline of this thesis

The aim of this thesis is to investigate the cognitive adverse effects of antiepileptic treatment in patients with refractory epilepsy. This thesis is divided in four parts. Part I starts with an overview of the available literature about the cognitive effects in adults and in children and also highlights the missing information (chapter 2). In part II, we discuss the cognitive functions that can be affected by antiepileptic treatment and some topics that will bridge the gap of our knowledge and thus fill the gaps identified in chapter 2. We focus on the cognitive profiles of two AEDs that have not been yet investigated; lacosamide, which is a relatively new drug (chapter 3) and ethosuximide which is an old, first-generation drug (chapter 4). Furthermore, we explore the behavioral and cognitive effects of an alternative antiepileptic treatment, the ketogenic diet (chapter 5) and focus on the absence of information of long-term chronic AED-use on cognitive development in children (chapter 6). In part III, the focus is on the clinical relevance of subjective reports. In this part, we not only discuss neuropsychological tests that are commonly used to assess cognition and cognitive side-effects, but we also focus on the subjectively perceived side-effects (chapter 7) and the profile of patients who are at risk for developing cognitive side-effects of antiepileptic drug treatment (chapter 8). Furthermore, we use a different method of assessment in a specific patient population, i.e. patients with intellectual disabilities (chapter 9). In part IV, we discuss our attempts identifying the neuronal substrates of cognitive side-effects, using MR spectroscopy and resting state fMRI (chapter 10 and 11). Chapter 12 provides a general discussion of this thesis and will elaborate on future implications of the results.

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Part I

Literature

Chapter 2

Cognitive side-effects of antiepileptic drugs

Based on:

DM IJff & AP Aldenkamp

Pediatric Epilepsy. New York: McGraw-Hill Professional 2012:424-436

Handbook of clinical neurology. Oxford: Elsevier Science 2013:707-718

Abstract

Although the causes of cognitive impairment in patients with epilepsy have not been completely elucidated, three factors are clearly involved: the underlying etiology of epilepsy, the effects of seizures or the epileptiform EEG discharges themselves, and the central nervous system effects of antiepileptic drugs (AEDs). All commonly used AEDs have some effect on cognitive function, and the effect may be substantial when crucial functions are involved, such as learning in children, or driving ability in adults, or when already vulnerable functions are involved, such as memory in elderly patients. For the commonly used AEDs, drug-induced cognitive impairment has been established for phenobarbital, phenytoin and topiramate. Mild effects were found for carbamazepine and valproate. Although the evidence is sketchy, oxcarbazepine and levetiracetam do not seem to have a negative impact on cognition. For lamotrigine, some mild cognitive activating effects were found. In adults, no cognitive effects were found for ethosuximide, rufinamide, tiagabine, and gabapentin, although the evidence requires confirmation. No studies are available for zonisamide. The effects for vigabatrin are inconclusive. For gabapentin, tiagabine, zonisamide, and rufinamide no studies in children are available.

Introduction

Cognitive impairment is the most common comorbid disorder in epilepsy.^{1,2} Memory impairments, mental slowing, and attentional deficits are the most frequently reported cognitive disorders.^{3,4} Such consequences may be more debilitating for a patient than the seizures; thus, it is worthwhile to explore the factors that lead to cognitive impairment. The exact cause of cognitive impairment in epilepsy has not been explored fully, but three factors clearly are involved: etiology, the seizures, and the “central” side-effects of drug treatment.⁵ Here we concentrate on the unwanted effects of antiepileptic medication on cognitive function. When evaluating this factor separately, it is imperative to realize that in clinical practice most cognitive problems have a multifactorial origin and that, for the most part, the three aforementioned factors, combined, are responsible for the “makeup” of a cognitive problem in an individual patient. Moreover, the factors are related, which causes therapeutic dilemmas in some patients when seizure control can only be achieved with treatments that are associated with cognitive side-effects.

The interest in the cognitive side-effects of antiepileptic drug (AED) treatment is of recent origin. The possibility that cognitive impairment may develop as a consequence or aftermath of epilepsy was raised as early as 1885 when Gowers described ‘epileptic dementia’ as an effect of the pathological sequela of seizures. Nonetheless, the topic was not coupled to antiepileptic drug treatment until the 1970s probably stimulated by the widening range of possibilities for drug treatment during that period (i.e., the introduction of carbamazepine and valproate).^{6,7} Since then, a plethora of studies have been published, the majority on the commonly used AEDs: valproate, carbamazepine, and phenytoin.

In the last decades, several new AEDs have been introduced. Although it is claimed that these drugs have different efficacy profiles and that some drugs are particularly efficacious in specific syndromes, head-to-head comparisons between the newer drugs and the commonly used drugs (such as carbamazepine and valproate) are rare. Nonetheless, meta-analyses such as the influential Cochrane reviews did not show significant differences in efficacy between the newer and classical drugs.^{8,9} Also, studies analyzing long-term retention did not show differences between the drugs.^{10,11}

Several studies have shown retention rate to be the best parameter of the long-term clinical usefulness of a particular drug.¹² Retention rate is considered to be a composite of drug efficacy and drug safety and expresses the willingness of patients to continue drug treatment. It is therefore the best standard for evaluating the clinical relevance of side-effects. The 1-year retention rate is reported to be not higher than 55% for topiramate¹³, 60% for lamotrigine, 58% for vigabatrin, and 45% for gabapentin.¹⁴ Long-term (mostly 3-year) retention is about 35% for all newer AEDs.¹⁵ Side-effects appear to be the major factor affecting long-term retention for most drugs.^{16,17}

In clinical practice, tolerability is therefore a major issue and the choice of a certain AED is at least partially based on comparison of tolerability profiles of the drugs. Also, the tolerability profiles of the newer drugs have become a more important issue in drug development, stimulated by the interest of regulatory agencies.¹⁷ Cognitive side-effects have been demonstrated to be one of the most important tolerability problems in chronic AED treatment.

Methodological issues

In evaluating studies of the cognitive effects of AEDs, we will follow an evidence-based approach.^{18,19} Randomized clinical trials with monotherapy in patients with newly diagnosed epilepsy represent the most accurate procedure for assessing the cognitive impact of AEDs.¹⁷ These studies are not clouded by the effect of concurrent or previous AED use and permit the accurate collection of non-drug baseline data that is required for determining whether a particular treatment affects cognitive processing (i.e., to isolate drug-induced impairments from those due to other sources such as the seizures). Data from such studies can be supplemented with information from studies using add-on or polytherapy designs. In these studies, the use of two AEDs makes identifying the components of the treatment that are responsible for the observed effects more complex. In many cases, however, patients with epilepsy require dual AED therapy before adequate seizure control is obtained; therefore, information from add-on studies does warrant consideration.

Also, data from healthy volunteers should be treated with caution. In general, the power of such studies is limited by small sample sizes, and drug-exposure periods are typically brief. It is possible that chronic treatment results in entirely different types of cognitive impairment that cannot be observed during short-term treatment. For example, such differences in side-effect profile between acute and long-term administration have been found with phenytoin. Moreover, volunteer studies do not provide information for children. Finally, the differing cerebral substrate in patients with epilepsy and healthy volunteers suggests that cognitive responses to AEDs may be different in these populations. Nonetheless, volunteer studies may provide an early insight into the cognitive effects of an AED and therefore provide a foundation for further studies in patients with epilepsy (see Vermeulen and Aldenkamp¹⁸ for a discussion of methodological aspects of cognitive drug trials in epilepsy).

The results will be discussed, distinguishing 'absolute effects' which are the effects of drug treatment against no-treatment (non-drugs) in the same subjects or in a control condition, which represents the most valuable information. Next, relative effects (comparing the cognitive effects of one drug with those of another drug) will be discussed. Although this is relevant clinical information, this comparison does not

exclude the possibility that two drugs are not different because they both impair cognitive function to the same extent.

Furthermore, we will discuss the data from pediatric studies. Cognitive side-effects of the antiepileptic drugs are of critical importance when prescribing these drugs in children because children with epilepsy have a higher risk of learning disabilities or more general problems with school progress. Children are potentially more susceptible to the adverse effects of AEDs than adults because of the effect of AEDs on neurodevelopment. Even a modest cognitive effect may therefore have consequences for neurodevelopment. Therefore, cognitive side-effects of the antiepileptic drugs have emerged as an important consideration when an antiepileptic drug is being selected for the treatment of childhood epilepsy.²⁰

Phenobarbital (PB)

The main anticonvulsant mechanism of action is the increase of the duration (not the frequency) of the GABA activated chloride ion channel opening, hence potentiating GABA mediated inhibitory neurotransmission.²¹ PB can also activate the GABA_A receptor in the absence of GABA, which is sometimes considered to be a mechanism leading to its sedative properties. PB is used for the treatment of epilepsy since the discovery of its antiepileptic effect by Hauptman in 1912.

Adults

The study by MacLeod et al. (1978) is available allowing the evaluation of the cognitive effects of phenobarbital relative to a non-drug condition. This study showed relative serious memory impairment in 19 patients with epilepsy.²² Comparisons with other AEDs are available from two studies showing inconsistent results. One revealed greater impairment for PB than phenytoin (PHT) or carbamazepine (CBZ) on visuomotor and memory tests while the other study did not show differences between PB and PHT or CBZ.²³⁻²⁴

Children

When the cognitive and behavior effects of this drug were assessed in toddlers in a randomized, placebo-controlled study of patients who had febrile seizures, no differences were found in IQ scores between placebo and phenobarbital groups after eight to twelve months of therapy, although this is debated in other studies.²⁵⁻²⁷ Schubert and colleagues (2005) reported evidence that phenobarbital may impair attention in children to a degree that an attentional deficit disorder may develop.²⁸ There may be a long-term adverse cognitive effect of phenobarbital on the language/verbal developmental skills like reading being acquired during the period of

treatment.²⁹ Comparisons with VPA in children showed impairment of intelligence scores after long-term PB-treatment.^{30,31}

Phenytoin (PHT)

The main anticonvulsant mechanism of action is use-dependent (voltage- and frequency dependent) sodium channel blocking.³² PHT binds to the fast inactivated state of the channel, reducing high frequency neuronal firing. PHT has a stronger effect on the sodium-channel than CBZ, delaying recovery stronger than CBZ. PHT may also have mild effects on the excitatory glutamate system and on the inhibitory GABA system. It is unknown which mechanism of action is responsible for the side-effects. PHT has been used as an antiepileptic drug since 1938 by Merritt and Putnam. For 20 years PHT was (together with PB) the universal treatment of epilepsy. PHT has excellent anticonvulsant properties and is used as a broad range AED.

Adults

For adults, five studies are available comparing phenytoin with a non-drug condition.³³⁻³⁷ These studies all reveal PHT-induced cognitive impairment in the areas of attention, memory and especially mental speed. The magnitude of the reported effects is moderate to large but all these studies were carried out in normal volunteers, which opens the possibility that these effects represent short-term outcomes of the drug. The results of head-to-head comparisons showed more cognitive impairment for PHT than for CBZ, although this is debated by others.^{22-24,36-38}

Children

For children one study is available using a withdrawal design, i.e. allowing to compare the effects of PHT with a non-drug condition. In this study antiepileptic drug treatment was withdrawn in 100 children and compared both to a non-drug control group and before-after withdrawal. The study did not show any severe cognitive effects.³⁹ This is in contrast with earlier studies that found severe effects in children.⁴⁰ In general, earlier studies used higher dosing, did not control for serum levels and mostly studied children in polytherapy. Moreover, the type of epilepsy is a confounder as more difficult epilepsies seem to be associated with more frequent use of PHT.

Ethosuximide (ESX)

ESX modifies the properties of voltage-dependent calcium channels, reducing the T-type currents and thereby preventing synchronized firing. The reduction is most prominent at negative membrane potentials and less prominent at more positive membrane potentials. Most of the effect is assumed to take place in thalamocortical relay neurons. ESX is introduced in 1960 and mainly used for the treatment of generalized absence seizures.

Adults

No controlled studies in adults are available.

Children

A recent study by Mandelbaum et al. (2009) showed mild and temporary attentional problems in children with idiopathic epilepsy (mostly absence seizures) in comparison to a non-treatment baseline.²⁰ However, more recently, a double-blind, randomized, controlled clinical trial in children with newly diagnosed childhood absence epilepsy showed that ESX was associated with fewer adverse attentional effects than valproic acid or lamotrigine.⁴¹

Valproate (VPA)

VPA, a fatty acid, is believed to possess multiple mechanisms of action. Several studies have demonstrated an effect on sodium channels that is different from PHT and CBZ. An effect on T-type calcium channels has also been demonstrated. Recent studies have, however, demonstrated that a predominant effect concerns the interaction with the GABA-ergic neurotransmitter system. More precisely, VPA elevates brain GABA levels and potentiates GABA responses, possibly by enhancing GABA synthesis and inhibiting degradation. Theoretically, such mechanisms of action may cause cognitive side-effects. Furthermore, VPA may augment GABA release and block the re-uptake of GABA into glia cells. VPA is one of the most effective drugs against generalized absence seizures.

Adults

Three studies allow the interpretation of absolute effects and showed mild to moderate impairment of psychomotor and mental speed.⁴²⁻⁴⁴ The comparison with other drugs showed lower performance of memory and visuomotor function compared to CBZ.²³

Children

One study reported 'no cognitive impairment' compared to a non-drug condition in a withdrawal design with children in remission.³⁹ A favourable profile compared to PB on tests for intelligence is found.^{30,31} An indirect effect of valproate is induced by hyperammonemia, resulting in mental slowing.⁴⁵

Carbamazepine (CBZ)

The main anticonvulsant mechanism of action is similar to that of PHT with a less 'slowing' effect in the recovery state than obtained for PHT. The mechanism of action is also voltage- and frequency dependent. CBZ was first synthesized in the early 1950's and introduced as an antiepileptic drug by Bonduelle in 1964 in Europe.^{46,47} CBZ is used for patients with partial complex seizures, with or without secondary generalization. Approval by the FDA for use in the United States followed much later (1978) because of concerns about serious hematological toxicity (e.g. aplastic anemia).

Adults

One study in normal volunteers reported 'no cognitive impairment' compared to a non-drug condition.³⁴ This is challenged by the group of Meador and coworkers that reported impairments of memory, attention and mental speed, largely the areas that may also be affected by PHT.^{36,37} When evaluating the comparisons of CBZ with other AEDs there are the conflicting results of the Italian study by Gallassi and coworkers, showing a more favourable profile compared with PHT and PB and the USA-based studies by Meador and coworkers that showed no differences compared with PHT and PB.^{23,24,36,37}

Children

Two studies in patients with epilepsy reported 'no cognitive impairment' compared to a non-drug condition in a withdrawal design with children in remission.^{39,48} The USA study of Mandelbaum et al. (2009) reported a persistence of attentional problems when newly diagnosed children with localisation-related epilepsy were treated over a period of one year.²⁰ This was compared to a non-drug baseline. Some effects on memory for CBZ are suggested, whereas VPA and PHT did not.^{49,50} In comparison with VPA, no differences were found.⁵¹

Oxcarbazepine (OXC)

OXC is a keto homologue prodrug of CBZ. It is structurally similar to CBZ, but has a different metabolic profile. In humans, the keto group is rapidly and quantitatively reduced to a monohydroxy derivative that is the main active anticonvulsant agent. Metabolism of OXC does not result in the formation of 10,11-epoxy carbamazepine that is considered the main metabolite causing side-effects. The mechanism of action is similar to CBZ, but OXC also reduces presynaptic glutamate release, possibly by reduction of high-threshold calcium currents. OXC was approved in the European Union in 1999 and is indicated for use as a monotherapy or adjunctive therapy for partial seizures with or without secondarily generalized tonic-clonic seizures in patients ≥ 6 years of age.

Adults

The effects of OXC on cognitive function have been evaluated in one study in healthy volunteers and in four studies in adults patients with epilepsy. A double-blind, placebo-controlled, crossover study was conducted in 12 healthy volunteers.⁵² The effects of two doses of OXC (150 mg/day and 300 mg/day) and placebo on cognitive function and psychomotor performance were compared. The treatment duration for each condition was 2 weeks. Cognitive function tests were administered before treatment initiation and 4 hours after the morning doses on days 1, 8, and 15. In this study, OXC improved performance on a focused attention task, increased manual writing speed, and had no effect on long-term memory processes.

In patients with epilepsy, four monotherapy comparative studies are available to evaluate the effects of OXC on cognitive functions in adult patients with newly diagnosed epilepsy. The first study was a double-blind, active-control study evaluating the effects of CBZ and OXC on memory and attention in 41 patients with newly diagnosed epilepsy.⁵³ The treatment duration was 1 year. Cognitive function and intelligence tests were administered before treatment initiation and after 1 year of treatment. The results indicated no deterioration of memory or attention with either CBZ or OXC.

The second study was an active-control study that evaluated the effects of CBZ, VPA, and OXC on intelligence, learning and memory, attention, psychomotor speed, verbal span, and visuospatial construction in patients with newly diagnosed epilepsy.⁵⁴ The treatment duration was 4 months. Cognitive function and intelligence tests were administered before treatment initiation and after 4 months of treatment. The results indicated no deterioration of cognitive function in any treatment group. Significant improvements in learning and memory tests were found for the CBZ- and OXC-treated patients. Improvements were also found in attention and psychomotor speed tests for the VPA-treated patients and partly for the CBZ-treated patients.

The third study was a double-blind, randomized, active-control study that evaluated the effects of PHT and OXC on memory, attention, and psychomotor speed in 29 patients with newly diagnosed epilepsy.⁵⁵ The treatment duration was 1 year. Cognitive function tests were administered before treatment initiation and after 6 and 12 months of treatment. The results indicated no significant differential cognitive effects between PHT and OXC during the first year of treatment in patients with newly diagnosed epilepsy who achieved adequate seizure control.

In the fourth study, three groups of 12 patients taking either CBZ, VPA, or PHT took a single 600-mg dose of OXC followed 7 days later by 3 weeks of treatment with OXC 300 mg thrice daily and matched placebo in random order.⁵⁶ Seven untreated patients, acting as controls, were prescribed the single OXC dose and 3 weeks of active treatment only. There were no important changes in cognitive function test results during administration of OXC compared with placebo.

Children

The effects in children have been studied in only one study, comparing OXC with CBZ and VPA.^{57,58} The study was an open-label, randomised, active-control, three-arm, parallel-group, 6-month study comparing 55 newly diagnosed patients on OXC monotherapy versus 57 patients taking CBZ or VPA. A broad set of cognitive areas were assessed, including intelligence. After a 6-month treatment period, no evidence for any detrimental change in comparison to baseline or the comparator (CBZ or VPA) was found. As in adults, some mild improvements were reported on the attentional tests.

Topiramate (TPM)

TPM is a sulfamate-substituted monosaccharide that has clearly multiple mechanisms of action.⁵⁹ TPM blocks neuronal sodium channels in a voltage- and frequency-dependent manner, it inhibits CA, it promotes the action of GABA at the GABA_A receptor complex, elevates GABA brain concentrations by about 60% at 3 and 6 hours after a single dose- an increase that is maintained with 4 weeks of TPM administration.⁶⁰ TPM is a carbonic anhydrase inhibiting agent that is effective in refractory chronic partial epilepsy.^{61,62}

Adults

During the initial add-on clinical trials, central nervous system (CNS)-related “cognitive” subjective complaints were frequently reported, including mental slowing, attentional deficits, speech problems, and memory difficulties.⁶¹ It should be mentioned, however, that higher target doses and faster titration schedules were used than are now common in clinical practice (see Faught et al.⁶² for a discussion of dose and titration

speed). Recent studies with TPM-treated patients have confirmed high levels of adverse cognitive effects based on subjective complaints.^{63,64} A follow-up study showed long-term retention of 30% for a 4-year follow-up.⁶⁵ For about half of the 70% of patients who discontinued treatment, side-effects were the major reason, with cognitive side-effects being most frequently mentioned.

A study of six normal volunteers used an acute dose of 2.8 mg/kg (~ 200 mg/day) followed by a titration to 5.7 mg/kg (~ 400 mg/day) in 4 weeks, resulting in weekly dose escalations of about 100 mg.⁶⁶ The rate at which TPM was escalated in this study was very similar to the dose escalation used in the initial TPM adjunctive-therapy trials,⁶¹ in which escalating the TPM dose to 200 or 400 mg/day over 2–3 weeks was associated with somnolence, psychomotor slowing, speech disorders, and concentration and memory difficulties.⁶⁵ The neuropsychometric changes were commensurate with the CNS effects. The cognitive effects of an acute starting dose of 200 mg/day were impairments of verbal function (word finding and verbal fluency) of approximately 2 standard deviations (a very serious impairment) and sustained attention. Titration to 400 mg/day in 4 weeks resulted in impairments of verbal memory and mental speed of >2 standard deviations.

Six studies involving patients with epilepsy are available. In a study by Meador (1997) with 155 patients with epilepsy, the effects of the gradual introduction of TPM as add-on (a 50-mg starting dose, followed by increments of 50 mg per week over 8 weeks) were compared with those of more rapid dose escalation (initial dose of 100 mg, followed by two consecutive weekly increments of 100 and 200 mg).⁶⁷ In a test battery of 23 variables representing selective attention, word fluency, and visuomotor speed, the subjects who were on a slow-titration schedule and treated with one background AED displayed TPM-associated score changes of more than one third but less than one standard deviation.

A study by Aldenkamp and colleagues (2000) was specifically designed to compare cognitive effects of TPM and VPA added to therapeutic dosages of CBZ in 59 patients with epilepsy.⁶⁸ In this study, a slow titration speed was used with a starting dose of 25 mg/day TPM and weekly increments of 25 mg. Moreover, the average achieved dose (approximately 250 mg) was relatively low. Neuropsychometric testing was conducted 8 weeks after the last dosage increase (20 weeks after the start of TPM therapy). The study therefore used optimal conditions (i.e., slow titration, relatively low dose, and a longer treatment period), allowing for patient habituation to the effects of TPM therapy. Nonetheless, cognitive impairment was found for verbal memory function both during titration and at end point.

In a study by Burton and Harden (1997), attention was assessed weekly in ten subjects receiving TPM over a 3-month period.⁶⁹ Four of nine subjects showed significant correlations between TPM dosage and forward digit span measured weekly, such that higher dosage was associated with poorer attention.

In a retrospective study by Thompson and colleagues (2000), the neuropsychological test scores of 18 patients obtained before and after the introduction of treatment with TPM (median dose 300 mg) were compared with changes in test performance of 18 patients who had undergone repeated neuropsychological assessments at the same time intervals.⁷⁰ In those patients taking TPM, a significant deterioration in many domains was found. The largest changes were found for verbal IQ, verbal fluency, and verbal learning.

In an open, prospective study, forty-one patients with intractable epilepsy initially received either TPM or tiagabine (TGB) as add-on treatment.⁷¹ Of these twenty-one patients were assessed at baseline; after a three month titration phase and after a three month maintenance phase. The patients were assessed on various aspects of cognitive functioning such as attention, memory, language and self-report mood and quality of life. The TPM group performed worse on measures of verbal fluency and working memory and reported more depression than the TGB group. They also felt that they were suffering from more adverse effects due to the TPM medication. However, TPM patients did report an increase in mental flexibility between titration and maintenance phase.

In another study, 21 patients with focal epilepsy treated with TPM worsened in the cognitive domains of cognitive speed and verbal fluency, as well as verbal and visual short-term memory compared to patients treated with LEV.⁷²

Children

Few studies have psychometrically measured cognitive changes in children on TPM which corroborate the findings in adults. A high percentage of children (>20%) suffer from a broad range of cognitive side-effects that persist even at assessments >1 year.⁷³

In a randomized, double-blind, placebo-controlled study comparing TPM in different dosages (50 mg/day and 100 mg/day) and placebo, the TPM 100 mg/day dose was associated with slowing in psychomotor reaction times.⁷⁴ Learning, memory and executive function were unchanged.

In another study, the digit symbol test and verbal learning memory test were administered at baseline and study endpoint in children treated with TPM started either in monotherapy or add-on therapy.⁷⁵ Cognitive testing revealed no significant changes during TPM therapy. Comparing pre-post differences, TPM monotherapy was associated with better cognitive outcomes than add-on therapy. However, these results of this 12-week open label study have to be interpreted with caution given the short study duration and the heterogeneity of the study population.

When the cognitive effects of TPM were compared with CBZ in children (5-15 years) with benign rolandic epilepsy after 28 weeks of treatment, patients who received CBZ showed an improvement on the subtest maze from the WISC-R and children with TPM had a poorer performance on the subtest arithmetic.⁷⁶ However, when the patients

who had maintained the minimum target dose were compared, the TPM group showed an improvement on the subtest object assembly compared to the CBZ treatment group.

Lamotrigine (LTG)

LTG is a phenyltriazine with weak antifolate activity. It was introduced in Europe in 1991 and in the United States in 1994. The main anticonvulsant mechanism of action is to block voltage-dependent sodium channels that result in voltage- and frequency-dependent inhibition of the channel. This suggests that the mechanism of action is similar to that of PHT and CBZ. However in LTG treatment, this mechanism prevents presynaptic excitatory neurotransmitter release and the extent to which the mechanisms of action differ from CBZ is debatable.⁷⁷ Clinical evidence indicates that LTG is effective against partial and secondarily generalized tonic-clonic seizures, as well as idiopathic (primary) generalized epilepsy.

Adults

A large number of cognitive studies are available for LTG (for an overview see Aldenkamp and Baker, 2001)⁷⁸. Six volunteer studies have been conducted with LTG. Doses of 120 mg and 240 mg did not produce a significant change in cognitive function compared with baseline when administered to 12 normal volunteers in an acute study of 1 day.⁷⁹ Similarly, five volunteers received LTG (acute dose 3.5 mg/kg and then titrated to a maximum of 7.1 mg/kg) in a single-blind manner and were assessed for change in cognitive function after 2 and 4 weeks.⁶⁶ There was no significant change in any of the neurocognitive measures relative to baseline performance.

LTG and CBZ have been compared in 12 healthy male volunteers and associations were made between the observed cognitive effects and plasma concentrations of these drugs.⁸⁰ The effects of these drugs were examined by means of adaptive tracking, which assesses eye-hand coordination and effects of attention, and eye movement tests. LTG treatment was not significantly different from placebo, but increased CBZ saliva concentrations were significantly associated with impaired adaptive tracking and smooth and saccadic eye movements.

The long-term effects of LTG and CBZ were compared in 23 volunteers in a 10-week crossover study.⁸¹ The neuropsychological battery in this study consisted of 19 instruments yielding 40 variables, including both subjective and objective measures. LTG showed better performance or fewer side-effects in 19 (48%) of the variables, while no statistically significant differences were seen in the remaining variables.

The cognitive and behavioral effects of LTG and TPM were compared in 47 healthy adults using a double-blind, randomized crossover design with two 12-week treatment periods.⁸² Neuropsychological evaluation included 17 measures yielding 41 variables of

cognitive function and subjective behavioral effects. Better performance on 33 (80%) variables was seen for LTG, but none for TPM. Even after adjustment for blood levels, performance was better on 19 (46%) variables for LTG, but none for TPM. Differences concerned both objective cognitive and subjective behavioral measures.

Finally, a study by Aldenkamp and colleagues (2002) in 30 volunteers (12 days of treatment, using a daily dose of 50 mg of LTG) showed evidence for a selective positive effect of LTG on cognitive activation, relative to both placebo and VPA.⁸³ Although the results of these volunteer studies provided us preliminary insight into the impact of LTG on cognition, the generalizability of the results from these studies to patients with epilepsy receiving long-term AED treatment is limited.

The effects of LTG on cognitive function have been compared with those of CBZ in patients with newly diagnosed epilepsy.⁸⁴ Patients completed tests of verbal learning and memory, attention, and mental flexibility at baseline and then periodically for up to 48 weeks. Significant differences favoring LTG over CBZ were observed with semantic processing, verbal learning, and attention. The authors concluded that LTG may have a favorable long-term effect on cognitive function when compared with CBZ.

Other studies have reported positive cognitive effects of LTG used as adjunctive therapy. Three independent double-blind, randomized, crossover studies have examined the cognitive effects of LTG used as add-on therapy.⁸⁵⁻⁸⁷ Two studies included patients with a history of partial seizures (at least once weekly during the preceding 3 months) who had received no more than two other AEDs or VPA or PHT monotherapy. Both studies also used two treatment periods (12 and 18 weeks), which were separated by a washout period (4 and 6 weeks). Despite the similarity in trial design and patients, there is some inconsistency between the findings of these studies. One study showed a marginal reduction in general "cerebral efficiency" (an indirect measure of cognitive function) following LTG treatment.⁸⁵ Conversely, significant improvements were reported in the second study and the third study when compared with TPM.^{86,87}

In an uncontrolled add-on study using CBZ as baseline drug, no deterioration on any of the cognitive tests was found after introducing LTG (200 mg).⁸⁸ LTG therapy in seven patients with epilepsy and mental retardation caused both positive and negative psychotropic effects.⁸⁹ These findings were based on the observations of parents and supervising staff. Positive effects included reduced irritability and increased compliance with simple instructions, while negative effects included behavioral deterioration with temper tantrums, restlessness, and hyperactivity. Similarly, a second study in 67 patients with mental retardation showed that following adjunctive treatment with LTG, social functioning was stable or improved in 90% of patients.⁹⁰

In addition to clinical studies that have assessed the impact of LTG on cognitive function, further evidence can be obtained from examining the effect of LTG on electroencephalographic (EEG) parameters. Overt EEG discharges can occur without any visible clinical correlate in many patients with epilepsy. These epileptiform episodes

may be associated with transient deterioration in cognitive function.⁹¹⁻⁹³ Data from several studies indicate that LTG may reduce spontaneous epileptiform discharges, which may partially explain the favorable cognitive profile of LTG. In five patients displaying spontaneous EEG discharges, a single dose of LTG (120 mg or 240 mg in addition to existing medication) resulted in a substantial reduction in spontaneous interictal discharges within a 24-hour period.⁹⁴

The effect of LTG add-on therapy in 11 patients with refractory partial seizures with or without secondary generalization has also been reported.⁹⁵ LTG was added to existing therapy consisting of CBZ with at least one additional AED. EEG recordings were made at rest with eyes closed, during an attentive task (blocking reaction induced by several episodes of eyes open lasting 8 to 9 seconds), during cognitive tasks, and while performing mental arithmetic. In addition, a battery of neuropsychological tests was carried out. Before LTG treatment, EEG data revealed a decrease in fast activity at rest and a reduction in alpha and beta bands during attentive and cognitive tasks. LTG treatment resulted in a selective increase in alpha reactivity and beta power during the attentive tasks with no other detectable changes. During cortical activation, subtle changes were observed that were taken as indicative of a slight improvement in attention. Neuropsychological evaluation revealed that following 3 months of LTG therapy, no deterioration in cognitive function had occurred.

The long-term effects of LTG on paroxysmal abnormalities have also been monitored with a computer-based analysis system.⁹⁶ Twenty-one patients with intractable epilepsy (twenty of whom were receiving multiple AED therapy) were evaluated before and after LTG treatment for EEG ictal events and number of spikes in a 10-minute period. Before LTG treatment, patients typically showed discharges characterized by diffuse spike-wave complexes. However, following a 4-month treatment period with LTG, ictal discharges disappeared and diffuse slow wave activity was seen with no adverse effect on background activity. Nineteen of the 21 patients also showed a reduction in seizure frequency.

