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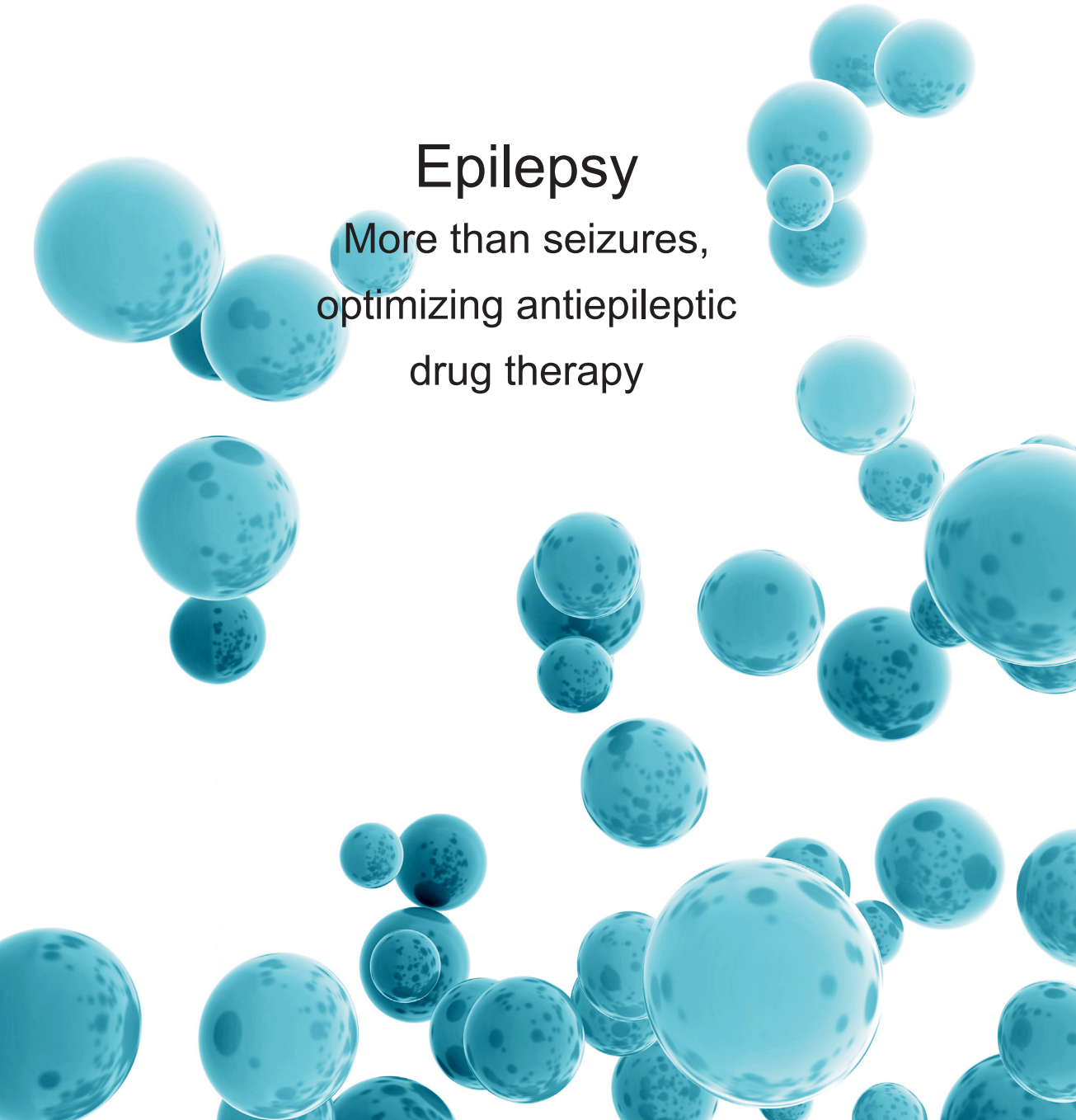
JUSSI MÄKINEN

Epilepsy

More than seizures, optimizing antiepileptic drug therapy



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ACADEMIC DISSERTATION
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Abstract

If the patient has recurrent seizures, if the diagnosis of epilepsy is conclusively established and if epilepsy surgery will most unlikely to be fruitful, then it is recommended that further attempts at optimizing the medical therapy should be pursued. During the last decade, a new antiepileptic drug (AED) has been introduced for clinical use on an almost annual basis. Convincing evidence for synergistic antiepileptic effects has not accumulated at a similar rate. Currently, the rational choice of AED combinations is often based on avoidance of pharmacological adverse-events (AEs) and patient comorbidities. The numerous emerging opportunities for combination therapy has also raised concerns of irrational polytherapy or overtreatment of epilepsy. This study aimed to enhance the options for clinical management of epilepsy by producing practical information for optimizing the AED treatment in terms of minimizing the AE while maximizing the therapeutic effect.

In the first part of the study, the impact of new antiepileptic drugs on overall outcome for patients with epilepsy was assessed. In 2014, a higher percentage of patients with polytherapy were seizure-free compared with the original analysis conducted ten years previously (22% vs. 30%). The most common pairing of 52 different combinations for duo-therapy was levetiracetam-oxcarbazepine.

We then analyzed the long-term retention rate (tolerability and efficacy combined) of eight most common AEDs in combination therapy and the effect of age and gender on retention rates were also assessed. The following 3-year retention rates were calculated: lacosamide 77%, lamotrigine 68%, levetiracetam 67%, clobazam 66%, topiramate 62%, zonisamide 60%, pregabalin 55%, and gabapentin 40%. Lacosamide, levetiracetam, and clobazam were the most effective AEDs in the elderly. The retention rate for pregabalin was higher in males (65%) than females (51%) whereas females had higher retention rates for both topiramate (72% vs. 58%) and zonisamide (67% vs. 57%). The retention rate was influenced by the sequence in which these AEDs had entered the market.

The third part of the study aimed to identify possible benefits and risk of transitioning from oxcarbazepine to eslicarbazepine acetate. In 65% of the

patients, the oxcarbazepine-related AEs were reduced after transition. No patient suffered an increase in seizure frequency following the transition.

The first choice, and comparator in clinical trials has been carbamazepine. During execution of this study, carbamazepine or oxcarbazepine where first-choice drugs for focal-onset epilepsy in Finland. However, concerns have been raised about whether patients on a potent enzyme inducer, such as carbamazepine, should be switched to non-inducing AEDs in order to avoid the long-term effects of enzyme induction. Twenty percent of the seizure-free patients on carbamazepine had recurrent seizures after carbamazepine discontinuation compared to 5% of those who continued with carbamazepine. A significant decrease in serum levels of total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), sex hormone binding globulin (SHBG), and increase in free testosterone were found in the discontinuation group compared with those who continued carbamazepine. Nonsignificant changes in triglycerides and vitamin D levels were detected.

Some patients with focal epilepsy might benefit from the newer AEDs as an adjunctive therapy to help achieve seizure-freedom. These data should encourage clinicians to continue active drug trials on those with persistent seizures. The retention rate appears to be influenced by the sequence in which these AEDs were introduced onto the market. There are differences in effectiveness between clobazam, gabapentin, lacosamide, lamotrigine, levetiracetam, pregabalin, topiramate, and zonisamide as adjunctive therapy for focal refractory epilepsy. The options for first line AEDs with similar mechanisms of actions should be considered if adverse events emerge, as our data indicate that safe transition can be accomplished. Discontinuation of carbamazepine in seizure-free patients seems to carry a moderate, but legitimate risk of relapse. Conversely, carbamazepine might have unfavorable effects on serum levels of TC, HDL, LDL, SHBG, and free testosterone. Most importantly, the importance of good communication between patient and treating physician is underlined in all situations.

Tiivistelmä

Epilepsialääkityksen optimointia tarvitaan, mikäli potilaalla esiintyy toistuvia epileptisiä kohtauksia, eikä epilepsiakirurgia tule kyseeseen. Kuluneen vuosikymmenen aikana kliiniseen käyttöön on tullut uusi epilepsialääke lähes vuosittain. Nykyisin epilepsian yhdistelmälääkehoito perustuu usein farmakologisesti epäedullisten yhdistelmien välttämiseen ja potilaan mahdollisten liitännäissairauksien huomioimiseen. Vaihtoehtoisten lääkeyhdistelmien runsas lukumäärä on herättänyt ajatuksia myös mahdollisista epäjohdonmukaisista lääkeyhdistelmistä ja liiallisesta hoidosta. Tämän tutkimuksen tarkoituksena oli tuottaa lisää käytännönläheistä tietoa epilepsian lääkehoidosta, jonka avulla pystytään entistä paremmin minimoimaan lääkitykseen liittyvät haitat ja toisaalta maksimoimaan teho.

Tutkimuksen ensimmäisessä osassa arvioitiin uusien epilepsialääkkeiden tehoa yhdistelmälääkehoidossa. Vuosien 2004-2014 välisenä aikana yhdistelmälääkehoitoa saavista kohtauksettomien potilaiden osuus oli merkittävästi lisääntynyt (22% vs. 30%). Tavallisin kahden epilepsialääkkeen yhdistelmä oli levetirasetaami-okskarbatsepiini.

Toisessa osatyössä analysoitiin kahdeksan yleisimmän epilepsialääkkeen käyttöä kolmen seurantavuoden aikana yhdistelmähoidossa. Lakosamidia käytti edelleen 77% kolmen vuoden kuluttua lääkityksen aloittamisesta, lamotrigiinia 68%:, levetirasetaamia 67%, klobatsaamia 66%, topiramaattia 62%, zonisamidia 60%, pregabaliinia 55% ja gabapentiinia 40%.

Seuraavaksi pyrittiin tunnistamaan mahdolliset hyödyt ja riskit, kun lääkitys vaihdetaan okskarbatsepiinista eslikarbatsepiiniasetaattiin. Kolmen seurantakuukauden aikana kahdella kolmasosalla okskarbatsepiiniin liittyvät lääkehaitat vähenivät lääkevaihdon myötä ilman kohtausalttiuden lisääntymistä.

Karbamatsepiini on epilepsian ensisijaislääke Suomessa sekä lääketutkimuksissa käytetty vertailuvalmiste. Karbamatsepiini on kuitenkin voimakas entsyymi-induktori, jonka pitkäaikaiskäyttöön saattaa liittyä epäedullisia muutoksia elimistön omissa endogeenisissä prosesseissa. Viimeisessä osatyössä selvitettiin karbamatsepiinin käytön lopettamisen vaikutuksia kohtaustilanteeseen ja toisaalta kolesteroli- sukupuolihormoni- ja D-

vitamiinitasoihin. Karbamatsepiinin käytön lopettamisen jälkeen viidesosa potilaista sai epileptisen kohtauksen puolen vuoden seuranta-aikana ja vastaavasti 5% karbamatsepiinia jatkaneista sai kohtausoireen. Seerumin kokonaiskolesterolin, HDL- ja LDL-lipoproteiinien, sukupuolihormoneja sitovan glubuliinin (SHBG) määrät vähenivät ja vapaa testosteroni pitoisuus suureni merkittävästi karbamatsepiinin lopettamisen myötä. D-vitamiinin pitoisuuksissa ei havaittu merkittäviä muutoksia.

Osa paikallisalkuista epilepsiaa sairastavista saattaa hyötyä uudemmista epilepsialääkkeistä kohtauksettomuuden saavuttamiseksi. Tämä tieto rohkaisee jatkamaan aktiivisia lääkehoitoponnisteluja, mikäli kohtauksia ei saada hallintaan. Tavallisimpien paikallisalkuisen epilepsian lisälääkkeiden osalta pidempiaikaista hoitovastetta on mahdollista ennustaa jo ennen lääkityksen aloittamista. Mikäli ensilinjan lääkitykseen liittyy merkittäviä haittoja, vaihtoa vastaavalla mekanismilla vaikuttavaan lääkkeeseen voidaan harkita, koska tutkimuksemme mukaan vaihto voidaan toteuttaa turvallisesti. Karbamatsepiinilääkityksen lopettamiseen kohtauksettomilta potilailta näyttää liittyvän kohtalainen, mutta hyväksyttävä kohtausten uusimisen riski. Toisaalta karbamatsepiini näyttää vaikuttavan epäedullisesti kokonaiskolesteroli-, HDL-, LDL-, SHBG-, ja vapaa testosteronipitoisuuksiin. Epilepsian lääkehoidossa kaikkein tärkeintä on kuitenkin, että päätökset lääkitykseen liittyen tehdään yhteisymmärryksessä potilaan ja hoitavan lääkärin kanssa.

Contents

List of original publications

The original publications will be referred to in the text by Roman numerals I-IV:

I Mäkinen J, Rainesalo S, Raitanen J, Peltola J. The effect of newer antiepileptic drugs in combination therapy. Epilepsy Res. 2017;132:15-20.

II Mäkinen J, Peltola J, Raitanen J, Alapirtti T, Rainesalo S. Comparative effectiveness of eight antiepileptic drugs in adults with focal refractory epilepsy: The influence of age, gender, and the sequence in which drugs are introduced onto the market. J Neurol. 2017;264:1345-53.

III Mäkinen J, Rainesalo S, Peltola J. Transition from oxcarbazepine to eslicarbazepine acetate: A single center study. Brain Behav. 2017;7:e00634.

IV Mäkinen J, Rainesalo S, Raitanen J, Saarinen J, Sandell S, Peltola J. Discontinuation of carbamazepine due to long-term effects of enzyme induction. Submitted.

Abbreviations

AE	Adverse-event
AED	Antiepileptic drug
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid
ANT	Anterior nucleus of the thalamus
AVM	Arteriovenous malformation
CBZ	Carbamazepine
CD	Cortical dysplasia
CI	Confidence interval
CLB	Clobazam
CNS	Central nervous system
CYP	Cytochrome P450
CZP	Clonazepam
DBS	Deep brain stimulation
DDD	Defined daily dose
DNET	Dysembryoplastic neuroepithelial tumour
EDTA	Ethylenediaminetetra-acetic acid
EEG	Electroencephalography
EI	Enzyme induction
ESL	Eslicarbazepine acetate
FDA	The Food and Drug Administration
FDG	Fluorodeoxyglucose
GABA	γ-aminobutyric acid
GBP	Gabapentin
GTC	Generalized tonic-clonic
HDL	High-density lipoprotein
HS	Hippocampal sclerosis
ICH	Intracerebral hemorrhage
LCM	Lacosamide
LDL	Low-density lipoprotein

LEV	Levetiracetam
LTG	Lamotrigine
MOA	Mechanism of action
MRI	Magnetic resonance imaging
OR	Odds ratio
OXC	Oxcarbazepine
PET	Positron emission tomography
PGB	Pregabalin
PHT	Phenytoin
PMD	Primidone
PRP	Perampanel
QOL	Quality of life
SHBG	Sex hormone binding globulin
T	Tesla
T3	Triiodothyronine
T4	Thyroxine
TPM	Topiramate
UGT	Uridine 5`-diphospho-glucuronyltransferase
VNS	Vagus nerve stimulation
VPA	Valproate
WHO	World Health Organization
ZNS	Zonisamide

1 Introduction

Epilepsy is the most common serious neurological disorder (Sander, 2003). Although the prognosis is generally good, approximately one-third of patients continue to have seizures despite appropriate deployment of antiepileptic drug (AED) therapy, resulting in substantial detrimental effects on individual health and the quality of life (QOL). If drug-resistant epilepsy could be recognized early, more decisive pharmacotherapy or early surgical intervention when indicated, could potentially improve these adverse consequences.

If the diagnosis of epilepsy is conclusively established and surgery will most likely not be fruitful, then further active drug trials should be pursued. There are two major questions, which drug to choose next and how to combine AEDs to achieve seizure control with minimal adverse drug effects. Unfortunately, there is scarcity of evidence on when and how to combine AEDs and the current treatment recommendations remain largely empirical. Nevertheless, some individuals will respond to their 4^{th} or 5^{th} AED, encouraging clinicians to continue active drug trials.

The ultimate goal of AED therapy is to restore a normal health-related quality of life, which is primarily dependent on achievement of seizure-freedom without clinically significant drug-related adverse-events (AEs). While the importance of complete seizure control cannot be overemphasized, recurrent seizures may potentially lead to overtreatment, resulting in a high probability of AEs, complex drug interactions and significant reduction of QOL. Moreover, enzyme inducing (EI) AEDs, including carbamazepine, are associated with vascular disease, osteoporosis and sexual dysfunction. It has been proposed that carbamazepine should not be regarded as a first-line AED in newly diagnosed epilepsy or even switching patients over to newer AED.

The purpose of this dissertation was to provide practical information in order to improve the quality of life in individuals with epilepsy by analyzing the effects of combination therapy on seizure frequency, determining the effectiveness of eight commonly used AEDs and reducing drug-related AEs by adjusting the AED therapy.

2 Review of the literature

2.1 Epileptic seizures and epileptic syndromes

An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity of the brain. Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures, the term also encompasses the neurobiological, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure (Fisher et al, 2005). Operationally epilepsy is defined by any of the following conditions: 1) At least two unprovoked (or reflex) seizures occurring >24 hours apart, 2) One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next ten years, 3) Diagnosis of an epilepsy syndrome (Fisher et al, 2014).

Seventy million people in the world have epilepsy, and there are between 34 and 76 new cases diagnosed per 100,000 every year (Ngugi et al, 2011). Epilepsy is considered to be resolved for individuals who either had an age-dependent epilepsy syndrome but are now past the applicable age or who have remained seizure-free for the last ten years and off AED therapy for at least the last five years (Fisher et al, 2014).

Epileptic seizures result from an excessive discharge in a population of hyper-excitable neurons. Typically, the seizures are generated in the cortical and hippocampal structures. The clinical manifestation of a seizure depends on its site of origin, time course and discharge outbreak (Avanzini and Franceschetti 2003). Focal epileptic seizures are conceptualized as originating within networks limited to one hemisphere and generalized seizures originate at some point within, and rapidly engaging, bilaterally distributed networks (Berg et al, 2010). Table 1 represents The International League Against Epilepsy (ILAE) new operational classification of seizure types (Fisher et al, 2017). Age at onset, cognitive and developmental antecedents and consequences, clinical neurological examination, EEG features, associated structural changes,

triggering or provoking factors and patterns of seizure occurrence with respect to sleep all contribute to epileptic syndromes. The ILAE´s new "roadmap" for the relevant classification of epilepsies for discussion is presented in Figure 1.

FIGURE 1. A framework for epilepsy classification (modified from Scheffer et al, 2016)

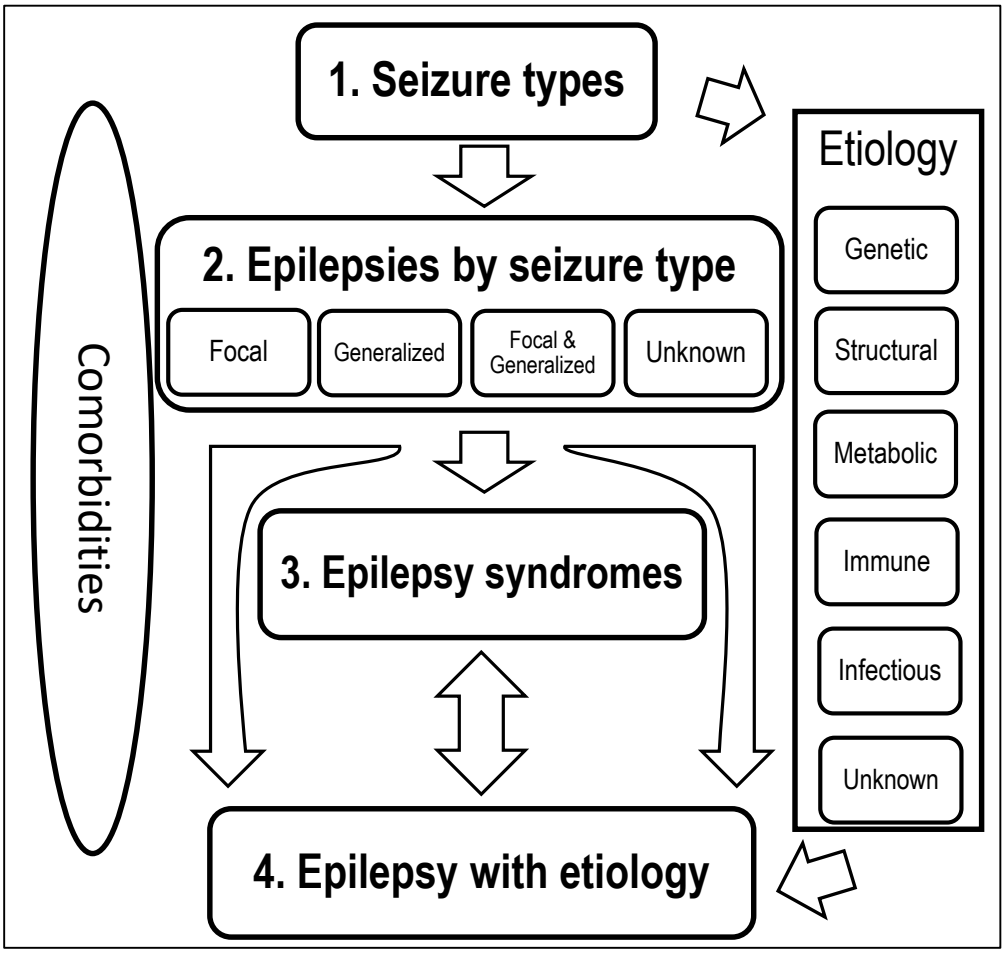


TABLE 1. The International League Against Epilepsy (ILAE) classification of seizure types

I FOCAL ONSET

Aware / Impaired awareness

A Motor Onset

- Automatisms
- Atonic
- Clonic
- Epileptic spasms
- Hyperkinetic
- Myoclonic
- Tonic

B Nonmotor Onset

- Autonomic
- Behavior arrest
- Cognitive
- Emotional
- Sensory

C Focal to bilateral tonic-clonic

II GENERALIZED ONSET

A Motor

- Tonic-clonic
- Clonic
- Tonic
- Myoclonic
- Myoclonic-tonic-clonic
- Atonic
- Epileptic spasms

B Nonmotor (absence)

- Typical
- Atypical
- Myoclonic
- Eyelid myoclonia

III UNKNOWN ONSET

A Motor

- Tonic-clonic
- Epileptic spasms

B Nonmotor

- Behavior arrest

C Unclassified

2.2 Etiology of epilepsy

Etiology is an important and major determinant of treatment, prognosis and clinical course as well as defining the choice of AEDs, duration of the treatment, possibilities for epilepsy surgery and probability of seizure-freedom. During the planning of this study The ILAE Commission for Classification of the Epilepsies had divided etiology of epilepsy into three categories: genetic, structural/metabolic and unknown cause (Berg et al, 2010). However, extension to six different etiological categories was introduced in the most recent classification (Scheffer et al, 2016). The concept of genetic epilepsy is that the epilepsy is the direct result of a known or presumed genetic defect(s) in which seizures are the core symptom of the disorder. According to the structural/metabolic etiology, there is a distinct structural or metabolic condition or disease that has been demonstrated to be linked with the increased risk of developing epilepsy. Unknown is meant to be viewed neutrally and to designate that the nature of the underlying cause is as yet unknown. The structural causes of epilepsy are presented on Table 2. The most common causes in adults are traumas, cerebrovascular/neurodegenerative diseases, tumors, hippocampal sclerosis (HS) and cortical dysplasia (CD). In childhood, epilepsy is often due to genetic, developmental and congenital factors.

TABLE 2. Structural causes of epilepsy based on neuroimaging (modified from Liimatainen et al, 2008)

A Central nervous system (CNS) infection

- Abscess
- Encephalitis
- Meningitis

B Cortical dysplasia (CD)

- Cortical dysgenesis
- Heterotopia
- Tuberosis sclerosis

C Dual pathology (HS associated with another brain lesion)

D Hippocampal sclerosis (HS)

E Other

- Demyelination
- Local diffuse atrophy
- Non-specific gliosis
- Non-specific signal change

F Other hippocampal abnormality

- Atrophy
- Demyelination
- Vascular malformation

G Poststroke

H Trauma

I Tumour

- Dysembryoplastic neuroepithelial tumour (DNET)
- Ependymoma
- Hamartoma
- Low-grade oligoastrocytoma
- Meningeoma

J Vascular lesion

- Anoxia
- Perinatal brain infarction

K Vascular malformation

- Arteriovenous malformation (AVM)
- Cavernous angioma
- Venous angioma

Confirmed head trauma or CNS infection prior to onset of epilepsy might be considered the cause of epilepsy despite normal neuroimaging.

2.3 Epileptogenesis

In approximately one third of the patients with epilepsy, the etiology remains unknown and furthermore, in patients with a known risk factor, only a minority of patients will develop epilepsy (Pitkänen et al, 2016). For example, the cumulative risk for seizures is nearly 12% at five years after intracerebral hemorrhage (ICH) or aneurysmal subarachnoid hemorrhage; independent risk factors include cortical involvement, age less than 65 years, acute seizures and blood volume over 10mL (Haapaniemi et al, 2014; Huttunen et al, 2015). Epileptogenesis refers to the development and extension of tissue capable of generating spontaneous seizures, resulting in the development of an epileptic condition and/or progression after the condition has become established (Pitkänen et al, 2013). Epileptogenesis refers to a period that arises after the occurrence of insult such as stroke or traumatic brain injury and ends at the time of the first spontaneous seizure (Pitkänen and Lukasiuk, 2011). In certain situations (e.g., encephalitis, prolonged febrile seizure, status epilepticus), epileptogenesis might begin during the insult. Furthermore, it has been postulated that molecular and cellular changes triggered by an epileptogenic insult can progress after the diagnosis of epilepsy (Pitkänen and Sutula, 2002; Pitkänen et al, 2009).

Epileptogenesis is a dynamic process that progressively transforms neuronal excitability, regularizes critical interconnections and requires intricate structural changes before the index seizure actually occurs. These alterations may include neurodegeneration, gliosis, axonal damage, blood-brain barrier damage, recruitment of inflammatory cells into brain tissue and reorganization of the molecular architecture of individual neuronal cells (Pitkänen and Lukasiuk, 2011).

Prevention of epileptogenesis is an unmet medical challenge but the underlying mechanisms suggest a wide spectrum of possible treatment targets. If antiepileptogenetic medication could be given prior to the onset of epilepsy, the disease development might prevent or delayed. Until then, the most efficient way to prevent epileptogenesis is prevention of a primary epileptogenic injury, for instance by wearing a helmet while riding a bike.

2.4 Outcome of epilepsy

2.4.1 Development of drug resistant epilepsy

Approximately 8-10% of the population has experienced at least one seizure in their lifetime and active epilepsy is affecting 0.5-1.0% of the population. Sixty percent of individuals who have their first epileptic seizure will never develop epilepsy. Three different prognostic groups are considered: 1) spontaneous remission as observed in childhood absences and benign epilepsy with centrotemporal spikes; 2) remission with treatment with AEDs; this occurs in most focal epilepsy and myoclonic juvenile epilepsy syndromes; 3) persistent seizures despite adequate treatment (Kwan and Sander, 2004). The etiology has an impact on seizure outcome. In a population-based study (n=360) conducted in Western Europe, remission was achieved in 80% of adult subjects with idiopathic generalized epilepsy, in 73% of unknown etiology and in 53% of symptomatic localization-related epilepsy (Picot et al, 2008). In another extensive hospital-based study, the remission rate was 82% in idiopathic generalized epilepsy, 45% in cryptogenic and 35% in symptomatic focal epilepsy (Semah et al, 1998).

Approximately 50% of the newly diagnosed adult patients with epilepsy respond to the first AED, whereas only 10% will have reached seizure-freedom with the second AED monotherapy (Kwan and Brodie, 2000). However, over 30% are thought to have drug-resistant seizures, of whom only a small minority can be helped by epilepsy surgery (Kwan et al, 2011) and some patients will respond to their 4^{th} or 5^{th} AED (Brodie et al, 2009).

2.4.2 Drug resistant epilepsy

First, it is necessary to rule out false refractoriness due to non-epileptic seizures, non-compliance and seizure-precipitating factors; video-electroencephalography (EEG) monitoring is often a very useful tool in this process. Different definitions for drug resistant epilepsy, often used interchangeably with medically refractory/intractable, or pharmacoresistant, have been appeared depending the context. The ILAE created a task force to define drug resistant epilepsy and their Consensus Proposal was published in 2010 (Kwan et al, 2010). According to the proposal, drug resistant epilepsy may be defined as a

failure of adequate trials of two tolerated and appropriately chosen and applied AED schedules (whether as monotherapies or in combination) to achieve sustained seizure-freedom. Seizure-freedom is defined as freedom from seizures for a minimum of 12 months or for a period lasting three times the longest pre-intervention inter-seizure interval. Furthermore, for the dosage that constituted an "adequate" trial for each drug, reference may be made to the World Health Organization (WHO)´s defined daily dose (DDD), which is the assumed average maintenance dose per day for a drug used for its main indication (WHO, 2016a) (Table 3). It has been proposed that primarily 50% or alternatively 75% of the DDD could be applied to the definition of drug resistant epilepsy when assessing what could be regarded as an "adequate" dose in defining treatment failure (Brodie et al, 2013).

The most crucial prognostic factor for long-term drug resistant epilepsy is the early response to the AEDs (Lossius et al, 1999; Mohanraj and Brodie, 2005). Structural causes of epilepsy (HS, CD, dual pathology, traumatic brain injury and hemorrhage) have been associated with refractoriness (Semah et al, 1998; Stephen et al, 2001; Blume, 2006; Hitiris et al, 2007; Gillioli et al, 2012). In a two year follow-up study, the influence of etiology on the changes of achieving seizure-freedom was evaluated in 119 patients with initially refractory focal epilepsy demonstrating that vascular malformation and dual pathology were the most refractory types with none of these patients being in remission at the end of the follow-up (Liimatainen et al, 2008). Time of epilepsy occurrence, localization of the epileptogenic zone, seizure frequency, neurological deficit at disease onset, multifocal spikes and the frequency of interictal spikes also have demonstrated prognostic value for drug resistant epilepsy (Beleza, 2009).

2.4.3 Burden of drug resistant epilepsy

The impact of epilepsy on an individual´s life is a combination of the physical consequences of seizures, influencing his/her social position and modifying psychological outcomes. Calculated in disability-adjusted life-years (DALYs), one quarter of the burden of neurological disorders is because of epilepsy (WHO, 2016b). This calculation does not take into account the effects of social exclusion and stigma or other detrimental aspects on families. Patients with drug resistant epilepsy are responsible for most of the burden of epilepsy, experiencing comorbid illnesses, psychological dysfunction, reduced QOL, increased risk of mortality and ultimately decreased life expectancy (Laxer et al,

2014). In addition, seizure-free patients have a higher proportion of depression, low self-esteem and more health-related concerns than would normally be expected (Hessen et al, 2008), which may affect negatively on the QOL (Hessen et al, 2009a).

For individuals with drug resistant epilepsy, optimizing QOL despite ongoing seizures becomes at least as important as continuing active drug trials. Although seizure-freedom is an important predictor for QOL, for those patients in whom this has not been achieved, sustained seizure frequency has a relatively minor influence on QOL compared to other factors e.g. mood and the adverse-events (AEs) of medication are much stronger predictors (Birbeck et al, 2002). Careful consideration is emphasized in order to avoid long-term AEs in exchange for a relatively short-term benefit (Roivainen et al, 2014). Even in those patients in remission, if it is achieved at the expense of unacceptable AEs, QOL may be poor. Noticeably, problems with memory, mood, tiredness, and behavior often represent a major disability but may either be misattributed, accepted or dismissed as an inevitable part of the condition by both physicians and patients (Mula and Cock, 2015). Furthermore, cognitive impairment can also be an AE of AEDs. In a withdrawal study with seizure-free patients on monotherapy, neuropsychological test results normalized significantly from 11% to 28% postwithdrawal with a relative risk of seizure relapse of 2.5 compared to those continuing medication (Lossius et al, 2008). Furthermore, executive functions may be markedly impaired during AED monotherapy (Hessen et al, 2009b).

If drug resistant epilepsy could be recognized early, more aggressive pharmacotherapy, early surgery, or neuromodulatory treatment when indicated, could potentially ameliorate these hazardous consequences.

2.4.4 Measuring the outcome of treatment with antiepileptic drugs

Each switch to some other AED may increase the probability of treatment failure and new or worsened side-effects (Sander, 2005). Data on AED performance based on clearly defined outcome measures are indispensable for physicians striving to meet the challenges of patient management. Ideally, the design of an AED clinical trial should be relevant to the real-world setting, provide reliable, valid, and comprehensive information on tolerability, efficacy, and QOL (Ben-Menachem et al, 2010). Multiple outcome measure parameters have been used: seizure-free rate, time to first seizure, time to N^{th} seizure, over

50% seizure reduction, percent seizure reduction, adverse effects, compliance, QOL and retention rate. The advantages and disadvantages of primary outcome measures are summarized in Table 3.

The regulatory trials typically focus on efficacy and dose response in refractory patients and usually do not meet the requirements for an ideal AED study design as it is critical also to understand the long-term treatment outcomes. Short-duration trials fail to observe natural patient discontinuation patterns, which might take a variable time period, even up to two years (Chung et al, 2007).

Table 3. The advantages and disadvantages of primary outcome measures with antiepileptic drugs (Modified from Ben-Menachem et al, 2010)

I OUTCOME MEASURE
A Percent seizure reduction
+ Widely accepted and mandated by the FDA and other regulatory agencies
+Comparative historic data available
-Requires prospective baseline and homogenous patient population with similarly high seizure frequency
-Usually short-term trials
B Responder rate (>50% seizure reduction)
+Accepted by European authorities
+Comparative historic data available
-Requires prospective baseline and homogenous patient population with similarly high seizure frequency
-Usually short-term trials
-Not sensitive to seizure worsening in some patients
C Time to first seizure
+Shows most important outcome
+Independent of baseline seizure rate
+Used in monotherapy studies
-Highly dependent on the length of study and responsiveness of the patient population
D Adverse-events
+Comparative historic data available
-Sometimes difficult to attribute to a specific drug in add-on studies
E Retention rate
+Naturalistic functional endpoint encompassing efficacy, QOL, tolerability and safety
+Functions as effectiveness or utility measure
+Longitudinal long-term data
+No prospective baseline required
-Requires longer trial attribution
-Less comparative historical data available
-Requires larger samples size
F Compliance
+Provides an indication of dose and schedule used
-Complex
-Direct measurements are invasive and impractical

FDA = the Food and Drug Administration; QOL = quality of life

2.4.4.1 Retention rate

The retention rate is calculated by measuring the time to treatment failure or study withdrawal for any reason. Retention rate encompasses both clinical outcomes and patient preferences and it is now considered as a primary measurement in AED studies (Chung et al, 2007; Bootsma et al, 2008; Peltola et al, 2009; Nakken et al, 2015). Ultimately, retention rate is a measure of a patient´s willingness to take a drug providing information that can be adapted readily to daily clinical practice. On the other hand, it is thought to reflect clinical effectiveness (tolerability and efficacy combined) and might also include total noncompliance as evaluated by discontinuation of medication (Ben-Menachem et al, 2010). The optimal trial duration is probably 2-3 years as if one has a shorter follow-up, especially less than one year, little or no differences might be observed (Bootsma et al, 2008). Otherwise, most of those who discontinue an AED within three years, will have already done so by two years (Peltola et al, 2009). Overall, the retention rate curves tend to decline linearly approximately 2-3 years until reaching a steady-state level.

2.5 Treatment of epilepsy

2.5.1 Drugs

The aim of the treatment of new-onset epilepsy, as well as drug-resistant epilepsy, is freedom from seizures with as few treatment related AEs as possible. The importance of accurate diagnosis in terms of seizure type, localization and the epilepsy syndrome cannot be overestimated since the choice of first AED will primarily be dependent on the diagnosis. Other individual features affecting the choice of AED include age, body weight, gender, fertility, lifestyle, other concomitant diseases and medications and AE profiles of the AEDs.

If a patient reaches seizure-freedom without AEs, the dose of AED should not be changed for at least a few years. However, if seizures continue, then the dose of AED should be raised until the seizure-freedom is obtained or AEs occur. An optional AED should be initiated if seizure control is not accomplished (Ben-Menachem, 2014).

If the first or second monotherapy improves seizure control although without producing seizure-freedom, the use of combination therapy is believed to be the most rational approach (Brodie MJ, 2005). Combination therapy seems to be effective in about one third of patients (Mohanraj and Brodie, 2005; Peltola et al, 2008). If the second AED leads to seizure-freedom, then the slow withdrawal of the first AED might be considered after conducting a risk/benefit assessment together with patient. The patient should be referred to a tertiary epilepsy center for further evaluation after the failure of two tolerated AEDs.

2.5.2 Rational polytherapy

Until the 1990s, the sodium channel blockers were in principle the only type of AED treatment, thus the era of rational polytherapy began in the middle of 1990s, when a number of new AEDs entered the market (Ferrendelli, 1995). Since then, an increased interest has triggered in optimizing combination therapy. Nowadays, the potential choices of AEDs as combination or monotherapy are so numerous that it is impossible to try every permutation in a single lifetime. The major questions are which AED to choose and how to combine AEDs in order to reach seizure-freedom?

Monotherapy has been considered as the gold standard for drug treatment of epilepsy but polytherapy might represent an unavoidable choice which should be carefully deliberated before instituting a treatment as this carries a significant risk of pharmacological interactions and AEs (Brigo et al, 2013). On the other hand, a minority of the patients may benefit considerably from a combination therapy (French and Faught, 2009). Several duo-therapies should be tested sequentially before adding a third drug (Brodie and Sills, 2011), a higher number of AEDs should be avoided if possible as it is highly unlikely that this strategy will lead to useful seizure reduction without AEs (Stephen and Brodie, 2002).

At the moment, the rational choice of AED combinations is based more on the avoidance of AEs than on evidence for synergic anticonvulsant effects and current practice recommendations remain empirical. Physicians have no clear evidence-based indications in their choice of a certain drug combination against specific types of epilepsy. The combination of lamotrigine-valproate has shown the best human evidence for synergy (Brodie and Yuen, 1997). Other useful combinations present in the literature are mostly reports from small patient groups or modest sample sizes including phenobarbital with phenytoin for

generalized tonic-clonic (GTC) seizures (Cereghino et al, 1975), valproate with ethosuximide for absence seizures (Rowan et al, 1983), carbamazepine with valproate or vigabatrin for partial seizures (Brodie et al, 1999) and lamotrigine with topiramate for several types of seizures (Stephen et al, 1998). The need for a national and most likely international data bank of all patients with epilepsy has been proposed so that data can be collated to help determine the best treatment for patients on a clinical basis in addition to experimental data while bearing in mind that the term rational polytherapy does not incorporate clinical information (McCabe, 2015). Another major issue is whether the area of seizure onset matters.

The new wave of polytherapy has also raised concerns if irrational polytherapy or overtreatment of epilepsy will lead to AEs, pharmacological interactions, reduced compliance and even an increased risk of mortality (Perucca and Kwan, 2005; Canevini et al, 2010). A poor initial diagnosis accompanied by the inappropriate choice of AED as the first therapy may lead to unfavorable events (Chaves and Sander, 2005), and a clinician might simply add further AEDs without re-evaluating the indication of the previously prescribed drug. Moreover, an inadequate knowledge of the mechanism of action (MOA) of AEDs and pharmacological interactions may lead to irrational polytherapies (Brigo et al, 2013), for example excessive neurotoxic AEs without increased efficacy have been reported after the combination of carbamazepine and lamotrigine (Besag et al, 1998).

In summary, reinforcement of a single pharmacological pathway is less effective than a combined effect on two distinct pathways (Brodie and Sills, 2011). The most successful combination of two drugs in laboratory studies seems to be a single mechanism drug combined with an AED known to possess multiple MOAs (Deckers et al, 2000). Guidance for combining antiepileptic drugs is presented in Table 4 and different mechanistic groups suitable for combination therapy are summarized in Table 5 (Brodie and Sills, 2011).

Table 4. Guidance for combining antiepileptic drugs (modified from Brodie and Sills, 2011)

Establish optimal dose of baseline agent
Add drug with multiple mechanisms
Avoid combining similar modes of action
Titrate new agent slowly and carefully
Be prepared to reduce the dose of original drug
Replace less effective drug if response still poor
Try range of different duo-therapies
Add third drug if still sub-optimal control
Device palliative strategy for drug resistant epilepsy

Table 5. Different mechanistic groups suitable for combination therapy (modified from Brodie and Sills, 2011)

1 SODIUM CHANNEL BLOCKERS
A Fast-activated state
Carbamazepine
Lamotrigine
Oxcarbazepine
Phenytoin
B Slow-inactivated state
Eslicarbazepine acetate
Lacosamide
2 CALCIUM CHANNEL BLOCKERS
A Low voltage activated channel
Ethosuximide
B High voltage activated channel
Gabapentin, Pregabalin
3 GABA-ERGIC DRUGS
A Prolongs chloride channel opening
Barbiturates
B Increased frequency of chloride channel opening
Clobazam, Clonazepam
C Inhibits GABA-transaminase
Vigabatrin
D Blocks synaptic GABA reuptake
Tiagabine
4 SYNAPTIC VESICLE PROTEIN 2A MODULATION
Brivaracetam
Levetiracetam
5 CARBONIC ANHYDRASE INHIBITION
Acetazolamide
6 INHIBITION OF GLUTAMATE TRANSMISSION
Perampanel
7 MULTIPLE PHARMACOLOGICAL TARGETS
Felbamate, Rufinamide
Sodium valproate
Topiramate
Zonisamide

GABA = γ-aminobutyric acid.

2.5.3 Molecular targets of antiepileptic drugs

AEDs are structurally and functionally diverse. Putative MOAs of AEDs and their efficacy in different seizure types are summarized in Table 6. AEDs can be categorized to membrane stabilizers, neurotransmitter release inhibitors, increased γ-aminobutyric acid (GABA)-mediated inhibitors and other mechanisms (Perucca and Mula, 2013). Membrane stabilizers reduce excitability by blocking sodium channels but gabapentin or oxcarbazepine might function via potassium channel activation although it is not their main MOA (Howard et al, 2011). Neurotransmitter release inhibitors consist of the α2δ and SV2A ligands. Gabapentin and pregabalin bind to the α2δ type 1 and 2 regulatory subunits of pre-synaptic (N, P/Q-type) voltage-gated calcium channels, reducing the calcium influx responsible for triggering neurotransmitter release (Bauer et al, 2010) causing a redistribution of calcium channels away from the cell surface rather than blocking them directly. Levetiracetam and brivaracetam binds to synaptic vesicle protein SV2A and are assumed to interfere with the release of the neurotransmitter from the storage vesicles (Lynch et al, 2004; Ma et al, 2015)). The mimetics of GABA are another group of AEDs; these either affect GABA metabolism (synthesis, re-uptake or breakdown) e.g. vigabatrin and valproate or act directly on GABAA receptors e.g. benzodiazepines (Howard et al, 2011). Perampanel is a selective, non-competitive, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist with a unique mechanism of action (French et al, 2012). Another group of drugs worthy of mention, the valproates, have several GABA-mediated mechanisms including altered synthesis, release, re-uptake and degradation (Loscher, 2002). Other mechanisms refer to synaptic vesicle modulation, carbonic anhydrase inhibition and chloride complex interaction.

TABLE 6. Molecular targets of antiepileptic drugs, their spectrum of efficacy and defined daily dose according to the World Health Organization (Modified from Howard et al, 2011, and Perucca and Mula, 2013)

	Na^+ channel blocker	Ca^+ channel blocker (channel subtype)	$GABA_A$ receptor activation ↑	Altered GABA re-uptake and breakdown	Inhibition of gluta-mate transmission (receptor subtype)	Other mechanism	Focal seizures	Primary GTC seizures	Absence seizures	Myoclonic seizures	DDD
I FIRST GENERATION											
Carbamazepine	++						+				1g
Clobazam			++				+	+	+	+	20mg
Clonazepam			++				+	+	+	+	8mg
Ethosuximide		++ (T)							+		1,25g
Phenobarbital		?	++		?	+	+	(+)		(+)	0,1g
Phenytoin	++						+				0,3g
Primidone	+		++				+	+		?	1,25g
Sodium valproate[a]	+	+ (T)		+	+ (NMDA)		+	+	+	+	1,5g
II SECOND GENERATION											
Felbamate	++	+ (L)	+		+ (NMDA)		+				2,4g
Gabapentin		++ (N, P/Q)	?			+	+				1,8g
Lamotrigine	++	++ (N,P/Q,R,T)	+		++ (NMDA,AMPA)	+	+	+	(+)	+	0,3g
Levetiracetam		+ (N)				++[c]	+	+	(+)	+	1,5g
Oxcarbazepine	++					+	+				1g
Pregabalin		++ (N, P/Q)					+				0,3g
Stiripentol[b]			++								1g
Tiagabine				++			+				30mg
Topiramate	++	+ (L)	++		++ (AMPA)	+	+	+		(+)	0,3g
Vigabatrin				++			+				2g

Table 6 (Continue)

	Na^+ channel blocker	Ca^+ channel blocker (channel subtype)	$GABA_A$ receptor activation ↑	Altered GABA re-uptake and breakdown	Inhibition of gluta-mate transmission (receptor subtype)	Other mechanism	Focal seizures	Primary GTC seizures	Absence seizures	Myoclonic seizures	DDD
Zonisamide	++	++(N,T,P)	+	?	+	+	+	(+)		+	0,2g
III THIRD GENERATION											
Brivaracetam						++[c]	+	+	(+)	+	0,1g
Eslicarbazepine acetate	++						+				0,8g
Lacosamide	++						+				0,3g
Perampanel					++ (AMPA)		+	+			8mg
Retigabine						++[d]	+				0,9g
Rufinamide	++					+	+				1,4g

GABA = γ-aminobutyric acid; GTC = generalized tonic-clonic; DDD = defined daily dose; NMDA = N-methyl-D aspartate; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid

Key: ++ = primary action, + = secondary action, ? = controversial

[a] Although many AEDs have more than one MOA, particularly valproate is thought to have no predominant MOA helping to explain its broad spectrum

[b] Indicated as an adjunctive therapy for treating Dravet syndrome

[c] Synaptic vesicle modulator (SV2A)

[d] Potassium channel blocker

2.5.4 Dibenzazepine family of antiepileptic drugs

The dibenzazepine family of AEDs contains carbamazepine (first generation), oxcarbazepine (second generation) which are relatives of eslicarbazepine acetate (third generation). Structurally, carbamazepine, oxcarbazepine and eslicarbazepine acetate all possess a dibenzazepine ring. Oxcarbazepine is an analogue of carbamazepine but with minor structural differences, which cause major differences in metabolism and induction of metabolic pathways. Eslicarbazepine acetate differs from carbamazepine and oxcarbazepine by the presence of a 5-carboxamide substitute at the 10,11 position (Keating, 2014). Blockade of voltage-gated sodium channel is the proposed MOA of all members of the dibenzazepine family (Bonifácio et al, 2001; Hebeisen et al, 2011), but eslicarbazepine acetate might even have a modulating action and be able to inhibit the slow activation of voltage-gated sodium channels (Hebeisen et al, 2015). Carbamazepine, oxcarbazepine and eslicarbazepine acetate are all effective against focal seizures but at least carbamazepine and oxcarbazepine may exacerbate absence and myoclonic seizures and should be avoided in patients with generalized epilepsy.

Oxcarbazepine and eslicarbazepine acetate share the same main active metabolite, eslicarbazepine (S-licarbazepine) (Schütz et al, 1986; Almeida and Soares-Da-Silva, 2007). Importantly, eslicarbazepine acetate is extensively metabolized to eslicarbazepine (94%), R-licarbazepine (5%) and oxcarbazepine (1%) whereas oxcarbazepine is metabolized to eslicarbazepine (78%) and R-licarbazepine (18%) (Nunes et al, 2013). The structural differences of carbamazepine and eslicarbazepine acetate mean that whereas carbamazepine metabolism is known to cause the generation of the toxic metabolite carbamazepine-10,11-epoxide, this metabolite is not formed from eslicarbazepine acetate (Benes et al, 1999).