LTG also showed a promising cognitive profile in elderly patients suffering from age-associated memory impairment.⁹⁷ A neuropsychological test battery in combination with auditory event-related potentials (ERPs) was used to measure the impact of LTG on cognitive function. LTG treatment caused a reduction in amplitude of the P₃₀₀ component of the ERP and a corresponding improvement in immediate and delayed visual memory and delayed logical memory. LTG may therefore improve simple memory functions in a memory-impaired elderly population.

Children

In the first placebo-controlled, double-blind, crossover study on the cognitive effects of lamotrigine in children with epilepsy, children with well-controlled or mild epilepsy were randomly assigned to add-on therapy with either lamotrigine followed by placebo or placebo followed by lamotrigine.⁹⁸ For children on VPA, LTG was titrated to

2 mg/kg/day (≤ 12 years old) or 150 mg/day (> 12 years old). For children not on VPA, lamotrigine was titrated to 10 mg/kg/day (≤ 12 years old) or 300 mg/day (> 12 years old). Each treatment phase was 9 weeks, the crossover period 5 weeks. A neuropsychological test battery was performed during EEG monitoring at baseline and at the end of placebo and drug phases. There were no cognitive effects for lamotrigine in adjunctive therapy found for children with epilepsy. A favorable cognitive profile was also reported after long-term treatment based on physicians' and parents' experience.⁹⁹ More positive changes were reported, most prominent in concentration and vigilance.

Levetiracetam (LEV)

LEV is structurally and mechanistically dissimilar to other AEDs. It is believed to bind to a specific, as yet undetermined, site on the synaptic plasma membrane. Moreover, LEV reduces the GABA turnover in the striatum by reducing GABA synthesis and increasing GABA metabolism. It is effective in reducing partial seizures in patients with epilepsy, both as adjunctive treatment and as monotherapy. LEV has many therapeutic advantages for patients with epilepsy. It has favorable pharmacokinetic characteristics (good bioavailability, linear pharmacokinetics, insignificant protein binding, lack of hepatic metabolism, and rapid achievement of steady-state concentrations) and a low potential for drug interactions. It is licensed for use as adjunctive treatment for partial seizures, with or without secondary generalization, in people aged over 16 years.

Adults

There are no controlled studies available. The small pilot study by Neyens et al. (1995) did not provide conclusions.¹⁰⁰ A prospective, multicenter, open-label study showed that adjunctive therapy or monotherapy with LEV in adult patients with epilepsy improved cognitive and neuropsychological functions such as recall and language.¹⁰¹ The recent study by Bootsma et al. (2009) showed favourable effects.¹⁰² In comparison to CBZ, LEV has a positive stimulating effect on cognition.¹⁰³

Children

The effects of adjunctive levetiracetam on memory and attention in children have been investigated in a randomized, double-blind, placebo-controlled study. No impairment in cognitive function was observed over the 8- to 12-week treatment period.¹⁰⁴ The behavioral and emotional effects of adjunctive LEV treatment in children and adolescents (4–16 years old) with uncontrolled partial-onset seizures were also evaluated in a randomized, double-blind, placebo-controlled study.¹⁰⁵ Patients received adjunctive LEV 20–60 mg/kg/day or placebo for 12 weeks. Selective aspects of

behavioral and emotional functioning, specifically aggressive behavior, were affected by adjunctive LEV treatment. However, no patient discontinued the trial because of aggressive behavior-related events.

Gabapentin (GBP)

GBP (1-(aminomethyl) cyclohexane-acetic acid) is a novel AED, currently used as add-on therapy in patients with partial and generalized tonic-clonic seizures. GBP is a cyclic GABA analogue, originally designed as a GABA agonist.¹⁰⁶ Further research has clearly shown a specific effect of GBP on GABA-ergic neurotransmitter systems, especially influencing GABA turnover. Investigations using nuclear magnetic resonance imaging spectroscopy have confirmed that GBP elevates GABA concentrations, specifically in the occipital cortex of patients with epilepsy.¹⁰⁷

Adults

Two volunteer studies and two clinical studies are available to interpret the cognitive effects. Martin et al. (1999) used an acute dose and rapid titration in six volunteers and did not find cognitive effects of GBP.⁶⁶ Meador et al. (1999) compared the cognitive effects of GBP and CBZ in 35 healthy subjects by using a double-blind, randomized, crossover design with two 5-week treatment periods. During each treatment condition, subjects received either GBP 2400 mg/day or CBZ (mean 731 mg/day).¹⁰⁸ Subjects were tested at the end of each AED treatment period and in four drug-free conditions (two pretreatment baselines and two post-treatment washout periods [1 month after each AED]). The neuropsychological test battery included 17 measures yielding 31 total variables. Significantly better performance on eight variables was found for GBP, but on no variables for CBZ. Comparison of CBZ and GBP with the nondrug average revealed significant statistical differences for 15 (48%) of 31 variables.

Leach et al. (1997) studied GBP in 21 patients in an add-on polytherapy study after 4 weeks of adjunctive therapy and found no change in psychomotor and memory tests. Drowsiness was more often found in higher dosing (2400 mg).¹⁰⁹

Mortimore et al. (1998) did also not find a difference between continued polytherapy and an add-on with GBP in measures of cognition or quality of life.¹¹⁰

Children

No studies are available.

Tiagabine (TGB)

TGB is a γ -aminobutyric acid (GABA) uptake inhibitor that is structurally related to the prototypic GABA uptake blocker nipecotic acid, but has an improved ability to cross the blood-brain barrier. TGB temporarily prolongs the presence of GABA in the synaptic cleft by delayed clearance. Clinical trials have shown that TGB is effective as add-on therapy in the management of patients with refractory partial epilepsy. As TGB was recently marketed, certain aspects of its development are unfinished.

Adults

Three cognitive studies are available. Dodrill and colleagues (1997) included 162 patients who received the following treatments: placebo (n=57), 16 mg/day TGB (n=34), 32 mg/day TGB (n=45), or 56 mg/day TGB (n=26) at a fixed-dose for 12 weeks after a 4-week dose titration period.¹¹¹ Eight cognitive tests and three measures of mood and adjustment were administered during the baseline period and again during the double-blind period near the end of treatment (or at the time of dropout). The results showed no cognitive effects of monotherapy with TGB at a low or high dose, but there was some evidence for mood effects of add-on treatment with TGB at higher dosing, possibly related to titration speed.

Thirty-seven patients with partial epilepsy were investigated in the add-on polytherapy study by Kälviäinen and colleagues (1996). The study protocol consisted of a randomized, double-blind, placebo-controlled, parallel-group add-on study and an open-label extension study.¹¹² During the 3-month double-blind phase at low doses (30 mg/day), TGB treatment did not produce any cognitive changes compared with placebo. TGB treatment also did not cause deterioration in cognitive performance during longer follow-up with successful treatment on higher doses after 6 to 12 months (mean 65.7 mg/day, range 30–80 mg/day) and after 18 to 24 months (mean dose 67.6 mg/day, range 24–80 mg/day).

Finally, Sveinbjornsdottir and colleagues (1994) conducted an open trial of 22 adult patients with refractory partial epilepsy followed by a double-blind, placebo-controlled, crossover trial in 12 subjects. Nineteen patients completed the initial open titration and fixed-dose phase of the study and 11 patients completed the double-blind phase.¹¹³ The median daily TGB dose was 32 mg during the open fixed-dose and 24 mg during the double-blind period. Neuropsychological evaluation did not show any significant effect on cognitive function in the open or double-blind phase.

Children

No studies available.

Vigabatrin (VGB)

VGB is an irreversible inhibitor of gamma- aminobutyric acid transaminase (GABA-T), the enzyme responsible for the catabolism of GABA. The mechanism of action of vigabatrin is attributed to irreversible enzyme inhibition of GABA-T and consequent increased levels of GABA. It is used as add-on medication in adult patients with complex partial seizures or as monotherapy in babies with infantile spasms.

Adults

A small sample showed no change from baseline when patients with partial epilepsy were treated with 2g VGB during six months.¹¹⁴ This finding was supported in a healthy volunteer study.¹¹⁵

Children

In a retrospective study with 84 children no serious cognitive impairment was found. In fact, a shorter period from onset of infantile spasms to treatment with VGB was associated with better cognitive outcome.¹¹⁶ In contrast, Gaily and colleagues (1999) reported cognitive impairments during treatment with VGB in a minority of their sample.¹¹⁷ However, also in this study the effect of epilepsy was not controlled.

Zonisamide (ZNS)

The anticonvulsant properties of ZNS were discovered through extensive testing of a variety of sulfonamide compounds. Like TPM, it has multiple mechanisms of action: blockade of voltage-gated sodium channels, reducing sustained repetitive firing, blocking T-type calcium channels, and inhibiting ligand binding to the GABA_A receptor. ZNS is also a carbonic anhydrase inhibiting drug, just as TPM. Although there is longer experience with ZNS in Japan (where it was developed), it is recently introduced in the USA and in Europe for partial onset seizures in refractory epilepsy.

Adults

Anecdotal clinical experience reveal a cognitive side-effect profile very similar to TPM but no controlled studies are available.

Children

No studies available.

Rufinamide (RUF)

RUF 331; 1-(2,6-difluoro-phenyl)methyl-1H-1,2,3-triazole-4-carboxamide) is a structurally novel compound which limits the frequency of sodium-dependent neuronal action potentials.

Adults

One study is available to assess the cognitive effects.¹¹⁸ The study used a multicentre, multinational double-blind, randomized, placebo-controlled parallel study design with 4 different doses of RUF (based on prior studies): 200 mg/day, 400 mg/day, 800 mg/day and 1600 mg/day as add-on to the existing medication. Cognitive assessments were performed at baseline (before the start with RUF treatment) and at endpoint (after 3 months of treatment). The most important finding is that for none of the cognitive tests a statistically significant worsening occurs for any of the doses of RUF when the period after 12 weeks of treatment was compared with the baseline before introducing RUF. Also, none of the comparisons between dose and placebo showed a statistically significant difference.

Children

No studies available.

Conclusion

A general conclusion that may be derived from most of the meta-analyses is that polypharmacy shows a relatively severe impact on cognitive function when compared with monotherapy, irrespective of the type of AEDs included.¹⁸ Two drugs that individually have mild cognitive effects may induce serious cognitive impairment when used together, possibly because of potentiation of tolerability problems.¹¹⁹

Possibly the most remarkable finding is that, although the severity of cognitive side-effects is generally considered to be mild to moderate for most AEDs, all commonly used AEDs have some impact on cognitive function.¹⁸ Such mild impact may be amplified in specific conditions and may become substantial in some patients when crucial functions are involved, such as learning in children or driving capacities in adults (often requiring millisecond precision), or when functions are impaired that are already vulnerable, such as memory function in the elderly.^{4,119} Moreover, the cognitive side-effects represent the long-term outcome of AED therapy; therefore, the effects may increase with prolonged therapy, which contributes to the impact on daily life functioning in refractory epilepsies.¹²⁰

The current evidence is summarized in Figure 2.1 and Table 2.1. Drug-induced cognitive impairment has been established for phenobarbital (that even may impact higher-order cognitive function, specifically attention and memory), phenytoin (mental slowing which seems only clinical relevant in higher dosing and in polytherapy) and topiramate (attention, mental slowing and verbal impairments/dysphasia). Mild effects, mostly psychomotor slowing, were found for carbamazepine (although there are conflicting reports between the USA-studies that report an impact on attention and the European studies that do not show cognitive impairment, a reason for this discrepancy may be selection bias or dosing) and valproate (does not seem to impair cognition if sufficiently controlled for hyperammonemia). Although the evidence is sketchy, oxcarbazepine and levetiracetam do not seem to have a negative impact on cognition. For lamotrigine, some mild cognitive activating effects were found. In adults, no cognitive effects were found for ethosuximide, rufinamide, tiagabine and gabapentin, although the evidence requires confirmation. No studies are available for zonisamide. The effects for vigabatrin are inconclusive. For gabapentin, tiagabine, zonisamide, and rufinamide no studies in children are available.

Figure 2.1 Dominant impairment per antiepileptic drug.

Table 2.1 Cognitive effects of AEDs.

	Adults		Children	
	Absolute effects (comparison with a non-drug condition)	Relative effects (impairment when compared with other antiepileptic drugs)	Cognitive effect	Area of cognitive impairment
Phenobarbital (PB)	1 study reporting impairment - Memory impairment	5 studies: 4 reporting impairment - Memory and visuomotor impairment when compared with PHT and CBZ - Impairment of intelligence after long-term treatment when compared to VPA	---	Memory and attention
Phenytoin (PHT)	5 studies all reporting impairment - attentional deficits, memory impairment and mental slowing (mental slowing most frequently reported)	6 studies, 1 reporting impairment - global cognitive impairment and mental slowing	-	At high dosing: mental speed
Valproate (VPA)	3 studies, all reporting mild impairment - psychomotor and mental slowing	4 studies, 1 reporting impairment - memory impairment	0	(caveat: hyperammonemia)
Carbamazepine (CBZ)	3 studies, 1 reporting impairment - attentional deficits and mental slowing	4 studies, none reporting impairment	0/-	Probably only an effect with high dosing
Oxcarbazepine (OXC)	1 study, reporting no impairment	4 studies, none reporting impairment	0/+	(improvement of attention)
Topiramate (TPM)	1 study, reporting impairment - attentional deficits, verbal impairments	6 studies, all reporting impairment - verbal impairments (especially word finding problems/dysphasia), memory impairment and mental slowing	---	Attention, memory and language function.
Lamotrigine (LTG)	6 studies, none reporting impairment and 4 reporting activating effects	7 studies, none reporting impairment; the majority reporting psychotropic effects (activation).	+	Attentional tests
Levetiracetam (LEV)	No studies	1 study, reporting no impairment	0	
Gabapentin (GBP)	1 study, reporting no impairment	3 studies, not reporting impairment	No information	
Tiagabine (TGB)	3 studies, none reporting impairment	No studies	No information	
Vigabatrin (VGB)	No studies	No studies	No information	
Ethosuximide (ESX)	No studies	No studies	0	
Zonisamide (ZNS)	No studies	No studies	No information	
Rufinamide (RUF)	No studies	1 study, reporting no impairment	No information	

Impairment (- mild; -- moderate; --- severe) or improvement (+ mild; ++ moderate; +++ profound), 0 = no impairment or improvement

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Part II

Bridging the gap of our knowledge

Chapter 3

Cognitive effects of lacosamide as adjunctive therapy in refractory epilepsy

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Abstract

Purpose

Lacosamide (LCM) is a novel antiepileptic drug (AED) with potential benefit as adjunctive treatment in patients with partial-onset seizures. As yet, limited information on cognitive effects of LCM is available, especially in real-life settings. In this open clinical prospective study, the cognitive effects of LCM were evaluated when used as adjunctive antiepileptic therapy in patients with refractory epilepsy.

Methods

We included 33 patients aged between 16 and 74 years (mean: 37 years). All patients had a localisation-related epilepsy. Patients were assessed at baseline before starting LCM treatment and during follow-up when the optimal clinical dose was achieved. Subjective complaints were evaluated using the SIDAED; effects on cognition were evaluated using the computerized visual searching task (CVST).

Results

The CVST showed significant faster information processing reaction times at the second evaluation ($p=.013$), which was not correlated with seizure control, type of epilepsy, age, gender, drug load, number of concomitant drugs, dose or duration of LCM treatment. On the SIDAED, patients complained more about their cognitive function at the second evaluation ($p=.005$). For the SIDAED, a positive correlation at follow-up was found between the total severity score and higher age ($r=.375$, $p=.031$), but not with epilepsy factors or treatment characteristics.

Conclusion

Screening of the cognitive effects of LCM showed that LCM does not have negative effects on information processing speed. As this is the most sensitive function for cognitive side effects of AEDs, LCM does not seem to induce the common negative cognitive effects. Remarkably, patients complained more, especially about their cognitive function, which is possible the 'doing better, feeling worse phenomenon'.

Introduction

Lacosamide (LCM) is a relatively recent introduced antiepileptic drug (AED). It was approved in Europe and USA in 2008 as adjunctive therapy for the treatment of partial-onset seizures in patients with epilepsy aged 16 and older in Europe and in patients 17 and older in the United States.¹ LCM is unique among existing antiepileptic drugs in that it has been shown to exert its anticonvulsant effects predominantly by enhancement of the slow inactivation of voltage-gated sodium channels without effecting fast inactivation.^{2,3} The post hoc analysis of pooled clinical data by Sack et al. (2010) suggests that there may be an improved tolerability for LCM in patients not on other sodium channel blockers (SCB's).⁴

The efficacy and safety of adjunctive LCM for partial-onset seizures was established in three multicenter, randomized, double-blind, placebo-controlled trials.⁵⁻⁷ Drug-induced adverse events with an incidence of at least 10% during the treatment period were general CNS and gastrointestinal effects (dizziness, nausea, diplopia, vision blurred, headache, vomiting, ataxia, fatigue, somnolence, vertigo, nasopharyngitis, abnormal coordination, nystagmus and tremor). All of these with the exception of headache appeared to be dose related and four of these adverse effects were greater for LCM than for placebo; dizziness [31% vs 8%], headache [13% vs 9%], nausea [11% vs 4%] and diplopia [11% vs 2%].⁷⁻⁸ A recent published meta-analysis of all available randomized controlled trials with LCM which included these three trials and seven trials with other disorders (neuropathic pain, migraine, fibromyalgia, knee osteoarthritis) found that these adverse events were more frequent reported in patients with drug-resistant epilepsy compared to other disorders.⁹ LCM was not associated with any adverse event unambiguously related to cognition in this analysis. However, Doty et al. (2013) criticised that no formal cognitive testing was performed in these randomized controlled trials.¹⁰

In none of the trials, cognitive side-effects were recorded as a dominant complaint, which is remarkable given the high incidence of reported cognitive side-effects in antiepileptic treatment.^{11,12} The only item indicative of cognitive dysfunction reported was memory impairment, but its association with LCM was limited and not significant. However, no formal cognitive testing was performed in any of these trials, and cognitive effects notoriously evade subjective detection, especially in cases where patient use the drug as a 'last resort'.^{9,10} In a long-term study rates of adverse events commonly attributed to other AEDs such as changes in cognition were low.¹³ Recently, the cognitive effects of LCM were compared with lamotrigine and topiramate suggesting a cognitive profile similar to lamotrigine and superior to that of topiramate.¹⁴

For our specific patient group (i.e., patients with refractory epilepsies in a tertiary epilepsy referral and care centre), data about the cognitive effects of LCM are important for clinical decision making. Cognitive complaints of the epilepsy, the seizures and the drugs may be confusingly entangled, limiting evaluation of the

effectiveness of a drug in an individual patient. Preferably, cognitive effects of LCM would be studied in a randomized clinical trial (RCT). However, rarely cognition is an outcome (primary or secondary) of the industry driven RCT's. The alternative reports of clinical experience (often case reports) has led, however, to a substantial delay in detecting and understanding some behavioral effects of antiepileptic drugs.¹⁵ Our study must therefore be seen as a systematic clinical audit, collecting information on the cognitive effects in the naturalistic clinical setting.

Methods

Subject selection

Patients who were scheduled to start with LCM between March 2009 and September 2011 were included. They were investigated before this drug was added to their current treatment and when they were using LCM. The study was approved by the local medical ethical committee.

Assessment procedures

Cognitive effects of LCM were assessed at two different times: at baseline before starting with this drug and at follow-up. The intervals between baseline and follow-up are variable because data were collected as part of normal clinical practice. The patient characteristics (age and sex), type of epilepsy, comedication, drug load, average dose of LCM, length of treatment with LCM at follow-up, efficacy and reasons for discontinuation of LCM were included in the database. Efficacy was evaluated by change in seizure frequency from baseline to follow-up using a 3-point scale; reduction in seizure frequency, seizure remission, or increase in seizure frequency.

Instruments

Patients were tested with two measurements: a standardized inventory to evaluate subjectively perceived cognitive side-effects and a neuropsychological test to assess possible effects independent of subjective complaints. Complaints were assessed using a list of 46 items with possible AED-related complaints, the SIDAED.^{16,17} A complete overview of the SIDAED is provided in the Appendix A. The included items form 10 categories: general CNS, behavior (increased irritability), depressive symptoms, cognitive function, motor problems and co-ordination, visual complaints, headache, cosmetic and dermatological complaints, gastrointestinal complaints, and sexuality and menses. For each item, the patient rates the severity of the complaint on a four-point Likert scale (no problem, mild, moderate, or serious problem). A total subjective complaints score was calculated for each patient from the SIDAED complaints

questionnaire, consisting of the number of mentioned complaints, weighing a mild score as 1, moderate as 2 and severe as 3 points. Thus, the range of the total severity complaints score could vary from 0 to 138. This questionnaire can be analysed in different ways: regarding the total reported complaints, the different categories and the different items. The SIDAED is chosen because the psychometric properties have been established¹⁶⁻¹⁸ and cognitive complaints can be measured relative to other domains.

The computerised visual searching task (CVST), an adaptation of Goldstein's visual searching task gives an indication of the visual (complex) information processing speed.¹⁹ A target grid pattern in the centre of the computer screen has to be compared with 24 surrounding patterns. Only one of them is identical to the target pattern. An example of this test is provided in the Appendix B. The patient is asked to react as fast as possible; reaction times are recorded. After each correct response, the central target pattern changes. The test consists of 24 different patterns and after 12 presentations the surrounding grids change. This task was included as slowing of central information processing is observed to be the dominant cognitive effect of most AED's and also the first sign of cognitive adverse effects.^{11,12}

Dosing and titration

The initial dose of 50 mg was increased at weekly intervals by 50 mg up to the recommended maintenance dose of 200 to 400 mg/day. However, the titration schedule was individualized in response to patient complaints and seizure frequency.

Statistical analysis

Data was analysed with SPSS version 21.0, Chicago, IL, USA. For analysing the neuropsychological data, paired sample t-tests were used. Pearson correlations were used to exclude for influential effects on the neuropsychological results. Patients characteristics (gender and age), epilepsy factors (seizure control and type of epilepsy) and treatment characteristics (number of concomitant drugs, drug load, dose and duration of LCM treatment) were taken into account. Because the SIDAED consisted of 10 different categories, a p-value ≤ 0.005 was considered significant for the subscales of the SIDAED. This more stringent criterion of significance was based on the Bonferroni adjustment for multiple tests. For the items of the SIDAED, a Bonferroni corrected p-value ≤ 0.001 was considered significant.

Results

Patient characteristics

A total of thirty-three patients were included in this study. Most patients (73%, n=24) were female. Mean age at baseline was 37 years (SD: 14.5). Most patients (58%, n=19) had a symptomatic localisation related epilepsy, 42% (n=14) had a cryptogenic localisation related epilepsy.

Five patients (15%) discontinued their LCM treatment before the second evaluation and were excluded for further analysis. Reasons for discontinuation were unsatisfactory therapeutic effect in two patients and side effects in three patients. These side-effects were tiredness, dizziness, coordination and balance problems.

The 28 remaining patients were using LCM treatment with a mean daily dose at follow-up of 298.2 mg/day (SD: 120.6). LCM was added to the anticonvulsant regimen. Twenty-one of 28 patients (75%) were taking LCM in addition to a SCB. Concurrent AEDs ranged from 1-4 (mean: 1.9, SD: 0.8). The majority of the patients were taking carbamazepine (43%), clobazam (32%), lamotrigine (25%) and levetiracetam (21%).

Mean follow-up time was 7 months (SD: 6, range 1–24). In nine patients (28%), co-medication was changed at follow-up; in five patients only the dose of co-medication was optimized, and in four patients, there was a medication switch in which LCM was added in exchange for one other anticonvulsant.

Seizure frequency was reduced in 50% (n=14) of the patients. In 12 patients (43%), LCM did not have an effect on seizure frequency. Two patients (7%) had more seizures than before treatment with LCM was started.

Patients characteristics and their clinical data are provided in Table 3.1.

Neuropsychological findings

The CVST showed significant faster information processing speed at the second evaluation ($t=2.644$, $p=.013$). At follow-up, patients showed an average increase of speed of more than three seconds (18%) on this task at follow-up (mean at baseline: 18.67 seconds; SD: 8.9; mean at follow-up: 15.40 seconds; SD: 7.5).

On the SIDAED, none of the patients mentioned zero complaints at baseline or follow-up. At baseline, before the start of treatment with LCM, the distribution of subjective complaints as measured by the SIDAED ranged from 3 to 36 (maximal range on the scale is 0-46), with a mean number complaints of 15.8 (SD:7.0). At second evaluation, the average rate of subjective complaints did not differ from baseline ($p=.431$) with a mean number of complaints of 16.8 (SD:8.5; range:1-35).

Table 3.1 Clinical characteristics of patients.

Patient	Sex	Age	Type of localisation-related epilepsy	Dosage LCM (mg) at second evaluation	Concurrent AED	Effect on seizure frequency	Treatment duration (LCM) at second evaluation (months)	Reason for discontinuation
1	F	74	Cryptogenic	200	PB 25 CLB 30	=	4	
2	F	44	Symptomatic	300	CBZ 600 CZP 1	-	5	
3	F	28	Symptomatic	200	PHT 350 OXC 1800 CLB 20	+	3	
4	F	62	Symptomatic	250	VPA 300 CLB 10	=	3	
5	F	59	Cryptogenic	400	CBZ 1000	=	3	
6	F	16	Symptomatic	Discontinued	-		Discontinued	Ineffectiveness
7	F	62	Cryptogenic	200	LEV 200 LTG 300 CLB 40	=	2	
8	F	45	Cryptogenic	100	LEV 500	-	24	
9	F	25	Cryptogenic	200	VPA 2250	-	1	
10	M	34	Symptomatic	300	LEV 3000 OXC 1200 LTG 500	=	3	
11	M	35	Symptomatic	Discontinued	-		Discontinued	Adverse events
12	F	19	Symptomatic	300	LTG 150	-	3	
13	M	18	Cryptogenic	400	OXC 2700 PGB 225	-	4	
14	F	37	Symptomatic	300	CBZ 1600 LTG 200	=	3	
15	F	50	Cryptogenic	200	GBP 1200 CBZ 600	-	4	
16	M	24	Symptomatic	600	LTG 550 TPM 200	=	10	
17	F	23	Symptomatic	400	AZM 500 CZP 3	=	12	
18	F	45	Symptomatic	250	CBZ 800 LTG 600	=	3	
19	F	19	Cryptogenic	300	VPA 1200 CBZ 1100	-	10	
20	M	47	Symptomatic	Discontinued	-		Discontinued	Ineffectiveness
21	M	25	Symptomatic	500	LEV 3000 CBZ 800 CLB 30	-	6	
22	M	51	Symptomatic	Discontinued	-		Discontinued	Adverse events
23	F	42	Cryptogenic	550	LEV 2000 PB 150	-	7	
24	F	44	Symptomatic	400	-	-	22	
25	M	29	Cryptogenic	150	CBZ 100 TPM 200	-	2	
26	F	29	Symptomatic	Discontinued	-		Discontinued	Adverse events
27	F	41	Cryptogenic	300	CBZ 1000	-	4	
28	F	22	Cryptogenic	200	LTG 175 CLB 20	=	17	
29	F	44	Symptomatic	400	CLB 20	-	8	
30	F	24	Cryptogenic	300	CBZ 800 CLB 10	+	2	
31	F	36	Symptomatic	250	PHT 187.5	-	3	
32	M	35	Symptomatic	200	CBZ 1400	=	10	
33	F	24	Cryptogenic	200	LEV 1000 CBZ 800 CLB 20	=	14	

AED: antiepileptic drug, LCM: lacosamide, PB: phenobarbital, CLB: clobazam, CBZ: carbamazepine, CZP: clobazepam, PHT: phenytoin, OXC: oxcarbazepine, VPA: valproate, LEV: levetiracetam, LTG: lamotrigine, PGB: pregabalin, GBP: gabapentin, AZM: acetazolamide, seizure frequency: reduction, +: increase, -: seizure remission, no effect.

A statistically significant effect was only found for the subscale cognitive complaints. For the other subscales, results did not yield statistical significance (see Figure 3.1). Both the severity of the cognitive complaints ($t=-3.367$, $p=.002$) as the number of the cognitive complaints ($t=-2.992$, $p=.005$) increased in the treatment phase. The mean severity score on the subscale cognitive function per item increased from 0.78 to 1.11 (see Table 3.2). At baseline, patients reported to experience on average 4.2 (SD:1.9) of the nine possible cognitive complaints. In the treatment phase, this was increased to an average of 5.3 (SD:2.4).

When analysing the 46 items, a significant higher severity score was found at the second evaluation for the following items from the cognitive function category; 'I have difficulty remembering names' ($t=-4.917$, $p<.000$), 'I notice I sometimes have difficulty expressing myself' ($t=-3.783$, $p<.000$), and 'I have difficulty finding the right words' ($t=-3.475$, $p=.001$)

Figure 3.1 Differences in the subscales of the SIDAED between baseline and follow-up.

Correlational analysis

A significant positive correlation was found at follow-up between processing speed and the SIDAED cognitive items 'I notice my reaction to others is slow' ($r=.465$, $p=.013$) and 'I notice my speech is slow' ($r=.467$, $p=.012$). Improvement of processing speed was associated with a decrease of complaints. No other cognitive complaints were correlated with the information processing task.

The improved information processing speed could not be explained by patient characteristics such as gender ($p=.712$) or age ($p=.771$), or by epilepsy factors such as seizure control ($p=.332$) or type of epilepsy ($p=.494$), or by treatment characteristics such as number of concomitant drugs ($p=.359$), drug load ($p=.927$) or dose ($p=.830$) and duration of LCM treatment ($p=.659$).

For the SIDAED, a positive correlation at follow-up was found between the total severity score and age ($r=.375$, $p=.031$). The older the patients, the more complaints were reported. Gender, epilepsy factors or other treatment characteristics did not affect the results.

Table 3.2 The mean reported severity score per item per subscale.

Subscale	Baseline	Follow-up
General CNS	0.80	0.94
Behavior (increased irritability)	0.55	0.56
Depressive symptoms	0.65	0.70
Cognitive function	0.78	1.11 *
Motor problems and co-ordination	0.54	0.60
Visual complaints	0.69	0.61
Headache	0.52	0.30
Cosmetic and dermatological complaints	0.40	0.41
Gastrointestinal complaints	0.35	0.38
Sexuality and menses	0.59	0.70

* $p \leq 0.05$

Discussion

Lacosamide is a relatively recent introduced AED with potential benefit as adjunctive treatment in patients with partial-onset seizures.²⁰ In this open clinical prospective study, the cognitive effects of LCM when used as adjunctive antiepileptic therapy in adolescent and adult patients with refractory epilepsy were evaluated in the real life setting.

During LCM treatment, we found a statistically significant improvement of information processing speed (increase of 18%). This function is generally impaired in individuals taking other AEDs.^{9,11,12} Speed of information processing is the most sensitive function affected by antiepileptic drug treatment; therefore this result is remarkable. However, activating effects have also been reported for lamotrigine.^{11,12,21,22} Ketter et al. (1999) divided AEDs in activating and sedating drugs, and our results suggest that LCM may be classified as a cognitive activating drug.²³ The results were not biased by interfering factors. The significant improvement of central information processing speed was not correlated with change in seizure frequency, type of epilepsy, age, gender, drug load, number of concomitant drugs or dose and duration of LCM treatment. Therefore, our

study suggest that LCM does not have a negative impact on this sensitive measurement.

There is a difference between the results of the objective cognitive assessment and the subjective patient report. Patients reported no increase in overall complaints from baseline to treatment phase. However, there is an increase in number and severity of cognitive complaints. More specifically, patients had more complaints about memory ('remembering names'), and language ('expressing themselves' and 'finding the right words'). On the other hand, correlational analysis showed a significant positive correlation at follow-up between processing speed and the SIDAED items 'I notice my reaction to others is slow' and 'I notice my speech is slow'. Improvement of processing speed was associated with a decrease of complaints. This concurs with the findings on the information processing task and these results in combination suggest that improvement of the processing speeds increases awareness in patients of other difficulties such as memory and language, which are generally not related to drug treatment but to the epilepsy. This improvement of adverse drug effect followed by an increased awareness of other cognitive difficulties can be described as the 'doing better, feeling worse phenomenon'.

None of the patients in our study discontinued LCM treatment because of the complaints about cognitive difficulties, which collaborates the result of the cognitive assessment. The reason for withdrawal was adverse events in three patients and unsatisfactory seizure control in two patients. The most common drug related adverse events were tiredness, dizziness, coordination and balance problems. This is in line with the study of García-Morales et al. (2011) who reported that about half of the patients who reported dizziness were taking other sodium channel blockers.²⁴ In our study, all patients who discontinued their LCM treatment were using a sodium channel modulator in combination. It has been suggested that neurotoxicity with LCM may be more likely with concomitant use of the more traditional voltage-gated sodium channel blockers such as carbamazepine, phenytoin, lamotrigine and oxcarbazepine due to a pharmacodynamic interaction.^{4,25-27} However, Wehner et al. (2009) and Stephen et al. (2011) concluded that LCM is as well tolerated in patients on traditional SCBs than on non-SCB's.^{28,29}

There are some methodological issues that limit the interpretation of our study. With respect to the neuropsychological outcome, this study has assessed the most commonly reported effect on cognition, but no tests using other cognitive functions has been used. Furthermore, preferably the rules of a randomised controlled trial would have been applied. However, generally, cognitive outcomes are not investigated in the industry driven RCT's when a new drug is in development. The alternative is then to study the effects in a naturalistic setting with limited protection against bias. Nonetheless, lacosamide is used in clinical practice and cognition is important for medical decision making. Our recommendation is that in new drug development of AEDs cognition is always used as outcome measure in the RCT's.

In conclusion, screening of the cognitive effects of LCM showed that LCM does not have negative effects on information processing speed. Further research is needed to investigate the other cognitive domains. However, as this is the most sensitive function for cognitive side effects of anti-epileptic drugs, LCM does not seem to induce the common negative cognitive effects. Possibly, it has a potential cognitive enhancing effect similar to that reported for lamotrigine.

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Appendix A

SIDAED list of subjective complaints

- 1 I have problems with my gums
- 2 I have lost weight
- 3 I have difficulty remembering names
- 4 I often feel drowsy and sleepy
- 5 I sometimes have to hold on to something to stop myself from falling
- 6 I forget all sorts of things, such as appointments
- 7 I find it hard to concentrate
- 8 I tire easily and have little energy
- 9 I am easily aggressive
- 10 I can only concentrate on something for short periods
- 11 I constantly walk into tables, doorposts etc.
- 12 I feel agitated and restless
- 13 I notice my reaction to others is slow
- 14 I cannot concentrate on the same thing for long periods of time
- 15 I notice my speech is slow
- 16 I constantly feel pressurized and excitable
- 17 I often suffer from dizzy spells
- 18 I have little appetite
- 19 My periods are irregular
- 20 I notice I sometimes have difficulty expressing myself
- 21 I often feel nauseous
- 22 I worry all day
- 23 I often suffer from diarrhea
- 24 My hands shake all the time
- 25 I have surplus saliva
- 26 I often suffer from double vision
- 27 I suffer from skin rash or other skin problems
- 28 I have gained weight
- 29 I think more slowly than I used to
- 30 I am easily irritated
- 31 I feel depressed and miserable
- 32 My bowel movement is often difficult
- 33 I have difficulty finding the right words
- 34 I am becoming less and less active
- 35 I cannot get to sleep and often lie awake
- 36 I am less often in the mood for sex
- 37 Sometimes I cannot do anything because of headaches
- 38 I suffer from hair loss
- 39 My vision is blurred
- 40 My hair growth has increased
- 41 When I want to pick up something, my hands start shaking
- 42 I do not feel capable of performing normal my daily activities
- 43 I often suffer from headaches
- 44 Making love has become less pleasant
- 45 I often suffer from stomach trouble
- 46 I often feel light-headed

Severity was stated as no problem/mild/moderate/serious problem.

Appendix B

Example of an item of the CVST from FePsy

Chapter 4

The cognitive profile of ethosuximide in children

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Abstract

Purpose

Although ethosuximide is one of the oldest anti-epileptic drugs (AEDs), little information is available about the cognitive side-effects of ethosuximide. Therefore, the aim of this study was to investigate the cognitive profile of ethosuximide.

Methods

In this cross-sectional study, we used an extensive neuropsychological test battery in patients with epilepsy aged 6-16 years who were treated with monotherapy ethosuximide. We evaluated the efficacy of the drug by seizure frequency (seizure free or not).

Results

We included 61 patients with a mean age of 9.4 years (SD:2.7) who used on average 686 mg/day (SD:245) ethosuximide as monotherapy. Ethosuximide was effective in the majority of the patients (70% were seizure free for at least 6 months at moment of inclusion). The total study population showed impairments of intelligence, visuomotor, and attentional function including activation/alertness. Comparisons between the well-controlled patients and patients who were not in remission showed significantly lower intelligence values and lower performance on the visual-perceptual and attentional tasks for the group with ongoing seizures. Our results suggested that the higher order cognitive dysfunctions (such as intelligence and visual-perceptual functions) may be regarded as seizure or aetiology effects and that the impaired fluid cognitive functions, such as activation/alertness, sustained auditory attention and attentional control or switching, were due to ethosuximide.

Conclusion

This study suggests the attentional dysfunction resulting in psychomotor slowing and alertness deficits may be regarded as effects of ethosuximide. Although no untreated baseline assessment was available, these effects are comparable to those of other AEDs, and ethosuximide may therefore be considered an AED with only mild effects on cognition. As ethosuximide is a first-line therapy for absence seizures in childhood, and drug-induced cognitive impairment may interfere with development, learning and academic achievement, these findings are of interest to clinicians who prescribe this drug, especially when informing parents.

Introduction

Approximately 10% of seizures in childhood epilepsy are absence seizures characterized by brief periods of unconsciousness that may be accompanied by automatic movements.¹ Generalized tonic-clonic seizures (GTCS) may occur in children with absences, especially late after seizure onset during adolescence.² Ethosuximide is effective as initial monotherapy in children with absence seizures.³ Furthermore, initially treated ethosuximide responders may have a lower risk of developing GTCS.⁴

Ethosuximide is one of the oldest anti-epileptic drugs (AEDs), developed in 1960 after the introduction of bromide, phenobarbital, phenytoin and primidone. Ethosuximide modifies the properties of voltage-dependent calcium channels, reducing the T-type currents and thereby preventing synchronized firing.⁵

The first publication concerning the effectiveness of this drug was published in 1958.⁶ Since then, the effect of ethosuximide has been studied in six randomized controlled trials (RCTs).⁷⁻¹² These RCTs were specifically performed to assess efficacy, although the three most recent RCTs also included one attentional test (the Conner's continuous performance test) to assess effects on cognition.¹⁰⁻¹² These studies showed that attentional dysfunction was more common in patients treated with valproic acid than in those treated with ethosuximide or with lamotrigine at 16-20 weeks of treatment¹⁰ and after 1 year of treatment.¹¹ However, these effects appeared to be caused by the epilepsy and not by ethosuximide.¹² A clinical study also reported attentional problems in children with absence seizures treated with ethosuximide,¹⁵ but this was a small and heterogeneous study in which not all patients had absence seizures.

No further information is available on the cognitive effects of ethosuximide. Therefore, the aim of this study was to investigate the entire cognitive profile of ethosuximide in children with absence seizures.

Methods

Subject selection

Patients with epilepsy aged 6-16 years who were referred to a tertiary referral centre for epilepsy and were treated with monotherapy ethosuximide were included in this cross-sectional study. All patients (parents) signed informed consent to use their data for research. Data on demographical and clinical characteristics such as treatment and seizure type and frequency were collected through medical records. These data are by nature retrospective. Patients were divided in two subgroups based on the efficacy of ethosuximide: a group that had been seizure free for at least 6 months and a group experiencing ongoing seizures. This division was based on clinical evaluation and a recent electroencephalogram (EEG).

Assessment procedure

The neuropsychological test battery consisted of two types of tests: (1) tests used to measure higher-order cognitive functions, such as intelligence, memory, and visual perceptual functions and (2) tests assessing fluid functions (functions that can easily fluctuate from moment to moment), such as attentional functions, speed of central information processing, motor speed, and alertness.^{14,15}

- **Intelligence:** The Wechsler Intelligence Scale for Children (WISC-III Dutch version) was used to measure the intellectual ability.¹⁶ The test consists of 11 subtests that generate a full-scale IQ (FSIQ), as well as a verbal IQ (VIQ) and a performance IQ (PIQ) and three indices: verbal reasoning (VR), perceptual organization (PO), and performance speed (PS).
- **Visual-perceptual functions:** The Beery Buktenica developmental test of visual-motor integration consists of a sequence of geometric forms of increasing difficulty that the patient copied on paper with a pencil.¹⁷ In the visual perception test, patients matched geometric forms to the in a given stimulus. In the motor coordination test, the patient traced shapes while remaining inside a double lined path, within a time limit.
- **Memory:** In the 15-word test (the Dutch version of the Rey Auditory Verbal Learning Test, AVLT), a list of 15 words was orally presented verbally five times. After every presentation, immediate recall (IR) was requested. A delayed recall (DR) was requested after a 20-min-interval.¹⁸
- **Alertness/activation:** In the reaction time measurements, patients had to react as quickly as possible to auditory stimuli presented at random intervals by a computer.^{14,21}
- **Central information processing speed:** In the computerized visual searching task (CVST), the subject had to compare a centred grid pattern against 24 surrounding patterns, one of which was identical to the target pattern.^{14,19}
- **Attention:** The Bourdon-Vos test is a cancellation test that assesses sustained attention. Patients were instructed to cross out the target items.²⁰ The Test of Everyday Attention for Children (TEA-Ch) is a standardized battery of tests for assessment across different attentional capacities.²¹ Four different subtests of the TEA-Ch were included: sky search which assessed selective/focused attention (patients had to find as many 'targets' as possible with similar distractors); score!, which assessed sustained attention (patients had to keep a count of the number of 'scoring' sounds they heard); creature counting, which assessed attentional control or switching (patients had to repeatedly switch between two activities in which time taken and accuracy were scored); sky search double task (DT), which assessed sustained and divided attention (patients were asked to combine two tasks; find targets in sky search and keep count of scoring sounds as in score!).

Statistical analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS, version 21.0 for Windows). The significance level was set at the 5% level. First, all neuropsychological test scores of the total study population were converted into z-scores (mean:0, SD:1; which indicates that z-scores between -1 and +1 are within the normal range). Age-matched norms for the general population were used as reference values. To investigate which cognitive domains were impaired in the total study population, comparisons with reference values were made with one-sample t-tests. Second, to eliminate possible interfering effects of the seizures on cognitive functions, differences in test results between seizure-free patients and patients with ongoing seizures were analysed with independent-sample t-tests. Third, to define the cognitive profile of ethosuximide, impaired cognitive functions of the total study population (that were significantly different from reference values and below a z-score of -1) that were not affected by seizure effects (not significantly different between seizure-free patients and patients with ongoing seizures) were regarded as effects of ethosuximide.

Results

In total, 61 patients were included in this study. In most of our patients (70%), ethosuximide was effective, resulting in seizure freedom, but some patients had ongoing seizures (30%). All patients had absence seizures, but a minority of the patients had also one or more GTCS in the past. Demographic and clinical characteristics of the study population are provided in Table 4.1.

Neuropsychological tests

Neuropsychological test results of the total study population were converted into z-scores and compared with reference values (Table 4.2). Significantly lower intelligence values were found for VIQ ($t=-2.265$, $p=.029$), PIQ ($t=-3.866$, $p<.001$), FSIQ ($t=-3.364$, $p=.002$), and PO ($t=-3.680$, $p=.001$). Furthermore, the score on the Beery visual motor integration was significantly lower ($t=-7.719$, $p<.001$), as well as the Beery motor coordination ($t=-3.658$, $p=.001$). Memory was not impaired. On the fluid cognitive functions, a significantly slower reaction time was found on all reaction time tasks (auditory dominant hand [DH] $t=4.637$, $p<.001$; auditory non-dominant hand [NDH] $t=4.754$, $p<.001$; visual DH $t=5.916$, $p<.001$; visual NDH $t=5.370$, $p<.001$). Attentional functions showed a lower performance for searching time ($t=-2.321$, $p=.027$), selective attention ($t=-2.507$, $p=.018$), sustained auditory attention ($t=-5.518$, $p<.001$), attentional control and switching for accuracy ($t=-2.984$, $p=.006$) and reaction time ($t=-4.960$, $p<.001$).

Table 4.1 Demographic and clinical characteristics.

	Total study population (n=61)			Seizure free patients (n=43)			Patients with ongoing seizures (n=18)		
	n	range		n	range		n	range	
Gender									
	Male	30 (49.2%)		21 (48.8%)			9 (50.0%)		
	Female	31 (50.8%)		22 (51.2%)			9 (50%)		
Mean age	At assessment (SD)	9.4 (2.7)	6-16	9.7 (2.8)	6-16		8.5 (2.2)	6-14	
	At onset of epilepsy (SD)	5.5 (2.9)	0-13	5.7 (3.1)	0-13		5.1 (2.3)	0-10	
AED	ESX in mg (SD)	685.9 (245)	250-1250	679.4 (242)	250-1250		701.4 (259)	250-1250	
	Duration of ESX use in years (SD)	1.2 (1.7)	0-6	1.3 (1.7)	0-6		.83 (1.4)	0-5	
Seizure type	Absences	61 (100%)		43 (100%)			18 (100%)		
	GTCS	8 (13.1%)		4 (9.3%)			18 (100%)		

ESX: ethosuximide, GTCS: generalized tonic-clonic seizures.

Table 4.2 Differences in neuropsychological test results compared with reference values.

Test	Total study population (n=61)				
	Mean	SD	Mean z-score	SD z-score	p
WISC-III VIQ	95.6	12.8	-.34	.85	.029*
WISC-III PIQ	91.1	15.0	-.61	1.01	<.001*
WISC-III FSIQ	92.7	14.3	-.53	.96	.002*
WISC-III VR	97.5	12.7	-.21	.83	n.s.
WISC-III PO	91.6	15.0	-.58	1.01	.001*
WISC-III PS	96.3	17.1	-.26	1.13	n.s.
Beery VMI	87.3	11.0	-.85	.73	<.001*
Beery VP	96.4	16.8	-.22	1.12	n.s.
Beery MC	87.6	16.2	-.83	1.08	.001*
AVLT IR (number correct)	42.1	10.2	.31	1.07	n.s.
AVLT DR (number correct)	8.5	2.9	-.15	1.02	n.s.
Auditory RT DH (ms)	362.3	90.3	-1.15	1.51	<.001*
Auditory RT NDH (ms)	345.8	76.3	-1.19	1.50	<.001*
Visual RT DH (ms)	398.1	94.7	-2.14	2.14	<.001*
Visual RT NDH (ms)	453.5	127.5	-2.44	2.61	<.001*
CVST (sec)	24.4	12.3	-.35	1.08	n.s.
Bourdon-Vos (reaction time)	16.3	5.4	-.28	1.53	n.s.
Teach Sky Search (number correct)	9.1	2.8	-.31	.93	n.s.
Teach Sky Search (time)	8.8	2.9	-.41	.98	.027*
Teach Sky Search (attention score)	8.6	3.1	-.47	1.04	.018*
Teach Score! (number correct)	6.9	3.1	-1.03	1.03	<.001*
Teach Creature Counting (number correct)	8.5	2.7	-.50	.89	.006*
Teach Creature Counting (time)	6.6	3.5	-1.12	1.18	<.001*
Teach Sky Search DT	9.3	2.9	-.24	.95	n.s.

TEA-Ch scores are shown in standard scores (mean:10, sd:3). AVLT: auditory verbal learning test, CVST: computerized visual searching task, DH: dominant hand, DR: delayed recall, DT: double task, FSIQ: full scale IQ, IR: immediate recall, MC: Motor Coordination, ms: milliseconds, NDH: non-dominant hand, NS: not significant, PIQ: performance IQ, PO: perceptual organization, PS: performance speed, RT: reaction time, sec: seconds, Teach: test of everyday attention for children, VIQ: verbal IQ, VMI: visual motor integration, VP: visual perception, VR: verbal reasoning, WISC: Wechsler intelligence scale for children. *p<.05

Seizure-free patients versus patients with ongoing seizures

Comparisons of the neuropsychological test results between the well-controlled patients and patients who were not in remission (Table 4.3), showed significantly lower intelligence values for the group with ongoing seizures (VIQ: $t=2.902$, $p=.006$; PIQ: $t=2.404$, $p=.021$; FSIQ: $t=2.752$, $p=.009$, VR: $t=2.854$, $p=.007$; PO: $t=2.026$, $p=.050$; PS: $t=2.302$, $p=.026$). Furthermore, the scores on the visual-perceptual tasks were significantly lower for this group (Beery visual motor integration: $t=-2.337$, $p=.024$; Beery visual perception: $t=2.465$, $p=.022$). For the attentional functions, a significantly lower performance for selective attention ($t=2.711$, $p=.011$) was found for the group with ongoing seizures, as well as for the accuracy ($t=2.121$, $p=.043$) as the reaction time ($t=3.066$, $p=.005$) of this task.

Table 4.3 Differences between seizure free patients and patients with ongoing seizures.

Test	Seizure-free patients (n=43)		Patients with ongoing seizures (n=18)		Seizure free vs.ongoing seizures
	Mean	SD	Mean	SD	p
WISC-III VIQ	98.5	11.5	86.1	12.8	.006*
WISC-III PIQ	94.7	13.2	82.9	14.8	.021*
WISC-III FSIQ	95.7	12.9	82.5	14.6	.008*
WISC-III VR	100.3	11.5	88.2	12.6	.007*
WISC-III PO	94.7	13.5	84.6	14.6	.050*
WISC-III PS	99.2	17.0	86.3	14.0	.026*
Beery VMI	89.6	10.3	81.3	11.0	.024*
Beery VP	101.4	14.9	83.7	15.8	.022*
Beery MC	89.3	15.6	82.8	18.7	n.s.
AVLT IR (number correct)	42.4	9.5	38.1	10.3	n.s.
AVLT DR (number correct)	8.7	2.9	7.8	2.9	n.s.
Auditory RT DH (ms)	342.0	70.6	404.6	113.8	n.s.
Auditory RT NDH (ms)	337.4	75.7	364.8	77.9	n.s.
Visual RT DH (ms)	377.7	80.0	421.1	101.2	n.s.
Visual RT NDH (ms)	423.32	123.4	476.3	103.0	n.s.
CVST (sec)	24.4	12.8	24.2	11.4	n.s.
Bourdon-Vos (reaction time)	16.2	5.4	17.1	6.7	n.s.
Teach Sky Search (number correct)	9.8	2.5	7.6	2.9	.043*
Teach Sky Search (time)	9.8	2.6	6.7	2.7	.005*
Teach Sky Search (attention score)	9.6	2.8	6.6	2.8	.011*
Teach Score! (number correct)	6.8	2.8	7.1	4.1	n.s.
Teach Creature Counting (number correct)	8.7	2.7	7.6	2.5	n.s.
Teach Creature Counting (time)	6.8	3.5	5.5	4.2	n.s.
Teach Sky Search DT	9.2	3.0	9.6	2.7	n.s.

TEA-Ch scores are shown in standard scores (mean:10, sd:3). AVLT: auditory verbal learning test, CVST: computerized visual searching task, DH: dominant hand, DR: delayed recall, DT: double task, FSIQ: full scale IQ, IR: immediate recall, MC: Motor Coordination, ms: milliseconds, NDH: non-dominant hand, NS: not significant, PIQ: performance IQ, PO: perceptual organization, PS: performance speed, RT: reaction time, sec: seconds, Teach: test of everyday attention for children, VIQ: verbal IQ, VMI: visual motor integration, VP: visual perception, VR: verbal reasoning, WISC: Wechsler intelligence scale for children. *p<.05.

Cognitive profile of ethosuximide

The significant lower scores on higher-order cognitive functions (such as intelligence and visual perceptual reasoning) in the total study population could be explained as seizure effects (or effects of a different underlying aetiology) because these functions scored significantly lower in patients with ongoing seizures than in patients in remission. The impaired fluid cognitive functions, such as activation, alertness, sustained auditory attention, and speed of attentional switching, could not be explained by the seizures/aetiology (did not differ between for seizure-free patients or patients with ongoing seizures) and may therefore be considered as the cognitive effects of ethosuximide. This is also shown in Figure 4.1, in which almost all cognitive domains of the seizure-free patients were within the normal range (z-score between -1

and +1) and were therefore not impaired, except for these fluid functions (which were below a z-score of -1).

Figure 4.1 Cognitive profile of ESM (in z-scores, between -1 and 1 is within the normal range) shows impaired alertness for ESM (scores below -1 which were not affected by the seizures). VIQ: Verbal IQ, PIQ: Performance IQ, FSIQ: Full Scale IQ, VR: Verbal Reasoning, PO: Perceptual Organization, PS: Performance Speed, VMI: Visual Motor Integration, VP: Visual perception, MC: Motor Coordination, AVLT: Auditory Verbal Learning Test, IR: immediate recall, DR: delayed recall, RT: reaction time, DH: dominant hand, NDH: non-dominant hand, CVST: computerized visual searching task, nr: number, DT: double task.

Discussion

Although ethosuximide is one of the oldest AEDs, its effect on cognition has not yet been established in great detail. A recent RCT assessing the efficacy of ethosuximide against other drugs used in absence seizures such as valproic acid and lamotrigine, suggested ethosuximide was superior.³ This was because of the higher adverse event rates and negative effects on attention found for valproic acid. However, only one attentional task was used in this comparative RCT. Hence, comprehensive information about the cognitive effects of ethosuximide is lacking.²²

Therefore, our study investigated the cognitive profile of ethosuximide monotherapy in children. By comparing the results for patients in remission with those for patients with ongoing seizures, the effects of the seizures could be separated from the effects of ethosuximide. Ethosuximide affected fluid 'attentional' functions, especially psychomotor speed and alertness. This type of side-effect is relatively mild with respect to interference with development and learning and does not differ from similar effects in other AEDs such as carbamazepine or oxcarbazepine.^{15,22,23} Apparently, mild

impairments in alertness and attentional function leading to cognitive slowing is a general reaction to AEDs.¹⁴

A previous study also showed (mild and temporary) attentional problems in a small group of children with idiopathic generalized epilepsy (mostly absence seizures) compared with the non-treatment baseline.¹³ However, whether this resulted from AED use or the epilepsy itself was unclear as patients included in this study were not seizure free and ethosuximide was used in most, but not all, patients. In two recent RCTs, the higher rate of attentional dysfunction found on one attentional task for valproic acid compared with ethosuximide or lamotrigine after 16-20 weeks of treatment¹⁰ persisted after 12 months of treatment.¹¹ This confirms our conclusions that cognitive effects for ethosuximide are mild.

Presumably, the main shortcoming of this study is that we did not assess the neuropsychological profile at baseline before ethosuximide treatment was started, which means we cannot compare performance on cognitive tests. This study was performed at a tertiary referral clinic wherein treatment was already started in most patients at referral as most received medication as soon as EEG findings confirmed the diagnosis. Furthermore, treatment effects on cognition can only be investigated in patients with absence seizures who are in remission. Results of an untreated baseline or an early baseline would always be a mixed bag of seizures effects and medication effects. Further confounding factors and methodological issues limit the interpretation of our study. Why some patients were more resistant to treatment than others is unknown. Although all patients had an idiopathic epilepsy, the underlying aetiology may nevertheless have an effect in patients with ongoing seizures. The gold standard design in this type of research would, of course, be an RCT with longitudinal follow-up. However, this is difficult to realize with a relative 'old drug'. Even with new medications, the initial regulatory trials almost never include cognition as an outcome measurement. Therefore, the 'next best' is then to study the effects in a naturalistic setting with limited protection against bias. As cognitive effects are important factors in medical decision making, we recommend that, in the development of new AEDs, cognition always be used as outcome measure in the industry driven RCTs.

Our study is the first that suggest a cognitive profile of ethosuximide and reveal an impact on attentional functions, especially on psychomotor speed and alertness. Such effects do interfere with development, learning and academic achievement, but only mildly compared with the effects of drugs on higher-order functions such as the effect of topiramate on language. As ethosuximide is considered a first-line therapy for absence seizures in childhood, and drug-induced cognitive impairment may interfere with development, learning and academic achievement, these findings are of interest to clinicians who prescribe this drug, especially when informing parents.

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Chapter 5

Cognitive and behavioural impact of the ketogenic diet in children and adolescents with refractory epilepsy: a randomized controlled trial

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Abstract

Purpose

The ketogenic diet (KD) is increasingly used for the treatment of refractory epilepsy in childhood because of the beneficial effect on seizure reduction. The aim of the current study was to objectively assess cognition and aspects of behavior during the first 4 months of a randomized controlled study in children and adolescents.

Methods

Participants from a tertiary epilepsy center were randomized to a KD group (intervention) or a care as usual (CAU) group (control). Follow-up assessments on cognition and behavior were performed approximately 4 months after initiation of the KD with a combination of parent report questionnaires and individually administered psychological tests for the children.

Results

A total of 50 patients were included for this study, 28 patients from the KD group and 22 patients from the CAU group. The KD group showed lower levels of anxious and mood-disturbed behavior and was rated as more productive. Cognitive test results showed an improvement of activation in the KD group.

Conclusion

This study showed a positive impact of the KD on behavioral and cognitive functioning in children and adolescents with refractory epilepsy. More specifically, an activated mood and cognitive activation were observed in patients treated with the KD.

Introduction

Epilepsy is a neurological disorder that is treated with antiepileptic drugs (AEDs) in the majority of the patients. However, AEDs are sometimes not efficacious. About one third of patients suffer from intractable epilepsy.¹ Furthermore, patients often experience side-effects that lead to discontinuation of the drug.² For these patients alternative nonpharmacological treatment options are available, including the ketogenic diet (KD). The KD was developed in the 1920s as a treatment for refractory epilepsy when few AEDs were available. The KD is a high-fat, low-carbohydrate diet that imitates the metabolic state of fasting while maintaining a normal number of calories. Body energy requirements while on a KD are met by lipolysis and β -oxidation of fatty acids rather than by the breakdown of carbohydrates. The exact anticonvulsant mechanism of action of the KD has not yet been elucidated.³ Side-effects of the KD are in the gastrointestinal domain such as constipation and vomiting.⁴

The effect of the KD has been studied in multiple observational studies⁵⁻¹⁰, reviews¹¹⁻¹⁵, and three randomized controlled trials (RCTs).^{4,16,17} The RCT of our study group showed that the KD was effective during the first four months in children and adolescents with refractory epilepsy compared with the care-as-usual (CAU) group. The most often reported side-effects were gastrointestinal symptoms. The focus of these studies is mainly on analyzing efficacy. Less attention has been paid to possible negative or positive effects of KD on behavioral function.

In the observational studies, the majority of parents reported improvements during treatment with the KD in their child's behavior¹⁸ and cognitive function,^{19,20} particularly with respect to attention/alertness,^{18,20} activity level, and socialization.^{20,21} Furthermore, the KD improves sleep quality in children with therapy-resistant epilepsy. The improvement in sleep quality seems to contribute to the improvement in attentional behavior.²² However, all these studies were focused on only one aspect of behavior and used only by-proxy reports with parent-rated questionnaires.

One study that used a combination of individually administered cognitive-oriented psychological tests and parent report questionnaires showed small trends toward improvement in the cognitive functioning and toward worsening in psychosocial adjustment.²³ However, the study group was small and there was no comparison with CAU. Therefore, the aim of the current study was to assess cognition and behavior in a prospective randomized controlled study in both children and adolescents.

Methods

Study population

Patients were children and adolescents with intractable epilepsy. Patients were eligible to participate if they met the following criteria: aged between 1 and 18 years and having uncontrolled seizures after trying two or more AEDs. Details of the exclusion criteria can be found elsewhere.²⁴ Eligible candidates and their parents were referred by their attending physician to the multidisciplinary KD team at epilepsy center Kempenhaeghe in the Netherlands, where they received detailed information about the study before giving their informed consent. This study has been approved by the ethics committee of the Academic Medical Center Utrecht, the Netherlands.

Procedure

Between July 2010 and August 2014, subjects were randomized to either the KD or to CAU after a 1-month baseline period. The KD group started after the baseline period with the ketogenic diet. The controls were treated and monitored according to good clinical practice. Both patient groups continued to take their AEDs without changes during baseline (except when medically indicated), during the 4 months waiting of the CAU group, and during the first 4 months of treatment with the KD. Assessments were performed at baseline, before randomization, and after a 4-month study period.

Mood and behavior

- The Profile of Mood States (POMS) was developed to identify and assess transient, fluctuating affective mood states: tension/anxiety, depression/dejection, anger/hostility, vigor/activity, fatigue/inertia and confusion/bewilderment. The POMS contains 65 self-report items using the 5-point Likert Scale. The test is used by proxy and requires parents to indicate for each word or statement how their child have been feeling in the past week. A higher score represents more mood impairment.²⁵
- The Personal Adjustment and Role Skills Scale – Third Edition (PARS-III) was specifically developed to measure psychosocial adjustment in children with chronic physical illness.²⁶ This instrument is a brief parent-completed index of youth psychosocial adjustment. The 28 items include six subscales: peer relations, dependency, hostility, productivity, anxiety-depression, and withdrawal. Higher scores indicate better psychosocial adjustment. The PARS-III is a reliable and valid index of youth psychosocial adjustment and can be used for both clinical screening and research purposes.²⁷
- The Strengths and Difficulties Questionnaire (SDQ) is a brief parent-reported behavioral screening questionnaire that provides balanced coverage of children and

young people's behaviors, emotions, and relationships.²⁸ The SDQ asks about 25 attributes that are divided into five relevant dimensions: namely emotional symptoms, conduct problems, hyperactivity, peer relations, and prosocial behavior. For all scales, except the prosocial scale, a higher score indicates more problems.

- The Hague Restrictions in Childhood Epilepsy Scale (HARCES) is a parent completed 10-item scale to assess impairments in daily functioning that are related to epilepsy.^{29,30} The scale measures the number of restrictions imposed because of seizures. Items reflect the frequency with which the child takes part in activities such as swimming, riding a bicycle, staying elsewhere overnight, and participating in physical education. The scale focuses on the extent to which epilepsy affects a child's ability to take part in everyday childhood activities. Respondents rate each item according to the degree to which the child's activity is limited by epilepsy; a higher score means more disabilities. Furthermore, parents are asked to rate the severity of the seizures, from not severe (low score) to very severe (highest score).
- The Social Emotional Questionnaire (SEV) is a DSM-IV oriented questionnaire to assess four domains of behavioral and social emotional dysfunction: attention deficit and hyperactivity disorders, oppositional defiant behavior and conduct disorders, anxiety and depression, and autism spectrum disorders.³¹ The questionnaire consists of 72 items and yields total scores for each of the four domains. A higher score indicates more problems.