Carbamazepine is a potent enzyme inducer reducing the levels of many drugs as well as endogenous substances metabolized by the cytochrome P450 (CYP) enzyme system. Furthermore, carbamazepine may accumulate when co-administered with inhibitors of CYP 3A4. Oxcarbazepine and eslicarbazepine acetate are weak inducers of CYP 3A4 (Mintzer, 2010); this enzyme is responsible for estrogen metabolism, and thus dibenzazepines may reduce the efficacy of oral contraceptive pills at high doses. CYP 2C19 is also weakly induced by oxcarbazepine and eslicarbazepine acetate, potentially reducing

plasma concentrations of drugs metabolized by this enzyme. Finally, oxcarbazepine has been found to cause the induction of CYP 3A5 (Brodie et al, 2013).

Typical AEs related to carbamazepine include nausea, headache, dizziness, sedation and tiredness whereas oxcarbazepine might cause drowsiness, headache and fatigue. Eslicarbazepine acetate has a similar AE profile to oxcarbazepine although side effects tend to be less frequent (Striano et al, 2006; Zaccara et al, 2013). Elevated levels of voltage-gated sodium blockers might cause blurred vision, diplopia, nystagmus, ataxia and tremor. Hyponatremia may also occur.

Some clinical and experimental findings suggest that eslicarbazepine acetate would be effective as oxcarbazepine but with less AEs (Peltola et al, 2015). Based on an observation that several dose-dependent neurological AEs occur almost invariably a few hours after the oxcarbazepine morning dose (Striano et al, 2006), it seems logical to link AEs to the oxcarbazepine peak concentration rather than to eslicarbazepine (its active metabolite), since the levels of the latter increase more slowly (Almeida and Soares-Da-Silva, 2007). As mentioned earlier, eslicarbazepine acetate is directly hydrolyzed to eslicarbazepine and it seems that it does not cause these morning-related oxcarbazepine characteristics.

What is the place of dibenzazepines in field of epilepsy at the moment? Both carbamazepine and oxcarbazepine are approved for the first-line monotherapy for focal seizures, however, EI and complex pharmacological interactions might be concerns favoring more modern AEDs; conversely economic considerations tend to favor the less-expensive carbamazepine. Theoretically eslicarbazepine acetate could be considered as a first-line AED for localization-related seizures and preferred over oxcarbazepine due to its better tolerability profile, but financial issues might delay this practice. There are certain situations in clinical practice in which it may be reasonable to switch patients from carbamazepine (significant vascular risk profile, drug interactions) or oxcarbazepine (oxcarbazepine-related AEs particularly following morning dosing or poor compliance with twice-daily dosing) to eslicarbazepine acetate.

2.5.5 Enzyme induction with antiepileptic drugs

Enzymes are biological catalysts and enzyme induction (EI) is a process in which a molecule (e.g. a drug) induces the expression of enzyme. In other

words, EI involves the synthesis of new enzyme molecules and the typical consequence of EI is an increased metabolism of the affected drug, leading to a decrease in its serum concentration and a reduced pharmacological effect (Brodie et al, 2013).

Biotransformation of a drug might be the most important determinant of its pharmacokinetic profile. Drug metabolism can be broadly divided into two categories: phase one (oxidation, reduction and hydrolysis) and phase two (conjugation). Phase one processes are mediated primarily by the cytochrome P450 (CYP) family of enzymes (Nelson et al, 1996), whereas conjugation reactions (phase two) are conducted mainly by the enzyme uridine 5`-diphospho-glucuronyltransferase (UGT) (Kiang et al, 2005). The activity of CYP and UGT isoenzymes can be influenced by genetic, environmental and endogenous factors, resulting in significant variation among individuals in drug metabolism (Brodie et al, 2013).

Altogether fifteen CYP isoenzymes are known to be involved in human drug metabolism; these enzymes are located intracellularly in endoplasmic reticulum and mitochondrial membranes (Nelson et al, 1996). CYP isoenzymes are typically associated with drug metabolism in the liver, but they are found in other tissues including brain, skin, kidney and lung (Pelkonen et al, 2008; Ghosh et al, 2010). CYP2C9, CYP2C19, CYP2D6, and CYP3A4 are responsible for the oxidative metabolism of 80% in the human liver with the last-mentioned CYP being responsible for the metabolism of the largest number of clinically used drugs as well as many endogenous substrates such as prostaglandins, steroid hormones and fatty acids (Brodie et al, 2013).

Nearly 40 years ago, EI was recognized as a pharmacological complication of epilepsy (Perucca, 1978) but awareness of its influence on the metabolism of several endogenous substrates is a much more recent finding (Nebert and Russell, 2002). Carbamazepine, phenytoin, primidone and phenobarbital are all inducing AEDs, sodium valproate is the only inhibiting AED while the new generation AEDs tend to have either mild or even non-inducing properties (Mintzer, 2010).

Due to its effects on endogenous metabolic pathways, EI can alter bone biochemistry, gonadal steroids and lipid markers. Patients with epilepsy have a significantly increased risk of fracture when compared to the general population (Pack, 2008), which has been attributed to the epileptic seizures and the use of inducing AEDs (Vestergaard et al, 2004; Carbone et al, 2010; Brodie et al, 2013). However, not all data supports this hypothesis (Stephen et al, 1999; Pack

et al, 2005). Inducing AEDs have been linked with abnormalities in sex hormone profiles, the potential for sexual dysfunction as well as the risk of hormonal contraception failure (Isojarvi, 1990; Morrell et al, 2001; Galimberti et al, 2009). However, these negative effects may be reversible even after years of treatment (Lossius et al, 2007). Carbamazepine is associated with an increase in the levels of serologic vascular risk markers including total cholesterol, triglycerides, low-density lipoprotein, lipoprotein(a), homocysteine and C reactive protein (Isojarvi et al, 1993; Bramswig et al, 2003; Linnebank et al, 2011; Chuang et al, 2012). The lipid-elevating effect seems to be specific to the use of inducing AEDs, because conversion from carbamazepine to oxcarbazepine reduced total cholesterol (Isojarvi et al, 1994) and also patients who changed from inducing AEDs to mild- or non-inducing AEDs showed similar results as well as healthy controls exposed to carbamazepine (Bramswig et al, 2003; Mintzer et al, 2009; Mintzer et al, 2012). Furthermore, a favorable change in the lipid profile after carbamazepine withdrawal has recently been reported using a prospective, randomized double-blind design (Lossius et al, 2015). Despite the fact that patients with epilepsy have significantly higher rates of cardiovascular and cerebrovascular disease (Gaitatzis et al, 2004) and inducing AEDs are clearly responsible for elevations of several vascular risk markers, there is a lack of reliable epidemiologic data which would have compared the rate of vascular events attributable to specific drugs. Interestingly, a recent population-based cohort study indicated that the use of EI AEDs might be associated with an increased risk of myocardial infarction when compared to the use of non-inducing AED (Renoux et al, 2015).

It is also well known that certain AEDs can affect thyroid hormones. According to a recent meta-analysis, carbamazepine was associated with a significant decrease in the levels of triiodothyronine (T3), thyroxine (T4) and free T4 (Zhang et al, 2016) and furthermore these changes could be reversed by treatment withdrawal (Lossius et al, 2009). The mechanism behind the positive association between AEDs and thyroid hormones remains unclear but it has been suggested that EI might play a significant role in this process (Zhang et al, 2016).

It is estimated that about one quarter of patients with epilepsy are prescribed two or more AEDs (Tsiropoulos et al, 2006) and this proportion increases to 75% among patients attending tertiary referral centers (Malerba et al, 2010). One study from Germany demonstrated that the percentage of EI AEDs for patients with active epilepsy was 35% in 2003 and 13% in 2008 cohort,

respectively (Strzelczyk et al, 2013). Additionally, there is a high probability that AEDs might be co-prescribed with other medications at some point. In elderly people with epilepsy, co-morbidities are common and many drugs including antihypertensives, statins, anticoagulants, psychoactive compounds and immunosuppressants all have clinically relevant interactions with the EI AEDs.

It has been suggested that inducing AEDs should not be recommended as first-line therapy in newly diagnosed epilepsy due the wide range of potential metabolic disturbances and complex drug interactions (Mintzer and Mattson, 2009; Mintzer, 2010; Zaccara and Perucca, 2014), especially when multiple effective and well-tolerated AEDs are now available. Furthermore, EI continues as long as the patient is being administered the inducer. Since it is impossible to predict health problems that might occur over the life span, it has been speculated that individuals on EI AEDs should be transitioned to newer AED (Brodie et al, 2013). At the very least, patients with EI AEDs should regularly been screened for potential detrimental signs of EI. If metabolic consequences are detected, some of these patients might be treatable but transitioning to newer AED may be a better practice as it might reduce complications, comorbidities and costs (Mintzer, 2010).

2.5.6 Surgery

Resective surgery is based on the removal of the entire epileptogenic area without causing a permanent neurological deficit. The epileptogenic zone is localized by magnetic resonance imaging (MRI), EEG findings (ictal and interictal), fluorodeoxyglucose-positron emission tomography (FDG-PET) and seizure semiology (Ryvlin et al, 2014). Surgery is effective treatment for patients with drug resistant epilepsy, leading to seizure-freedom in up to 70% of patients (Engel et al, 2003; Neligan et al, 2012). More than half of the procedures are anterior temporal lobe resections while mesial temporal lobe epilepsy associated with HS leads to temporal lobe resections in around 60% of the patients.

Early identification of potential candidates for surgery is of major importance as surgical intervention early in the course of drug-resistant epilepsy is superior to further medical trials (Jóse et al, 2005; Engel et al, 2012). The most important reason for the delay to surgery is the dynamic pattern of epilepsy with seizure-free periods lasting one year or oven longer, even after the epilepsy has been

defined as drug-resistant (Jobst and Cascino, 2015). On the other hand, there is a considerable possibility that seizures may improve with a trial of new AED (Langfitt and Wiebe, 2008; Liimatainen et al, 2008). Another cause for delay in surgery is the late referral of patient to a specialized center by the treating physician, which is also reflected by the long interval between diagnosis of drug-resistance and surgery, which can be as long as 30 years (Jobst and Cascino, 2015). The recent ILAE definition for drug-resistant epilepsy may be a practical tool to minimize this delay. However, according to Jobst and Cascino, 2015, the ILAE criteria would not have led to earlier identification of patients with drug-resistant epilepsy than formerly used definitions as it took an average of 13 years until these patients' epilepsy could be considered to be drug-resistant. Further, the development of MRI technology allows more accurate diagnostic approach as demonstrated in a recent paper, where 7 Tesla (T) MRI revealed structural lesions in 6 out of 21 (29%) patients with focal epilepsy and normal conventional (1.5 or 3T) MRI (De Ciantis et al, 2016). Four out of these six patients underwent surgery and histopathology showed focal cortical dysplasia in all cases.

2.5.7 Neuromodulation

When pharmacological and surgical treatments are ineffective or not viable options, neuromodulatory techniques could be considered as a means for controlling or reducing persistent seizures and improving the QOL in patients with refractory epilepsy. Vagus nerve stimulation (VNS) and deep brain stimulation (DBS) are currently the predominant treatment modalities being used. One advantage of these treatments is the consistently noted continuous improvement in seizure control with time. The stimulator and the battery are typically implanted in the chest wall with easy access to adjust the parameters.

The trial-based use of VNS for epilepsy began in 1988 with the official approval granted in 1994 in Europe and in 1997 in the United States and Canada (Hassan and Al-Quliti, 2014). The vagus nerve has a significant role in the autonomic parasympathetic control of the heart and digestive tract and in the conveyance of sensory information regarding various internal organs to the CNS. VNS is designed to stimulate only the peripheral vagus nerve that terminates in the nucleus of the tractus solitarius in the medulla (Bolden et al, 2015). However, the exact mechanism by which VNS reduces seizures remains unclear.

For adults with focal refractory epilepsy, DBS of the anterior nucleus of the thalamus (ANT) is now approved as an adjunctive therapy in Europe (Fisher et al, 2010). A stereotactic approach is applied to implant multi-contact depth electrodes into the ANT in DBS. The mechanism of action behind DBS is not well understood but it is hypothesized to induce a disruption of unopposed network activity. High frequency DBS might block epileptiform activity in the cortex whereas low-frequency DBS may synchronize cortical activity (Bolden et al, 2009).

3 Purpose of the study

The purpose of this thesis was to provide practical data in order to improve the quality of life in individuals with epilepsy by minimizing the adverse-events and maximizing the efficacy of the antiepileptic drug therapy. The more specific purposes of the study were:

1. To assess the impact of the increasing range of newer antiepileptic drugs on the clinical outcome

2. To evaluate the effects of age and gender on long-term retention rates for eight of the most commonly used antiepileptic drugs as adjunctive therapy

3. To investigate the differences between oxcarbazepine and eslicarbazepine acetate in terms of tolerability and efficacy

4. To provide practical information related to discontinuation of carbamazepine due to concerns about the long-term effects of enzyme induction

4 Materials and methods

4.1 Definitions

Epilepsy was defined as a disorder with 1) at least two unprovoked (or reflex) seizures, occurring >24 h apart; or 2) one unprovoked seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years for example, on account of some underlying etiology or status epilepticus (Fisher et al, 2014).

Data concerning patient background, medical history, current and previous AED use, duration of therapy, and reasons for treatment discontinuation were retrospectively collected from the hospital records by doctorand. All modern AEDs during the time of studies were available except for brivaracetam and perampanel, which were not licensed in Finland at that time. The seizure frequency from the previous year was recorded; seizure-free patients had not experienced any seizures during the previous year.

Adult patients with focal epilepsy treated in Tampere University Hospital were identified cross-sectionally from the hospital patient registry 31.12.2014 (study I,II,IV) using ICD-10 diagnostic codes for focal and unclassifiable epilepsy (G40.1X, G40.2X, and G40.9). Patients with moderate or severe mental retardation, dementia, or malignant high-grade brain tumours and epilepsy were excluded.

The etiologies were classified into either known or unknown etiologies (Scheffer et al, 2016).

Refractory epilepsy was defined as having persistent seizures after trials of at least two AEDs with maximally tolerated doses (sequentially or in combination therapy) (Kwan et al, 2010). The intensity of AEs was classified as mild, moderate, or severe. A mild AE was defined as a symptom not interfering with daily activities, moderate as interfering but not preventing daily life activities and severe as incapacitating with respect to at least some daily activities.

4.2 Study patients

The study patients were treated in the Outpatient Clinic of Neurology and Rehabilitation, Tampere University Hospital. Additionally, patients from Central Hospitals of Seinäjoki and Vaasa were included in the study IV.

4.2.1 Patients in studies I and II

396 patients with polytherapy were included in the study I (Table 7). Study II included 507 patients with focal refractory epilepsy who had ever used at least one of the following AEDs: clobazam, gabapentin, lacosamide, lamotrigine, levetiracetam, pregabalin, topiramate or zonisamide (Table 8). Overall, 22% of the patients were treated with monotherapy, 43% with duo-therapy, 30% with triple therapy, and 5% were being administered four AEDs (II).

Table 7. Clinical characteristics of the study patients in study I (Study I, reprinted with permission)

Number of antiepileptic drugs	2	3	4	total
N	218	151	27	396
Sex				
Female	116	75	14	205
Male	102	76	13	191
Mean age (years)	51.1	45.6	39.7	48.2
Mean duration of epilepsy (years)	22.0	23.5	27.6	23.0
Etiology				
Known	153	95	16	264
Unknown	65	56	11	132
Seizure frequency				
Seizure-free	83	30	4	117
Persistent seizures	135	121	23	279

Table 8. Clinical characteristics of the study patients in study II (Study II, reprinted with permission)

N	507
Sex	
Female	259
Male	248
Mean age (years)	48.4
Mean duration of epilepsy (years)	23.0
Etiology	
Known	220
Unknown	287

4.2.2 Patients in the study III (Table 9)

Twenty three patients with focal epilepsy were included applying following inclusion criteria: (1) current treatment with oxcarbazepine; (2) oxcarbazepine-related moderate or severe tolerability problems which affected the patient's daily life; (3) transition from oxcarbazepine to eslicarbazepine acetate was performed due to oxcarbazepine-related AEs; and (4) transition was undertaken before 30 November 2015.

Table 9. Clinical characteristics of the study patients for study III (Study IIII, reprinted with permission)

N	23
Sex	
Female	14
Male	9
Mean age (years)	41.8
Mean duration of epilepsy (years)	14.4
Etiology	
Known	17
Unknown	6
Refractory epilepsy	18
Seizure frequency	
Seizure-free	11
Persistent seizures	12
Mean OXC dose (mg/day)	1152
Final ESL dose (mg/day)	1095

AED; antiepileptic drug, OXC; oxcarbazepine, ESL; eslicarbazepine acetate

4.2.3 Patients in the study IV (Table 10)

A total of 58 patients who were currently treated with carbamazepine (monotherapy or polytherapy) and whose treating epileptologist had recommended that they should discontinue carbamazepine due to concerns about the long-term effects of EI were included in study IV. Those who were converted from carbamazepine to some other AED due to incomplete seizure control, adverse events, drug interactions or any other reason than possible long-term effect of EI, were excluded.

Table 10. Clinical characteristics of study patients in study IV (Study IV, reprinted with permission)

Carbamazepine status at baseline	Continue	Discontinue
N	24	34
Sex		
Female	13	19
Male	11	15
Mean age (years)	52.6	49.1
Refractory epilepsy	9	15
Seizure frequency		
Seizure-free	21	20
Persistent seizures	3	14
Statin use	2	5
Mean duration of epilepsy (years)	34.4	30.3
Duration of CBZ treatment (years)	29.0	23.7
Daily dose of CBZ (mg/day)	810	750
Total cholesterol (mmol/l)	5.7	5.9
HDL (mmol/l)	1.8	2.0
LDL (mmol/l)	3.6	3.7
Trigyceride (mmol/l)	1.3	1.1
SHBG (nmol/l)	115.5	100.4
Free testosterone (pmol/l)	212.8	156.9
Vitamin D (nmol/l)	80.2	78.1

CBZ; carbamazepine, HDL; high-density lipoprotein, LDL; low-density lipoprotein, SHBG; sex hormone-binding globulin

4.3 Methods

4.3.1 Polytherapy study

In 2004, a cross-sectional evaluation of 193 subjects with focal epilepsy treated with polytherapy had been undertaken in Tampere University Hospital (Peltola et al, 2008). Now 10 years later, this analysis was repeated.

4.3.2 Retention rate study

Three year retention rates were evaluated for eight of the most commonly used AEDs as adjunctive therapy. Vigabatrin was excluded from the final analysis due to low number of cases (N=37). In addition, the effects of age and gender on retention rates were assessed of all eight AEDs. The following classifications were made for the subgroup analyses. Age was categorized into two groups: < 60 years of age and ≥ 60 years of age. Finally, each drug was analyzed in terms of annual prescriptions and withdrawals from the introduction of the drug in Finland up to the final assessment point.

4.3.3 Transition study

All subjects were being treated with immediate-release oxcarbazepine. The dosages of concomitant AEDs remained unchanged during the transition period. Tolerability problems related to oxcarbazepine were categorized addressing neurological AEs of new generation sodium-blockers (somnolence, dizziness, vertigo, ataxia/coordination abnormal, diplopia, nystagmus, fatigue, tremor, headache, nausea, vomiting). Patients were transitioned overnight from oxcarbazepine to eslicarbazepine acetate and retrospectively followed up for three months by clinicians. The target dose of eslicarbazepine acetate was calculated using a dose ratio 1:1 depending on the pretransition oxcarbazepine dose. If the dose ratio did not correspond to an exact eslicarbazepine acetate dose, then the closest lower eslicarbazepine acetate dose was used. The last administration of oxcarbazepine was the morning dose followed by the first intake of eslicarbazepine acetate in the evening of the same day. After 1 and 3 months, an evaluation of the effects of the transition was made in terms of tolerability and efficacy. Patients were dichotomized by outcome in terms of AEs after being switched from oxcarbazepine to eslicarbazepine acetate.

4.3.4 Long-term effects of enzyme induction study

Discontinuation meant either conversion from carbamazepine to newer AED or slow withdrawal of carbamazepine (discontinuation group). Patients who preferred to continue on carbamazepine were designated as a retrospective control group for comparison with those undergoing carbamazepine

discontinuation. The decisions concerning discontinuation were made purely on clinical grounds. In all cases, an individual therapeutic plan was undertaken by the treating epileptologist for the patient´s benefit. The rate of initiation of therapy with the new AED and the tapering off of carbamazepine were arranged at the discretion of the treating epileptologist and were individualized for each patient. The minimum target dose for the new AED was 800 mg daily for eslicarbazepine acetate, 200 mg daily for lacosamide, 1000 mg daily for levetiracetam and 900 mg for gabapentin. The use of other potent inducing AEDs is very limited in our district and therefore excluded from the study.

4.3.4.1 Blood samples

All blood samples used in the current study were measured as a part of routine clinical practice related to the use of EI AEDs. Venous blood samples were collected into tubes containing ethylenediaminetetra-acetic acid (EDTA) as anticoagulant after a minimum of 12 hours of fasting during scheduled outpatient visits (IV). The following serum variables were analyzed: total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, 25-hydroxyvitamin D, sex hormone binding globulin (SHBG), and free testosterone. Among women with epilepsy, sex hormone profiles are not routinely measured due to complicated interpretations with respect to the menstrual cycle. Laboratory analyses were performed in the Centre of Laboratory Medicine, Tampere University Hospital.

In case of carbamazepine discontinuation, control blood samples had been obtained at least 3 months after the last dose of carbamazepine in order to observe the possible improvement in laboratory parameters after the medication switch. In case of carbamazepine continuation, blood samples are controlled regularly as a part of clinical practice. The design of the study entailed each patient having blood drawn after a minimum of 12 hours of fasting on 2 occasions: first at baseline, while taking carbamazepine; a second time three months after the last dose of carbamazepine or 3-12 months after baseline while still taking carbamazepine.

4.4 Statistical analyses

Chi-square test was used to analyze differences between groups and categorical variables, and based on the assumption of normality, Student´s T-test or Mann-Whitney U-test was applied for continuous variables. The background and medical characteristics of the patients are reported as means and ranges or proportions.

Statistical significance was evaluated using a chi-square test when comparing the proportion of seizure-free subjects with different numbers of AEDs. A two-sample z-test was used to compare the proportions from studies in 2004 and 2014. Student´s T-test was used for comparing mean differences of changes between the two groups. Both unadjusted and adjusted logistic regression models were used to analyze seizure-freedom and the effect of year (2004 vs. 2014) on seizure-freedom. The covariates considered were age, gender, etiology, and duration and type of epilepsy.

The Kaplan-Meier method was used to obtain a product-limit estimate of the retention rate and comparisons between the retention curves were analyzed using a log-rank tests. Bonferroni correction was used for multiple comparisons.

Changes in serum samples were calculated as a difference between the end of the follow-up and baseline and were reported as means and standard deviations. Five serum samples (HDL, LDL, triglycerides, SHBG, and vitamin D) were standardized in order to have them on the same scale. After standardization, the sum of five variables (z-sum) was calculated so that the greater value of z-sum corresponded to a better total situation. Binary logistic regression analysis was used to estimate the association between groups and seizure recurrence 6 months after baseline. No essential changes in the estimate of group variable were found after adjustments for potential confounders (age, gender, and the number of prior AEDs) and therefore only results from unadjusted models were reported. After fitting logistic regression models, predicted probabilities for seizure recurrence at 6 months after baseline were calculated by converting the odds.

All analyses were conducted using Stata statistical software version 13.1 (StataCorp, College Station, Texas, USA). For statistical tests, p-value < 0.05 was considered significant.

4.5 Ethical aspects

This was a non-interventional, retrospective, observational study (I-IV) based on individual-level hospital patient data. Access to patient records was based on decision made by the Head of Science Centre, Tampere University Hospital research and innovation services, Science Center. Authorization for using the hospital medical records in Central Hospitals of Seinäjoki and Vaasa (study IV) were granted by the regulatory authority responsible for the administration of said data in Finland, that is, the respective hospital districts.