Neuropsychological assessment

- The Dutch version of the Peabody Picture Test (PPVT-III) assesses receptive vocabulary.³² The child has to point to one of four pictures corresponding to the examiner's stimulus word. Raw scores can be converted to age-equivalent standard scores (mean:100, standard deviation: 15). This measurement is often used as a reliable predictor of general cognitive functioning in children and adults.³³
- The Beery Developmental Test of VMI is a widely used paper-and-pencil test that assesses the extent to which individuals can integrate their visual and motor abilities.³⁴ Subjects are asked to copy a developmental sequence of 24 geometric forms. Raw scores are converted into standardized scores (mean: 100, standard deviation: 15).
- Additionally, different subtests from the FePsy neuropsychological computerized test battery were conducted.³⁵ *Simple reaction time measurements* on either visual (a white square) or auditory stimuli assess alertness functions and speed of activation of the information processing system. In the *binary choice reaction test*, the subject has to react in a different way to two dissimilar stimuli (a red square presented on the left side of the screen and a green square presented on the right side) which assesses the speed of central information processing. In both tasks, reaction times in milliseconds are provided (with a higher score indicating a slower reaction time). In the *tapping task*, speed of finger tapping is measured for the index finger of the right

and left hands, separately. Number of taps is recorded and a higher score indicates more motor activation and fluency.

Statistical analysis

Data analyses were performed using SPSS version 21 for Windows. The level of significance was set at $p < .05$ (p-values were 2-sided). Independent t-tests were performed to check for differences between the KD group and the CAU group at baseline and at end-point (4 months). Correlations between seizure reduction and the behavioral and cognitive data were investigated using Pearson's correlations.

Results

Between August 2010 and August 2014, a total of 58 patients were included in the study. One patient dropped out of the study before randomization, and seven patients dropped out after randomization: six from the CAU group (because of dissatisfaction regarding the randomization result) and one patient from the KD group (because of spontaneous seizure reduction), leaving 50 patients who were investigated at baseline (28 patients from the KD group (56%) and 22 patients from the CAU group). The demographic and clinical characteristics of the study population are shown in Table 5.1. Furthermore, of these 50 included patients, eight patients dropped out before the study endpoint of 4 months (five patients from the KD group and three patients from the CAU group). The effectiveness of the KD in our study population is described elsewhere.¹⁷

Mood and behavior

The results of the mood and behavior questionnaires are provided in Table 5.2.

On the POMS, differences between groups at baseline were found. Patients randomized to the KD group had higher tension/anxiety levels, higher anger/hostility levels, and higher confusion/bewilderment levels. These differences were not statistically significant at the 4-month follow-up because of the reduction in anxiety/tension/hostility levels in the KD patients. At the 4-month follow-up, the patients from the KD group had a higher score on the subscale 'vigor' ('energy') than the patients from the CAU group ($p = .005$). There was a positive correlation with seizure reduction in the KD group ($r = .622$, $p = .004$). The greater the seizure reduction, the higher the vigor score.

On the PARS, no significant differences were found at baseline. At the 4-month follow-up, parents reported for the KD group a higher score on the subscale 'productivity' than for the CAU group ($p = .039$). There was no significant correlation with seizure reduction.

Table 5.1 Demographic and clinical characteristics at baseline.

	KD N=28	%	CAU N=22	%
Gender				
Male	20	71.4	9	40.9
Female	8	28.6	13	59.1
Age				
at trial initiation (range)	7.6 (2.1-16.5)		8.1 (1.1-15.7)	
at seizure onset	2.3 (0-8)		1.9 (0-10)	
Type of epilepsy				
Syndrome	10	35.7	4	18.2
Generalized	5	17.9	6	27.3
Localization related	13	46.4	12	54.5
Etiology of epilepsy				
Genetic	7	25	1	4.5
Structural-metabolic	2	7.1	10	45.5
Unknown	19	67.9	11	50
Seizure frequency during baseline				
<1 month	1	3.6	0	-
≥1 month	3	10.7	3	13.6
≥1 week	14	50	16	72.7
Daily	10	35.7	3	13.6
Number of AEDs tried before start AED				
Three	3	10.7	4	18.2
Four	4	14.3	5	22.7
Five	9	32.1	3	13.6
Six	5	17.9	3	13.6
Seven	2	7.1	1	4.5
Eight	4	14.3	2	9.1
Nine	1	3.6	4	18.2
Number of AEDs at start KD				
None	0	-	1	4.5
One	3	10.7	4	18.2
Two	13	46.4	8	36.4
Three	9	32.1	5	22.7
Four	3	10.0	2	9.1
Five	0	-	2	9.1
Type of KD				
Classical	2	7.1		
MCT	20	71.4		
Only Ketocal	5	17.9		
Mixture	1	3.6		
VNS tried before KD				
Yes	1	3.6	1	4.5
No	27	96.4	21	95.5
Epilepsy surgery in the past				
Yes	1*	3.6	0	-
No	29	96.4	22	100

KD: Ketogenic diet, CAU: Care as usual, AEDs: Antiepileptic drugs, MCT: Medium-chain triglycerides, VNS: Vagus nerve stimulator, ADHD: Attention deficit hyperactivity disorder, ADD: Attention deficit disorder.

* One patient from the KD-group had a corpus callosotomy in the past.

There were no significant differences between the groups on the SDQ, either for the baseline and the 4-month follow-up assessments.

On the HARCES, no differences were found at baseline. At the 4-month follow-up, the severity of the seizures of the KD group was reported as less severe compared to the CAU group ($p=.038$). There was a negative correlation with seizure reduction in the KD group ($r=-.718$, $p\leq.000$). The more severe the seizures were perceived, the less the seizure reduction.

On the SEV, no differences were found at baseline. At the 4-month follow-up, parents reported less anxious and mood disturbed behavior for the KD group than for the controls ($p=.049$). There was no significant correlation with seizure reduction.

Table 5.2 Differences in mood and behavior between KD vs. CAU.

Assessment	Baseline			Endpoint		
	KD	CAU	p	KD	CAU	p
POMS tension / anxiety	11.39	7.15	.005*	9.20	9.63	n.s.
POMS depression / dejection	9.35	7.15	n.s.	6.47	5.71	n.s.
POMS anxiety / hostility	10.39	6.62	.042*	8.80	8.13	n.s.
POMS vigor / activity	19.39	19.29	n.s.	20.86	16.50	.005*
POMS fatigue / inertia	9.67	7.93	n.s.	8.20	8.63	n.s.
POMS confusion / bewilderment	11.00	6.08	.005*	8.27	9.38	n.s.
PARS-III peer relations	8.68	7.87	n.s.	8.36	8.00	n.s.
PARS-III dependency	10.37	9.27	n.s.	9.92	8.33	n.s.
PARS-III hostility	18.37	18.00	n.s.	18.62	17.83	n.s.
PARS-III productivity	8.58	7.07	n.s.	9.31	7.42	.039*
PARS-III anxiety-depression	19.26	18.40	n.s.	20.77	18.17	n.s.
PARS-III withdrawal	11.53	11.80	n.s.	13.31	12.92	n.s.
SDQ emotional symptoms	3.43	2.54	n.s.	2.00	2.50	n.s.
SDQ conduct problems	1.86	1.15	n.s.	1.31	1.83	n.s.
SDQ peer relations	3.33	2.31	n.s.	2.75	2.83	n.s.
SDQ hyperactivity	6.10	6.54	n.s.	4.81	4.92	n.s.
SDQ prosocial behavior	6.47	6.54	n.s.	7.31	7.00	n.s.
HARCES restrictions	25.80	25.21	n.s.	24.06	23.00	n.s.
HARCES rating severity of seizures	8.24	8.32	n.s.	6.06	7.29	.038*
SIDAED general CNS	5.44	3.77	n.s.	3.90	3.11	n.s.
SIDAED behavior / increased irritability	3.25	2.45	n.s.	1.59	1.44	n.s.
SIDAED depressive symptoms	2.07	2.00	n.s.	0.90	1.94	n.s.
SIDAED cognitive functions	9.85	7.71	n.s.	6.25	7.29	n.s.
SIDAED motor coordination	1.89	1.59	n.s.	0.90	1.22	n.s.
SIDAED visual complaints	0.00	0.27	n.s.	0.00	0.11	n.s.
SIDAED headache	1.07	0.43	n.s.	0.25	0.39	n.s.
SIDAED cosmetic and skin	2.07	2.86	n.s.	1.27	2.44	n.s.
SIDAED gastrointestinal complaints	2.29	1.68	n.s.	3.29	1.44	.000*
SEV attention deficit and hyperactivity	29.85	28.69	n.s.	26.60	25.22	n.s.
SEV social problem behavior	16.65	13.00	n.s.	15.67	10.78	n.s.
SEV anxious and mood-disturbed behavior	13.45	12.92	n.s.	8.73	15.22	.049*
SEV autistic behavior	8.10	7.69	n.s.	5.93	7.78	n.s.

* $p<.05$, n.s.: not significant.

Neuropsychological investigation

Table 5.3 shows the neuropsychological differences between both groups at baseline and endpoint. At baseline and endpoint, a statistically significant difference was found between the KD group and the control group for word comprehension on the Peabody Picture Test (baseline: $p=.036$, endpoint: $p=.006$). Patients from the KD group had a higher score than patients from the control group. There was no significant correlation with seizure reduction. At baseline, significantly higher scores were found on two of the four simple reaction time activation tests for the KD group. These differences disappeared at the 4-month follow-up because of improvement of scores in the KD group.

Table 5.3 Differences in neuropsychological investigation between KD vs. CAU.

Assessment	Baseline			Endpoint		
	KD	CAU	p	KD	CAU	p
PPVT-III	92.67	81.27	.036*	96.30	82.56	.006*
Beery VMI	85.93	81.40	n.s.	87.73	81.56	n.s.
FePsy auditory reaction time DH	672.85	445.44	.031*	474.40	455.22	n.s.
FePsy auditory reaction time NDH	649.23	484.11	n.s.	564.90	487.67	n.s.
FePsy visual reaction time DH	757.58	572.78	n.s.	624.10	517.29	n.s.
FePsy visual reaction time NDH	785.33	567.89	.023*	745.60	566.86	n.s.
FePsy binary choice reaction time	671.38	518.78	n.s.	564.40	579.00	n.s.
FePsy tapping DH	32.86	34.78	n.s.	34.42	34.34	n.s.
FePsy tapping NDH	30.79	30.22	n.s.	34.12	29.89	n.s.

* $p<.05$, n.s.: not significant, DH: dominant hand, NDH: non-dominant hand.

Discussion

This RCT shows a positive cognitive and behavioral effect of the KD in children and adolescents. With respect to mood, patients on the KD showed higher levels of mood problems at baseline. These problems, however, disappeared at the 4-month follow up because of reduction in anxiety/tension/hostility levels in the KD patients. With respect to social emotional functioning, patients from the KD group showed lower levels of anxious and mood-disturbed behavior at 4 months, which were independent of the improved seizure control. Furthermore, they had a higher productivity at 4 months (e.g. continued working until it was finished and even though it was difficult without encouragement) which was also independent of the seizure reduction. Cognitive test results showed a higher receptive vocabulary for patients randomized to the KD at 4 months, which already existed at baseline and was independent of the improved seizure control. This seems to be a baseline characteristic of the patients without a relation to the KD. Furthermore, patients on the KD showed slower reaction times at baseline. This mental slowing, however, disappeared at the 4-month follow-up because

of improvement of activation of the KD patients and appears not to be an effect of improved seizure control. Both patient groups continued to take their AEDs without changes. Therefore, these findings could not be an effect of the medication. Figure 5.1 summarizes the obtained KD-related effects on mood and cognition.

Figure 5.1 Summary of the KD effects on mood and cognition.

To our knowledge, this is the first RCT that evaluated the cognitive and behavioral effect of the KD versus a control group. Furthermore, little research is done in this area in children and adolescents, which makes it difficult to compare our results with previous findings. The activated cognition found in our study is consistent with previous reports of children on the KD showing increased mental alertness^{18,21,36,37}, improved attention^{20,21}, and improved cognition.^{19,20,23} The activated mood and behavior during the KD is consistent with previous findings reporting improvement in activity level and socialization²¹ but in contrast with an earlier observational study.²³ Based on these improvements, extensive objective neuropsychological investigation and systematic questionnaires during the KD seem to be unnecessary. However, this was a group approach. Of course, there is some interindividual variability, so vigilance with monitoring of cognitive functions and emotional well-being is always advised. Furthermore, it is not clear how these effects evolve over the long-term. Therefore, further research focusing on the chronic effects of the KD on cognition and behavior of children is needed.

This study has some limitations. Both the classical and MCT KD protocols was used. However, these are comparable in efficacy and tolerability.³⁸ The dropout rate in our

study population is 16% and therefore relatively high. However, previous research showed that 96% of the KD users who discontinued the diet would recommend this nonpharmacological treatment option to others,³⁹ and more than half of them recommend starting the KD before trying AEDs. This indicates that, although compliance to the KD is difficult because of practical issues, the KD is recommended. We used by-proxy measures for assessing the impact of the KD on behavior which could be influenced by the efficacy of the diet. Therefore, the results were correlated with seizure reduction. Although the KD group had a significantly higher level of cognitive functioning than the CAU group, we used neuropsychological tests which could be used in the majority of the patients because they matched their cognitive age and chronological age levels which made comparison of the results across the study population possible.

In conclusion, this RCT showed a positive impact of the KD on behavioral and cognitive functioning in children and adolescents with refractory epilepsy. Moreover, some improvements during treatment with the KD were observed in this study population. This activated mood and cognitive activation was not related to reduction in seizure frequency and corresponds with the well-known effects of the KD. It also contributes to the growing motivation for consideration of the KD as a treatment option in childhood refractory epilepsy.

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Chapter 6

Long-term impact of antiepileptic drug treatment on cognitive development

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Submitted

Abstract

Purpose

Children with epilepsy are at increased risk for cognitive impairment and difficulties in learning that may affect school performance, in which long-term anti-epileptic drug (AED) therapy likely plays a role. This study focused on the impact of long-term AED treatment, specifically with carbamazepine (CBZ) and valproate (VPA), on cognitive development.

Methods

Epilepsy patients aged 6-16 years, who were treated ≥ 6 months with monotherapy CBZ or VPA from the epilepsy onset and without any switch to other medication in the past were included in this cross-sectional study. Outcome measures included the Wechsler Intelligence Scale for Children-III (WISC-III) and other cognitive tests assessing alertness, information processing speed and memory.

Results

In total, 50 patients aged 6-16 were included (CBZ $n=21$ and VPA $n=29$). The two groups did not differ in demographical and epilepsy related characteristics such as gender, type of epilepsy, seizure frequency, age, drug load, and duration of drug treatment. Patients on CBZ had significantly lower intelligence values than patients on VPA. There were no other differences found in the cognitive profile.

Conclusion

Our study suggested that chronic use of AEDs has a detrimental impact on cognitive development during childhood, possibly through accumulating effect of drug-induced impairments on cognitive developmental processes.

Introduction

Cognitive impairment is a common problem in patients with epilepsy.¹ Children with epilepsy have a higher risk of learning disabilities and poor academic performance, because of the neurological disorder and related issues.² The etiology of cognitive impairment in people with epilepsy is multi-factorial. Many factors such as premorbid brain dysfunction, age at onset, etiology, type, frequency, severity, and duration of seizures and treatment can adversely affect cognition.^{1,3} Cognitive side-effects of the antiepileptic drugs (AEDs) have emerged as an important consideration when an AED is being selected for the treatment of childhood epilepsy.⁴ The first formal studies on the cognitive side effects of AEDs were published in the early 1970's⁵ and many followed since then. However, most regulatory trials are carried out in adults,⁶ even recently, which limits the generalization of findings to children.⁷

The cognitive effects of AEDs are, therefore, still in debate. Carbamazepine (CBZ) and valproate (VPA), commonly used first line AEDs in newly diagnosed epilepsy, are considered to have comparable and mild effects on cognitive functioning.⁸⁻¹⁰ However, there have been reports that in children the outcome is less favourable for CBZ over a longer period of time.^{4,11,12}

Most studies, however, have a limited duration with trial durations mostly not exceeding the 12 weeks period and base the detrimental effects of CBZ on non-controlled extensions of trials. Meanwhile, there still remains a large contrast between the average trial duration that has provided us with the current knowledge and clinical practice with treatment durations of years instead of weeks. In the past, concern has been expressed about long-term effects of AED use on cognitive development in children.^{13,14}

Theoretically, children are potentially more susceptible to the adverse effects of AEDs than adults because of the potential effect of AEDs on brain maturation and hence on neurodevelopment. Subtle effects on the fluid cognitive functions leading to attentional or arousal deficits could, therefore, accumulate over time and result in deficits in higher-order cognitive functions such as memory or learning.^{2,3,15} Early identification of possible long-term AED-induced impacts on cognitive development is crucial to avoid future negative educational, occupational and social outcomes.¹⁶ During the development of oxcarbazepine, a compound related to CBZ, similar concerns were expressed by the regulatory agents and therefore a trial was designed with much longer duration and cognitive development (among others intelligence) as outcome.^{17,18} However, also that trial was limited to six months, which is still in contrast with normal treatment duration in clinical practice.

Our study, therefore, focused on the impact of long-term AED treatment, specifically with CBZ and VPA, on cognitive development in children with epilepsy. Long-term is defined in our study as ≥ 6 months of treatment.

Methods

Subject selection

Epilepsy patients aged 6-16 years who were referred to a tertiary referral centre for epilepsy and were treated ≥ 6 months with monotherapy CBZ or VPA were included in this cross-sectional study. Only patients were included who had been on monotherapy CBZ or VPA from the epilepsy onset and without any switch to other medication in the past. Data about demographical and clinical characteristics were collected through medical records.

Type of epilepsy was divided in localization related epilepsy (cryptogenic, symptomatic or idiopathic), generalized epilepsy (idiopathic) or not yet classified (non-classified). Seizure frequency was divided in three groups; seizure free for at least 6 months, a seizure reduction of $\geq 50\%$ or seizure reduction of $< 50\%$. Drug load for each individual patient was estimated as the sum of the prescribed daily dose (PDD)/defined daily dose (DDD), where DDD corresponds to the assumed average maintenance daily dose of a drug prescribed for its main indication (World Health Organization).¹⁹

Assessment procedures

The assessment procedure consisted of two types of tests, see Table 6.1. Tests that have been demonstrated to be sensitive to cognitive side-effects of AEDs. These tests assess fluid functions (functions that are state-dependent and can easily fluctuate), such as attentional function, speed of central information processing, psychomotor speed and alertness.²⁰ To assess possible long-term effects of AEDs on development, tests were used measuring higher-order stable cognitive function: memory and intelligence.

Furthermore, the Wechsler Deterioration Index (WDI) was used to estimate the premorbid intellectual ability of our study population.^{21,22} The WDI for each individual patient was estimated, which subtracts the sum of the scaled scores on the 'hold' subtests from those achieved on 'don't hold' subtests/ 'hold' subtests. 'Hold' subtests (Vocabulary, Information, Object Assembly, and Picture Completion) were thought to be insensitive to deterioration in cognitive or brain functions, while 'don't hold' subtests (Digit Span, Similarities, Coding, and Block Design) were felt to decrease significantly in the face of insults to brain functions.²³

Table 6.1 Assessment protocol.

Fluid state-dependent functions	Psychomotor speed / alertness / attention	Simple reaction time measurements: the patients had to react as quickly as possible on auditory stimuli that were presented at random intervals by the computer, activation and alertness are measured by these tests and a strong motor component is involved. ²⁴
	Central information processing speed	Binary choice reaction-time measurement: a reaction time test with a decision component. The patient has to react differentially to a red square on the left side of the screen and to a green square at the right side of the screen. The reaction time does not only reflect motor speed, but also the decision making process. ²⁴ Computerized visual searching task: an adaptation of Goldstein's Visual Searching Task. A centred grid pattern has to be compared with 24 surrounding patterns. Only one of them is identical to the target pattern. The test consists of 24 trials and gives an indication of the information processing speed and perceptual mental strategies. ²⁴
Higher-order cognitive functions	Intelligence	Processing Speed from the WISC-III. ²⁵ Wechsler Intelligence Scale for Children-III measures intellectual ability which is expressed in Full Scale IQ (FSIQ), Verbal IQ (VIQ), Performance IQ (PIQ) with a mean IQ:100, SD:15. ²⁵
	Memory	The 15 word test, a Dutch version of the Rey Auditory Verbal Learning Test (AVLT): a list of 15 words is orally presented five times. After every presentation, immediate recall (IR) is requested. A delayed recall (DR) is requested after a 20 minutes interval. ²⁶

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS, version 21.0 for Windows). To check if there are any differences between both groups in demographical and epilepsy related characteristics Pearson's chi-square tests were performed for the categorical variables (gender, type of epilepsy, seizure frequency) and independent samples t-tests were used for the continuous variables (age, drug load, and duration of drug treatment). Differences in test results between the two groups were analyzed with two-sided independent samples t-tests. Significance level was set at the 5% level.

Results

Demographics

We enrolled a total of 50 children in this study: the total cohort consists of 21 patients using CBZ and 29 patients using VPA. In both treatment groups, the mean age at start treatment was 7 years (range 4-15). The mean duration of AED treatment was approximately two years (with a range from 6 months up to 8 years). The clinical and

demographic characteristics of these groups are summarized in Table 6.2. The two groups did not differ in demographical and epilepsy related characteristics such as gender, type of epilepsy, seizure frequency, age, drug load, and duration of drug treatment. Furthermore, the WDI showed no significant difference between the CBZ group and the VPA group ($t=.209$, $p=.835$), which indicated that there was no difference in premorbid intellectual ability between both groups.

Table 6.2 Demographical and clinical characteristics.

		CBZ-group (n=21)		VPA-group (n=29)		p	
		N	%	N	%		
Gender	Male	8	38.1	11	37.9	n.s.	
	Female	13	61.9	18	62.1		
Type of epilepsy	Cryptogenic localization related	8	38.1	9	31	n.s.	
	Symptomatic localization related	1	4.8	4	13.8		
	Idiopathic localization related	6	28.6	4	13.8		
	Idiopathic generalized	1	4.8	7	24.1		
	Non-classified	5	23.8	5	17.2		
Seizure frequency	Seizure free >6 months	12	57.1	17	58.6	n.s.	
	Seizure reduction $\geq 50\%$	8	38.1	12	41.4		
	Seizure reduction <50%	1	4.8	0			
Age (in years)		M	SD	Range	M	SD	Range
	At assessment	10.1	2.6	6-15	10.3	2.8	6-16
	At onset epilepsy	6.3	3.1	1-12	6.2	3.8	1-15
	At start treatment	7.8	2.4	4-12	7.7	3.1	4-15
AED	Daily dosage (mg)	553.3	240.6	120-960	760.3	358.1	160-1800
	Drug load	.55	.24	.12-.96	.51	.24	.11-1.20
	Duration of AED use (years)	1.86	1.6	0-6	2.1	2	0-8

n.s.: not significant

Neuropsychological test results

When the two treatment groups were compared, no significant differences were found on the fluid, state-dependent functions such as alertness and information processing speed, see Table 6.3. On the stable, higher-order cognitive function, no significant differences in memory performance were found between the CBZ group and the VPA group. For intelligence values, the CBZ group scored significantly lower than the VPA group (FSIQ $t = -2.264$, $p = .028$, VIQ: -2.328 , $p = .024$), see Figure 6.1.

Table 6.3 Neuropsychological test results.

	Assessment	CBZ		VPA		p
		Mean	SD	Mean	SD	
Fluid state-dependent functions	Auditory reaction time DH (ms)	331.6	101.1	325.8	86.1	n.s.
	Auditory reaction time NDH (ms)	363.8	108.9	357	115.4	n.s.
	Binary choice reaction time (ms)	430.5	83.5	448.7	147	n.s.
	CVST (sec)	18.9	8.4	23.5	14.7	n.s.
	Processing Speed (WISC-III)	88.9	17.5	94.6	19.4	n.s.
Higher-order cognitive functions	AVLT IR	40.9	14.1	42.4	13.5	n.s.
	AVLT DR	8.0	3.7	8.4	3.6	n.s.
	FSIQ	84.8	14.2	93.1	11.8	.028*
	VIQ	85.8	12	94	12.4	.024*
	PIQ	87	16.5	93.9	12.3	n.s.

DH: dominant hand, NDH: non dominant hand, ms: milliseconds, CVST: computerized visual searching task, AVLT: auditory verbal learning task, IR: immediate recall, DR: delayed recall, FSIQ: full scale IQ, VIQ: verbal IQ, PIQ: performance IQ, n.s.: not significant. * $p < .05$

Figure 6.1 Outcome of IQ of patients with monotherapy CBZ or VPA.

Discussion

This clinical comparative cohort study investigated the long-term impact of AED treatment on cognitive development in children. Two types of results were found: on tests assessing fluid, state-dependent functions we did not find statistically significant differences between children treated with CBZ versus children treated with VPA. This confirms earlier reports of no differences between these AEDs on such functions.^{7,10} Our study showed that this remains stable over time. Although there were no differences found, this only expresses equivalence but still may imply that both drugs impair such fluid function to the same extent. Moreover, it has been suggested that such effects could accumulate over longer periods.¹⁷ Consequently, these accumulating

effects can potentially affect stable, higher-order cognitive functions. On tests assessing higher-order and more stable cognitive functions, our study demonstrated an effect on intelligence, specifically for CBZ. Children on CBZ scored statistically significantly lower on intelligence measures than children on VPA. More specifically, the difference between the two AEDs for Verbal IQ and Full Scale IQ were statistically significant but not for Performance IQ which includes more fluid cognitive functions and emphasizes more on speed factors.

Our results are consistent with Piccillini et al. (2010) who found that children treated with CBZ, but not with VPA, had a mild deterioration of IQ after one year of therapy.¹² Forsythe and co-workers (2001) found that carbamazepine in moderate dosage adversely affected memory in children, whereas VPA did not.¹¹ The USA study of Mandelbaum et al. (2009) reported a persistence of impairment of reaction times when children with newly diagnosed localisation-related epilepsy were treated with CBZ over a period of one year.⁴ This was compared to a non-drug baseline. Our results are inconsistent with previous findings of Chen et al. (2001) who found no significant differences in the WISC-R between VPA and CBZ treated for one year, and after complete withdrawal of the treatment.⁹ However, that study only included seizure free children while our study included children with an active epilepsy.

Our findings confirmed the hypothesis by Drane and Meador (1996) who suggested that dysfunction in areas such as arousal, attention, and psychomotor functioning can contribute to deficits in higher cognitive processes such as memory and learning over time.¹⁵ Loring and Meador (2004) concluded from their studies that long-term AED therapy is at least one of the components that contribute to the increased risk for cognitive impairment, and difficulties in learning that may affect school performance in children with epilepsy.²

Knowledge of the mechanisms of action of AEDs is essential to explain the occurrence of side-effects.²⁷ Cross (2010) concluded that AEDs may have different effects in the immature brain because of its impact on neuroreceptor function which may interfere with normal maturation.¹³ One explanation for the cognitive effects on the long-term may be found in the different mechanisms of action of these drugs. VPA is predominantly a GABA-ergic drug with a more temporarily effect whereas CBZ stabilize the inactive form of the voltage ion channel,²⁸ inducing a more permanent change. Currently, we use Magnetic Resonance Spectroscopy (MRS) that enables *in vivo* measurements of neurotransmitter and other brain metabolite concentrations and may provide us more insight in the metabolism of AEDs. Another explanation may be found in brain activity, as assessed by functional Magnetic Resonance Imaging (fMRI). In adult epilepsy patients, chronic epilepsy causes cognitive deficits in intellectual functioning, by loss of network efficiency.²⁹ The role of AED use remained unclear in such studies but must certainly not be underestimated.

The main shortcoming of this study is that we did not assess the neuropsychological profile at baseline, before AED treatment was started. Because this study was

performed at a tertiary referral clinic, treatment was already started in most patients at referral. We used the WDI to estimate the premorbid intellectual ability of our study population. There was no significant difference in the WDI between the treatment groups at baseline, before treatment was started. Additionally, in a limited number of children (5 on CBZ and 7 on VPA) we did have data on their intelligence prior to treatment. These data also suggested no differences in IQ's between the CBZ and the VPA group before treatment was started. It may be assumed that these groups were comparable in their intellectual performance before antiepileptic drug treatment was started.

To conclude, our study emphasized the need to study effects of chronic AED use, especially in children. Furthermore, our study suggests that chronic use of AEDs has a detrimental impact on cognitive development during childhood and may impact higher-order cognitive functions and even intelligence, possibly through accumulating effect of drug-induced impairments of fluid function on cognitive developmental processes.

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Part III

Clinical relevance of subjective reports

Chapter 7

Subjectively perceived side-effects of antiepileptic drugs in chronic refractory epilepsy

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Abstract

Purpose

Antiepileptic drugs (AEDs) can cause side-effects. Patient-reported side-effects due to this type of medication are very common, but thus far only investigated in community based populations. We investigated the subjectively perceived side-effects of anti-epileptic drug treatment in patients with refractory epilepsy.

Methods

A non-selected group, of patients visiting the outpatient department between September 2011 and November 2011 was invited to complete a questionnaire only if they had experienced side-effects of their AED treatment during last year. The questionnaire, the SIDAED, assessed four different categories; cognition, mood, cosmetics and general health. Subgroup analyses were based on their medication use: mono- or polytherapy, older and newer AEDs and AEDs with a high or a low risk for cognitive and behavioral/mood side-effects.

Results

In total, 203 patients or their relatives completed the questionnaire. Mean age of the patients was 37 years (2-81). Most reported complaints (85%) were about their general health followed by cognition, mood and cosmetics. Subgroup analyses showed no differences between patients using monotherapy or polytherapy. Also, no differences were found between patients using older AEDs or newer drugs. Patients using AEDs with a high risk for side-effects, did complain more about their mood but not about their cognition. Regression analysis showed that using a high risk AED for behavioral side-effects contributed significantly to the total experienced side-effects.

Conclusion

In conclusion, our study illustrates that patients are a reliable respondent to indicate side-effects despite of their refractory epilepsy. Particularly, mood complaints due to antiepileptic drugs (such as levetiracetam) are correctly noticed.

Introduction

The best possible outcome of antiepileptic drug (AED) treatment is to achieve complete seizure freedom without adverse events. However, AEDs are frequently accompanied by a variety of side-effects. The prevalence of AED-related subjective complaints in routine clinical practice in a community-based population was almost 60%.¹ The two domains which yielded the highest prevalence of complaints are general CNS-related complaints (68%) and cognitive complaints (62%). The most frequently reported complaints within the general CNS-related domain are fatigue and tiredness. Memory problems and concentration difficulties are most frequently reported within the cognitive domain. Mood and behavioural complaints such as agitation or irritability and depression are reported less frequently (22%). Another study reported a prevalence of 67% of moderate to severe subjective complaints of patients who were considered to be well-controlled (defined as unchanged medication for the last six months).² Cognitive complaints were reported most frequently. Furthermore, patients on polytherapy reported more side-effects than patients on monotherapy.¹⁻³

The new antiepileptic drugs such as lamotrigine (LTG), levetiracetam (LEV), oxcarbazepine (OXC), gabapentin (GBP), pregabalin (PGB) and lacosamide (LCS) seem to be similar to the older compounds in efficacy, but superior in tolerability.⁴ Cognitive complaints, related to confirmed cognitive dysfunction has been reported with almost all the older drugs and especially for phenobarbital (PB), phenytoin (PHT) and vigabatrin (VGB).^{4,5} Some newer AEDs such as topiramate (TPM) and zonisamide (ZNS) are also known to cause significant cognitive side-effects: both have diffuse cognitive effects, as well as specific effects on language and memory.⁵⁻⁹ This concurs with the patient-reported cognitive side-effects that are more common with TPM, followed by ZNS and phenytoin (PHT) and are least likely to be reported with GBP, valproate (VPA), LTG and carbamazepine (CBZ).¹⁰⁻¹¹ Furthermore, the newer anti-epileptic drug LEV is known for its high-risk to cause mood effects.¹²⁻¹³ Mood side-effects are therefore most common in patients-reports with (LEV).^{14,15} The subjective reports about these drugs seem to be by and large equivalent to measured cognitive effects of these AEDs.^{16,17}

Negative consequences of the antiepileptic drugs necessitate interventions ranging from minor interventions such as drug switches to very expensive hospitalization. It is estimated that side-effects due to antiepileptic drugs have a major impact on health care costs which can be as high as €20.751 (US \$26.675) per patient per year.¹⁸ It is desirable to reduce these costs to a level as low as possible. Earlier studies already showed that side-effects are more important for patients than efficacy in long-term treatment and that long-term retention time is mainly based on subjectively perceived side-effects.¹⁹ Previous research showed also that subjectively perceived side-effects about cognitive functions are used as a sensitive screening instrument for clinical practice which can help to identify who is at risk and needs further referral for neuropsychological assessment while keeping the burden on financial and time

resources to a minimum.²⁰ This allows screening at an early stage and minimizes the use of expensive assessment facilities.

In addition to the community-based studies from our group,^{1,2,21} we attempted to investigate the impact of subjective complaints in a hospital-based study, in patients with chronic refractory epilepsy. In the community based studies most patients were in remission or they had only infrequent seizures and most were on low dose monotherapy. In the patient population of a tertiary referral center most patients have frequent seizures, are afraid of status epilepticus, and often use high dosing polytherapy. Within this study we also focused on subgroup comparisons. Firstly, a combination of AEDs can produce negative interactions which can lead to side-effects. Separate subgroup analyses were, therefore, performed to check for differences between patients on monotherapy or polytherapy. Secondly, as side-effects of AEDs are claimed to have less effects in the newer generation of AEDs, differences between the newer and older generation of AEDs were compared. Thirdly, some drugs are known to have a higher risk for side-effects than others. Therefore a high-risk group was compared with a low-risk group.

Methods

Procedure

All epilepsy patients using antiepileptic drugs, who visited our tertiary epilepsy center Kempenhaeghe, Heeze, The Netherlands, between September 2011 and November 2011, received a patient information letter by mail including an invitation to complete a questionnaire.¹⁸ Patients were invited to complete the questionnaire only when they had experienced side-effects of the AEDs during the previous 12 months. The questionnaire could either be completed digitally via the internet or on paper. For young children and patients with severe mental retardation, proxy measures were used. All participants (patients, parents or caregivers) gave their informed consent.

Questionnaire

The questionnaire was specifically developed for this study and was subdivided into five different categories of commonly reported side-effects. The SIDE effects of AED treatment questionnaire (SIDAED)², developed by our group, was used as the basis for the questionnaire. The original 10 side-effect categories of the SIDAED were compressed into four categories in order to focus on the most commonly reported side-effects. The categories used in this study were: cognition, cosmetic, mood and general health (i.e. general CNS, vision, headache, gastrointestinal, sexuality/menses complaints).

Subgroup and statistical analysis

The subgroup analyses were performed using independent t-tests with SPSS version 21.0, Chicago, IL, USA. A p-value of ≤ 0.05 was considered significant. Linear regression analysis was used to evaluate the impact of the treatment factors (mono vs. polytherapy, old vs. new AEDs and cognitive/behavioral high vs. low risk AEDs) on the total number of complaints.

Results

Demographic and clinical characteristics

In total, 1386 epilepsy patients received the request to complete a questionnaire. In total, 210 patients completed the questionnaire. Although we asked patients only to fill out the questionnaire when they had experienced any side-effect during the previous 12 months, seven patients returned the forms reporting no side-effects. These patients were excluded from the analysis, yielding a total of 203 patients reporting side-effects (14.6%).

Main characteristics of the 203 patients are shown in Table 7.1. Mean age was 37 years, with a range from 2 to 81 years. Most patients were treated with polytherapy (range 2-6 AEDs). Most patients used LTG as AED during the last 12 months, followed by LEV, CBZ, VPA and CLB. OXC, TPM, PHT, PGB, GBP, LCS, PB and ethosuximide (ESX) were used less frequently. AEDs that were only used by one patient were primidone, ZNS, VGB and acetazolamide. These drugs were grouped as 'other drugs' (3.0%). Most of the patients were treated with a combination of an older (such as CBZ, VPA, PB, PHT, ETX or benzodiazepines) and a newer (such as LTG, LEV, OXC, GBP, PGB, LCS, TPM) anti-epileptic drug during the last 12 months. Table 7.2 shows that in monotherapy LTG, VPA, CBZ and LEV are mostly used and OXC and TPM are used less frequently.

Based on the literature,^{16,17,22} we grouped PB, PHT, TPM, ZNS, and VGB as drugs with a high risk for side-effects. The other AEDs are grouped as AEDs with a low risk for side-effects except LEV which is known for its behavioral effect but has no cognitive side-effects.²³ Therefore, this drug is only added in the behavioral high risk group and not in the cognitive high risk group. During the last 12 months 16% of the patients used at least one of the cognitive high risk drugs and 46.8% of the patients used at least one of the behavioral high risk AEDs.

Table 7.1 Demographic and clinical characteristics (N=203).

	N	%
Age mean (range)	37 (2 – 81)	
Gender		
Male	101	49.8
Female	102	50.2
Mono vs polytherapy		
Monotherapy	67	33.0
Polytherapy	136	67.0
Number of different AEDs per patient		
Two	71	35.0
Three	40	19.7
Four or more	25	12.3
AED use during the last 12 months		
LTG	77	37.9
LEV	68	33.5
CBZ	68	33.5
VPA	65	32.0
CLB	50	24.6
Other BZP	15	7.4
OXC	27	13.3
TPM	15	7.4
PHT	10	4.9
PGB	11	5.4
GBP	8	3.9
LCS	7	3.4
PB	7	3.4
ESX	6	3.0
Other AEDs	5	2.5
Old versus new AEDs		
Old AEDs	48	23.6
New AEDs	54	26.6
Combination of old and new AEDs	101	49.8
Low risk versus high risk AEDs		
Cognitive low risk AEDs	170	83.7
Cognitive high risk AEDs	33	16.3
Behavioral low risk AEDs	108	53.2
Behavioral high risk AEDs	95	46.8

LTG: lamotrigine, LEV: levetiracetam, CBZ: carbamazepine, VPA: valproate, CLB: clobazam, BZP: benzodiazepines, OXC: oxcarbazepine, TPM: topiramate, PHT: phenytoin, PGB: pregabalin, GBP: gabapentin, LCS: lacosamide, PB: phenobarbital, ESX: ethosuximide. Old AEDs: CBZ, VPA, BZP, PB, PHT, ESX. New AEDs: LTG, LEV, OXC, GBP, PGB, LCS, TPM. High-risk AEDs: PB, PHT, TPM, ZNS, VGB. LEV is only added for the behavioral high-risk AEDs.

Table 7.2 AED use in monotherapy patients.

	N	%
LTG	14	20.9
VPA	13	19.4
CBZ	13	19.4
LEV	12	17.9
OXC	6	9.0
TPM	4	6.0
CLB	3	4.5
PHT	1	1.5
Other BZP	1	1.5

LTG: lamotrigine, VPA: valproate, CBZ: carbamazepine, LEV: levetiracetam, OXC: oxcarbazepine, TPM: topiramate, CLB: clobazam, PHT: phenytoin, BZP: benzodiazepines.

Type of side-effects

The largest group of patients (38%, n=78) reported problems in three of the five categories, 24% (n=49) reported to have side-effects in two of the categories, 23% (n=47) reported side-effects in four of the categories, 12% (n=24) reported problems in one of the five categories and five patients (3%) reported to have problems in all categories (see Figure 7.1). Most of the patients (85%) had experienced some kind of general health side-effect due to AEDs during the last 12 months, such as sleep problems and fatigue, motor and balance problems, headache and dizziness (see Table 7.3). Cognitive side-effects were the second most commonly reported problem among the patients (77%). Most described cognitive complaint was memory problems and to a lesser extent concentration problems, language difficulties, mental slowing and problems with information processing. Behavioral side-effects were reported in 69% of the patients. Most commonly described mood complaint was a depressive mood, irritable and angry or agitated behavior. Cosmetic side-effects such as skin rash, weight problems and gum problems occurred in 42% of the patients and 7% reported other side-effects that could not be classified. Only in the cosmetic category of the questionnaire there was a significant difference between males and females. More females reported cosmetic problems during the last 12 months ($t=-2.229$, $p=.027$). Only in the mood category, there was a significant negative correlation found for age ($r=-.141$, $p=.044$); the younger the patients, the more mood complaints were reported.

Figure 7.1 Number of side-effects.

Table 7.3 Type of side-effect and complaints.

	N	%	Type of complaints	% *
General health complaints	172	84.7	Fatigue and sleep problems	62
			Motor and balance problems	29
			Headache	24
			Dizziness	23
			Gastrointestinal problems	14
			Nausea	13
Cognitive complaints	157	77.3	Memory problems	73
			Concentration problems	29
			Language difficulties	25
			Mental slowing	13
Mood complaints	139	68.5	Depressive mood	37
			Irritable and angry behavior	36
			Agitated behavior	20
			Mood swings	16
			Aggressive behavior	13
			Anxious behavior	5
Cosmetic complaints	86	42.4	Skin rash	45
			Weight problems	44
			Problems with gums	26
			Hair loss	15
			Itch	4
			Shaking hands	4

* patients can have problems in more than one area.

Subgroup analyses

No differences were found between the mono- and the polytherapy group; patients on polytherapy did not report more side-effects than patients on monotherapy (see Table 7.4). For the comparison between the older and the newer AEDs, patients who used a combination of these medication regimens were not taken into account. There were also no differences between the old and new AEDs; patients who used older AEDs did not experience more side-effects than patients who were treated with newer AEDs.

Furthermore, there were also no differences between the cognitive risk groups; the cognitive high risk group did not report more side-effects than the cognitive low risk group. However, there was a significant difference between the behavioral risk groups for the mood complaints ($t=-2.776$, $p=.006$) and total number of complaints ($t=-2.221$, $p=.027$); patients from the behavioral high risk group did have significantly more problems than patients from the behavioral low risk group, especially concerning their mood.

Table 7.4 p-values for the different subgroup analyses.

Type of side-effect	mono vs. poly	old vs. new	Cognitive low risk vs. high risk	Behavioral low risk vs. high risk
Cognition	.772	.699	.492	.235
Mood	.549	1.000	.305	.006*
General health	.466	.955	.614	.843
Cosmetic	.309	.962	.696	.620
Total	.248	.991	.925	.027*

* $p \leq .05$

Linear regression analysis

Thus far, each comparison was made independently from the other treatment regimen. However, subgroup divisions are correlated. Therefore, regression analysis was performed with total number of complaints as dependent variable and 1) mono vs. polytherapy, 2) old vs. new AED, 3) cognitive high vs. low risk AED and 4) behavioral high vs. low risk AED as predictors. A backward procedure was used. Although both the cognitive and behavioral high vs. low risk AEDs contributed significantly (F -value:3.044, $p=.05$), the procedure identified a one-factor solution as the strongest predictor of the total complaints: a behavioral high risk AED (F -value:4.932, $p=.027$). The total percentage of explained variance was 2.4%.

Discussion

This study compared subjective reported side-effects among different AED treatments in a population referred to a tertiary epilepsy center. No more than 15% of the patients who visited the outpatient clinic reported to have side-effects. It is unlikely that this is due to the absence of side-effects. Rather this percentage reflects the weight the patients with chronic refractory epilepsy attribute to side-effects. Side-effects are commonly reported in community based studies in which the majority of the patients are in remission. In our population, much more importance is probably attributed to the seizures and, hence, the importance of the efficacy of the drugs.

Of the patients who did report side-effects, most had experienced some complaints in their general health, cognition or mood due to their AEDs during the last 12 months. Cosmetic side-effects occurred in a minority of the patients; more in females than males which is consistent with previous literature.²⁴ In our specific population, polytherapy did not induce more complaints than monotherapy. This is inconsistent with previous literature who did report more side-effects¹⁻³ and a lower quality of life²⁵ for polytherapy. This probably again illustrates a different efficacy/tolerability attribution in our patient group compared to studies in the community. Furthermore, the generation of the AEDs (older versus newer) was not relevant. The newer AEDs have been thought to have decreased the incidence of certain side-effects such as cosmetic side-effects when compared with older antiepileptic medication.^{24,26} However, previous research showed that there was no difference between patients using newer versus classic AEDs in their quality of life.²⁵ Moreover, patients with a high-risk AED for cognitive side-effects did not complain more about their cognitive functions than patients with a cognitive low-risk AED. However, when LEV was added to this high risk AED group, patients with a high risk AED for behavioral side-effects did complain more about their mood than patients with a behavioral low-risk AED. As shown in our regression analysis, using a high risk AED for behavioral side-effects contributed significantly to the total experienced side-effects. Note, however, that the percentage explained variance is low, indicating that the complaints are also related to other factors, in this group probably the epilepsy. The mood complaints of patients using LEV treatment were an essential factor in our study and is in line with a number of studies and meta-analyses.²⁷⁻³⁰ LEV had an adverse event profile within the range of the other older drugs like PHT but with a different profile; self-reported anger and hostility were particularly frequent.^{13,15}

The primary limitation of our study stem from self-reporting. The side-effects were subjectively reported. Our study therefore critically relied on the validity and reliability of subjective self-report as no formal neuropsychological testing was used. Nevertheless, this is a naturalistic situation and the assessment of possible side-effects of AEDs in routine daily care of patients with epilepsy is based on these same self-reports which can be used as a sensitive screening instrument.²⁰

In conclusion, our study illustrates that patients are a reliable respondent to indicate side-effects despite of their refractory epilepsy. Particularly, mood complaints due to antiepileptic drugs (such as LEV) are correctly noticed.

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Chapter 8

Cognitive adverse effects of antiepileptic drug treatment; how to recognize who is at risk

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Abstract

Introduction

Patients with epilepsy can have major benefits from AEDs. Cognitive adverse effects and subjective complaints are very common. Being able to predict which patient is at risk for developing cognitive adverse effects would be of great value in avoiding unnecessary cognitive tests. The aim of this study was to determine the profile of patients at risk for developing cognitive adverse effects of AED treatment in chronic epilepsy.

Method

In this cross-sectional study, patients with localisation related epilepsy taking lamotrigine or levetiracetam (low risk group) and phenytoin or topiramate (high risk group) were included. A neuropsychological assessment was used to evaluate the cognitive impairments and questionnaires were used to assess mood and subjective perceived adverse effects.

Results

This study included 53 patients (low risk group n=32 and high risk group n=21). The high risk group had a significantly slower information processing speed than the low risk group. No other significant differences in cognition, mood or subjective complaints were found. A backward linear regression analysis identified duration of epilepsy and subjectively complaints of the AED treatment as the strongest indicators of mental slowing for the whole study population.

Conclusion

This study confirms that patients taking high risk AEDs have drug-induced cognitive impairment, expressed as slowing of central information processing. This mental slowing can be predicted by a longer duration of epilepsy and the presence of subjectively perceived adverse effects of the AED treatment. Although there were some methodological issues, this study revealed that patients with chronic epilepsy complaining about their AED treatment may be regarded as being at risk for developing cognitive adverse effects. In clinical practice, further neuropsychological assessment is indicated for these patients.

Introduction

Epilepsy is treated in the majority of patients with AEDs. One of the complications of AED-treatment is the occurrence of adverse effects. Cognitive adverse effects are among the most frequent complaints by patients¹ as well as the most frequently demonstrated drug-induced impairments.² In general, these adverse effects involve 'fluid' attentional-type of functions, especially slowing of central information processing.³ The risk of impaired cognition due to AED treatment differs between AEDs.^{2,4} AEDs considered to have a high risk for cognitive adverse effects are for example phenytoin (PHT) and topiramate (TPM), especially relative to low risk AEDs such as lamotrigine (LTG) and levetiracetam (LEV).⁵⁻¹⁰ These latter drugs may even have activating effects on cognition. Drugs such as carbamazepine (CBZ), oxcarbazepine (OXC), or valproate (VPA) can be regarded as intermediate drugs.¹¹⁻¹⁴

Although some of the epilepsy guidelines advise to monitor for cognitive adverse effects when administering high risk drugs,¹⁵ many patients may not experience such effects while patients taking low risk drugs may have serious cognitive adverse effects.^{16,17} Apparently, risk category alone is not a sufficient predictor for cognitive problems which are also influenced by other factors. Ortinski and Meador (2004) reported that an earlier onset of seizures leads to more severe cognitive adverse effects of AEDs, possibly due to a longer accumulation of effects.¹⁸ In addition, not only the type of medication, but also drug load may negatively affect cognitive function.¹⁹ Furthermore, the mood status of patients may impact the perception of the cognitive adverse effects and lead to more complaints.^{20,21}

Being able to predict which patient is at risk for developing cognitive adverse effects could be of great value in avoiding unnecessary cognitive tests, when a review of antiepileptic medication might be more appropriate. The important question is whether cognitive adverse effects of AED treatment can be predicted by risk category alone or in combination with other factors. Other possible factors include the severity of the epilepsy, additional treatment characteristics such as drug load, or subjective complaints of the AED treatment. The present study was therefore set up to determine the risk profile of patients for developing cognitive adverse effects of AED treatment in chronic epilepsy in a cross-sectional study design.

Methods

Patients

All patients were consecutively included from the outpatient clinic of our tertiary epilepsy centre (Kempenhaghe). All subjects gave written informed consent and approval by the local Medical Ethical Committee was obtained. The inclusion criterion

for this study was localization-related epilepsy which was treated with AEDs. The following patient data were collected: gender, age, educational level (converted into the American education system), epilepsy characteristics (duration and type of epilepsy, type of seizure and seizure frequency), and AED use. These drugs were subdivided into two risk categories based on the cognitive risk:^{2,22} LEV and LTG were included in the 'low risk' category, and PHT and TPM in the 'high risk' category. Patients were allowed to use one add-on drug of the mild category (CBZ, OXC or VPA). Drug load was calculated for each individual patient as the sum of the prescribed daily dose (PDD)/defined daily dose (DDD), where DDD corresponds to the assumed average maintenance daily dose of a drug, prescribed for its main indication.²³

Neuropsychological assessment

A neuropsychological test battery was used which included tasks that have been demonstrated to be sensitive for cognitive adverse effects, because they assess fluid functions such as alertness, attention, and central information processing speed. Furthermore, we included tests that assess psychomotor speed, memory, language and cognitive ability, because high risk drugs may also impact the higher-order cognitive functions.² We used questionnaires to measure mood and subjective complaints about AED treatment.

Alertness / attention / information processing speed

- Simple Reaction-Time Measurement: The reaction time for simple auditory tones or visual stimuli is measured.²⁴
- Binary Choice Reaction Test (BCRT): The subject has to react differentially to a red square, presented on the left hand side of the computer screen, then to a green square, presented on the right side.³
- Computerised Visual Searching Task (CVST): The task consists of finding a grid pattern out of 24, which matches the one in the centre of the screen.³

Psychomotor speed

- Finger Tapping Test: Speed of finger tapping is measured for the index finger of the dominant hand; five times for a period of 10 seconds each.³

Memory

- Recognition of words and figures: Six words and four figures are presented. After a delay, the target item has to be recognised amongst a series of distracters.²⁴
- The Rey's Auditory Verbal Learning Test (AVLT), testing memory and learning.²⁵ A list of 15 words is orally presented five times. After every presentation, immediate recall is requested. A delayed recall is requested after a 20 minutes interval.

Language

- The Lindeboom Naming task; naming of images, measuring word retrieval.²⁶

Cognitive abilities

The Raven's Standard Progressive Matrices, measuring global cognitive functioning.²⁷ It provides a measure of the capacity to observe, solve problems, and learn. This test includes multiple choice tests of abstract reasoning in which patients are asked to identify the missing element required to complete a pattern.

Mood

- Profile of mood states (POMS), Dutch language version measures state-dependent mood changes for the previous week according to adjectives.²⁸ Ratings are scored for six mood states: tension-anxiety, depression-dejection, anger-hostility, fatigue-inertia, confusion-bewilderment and vigour-activity. A Total Mood Disturbance (TMD) can be calculated by adding the scores for Tension, Depression, Anger, Fatigue and Confusion and then subtracting the score for Vigour.

Subjective complaints

- SIDAED (SIDEffects of AEDs). Three categories from the original version were included; behaviour (increased irritability), depressive symptoms and cognitive function.²⁹ For each item the patient rates the severity of the complaint on a four-point Likert scale (0=no problem, 1=mild, 2=moderate, or 3=serious problem).
- The A-B neuropsychological assessment schedule (ABNAS) measures seven critical domains of cognition (tiredness/fatigue, hyper-excitability, slowing (mental and motor), memory impairment, attention disorders, and impairment of motor coordination and language disorders).³⁰ For each item, the patient rates the severity of the complaint, again on a four-point Likert scale.

Subgroup and statistical analysis

Statistical analyses were performed with SPSS version 21 for Windows (SPSS Inc., Chicago, IL, USA). To check if there are any differences between the treatment groups in demographical and epilepsy related characteristics, independent samples t-tests were used for the continuous variables (age, drug load, and duration of epilepsy), and Pearson's chi-square tests were performed for the categorical variables (gender, educational level, type of epilepsy and seizure, seizure frequency). Furthermore, independent samples t-tests were performed to check for differences between the groups on the neuropsychological test results and the questionnaires. Backward linear regression analyses were applied to determine which measurements predicted

cognitive adverse effects and which patients were at risk for developing drug-induced cognitive adverse effects.

Results

Demographics and clinical characteristics

In total, 53 patients were included in this study. The demographic and clinical characteristics are summarized in Table 8.1. The groups differed significantly in age; patients from the high risk group were older than the low risk group ($p=.018$). There were no significant differences in gender, educational level, duration of epilepsy, type of epilepsy or seizures, seizure frequency or drug load.

Table 8.1 Demographics and clinical characteristics.

		Low risk (n=32)	High risk (n=21)	p
Gender (%)	Male	12 (37.5)	8 (38.1)	n.s.
	Female	20 (62.5)	13 (61.9)	
Age	At assessment (SD)	42.8 (13.4)	51.9 (12.9)	.018*
	Range	22-69	20-69	
	At onset epilepsy (SD)	16.8 (14.2)	20.6 (13)	n.s.
	Range	2-68	6-52	
	Duration of epilepsy (SD)	26.1 (13.1)	31.5 (15.7)	n.s.
	Range	1-52	1-59	
Educational level (%)	Elementary school	2 (6.3)	1 (4.8)	n.s.
	High school diploma	4 (12.5)	4 (19.0)	
	Associate's degree	14 (43.8)	10 (47.6)	
	Bachelor's degree	12 (37.5)	6 (28.6)	
Type of epilepsy (%)	Symptomatic	11 (34.4)	6 (28.6)	n.s.
	Non symptomatic	21 (65.6)	15 (71.4)	
Type of seizures (%)	Tonic-clonic	22 (68.8)	13 (61.9)	
	Other	10 (31.3)	8 (38.1)	
Seizure frequency (%)	Weekly	1 (3.1)	-	n.s.
	Monthly	6 (18.8)	1 (4.8)	
	Annually	6 (18.8)	4 (19.0)	
	Seizure free	19 (59.4)	16 (76.2)	
AED (%)	Monotherapy	16 (50.0)	8 (38.1)	n.s.
	Polytherapy	16 (50.0)	13 (61.9)	
	LTG	19 (55.9)	-	
	LEV	13 (38.2)	-	
	TPM		5 (23.8)	
	PHT		16 (76.2)	
Add-on	CBZ	11 (34.4)	6 (28.6)	
	OXC	3 (9.4)	-	
	VPA	2 (6.3)	6 (28.6)	
	Drugload (SD)	1.6 (.7)	1.5 (.7)	

* $p<.05$, n.s.: not significant.

Neuropsychological assessment

Most neuropsychological functions were in the normal range, except the reaction times on visual stimuli and the CVST reaction time, which were slower than normal for the high risk group. Furthermore, the outcomes of most tasks were not significantly different between the groups (Table 8.2). Only the CVST, a test assessing speed of central information processing, showed a significant difference between the low and the high risk group; patients from the high risk group performed this task significantly slower ($t=-2.053$, $p=.045$). Furthermore, a trend was found on the auditory reaction time test ($t=-1.924$, $p=.065$), which assesses activation.

Table 8.2 Neuropsychological assessment.

Assessment	Low risk Mean (SD)	High risk Mean (SD)	p
Auditory reaction time DH (ms)	240.6 (51.4)	283.3 (93.0)	n.s.
Auditory reaction time NDH (ms)	236.2 (53.3)	257.1 (95.3)	n.s.
Visual reaction time DH (ms)	310.4 (50.8)	321.1 (70.3)	n.s.
Visual reaction time NDH (ms)	319 (65.3)	344.9 (117.4)	n.s.
Binary choice reaction time (ms)	468.9 (124.6)	487.5 (174.6)	n.s.
CVST reaction time (sec)	13.3 (5.4)	16.6 (5.9)	.045*
Tapping DH	54.5 (8.1)	55.9 (9.0)	n.s.
Tapping NDH	50.3 (8.0)	50.9 (9.3)	n.s.
Recognition words	19.0 (3.3)	18.3 (3.5)	n.s.
Recognition figures	7.1 (2.1)	7.0 (2.0)	n.s.
Rey AVLT immediate recall	40.9 (8.1)	40.7 (8.8)	n.s.
Rey AVLT delayed recall	8.1 (2.6)	8.1 (3.2)	n.s.
Raven total number correct	43.3 (5.9)	43.5 (5.5)	n.s.
Lindeboom Naming Task	14.8 (.5)	14.6 (.9)	n.s.

* $p<.05$ DH: dominant hand, NDH: non-dominant hand, ms: milliseconds, sec: seconds, n.s.: not significant.

Mood and subjective complaints

There were no significant differences in mood or subjective complaints between the two treatment groups (see Table 8.3). Patients did not differ in their reported adverse effects of AED-treatment concerning their cognition (mental slowing, memory, attention, language), behaviour and mood (fatigue or hyper-excitability).

Linear regression analyses

To confirm the results presented in Table 8.2, but to remove the effect of shared correlation between the tests, a linear regression analysis was performed. Only tests considered sensitive to drug effects,³ i.e. tests assessing fluid functions (auditory reaction time, visual reaction time, BCRT, CVST), were included. The cognitive risk category was used as dependent variable. A backward procedure was used. The procedure identified a two-factor solution as the strongest indicator of the cognitive

risk category: the CVST and the auditory reaction-time task (F-value: 3.061, $p=.037$). This is in line with the results of t-testing as presented in Table 8.2. However, the auditory reaction task has the strongest effect ($r=.289$, $p=.018$), followed by the CVST ($r=.276$, $p=.023$).

We subsequently created a new variable which was called the 'mental slowing score', defined as the sum of the auditory reaction time performed with the dominant hand and the reaction time for the CVST. A higher score indicates more mental slowing. In a second step, a linear regression analysis was performed with the mental slowing score as dependent variable and age as demographic variable (because of the age-difference between the groups), duration and type of epilepsy as indicators of the epilepsy severity, drug load as medication factor, total mood disturbance as indicator of mood and subjective complaints (sum of total ABNAS-score and total SIDAED-score) as independent variables. A backward procedure was used. The procedure identified a two-factor solution as the strongest predictor of mental slowing: duration of epilepsy and subjective complaints (F-value: 4.262, $p=.020$). The total of subjective complaints ($r=.302$, $p=.015$) had the strongest effect, followed by duration of epilepsy ($r=.223$, $p=.056$).

Table 8.3 Mood and subjective complaints.

Questionnaires	Low risk Mean (SD)	High risk Mean (SD)	p
POMS tension/anxiety	12.2 (4.9)	10.1 (5.7)	n.s.
POMS depression/dejection	9.5 (7.9)	10.9 (12.9)	n.s.
POMS anxiety/ hostility	9.1 (6.6)	8.1 (8.5)	n.s.
POMS vigor	18.4 (6.0)	18.1 (6.6)	n.s.
POMS fatigue	8.4 (5.4)	6.9 (6.0)	n.s.
POMS confusion	10.7 (4.9)	9.2 (5.1)	n.s.
POMS total mood disturbance	31.6 (26.1)	27.1 (32.8)	n.s.
ABNAS number of complaints	10.6 (6.9)	8.7 (7.6)	n.s.
ABNAS total	15.8 (14.3)	14.0 (15.1)	n.s.
SIDAED number of complaints	6.1 (4.6)	6.6 (5.6)	n.s.
SIDAED behaviour	2.1 (2.3)	1.6 (2.9)	n.s.
SIDAED depressive symptoms	1.8 (2.5)	2.4 (2.8)	n.s.
SIDAED cognitive functions	5.7 (5.4)	6.8 (6.9)	n.s.
SIDAED total	19.1 (15.7)	18.9 (20.7)	n.s.

n.s.: not significant

Discussion

Patients taking AEDs with a high risk for cognitive adverse effects had a slower information processing speed than patients taking low risk AEDs. Linear regression analysis revealed that mental slowing was determined by two tasks, namely the CVST

and the auditory reaction task. This drug-induced mental slowing appeared to be predicted by subjective complaints and the duration of epilepsy.

Our results are in line with previous neuropsychological studies that consistently identify 'speed factors' as the most sensitive area in relation to drug treatment.³¹⁻³³

Only the CVST and simple reaction time measurements showed a significant effect and are therefore useful parameters to screen for cognitive adverse effects of AEDs, which is consistent with previous findings.³ Moreover, this study confirms that the presence of subjective complaints due to AED-treatment is a reliable indicator of cognitive adverse effects.^{1,30} Subjective complaints in patients with chronic epilepsy should therefore be taken seriously and should lead to referral for neuropsychological assessment. This study confirms furthermore that a longer duration of epilepsy is associated with more drug-induced cognitive impairments.^{18,34}

Previous research of our group using fMRI showed that chronic epilepsy is associated with global brain network changes and impaired white matter connectivity.^{35,36}

Although the effects of AEDs were not separately investigated in this study, one can speculate that the resulting vulnerable brain may be more susceptible to adverse effects of AEDs. So far, there is a scarcity of fMRI studies investigating drug-related changes of brain activity and function.³⁷ The mechanisms underlying the cognitive effects caused by AEDs are therefore poorly understood. Further research needs to investigate the neuronal mechanisms underlying this cognitive impairment due to AED-treatment, which may explain why cognitive functioning of some patients with epilepsy is impaired by AEDs while it is not affected in other patients.³⁸

There are some confounding factors and methodological issues that limit the interpretation of our study. Although duration of epilepsy was included in this study, treatment had already been started in most patients at referral because this study was performed at a tertiary referral clinic. It is therefore unknown when treatment was started in our study population. Although the sample size was relatively small, especially in the high risk group, it allowed us to detect moderate effects.³⁹ Undoubtedly, more effects would have been detected with larger sample sizes, however, not necessarily increasing the clinical relevance of our findings. Furthermore, our findings were in line with our expectations based on literature; slowing of central information processing is an important cognitive 'marker' of AED-induced side-effects and longer duration seems to represent chronicity of treatment. Although we tried to include comparable patients groups, age was not equally distributed across treatment groups, suggesting that our study population was biased, which is another limitation of our study. However, patients did not differ in their educational level and global cognitive functioning (as assessed with the Raven test), which suggests that these groups are comparable in their performance on general neuropsychological tests. Moreover, regression analysis in which age was included, showed that age did not significantly contribute to cognitive impairment in AED-treated patients.