5 Results

5.1 The effect of newer antiepileptic drugs in combination therapy

Fifty-five percent of the subjects with combination therapy were being treated with two AEDs, 38% received three and 7% four AEDs. Eighty three out of 218 subjects (38%) were seizure-free on duo-therapy and furthermore 30 out of 151 receiving three AEDs (20%) were seizure-free. Four out of 27 subjects (15%) administered four AEDs were seizure-free. Subjects with three or four AEDs were less likely to be seizure-free compared to those being treated with two AEDs (odds ratio [OR] 2.7, 95% confidence interval [CI] 1.6-4.4). Temporal lobe epilepsy was the most common type of epilepsy (N=161, 41%).

In all, 52 different combinations of two AEDs were being used (Table 11). Subjects with three AEDs (N=151) had 80 different combinations; the most common combinations included lamotrigine-topiramate-valproate (N=7), levetiracetam-oxcarbazepine-topiramate (N=5), levetiracetam-oxcarbazepine-pregabalin (N=5), clobazam-lacosamide-topiramate (N=5), clobazam-lacosamide-zonisamide (N=5). All the subjects being treated with four AEDs had their own distinctive combinations. The mean and median doses of individual AEDs are summarized in Table 12. Table 13 presents comparisons with the results from 2004.

Seizure-freedom on duo-therapy was found to be more frequent in 2014 compared to 2004 in the unadjusted model, especially after adjusting for covariates. Instead, in those subjects administered three or four AEDs, the findings do not reach statistical significance. Compared to patients on duo-therapy in the 2004 analysis, patients with two AEDs in the 2014 analysis had higher possibility of being seizure-free (OR 2.00, 95% CI 1.20-3.33; p=0.008). Among those with 3 or 4 AEDs, patients in 2014 had a 2.60 times higher odds of attaining seizure remission compared to patients in the earlier study (OR 2.60, 95% CI 0.90-7.49; p=0.076).

Table 11. The number of subjects with two antiepileptic drug combinations (n=218) (Study I, reprinted with permission)

	LEV	LTG	TPM	GBP	PGB	ZNS	TGB	VGB	OXC	CBZ	VPA	CLB	CZP
LEV													
LTG	13												
TPM	4	8											
GBP	2	1	1										
PGB	2	6	1										
ZNS		7			1								
OXC	29		2		5	2	1						
CBZ	19	1	7	1	8	2	1	1					
VPA	5	10											
CLB	2	2		1	1	2			4	5			
CZP		1		1					1	1			
PHT	1												
PMD										1			
LCM	17		11		1	2			1		4	6	1
ESL	6				2	1						1	
PRP									1				

LEV = levetiracetam; LTG = lamotrigine; TPM = topiramate; GBP = gabapentin; PGB = pregabalin; ZNS = zonisamide; OXC = oxcarbazepine; CBZ = carbamazepine; VPA = valproate; CLB = clobazam; CZP = clonazepam; PHT = phenytoin; PMD = primidone; LCM = lacosamide; ESL = eslicarbazepine acetate; PRP = perampanel

Table 12. The doses (mg/day) of individual antiepileptic drugs (AEDs) (Study I, reprinted with permission)

	Two AED combinations			Three or four AED combinations			DDD (mg)
	N	Mean	Range	N	Mean	Range	
Levetiracetam	100	1737	1000-3000	78	2042	100-3500	1500
Carbamazepine	47	859	200-1600	30	763	300-1200	1000
Oxcarbazepine	46	1187	600-1800	42	1279	600-2400	1000
Lacosamide	43	395	100-600	56	413	200-600	300
Lamotrigine	49	341	100-600	54	336	25-600	300
Topiramate	34	292	100-600	51	361	50-1000	300
Pregabalin	28	399	150-600	40	443	75-600	300
Clobazam	24	16	5.0-30	71	22	5.0-80	20
Valproate with lamotrigine	10	1210	900-1500	26	1419	500-3000	1500
Valproate without lamotrigine	9	1389	500-2000	12	1342	1000-1800	1500
Zonisamide	17	365	200-500	49	359	200-600	200
Eslicarbazepine	10	1100	800-1600	13	1262	800-2000	800
Gabapentin	7	2486	1200-3600	6	1917	1200-3600	1800
Clonazepam	5	1.9	1.0-8.0	10	2.7	0.4-0.6	8
Tiagabine	2	25	20-30	2	65	30-100	30
Vigabatrin	1	2000	2000-2000	1	3000	3000-3000	2000
Phenytoin	1	250	250-250	1	300	300-300	300
Primidone	1	500	500-500	-	-	-	1250
Perampanel	1	4.0	4.0-4.0	8	9.3	4.0-12	8

DDD = defined daily dose

5.2 Effectiveness of antiepileptic drugs

We estimated the following 3-year retention rates: clobazam 66%, gabapentin 40%, lacosamide 77%, lamotrigine 68%, levetiracetam 67%, pregabalin 55%, topiramate 62%, and zonisamide 60%. The log-rank test detected a significant variation between the AEDs (p=0.001). In pairwise comparison, the retention rates of lacosamide (p=0.003), lamotrigine (p=0.01), and levetiracetam (p=0.04) were significantly increased compared to gabapentin even after Bonferroni correction. Other statistically significant differences between the retention rates could not be identified in the pairwise comparison.

The reasons for discontinuation in those patients who terminated the particular AED within the 3-year follow-up period are shown in Table 14. The results of the subgroup analyses in which the patients were categorized according either to age or gender are summarized in Table 15. The annual number of initiations and discontinuations for lacosamide, levetiracetam, pregabalin, topiramate, and zonisamide used as an adjunctive therapy in focal refractory epilepsy from 1995 to 2014 are illustrated in Figure 2.

Table 13. Subjects with localization-related epilepsy on combination therapy (Study I, reprinted with permission)

Year of analysis	N	Combination therapy (%)	Seizure-free on combination therapy	Seizure-free on two AEDs (%)	Seizure-free on three AEDs (%)	Seizure-free on four AEDs
2004	395	193 (48.9)	41 (21.6)	36 (27.3)	5 (10)	-
2014	507	396 (78.1)	117 (29.9)	83 (38.4)	30 (20.3)	4 (14.8)
			p=0.042	p=0.040	p=0.11	p=0.24

AED = antiepileptic drug

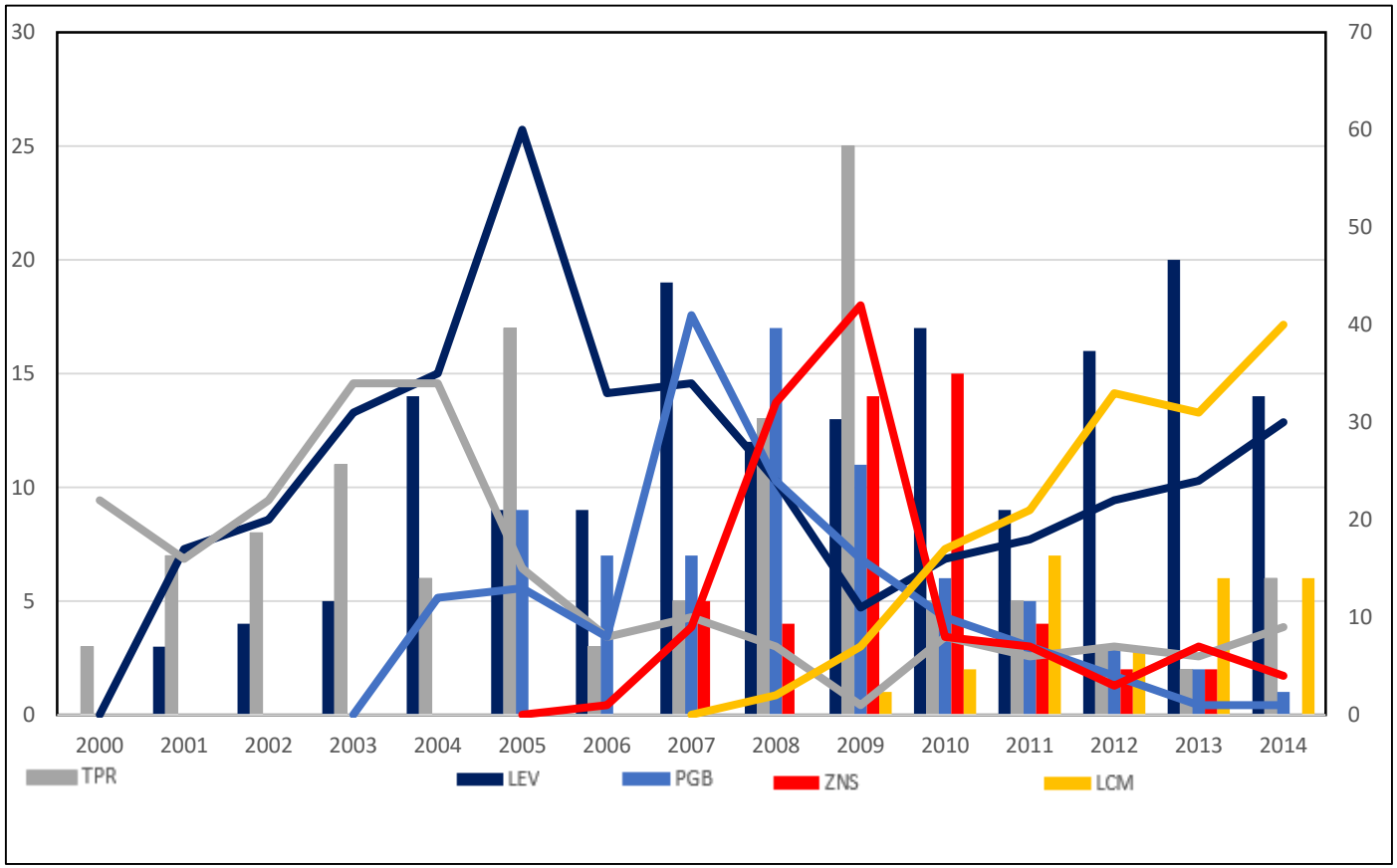
Table 14. Reason for discontinuation of one of the tested antiepileptic drugs and mean duration (months) of treatment in subjects who discontinued the drug (Study II, reprinted with permission)

	Discontinued	Lack of efficacy		Adverse effect		Lack of efficacy+adverse effect		Other reason	
	N	%	Duration	%	Duration	%	Duration	%	Duration
Clobazam	38	42.1	15.6	36.8	5.9	5.3	14.6	15.8	13.8
Gabapentin	38	73.8	12.5	10.5	10.2	10.5	13.3	5.2	2.1
Lacosamide	26	19.2	7.3	50.0	4.7	7.7	6.0	23.0	2.9
Lamotrigine	54	53.7	12.0	31.5	3.6	5.6	7.5	9.3	12.8
Levetiracetam	100	49.0	8.6	34.0	5.9	8.0	12.4	9.0	5.7
Pregabalin	56	39.3	8.9	41.0	9.0	16.1	10.8	3.6	17.1
Topiramate	65	24.6	12.7	52.3	9.1	15.4	17.7	7.7	9.8
Zonisamide	37	46.0	9.6	29.7	5.6	16.2	8.2	8.1	1.0

Table 15. The effect of age and gender on retention rates of the eight antiepileptic drugs (Study II, reprinted with permission)

	Three-year retention rate			
	Age (years)		Gender	
	<60	≥60	Female	Male
Clobazam	68.0	73.9	68.0	70.0
Gabapentin	43.7	47.7	45.6	44.4
Lacosamide	76.7	80.0	80.6	74.0
Lamotrigine	67.0	61.4	66.1	64.6
Levetiracetam	71.6	74.5	72.6	72.1
Pregabalin	53.7	71.9	53.2	62.2
Topiramate	61.0	68.6	69.8	56.3
Zonisamide	64.8	50.8	68.2	57.2

Figure 2. The number of annual initiations (*curves, right column*) and discontinuations (*bars, left column*) for antiepileptic drugs used as an adjunctive therapy in focal refractory epilepsy from 2000 to 2014 (Study II, reprinted with permission)

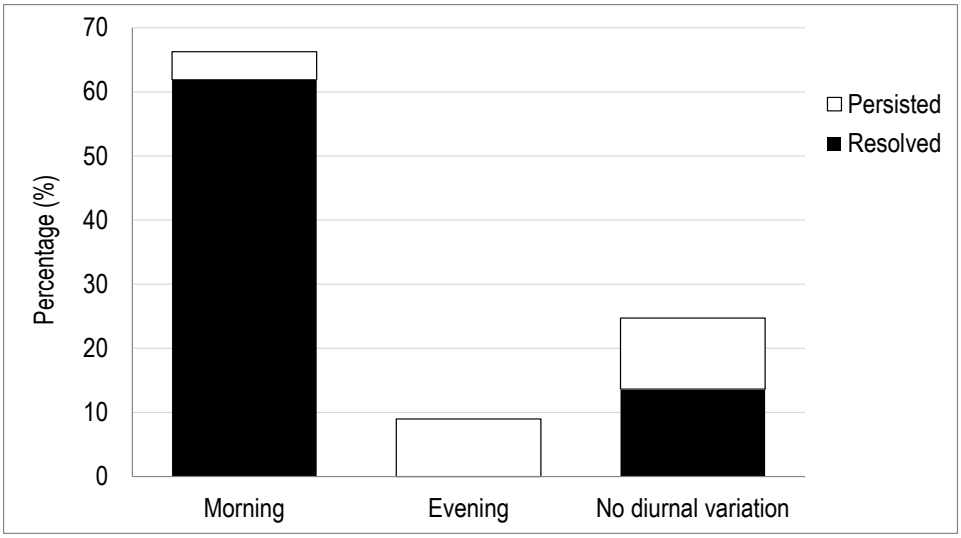


5.3 Transition from oxcarbazepine to eslicarbazepine acetate

Oxcarbazepine-related AEs in fifteen (65%) patients had resolved after transition at the three month follow-up. Two thirds of the AEs occurred in the morning and the vast majority (93%) of them resolved after transitioning from oxcarbazepine to eslicarbazepine acetate (Figure 3). Those AEs presenting without diurnal variation tended to be more persistent after the transition. The most common AEs related to oxcarbazepine were fatigue (48%), somnolence (44%), vertigo (26%), dizziness (22%), and ataxia (17%). The three most common concomitant AEDs were levetiracetam, topiramate, and clobazam.

No patient experienced an increase in seizure frequency following the transition. The incidence of eslicarbazepine acetate-related AEs was 39% at one month and 13% at the three month follow-up; however, all patients continued eslicarbazepine acetate throughout the study period. Most of the AEs attributed to eslicarbazepine acetate were mild although some were moderate in intensity. During the hospitalization period, two patients reported headache, but no changes in seizure frequency or duration were observed.

FIGURE 3. Diurnal variation and the three month outcome of oxcarbazepine related adverse events after transition to eslicarbazepine acetate (Study III, reprinted with permission)



5.4 Long-term consequences of enzyme induction

Of the 58 patient participating in the study, 24 decided to continue with carbamazepine, 10 were withdrawn from carbamazepine without switching to some other AED, and 24 were converted from carbamazepine to some other AED (eight to eslicarbazepine acetate, eight to lacosamide, seven to levetiracetam, and one to gabapentin). The main reasons affecting individual decisions to continue with carbamazepine were as follows; 11 were anxious that there would be seizure-relapse, seven were afraid of losing their job and/or driver´s license should a seizure occur, two were not concerned about the long-term effects of EI, with the final four subjects deciding for reasons best to known themselves.

There were significant differences between the groups with respect to seizure-freedom and mean free testosterone levels. Recurrent seizures were more frequent, and the testosterone level was lower in the discontinuation group at baseline as compared to the continuation group. The time between the first and second blood samplings in these patients ranged from 91 to 334 days (mean: 141 days).

Compared to those who continued the carbamazepine treatment, patients in the carbamazepine discontinuation group displayed significant decreases in serum total cholesterol (15%), HDL (10%), LDL (19%), and SHBG (18%) concentrations (Table 16, Figure 4). In men, the free testosterone level was significantly increased (39%) in the carbamazepine discontinuation group compared to those who continued with carbamazepine medication. There were no significant changes in the serum concentrations of triglyceride and vitamin D.

Seizure outcome data is summarized in Table 17. Two patients suffered a sporadic seizure during the titration period with the new drug. In contrast, none had withdrawal seizures due to the tapering-off of the carbamazepine medication. Data from these seizures are not included here. Table 18 demonstrates unadjusted odds ratios for the various subgroups relative to their seizure status at baseline. The logistic regression model was adjusted for covariates (age, gender, and number of prior AEDs) but this did not lead to results that differed markedly to those obtained with the unadjusted model (data not shown). Table 19 presents probabilities for seizure recurrence six months after baseline in the various subgroups of previously seizure-free patients. The probabilities are based on results of the logistic regression model (Table 18).

Table 16. Laboratory data after baseline (sampling 2) and comparison of laboratory parameters between sampling one (baseline) and sampling two (Study IV, reprinted with permission)

	CBZ status at baseline			Change from sampling 1 to sampling 2		
	Continue (n=24)	Discontinue (n=34)	p	Continue (n=24)	Discontinue (n=34)	p
TC, mmol/l (SD)	5.7 (1.2)	5.0 (1.1)	0.014	-0.01 (0.58)	-0.95 (1.05)	<0.001[1]
HDL, mmol/l (SD)	1.8 (0.7)	1.8 (0.5)	0.61	0.04 (0.16)	-0.24 (0.38)	0.002[1]
LDL, mmol/l (SD)	3.4 (1.1)	3.0 (0.9)	0.11	-0.10 (0.60)	-0.64 (0.90)	0.013[1]
Triglyceride, mmol/l (SD)	1.24 (0.75)	0.97 (0.41)	0.23	-0.01 (0.45)	-0.12 (0.42)	0.23[2]
SHBG, nmol/l (SD)	124.7 (88.8)	82.1 (40.3)	0.042	9.1 (18.0)	-18.4 (39.9)	<0.001[2]
FT, pmol/l (SD)*	212.9 (80.2)	218.1 (93.6)	0.92	0.09 (22.5)	61.2 (91.8)	0.017[2]
Vitamin D, nmol/l (SD)	80.3 (31.3)	81.4 (27.2)	0.89	0.1 (19.2)	3.3 (22.4)	0.58[1]
z-score sum**	-0.84 (2.84)	0.59 (2.06)	0.030	-0.48 (1.65)	0.34 (1.61)	0.064[1]

FT = free testosterone; HDL = high-density lipoprotein; LDL = low-density lipoprotein; SD = standard deviation; SHBG = sex hormone-binding globulin; TC = total cholesterol

[1] Student's T-test

[2] Mann-Whitney U-test

* n = 26 (men only)

** The sum of standardized values of HDL, LDL, triglyceride, SHBG, and vitamin (z-sum) was calculated so that the greater value of z-sum corresponds to the better total situation

Table 17. Seizure outcomes at 6 months after baseline (Study IV, reprinted with permission)

Seizure status at baseline	CBZ status at baseline	N	Seizure-free after baseline (%)	Recurrent seizure after baseline (%)
Seizure-free	Continue	21	20 (95.2)	1 (4.8)
	Discontinue	20	16 (80.0)	4 (20.0)
Not seizure-free	Continue	3	0 (0)	3 (100)
	Discontinue	14	1 (7.1)	13 (92.9)

Table 18. Odds of seizure recurrence 6 months after baseline, among various subgroups relative to seizure status at baseline (seizure-free or not seizure-free) (Study IV, reprinted with permission)

Comparison	Odds ratio	95% CI	p
Seizure-free at baseline, CBZ discontinue vs. continue (n=41)	5.00	0.51-49.3	0.17
Seizure-free at baseline, CBZ withdrawal vs. continue (n=28)	8.00	0.60-106.9	0.12
Seizure-free at baseline, CBZ switch to other AED vs. continue (n=34)	3.64	0.30-44.8	0.31

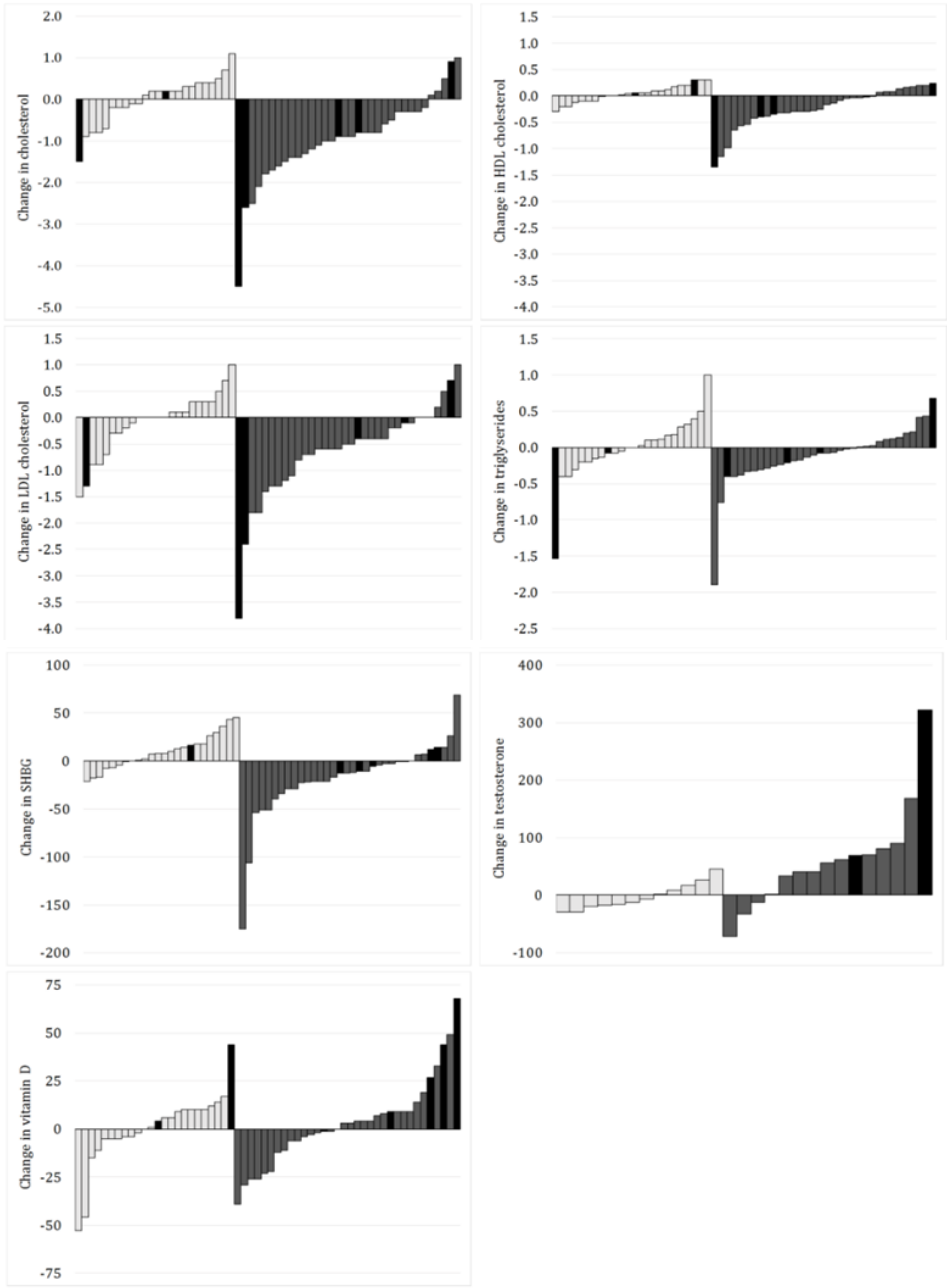
AED = antiepileptic drug; CBZ = carbamazepine; CI = confidence interval

Table 19. Probabilities for seizure recurrence 6 months after baseline among various subgroups relative to seizure status at baseline (seizure-free or not-seizure-free) (Study IV, reprinted with permission)

Comparison	Seizure recurrence probabilities	Difference
Seizure-free at baseline, CBZ discontinue vs. continue (n=41)	20.0% vs. 4.8%	15.2 pp
Seizure-free at baseline, CBZ withdrawal vs. continue (n=28)	28.6% vs. 4.8%	23.8 pp
Seizure-free at baseline, CBZ switch to other AED vs. continue (n=34)	15.4 vs. 4.8%	10.6 pp

AED = antiepileptic drug; CBZ = carbamazepine; PP = percentage point

Figure 4. Change in laboratory parameters in patients who continued with carbamazepine and in those with carbamazepine discontinuation. Each bar shows the absolute change in the laboratory parameter between the first and second samplings for individual subjects, with 24 patients who continued CBZ shown in white on the left, and the 34 patients who discontinued CBZ in grey on the right. A black bar indicates a statin user. (Study IV, reprinted with permission)



5.5 Summary of the results

I In 2014, a higher percentage of patients with polytherapy (117 out of 396; 30%) were seizure-free compared with the original analysis conducted ten years previously (22%) (p=0.042). Eighty three out of 218 (38%) subjects on duo-therapy were seizure-free (27% in 2004) (p=0.0040); in the 151 receiving triple therapy, there were 30 (20%) seizure-free subjects (10% in 2004). Four out of 27 subjects (15%) with four AEDs were seizure-free (0% in 2004). The most common pairing of 52 different combinations for duo-therapy was levetiracetam-oxcarbazepin. Eighty different AEDs regimens were being used in the patients administered three AEDs.