In conclusion, this study confirms that patients taking high risk AEDs have more drug-induced cognitive impairments, expressed as slowing of central information processing. This mental slowing can be predicted by a longer duration of epilepsy and the presence of subjectively perceived adverse effects of AED-treatment. In clinical practice, patients with chronic epilepsy complaining about their AED-treatment may be regarded as being at risk for developing cognitive adverse effects in which further neuropsychological assessment is indicated.

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Chapter 9

**Effect of chronic high risk antiepileptic drug use on
functional status; a ten year follow-up study using
the Barthel Index**

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Submitted

Abstract

Background

The prevalence of epilepsy among people with ID is much higher than in the general population. Chronic treatment with high risk medication is more common in this population. The aim of this longitudinal, clinical study is to investigate the impact of 'high risk' AEDs on functional status in patients with ID.

Methods

The Barthel Index was used yearly to assess the functional status of every adult patient with epilepsy who lived in the long-stay care facility of Kempenhaeghe. Number and type of seizures were also recorded. Phenobarbital, levetiracetam, phenytoin, topiramate were selected as 'high risk' AEDs. Other AEDs were classified as 'low risk' medication.

Results

There was a consistent trend on the long-term for lower functional status for the 'high risk' AED-group. The decreasing Barthel scores over the ten year period was not affected by AED regimen or type of seizures, but due to an increasing age and related to level of ID.

Conclusion

In comparison to the demographic effects of the patients, AED-treatment has no impact on the functional status in patients with epilepsy and ID. Furthermore, chronic use of high risk AEDs does not lead to a decline in activities of daily living in this patient population.

Introduction

The prevalence of epilepsy among people with intellectual disabilities (ID) is much higher than in the general population.¹ In people with intellectual disabilities, one in five will have epilepsy (22%), whereby prevalence increased with increasing level of intellectual disability.² Previous research showed that patients with intellectual disabilities and epilepsy have more physical impairments than those without epilepsy.² Seizures in this population are often complex and difficult to treat. A complicating factor is that treatment in this population is often chronic (or even lifelong) treatment. Although the adverse events in this population are similar to the adverse events in patients with epilepsy and without intellectual disabilities,³ the chronicity or treatment as such may impact daily function especially with high risk medication.

From studies in the general epilepsy population it is known that all commonly used antiepileptic drugs (AEDs) have some effect on cognitive functions and on mood, although some agents have a more profound effect.⁴ From the older agents, phenobarbital (PB) induces the most severe cognitive impairment.^{4,5} Phenytoin (PHT) may also have a substantial impact on cognitive function with declines in concentration, memory, visuomotor functions, intelligence and mental speed.^{4,5} Among the new AEDs, topiramate (TPM) seems to have a large negative impact on cognition.^{6,7} Levetiracetam (LEV) is associated with an increased risk of developing behavioural, mood and even psychiatric side-effects such as irritability and aggression,⁸ which is more frequently seen in people with ID.⁹ Long-term exposure to such medications may lead to severe impact over time, even detectable as change in functional status.

The Barthel Index (BI) was first published in 1965 and is widely used as measure of functional status because of its validity, reliability, and sensitivity.¹⁰ Its use for research and clinical practice is recommended in people with ID.¹¹ The BI was originally developed to assess the change in functional status in patients with neurologic or musculoskeletal disorders¹² but is also used in the setting of brain tumors and brain metastases,¹³⁻¹⁶ and in patients with multiple sclerosis and stroke.¹⁷⁻¹⁸

In epilepsy, patients receiving drug treatment did not significantly differ in their need for aid in their activities of daily living (ADL) than patients receiving surgical treatment.¹⁹ Level of dependence in ADL is mostly assessed in patients aged 60 years and over. Some reports suggests that there is a greater risk of impairment of ADL among noninstitutionalized people using psychoactive drugs such as anticonvulsants.²⁰ Also in patients living in nursing homes, level of functional dependence was more severe in AED users, both in those with and without a history of epileptic seizures, than in non AED users, even in spite of their significantly younger age.^{21,22} However, all AED users were also taking other drugs than AEDs including drugs that may interact with AEDs such as antipsychotics. In patients with dementia due to Alzheimer's disease, AEDs were associated with lower instrumental functionality.²³

Some reports focused on specific AEDs in particular. In a small number of adult patients with brain tumor-related epilepsy treated with monotherapy LEV, a significant worsening after 6 months follow-up was found on the BI.²⁴ However, in patients with post stroke partial seizures or generalized tonic-clonic seizures, the impairment of the ADL was greater for carbamazepine than for LEV-treatment.²⁵ In stroke patients, a 'detrimental' drug group which included PB and PHT was compared with a 'neutral' drug group and showed a lower degree of independence in ADL.²⁶

However, there is no information available of the effects of AED use on functional status in adult epilepsy patients with ID. It may be hypothesised that 'high risk' AEDs also have a more deleterious impact on ADL than 'low risk' AEDs and therefore lead to a faster decline of functional status. The aim of this study is therefore to investigate the impact of 'high risk' AEDs on functional status over time in patients with ID.

Methods

Study population

This study was performed at the long-stay care facility of Kempenhaeghe. Adult patients (18 years and older) with chronic, refractory epilepsy were included in this longitudinal, clinical study. Patients had either a mild (IQ: 50-70), moderate (IQ: 35-50), severe (IQ: 20-35) or profound intellectual disability (IQ < 20). During the study period, between January 2005 and January 2014, number of seizures and type of seizures were recorded. Patients were only included if they still had seizures, which were classified in minor seizures such as partial seizures, myoclonic seizures and absences, or major seizures such as tonic seizures, tonic-clonic seizures and atonic seizures. AED use was controlled every year. Patients who switched from the 'low risk' group to the 'high risk' group or vice versa during the study period were excluded. Due to their negative effects on cognitive or behavioural functioning, PB, LEV, PHT and TPM were selected as 'high risk' AEDs. Other AEDs were classified as 'low risk' AEDs. Patients were categorised according to their AEDs associated with the greatest risk.

Assessment of functional status

The Barthel Index of Activities of Daily Living was used for assessment of functional status. Ten primary activities of daily living such as feeding, bathing, grooming, dressing, bowels, bladder, toilet use, transfers, mobility and stairs are scored, each with two to four response categories (see Appendix). The number of points is based on the amount of help a patient needs. The highest score means that this activity can be performed independently. Minimum total score is 0 (completely dependent), maximum total score is 20 (completely independent). The functional state was routinely assessed every year, at all time points, for every patient by their professional caregiver.

Data analysis

Data were analyzed with the Statistical Packages for the Social Sciences SPSS version 21.0 for Windows. First, to compare the 'high risk' group with the 'low risk' group, independent samples t-tests were performed for every time point. Furthermore, as level of ID and seizure type may affect these results, subgroup comparisons were made using ANOVA or independent samples t-tests. Second, to control for possible interfering effects of the demographics (age and level of ID) and epilepsy characteristics (seizure type) on functional status, a general linear model was chosen for the repeated measurement analysis testing the effects of AED ('low risk' versus 'high risk') on the BI after controlling for age, level of ID and seizure type as covariates. In case of a significant ($p < .05$) Mauchly's W test for sphericity, the corrected Greenhouse Geissers F was used.

Results

Demographic characteristics

In total, 153 patients were included in this study. The study group consisted of 89 men (58%) and 64 women (42%). Mean age at screening was 42 years. More than half of the patients (56%) used at least one 'high risk' AED. In both groups, most patients had a moderate intellectual disability, and had both minor and major seizures. The demographic and clinical characteristics are presented in Table 9.1.

Table 9.1 Demographic and clinical characteristics.

	Low risk AED (n=68)		High risk AED (n=85)	
	N	%	N	%
Gender				
Male	36	52.9	53	62.4
Female	32	47.1	32	37.6
Mean age at baseline	42.3	(SD:13.4)	42.8	(SD:11.6)
(range)	(18-72)		(21-63)	
Intellectual disability				
Mild	17	25.0	17	20.0
Moderate	24	35.3	34	40.0
Severe	16	23.5	20	23.5
Profound	11	16.2	14	16.5
Seizure type				
Minor	11	16.2	8	9.4
Major	57	83.8	77	90.6

Functional status

Figure 9.1 shows a consistent trend for lower scores for the 'high risk' AED-group on functional status than for the 'low risk' AED-group, which remain constant over the study period. These differences did not reach the statistical significance level (Table 9.2).

Level of ID affected the functional status of patients, which was significant ($p < .000$) during the whole study period (Table 9.2). Although there was a consistent trend for lower scores for patients with both minor and major seizures on functional status than for patients with only minor seizures (Table 9.2), which remain constant over the study period (Figure 9.2), this only reached the statistical significance level in 2006 ($t = 1.982$, $p = .049$).

Figure 9.1 Effect of AED on functional status.

Table 9.2 Mean Barthel scores.

Year	AED-group			Intellectual Disability					Seizure type		
	Low risk	High risk	p	Mild	Moderate	Severe	Profound	p	Minor	Major	p
2005	12.4	10.9	n.s.	16.3	13.7	9.7	2.6	$\leq .000^*$	14.2	11.2	n.s.
2006	12.6	11.3	n.s.	16.6	14.0	10.3	2.7	$\leq .000^*$	14.7	11.5	.049*
2007	11.5	10.8	n.s.	15.2	13.1	10.1	2.2	$\leq .000^*$	13.7	10.7	n.s.
2008	11.6	10.6	n.s.	15.5	13.0	10.1	1.7	$\leq .000^*$	13.6	10.6	n.s.
2009	11.3	10.3	n.s.	15.1	12.3	10.1	1.8	$\leq .000^*$	13.0	10.4	n.s.
2010	11.2	10.5	n.s.	15.7	12.5	9.8	1.8	$\leq .000^*$	13.0	10.5	n.s.
2011	10.7	9.9	n.s.	14.4	11.9	9.4	1.7	$\leq .000^*$	12.5	9.9	n.s.
2012	11.2	9.7	n.s.	14.7	12.2	9.0	2.1	$\leq .000^*$	12.2	10.1	n.s.
2013	11.0	9.9	n.s.	14.5	12.33	9.3	1.8	$\leq .000^*$	11.8	10.2	n.s.
2014	10.6	9.7	n.s.	14.3	12.0	8.8	2.0	$\leq .000^*$	12.1	9.8	n.s.

* $p < .05$, n.s.: not significant.

Figure 9.2 Effect of type of seizures on functional status.

Repeated measures were performed to test whether there was an effect for AED-treatment over time, so throughout the 10 years, when controlling for age, level of ID and seizure type. There was no significant effect of time ($F=.487$, $p=.882$) which shows that there is no change in BI scores across the ten year period. After adjusting for age, level of ID and seizure type, there was no significant difference on the BI between the AED-treatment groups ($F=.708$, $p=.401$). The covariates age ($F=5.121$, $p=.025$) and level of ID ($F=109.219$, $p<.001$) were significantly related with the change in Barthel scores during the study period while seizure type was not ($F=2.133$, $p=.146$).

Discussion

Our study demonstrated that type of AED does not influence functioning in daily activities, even on the long-term. Although there was a consistent trend for AEDs with a high risk for cognitive or behavioural effects to have a lower functional status compared to 'low risk' AEDs, this did not reach the statistical significant level. Furthermore, the change in Barthel scores over the ten year period was not affected by AED regimen or type of seizures. Naturally, level of functional dependency decreases over time due to an increasing age and was, as expected, affected by level of ID. So, in comparison to the demographic effects of the patients and the effect of the epilepsy, AED treatment has no impact on the functional status in patients with epilepsy and ID. Previous research showed a more severe level of functional dependence in AED users compared to non AED users²⁰⁻²³ but no distinction was made between different AEDs. Moreover, these studies included only patients aged 60 years and over and the AEDs

were not only and solely used for epileptic seizures. Our study is the first that investigated the impact of different AEDs on functional status in patients with ID. We found no effect of AED treatment which is inconsistent with previous research in which a greater impairment of ADL is reported in AEDs such as PB, PHT and LEV.^{24,26} However, there is some inconsistency about specific AEDs effects on functional status in literature.^{25,27} The demographic effects on dependence in ADL found in our study are in line with previous findings which showed that the degree of independence in ADL is primarily determined by level of ID¹¹ and is influenced by age.²⁶

In this study, we selected four 'high risk' AEDs based on previous research which were used throughout the longitudinal study period. These 'high risk' AEDs are used in polytherapy in this study population, which is a limitation of this study. However, reduced functional abilities were more observed in monotherapy than in polytherapy.²² Further research is needed in this area to provide a more thorough understanding of the long-term effects of AED treatment in people with epilepsy and ID. Presumably, the focus should then be on more subtle effects than the functional status that we studied. In conclusion, although there was a systematic trend for high risk medication to have a greater negative impact on functional status, chronic use of 'high risk' AEDs does not lead to a decline in functional status of patients with ID. Furthermore, type of epileptic seizures has no effect. The largest effects were found for demographic characteristics. Over time, a trend was found of lowering functional status, explained by increasing age and related with level of ID. Our main conclusion is that chronic AED use has no impact on the functional status in patients with ID and do not lead to a decline in ADL in this patient population.

Appendix

Barthel Index	
Activity	Score
Bowels	0 = incontinent 1 = occasional accident 2 = continent
Bladder	0 = incontinent of catheter 1 = occasional accident 2 = continent
Grooming	0 = needs to help with personal care 1 = independent
Toilet use	0 = independent 1 = needs some help 2 = independent
Bathing	0 = dependent 1 = independent
Feeding	0 = unable 1 = needs help (cutting or spreading) 2 = independent
Transfers (bed to chair and back)	0 = unable 1 = major help 2 = minor help 3 = independent
Mobility	0 = immobile 1 = wheelchair dependent 2 = walks with help of one person 3 = independent
Dressing	0 = dependent 1 = needs help but can do about half unaided 2 = independent
Stairs	0 = unable 1 = needs help 2 = independent
Maximum score	20

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Part IV

AEDs and the brain

Chapter 10

Glutamate concentrations vary with antiepileptic drug use and mental slowing

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Abstract

Objective

Although antiepileptic drugs (AEDs) are effective in suppressing epileptic seizures, they also induce (cognitive) side effects, with mental slowing as general effect. This study aimed to assess whether concentrations of MR detectable neurotransmitters, glutamate and GABA, are associated with mental slowing in patients with epilepsy taking AEDs.

Methods

Cross-sectional data were collected from patients with localization-related epilepsy using a variety of AEDs from three risk categories, i.e. AEDs with low, intermediate, and high risks for developing cognitive problems. Patients underwent 3T MR spectroscopy, including a PRESS (n=55) and MEGA-PRESS (n=43) sequence, to estimate occipital glutamate and GABA concentrations, respectively. The association was calculated between neurotransmitter concentrations and central information processing speed, which was measured using the Computerized Visual Searching Task (CVST), and compared between the different risk categories.

Results

Combining all groups, patients with lower processing speeds had lower glutamate concentrations. Patients in the high risk category had a lower glutamate concentration and lower processing speed compared with patients taking low risk AEDs. Patients taking intermediate risk AEDs also had a lower glutamate concentration compared with patients taking low risk AEDs, but processing speed did not differ significantly between those groups. No associations were found between the GABA concentration and risk category or processing speed.

Conclusion

For the first time a relation is shown between glutamate concentration and both mental slowing and AED use. It is suggested that the reduced excitatory action, reflected by lowered glutamate concentrations, may have contributed to the slowing of information processing in patients using AEDs with higher risks for cognitive side effects.

Introduction

Although antiepileptic drugs (AEDs) are effective in suppressing epileptic seizures, they may also induce side effects. These side effects can strongly affect the quality of life of patients, with slowing of central information processing speed as dominant cognitive effect of most AEDs and also the first sign of cognitive adverse effects.^{1,2} Cognitive side effects are commonly seen among the different AED regimes, but the occurrence and severity varies between different AEDs. The newer AEDs lamotrigine and levetiracetam are suggested to have no adverse, and maybe even beneficial, cognitive effects, while topiramate is known for its deleterious cognitive effects. Other AEDs, such as valproate or carbamazepine, are associated with milder cognitive effects.^{1,3,4}

AEDs aim to control for epileptic seizures via a number of distinct mechanisms of action, which can be subdivided in suppression of the excitatory mechanisms or enhancement of inhibitory mechanisms.⁵ Although cognitive side effects are likely to result from the anticonvulsant activity of the AEDs, these effects cannot be linked to any particular mechanism of action, and other mechanisms might be involved as well.⁶ It has been hypothesized that especially AEDs with mechanisms acting on the γ -aminobutyric acid (GABA) system cause cognitive side effects, but similar side effects are also induced by AEDs with other mechanisms of action.⁷ Furthermore, it is currently not possible to predict which patients will suffer from these side effects and who will not. However, compliance to AED therapy relies on efficacy as well as tolerance to side effects.

In vivo measurements of the main inhibitory and excitatory neurotransmitters GABA and glutamate can be provided by proton magnetic resonance spectroscopy (¹H-MRS). In healthy individuals, higher GABA concentrations and lower glutamate concentrations have been associated with better cognitive performance.⁸⁻¹⁰ Previous studies also showed that AED treatment can be associated with altered neurotransmitter concentrations.¹¹ Although several studies have been performed to associate GABA and glutamate concentrations with seizure control,¹²⁻¹⁴ to our knowledge the association with cognitive side effects has not been investigated yet. The aim of this cross-sectional study was to assess whether GABA and glutamate concentrations can be linked to cognitive functioning, in terms of decreased processing speed, in epilepsy patients on long-term AED treatment.

Methods

Patients

Patients with localization-related epilepsy, recruited from our tertiary epilepsy referral center, were included in this study. Inclusion criteria were an age between 18 and

70 years and no contra-indications for MRI (metal implants, claustrophobia, or pregnancy). This study was approved by the local Medical Ethical Committee and written informed consent was obtained from all patients before the examination.

To obtain a variation in information processing speed, three groups of patients using different AEDs were included. The groups were defined according to Samarasekera and colleagues,¹⁵ based on the known risk for developing cognitive side effects: a low risk category (levetiracetam and lamotrigine), an intermediate risk category (valproate, carbamazepine, oxcarbazepine and phenytoin), and a high risk category (topiramate). Both patients on mono- as polytherapy were included, but patients took maximal two different AEDs. Patients on polytherapy were classified according to the AED in the highest risk category.

Neuropsychological investigation

Information processing speed was used as a measure for cognitive side effects, as slowing of central information processing speed is the most common side-effect of AEDs.² For this, the Computerized Visual Searching Task (CVST) was used.¹⁶ In this task, a centered grid pattern has to be compared to 24 surrounding grid patterns. Participants have to find the grid pattern identical to the centered pattern. The score is the average time needed to complete this task. Additionally, as global cognitive abilities are assumed to be unaffected by AEDs,² the Raven Standard Progressive Matrices was performed to correct for possible variation in cognitive abilities between the patients.¹⁷ This is a non-verbal reasoning test, in which participants have to identify the figure that is required to fulfill a series of eight other figures.

Data acquisition

MR data were acquired on a 3.0T MR scanner equipped with an 8-channel head coil (Philips Achieva, Philips Medical Systems, Best, the Netherlands). Glutamate concentrations were measured using a PRESS sequence (T_E/T_R : 35/2000 ms, 128 averages, VAPOR water suppression). GABA edited MR spectra were acquired using a MEGA-PRESS sequence (T_E/T_R 68/2000 ms, 320 averages, with editing pulses at 1.9 (ON) and 7.46 ppm (OFF) interleaved in 40 blocks, MOIST water suppression). Both spectra were acquired from the same $3 \times 3 \times 3 \text{ cm}^3$ voxel located around the parieto-occipital sulcus (Figure 10.1). This location has an optimal signal-to-noise and is commonly selected in MRS studies.¹⁸ To estimate the water signal, separate scans without water suppression were made directly after the PRESS and MEGA-PRESS scans (with T_E/T_R 35/2000 ms and 128 averages, or T_E/T_R 68/2000 ms and 8 averages, respectively). Additionally, a T1-weighted scan was made to determine the voxel composition (voxel size $1 \times 1 \times 1 \text{ mm}$, flip angle 8° , 3D fast spoiled gradient echo sequence, $T_E/T_1/T_R$ 4.8/1022/8.3 ms, 180 slices).

Figure 10.1 Example of the voxel placement (A), a PRESS spectrum with the LCModel fit (in red), which fits a linear combination of metabolite spectra (B), and a MEGA-PRESS spectrum with the GANNET fit (in red), which only fits the GABA+ peak (GABA + co-edited macromolecules) (C). Individual glutamate or GABA fits are displayed in the figures as well.

Data analysis

PRESS spectra were analyzed using LCModel (version 6.3-1L). LCModel fits the spectrum with a linear combination of individual metabolite spectra.¹⁹ A standard basis set with sixteen different simulated metabolite spectra was used in this analysis and spectra were analyzed within the resonance frequency range from 0.2 to 4.0 ppm. In addition to glutamate, tNAA (N-acetyl aspartate + N-acetylaspartylglutamate), tCho (phosphorylcholine + glycerophosphorylcholine), and tCr (creatine + phosphocreatine) concentration estimates were collected for further analyses.

Gannet (version 2.0) was used for the preprocessing and quantification of the GABA+ concentration (i.e. GABA and co-edited macromolecules).²⁰ The GABA peak is fitted to a Gaussian model curve. Gannet is designed for GABA+ quantification, but also enables Glx quantification from MEGA-PRESS spectra.²¹ Gannet has the advantage that it also includes frequency and phase corrections.^{22,23} MEGA-PRESS scans are more vulnerable for field drifts and movement artefacts than typical PRESS scans due to addition of an editing pulse and subtraction of ON and OFF scans to obtain difference spectra, potentially leading to subtraction artifacts. Frequency correction can reduce quantification errors.²² All spectra were visually inspected on subtraction artifacts and adequate noise levels.

Repeatability of these methods was tested in five healthy volunteers (age 29 ± 4 year, four male), who underwent two PRESS and MEGA-PRESS scans immediately after each other. The results showed a coefficient of variation of 2.1%, 5.6% and 3.9% for glutamate (using PRESS/LCModel), Glx (using MEGA-PRESS/Gannet) and GABA+, respectively. Because of the better coefficient of variation of glutamate estimations with PRESS than Glx estimations with MEGA-PRESS, and because of a moderate concordance between these measurements in the included patients (Pearson

correlation coefficient=0.31, $p=0.046$), only glutamate measurements with PRESS were considered in this study.

All concentrations are reported relative to the unsuppressed water signal from the same volume. FMRIB's Automated Segmentation Tool (FAST), part of FSL (version 5.0.1), was applied to determine the voxel composition in terms of grey matter, white matter, and cerebral spinal fluid (CSF) content.^{24,25} Assuming that the neurometabolites are only present in the grey and white matter, the concentrations relative to the water signal were corrected for the CSF content of the voxel. Therefore, the neurometabolite concentrations were divided by the sum of the grey and white matter fractions.

Statistical analysis

Associations between the neurometabolite concentrations (i.e. glutamate, GABA+, tNAA, tCho, and tCr) and CVST were tested with linear regression analysis, with CVST as dependent variable and the concentrations as independent variables. Separate analyses were performed for each neurometabolite. Besides the neurometabolite concentration, age and the percentage correct answers in the Raven test (as measure for intelligence) were added to these analyses as independent variables, as the information processing speed usually correlates with age and cognitive abilities.

To test whether the neurometabolite concentrations varied with risk degree an ANCOVA (analysis of covariance) test was applied, with the neurometabolite concentrations as outcome variable and the risk categories as fixed factors. Covariates in the analyses were age, gender, and the grey matter fraction in the voxel (grey matter fraction divided by the sum of the white and grey matter fractions). In case of significant group effects, post-hoc tests (Students t-tests) were applied to test for individual group differences.

To check for possible confounding effects, the analyses were repeated with drug load (defined as the ratio of the prescribed daily dose to the defined daily dose²⁶), having symptomatic epilepsy, or epilepsy severity added as additional covariate. Epilepsy severity was defined by a composed score ranging from 0-7 based on seizure type (tonic-clonic:1, other:0), previous occurrence of status epilepticus (yes:1, no:0), seizure-related injury (yes:1, no:0), and seizure frequency (seizure free:0, yearly:1, monthly:2, weekly:3, daily:4). In all analyses, p -values <0.05 were considered significant.

Results

Patient characteristics

Fifty-eight patients were included in this study. Three of these patients did not finish the MRI examination due to claustrophobia, resulting in suitable data of 55 patients for further analysis. Seventeen of the 55 patients had symptomatic epilepsy. MRI lesions

included cerebral atrophy (6), cortical dysplasia's (5), infarctions (3), malformations (1), tumors (1), and cysts (1). The remaining 38 patients had non-symptomatic epilepsy.

The low and intermediate risk group differed significantly age and drug load (Table 10.1). Furthermore, the number of patients taking polytherapy was significantly higher in the intermediate and high risk category than in the low risk category. Patients in the different risk categories did not differ significantly in educational level, seizure frequency, epilepsy severity score, or years since epilepsy onset.

The CVST reaction time ranged from 7.3 to 30.8 s (mean $\pm$ sd in a normal adult population: 10.3 $\pm$ 4.1 s [26]). Both the patients taking intermediate-risk as high risk AEDs had a significantly lower processing speed compared with patients taking low-risk AEDs ($p=0.003$ and $p=0.042$, respectively, Table 10.1). When age, gender, and the percentage correct answers in the Raven test were added as covariates to this analysis (ANCOVA), there was a significant effect of risk category ($p=0.009$). Post-hoc tests revealed a significant longer CVST reaction time in the intermediate ($p=0.035$, adjusted mean difference 3.5 s), and in the high risk category ($p=0.004$, adjusted mean difference 7.8 s), compared with patients taking low risk AEDs. The CVST reaction time did not differ significantly between the intermediate and high risk group. All participants had a Raven score above the 5th percentile of a normal, age-matched adult population, and the Raven score was not significantly different between the groups.

Spectroscopy results

The quality of the PRESS spectra was adequate in all patients. Visual inspection did not reveal spectra of insufficient quality, all spectra had a signal-to-noise ratio above 20, and the Cramér-Rao lower bounds (CRLB) of glutamate were below 10%. Forty-three MEGA-PRESS spectra were included in the statistical analysis (15 from the low risk group, 26 from the intermediate risk group, and 2 from the high risk group). In four patients, no MEGA-PRESS data were available because of acquisition problems, and another eight MEGA-PRESS scans were excluded due to insufficient quality of the spectrum. The error of the GABA fit was below 15% in the remaining spectra, while the mean absolute drift of the water peak between two subsequent blocks was 0.009 $\pm$ 0.004 ppm.

Across all participants, the glutamate and GABA concentrations were 9.3 $\pm$ 0.8 i.u. (institutional units) and 1.7 $\pm$ 0.4 i.u., respectively (mean $\pm$ sd). tNAA, tCr, and tCho concentrations were 9.0 $\pm$ 0.5 i.u., 6.8 $\pm$ 0.6 i.u., and 1.2 $\pm$ 0.2 i.u., respectively.

The CVST reaction time was significantly associated with glutamate concentration ($\beta=-3.1$, $p=0.001$, with correction for age and global intelligence), indicating that patients with a lower processing speed had a lower glutamate concentration (Figure 10.2). The CVST reaction time was not significantly associated with the GABA ($p=0.45$), tNAA ($p=0.99$), tCr ($p=0.82$), or tCho ($p=0.13$) concentrations.

Table 10.1 Patient characteristics for the three risk categories^a. Results are displayed for the participants included in the PRESS analysis.

	Low risk (n=16)	Intermediate risk (n=34)	High risk (n=5)
General			
Male/female	5/11 (31/69%)	16/18 (47/53%)	0/5 (0/100%)
Age (years) ^b	39.5±13.4	50.7±12.5 [*]	42.4±15.8
Educational level ^c	5 (range 2-6)	5 (range 2-7)	5 (range 4-6)
Epilepsy-related			
Symptomatic/non-symptomatic	2/14 (13/88%)	15/19 (44/56%)	0/5
Seizure frequency			
Weekly	0	1 (3%)	0
Monthly	4 (25%)	3 (9%)	0
Yearly	2 (13%)	6 (18%)	2 (40%)
Seizure free	10 (63%)	24 (71%)	3 (60%)
Years since epilepsy onset ^b	22.7±11.7	30.4±13.4	26.8±23.3
Epilepsy severity score ^b	1.4±0.8	1.2±1.0	1.0±0.7
AED-related			
Mono-/polytherapy	16/0	8/26 (24/77%) [*]	3/2 (60/40%) [†]
Medication type			
CBZ	0	17 (50%)	1 (20%)
LEV	7 (44%)	6 (18%)	0
LTG	9 (56%)	10 (29%)	1 (20%)
OXC	0	4 (12%)	0
PHT	0	16 (47%)	0
TPM	0	0	5 (100%)
VPA	0	7 (21%)	1 (20%)
Drug load ^{b,d}	1.3±0.6	1.8±0.7 [*]	1.2±1.0
Neuropsychological results			
CVST reaction time ^b	11.5±2.9	15.7±6.4 [*]	20.2±6.7 [†]
Raven (% correct answers) ^b	71.7±10.3%	73.2±10.1%	71.7±3.1%

Differences between the risk groups were tested using a Fisher's exact test (gender, symptomatic epilepsy, mono/polytherapy), a Mann-Whitney test (educational level, seizure frequency, epilepsy severity score), or a student's t-test (all remaining variables). ^{*} indicates significant differences between the low and intermediate risk category ($p<0.05$); [†] indicates differences between the low and high risk category ($p<0.05$). ^a Low risk: lamotrigine (LTG), levetiracetam (LEV); Intermediate risk: valproate (VPA), carbamazepine (CBZ), oxcarbazepine (OXC) and phenytoin (PHT); High risk: topiramate (TPM); ^b mean ± standard deviation; ^c Median (range). Scores are according to Verhage (1964), range 1 (did not finish primary school) to 7 (Master's degree); ^d The drug load is defined as the ratio of the prescribed daily dose to the defined daily dose (26)

The glutamate and GABA concentrations are illustrated for the different groups in Figure 10.3. A significant effect of cognitive risk category on the glutamate concentration was observed ($p=0.028$, ANCOVA, with age, gender, and grey matter fraction as covariates). Post-hoc tests showed a significantly lower glutamate concentration in the intermediate risk category than in the low risk category ($p=0.021$, adjusted mean difference 0.49) and in the high compared with the low risk category ($p=0.032$, adjusted mean difference 0.72). The intermediate and high risk categories did not differ significantly in the glutamate concentrations ($p=0.47$). Risk category did not

have a significant effect on the GABA ($p=0.83$), tNAA ($p=0.47$), tCho ($p=0.085$), or tCr ($p=0.17$) concentration.