II The following 3-year retention rates were calculated: lacosamide 77% (n=137), lamotrigine 68% (n=177), levetiracetam 67% (n=319), clobazam 66% (n=130), topiramate 62% (n=178), zonisamide 60% (n=103), pregabalin 55% (n=127), and gabapentin 40% (n=66). Lacosamide, levetiracetam, and clobazam were the most effective AEDs in the elderly. The retention rate for pregabalin was higher in males (65%) than females (51%) whereas females had higher retention rates for both topiramate (72% vs. 58%) and zonisamide (67% vs. 57%). The retention rate was influenced by the sequence in which these AEDs had entered the market.

III In fifteen (65%) out of 23 patients, the oxcarbazepine-related AEs were reduced after transition. In particular, most of (93%) the AEs that presented in the morning resolved after transition to eslicarbazepine acetate. No patient suffered an increase in seizure frequency following the transition. The incidence of eslicarbazepine acetate -related AEs was 39% at one month and 13% at three month follow-up; however, all patients continued eslicarbazepine acetate throughout the study period.

IV Twenty patients had been seizure-free on carbamazepine; 4 (20%) had recurrent seizures after carbamazepine discontinuation compared to one (5%) of those who continued with this AED. Seizure-free patients had a five- fold elevated odds of seizure recurrence if carbamazepine was

discontinued (95% CI 0.51-49.3; p=0.17). A significant decrease in serum levels of TC, LDL, HDL, and SHBG as well as a significant increase in that of free testosterone were found in the discontinuation group compared with those who continued carbamazepine. Nonsignificant changes in triglycerides and vitamin D levels were detected.

6 Discussion

6.1 The effect of newer antiepileptic drugs in combination therapy

The main finding of our study is that at least one year seizure-freedom with polytherapy had been achieved in 30% of the patients in the 2014 cohort, which is significantly higher than the value of 22% in the original analysis which was conducted in 2004 (p=0.042). The second significant finding is that in patients with duo-therapy, the rate of seizure-freedom increased from its 2004 value of 27% to 38% in 2014 (p=0.040). Furthermore, there is a trend towards improved possibilities for seizure-freedom in patients with three or four AEDs although these trends were not statistically significant. These results may indicate that some of the newer AEDs might be useful in combination therapy on the route to seizure-freedom. As far as we are aware, only one such pair of studies has been previously published (Stephen and Brodie 2002; Stephen et al, 2012). In the 2012 analysis conducted by Stephen et al., sustained seizure-freedom with more than one AED was achieved in 20% of patients, which is an almost identical percentage as the 21% reported by that group in their 2002 study (Stephen and Brodie 2002) indicating that despite the introduction of six new AEDs in the intervening decade, no substantial impact on the likelihood of producing seizure-freedom had been achieved. The rate of seizure freedom from these two studies is similar to our 2004 cohort. One explanation for the comparable results might be that the most common duo-therapies (lamotrigine-valproate, carbamazepine or oxcarbazepine combined to topiramate or levetiracetam) were analogous in our 2004 analysis and furthermore in the 2012 analysis by Stephen et al. the most common combinations remained the same as in their 2002 study (Stephen and Brodie 2002) i.e. lamotrigine-valproate, phenytoin-phenobarbital and carbamazepine combined with gabapentin, valproate or lamotrigine.

The use of polytherapy has become more frequent in our center i.e. whereas only 49% (222/395) of the subjects received combination therapy in 2004, by 2014 that value had risen to 78% (396/507). The number of different duo-therapy combinations has increased from 38 to 52 and different triple-therapy combinations from 40 to 80 during a time frame of a single decade. From a

clinical standpoint, the increased number of different combinations emphasizes the challenges related to the evaluation of the efficacy and tolerability of given combinations. However, direct comparison about the success of different combinations is not possible because AEDs have been introduced into the market at different time points (Peltola et al, 2008). At the time of this analysis in 2014, perampanel and brivaracetam were not licensed and eslicarbazepine acetate was not fully reimbursed in Finland.

In the current analysis, the most common individual combination was levetiracetam and oxcarbazepine followed by combinations of carbamazepine and levetiracetam, and lacosamide and levetiracetam representing the ideology of rational polytherapy; a sodium channel blocker combined with another AED with a different mechanism of action. In the three or four drug combinations, levetiracetam and clobazam were the most commonly used AEDs whereas in the two drug combinations, clobazam was used infrequently; in our center, clinicians prefer to prescribe clobazam most frequently when proceeding to triple-therapy. As hypothesized in the previous study (Stephen et al, 2012), the different combinations could simply express personal preferences of the treating physicians, but on the other hand, similar results have been shown in laboratory studies (Brodie and Sills 2011). In the two data sets, we were not able to identify any of the combinations as being clearly more successful than the others. In a previous study on combination therapy, the most common combinations in seizure-free patients with epilepsy were sodium valproate-lamotrigine, carbamazepine-sodium valproate and phenobarbital-phenytoin (Stephen et al, 2012).

The mean doses for AEDs used in combination therapy were mostly equal or marginally higher than the World Health Organization (WHO) defined daily doses (2016) suggesting that the overall drug load was not excessive in our patients. However, little is known about the actual optimal doses in polytherapy and there is a considerable risk of overtreatment if the physician prescribes unnecessarily high doses (Brigo et al, 2013). On the other hand, it has been suggested that if seizure-freedom is not achieved with 2 or 3 AEDs, drug substitution rather than addition will result in a better outcome (Stephen et al, 2012); an approach which may also reduce overtreatment in epilepsy (Brigo et al, 2013) and minimize adverse-events related to combination therapy.

In addition to efficacy, some newer AEDs seem to display a better side-effect profile and furthermore, they undergo fewer interactions compared to the older drugs, especially concerning the long-term adverse-events such as issues related

to enzyme induction. Subjects who become seizure-free at low doses of AEDs have enjoyed improvements in quality of life measures (Marson et al, 2007). Nonetheless, also in patients with combination therapy and persistent seizures, the quality of life may still be improved; the correlation between quality of life and medication-related adverse-events is much stronger than that between quality of life and seizure frequency (Ben-Menachem et al, 2010; Gillian et al, 2004).

6.2 Effectiveness of antiepileptic drugs

The most crucial finding in our study was that the retention rate appeared to be influenced by the sequence in which these AEDs were introduced onto the market and this "latest drug phenomena" should be taken into account when assessing the effectiveness of AEDs. Furthermore, we calculated the following long-term retention rates; lacosamide 77%, lamotrigine 68%, levetiracetam 67%, clobazam 66%, topiramate 62%, zonisamide 60%, pregabalin 55% and gabapentin 40%.

An ideal study design should be relevant to real-world settings and provide encompassing measures of efficacy and tolerability assessed with reliable and valid tools. This requirement is usually not fulfilled in regulatory trials, which focus on efficacy and dose response in refractory patients. Often in these clinical trials, the dosage range tends to be high, the titration schedule too rapid and the follow-up period very short. In contrast, the retention rate is considered to be a compound measure of drug efficacy, safety and compliance, ultimately expressing the willingness of patient to take the drug.

It has been hypothesized that the retention rate can be influenced by the sequence in which these AEDs are introduced onto the market (Zaccara et al, 2006), but as far as we are aware, this has not been actually determined previously. In Finland, after authorities have given approval for full reimbursement, a new AED is made available free of charge for its licensed indication and the clinician can prescribe this drug to suitable patients. As shown in Figure 3, the use of a new AED significantly increases once full reimbursement is approved. Patients being administered AEDs that were marketed first could have discontinued that treatment after a new drug became available, as demonstrated in Figure 3. For example, topiramate entered the full reimbursement market in the year 2000; its peak of treatment discontinuations

occurred in 2005 when a new AED (levetiracetam) became available. Similarly in 2007; many patients receiving levetiracetam terminated its use because of the availability of new drug (pregabalin). Finally, the number of annual discontinuations for pregabalin increased in 2008 when yet another AED (zonisamide) received full reimbursement approval. At the time of analysis, lacosamide was the latest AED which had been awarded full reimbursement (2012) and the peak of withdrawals from this drug had still not been observed by the end of year 2014. Additionally, lacosamide could have been tested in a more drug resistant cohort of patients. Our results suggest that the retention rate appears to be influenced by the sequence in which these AEDs have been introduced onto the market. This "latest drug phenomena" should be taken into account in the long-term retention rate studies, when comparing the effectiveness of subsequently marketed AEDs.

In the subgroup analysis, the effects of age and gender on retention rates of all eight AEDs were studied. Despite the well-known modifications in AED pharmacokinetics and pharmacodynamics in the elderly, we found only one retrospective, uncontrolled study of older patients (≥55 years) with epilepsy which would have evaluated effectiveness by comparing 12-month retention rates of 10 different AED (Arif et al, 2009). In our study, lacosamide was the most effective AED in the elderly as measured by its three year retention rate, followed by levetiracetam and clobazam. Zonisamide and gabapentin were the least effective drugs. Our results are similar to those of Arif et al, 2009 with one exception. In our study, lamotrigine had the third lowest retention rate (63%) in contrast to that previous study, in which lamotrigine had the highest retention rate (79%). The differences might be explained by the limited number of patients receiving each AED in both studies.

Surprisingly, very little is known about the effectiveness of AEDs between females and males in the light of long-term retention rate studies. We could not identify any study focusing on this topic. Three year retention rate for pregabalin was higher in males (62%) than females (53%) whereas females had a higher retention rate for both topiramate (70% vs. 56%) and zonisamide (68% vs. 57%). In fact, topiramate was the third best tolerated AED in females. However, results did not reach statistical significance due to limited number of patients. One might hypothesize that these results would reflect cosmetic side effects of AEDs to which females tend to be more prone, as pregabalin is associated with gaining weight whereas both topiramate and zonisamide might cause a loss of body weight (Ben-Menachem 2007).

Direct comparison of the AEDs is difficult based on the nature of the current study, but it might be worthwhile noting the characteristics of the patients receiving different drugs. The number of patients on each AED was relatively high (over 125 patients) with the exceptions of zonisamide (N = 103) and gabapentin (N = 66). Females and males were equally represented in all of the groups. The known etiology for focal seizures has been considered as a marker of pharmacoresistance (Liimatainen et al, 2008). The majority of the patients receiving levetiracetam, lamotrigine and zonisamide had a known etiology. The mean duration of epilepsy varied from 17 years (lacosamide) to 27 years (gabapentin and lamotrigine) highlighting the refractory nature of our patient cohort. The mean doses for all eight AEDs were mostly equal or marginally higher than the World Health Organization (WHO) defined daily doses, suggesting that the overall drug load was not excessive in our patients. Finally, generally is known how much drug resistance is influenced by previous unsatisfactory treatments. As the majority of the patients on lamotrigine, topiramate, pregabalin, zonisamide, clobazam and gabapentin had previously tried a minimum of four AEDs, these cohorts must be characterized as being highly drug resistant. These observations might indicate that patients with a known etiology or/and high number of previous AEDs had more severe epilepsy which could have detrimentally influenced their long-term retention rate. On the other hand, percentage of patients who have previously taken more than 4 AEDs varies from almost 70% with gabapentin, to almost 40% with lacosamide. Incidentally, lacosamide resulted the AED with the best retention rate. This data weaken the observation that lacosamide has a better retention. Overall, no major differences were found with respect to any of the demographical or clinical variables, which allows us to compare these eight AEDs and to hypothesize that differences in their long-term retention rates are drug-related.

6.3 Transition from oxcarbazepine to eslicarbazepine acetate

The main objective of this study was to evaluate the tolerability of a switch from oxcarbazepine to eslicarbazepine acetate by applying a sufficiently long follow-up period. Our study demonstrates that patient satisfaction improved in terms of reduced AEs after the switch from oxcarbazepine to eslicarbazepine acetate in 65% of the subjects without any corresponding increase in seizure frequency. This finding is similar to a previous study demonstrating that 15 out of 26

patients who were transitioned from oxcarbazepine to eslicarbazepine acetate due to oxcarbazepine-related AEs, no longer experienced AEs after the change (Villanueva et al, 2014). Furthermore, we showed that if oxcarbazepine-related AEs are particularly evident in the morning, nearly all of them will be resolved after the transition to eslicarbazepine acetate, which indicates that these AEs are linked to the oxcarbazepine peak concentration in cerebrospinal fluid and plasma (Keating 2014). These findings might help a clinician to assess whether a patient´s complaints of neurological AEs are related to oxcarbazepine, especially in complex situations e.g. when there are several AEDs, comorbidities (e.g. depression, sleeping problems), and persistent seizures.

The secondary objective was to assess the efficacy of eslicarbazepine acetate. Our results indicate that a switch from oxcarbazepine to eslicarbazepine acetate was effective and well tolerated during a 3 month follow-up period. Clearly, the fact that none of the patients had an increased seizure frequency is at least as important as the seizure reduction observed in a small proportion of the patients. Furthermore, we did not note any specific concerns indicating that the transition from oxcarbazepine to eslicarbazepine acetate has to be conducted in an inpatient setting, as arranged earlier in our center. Transition from oxcarbazepine to eslicarbazepine acetate can be safely carried out in an outpatient setting.

There were slight differences on how the switch from oxcarbazepine to eslicarbazepine acetate was conducted in our center in comparison to the previous study (Schmid et al, 2016). In that study, the last intake of oxcarbazepine was the evening dose followed by first intake of eslicarbazepine acetate on the evening of the next day. In our study, the last administration of oxcarbazepine was the morning dose followed by the first intake of eslicarbazepine acetate already in the evening of the same day. The initiation dose of eslicarbazepine acetate was similar in both studies as a ratio 1:1 between oxcarbazepine and eslicarbazepine acetate were utilized.

6.4 Long-term consequences of enzyme induction

The major feature of current study is its practical relevance for those patients currently receiving carbamazepine treatment. We show here that carbamazepine discontinuation produces a broad spectrum of significant changes in serum concentrations of total cholesterol, HDL, LDL, SHBG, and testosterone whereas

previous studies have focused on single metabolic pathways. In spite of the relatively modest sample size, the significance of the findings attests to the robust nature of the effect. The overall consequence of these changes would be expected to result in a considerable decline in the risk for ischemic vascular disease and sexual dysfunction in men. Additionally, we systematically assessed the seizure outcome of carbamazepine discontinuation in various subgroups.

In the current study, approximately 40% of the patients were ultimately not willing to discontinue carbamazepine even though they had initially expressed acquiescence towards an evaluation of metabolic side-effects related to carbamazepine. Most patients had been seizure-free with carbamazepine for decades without experiencing any noticeable side effects. On the other hand, ageing is the most important risk factor for vascular events. However, a significant proportion of patients decided to continue carbamazepine despite their appreciation of the possible risks related to the long term effects of EI. The importance of good communication between patient and treating physician is underlined in these situations.

The inclusion of a control group in our study has added an important methodological feature missing from all previous outcome investigations with one exception (Wang et al, 2013). However, in that study, all switched patients were initially taking phenytoin or carbamazepine, whereas the controls were being treated with a diverse group of 10 different AEDs. We compared the patients who discontinued carbamazepine to those taking carbamazepine who continued taking carbamazepine. We detected a 5% rate of spontaneous recurrence in previously seizure-free patients who continued with carbamazepine during the six months' follow-up period, which is similar to the values from a previous investigation (Candrilli et al, 2010). In contrast, there was a 20% risk of seizure recurrence in seizure-free patients who discontinued carbamazepine.

One of the major features of the current study is of practical significance, since we were able to calculate probabilities for seizure recurrence among various subgroups (Table 18). The recurrence rate after carbamazepine withdrawal resulted in an approximately 24 percentage point incremental additional risk of seizure recurrence. Similarly, converting carbamazepine to some other AED in seizure-free patients resulted in an 11 percentage point additional risk of recurrent seizures. We also calculated the odds of seizure recurrence in seizure-free patients, but the absolute differences might be more interesting from the clinician's perspective.

Most of the epidemiological data emphasizes that patients with epilepsy have an increased risk of developing cardiovascular and cerebrovascular disease as compared to the general population (Annegers et al, 1984, Jansky et al, 2009). Furthermore, Sillanpää et al, 2015 conducted a population-based cohort study and demonstrated that there was a striking increase in magnetic resonance imaging (MRI) abnormalities related to cerebrovascular disease in patients with epilepsy compared to healthy controls at the age of 45 years. Following an extensive meta-analysis, Lossius et al, 2016 concluded that a decrease in LDL of 0.51 mmol/l, similarly to the decline detected in our patients, could reduce the overall mortality by five percentage points and cardiovascular mortality by 11% (CTT Collaboration et al, 2010). Based on the above findings, atherosclerotic vascular disease appears to be a genuine risk in the epileptic population. However, contradictory data do exist (Luoma et al, 1985, Nakken and Kornstad 1998, Sudhop et al, 1999).

We observed that there was a decrease in serum concentrations of total cholesterol, HDL, and LDL following discontinuation of carbamazepine. These results are rather similar to those seen when patients were either switched from carbamazepine to some other AED or alternatively carbamazepine was withdrawn (Isojärvi et al, 1994, Mintzer et al, 2009, Wang et al, 2013, Lossius et al, 2016).

Most statins are extensively metabolized by the CYP system; one might expect that there would be reduced serum levels of these drugs in the presence of an enzyme inducer (Brodie et al, 2013). However, patients taking statins had been excluded from all previous studies investigating this topic. In the current study, some of the patients receiving statins displayed moderate declines in the lipid profile, others exhibited rather major declines e.g. 4.5 mmol/l total cholesterol or 3.7 mmol/l LDL (Figure 4). Although the number of patients with statins was low and caution is necessary when considering the clinical implications of this finding, one might postulate that patients receiving statin therapy should avoid carbamazepine treatment.

We detected a significant decrease in SHBG levels in both genders following carbamazepine discontinuation. In addition, there was a significant increase in the free testosterone level in men after carbamazepine discontinuation. This corresponds well with clinical experience that some men enjoy improvements in sexual function after carbamazepine discontinuation. The design of our study meant that we were not able to assess the sex hormone profiles of females as it

is not convenient in clinical practice to request the patient to come to the clinic to provide a blood sample at a fixed time point relative to her menstrual cycle.

Unexpectedly, discontinuation of carbamazepine was not associated with any increase in serum vitamin D concentrations. Several factors might be speculated to account for this phenomenon. Firstly, extensive variability was also seen in the carbamazepine continuation group in vitamin D levels, which might be related to seasonal changes of sunlight exposure with respect to the time of year. Secondly, vitamin D supplements are prescription–free and widely used in Finland and their use could not be controlled in this retrospective analysis. In the northern hemisphere at latitudes greater than around 40°N (north of Barcelona), from October to March, the sunlight is not strong enough to trigger the synthesis of vitamin D in the skin.

6.5 Strengths and limitations of the study

The major feature of the current study is its practical importance on behalf of those patients with focal epilepsy. Another strength of our study was a comprehensive, well examined patient population with a detailed and accurate classification of epilepsies. The proportion of unclassified epilepsies was remarkably low.

Some points must be borne in mind when drawing conclusions from this study. All patients were from a single center (except study IV), which limits the external validity of findings. This was a retrospective study, not a prospective randomized controlled trial, complicating the comparability of patients in the different groups. As in all retrospective analysis, we were not able to control exposure or outcome assessment, we relayed on others for accurate recordkeeping. Further, the retrospective aspect may introduce selection bias and mis-classification or information bias. However, most of these clinical questions could not be adequately answered in a double-blind randomized study. It is not unlikely that physician preference/bias played a role in drug selection and decisions to modify certain AED treatments, but no statistical method can remove or fully account for this effect (Arif et al, 2009). The lack of systematic titration data for AEDs is a limitation of study, as too rapid titration might have an effect on tolerability. For certain AEDs, the number of patients was relatively small, this was particularly true in the transition from oxcarbazepine to eslicarbazepine acetate study. However, when considering the

results and conclusions emerging from the transition study, the number of patients can be viewed as justified. Moreover, since the seizure data was gathered only from the previous year, we were unable to eliminate the possibility of a remitting-relapsing pattern, which is believed to be present in as many as 16% of patients with epilepsy i.e. the patients fluctuate between periods of seizure-freedom and recurrence (Brodie et al, 2012).

6.6 Summary of the discussion

I Combined data from these two studies indicate that some patients with focal epilepsy might benefit from newer AEDs as an adjunctive therapy with the possibility they could acquire seizure-freedom.

II We provide important information about practical aspects of these eight AEDs, revealing that there are differences in their effectiveness as adjunctive treatment for focal refractory epilepsy. Most importantly, the retention rate appears to be influenced by the sequence in which these AEDs are introduced on to the market.

III Patients currently receiving oxcarbazepine and experiencing intolerable AEs benefit from switching to eslicarbazepine acetate in order to maintain seizure control while improving AED tolerability. This is particularly true if the AEs are most evident following morning dosing. Transition can be performed safely in an outpatient setting achieving both cost effectiveness and patient comfort.

IV Carbamazepine might exert an unfavorable impact on serum levels of TC, LDL, HDL, SHBG, and free testosterone. Conversely, discontinuation of carbamazepine in seizure-free patients seems to carry a moderate, but legitimate risk of relapse.

7 Summary and conclusions

The topic of this study was related to the assessment of treatment responses in patients with focal epilepsy. To summarize, this dissertation will be beneficial in the clinical management of epilepsy by producing practical information for optimizing the AED treatment in terms of minimizing the AEs while maximizing the therapeutic effect. The ultimate goal was to improve the QOL of the patients with epilepsy.

According to our present studies, we can draw the following inferences.

1. It seems that some patients with focal epilepsy might benefit from the newer AEDs as an adjunctive therapy to help achieve seizure-freedom. These data should encourage clinicians to continue active drug trials on those with persistent seizures.

2. The retention rate appears to be influenced by the sequence in which these AEDs were introduced onto the market. There are differences in effectiveness between clobazam, gabapentin, lacosamide, lamotrigine, levetiracetam, pregabalin, topiramate, and zonisamide as adjunctive therapy for focal refractory epilepsy. The value of retention rate studies as a valuable information source for the physician is highlighted.

3. Patients suffering from oxcarbazepine-related AEs improve in terms of tolerability after a switch to eslicarbazepine acetate with maintaining seizure control. This improvement is more pronounced if the oxcarbazepine-related AEs are most evident following the morning dosing of oxcarbazepine.

4. Carbamazepine is responsible for a deterioration in the lipid profile, alterations in male reproductive function, and potential drug interactions, which makes the use of carbamazepine problematic. With regard to the potential for chronic adverse-effects related to EI, the

practice of switching carbamazepine patients to non-inducing AED might be worth consideration.

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The effect of newer antiepileptic drugs in combination therapy

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ABSTRACT

Purpose: To assess the impact of the new AEDs on overall outcome for patients with epilepsy.
Methods: In 2004, the effect of combination therapy on seizure frequency in adult patients with focal epilepsy was evaluated in a cross-sectional study in our center. We repeated this analysis ten years and eight new antiepileptic drugs (AED) later.
Results: In 2014, a higher percentage of patients with polytherapy (117 out of 396; 30%) were seizure-free compared with the original analysis (22%) ($p = 0.042$). Eighty three out of 218 (38%) subjects on duo-therapy were seizure-free (27% in 2004) ($p = 0.040$); in the 151 receiving triple therapy there were 30 (20%) seizure-free subjects (10% in 2004). Four out of 27 subjects (15%) with four AEDs were seizure-free (0% in 2004). The most common pairing of 52 different combinations for duo-therapy was levetiracetam-oxcarbazepine. Eighty different AEDs regimens were being used in the patients administered three AEDs.
Conclusion: Our combined data from these two studies indicate that some patients with focal epilepsy might benefit from newer AEDs as an adjunctive therapy in the hope they could acquire seizure freedom.
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1. Introduction

The target of all epilepsy treatment is seizure freedom for the patient with as few antiepileptic drug (AED) related adverse-events as possible. If the first or second monotherapy improves seizure control but does not achieve seizure-freedom, combination therapy should be considered (Brodie, 2005). Combination therapy has been shown to be successful in about 20–30% of patients (Mohanraj and Brodie, 2005; Peltola et al., 2008). If the patient has recurrent seizures, if the diagnosis of epilepsy is conclusively established and if epilepsy surgery will most likely not be beneficial, then it is recommended that further attempts at optimizing the medical therapy should be pursued (Ben-Menachem, 2014). The major issues are i) which AED to choose and ii) how to combine different AEDs in order to reach seizure freedom. The best human evidence for synergistic effect of two AEDs in combination therapy exists for pairing valproate with lamotrigine (Brodie and Yuen, 1997). Currently, the rational choice of AED combinations is based more on the avoidance of pharmacological adverse effects rather than on convincing evidence for synergistic anticonvulsant effects (French and Faught, 2009). On the other hand, it has been demonstrated that some individuals will respond even to their 4th or 5th treatment schedules (Brodie et al., 2009). The new wave of combination therapy has also raised concerns of irrational polytherapy or overtreatment of epilepsy causing tolerability problems, pharmacological interactions, reduced compliance and increased risk of mortality (Brigo et al., 2013; Canevini et al., 2010; Perucca and Kwan, 2005).

There is currently little evidence to guide the physician when and how to combine AEDs. Therefore current treatment recommendations remain largely empirical. Moreover, a wide range of modern AEDs are available, some claimed to have better tolerability profiles and fewer interactions than the older AEDs. In 2004, a cross-sectional evaluation of 193 subjects with focal epilepsy treated with polytherapy was undertaken in Tampere University Hospital (Peltola et al., 2008). During the past decade, a further eight new AEDs (eslicarbazepine acetate, lacosamide, perampanel, pregabalin, retigabine, rufinamide, stiripentol and zonisamide) have been introduced for the adjunctive treatment of epilepsy in Finland. Now 10 years later, we have repeated this analysis to assess the impact of the increasing range of newer drugs on the clinical outcome. The majority of refractory patients in the Tampere University Hospital district (population of 505 000) are monitored in our clinic. Only some elderly patients and those patients with mental retardation are treated elsewhere.

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2. Materials and methods

The study was carried out at the Outpatient Department of Neurology, Tampere University Hospital. Patients with focal epilepsy treated in our department 31.12.2014 were identified from the hospital patient registry using ICD-10 diagnostic codes for focal and unclassifiable focal epilepsy (G40.1X, G40.2X and G40.9). Only subjects with polytherapy were included in this study (n = 396). The information of patient characteristics was collected retrospectively from the medical records. Subjects were classified according to ILAE guidelines (Anon., 1989) for epilepsy type into temporal lobe epilepsy, frontal lobe epilepsy, parietal/occipital lobe epilepsy or multifocal epilepsy based on seizure characteristics, EEG and imaging findings, and in some patients on ictal video-EEG recordings. The etiologies were classified into either known (structural, metabolic, infectious) or unknown etiology (Scheffer et al., 2016); in the 2004 analysis, the etiologies had been classified similarly but with older terminology (remote symptomatic or cryptogenic). The seizure frequency was recorded for the previous year prior to the last visit date; seizure-free subjects had not experienced any seizures during the previous year. The AEDs currently used, information on doses, and duration of present regimen were registered. The study was approved by the Ethics Committee of the Tampere University Hospital.

According to local treatment guidelines, all adult (>16 years) patients with refractory epilepsy—except patients with moderate or severe mental retardation, those elderly patients with controlled epilepsy and patients with post-stroke epilepsy—in Pirkanmaa Hospital District (population of 505 000) are treated and followed-up in our institution. Our department also serves as a secondary referral center for refractory patients for a population of about 1 million including five central hospitals. The patients were monitored and regularly reviewed by three epileptologists in 2004 and 2014 analysis. Residents of neurology have monitored patients sporadically as a part of their degree. Patients with active epilepsy are reviewed between 1 and 3 months by epilepsy nurse or epileptologist. In addition, some of the patients had epilepsy surgery or other lesional surgery or were under presurgical or neuromodulative treatment evaluation, but none underwent operation during the follow up. No strict upper age limit was used. There has been participants in randomized controlled AED trials from our institution. However, these patients are treated and followed up in separate scientific clinic (Finn-Medi) and therefore not included in the current study.

Statistical significance was evaluated using a chi-square test when comparing the proportion of seizure-free subjects with different numbers of AEDs. Two-sample z-test was used to compare the proportions from studies in 2004 and 2014. Chi-square test was used for testing group differences for categorical variables. Independent *t*-test was used for comparing mean differences of changes between the two groups. An unadjusted and adjusted logistic regression models were used to analyze seizure freedom and the effect of year (2004 vs. 2014) on seizure freedom. The covariates considered were age, gender, etiology, duration of epilepsy and type of epilepsy. Confidence intervals (CI) are likelihood-based. The results were considered to be statistically significant if $p < 0.05$. All analyses were performed with Stata Statistical Software version 13.1.

3. Results

In the 2014 analysis, a total of 507 subjects with focal epilepsy were identified from a computerized patient database. One hundred and eleven subjects were excluded because they were receiving monotherapy, and thus 396 subjects on polytherapy were included in this study. There were significant differences between the groups in age and type of epilepsy (Table 1). Patients were significantly younger (41.6 vs. 48.2) on 2004 analysis than 2014. Further, temporal and frontal lobe epilepsies were more common in 2004 study.

Fifty-five percent of the subjects with combination therapy were being treated with two AEDs, 38% received three and 7% four AEDs. Eighty three out of 218 subjects (38%) were seizure-free on duotherapy and furthermore 30 out of 151 receiving three AEDs (20%) were seizure-free. Four out of 27 subjects (15%) administered four AEDs were seizure-free. The clinical characteristics of the seizure-free patients are presented in Table 2. Subjects with three or four AEDs were less likely to be seizure-free compared to those being treated with two AEDs (OR 2.7, 95% CI 1.6–4.4). Temporal lobe epilepsy was the most common type of epilepsy (N = 161, 41%) whereas 85 (21%) subjects had frontal lobe epilepsy, 37 (9%) had multifocal epilepsy and 24 (6%) suffered from parieto-occipital epilepsy.

The most common combinations with two AEDs included levetiracetam-oxcarbazepine (N = 29), carbamazepine-levetiracetam (N = 19), lacosamide-levetiracetam (N = 17), lamotrigine-levetiracetam (N = 13), lacosamide-topiramate (N = 11) and lamotrigine-valproate (N = 10). In all, 52 different combinations of two AEDs were being used (Table 3). The different combinations with the most seizure-free subjects were levetiracetam-oxcarbazepine (N = 15), carbamazepine-levetiracetam (N = 12), lamotrigine-levetiracetam (N = 7), lamotrigine-valproate (N = 7), levetiracetam-valproate (N = 4) and lamotrigine-topiramate (N = 4).

Subjects with three AEDs (N = 151) had 80 different combinations; the most common combinations included lamotrigine-topiramate-valproate (N = 7), levetiracetam-oxcarbazepine-topiramate (N = 5), levetiracetam-oxcarbazepine-pregabalin (N = 5), clobazam-lacosamide-topiramate (N = 5) and clobazam-lacosamide-zonisamide (N = 5). All of the subjects being treated with four AEDs had their own distinctive combinations. The mean and median doses of individual AEDs are summarized in Table 4. In this analysis, the most frequently used AEDs were levetiracetam (N = 100), lamotrigine (N = 49) and carbamazepine (N = 47) for two drug combinations and levetiracetam (N = 33), clobazam (N = 25) and lacosamide (N = 22) for three drug combinations. Table 5 presents comparisons with the results from 2004.

Table 6 shows unadjusted and adjusted odds ratios for covariates. Seizure freedom on duotherapy was found to be more frequent in 2014 compared to 2004 in unadjusted model and especially after adjusting for covariates. Instead, on those with 3 or 4 AEDs findings do not abundantly reach statistical significance. Compared to patients on duotherapy in 2004 analysis, patients with 2 AEDs on 2014 analysis had 2.00 times higher odds of being seizure free (odds ratio [OR] 2.00, 95% confidence interval [CI] (1.20–3.33); p = 0.008). Among those with 3 or 4 AEDs, patients on 2014 had 2.60 times higher odds of attaining seizure remission compared to patients in earlier study (OR 2.60, 95% CI 0.90–7.49; p = 0.076).

4. Discussion

The main finding of our study is that at least one year seizure-freedom with polytherapy had been achieved in 30% of the patients in the 2014 cohort, which is significantly higher than the value of 22% in the original analysis from 2004 (p = 0.042). The second significant finding is that in patients with duo-therapy, the rate of seizure-freedom increased from its 2004 value of 27%–38% in 2014 (p = 0.040). Furthermore, there is a trend towards improved possibilities for seizure-freedom in patients with three or four

Table 1
Comparison of clinical characteristics of patients with combination therapy between 2014 and 2004.

Characteristics	Year of analysis, 2014				Year of analysis, 2004				p
	Number of antiepileptic drugs (AED)				Number of antiepileptic drugs (AED)				
	2	3	4	Total	2	3	4	Total	
Total (n)	218	151	27	396	135	50	8	193	
Gender									0.82
Male (%)	47	50	48	48	45	60	50	49	
Female (%)	53	50	52	52	55	40	50	51	
Mean age (SD)	51.1 (15.5)	45.6 (16.2)	39.7 (11.7)	48.2 (15.9)	43.4 (14.3)	37.6 (13.0)	36.7 (13.6)	41.6 (14.1)	<0.001
Type of epilepsy									0.018
Temporal lobe epilepsy (%)	45	38	22	41	44	48	75	46	
Frontal lobe epilepsy (%)	17	25	37	21	24	42	13	28	
Parieto/occipital epilepsy (%)	6	6	4	6	10	0	0	7	
Multifocal epilepsy (%)	6	11	26	9	3	8	13	5	
Focal epilepsy with undefined onset (%)	25	20	11	22	19	2	0	14	
Mean duration of epilepsy (years) (SD)[a]	22.0 (16.3)	23.5 (15.8)	27.6 (12.5)	23.0 (15.9)	21.2 (15.5)	25.4 (13.5)	17.3 (12.0)	22.2 (15.0)	0.56
Etiology[b]									0.42
Known (%)	70	63	60	67	66	53	86	63	
Unknown (%)	30	37	40	33	34	47	14	37	
Seizure frequency[c]									0.047
Seizure-free (%)	38	20	15	30	28	10	0	22	
Persistent seizures (%)	62	80	85	70	72	90	100	78	

[a] Missing information: 2 in 2 AED.
[b] Missing information: 8 in 2 AED, 6 in 3 AED and 6 in 4 AED.
[c] Missing information: 5 in 2 AED and 3 in 3 AED.

Table 2
Clinical characteristics of seizure-free patients compared with patients with persistent seizures.

	Seizure-free	Persistent seizures	OR (95 % CI)	p
Antiepileptic drugs (AED)				
2 (%)	71	50	1.00	
3 or 4 (%)	29	50	2.65 (1.60–4.40)	<0.001
Mean age	46.6	49.3	1.02 (1.01–1.04)	0.006
Gender				
Male (%)	50	47	1.00	
Female (%)	50	53	1.16 (0.72–1.87)	0.53
Mean duration of epilepsy (years)	22.0	23.4	0.98 (0.97–1.00)	0.066
Type of epilepsy				
Temporal lobe epilepsy (%)	46	40	1.00	
Frontal lobe epilepsy (%)	24	19	0.85 (0.45–1.58)	0.60
Parieto/occipital epilepsy (%)	4	8	2.64 (0.82–8.50)	0.10
Multifocal epilepsy (%)	4	11	3.00 (0.97–9.30)	0.057
Onset not defined (%)	22	22	1.25 (0.67–2.32)	0.48
Etiology				
Known (%)	67	67	1.00	
Unknown (%)	33	33	0.99 (0.59–1.64)	0.96
Mean number of previously tried AEDs	2.7	3.8	1.27 (1.13–1.43)	<0.001

OR = odds ratio; CI = confidence interval.

AEDs although these trends were not statistically significant. These results may indicate that some of the newer AEDs might be useful in combination therapy on the route to seizure-freedom. As far as we are aware, only one such pair of studies has been published previously (Stephen and Brodie, 2002; Stephen et al., 2012). In the 2012 analysis by Stephen et al. sustained seizure-freedom with more than one AED was achieved in 20.4% of patients, which was an almost identical percentage as the 20.5% reported by that group in their 2002 study (Stephen and Brodie, 2002) indicating that despite the introduction of six new AEDs in the intervening decade, no substantial impact on the likelihood of producing seizure-freedom had been achieved. The rate of seizure freedom from these two studies is similar to our 2004 cohort. One explanation for the comparable results might be that the most common duo-therapies (lamotrigine-valproate, carbamazepine or oxcarbazepine combined to topiramate or levetiracetam) were analogous in our 2004 analysis and in the 2012 analysis by Stephen et al. The most common combinations in their 2002 study (Stephen and Brodie, 2002) had been lamotrigine-valproate, phenytoin-phenobarbital and carbamazepine combined with gabapentin, valproate or lamotrigine.

There were certain differences in clinical characteristics of the patients with combination therapy when comparing 2004 and 2014 studies. The proportion of patients with known etiology had risen from 63.7% to 66.7% due to advances in neuroimaging. The percentage of multifocal epilepsy had moderately increased in those patients with more than two AEDs. Combination therapy has also become more complex during the past decade; the number of patients with three or four AEDs had tripled but there were only one and half times more patients being administered two AEDs. These clinical characteristics suggest that the study population in the 2014 analysis was at least as refractory as that examined in our original analysis in 2004.

As is generally known, age, duration of epilepsy and multifocal epilepsy are associated with persistent seizures; this was evident also in our analysis. The mean number of previously tried AEDs

Table 3
The number of subjects with two antiepileptic drug combinations (n = 218).

	LEV	LTG	TPM	GBP	PGB	ZNS	TGB	VGB	OXC	CBZ	VPA	CLB	CZP
LEV													
LTG	13												
TPM	4	8											
GBP	2	1	1										
PGB	2	6	1										
ZNS		7			1								
TGB													
VGB													
OCX	29		2		5	2	1						
CBZ	19	1	7	1	8	2	1	1					
VPA	5	10											
CLB	2	2		1	1	2			4	5			
CZP		1		1					1	1			
PHT	1												
PMD										1			
LCM	17		11		1	2			1		4	6	1
ESL	6				2	1						1	
PRP									1				

LEV = Levetiracetam; LTG = Lamotrigine; TPR = Topiramate; GBP = Gabapentin; PGB = Pregabalin; TGB = Tiagabine; VGB = Vigabatrin; ZNS = Zonisamide; OCX = Oxcarbazepine; CBZ = Carbamazepine; VPA = Valproate; CLB = Clobazam; CZP = Clonazepam; PHT = Phenytoin; PMD = Primidone; LCM = Lacosamide; ESL = Eslicarbazepine; PRP = Perampanel.

Table 4
The doses (mg/day) of individual antiepileptic drugs (AEDs).

	Two AED combinations				Three or four AED combination				DDD (mg)
	N	Mean	Median	Range	N	Mean	Median	Range	
Levetiracetam	100	1737	1500	1000–3000	78	2042	2000	100–3500	1500
Carbamazepine	47	859	800	200–1600	30	763	775	300–1200	1000
Oxcarbazepine	46	1187	1200	600–1800	42	1279	1200	600–2400	1000
Lacosamide	43	395	400	100–600	56	413	400	200–600	300
Lamotrigine with valproic acid	10	198	200	100–550	26	306	200	25–300	300
Lamotrigine without valproic acid	39	372	400	100–600	28	363	400	100–600	300
Topiramate	34	292	300	100–600	51	361	400	50–1000	300
Pregabalin	28	399	413	150–600	40	443	475	75–600	300
Clobazam	24	16	15	5.0–30	71	22	20	5–80	20
Valproate with lamotrigine	10	1210	1200	900–1500	26	1419	1500	500–3000	1500
Valproate without lamotrigine	9	1389	1500	500–2000	12	1342	1500	1000–1800	1500
Zonisamide	17	365	400	200–500	49	359	300	200–600	200
Eslicarbazepine	10	1100	1200	800–1600	13	1262	1200	800–2000	800
Gabapentin	7	2486	2800	1200–3600	6	1917	1350	1200–3600	1800
Clonazepam	5	19	4.0	1.0–8.0	10	2.7	2.1	0.4–6.0	8
Tiagabine	2	25	25	20–30	2	65	65	30–100	30
Vigabatrin	1	2000	2000	2000–2000	1	3000	3000	3000–3000	2000
Phenytoin	1	250	250	250–250	1	300	300	300–300	300
Primidone	1	500	500	500–500	–	–	–	–	1250
Perampanel	1	4.0	4.0	4.0–4.0	8	9.3	9.0	4.0–12	8
Phenobarbital	–	–	–	–	2	190	190	180–200	100
Acetazolamide	–	–	–	–	1	250	250	250–250	900
Retigabine	–	–	–	–	1	900	900	900–900	900

DDD = Defined daily dose.

Table 5
Subjects with localization-related epilepsy on combination therapy.

Year of analysis	N	Combination therapy (%)	Seizure-free on combination therapy (%)	Seizure-free on two AEDs (%)	Seizure-free on three AEDs (%)	Seizure-free on four AEDs (%)
2004	395	193 (48.9)	41 (21.6)	36 (27.3)	5 (10)	–
2014	507	396 (78.1)	117 (29.9)	83 (38.4)	30 (20.3)	4 (14.8)
			p = 0.042	p = 0.040	p = 0.111	p = 0.247

in seizure-free patients was 0.7 in 2004 analysis and 2.7 in 2014 analysis suggesting that on average, it required a trial with a fourth AED before the patient enjoyed seizure freedom without intolerable adverse-events. Subjects with persistent seizures had tried on average 1.2 previous AEDs in 2004 and 3.8 in 2014, underlining the refractory nature of study population in the later analysis.

Monotherapy remains the golden standard treatment being sought by the majority of the patients with epilepsy but those with persistent seizures may benefit significantly from some form of combination therapy. In theory, seizure freedom can be pursued by combining AEDs with different mechanisms of action in order to achieve a synergistic effect (Guimarães and Ribeiro, 2010). The use of rational polytherapy has become more frequent in our center i.e. whereas only 49% of the subjects received combination therapy in 2004, by 2014 that value had risen to 78%. The number of different duo-therapy combinations has increased from 38 to 52 and different triple-therapy combinations from 40 to 80 during a time frame of a single decade. From a clinical standpoint, the increased num-

Table 6
Unadjusted and adjusted logistic regression models for 2 and 3 or 4 AEDs.

Characteristic (referent)	2 AEDs				3 or 4 AEDs			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	P	OR (95% CI)	P
Year (2004)	1.60 (1.00–2.56)	0.049	2.00 (1.20–3.33)	0.008	2.56 (0.95–6.88)	0.063	2.60 (0.90–7.49)	0.076
Age			0.98 (0.96–1.00)	0.012			1.01 (0.98–1.03)	0.52
Epilepsy type (TLE)								
FLE			0.94 (0.51–1.73)	0.85			1.18 (0.49–2.82)	0.71
PLE/OLE			0.20 (0.06–0.69)	0.011			1.71 (0.37–7.89)	0.49
Multifocal			0.28 (0.07–1.04)	0.057			0.38 (0.33–2.81)	0.22
Undefined onset			0.86 (0.46–1.59)	0.62			0.96 (0.33–2.81)	0.94
Gender (female)			1.03 (0.64–1.65)	0.90			1.64 (0.79–3.43)	0.19
Duration of epilepsy			1.01 (0.99–1.02)	0.37			0.99 (0.96–1.01)	0.34
Etiology (unknown)			0.66 (0.40–1.08)	0.099			1.74 (0.79–3.84)	0.17

AED = Antiepileptic drug; CI = Confidence interval; FLE = Frontal lobe epilepsy; OLE = Occipital lobe epilepsy; OR = Odds ratio; PLE = Parietal lobe epilepsy; TLE = Temporal lobe epilepsy.

ber of different combinations emphasizes the challenges related to evaluation of the efficacy and tolerability of given combinations. However, direct comparison about the success of different combinations is not possible because AEDs have been introduced to the market at different time points (Peltola et al., 2008). At the time of analysis in 2014, perampanel and brivaracetam were not licensed and eslicarbazepine acetate was not fully reimbursed in Finland.

In the current analysis, the most common individual combination was levetiracetam and oxcarbazepine followed by combinations of carbamazepine and levetiracetam, and lacosamide and levetiracetam representing the ideology of rational polytherapy; a sodium channel blocker combined with another AED with a different mechanism of action. In the three or four drug combinations, levetiracetam and clobazam were the most commonly used AEDs whereas in two drug combinations clobazam was used infrequently; in our center, clinicians prefer to prescribe clobazam most frequently when proceeding to triple-therapy. As hypothesized in the previous study (Stephen et al., 2012), the different combinations could simply express personal preferences of the treating physicians, but on the other hand similar results have been shown in laboratory studies (Brodie and Sills, 2012). In the two data sets, we were not able to identify any of the combinations as being clearly more successful than the others. In a previous study on combination therapy, the most common combinations in seizure-free patients with epilepsy were sodium valproate-lamotrigine, carbamazepine-sodium valproate and phenobarbital-phenytoin (Stephen et al., 2012).

The mean doses for AEDs used in combination therapy were mostly equal or marginally higher than the World Health Organization (WHO, 2016) defined daily doses (2016) suggesting that overall drug load was not excessive in our patients. However, little is known about the actual optimal doses in polytherapy and there is a considerable risk of overtreatment in terms of unnecessarily high doses (Brigo et al., 2013). On the other hand, it has been suggested that if seizure-freedom is not achieved with 2 or 3 AEDs, drug substitution rather than addition will result in better outcomes (Stephen et al., 2012); an approach which may also reduce overtreatment in epilepsy (Brigo et al., 2013) and minimize adverse-events related to combination therapy.

This study and also the original analysis have some limitations. This was not a randomized trial complicating the comparability of subjects on different AEDs. Moreover, the analysis was retrospective and subjects had variable clinical histories (duration of epilepsy, arrival to the study hospital). Furthermore, the homogeneity of study population was magnified by limiting the analyses only to those subjects with focal epilepsy and polytherapy being followed in a single center. As in the original article (Peltola et al., 2008), the lack of a uniform treatment guideline helps the evaluation of individual AEDs, as the variability in the order in which AEDs are introduced improves comparability between the combinations i.e. we are not comparing against a fixed sequence of AEDs. Sodium-channel blockers (carbamazepine/oxcarbazepine/phenytoin) had been combined into a single group in the original analysis but in current study this was considered inadequate due to increased number of sodium-channel blockers and differences on their detailed mechanism of action (inhibition of the slow/fast activation of voltage-gated sodium-channel). Moreover, since the seizure data was gathered only from the previous year, we were unable to eliminate the possibility of remitting-relapsing pattern, which is believed to be present in as many as 16% of patients with epilepsy i.e. the patients fluctuate between periods of seizure freedom and recurrence (Brodie et al., 2012). However, the data from our 2004 cohort was evaluated in a similar way as in the 2014 cohort probably nullifying the effect of relapsing-remitting pattern in our comparison.