The additional analyses, with epilepsy severity score, drug load, or having symptomatic epilepsy added as covariates, showed comparable results as the analyses without these additional covariates (<10% change in effect size). Furthermore, epilepsy severity, drug load, or having symptomatic epilepsy were not significant covariates in any of the analyses.

Figure 10.2 Association of the glutamate concentration and CVST reaction time.

Patients with lower glutamate concentrations, had a longer CVST reaction time, i.e. a lower processing speed, than patients with higher glutamate concentrations. The depicted line represents the uncorrected linear regression estimate to guide the eye. This association remained significant after correction for age and global intelligence ($\beta=-3.1$, $p=0.001$). From the graph it can be noticed that patients taking low risk AEDs (open circles), had high glutamate concentrations and low CVST reaction times, while lower glutamate concentrations and higher CVST reaction times were only measured in patients taking intermediate (grey circles) or high risk (black circles) AEDs. CVST: computerized visual searching task.

Figure 10.3 Glutamate (A) and GABA (B) concentrations for the three risk groups. Concentrations are relative to the water concentration, corrected for the cerebral spinal fluid content of the voxel, and displayed in institutional units. Low risk category: lamotrigine or levetiracetam; Intermediate risk category: carbamazepine, oxcarbazepine, phenytoin or valproate; High risk category: topiramate. Standard deviations are displayed with error bars. * indicate significant differences ($p < 0.05$), when adjusted for age, gender, and grey matter fraction.

Discussion

This study assessed associations between neurotransmitter concentrations, AED treatment, and cognitive functioning in patients with epilepsy. Lower glutamate concentrations were associated with a lower processing speed, the most common type of drug-induced cognitive impairment. Furthermore, patients taking AEDs from higher risk category had lower glutamate concentrations than patients taking AEDs from lower risk categories. No significant associations were found between the GABA+ concentration and risk category or processing speed.

Glutamate concentrations and cognitive slowing

To our knowledge, this is the first study showing associations between neurotransmitter concentrations and drug-induced cognitive side effects (i.e. mental slowing) in patients with epilepsy. Studies in other diseases did also show associations between the glutamate concentration and cognitive functioning, but the variety of the applied cognitive tests is large, and both positive and negative associations have been found.²⁷ Different explanations are proposed for these associations. For instance, it is hypothesized that neurotoxic effects of high glutamate concentrations affect cognitive functioning,²⁸ that a higher GABA/glutamate concentration improves decision-making,⁸ or that glutamate concentration acts as a marker for neuronal integrity.²⁹ Precise associations between glutamate and cognitive function and the underlying mechanisms may depend on the specific disease and cognitive functions being studied.

The glutamate concentration measured by MRS is a combination of glutamate functioning as neurotransmitter and glutamate stored in synaptic vesicles and metabolic pools. Although the precise mechanisms are unknown, the glutamate concentration appears to be roughly linearly related to excitatory activity, possibly due to its involvement in the glucose metabolism in the brain.^{30,31} As AEDs generally tend to suppress (abnormal) brain activity,⁵ it seems likely that the lower glutamate concentrations in this study reflect more suppressed brain activity, which may be associated with a slowing of information processing at the downside of this effect.

AED use and glutamate concentrations

Although differences in glutamate concentrations were observed between the different risk category, none of the known mechanisms of action of AEDs are likely to affect the glutamate concentration directly.⁵ However, it is possible that modulation of the sodium channels, seen in PHT, CBZ, OXC, TPM, and VPA, which blocks high frequency repetitive action potentials, indirectly decrease the glutamate release. Three previous longitudinal studies showed no changes in the Glx concentration (glutamate and its precursor glutamine combined) after VPA use, or glutamate concentrations after TPM or LEV use,³²⁻³⁴ AEDs which were also used in the current study. Taken together, the

current study does not provide evidence that AEDs from different risk categories alter glutamate concentrations directly, but the results do suggest a link between glutamate concentration and mental slowing due to AED use.

GABA

In this study, no associations were found between the GABA concentration and information processing speed or cognitive risk category, in contrast to the hypothesized involvement of GABAergic mechanisms in cognitive side effects of AEDs.^{7,35} Existing associations might have been undetected in this study due to the small group size. Due to exclusion of MEGA-PRESS spectra, this group size was smaller compared with the other results (n=43 versus n=55). Also confounding effects of the different AEDs might have had different effects on the GABA concentration. For instance, both TPM and LTG are suggested to increase the GABA concentration, but a higher increase was reported with TPM use than with LTG use.³⁶ Using the current clinical study design, it is not feasible to assess distinct effects of the different AEDs, due to the many different combinations of AEDs which were being used by the included patients. However, it cannot be excluded that for individual AEDs, also GABA concentrations are associated with cognitive functioning.

Other neurometabolites

tNaa, tCho, and tCr concentrations were not significantly associated with CVST reaction time nor risk group in this study, while previous studies did show associations with for example NAA and information processing speed³⁷ or executive functioning³⁸ in healthy elderly populations. Age-specific mechanisms may underlie these associations, that cannot be generalized to other study populations. For instance, NAA is considered a marker for neuronal integrity and is often associated with cognitive functioning. However, cognitive side effects of AED use are reversible, and therefore not likely to be accompanied by neuronal cell damage as might be the case in aging. Previous studies have not reported associations with tNAA, tCho, or tCr and AED use.¹¹

Study considerations

This study was performed in patients with epilepsy on long-term AED treatment, which is most relevant for clinical practice. However, adherent to these studies is the heterogeneity of the study population and the different combinations of AEDs that were taken. An important possible confounder in this study is whether patients were on mono- or polytherapy, which largely coincides with taking AEDs from the low- or intermediate risk category. Importantly, polytherapy itself is already associated with higher risk on cognitive side effects.³⁹ It can furthermore not be excluded that both glutamate concentrations and processing speed were affected by epilepsy

characteristics or underlying causes rather than AED use. Future studies are needed to distinguish these factors, and to clarify the precise, causal relationship between neurotransmitter concentrations, AED use, and cognitive side effects.

Because of its negative cognitive side effects, topiramate is not commonly prescribed in our epilepsy center. This resulted in a limited number of patients taking high risk AEDs in this study, but the results of this group are in line with the results from the intermediate risk category. The lack of significant differences between the intermediate and high risk category might therefore be due to the small group size of the high risk category.

The MRS measurements used in this study showed good repeatability. However, the low concordance between glutamate estimations from PRESS and Glx from MEGA-PRESS is striking. A possible explanation is the presence of macromolecules in one of these spectra, but future studies are prompted to investigate this topic. A final consideration regarding MRS measurements is the voxel location. As in many previous studies, the occipital lobe was chosen because it gives the best signal-to-noise ratio.^{18,22} However, regions important for cognitive processes include the prefrontal cortex and subcortical structures, and not the occipital lobe.⁴⁰ Currently, it remains to be determined whether relevant spatial variations exist in the neurotransmitter concentrations in relation to adverse cognitive effects.

Future perspectives

Currently, it is not possible to predict which patients will or will not suffer from these side effects, while this would aid clinical decision making. The results of this study show potential of glutamate measurements as a candidate biomarker. In order to predict these side effects, it is necessary to first longitudinally assess changes in neurotransmitter concentration, to see whether the differences in glutamate levels possibly precede the cognitive problems or coincide with the cognitive problems.

Conclusions

For the first time a relation is shown between the lowered glutamate concentration and both AED use and mental slowing in patients with epilepsy. This observation hints at a possible contribution to a neurobiological mechanism of mental slowing due to AED use. More knowledge about this relation might help to explain why some patients with epilepsy experience cognitive side effects while the cognitive function of other patients is not affected by AEDs. Future studies with MRS and AEDs are warranted to further elucidate more details of underlying mechanisms.

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Chapter 11

Chronic AED use and functional network efficiency

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Submitted

Abstract

Purpose

Cognitive side effects, such as slowing of central information processing, is a common complication of antiepileptic drug (AED) treatment. To increase our insight in the neuronal mechanisms underlying such cognitive side-effects, the relation between functional MR-acquired brain network measures, AED use, and cognitive function was investigated.

Methods

Three groups of patients with epilepsy with a different risk profile for developing cognitive side effects were included: a 'low risk' category (lamotrigine or levetiracetam), an 'intermediate risk' category (carbamazepine, oxcarbazepine, phenytoin, or valproate) and a 'high risk' category (topiramate). Brain connectivity was assessed using resting state functional MRI and graph theoretical network analysis. The Computerized Visual Searching Task (CVST) were used to measure central information processing speed and global cognitive performance, respectively.

Results

Central information processing speed was lower in patients taking AEDs from the intermediate and high risk categories, compared with patients from the low risk category. Patients from the high risk category had a higher global efficiency compared with the other patients, while the global efficiency did not differ between the low and intermediate risk category.

Conclusion

The results of this study indicated that only topiramate could be associated with altered improved graph measures reflecting more globally efficient networks, which might be a mechanism to compensate for the cognitive slowing. Alterations in functional brain network organization may be only subtle and measureable in patients with more severe cognitive side effects.

Introduction

Epilepsy is generally treated with antiepileptic drugs (AEDs). A persistent problem in AED treatment is the occurrence of adverse events among which cognitive side effects are commonly seen.^{1,2} The cognitive side effects account for a high percentage of the disease burden³ and lead to early drug discontinuation.⁴ The prevalence and severity of the cognitive side effects varies among different AEDs. Several AEDs, such as topiramate, are associated with cognitive problems such as language deficit (anomia), while other AEDs such as lamotrigine seem to induce less cognitive side effects or even have activating effects.⁵ Despite specific differences, a decreased central information processing speed is commonly observed among the different AEDs to some extent.²

AEDs control epileptic seizures via several distinct mechanisms, such as enhancement of GABAergic inhibition, reduction of glutamatergic neurotransmission, or modulation of the voltage-gated ion channels.⁶ Changes in brain metabolic processes also affect healthy brain activity, and are likely to be responsible for cognitive side effects.¹ Functional magnetic resonance imaging (fMRI) enables assessment of this brain activity, and can be employed to measure combined effects of different mechanism of action of AEDs.⁷ Several fMRI studies have shown altered brain activity patterns in healthy participants⁸ or patients with epilepsy^{9,10} treated with AEDs. For instance, altered brain activity patterns appeared to be associated with language impairments when taking topiramate.¹¹⁻¹³

Cognitive functions are mediated by the concerted action of multiple and distributed brain regions. These brain regions show correlations of their fMRI time signals, which is commonly interpreted as functional connectivity. Collectively, these functional connections form a brain network, which can be analyzed and characterized using graph theoretical analysis. Brain networks appear to be efficient networks, characterized by a high functional segregation and integration, i.e. different brain regions form densely interconnected groups, enabling specialized information processing, and also rapid communication between distributed brain regions. Several graph measures are available to quantify these characteristics.¹⁴

Cognitive performance has been associated with the efficiency of functional brain networks,^{15,16} while impaired functional brain networks have been associated with cognitive decline in epilepsy.^{17,18} Furthermore, associations between drug load, cognition and graph measures were shown in one of these studies, although this was not the main focus of the current study.¹⁷ Another study associated the use of carbamazepine with altered graph measures when compared with other AEDs, but did not investigate the relation with cognitive effects.¹⁹ In the current study, we aim to test whether chronic use of AEDs, associated with a high risk for cognitive side-effects, affects functional resting-state network measures differently than long-term use of AEDs associated with milder cognitive side-effects. Furthermore, we will test whether

functional resting-state network measures are associated with impaired cognitive functioning.

Methods

Patients

Three groups of patients with epilepsy were compared in this observational, cross-sectional study. These groups were subdivided based on the AEDs that were being used, in accordance to Samarasekera et al.²⁰ The first group, the low risk category, consisted of patients using lamotrigine or levetiracetam. Patients taking carbamazepine, oxcarbazepine, phenytoin, or valproate were included in the intermediate risk category, while the high risk category comprised patients taking topiramate. Patients on polytherapy took at most two different AEDs and were categorized according to their AED associated with the greatest cognitive risk. By including patients with AEDs from the three risk groups, a range in slowing of information processing speed is set out for.

All patients were clinically diagnosed with localization-related epilepsy and aged between 18 and 70 years. The patients were recruited from our tertiary epilepsy referral center. Participants not eligible for MRI, because of metal implants, claustrophobia, or pregnancy, were excluded from this study. Furthermore, patients did not experience seizures at least 12 hours prior to MRI. This study was approved by the local Medical Ethical Committee and all participants provided written informed consent.

Neuropsychological investigation

Cognitive functioning was assessed by two neuropsychological tasks. The Computerized Visual Searching Task (CVST) was used to measure visual (complex) information processing speed.²¹ Slowing of this central information processing speed is a common side effect of AEDs,²² and therefore the CVST is considered to be sensitive for treatment effects.²³ With the CVST, a centered grid is shown surrounded by 24 other grid patterns. Participants have to find the (only) grid identical to the centered one as fast as possible. The Raven Standard Progressive Matrices was administered to assess global cognitive performance. This is a non-verbal reasoning test which gives an indication of fluid intelligence.²⁴ Previous studies suggested that intelligence stays relatively unaffected by AEDs.²³

Epilepsy severity

As several epilepsy related characteristics might affect functional brain networks,²⁵ a score was composed to account for these effects. This epilepsy severity score was assessed in all patients and compared between the different risk categories. Epilepsy severity was characterized using a summarized score between zero and seven, composed by the sum of subscores for seizure type (tonic-clonic: 1, other: 0), previous occurrence of status epilepticus (yes: 1, no:0), seizure-related injury (yes:1, no:0) and seizure frequency (seizure free: 0, yearly: 1, monthly: 2, weekly: 3, daily: 4).

MRI data acquisition

MRI data were acquired on a 3.0T MRI scanner equipped with an 8-channel head coil (Philips Achieva, Philips Medical Systems, Best, the Netherlands). The scanning protocol included resting-state functional MRI and a T1-weighted scan. Functional MRI data were acquired using whole-brain single-shot multi-slice echo planar imaging (EPI) sequence sensitive to the blood-oxygen-level-dependent (BOLD) effect (195 volumes, 32 slices, in-plane resolution 2x2 mm, 4 mm thick slices, repetition time 2000 ms, echo time 35 ms, flip angle: 90°, acquisition time: 7 min). A 3D T1-weighted scan was acquired for anatomic reference (voxel size 1x1x1 mm, repetition time 8.3 ms, echo time 4.8 ms, inversion time 1022 ms, 180 slices, flip angle 8°, acquisition time 6 min).

Data preprocessing

Preprocessing of the functional images was performed using SPM8 (Wellcome Department of Cognitive Neurology, London, UK). The functional images were corrected for differences in slice timing and head movement, coregistered to the T1 image and spatially (FWHM 6 mm) and temporally filtered (band pass 0.01–0.1 Hz). The BOLD signal originating from the white matter and ventricles, which is assumed to reflect physiological noise,²⁶ and the six translation and rotation parameters obtained from the motion correction were deregressed from the BOLD signal.

The T1-weighted scan was parcellated into 82 cortical and subcortical brain regions using FreeSurfer v5.1.0 (The General Hospital Corporation, Boston MA, USA). Subsequently, a connectivity matrix was created by calculating the Pearson's correlation coefficient between the average (deregressed) BOLD time signal of each combination of two regions. Negative correlations were set to zero. The correlation values were thresholded, based on the average connectivity matrix, to obtain connectivity matrices with only the strongest connections. The number of included connections was varied, with sparsity levels ranging from 0 to 0.9 (0 is fully connected, whereas 1 indicates no connections).

Data analysis

The Brain Connectivity Toolbox¹⁴ was employed to compute graph measures for each individual connectivity matrix. The clustering coefficient and the characteristic path length are commonly used to characterize the functional segregation and integration, respectively. The clustering coefficient quantifies the fraction of a node's neighbor that are also connected to each other. The characteristic path length is defined as the average shortest distance (the inverse correlation coefficient) between all pairs of nodes. As, in sparse networks, a single weak connection can result in a large, or even infinite average path lengths, global efficiency was computed instead of characteristic path length, which avoids this effect by using inverse path lengths.²⁷

One hundred null models of the connectivity matrices were computed by randomizing the connections of the original matrices, while preserving the degree and weight distribution.²⁸ The graph measures were divided by the mean global efficiency and clustering coefficient of these null models, providing a normalized global efficiency (E_g) and clustering coefficient (γ).

Statistical analysis

To test whether the clustering coefficient and global efficiency differed between the risk categories, an analysis of covariance (ANCOVA) was applied with the graph measures as outcome, cognitive risk category as fixed factor and age as covariate. Associations with cognition were assessed with linear regression analysis, with CVST time as outcome, and E_g or γ , age, and the percentage correct answers in the Raven test as independent variables. To assess whether these results were affected by confounders, these analyses were repeated with gender, epilepsy severity score, or drug load (ratio of prescribed daily dose to defined daily dose²⁶) added to the regression analyses as additional covariates. All statistical analyses were performed in Matlab (version R2012b). P-values lower than 0.05 were considered significant.

Results

In total, 58 patients were included in this study. Three of these patients did not finish the procedures due to claustrophobia, resulting in 16 patients taking AEDs from the low risk category, 34 taking AEDs from the intermediate risk category, and 5 taking high risk AEDs. The age and drug load were significantly higher in the intermediate risk category than in the low risk category (Table 11.1). Also the number of patients on polytherapy was significantly higher in the intermediate risk category compared with the low risk category, while the high and low risk categories significantly differed in number of patients on polytherapy. The risk categories did not differ in gender distribution, educational level, or epilepsy severity.

Table 11.1 Patient characteristics for the three risk categories.^a

	Low risk (n=16)	Intermediate risk (n=34)	High risk (n=5)
General			
Male/female	5/11 (31/69%)	16/18 (47/53%)	0/5 (0/100%)
Age (years) ^b	39.5±13.4	50.7±12.5*	42.4±15.8
Educational level ^c	5 (range 2-6)	5 (range 2-7)	5 (range 4-6)
Epilepsy-related			
Symptomatic/non-symptomatic	2/14 (13/88%)	15/19 (44/56%)	0/5
Seizure frequency			
Weekly	0	1 (3%)	0
Monthly	4 (25%)	3 (9%)	0
Yearly	2 (13%)	6 (18%)	2 (40%)
Seizure free	10 (63%)	24 (71%)	3 (60%)
Years since epilepsy onset ^b	22.7±11.7	30.4±13.4	26.8±23.3
Epilepsy severity score ^b	1.4±0.8	1.2±1.0	1.0±0.7
AED-related			
Mono-/polytherapy	16/0	8/26 (24/77%)*	3/2 (60/40%) [†]
Medication type			
CBZ	0	17 (50%)	1 (20%)
LEV	7 (44%)	6 (18%)	0
LTG	9 (56%)	10 (29%)	1 (20%)
OXC	0	4 (12%)	0
PHT	0	16 (47%)	0
TPM	0	0	5 (100%)
VPA	0	7 (21%)	1 (20%)
Drug load ^{b,d}	1.3±0.6	1.8±0.7*	1.2±1.0

Differences between the risk groups were tested using a Fisher's exact test (gender, symptomatic epilepsy, number of different AEDs), a Mann-Whitney test (educational level, seizure frequency, epilepsy severity score), or a student's t-test (all remaining variables). * indicates significant differences between the low and intermediate risk category ($p < 0.05$); [†] indicates differences between the low and high risk category ($p < 0.05$).

^a Low risk: lamotrigine (LTG), levetiracetam (LEV); Intermediate risk: valproate (VPA), carbamazepine (CBZ), oxcarbazepine (OXC) and phenytoin (PHT); High risk: topiramate (TPM); ^b mean ± standard deviation; ^c Median (range). Scores are according to Verhage (1964), range 1 (did not finish primary school) to 7 (Master's degree)

Neuropsychological assessment

The results of the CVST and the Raven task are summarized in Table 11.2. The CVST reaction time was slower than the normal range (range: 7.3 to 30.8 s, while the mean±sd was 10.3±4.1 s in normal population²⁹). A significant effect of risk category on CVST reaction time was observed, which remained significant when controlling for age, gender, and global cognitive level ($p = 0.009$, ANCOVA). Post-hoc tests showed significant differences in CVST between the low and intermediate risk category ($p = 0.035$, estimated adjusted mean difference 3.5 s), and between the low and high risk category ($p = 0.004$, adjusted mean difference 7.8 s). No significant differences were found between the percentage correct answers Raven scores of the different risk categories.

Table 11.2 Results of the neuropsychological investigation, represented as mean $\pm$ standard deviation for each risk category.

Risk category	Cognitive test results	
	CVST (s) ^a	Raven ^b
Low risk	11.5 $\pm$ 3.0	70.8 $\pm$ 10.0%
Intermediate risk	15.6 $\pm$ 6.5	73.3 $\pm$ 10.1%
High risk	18.1 $\pm$ 5.6	72.5 $\pm$ 2.9%
<i>p</i> -value ^c	0.008	0.85

^a mean reaction time on the Computerized Visual Searching Task (CVST)²¹; ^b Percentage correct answers on the Raven Standard Progressive Matrices²⁴; ^c Tested with ANOVA.

Network topology

Of the 55 included patients, seven were excluded from further analysis: one patient was excluded because of excessive head motion (maximum head movement of 8.0 mm, while the maximum head movement was below 1.5 mm in all other patients), one because of a deeper large lesion mass, and five patients were excluded because of a failure to automatically parcellate the cortex, due to cortical abnormalities. The analysis was therefore performed on 48 patients: 15 patients taking AEDs from the low-risk category, 29 patients taking AEDs from the intermediate risk category and 4 patients taking the high risk medication. The maximum head displacement did not differ between the three risk categories.

The functional networks were fully connected and showed small-world characteristics within the sparsity range 0.32-0.66 (which was defined as γ/λ significantly larger than one, with γ the normalized clustering coefficient, and λ the normalized characteristic path length). Only the sparsity levels within this range were considered for further analyses. The ANCOVA test revealed significant effects of risk category on Eg at most sparsities within this sparsity range (Figure 11.1). Post-hoc tests showed a significantly higher Eg for patients from the low category compared with the high risk category, and for patients from the intermediate category compared with the high risk category. Eg or γ did not differ significantly between patients from the low and intermediate risk categories ($p>0.2$ at all sparsity levels), and no significant associations were observed between γ or Eg and CVST time ($p>0.15$ at all sparsity levels). Gender, epilepsy severity score, or drug load were not significantly associated with the γ , Eg , or CVST reaction time, and the results of these adjusted analyses were consistent with the results of the analyses without these additional covariates (<10% change in effect size of the variable of interest).

Figure 11.1 Mean clustering coefficient (A, C) and global efficiency (B, D) for each risk category. Both clustering coefficient and global efficiency are normalized, i.e. the measures are divided by the clustering coefficient and global efficiency of random networks. A and B show the graph measures as a function of sparsity, while B and D show the results at a single sparsity level. Error bars show standard deviations, while the asterisks indicate significant differences between the risk categories ($p < 0.05$, with age included as covariate).

Discussion

The current study investigated whether patients taking AEDs with a different risk for cognitive side-effects have different functional brain topologies. To this end, we included epilepsy patients with chronic AED treatment with different risk profiles, i.e. a low risk category, intermediate-risk, and high risk category. Furthermore, we assessed whether cognitive problems, in terms of a decreased central information processing speed, could be associated with the functional brain organization.

A higher global efficiency was shown in the patients taking TPM (the high risk category), compared with patients taking the low and intermediate risk AEDs. The directionality of this difference is strikingly, as this result seems to contradict the cognitive side effects

of TPM. The global efficiency is suggested to be particularly important for more complex cognitive tasks, for which different brain areas are involved.³⁰ The ‘better’ global efficiency in TPM users might however be interpreted as a compensatory mechanism, or could be explained by a ‘survivor effect’. As patients with side effects are more likely to switch to other AEDs, it is likely that these patients are less vulnerable for cognitive problems. The higher global efficiency in the high-risk group might therefore reflect a lower susceptibility for cognitive side effects of these patients.^{31,32} However, these patients did have a lower processing speed compared with the other patients, which argues against this explanation and for a compensatory mechanisms.

No differences in graph measures were observed between the patients groups taking AEDs from the low and from the intermediate risk category. It is possible that the effects of TPM on brain organization are more pronounced compared with effects of other AEDs, but TPM can also have distinctive effects on brain organization. TPM is suggested to have a unique cognitive profile, with specific effects on verbal fluency. Moreover, it has multiple mechanisms of action, and both these mechanisms and its chemical structure differ from other AEDs.³³

Furthermore, no associations were found between processing speed and graph measures, in contrast to a previous study that showed not only associations between intellectual decline and a lowered clustering coefficient in patients with epilepsy, but also with increasing drug load.¹⁷ The latter suggests that the intellectual decline (which was based on intelligence tests) was a side effect of the AED treatment, but this could also result from differences in epilepsy characteristics. That study included more patients with a high drug load (15% of the patients had a drug load higher than 3) than the current study (no drug loads higher than 3 in the included patients), thus it is possible that the effects on graph measures are only measureable in patients with higher drug loads or AEDs with high risks on cognitive complaints.

The measured information processing speed covered the whole range from normal to a clearly affected processing speed, and patients taking AEDs known to induce cognitive side effects, showed lower processing speeds than patients with lower risk AEDs. These results could therefore not explain the lack of associations between graph measures and information processing speed, or the lack of differences in graph measures between the low and intermediate risk category. Also no trends were shown, while the total number of participants (48), and the number of patients in the low (16) and intermediate risk categories (34) were relatively large, making it unlikely that this lack of findings were due to limited power.

All included patients in the current study were diagnosed with localization-related epilepsy. Epilepsy is associated with a decreased global efficiency and increased clustering coefficient, although some studies showed a decreased clustering coefficient in patients with epilepsy.³⁴ It is therefore plausible that the functional brain networks of

all three groups of patients in this study were already altered compared with healthy participants, irrespective of AED treatment.

This study has several limitations. Although we tried to include comparable patient groups, the risk categories differed in age and drug load, suggesting that our study population is biased. Therefore, the analyses were corrected for these characteristics by including age and drug load as covariates. Besides these characteristics, also other factors could have confounded our results, such as the location of the epileptic focus or effects of AEDs on the neurovascular coupling, which should be assessed in separate studies.³⁵ Finally, no information is available about changes over time and causality due to the cross-sectional design.

Conclusions

No differences in functional network graph measures could be detected between patients with epilepsy after chronic use of AEDs with a different risks on cognitive side effects. Only patients taking TPM, which has a high risk for developing cognitive side effects, showed a more efficient brain network topology, which might be a compensatory mechanism. Also no associations were found between the graph measures and the measured cognitive impairments, specifically slowing of central information processing. Alterations in functional brain network organization may be only subtle and measureable in patients with more severe cognitive side-effects.

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Chapter 12

General discussion

General discussion

Epilepsy is a neurological disorder that is estimated to affect almost 70 million people worldwide.^{1,2} The highest incidence is found in children.³ The prevalence of epilepsy among people with intellectual disabilities is much higher than in the general population with one in five having epilepsy (22%).⁴ In the majority of the patients, epilepsy is treated with anti-epileptic drugs (AEDs) to prevent seizures. About one third of patients suffer from drug refractory epilepsy.⁵ For these patients additional nonpharmacological treatment options are available, such as epilepsy surgery, vagus nerve stimulation and the ketogenic diet.

The best possible outcome of AED-treatment is to achieve complete seizure freedom without adverse events. However, one of the complications of AED-treatment is the occurrence of side-effects, especially in the cognitive domain.^{6,7} These cognitive side-effects may even outbalance the effectiveness of the drug which limits the compliance. Cognitive side-effects are therefore an important aspect of establishing overall treatment effectiveness.

The aim of this thesis was to investigate the cognitive adverse effects of anti-epileptic treatment in patients with refractory epilepsy. This thesis was divided in four parts that has provided information and allows attempting answering five pertinent clinical questions:

What kind of cognitive functions can be affected by antiepileptic drug therapy?

All commonly used AEDs have some effect on cognitive function. The severity of impaired cognition due to treatment differs per AED. From the older agents, phenobarbital (PB) induces the most severe cognitive impairment, especially on memory and visuomotor functions.⁸ Another AED of the first generation, phenytoin (PHT) may also have a substantial impact on cognitive function with impairments in concentration, memory and mental speed.⁹ Mild to moderate impairments of psychomotor and mental speed are described for valproate (VPA) and carbamazepine (CBZ).¹⁰ No cognitive impairments are described for oxcarbazepine (OXC) in adults¹¹ and children.^{12,13} Among the newer AEDs, topiramate (TPM) potentially has a severe negative impact on cognition, especially on verbal function.¹⁴ The cognitive side-effect profile of zonisamide (ZNS) is regarded to be comparable with TPM.¹⁵ This is contrary to lamotrigine (LTG) and levetiracetam (LEV) that may even have activating effects on cognition.^{16,17} However, LEV is associated with an increased risk of developing behavioral, mood and even psychiatric side-effects such as aggressiveness, irritability and hostility.¹⁸

Higher-order cognitive functions that are more stable, reasoning functions, such as intelligence or memory are only affected by AEDs from the very first generation and the newer drug TPM and ZNS. The most common cognitive area that is affected by drug

treatment are attentional related state dependent ‘fluid functions’ in particular psychomotor speed and speed of central information processing.^{19,20} The dominant cognitive impairment per AED is schematically shown in Figure 12.1. In addition to literature, the neuropsychological profile of two AEDs (one drug from the older generation and one from the newest generation) were discussed in this thesis. Lacosamide is positioned in the class of activating drugs on cognition, comparable with lamotrigine. Ethosuximide is positioned in the class of drugs with mild effects on cognition, comparable to e.g. carbamazepine and oxcarbazepine.

Figure 12.1 Dominant impairment per antiepileptic drug.
Adapted from: IJff, DM and Aldenkamp, AP. Comorbidities of treatment with antiepileptic drugs. In Duchowny, Cross, and Arzimanoglou (Eds.), *Pediatric Epilepsy*, New York: McGraw-Hill Professional, 2012.

Are the cognitive side-effects of nonpharmacological treatment options comparable to AED-treatment?

Nonpharmacological treatment options such as epilepsy surgery, vagus nerve stimulation and the ketogenic diet are available for patients with drug-resistant epilepsy, also for children. As opposed to AEDs, there are no negative effects on cognition reported for vagus nerve stimulation.²¹ In children treated with the ketogenic diet an activated mood and cognitive activation was observed.²² Similar reports are available for successful epilepsy surgery.^{23,24} This positions the nonpharmacological

treatment options in the same class as the activating AED such as lacosamide, which has also been reported in literature for lamotrigine²⁵ or oxcarbazepine.¹¹⁻¹³

Has chronic use of AEDs a detrimental impact on cognitive development during childhood?

Current knowledge is mostly based on research with trial durations of weeks instead of years which is in contrast with clinical practice. Furthermore, data in children are limited. As AEDs may have an effect on brain maturation and hence on neurodevelopment, children are potentially more susceptible to the adverse effects of AEDs than adults.²⁶ Concern has therefore been expressed about long-term effects of AED use on cognitive development in children²⁷ which was confirmed by one of our studies in this thesis (chapter 6).

How useful are subjective reports for indicating cognitive side-effects?