In addition to efficacy, some newer AEDs seem to display a better side-effect profile and to have fewer interactions compared to the older drugs, especially concerning the long-term adverse-events such as issues related to enzyme induction. Subjects who become seizure-free at low doses of AED have shown improvement in quality of life measures (Marson et al., 2007). Nonetheless, also in patients with combination therapy and persistent seizures, the quality of life may also be improved; the correlation between quality of life and medication-related adverse-events is much stronger than that between quality of life and seizure frequency (Ben-Menachem et al., 2010; Gillian et al., 2004).

5. Conclusion

The proportion of subjects benefiting from combination therapy in our institution has increased from 22% to 30% during the last decade. The most common two-drug combination was levetiracetam-oxcarbazepine. If one considers the outcomes of these two studies separated by 10 years, then it seems that some patients with focal epilepsy might benefit from the newer AEDs as an adjunctive therapy to help them achieve reach seizure freedom. Furthermore, these data should encourage clinicians to continue active drug trials on those patients with persistent seizures. In future studies, the usefulness of combination therapy on different seizure types should be evaluated as there might be other significant clinical benefits such a decrease in the frequency or severity of tonic-clonic convulsions or other seizure types even without achieving complete seizure freedom. The term rational polytherapy does not incorporate clinical information, therefore it

has been proposed that an international data bank of all patients with epilepsy should be established to help determine the best treatment for patients on a clinical basis in addition to experimental data (McCabe, 2015).

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ORIGINAL COMMUNICATION

Comparative effectiveness of eight antiepileptic drugs in adults with focal refractory epilepsy: the influence of age, gender, and the sequence in which drugs were introduced onto the market

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Abstract The first objective was to determine the long-term retention rate of eight antiepileptic drugs (AEDs) commonly used as adjunctive therapy in adults with focal refractory epilepsy. Second, we assessed the effects of age and gender on retention rates. Third, we examined if the retention rate could be influenced by the sequence in which the AEDs had entered the market. Patients with focal refractory epilepsy treated with any of the eight AEDs in Tampere University Hospital were identified retrospectively ($N = 507$). Retention rates were evaluated with the Kaplan–Meier method. Follow-up started at the first date of treatment and each individual was followed a maximum of 36 months. We calculated the following 3-year retention rates: lacosamide 77.1% ($N = 137$), lamotrigine 68.3% ($N = 177$), levetiracetam 66.7% ($N = 319$), clobazam 65.6% ($N = 130$), topiramate 61.6% ($N = 178$), zonisamide 60.4% ($N = 103$), pregabalin 54.6% ($N = 127$), and gabapentin 40.2% ($N = 66$). Lacosamide, levetiracetam, and clobazam were the most effective AEDs in the elderly. The retention rate for pregabalin was higher in males (65%) than females (51%) whereas females had higher retention rates for both topiramate (72 vs. 58%) and zonisamide (67 vs. 57%). The retention rate was influenced by the sequence in which these AEDs entered the market. We provide important information about practical aspects of these eight AEDs, revealing that there are differences in their effectiveness as adjunctive treatment for focal refractory epilepsy. Most importantly, the retention rate appears to be influenced by the sequence in which these AEDs were introduced onto the market.

Keywords Antiepileptic drugs · Epilepsy · Retention rate · Effectiveness

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Introduction

Epilepsy is a chronic disorder that often requires lifelong treatment with antiepileptic drugs (AEDs). During the last decade, a new AED has been introduced for clinical use almost on an annual basis. This makes it increasingly difficult for the clinician to make a rational choice about which AED to select for which patient, especially in patients with drug-resistant epilepsy. It has been claimed that the choice of an AED is currently more empirical than evidence based [1]. The tolerability and efficacy of new AEDs have been demonstrated in regulatory trials, but their strict entry and dosing criteria limit the amount of useful data that can be utilized in clinical practice [2].

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Both the International League Against Epilepsy (ILAE) and the European Medicines Agency (EMEA) have emphasized the importance of gathering long-term retention data as a relevant endpoint for clinical trials of AEDs [3, 4], since this provides information that can be applied readily to everyday practice [5]. The long-term retention rate of patients on their AED treatment is accepted as one of the clearest reflections of the drug's true therapeutic effectiveness (i.e., it combines aspects of efficacy and tolerability) [6].

First, we evaluated the long-term retention rates for eight of the most commonly used AEDs as adjunctive therapy in our institution in patients with focal refractory epilepsy: clobazam, gabapentin, lacosamide, lamotrigine, levetiracetam, pregabalin, topiramate, and zonisamide. Brivaracetam and perampanel were excluded from the analysis because they were not licensed in Finland at the time of this analysis, eslicarbazepine acetate because it was not fully reimbursed, and carbamazepine, oxcarbazepine and sodium valproate because they are extensively administered as the first-line therapy for new-onset epilepsy [7]. The poor long-term retention rate for tiagabine (38.2%) in our center had been determined earlier based on an analysis conducted in 2004 [8]; since then, tiagabine has not been prescribed in our institution and, therefore, it was excluded from the current study. Vigabatrin was included in the early phase of the analysis, but excluded from the final analysis due to low number of cases ($N = 37$).

Second, we assessed the effects of age and gender on retention rates of all eight AEDs due the fact that currently there is a lack of specific prescribing guidance for these subgroups of people with epilepsy [9].

It has been speculated, but not confirmed earlier, that the retention rate could be influenced by the sequence in which AEDs have been introduced into market [10]. Therefore, we analyzed each drug in terms of annual prescriptions and withdrawals from the introduction of the drug in Finland up to the final assessment point.

Materials and methods

Patients with focal refractory epilepsy (age $\geq$18 years) treated in Tampere University Hospital from January 1, 2004, to December 30, 2014 were identified from the hospital patient registry using ICD-10 diagnostic codes for focal and unclassifiable epilepsy (G40.1X, G40.2X, and G40.9). Refractory epilepsy was defined as having seizures after trials of at least two AEDs with maximally tolerated doses either sequentially or in combination therapy. However, patients ranging from 4 to 16% demonstrate only one prior AED in Table 1. To clarify Table 1, prior AEDs are defined as priory initiated and tapered off due to inefficacy. In patients with one prior AED, the second AED failed to achieve complete seizure freedom, but it was continued due to clinical reasons (i.e., partial effect on seizure duration or frequency) and third AED was initiated as a combination therapy with the second AED. We included patients with focal refractory epilepsy who had ever used at least one of the following AEDs: clobazam, gabapentin, lacosamide, lamotrigine, levetiracetam, pregabalin, topiramate, or zonisamide ($N = 507$). All patients started these AEDs as adjunctive therapy. Overall, 21.9% of the patients were treated with monotherapy, 43.0% with duotherapy, 29.7% with triple therapy, and 5.4% were being administered four AEDs. We retrospectively reviewed patient background, medical history, current and previous AED use, duration of therapy, and reasons for treatment discontinuation. The etiologies were classified into either known (structural, metabolic, infectious) or unknown etiologies [11]. The majority of the refractory patients in the Tampere University Hospital district (population of 505,000) are monitored in our clinic and only some elderly as well as those patients with moderate or severe mental retardation are treated elsewhere.

The following classifications were made for the subgroup analyses. Age was categorized into two groups: $<$60 years of age and $\geq$60 years of age and the subjects were also subdivided by gender.

The background and medical characteristics of the patients are reported as means and ranges or proportions. The Kaplan–Meier method was used to obtain a product-limit estimate of the retention rate and comparisons between the retention curves were analyzed using log-rank tests. Significance was determined as $p < 0.05$. Bonferroni correction was used for multiple comparisons. Follow-up started on the first date of treatment and each person was followed for a maximum of 36 months. Follow-up lasted until discontinuation of the treatment (event), death, or the end of the follow-up (range from 2 days to 36 months). All analyses were performed with Stata Statistical Software version 13.1.

Results

Clinical and demographic data on the patients treated with each AEDs are summarized in Table 1. Retention curves for all AEDs are presented in Fig. 1. We estimated the following 3-year retention rates: clobazam 65.6%, gabapentin 40.2%, lacosamide 77.1%, lamotrigine 68.3%, levetiracetam 66.7%, pregabalin 54.6%, topiramate 61.6%, and zonisamide 60.4% (Table 2). Log-rank test showed significant variation between the AEDs ($p = 0.0001$). In pairwise comparison, lacosamide ($p = 0.003$), lamotrigine ($p = 0.01$), and levetiracetam ($p = 0.04$) retention was

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Table 1 Demographic and medical characteristics of the patients

	Clobazam	Lamotrigine	Gabapentin	Topiramate	Levetiracetam	Pregabalin	Zonisamide	Lacosamide
Year of introduction onto the Finnish market	1988	1994	1995	1999	2001	2004	2007	2009
Date of full reimbursement	1.1.1990	1.7.1996	1.7.1996	1.9.2000	1.1.2005	1.7.2007	1.11.2008	1.1.2012
N	130	177	66	178	319	127	103	137
Sex								
Female (%)	48.5	55.4	54.5	48.3	49.8	51.2	49.5	51.1
Male (%)	51.5	44.6	45.5	51.7	50.2	48.8	50.5	48.9
Etiology								
Known (%)	29.6	58.7	30.0	34.2	66.5	37.8	56.3	33.5
Unknown (%)	70.4	41.3	70.0	65.8	33.5	62.2	43.7	66.5
Duration of epilepsy (years)								
Mean	20.7	27.1	27.3	23.5	20.2	25.4	23.5	16.6
Range	0–72	1–72	2–63	0–72	0–70	2–70	2–63	0–63
Age								
Mean	44.6	48.1	51.7	49.2	50.6	46.4	42.7	54.0
Range	19–85	19–85	24–85	20–85	19–85	19–85	19–76	21–85
Number of prior AEDs*								
1 (%)	11.8	8.9	4.5	7.9	16.3	7.4	4.9	16.3
2 (%)	15.0	14.8	7.6	14.7	21.5	9.2	7.8	18.8
3 (%)	17.4	17.5	18.2	18.4	20.6	17.6	21.3	25.2
≥4 (%)	55.8	58.8	69.7	59.0	41.6	65.8	66.0	39.7

AED Antiepileptic drug

* Defined as initiated and withdrawn due to inefficacy

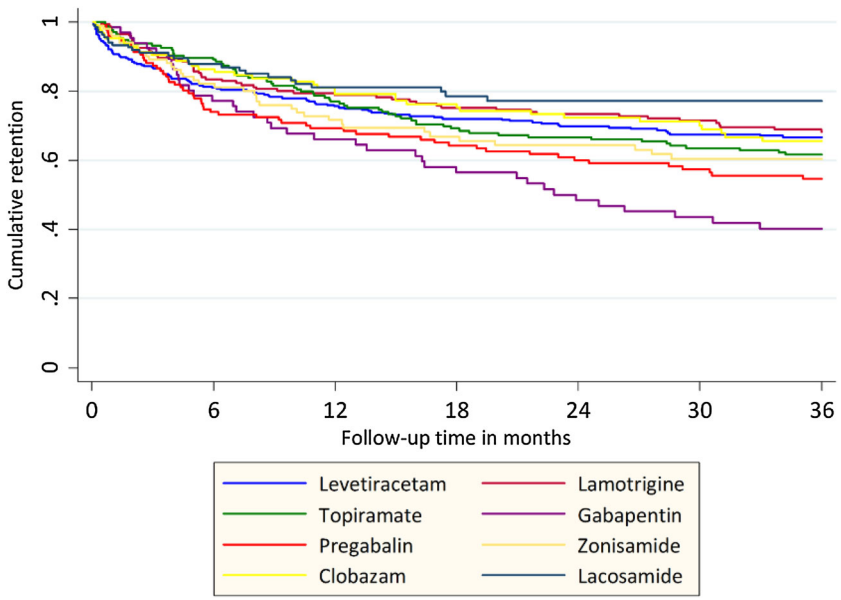

Fig. 1 Retention rates for clobazam, gabapentin, lacosamide, lamotrigine, levetiracetam, pregabalin, topiramate, and zonisamide in patients with focal epilepsy by Kaplan–Meier analysis

significantly increased compared to gabapentin after Bonferroni correction. Other statistically significant differences between the retention rates could not be identified in pairwise comparison.

The reasons for discontinuation by those patients who terminated a particular AED within the 3-year follow-up period are shown in Table 3. The results of the subgroup analyses in which the patients were categorized according

Table 2 Mean duration (months) of treatment and mean dose (mg per day) of AEDs for all patients, patients who discontinued the drug, and for those who continued the treatment

	All patients			Discontinued			On medication			Three-year retention rate	
	n	Duration Mean (range)	Dose Mean (range)	*n*	Duration Mean (range)	Dose Mean (range)	*n*	Duration Mean (range)	Dose Mean (range)	%	95% CI
Levetiracetam	319	23.4 (0–36)	2001 (100–3500)	138	15.5 (0–36)	2271 (250–3500)	181	29.3 (0–36)	1800 (100–3500)	66.7	61.0–71.8
Lamotrigine	177	26.1 (0–36)	305 (25–800)	71	16.5 (0–36)	297 (50–800)	106	32.6 (0–36)	310 (25–550)	68.3	60.6–74.7
Topiramate	178	24.8 (0–36)	326 (30–1600)	97	19.5 (1–36)	338 (30–1600)	81	31.2 (0–36)	311 (50–600)	61.6	53.8–68.5
Pregabalin	127	22.8 (0–36)	415 (25–600)	62	12.1 (0–36)	415 (25–600)	65	33.0 (10–36)	415 (75–600)	54.6	45.4–63.0
Zonisamide	103	21.1 (0–36)	354 (25–600)	39	9.9 (0–36)	349 (25–600)	64	27.9 (1–36)	356 (200–600)	60.4	49.5–69.6
Clobazam	130	22.4 (0–36)	21.8 (2–200)	50	17.1 (0–36)	23.6 (2–200)	80	25.7 (0–36)	20.7 (5–80)	65.6	55.7–73.8
Lacosamide	137	16.9 (0–36)	396 (100–600)	28	7.7 (0–36)	363 (200–600)	109	19.2 (0–36)	405 (100–600)	77.1	67.8–84.0
Gabapentin	66	20.8 (1–36)	2692 (900–4800)	55	19.5 (1–36)	2804 (900–4800)	11	27.5 (6–36)	2136 (900–3600)	40.2	28.1–52.0

Missing information

Dose of levetiracetam, three patients (discontinued)

Dose of lamotrigine, four patients (discontinued)

Dose of topiramate, two patients (discontinued)

Dose of pregabalin, one patient (discontinued)

Dose of clobazam, one patient (discontinued)

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Table 3 Reason for discontinuation of one of the tested antiepileptic drugs and mean duration (months) of treatment in subjects who discontinued the drug

	Discontinued	Lack of efficacy			Adverse effect			Lack of efficacy and adverse effect			Other reason		
	n	*n*	%	Duration	*n*	%	Duration	*n*	%	Duration	*n*	%	Duration
Clobazam	38	16	42.1	15.6	14	36.8	5.9	2	5.3	14.6	6	15.8	13.8
Gabapentin	38	28	73.8	12.5	4	10.5	10.2	4	10.5	13.3	2	5.2	2.1
Lacosamide	26	5	19.2	7.3	13	50.0	4.7	2	7.7	6.0	6	23.0	2.9
Lamotrigine	54	29	53.7	12.0	17	31.5	3.6	3	5.6	7.5	5	9.3	12.8
Levetiracetam	100	49	49.0	8.6	34	34.0	5.9	8	8.0	12.4	9	9.0	5.7
Pregabalin	56	22	39.3	8.9	23	41.0	9.0	9	16.1	10.8	2	3.6	17.1
Topiramate	65	16	24.6	12.7	34	52.3	9.1	10	15.4	17.7	5	7.7	9.8
Zonisamide	37	17	46.0	9.6	11	29.7	5.6	7	16.2	8.2	3	8.1	1.0

either to age or gender are summarized in Table 4. The annual number of initiations and discontinuations for lacosamide, levetiracetam, pregabalin, topiramate, and zonisamide used as an adjunctive therapy in focal refractory epilepsy from 1995 to 2014 are illustrated in Fig. 2.

Discussion

The most crucial finding in our study was that the retention rate appeared to be influenced by the sequence in which these AEDs were introduced onto the market and this "latest drug phenomena" should be taken into account when assessing the effectiveness of AEDs. Furthermore, we calculated the following long-term retention rates: lacosamide 77%, lamotrigine 68%, levetiracetam 67%, clobazam 66%, topiramate 62%, zonisamide 60%, pregabalin 55%, and gabapentin 40%. All patients fulfilled the ILAE's definition of pharmacoresistance [12].

An ideal study design should be relevant to real-world settings and provide encompassing measures of efficacy and tolerability assessed with reliable and valid tools. This requirement is usually not fulfilled in regulatory trials, which focus on efficacy and dose response in refractory patients. Often in these clinical trials, the dosage range tends to be high, the titration schedule too rapid and the follow-up period very short. In contrast, the retention rate is considered to be a compound measure of drug efficacy, safety, and compliance, ultimately expressing the willingness of patient to take the drug.

Table 4 The effect of age and gender on retention rates of the eight antiepileptic drugs

	Three-year retention rate					
	Age (years)			Gender		
	<60	≥60	*p*	Female	Male	*p*
Clobazam	68.0	73.9	0.57	68.0	70.0	0.98
Gabapentin	43.7	47.7	0.68	45.6	44.4	0.77
Lacosamide	76.7	80.0	0.93	80.6	74.0	0.64
Lamotrigine	67.0	61.4	0.56	66.1	64.6	0.84
Levetiracetam	71.6	74.5	0.67	72.6	72.1	0.98
Pregabalin	53.7	71.9	0.12	53.2	62.2	0.45
Topiramate	61.0	68.6	0.30	69.8	56.3	0.085
Zonisamide	64.8	50.8	0.35	68.2	57.2	0.24

It has been hypothesized that the retention rate can be influenced by the sequence in which these AEDs are introduced onto the market [10], but as far as we are aware, this has not been actually determined previously. In Finland, after authorities have given approval for full reimbursement, a new AED is made available free of charge for its licensed indication and the clinician can prescribe this drug to suitable patients. As shown in Fig. 2, the use of a new AED significantly increases once full reimbursement is approved. Patients being administered AEDs that were marketed first could have discontinued that treatment after a new drug became available, as demonstrated in Fig. 2. For example, topiramate entered the full reimbursement market in the year 2000; its peak of treatment discontinuations occurred in 2005 when a new AED (levetiracetam) became available. Similarly, in 2007, many patients receiving levetiracetam terminated its use because of the availability of new drug (pregabalin). Finally, the number of annual discontinuations for pregabalin increased in 2008 when yet another AED (zonisamide) received full reimbursement approval. At the time of analysis, lacosamide was the latest AED which had been awarded full reimbursement (2012) and the peak of withdrawals from this drug had still not been observed by the end of year 2014. Additionally, lacosamide could have been tested in a more drug-resistant cohort of patients. Our results suggest that the retention rate appears to be influenced by the sequence in which these AEDs have been introduced onto the market. This "latest drug phenomena" should be taken into account in the long-term retention rate studies, when

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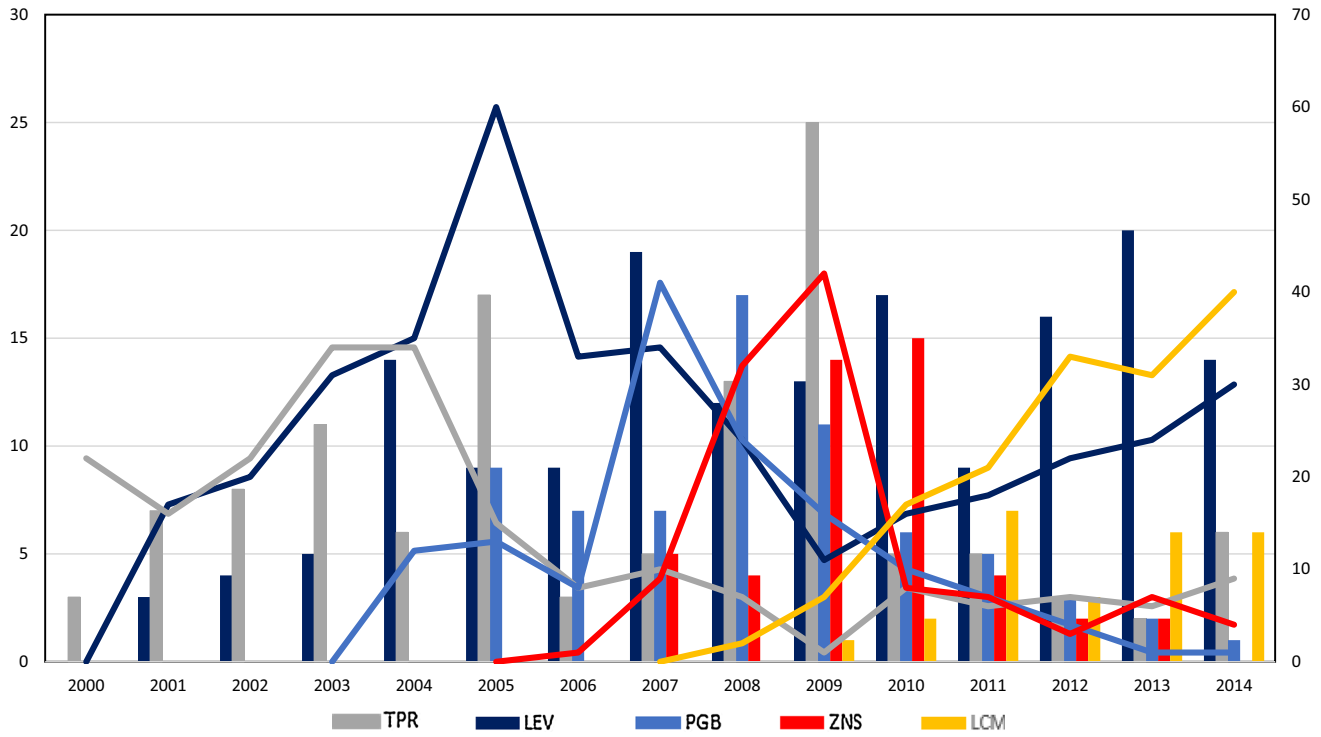

Fig. 2 The number of annual initiations (*curves*, *right column*) and discontinuations (*bars*, *left column*) for antiepileptic drugs used as an adjunctive therapy in focal refractory epilepsy from 2000 to 2014. The location of color code indicates the year of full reimbursement for each antiepileptic drug in Finland

comparing the effectiveness of subsequently marketed AEDs.

In the subgroup analysis, the effects of age and gender on retention rates of all eight AEDs were studied. Despite the well-known modifications in AED pharmacokinetics and pharmacodynamics in the elderly, we found only one retrospective, uncontrolled study of older patients (≥55 years) with epilepsy which would have evaluated effectiveness by comparing 12-month retention rates of ten different AED [9]. In our study, lacosamide was the most effective AED in the elderly as measured by its 3-year retention rate, followed by levetiracetam and clobazam. Zonisamide and gabapentin were the least effective drugs. Our results are similar to those of Arif et al. [9] with one exception. In our study, lamotrigine had the third lowest retention rate (63%) in contrast to that previous study, in which lamotrigine had the highest retention rate (79%). The differences might be explained by the limited number of patients receiving each AED in both studies.

Surprisingly, very little is known about the effectiveness of AEDs between females and males in the light of long-term retention rate studies. We could not identify any study focusing on this topic. Three-year retention rate for pregabalin was higher in males (62%) than females (53%) whereas females had a higher retention rate for both topiramate (70 vs. 56%) and zonisamide (68 vs. 57%). In fact, topiramate was the third best tolerated AED in females. However, results did not reach statistical significance due to limited number of patients. One might hypothesize that these results would reflect cosmetic side effects of AEDs to which females tend to be more prone, as pregabalin is associated with gaining weight whereas both topiramate and zonisamide might cause a loss of body weight [13].