Following the community-based studies which were published previously,^{6,28} we assessed the value of subjective complaints, now in a hospital-based population, i.e. in patients with chronic refractory epilepsy visiting the outpatient departments of our tertiary referral center. Most reported complaints were about their general health (85%), followed by cognition (77%), mood (69%) and cosmetics (42%). Although previous reports showed the highest rate of intolerable cognitive complaints for TPM,²⁹⁻³¹ patient-perceived complaints could not distinguish the AEDs associated with a greater risk of cognitive dysfunction such as TPM, PB, PHT or ZNS in our patient population.³² However, regression analysis showed that using a high risk AED for behavioral side-effects (such as LEV) contributed significantly to the total subjectively experienced side-effects and to mood effects. This indicates that subjective cognitive complaints may be less reliable than subjective mood reports.

The usefulness of patient-based reports in detecting the adverse effects of AEDs on cognitive function is still in debate. Although it may identify patients who are at risk for developing drug-induced cognitive impairment^{33,34} which was confirmed in this thesis (chapter 8), complaints may reflect depressed mood instead of cognitive impairments.³⁵⁻³⁷ It is therefore suggested to use a combination of subjective and objective assessments of cognition, including caregivers reports.³⁸ Subjective self-reports or cognitive tests are, however, not possible for every patient. Patients with intellectual disabilities are less likely to report cognitive side-effects due to difficulty detecting subtle forms of cognitive impairment in intellectually disabled patients and underreporting.²⁹ We therefore used a new approach, assessing the effects of AEDs on functional status using long-term follow up with caregiver reports on the Barthel Index of Activities of Daily Living in this patient population.

What is the effect of AED-treatment on the brain?

As some patients may be more susceptible to cognitive impairments due to antiepileptic treatment than others,³⁹ a better understanding of neuronal mechanisms of action causing cognitive side-effects is needed to improve the tolerability of antiepileptic treatment. One mechanism of action is neurotransmitter-related. Some of the AEDs are thought to affect GABAergic mechanisms directly or to alter the glutamate concentrations indirectly by decreasing the sensitivity of the glutamate receptors.⁴⁰ Neurotransmitter concentrations and brain activity can be measured using MR spectroscopy (MRS) and functional MR imaging (fMRI) respectively. Although there is a scarcity of clinical MR-studies investigating the effectiveness of AEDs, these techniques provide biomarkers that may predict treatment outcomes in the individual patient and enable assessment of mechanisms of cognitive side-effects.^{41,42} fMRI-studies suggest that several AEDs such as CBZ,⁴³ LEV,⁴⁴ VPA,⁴⁵ and TPM⁴⁶⁻⁴⁸ have effects on cognitive brain networks in patients with epilepsy. Based on our clinical MRI studies using MR spectroscopy and resting-state functional MR imaging to investigate the effects of AED-treatment on brain function and brain activity, respectively, we concluded that drug-induced slowing of central information processing speed is associated with reduced excitatory neurotransmitter function and subtle changes in brain connectivity.^{49,50} Such alterations in neurotransmitters and brain organization may therefore underlie the development of cognitive side-effects.

How to proceed from here?

Implications for clinical practice

A neuropsychological investigation is commonly used to obtain a neurocognitive profile for an individual patient in relation to subjective complaints, type of AED, and drug load. Valid and reliable screening instruments are however, necessary on the one hand for early detection of side-effects, on the other hand to avoid unnecessary referral for costly and time-consuming neuropsychological investigations. Our work has shown that a screening instrument may be based on the subjective complaints of the patients, under the condition of structural assessment. A subjective complaint list, focused on assessing cognitive side-effects such as the ABNAS³⁴ or focused on a broader range of side-effects including the cognitive domain such as the SIDAED,⁶ may be helpful. Other questionnaires exist and are available in the public domain. Such questionnaires can be completed online or in the waiting room prior to a consultation for clinical practice. To objectify the subjective complaints, a neuropsychological investigation can be used. We have demonstrated that fluid cognitive functions are most sensitive for the cognitive impact of AEDs and in particularly information processing speed. Even mild effects on fluid functions must therefore be controlled with neuropsychological follow-up when longer treatment durations (i.e. years) are necessary, especially in children to

avoid interference with normal cognitive development. Computerized cognitive assessment to monitor alertness, information processing speeds and other attentional functions has the advantage of reducing assessment time to a mere 20 minutes and the immediate availability of test results for advising the patients.⁵¹ In many occasions, assessment of potential cognitive side-effects requires repeated testing and a short focused test battery is then an advantage.

Implications for future research

The most preferable research design to investigate the impact of AEDs, would be a longitudinal, double-blind, randomized controlled trial in patients (adults and children) with newly diagnosed epilepsy with a non-medicated baseline. These studies are not affected by concurrent or previous AED use, heterogeneous patient populations, or the seizures. However, this optimal research design is not achievable in our patient population because in most patients, treatment is already started before referral to our tertiary referral clinic and the epilepsy syndrome may be unclear or misdiagnosed.

As cognitive outcomes are usually not investigated in the industry driven randomized controlled trials when a new drug is in development, it is only possible to speculate about the potential impact on cognition based on the mechanism of action.⁵² The alternative is to study the effects in a naturalistic setting with limited protection against bias. We therefore recommend that when new AEDs become available for clinical practice, networks of centers are formed to identify the cognitive profile of the new drug as soon as possible. Possibly tertiary epilepsy centers can serve as an organizational 'hub' in such networks. We have to close the gap between introduction of a drug and the identification of its cognitive and mood profile. Levetiracetam was internationally introduced in clinical practice in 1999/2000 but the very first publication describing its possible psychiatric effects was 4-5 years later.⁵³ From 2007/2008 first publications appeared that the increased irritability is not a rare, but rather a common side-effect of this AED.

Furthermore, most studies have a limited duration with trials mostly not exceeding the 12-weeks period, which is in contrast with treatment durations of years instead of weeks in clinical practice. Especially in more vulnerable groups such as children or patients with intellectual disabilities, in which chronic anti-epileptic treatment may impact cognitive developmental processes by accumulating effects, this is an important issue. Therefore, more research is needed to investigate the effects of chronic anti-epileptic treatment, in particular in children and patients with intellectual disabilities. These studies should also focus on useful parameters to assess side-effects. Although neuropsychological testing is not always possible in patients with intellectual disabilities, the focus should be on more subtle effects than the functional status that we studied. A possible new technique to investigate drug-induced impairments may be eye tracking which measures eye positioning and eye movements, and can also be used in these more specific patient populations. Future studies should also focus on the

usefulness of MR-based biomarkers and more advanced MR-technologies such as Magnetic Resonance Spectroscopy imaging of the prefrontal cortex.

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Summary

Summary

Chapter 1, the general introduction, provides background information on epilepsy and antiepileptic treatment. Also, the main research questions and the structure of this thesis is provided.

Chapter 2 gives an overview of the current knowledge on the cognitive effects of all commonly used antiepileptic drugs. A relatively large number of studies are available for adults but for children the evidence is sketchy. Phenobarbital has serious cognitive effects that may even impact higher-order cognitive function. Phenytoin may also have an impact on higher-order cognitive function, specifically on memory, mental speed and concentration. Valproate and carbamazepine do not seem to impair cognition to a great extent. No detrimental effect on cognitive function is described for oxcarbazepine. Among the newer antiepileptic drugs, there is clear evidence for drug-induced cognitive impairment in language function for topiramate and zonisamide. Levetiracetam and lamotrigine may have a cognitive enhancing effect, especially on attentional function. For other antiepileptic drugs, including the drugs from the newest generation, the data are inconclusive.

Chapter 3 presents the cognitive effects of lacosamide, a relatively new antiepileptic drug therapy with potential benefit as adjunctive treatment in patients with partial onset seizures. None prior studies on the cognitive effects of lacosamide were available. Thirty-three patients with localization related epilepsy between 16-74 years were assessed at baseline before starting lacosamide treatment and during follow-up when the optimal clinical dose was achieved. Although patients had a significantly faster information processing speed (which could not be explained by improved seizure control), they complained more about their cognitive function than before using this drug. This was described as the 'doing better, feeling worse' phenomenon due to an increased awareness of patients of other cognitive difficulties.

Chapter 4 presents the cognitive effects of ethosuximide which is one of the oldest antiepileptic drugs. Nonetheless, information on the cognitive effects of this antiepileptic drug was almost completely absent. Sixty-one patients aged 6-16 years treated with monotherapy ethosuximide for their absence seizures were investigated with a neuropsychological test battery. Treatment was effective in the majority of these patients; 70% were seizure free for at least 6 months. The higher-order cognitive functions (such as intelligence, memory and visual-perceptual functions) were affected by the seizures but not by the treatment. The fluid cognitive functions, such as activation, alertness, sustained auditory attention and attentional control or switching, showed mild impairments that were attributed to ethosuximide. It was concluded that

the cognitive impact on psychomotor slowing and alertness of this drug is mild, which is comparable to other antiepileptic drugs such as carbamazepine or oxcarbazepine.

For patients with drug-resistant epilepsy, nonpharmacological treatment options are available. **Chapter 5** evaluates the cognitive and behavioral impact of the ketogenic diet which is a high-fat, low-carbohydrate diet. In this randomized controlled trial, the performance of 28 patients using the ketogenic diet was compared with 22 patients from the care as usual (control) group. Follow-up assessments at four months showed lower levels of anxious and mood disturbed behavior for the ketogenic diet-group who was also rated as more productive. Cognitive test results showed an improvement of activation in the ketogenic diet-group. Overall, an activated mood and cognitive activation was observed in patients treated with the ketogenic diet which lead to the conclusion that the ketogenic diet has a positive impact on behavioral and cognitive functioning in children and adolescents with refractory epilepsy.

Chapter 6 discusses the impact of long-term treatment with antiepileptic drugs on cognitive development. Fifty patients with epilepsy, aged 6-16 years, who had been treated with monotherapy with either carbamazepine or valproate since epilepsy onset and without any switch to other medication in the past were included in this study. Both treatment groups had a mean treatment duration of approximately two years and were comparable in demographical and epilepsy related characteristics. Cognitive tests assessing 'fluid functions' such as alertness or information processing speed showed no differences between both groups. Apparently, both drugs affected these functions to the same extent. However, patients on carbamazepine had significant lower intelligence values than patients on valproate. These findings suggest that chronic use of carbamazepine may impact higher-order cognitive function and even intelligence over longer periods of time, possibly through accumulating effect of drug-induced impairments on cognitive developmental processes. This emphasizes the need to study effects of chronic use of antiepileptic drugs, especially in children.

Chapter 7 describes the subjectively perceived side-effects of antiepileptic drug treatment in patients with chronic refractory epilepsy visiting the outpatient departments of a tertiary referral center. In total, 203 patients completed the questionnaire. Mean age of the patients was 37 years (2-81). Most reported complaints were about their general health (85%), followed by cognition (77%), mood (69%) and cosmetics (42%). This study found no differences in the rate and type or severity of complaints between patients using polytherapy versus monotherapy and between patients using older versus newer medication. Patients using antiepileptic drugs with a high risk for side-effects did complain more about their mood but not about their cognition.

Chapter 8 reports the profile of patients who are at risk for developing cognitive side-effects of antiepileptic drug treatment. Fifty-three patients aged 20-69 years using antiepileptic medication were divided in a low risk group (levetiracetam or lamotrigine) and a high risk group (phenytoin or topiramate). Patients in the high risk group were slower on a central information processing task than patients in the low risk group. This drug-induced mental slowing appeared to be predicted by subjective complaints about the antiepileptic drug treatment and the duration of epilepsy. In clinical practice, patients with chronic epilepsy complaining about their treatment may be regarded as at risk for developing cognitive side-effects justifying referral for specialized neuropsychological assessment.

Chapter 9 evaluates the impact of chronic use of 'high risk' antiepileptic medication on functional status in patients with intellectual disabilities. The Barthel Index of Activities of Daily Living was used in 153 patients, aged 18-72 years, over a ten year period. This study showed that chronic treatment with 'high risk' medication did not lead to a faster decline of functional status than 'low risk' medication. Furthermore, type of epileptic seizures had no effect. Naturally, level of functional dependency decreases over time due to an increasing age and was affected by level of intellectual disability. Based on this study, it was concluded that, compared to the demographic effects of the patients, antiepileptic drug treatment had no additional negative impact on the functional status in patients with epilepsy and intellectual disabilities.

Chapter 10 and **chapter 11** describe the effects of drug-induced impairment on brain function and brain activity. For these MR-studies, 55 patients using a variety of antiepileptic drugs from three categories with different risks for cognitive side-effects, i.e. a low (levetiracetam or lamotrigine), intermediate (carbamazepine, oxcarbazepine, valproate or phenytoin), and a high (topiramate) risk, were investigated with different assessments. Cognition was assessed with the Computerized Visual Searching Task (CVST). Brain connectivity was assessed using resting state functional MRI and graph theoretical network analysis and patients underwent MR spectroscopy. These studies showed that patients with lower processing speeds had lower glutamate concentrations. Furthermore, the functional brain organization for patients in the highest risk category was altered and associated with the drug-induced mental slowing. These studies suggest that mild alterations in neurotransmitter concentration levels and functional brain network organization may have contributed to the development of cognitive side-effects.

In **chapter 12**, the general discussion, the results of all studies are discussed by answering five pertinent clinical questions. Furthermore, the discussion suggests implications for clinical practice and future research.

Samenvatting

Samenvatting

Hoofdstuk 1, de algemene inleiding, verstrekt achtergrondinformatie over epilepsie en over anti-epileptische medicatie. Ook de belangrijkste onderzoeksvragen en de opzet van dit proefschrift is weergegeven.

Hoofdstuk 2 geeft een overzicht van de huidige kennis over de cognitieve bijwerkingen van alle algemeen gebruikte anti-epileptica. Een relatief groot aantal studies zijn beschikbaar voor de interpretatie van effecten bij volwassenen maar voor kinderen zijn er veel minder studies en gegevens. Fenobarbital heeft ernstige cognitieve bijwerkingen die zelfs de hogere-orde cognitieve functies en dan met name het geheugen kunnen beïnvloeden. Fenytoïne kan eveneens hogere-orde cognitieve functies beïnvloeden, met name de mentale snelheid, concentratie en het geheugen. Valproaat en carbamazepine zijn middelen die in de regel slechts een mild effect hebben op met name de fluïde cognitieve functies (functies die sterk kunnen wisselen, zoals aandachtsfuncties). Hetzelfde geldt ook voor het medicament oxcarbazepine. Van de nieuwere anti-epileptica zien we enerzijds activerende effecten voor levetiracetam en lamotrigine, anderzijds stoornissen van een hogere-orde cognitieve functie, namelijk de taalfunctie voor topiramaat en zonisamide. Voor de andere anti-epileptica, waaronder ook medicamenten van de nieuwste generatie, zijn feitelijk geen gegevens voorhanden.

Hoofdstuk 3 beschrijft de cognitieve effecten van lacosamide, een relatief nieuw anti-epilepticum dat gebruikt wordt bij partiële epilepsie. Er waren geen eerdere studies naar de cognitieve effecten van lacosamide beschikbaar en tijdens de voor de registratie noodzakelijke gerandomiseerde klinische studies is niet op cognitie gelet. Drieëndertig patiënten met een gelokaliseerde epilepsie, tussen 16-74 jaar oud, werden onderzocht op baseline (voordat gestart werd met de lacosamide behandeling) en tijdens de follow-up (wanneer de optimale klinische dosering was bereikt). De patiënten toonden enerzijds een significant snellere centrale informatieverwerkingssnelheid (niet samenhangend met een verbeterde aanvalscntrole). Anderzijds klaagden ze meer over hun cognitief functioneren. Dit is in de literatuur eerder beschreven als het 'doing better, feeling worse' fenomeen, dat het gevolg is van een verhoogd besef van patiënten op andere cognitieve problemen.

Hoofdstuk 4 beschrijft de cognitieve effecten van ethosuximide, een van de anti-epileptica van de eerste generatie. Desalniettemin was informatie over de cognitieve bijwerkingen van dit anti-epilepticum nauwelijks aanwezig. Eenenzestig patiënten in de leeftijd 6-16 jaar die behandeld werden met monotherapie ethosuximide voor hun absences werden onderzocht met een neuropsychologische testbatterij. Behandeling was effectief bij het merendeel van onze patiënten: 70% was minstens 6 maanden

aanvalsvrij. De hogere-orde cognitieve functies zoals intelligentie, geheugen en visueel-perceptuele functies werden beïnvloed door de aanvallen maar niet door de behandeling. De fluïde cognitieve functies zoals activatie, alertheid, volgehouden auditieve aandacht, aandachtscontrole en het switchen van de aandacht, toonden milde verstoringen die toegeschreven werden aan de ethosuximide. Geconcludeerd werd dat de cognitieve bijwerkingen van dit anti-epilepticum mild zijn en het daarmee gerangschikt kan worden in de klasse middelen zoals carbamazepine of oxcarbazepine.

Voor patiënten met een medicatie-resistente epilepsie zijn er non-farmacologische behandelingsopties beschikbaar. **Hoofdstuk 5** evalueert de cognitieve en gedragsmatige effecten van het ketogeen dieet, dat een vetrijk en koolhydraatarm dieet is. In deze gerandomiseerde gecontroleerde studie werd de prestatie van 28 patiënten die het ketogeen dieet gebruikten vergeleken met 22 patiënten die de gebruikelijke zorg kregen en als controlegroep dienden. Follow-up metingen na vier maanden toonden voor de ketogeen dieet-groep een betere stemming en productiever gedrag. Cognitieve test resultaten toonden een verbeterde activatie bij de ketogeen dieet-groep. Dit leidde tot de conclusie dat het ketogeen dieet een positief effect heeft op het gedragsmatige en cognitieve functioneren bij kinderen en adolescenten met refractaire epilepsie.

Hoofdstuk 6 bespreekt het effect van chronische behandeling met anti-epileptica op de cognitieve ontwikkeling bij kinderen. Vijftig patiënten met epilepsie, in de leeftijd 6-16 jaar, die sinds het debuut van de epilepsie uitsluitend behandeld werden met monotherapie carbamazepine of valproaat werden in deze studie geïnccludeerd. Beide groepen hadden een gemiddelde behandelduur van bijna twee jaar en waren vergelijkbaar in demografische en epilepsie gerelateerde kenmerken. Cognitieve testen die de fluïde cognitieve functies meten zoals de alertheid en informatieverwerkings-snelheid toonden geen verschillen tussen beide groepen. Klaarblijkelijk beïnvloedden deze anti-epileptica deze functies in dezelfde mate. Patiënten die carbamazepine gebruikten, hadden echter significant lagere intelligentiewaarden dan patiënten die valproaat gebruikten. Deze bevindingen suggereren dat chronisch gebruik van carbamazepine de hogere-orde cognitieve functies kan aantasten na een langere periode. Mogelijk is er sprake van accumulerende effecten waarbij langdurige verstoringen van fluïde cognitieve processen uiteindelijk ook kunnen leiden tot afwijkingen in de cognitieve ontwikkeling. Dit benadrukt de noodzaak om de effecten van chronisch gebruik van anti-epileptica te onderzoeken, vooral bij kinderen.

Hoofdstuk 7 beschrijft de subjectieve klachten over bijwerkingen door patiënten met een chronische, refractaire epilepsie die de polikliniek van een derdelijns instelling bezochten. In totaal werden 203 patiënten geïnccludeerd. De meest gerapporteerde klachten gingen over de algemene gezondheid (85%), gevolgd door klachten over het cognitief functioneren (77%), de stemming (69%) en het uiterlijk (42%). In dit

onderzoek werden er geen verschillen gevonden in het aantal of de ernst van de klachten tussen patiënten die polytherapie en monotherapie gebruikten. Dit gold ook voor de patiënten die oudere versus nieuwere medicatie gebruikten. Patiënten die een anti-epilepticum gebruikten met een hoog risico op bijwerkingen, klaagden meer over hun stemming maar niet over hun cognitie.

In **hoofdstuk 8** wordt onderzocht of het mogelijk is het risico op het ontwikkelen van cognitieve bijwerkingen van anti-epileptica te voorspellen. Drieënvijftig patiënten, in de leeftijd 20-69 jaar die medicatie gebruikten werden in een laag risico groep (levetiracetam of lamotrigine) en een hoog risico groep (fenytoïne of topiramaat) verdeeld. Patiënten in de hoge risico groep waren trager op een centrale informatie-verwerkingstaak. Deze door medicatie veroorzaakte mentale traagheid was gecorreleerd met subjectieve klachten over de anti-epileptische behandeling en met de duur van de epilepsie. Patiënten met chronische epilepsie die klagen over hun medicatie, lopen inderdaad risico op het ontwikkelen van cognitieve bijwerkingen. Dergelijke klachten moeten serieus genomen worden en doorverwijzing voor neuropsychologisch onderzoek is dan nuttig.

Hoofdstuk 9 evalueert de invloed van het gebruik van hoog risico anti-epileptische medicijnen op de activiteiten van het dagelijks leven van patiënten met een verstandelijke beperking. De Barthel Index van 153 patiënten, in de leeftijd 18-72 jaar, werd gevolgd gedurende een periode van 10 jaar. Dit onderzoek toonde dat chronische behandeling met hoog-risico medicatie niet leidt tot een meetbare achteruitgang in het uitvoeren van algemeen dagelijkse handelingen dan laag-risico medicatie. Aanvalstype bleek eveneens geen effect te hebben. De functionele status vermindert (wat leidt tot een toename van afhankelijkheid) gedurende deze periode door algemene factoren als veroudering en de mate van verstandelijke beperking. Op basis van dit onderzoek werd geconcludeerd dat anti-epileptische medicatie geen additioneel negatief effect heeft op de algemeen dagelijkse handelingen in de groep patiënten met epilepsie en een verstandelijke beperking.

In **hoofdstuk 10** en **hoofdstuk 11** worden de onderzoeken gerapporteerd naar neuronale achtergronden van cognitieve bijwerkingen. Voor deze MRI-studies werden 55 patiënten ingedeeld in drie categorieën op basis van hun medicatie: een groep met een laag risico op cognitieve bijwerkingen (levetiracetam of lamotrigine), een tussengroep (carbamazepine, oxcarbazepine, valproaat of fenytoïne) en een hoge risicogroep (topiramaat). Zij werden op verschillende manieren onderzocht. De snelheid van centrale informatieverwerking (mentale snelheid) als meest gevoelige functie voor de cognitieve effecten van anti-epileptica, werd vastgesteld met de FePsy gecomputeriseerde visuele zoektaak (CVST). Hersenconnectiviteit werd bepaald door het gebruik van functionele MRI tijdens rust en graaf theoretische analyse methodes en

patiënten kregen MR spectroscopie. Deze onderzoeken toonden aan dat patiënten met een lagere centrale verwerkingssnelheid, lagere glutamaat concentraties hadden. De functionele hersenorganisatie voor patiënten in de hoogste risicoklasse was veranderd en geassocieerd met de door medicatie geïnduceerde mentale vertraging. Deze studies suggereren dat milde veranderingen in neurotransmitter concentratie niveaus en functionele hersen netwerkorganisatie kunnen hebben bijgedragen aan de ontwikkeling van cognitieve bijwerkingen.

In **hoofdstuk 12**, de algemene discussie, worden de resultaten van alle studies besproken door het beantwoorden van vijf belangrijke, klinische vragen. Bovendien worden er aanbeveling gegeven voor in de klinische praktijk en voor vervolgonderzoek.

Valorisation

Valorisation

Relevance

Worldwide, about 70 million people are estimated to have epilepsy.^{1,2} Epilepsy is characterized by recurrent unprovoked seizures. Seizure control is imperative for medical reasons but also because the unpredictable paroxysmal nature of the symptoms (seizures), as well as feeling of loss of control may negatively impact the psychosocial situation affecting the emotional state, coping and consequently, quality of life. Moreover, some objective limitations go with the diagnosis with impact on the social position, such as losing driving license, or restrictions in some sports (such as swimming) as well as occupational limitations.

In most patients with epilepsy, antiepileptic drug (AED) treatment is the first choice of treatment. The best possible outcome of AED treatment is to achieve complete seizure freedom without adverse events. However, AED-induced cognitive side-effects are a major issue in the treatment of epilepsy. Deficiencies in attention, memory, language ability and reaction time are frequently reported side-effects of AEDs.³ All AEDs have the potential for adverse effects on cognitive functioning. However, variability between types of drugs and individuals is considerable. Therapeutic dilemmas arise when reduction of seizure frequency can only be accomplished with medication that is associated with cognitive side-effects. As side-effects of AEDs have a major impact on health care costs⁴ and given that most patients with epilepsy consider the adverse cognitive effects of antiepileptic medication to substantially influence their quality of life,⁵ and to be an important reason for AED discontinuation,^{6,7} the possibility of side-effects should be taken into the medical decision making as a top priority in the choice of AEDs or in the need to switch.

Target groups

The results of this thesis are relevant for patients with epilepsy and all physicians who treat patients with epilepsy (such as neurologists, child neurologists, general practitioners, pediatricians). Nowadays, as some AEDs are also used for other diseases such as migraine (valproate, topiramate) and neuropathic pain (carbamazepine, gabapentin, pregabalin), this makes this thesis also of interest for psychiatrists who should be aware of the cognitive effects of AED use.

Patients should be informed about the possible negative effects of an AED on their cognition. Furthermore, the outcomes of this thesis help to identify patients with epilepsy at risk for developing cognitive side-effects in an early stage. We paid special attention to subjective reports e.g. self-reported complaints and caregiver reports. Early recognition of patients with epilepsy at risk for cognitive impairments due to treatment through screening procedures can lead to early interventions in their

treatment strategies. Monitoring cognition and discussing their side-effects should be common in clinical practice when starting or changing AED treatment.

This results of this thesis are also interesting for pharmacologists and the pharmaceutical industry. In the industry-driven regulatory trials only a limited number of subjectively reported side-effects are recorded (using fixed systems such as the WHO-ART system). Objective assessment of side-effects is generally not included. We have highlighted the relevance of taking cognition as an outcome measurement in the randomized controlled trials. Until this is realized, identification of the cognitive profile of new drugs available for clinical practice in the naturalistic setting is a good, but slow, alternative.

Activities

The research described in this thesis have led to a more understanding of the cognitive adverse effects of AEDs in patients with refractory epilepsy. It has given an overview of the available literature about the cognitive functions that can be affected by antiepileptic treatment in adults and in children and has discussed some of the missing information. Furthermore, the focus has been not only at detecting side-effects, but a start has been made to explain why side-effects occur in specific patients in reaction to specific drugs. We used two (MR-)techniques to identify the neuronal substrates of cognitive side-effects.

The results of this thesis are published (or submitted) in international peer-reviewed journals and are discussed during (poster)presentations at (inter)national symposia. Furthermore, in the Dutch guidelines for epilepsy it is stated that a neuropsychological screening is indicated when cognitive deficits due to medication are reported and for patients using AEDs with a high risk for cognitive effects (such as phenobarbital, phenytoin or topiramate) or for behavioral effects (levetiracetam).

Innovation

Although the first studies about the cognitive side-effects of AED-treatment are from the late 1970's,⁸ many newer AEDs became available of which the cognitive effects were unknown. Furthermore, evidence was and is clearly lacking for children compared to adult patients with epilepsy. In the last part of this thesis (chapter 12), five pertinent clinical questions could be answered based on the results discussed in this thesis. Some of these questions were also raised by the so-called 'anti-epileptic drug committee' ('Geneesmiddelen commissie') of our epilepsy center. This committee consisting of six neurologists, one pharmacist, three trial nurses, one clinical chemist, and one neuropsychologist is meeting every month to discuss the progress of all drug-related research that is performed in our center. This includes the implementation of the pharmacological studies initiated by the industry but also of investigator driven studies.

Implementation

The results of this thesis can be used in clinical practice and for further research implications which are also discussed in the discussion part of this thesis. We have highlighted that screening instruments can be used for early detection of side-effects that can be confirmed with a neuropsychological investigation. It is not known whether and when our recommendations for the pharmaceutical industry and for clinically driven studies will be implemented. At this moment, we are gathering data of patients with epilepsy using AEDs performing computerized cognitive tasks (assessing alertness and information processing speed) simultaneously with eye tracking, which measures eye positioning and eye movements. This might possibly be a new useful technique to investigate drug-induced impairments.

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Dankwoord

Dankwoord

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Op de eerste plaats aan alle patiënten die hebben deelgenomen aan de wetenschappelijke onderzoeken. Of het nu ging om een afname van 'slechts' enkele korte taken of een hele uitgebreide MRI-studie, steeds weer werd ik aangenaam verrast door het enthousiasme en de motivatie van de deelnemers. Zelfs als er een flinke afstand voor overbrugd moest worden (en dat soms tot twee keer toe wanneer de scans niet voldoende bruikbaar bleken te zijn). Zonder deze bereidwillige patiënten is het uitvoeren van wetenschappelijk onderzoek niet mogelijk.

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Curriculum Vitae

Curriculum Vitae

Dominique Mistral IJff werd op 3 mei 1987 geboren in Weert en groeide op in Waalre. Na het behalen van haar VWO-diploma in 2005 aan het Van Maerlantlyceum in Eindhoven, verhuisde ze naar Amsterdam. Van 2005 tot 2010 studeerde zij klinische neuropsychologie aan de Universiteit van Amsterdam. Naast haar studie werkte ze als pedagogisch medewerker bij Unieke Kinderopvang in Amsterdam. Tijdens de zomervakanties werkte ze als begeleider in de dagelijkse zorg en activiteiten van volwassenen en kinderen met epilepsie bij het Epilepsiecentrum Kempenhaeghe in Heeze, waar haar interesse voor epilepsie groeide. In het laatste jaar van haar tweejarige master Gezondheidszorgpsychologie verrichte zij een klinische stage en een wetenschapsstage te Kempenhaeghe. Hieruit volgde de eerste publicatie waar ze aan heeft bijgedragen over het cognitieve en gedragsmatige profiel van kinderen met een frontaalkwab-epilepsie. Na haar afstuderen werkte zij 3 jaar als psycholoog bij de Gedragswetenschappelijke Dienst van Kempenhaeghe. In september 2013 startte zij aldaar met de postdoctorale opleiding tot GZ-psycholoog in combinatie met haar promotieonderzoek. Momenteel rondt ze het klinische gedeelte van haar opleiding af. In de toekomst ambieert ze het combineren van patiëntenzorg met wetenschappelijk onderzoek.

Dominique Mistral IJff was born on May 3rd 1987 in Weert. She was raised in Waalre. After graduating her secondary school education in 2005 at the Van Maerlantlyceum in Eindhoven, she moved to Amsterdam. She studied clinical neuropsychology at the University of Amsterdam from 2005 to 2010. During her study, she worked as a day care worker at Unieke Kinderopvang in Amsterdam. During summer, she assisted in the daily care and activities of adults and children with epilepsy at the Epilepsy Center Kempenhaeghe in Heeze, which resulted in a growing interest in epilepsy. During the last year of her two-year master Health Care Psychology, she performed a clinical internship and a research internship. This research internship resulted in a first publication in which she contributed about the cognitive and behavioral findings in children with frontal lobe epilepsy. After graduating, she started working as a psychologist at the Department of Behavioral Sciences at Kempenhaeghe. In September 2013, she started with the postgraduate program to become a registered mental-health psychologist in combination with her PhD-research. Currently, she is finishing the clinical part of her post-graduate program. In the future, she aspires to combine patient care with clinical research.

List of publications

List of publications

In this thesis

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