The highest retention rate was found for lacosamide (77%), which is exactly the same percent as in prospective audit with adjunctive lacosamide in focal uncontrolled epilepsy conducted in the Western Infirmary in Glasgow, Scotland [14]. In a large cohort with medically refractory epilepsy, the retention rate for lacosamide was 62% at 1 year, 45% at 2 years, and 35% at 3 years [15]. This difference may be explained by the differences in study populations. Novy et al. [15] conducted the study in a tertiary referral center in which each new assessment selects patients who did not respond to a number of previous AEDs (87% to at least six prior AEDs), i.e., the population is becoming increasingly refractory [5] in comparison to our study which was performed in a secondary epilepsy center. Furthermore, in our clinic, lacosamide is often used in the early phase as an adjunctive therapy with a low number of prior AEDs and this improved the possibility of its efficacy and thus higher retention. The discontinuation of the lacosamide has been

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mainly due to the adverse events (50%) rather than the drug's lack of efficacy (19%). This finding is in line with most of earlier studies [14, 16, 17] but contrary to Novy et al. [15].

Lamotrigine had the second highest long-term retention rate, i.e., 68% which agrees well with the findings in the previous studies (69–74% at 2–3 years) [6, 8, 18]. Nonetheless, a study executed in a tertiary referral center found a significantly lower retention rate of 40% at 3 years [19]. Lamotrigine is known to be well tolerated [6, 8] and this was the case also in our study.

Levetiracetam had the third highest retention rate at 3 years (67%). Other studies have reported similar outcomes [8, 18, 20], but one report found a poorer outcome, i.e., a retention rate of 46% at 2 years [6]. In our study, adverse events were the cause of discontinuation in only 34% of the cases suggesting that this drug has a favorable tolerability profile.

The retention rate for clobazam was good: 66% of the patients continued the treatment for 3 years. There are very limited data on the long-term retention rate for clobazam treatment. Indeed, we found only one study ($N = 54$) which was conducted with highly refractory patients (mean of 8 previous AEDs) reporting a 12-month retention rate (61%) for clobazam [21]. In our audit, clobazam's discontinuation was equally often due to its adverse effects and its lack of efficacy. According to our results, clobazam can be considered a safe and effective AED. The good long-term retention rate also indicates that the tolerance issues related to adjunctive clobazam treatment might have been overestimated.

Topiramate had a retention rate of 62% following closely behind clobazam. The majority of previous studies have reported significantly lower long-term retention rates between 30 and 50% for topiramate [6, 18, 19, 22, 23]. Perhaps this is attributable to the divergences between the study populations. In our study, as in previous reports, adverse events were the most prominent reason for discontinuation of topiramate treatment out of all of the evaluated eight AEDs. Our results imply that if the patient tolerates the acute toxic effects of topiramate then this is a good indicator of long-term retention, since most withdrawals occur within the first year. This fact has also been mentioned by other investigators [6, 18, 23].

The retention rate of zonisamide after 36 months as adjunctive therapy in adult patients with refractory focal epilepsy was 60%. One Scandinavian study with a similar patient cohort to ours reported a 12-month retention rate of 54% for zonisamide [24]. Other studies have estimated 45–65% retention rates after 12-month zonisamide treatment [18, 23, 25]. One study with a large cohort from a tertiary epilepsy center reported a 3-year retention rate of 30% [26]. Here, the drug was fairly well tolerated, with only 30% of the subjects discontinuing therapy due to adverse events, in line with an earlier study [24]. In our study, the majority of those patients who discontinued because of tolerability problems did so during the first 150 days after initiation of zonisamide therapy.

Pregabalin appeared to be one of least well-tolerated AEDs in our study with a retention rate of 55%. In recent years, almost all publications with pregabalin have been addressing different indications other than epilepsy. Surprisingly, we found only one report from a tertiary referral center which would have addressed the long-term outcome in a large group of patients. In this study with 402 patients, the estimated 2.5-year retention rate was 32% [27]. In their prospective audit, Stephen et al. [28] showed that 50% of those patients treated with pregabalin remained on the drug whereas 46% discontinued the treatment due to adverse events, a similar number as noted here (41%).

Gabapentin was the drug producing the greatest number of complexities leading to discontinuation, with a retention rate of only 40%, a value in line with one earlier report [8]. The data on long-term retention with gabapentin are very limited. We found that 74% of discontinuations were due to a lack of efficacy and only 11% were attributable to adverse events. Our findings support the impression that gabapentin might be better tolerated than several other AEDs, but it seems to possess relatively limited efficacy.

Direct comparison of the AEDs is difficult based on the nature of the current study, but it might be worthwhile noting the characteristics of the patients receiving different drugs. The number of patients on each AED was relatively high (over 125 patients) with the exceptions of zonisamide ($N = 103$) and gabapentin ($N = 66$). Females and males were equally represented in all the groups. The known etiology for focal seizures has been considered as a marker of pharmacoresistance [29]. The majority of the patients receiving levetiracetam, lamotrigine, and zonisamide had a known etiology. The mean duration of epilepsy varied from 17 years (lacosamide) to 27 years (gabapentin and lamotrigine) highlighting the refractory nature of our patient cohort. The mean doses for all eight AEDs were mostly equal or marginally higher than the World Health Organization (WHO)-defined daily doses, suggesting that the overall drug load was not excessive in our patients [30]. Finally, generally it is known how much drug resistance is influenced by previous unsatisfactory treatments. As the majority of the patients on lamotrigine, topiramate, pregabalin, zonisamide, clobazam, and gabapentin had previously tried a minimum of four AEDs, these cohorts must be characterized as being highly drug resistant. These observations might indicate that patients with a known etiology or/and high number of previous AEDs had more severe epilepsy which could have detrimentally influenced their long-term retention rate. On the other hand, percentage of

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patients who have previously taken more than four AEDs varies from almost 70% with gabapentin, to almost 40% with lacosamide. Incidentally, lacosamide resulted as the AED with the best retention rate. These data weaken the observation that lacosamide has a better retention. Overall, no major differences were found with respect to any of the demographical or clinical variables, which allows us to compare these eight AEDs and to hypothesize that differences in their long-term retention rates are drug related.

A variety of factors may have influenced these retention rates. The mean times to intolerability were in the range of 3.6 (lamotrigine) to 10.2 months (gabapentin). These data might indicate that only a minority of the intolerable adverse events could have been due to rapid titration. Furthermore, if patients terminated treatment with one drug due to adverse events, this was most likely to occur during the first 12 months. This might indicate that if adverse events of an AED do not appear relatively early, they are unlikely to appear after years of treatment as observed in an earlier study [9]. The time to reach a conclusion about insufficient efficacy took somewhat longer, 9–13 months with most of the drugs, ranging from only 7 months with lacosamide up to 16 months with clobazam.

Some points must be kept in mind when drawing conclusions from this study. All patients were from a single center, which limits external validity of findings. Retrospective nature and the lack of available comparative data are the main disadvantages of retention rate analysis with the current study not being an exception. Furthermore, patients were not randomized to receive any particular AED. Quite likely, physician preference/bias played a role in drug selection and decisions to withdraw certain AED treatments, but no statistical method can remove or fully account this effect [9]. The lack of systematic titration data for AEDs is a limitation of study, as too rapid titration might have an effect on tolerability. For certain AEDs, the number of patients is relatively small, this is particularly true in the subgroup analysis of elderly patients. Therefore, it might be most appropriate to compare our results with those from other pragmatic studies evaluating retention with adjunctive AEDs in adult patients with refractory focal epilepsy. Even in those cases, the different methodologies and study populations may allow only indirect comparison. However, tolerability has been evaluated analogously in all studies, i.e., the percentage of patients terminating drug treatment because of adverse events.

In conclusion, the retention rate appears to be influenced by the sequence in which these AEDs were introduced onto the market. Our study provides important information of many practical aspects of the AED therapy and indicates that there are differences in effectiveness between clobazam, gabapentin, lacosamide, lamotrigine, levetiracetam, pregabalin, topiramate, and zonisamide as adjunctive treatment for focal refractory epilepsy. Those AEDs that are modestly efficacious but associated with a good tolerability profile might perform better than drugs that are more efficacious with significant tolerability problems. The value of retention rate studies as a valuable information source for physicians is highlighted.

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Compliance with ethical standards

Ethical standards This was a non-invasive, retrospective study, which does not oblige ethics committee approval according to Finnish Law on Research. Access to patient records based on decision made by Head of Science Centre, Tampere University Hospital research and innovation services, Science Center.

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ORIGINAL RESEARCH

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Transition from oxcarbazepine to eslicarbazepine acetate: A single center study

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Abstract

Objectives: There is limited clinical evidence for comparison between oxcarbazepine (OXC) and eslicarbazepine acetate (ESL) in terms of tolerability, or how to execute the change from OXC to ESL. We report the process of transitioning patients with focal epilepsy from previous OXC treatment to ESL due to tolerability problems. The rationale for change from OXC is reported, and the outcome with respective to this rationale is analyzed in terms of tolerability and efficacy.

Materials and Methods: The subjects were transitioned overnight from OXC to ESL in a hospital inpatient setting. An evaluation of the effects of the transition was made after 1 and 3 months. All adverse events (AEs) were recorded following the transition period. Subjects were classified by outcome in terms of AEs.

Results: Twenty-three subjects were transitioned from OXC to ESL. Fifteen patients OXC-related AEs reduced significantly after transition. Particularly, most of (93%) the AEs presented in the morning resolved after transition to ESL. No patient had an increase in seizure frequency following the transition. The incidence of ESL-related AEs was 39% at 1 month and 13% at 3 month follow-up; however, all patients continued ESL throughout the study period.

Conclusions: This study demonstrates that patients suffering from OXC-related AEs improve in terms of tolerability after a switch to ESL with maintaining seizure control. This improvement is more pronounced if the OXC-related AEs are most evident following morning dosing of OXC. Transition can be safely executed in an outpatient setting.

KEYWORDS

epilepsy, eslicarbazepine acetate, oxcarbazepine, tolerability, treatment transition

1 | INTRODUCTION

Epilepsy has an annual incidence of about 50 per 100,000 and prevalence between 5 and 10 per 1,000 (Sander, 2003). Monotherapy with an antiepileptic drug (AED) is sufficient to achieve seizure control without intolerable adverse events (AEs) approximately in 60% of patients (Stephen & Brodie, 2012). AEs related to AEDs impact negatively on health-related quality of life, cause a significant source of disability, and may lead to low adherence to the treatment or treatment discontinuation (Stephen & Brodie, 2012).

In adults (>18 years), oral eslicarbazepine acetate (ESL) is approved in the EU as an adjunctive therapy with partial onset seizures with or

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without secondarily generalization and in the US as a monotherapy or adjunctive treatment of partial-onset seizures (Aptiom®; Zebinix®). ESL is a third-generation member of the dibenzazepine family, which also includes carbamazepine (CBZ) and oxcarbazepine (OXC; Keating, 2014; Zaccara, Giovanelli, Cincotta, & Verrotti, 2015). Blockade of voltage-gated sodium channel (VGSC) is the proposed mechanism of action for CBZ, OXC, and ESL (Keating, 2014), but ESL has been shown to have a modulating action and inhibits the slow activation of VGSC (Hebeisen et al., 2015) and also an effect on Cav3.2T-type Ca^{2+} channels (Doeser et al., 2015). ESL is a prodrug that is metabolized to its major active metabolite eslicarbazepine (S-licarbazepine) and to the minor active metabolites (R)-licarbazepine and OXC, which are mainly eliminated by renal excretion (both unchanged and glucuronide conjugate forms; Keating, 2014). Half-life terminal elimination of ESL in plasma concentrations varies between 20–24 hr allowing once-daily administration regimen (Perucca et al., 2011). Maximum plasma concentrations of ESL were reached in median 2.0–2.5 hr (Almeida & Soares-Da-silva, 2004). Steady state is reached in 4–5 days (Elger, Halász, Maia, Almeida, & Soares-Da-silva, 2009).

Eslicarbazepine acetate is efficacious and well tolerated as adjunctive therapy in drug-resistant focal epilepsies at doses of 800 and 1,200 mg once-daily (Ben-Menachem et al., 2010; Elger et al., 2009; Gil-Nagel, Lopes-Lima, Almeida, Maia, & Soares-Da-silva, 2009; Gil-Nagel et al., 2013; Sperling et al., 2015). Dizziness, vertigo, abnormal coordination, ataxia, diplopia, fatigue, somnolence, and headache are most often reported and frequent AEs in controlled clinical trials (Sperling et al., 2015) and to a lesser degree when used as the only adjunctive AED (Holtkamp, McMurray, Bagul, Sousa, & Kockelmann, 2016). It was noted in one study that switching from OXC to ESL (dose ratio 1:1) was associated with better tolerability during ESL treatment (Villanueva et al., 2014). Recent meta-analysis compared the tolerability of ESL, OXC, and lacosamide (LCM) showing that patients with OXC withdrew from the treatment more frequently than patients with ESL or LCM (Zaccara, Giovanelli, Maratea, Fadda, & Verrotti, 2013). Furthermore, some side-effects (diplopia, ataxia, abnormal coordination) were significantly more frequent in OXC-treated patients compared to ESL and LCM. ESL-related hyponatremia varies from 1.2% to 8.8% between different studies (Halasz et al., 2010; Hufnagel et al., 2013; Villanueva et al., 2014; Zaccara et al., 2013). The difference can be explained in terms of dosage used, population characteristics, and cut-off used to define hyponatremia. These data suggest, that ESL might share similar efficacy compared to OXC, but with less AEs. Several dose-dependent neurological AEs occur intermittently and appear almost always a few hours after OXC administration (Striano et al., 2006). It seems reasonable to relate AEs to OXC peak concentration rather than to the active metabolite eslicarbazepine, which levels increase more slowly (Keating, 2014). ESL is directly metabolized to eslicarbazepine with minor concentrations of r-licarbazepine and OXC (Almeida & Soares-Da-silva, 2007).

At present, there is only one study documenting that overnight switch from OXC to ESL seemed to be safe and result in significant improvements in AEs, quality of life, and alertness (Schmid et al., 2016). However, that study focused on acute effects following the transition leaving long-term effects of such transition related to tolerability and efficacy still unclear.

We provide 3 month follow-up data when transitioning patients with focal epilepsy from previous OXC treatment to ESL in a standardized clinical setting. The rationale for change from OXC is reported, and 3 month outcome with respective to this rationale is analyzed in terms of tolerability (the main objective) and efficacy (the secondary objective).

2 | MATERIAL AND METHODS

We identified all the patients (age at least 18 years) with focal epilepsy followed in the Department of Neurology in Tampere University Hospital, Finland from the patient registry. Following inclusion criteria were applied: (1) current treatment with OXC; (2) OXC-related moderate or severe tolerability problems which affected daily life; (3) transition from OXC to ESL was performed due to OXC-related AEs; and (4) transition was undertaken before 30 November 2015. The dosages of concomitant AEDs remained unchanged during the transition period. All subjects were on immediate-release OXC as extended-release OXC is not available in Finland. Information on the patient characteristics was obtained retrospectively from the medical records.

Tolerability problems related to OXC were categorized as in recent meta-analysis (Zaccara et al., 2013) addressing neurological AEs of new generation sodium-blockers (somnolence, dizziness, vertigo, ataxia/coordination abnormal, diplopia, nystagmus, fatigue, tremor, headache, nausea, vomiting). Patients were classified according to ILAE guidelines to temporal, frontal, parietal, occipital, multifocal, or unclassifiable epilepsies based on seizure characteristics, EEG and imaging findings and for some patients on ictal video-EEG recordings (CoCaTotILA, 1989). The etiologies were divided into remote symptomatic and unknown. The seizure frequency from the previous year was recorded; seizure-free patients did not have any seizures during the previous year. Refractory epilepsy was defined as having persistent seizures after trials of at least two AEDs with maximally tolerated doses (sequentially or in combination therapy).

Patients were transitioned overnight from OXC to ESL in a hospital inpatient setting on the day of arrival and the patients were followed up to 3 months by clinicians. The target dose of ESL was calculated using an OXC:ESL dose ratio 1:1 depending on the pretransition OXC dose. If the 1:1 dose ratio did not correspond to an exact ESL dose, then the closest lower ESL dose was used. The last intake of OXC was the morning dose followed by the first intake of ESL in the evening of the same day. After 1 and 3 months an evaluation of the effects of the transition was made in terms of tolerability, which was main purpose of this study. Efficacy in terms of seizure change was evaluated at 1 and 3 months after transitioning. All AEs and their intensity (mild, moderate, severe) were recorded and reported following the transitioning period. Mild was defined as a symptom not interfering with daily activities, moderate as interfering but not preventing daily life activities and severe as incapacitating at least part of daily activities. Patients were dichotomied by outcome in terms of AEs after switched from OXC to ESL.

This was a noninvasive, retrospective study, which does not oblige ethics committee approval according to Finnish Law on Research. Access to patient records based on decision made by Head of Science Centre, Tampere University Hospital research and innovation services, Science Center.

TABLE 1 Demographic and medical characteristics of the patients

Number of patients	23
Sex	
Female, *N* (%)	14 (60.9)
Male, *N* (%)	9 (39.1)
Mean age; years (range)	41.8 (22–69)
Mean duration of epilepsy; years (range)	14.4 (2–62)
Etiology	
Remote symptomatic, *N* (%)	17 (73.9)
Unknown, *N* (%)	6 (26.1)
Refractory epilepsy, *N* (%)	18 (78.2)
Seizure frequency	
Seizure free (during previous year), *N* (%)	11 (47.8)
Persistent seizures, *N* (%)	12 (52.2)
Mean OXC dose; mg/day (range)	1,152 (600–1,800)
Final ESL dose; mg/day(range)	1,095 (800–2,000)
Number of concomitant AEDs, *N* (%)	
0	3 (13.0)
1	9 (39.2)
2	10 (43.5)
3	1 (4.3)
Number of prior AEDs, *N* (%)	
1	3 (13.0)
2	5 (21.8)
3	6 (26.1)
4	3 (13.0)
≥5	6 (26.1)

AEDs, antiepileptic drugs; ESL, eslicarbazepine acetate; OXC, oxcarbazepine.

3 | RESULTS

We identified 23 patients, who were transitioned from OXC to ESL because of OXC-related AEs. Demographic and medical characteristic of the subjects are presented in Table 1. Three most common concomitant AEDs were levetiracetam, topiramate, and clobazam. AEs related to OXC before transition to ESL are described in Figure 1. Fifteen (65.2%) patients OXC-related AEs resolved after transition at 3 months follow-up and this was the case in 14 patients at 1 month follow-up. Furthermore, the timing of the AEs over the day with respect to their persistency was analyzed and the results are shown in Figure 2. Two thirds (66.5%) of the AEs occurred in the morning and most of them (93.4%) resolved after transitioning OXC to ESL. AEs presenting all day or evening tended to be more persistent after transition.

The most intolerable single OXC-related AEs were somnolence, dizziness, and diplopia. Fatique, somnolence, tremor, diplopia, and nausea mostly resolved after transition. A clear tendency that some AEs would have been more persistent than others, especially in the morning, was not observed. However, dizziness and coordination problems were the commonest AEs that persisted after transition.

The effects of the transition from OXC to ESL on seizure frequency are summarized in Table 2. AEs occurring after transition related to ESL are shown in Figure 3. The incidence of AEs was higher at 1 month (39.1% [9/23]) than at 3 month follow-up (13.0% [3/23]). However, no treatment discontinuations occurred and all patients continued ESL throughout the study period. Most of the AEs attributed to ESL were mild and some moderate in intensity. The dose-dependent increase in AEs frequency was not noticed.

Changes in seizure frequency or duration were not observed during the transition period in a hospital inpatient setting. Two patients reported headache during the hospitalization, but at 1 and 3 month follow-up this AE was not observed in these patients any more. None of those patients who had AEs during the follow-up did report tolerability problems during the hospitalization.

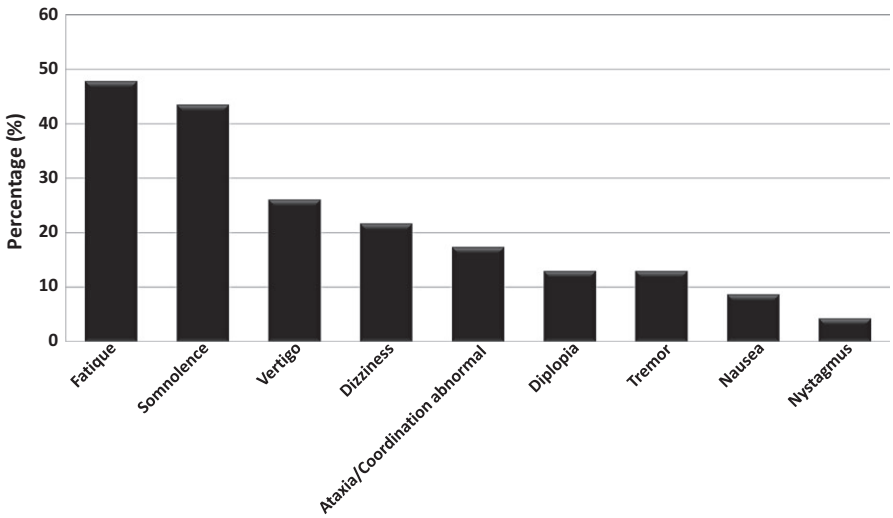

FIGURE 1 Adverse-events related to oxcarbazepine. One or more adverse-event can be present on a single subject

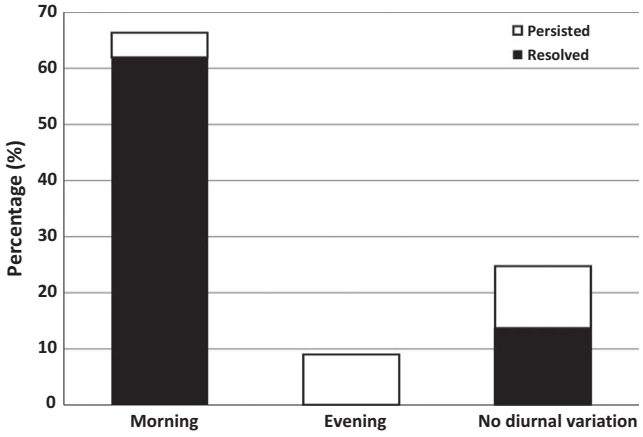

FIGURE 2 Diurnal variation and 3 month outcome of oxcarbazepine-related adverse events after transition to eslicarbazepine acetate

4 | DISCUSSION

The main objective of this study transitioning patients with focal epilepsy from OXC to ESL due to typical OXC-related AEs was to evaluate the tolerability during sufficiently long follow-up period. Our study demonstrates that patient satisfaction improved significantly in terms of reduced AEs after switching from OXC to ESL in 65% of the subjects without increase in seizure frequency. This finding is similar to a previous study demonstrating that 15 of 26 patients who were transitioned from OXC to ESL due to OXC-related AEs no longer had AEs after the change (Villanueva et al., 2014). Furthermore, we showed that if the OXC-related AEs are most evident in the morning (following morning dosing), nearly all of them (93%) dissolved after transition to ESL indicating a relation to OXC peak cerebrospinal fluid and plasma concentration as suggested earlier (Keating, 2014). These findings might help clinician in everyday practice to assess whether patient's complaints of neurological AEs related to OXC, especially in complex situations; several AEDs, comorbidities (e.g. depression, sleeping problems) and, persistent seizures.

The secondary objective was to assess the efficacy of ESL. The results of this study indicated that when switched from OXC, ESL was effective and well tolerated during 3 months follow-up. During previous year 12 patients had persistent seizures and after changing from OXC to ESL in one patient seizure frequency reduced by 50% and in another patient by 30%. Moreover, in two patients seizure duration shortened without change in seizure frequency. Altogether four patients of 12 achieved reduction in seizure frequency or duration. Nevertheless, the fact that none of the patients had increased seizure frequency is at least as important as seizure reduction in small proportion of the patients.

Earlier expert group's opinion hypothesized there might be situations in which it may be reasonable to convert patients from OXC to ESL; most appropriately those who experience OXC-related AEs or have poor compliance with twice-daily OXC dosing (Peltola et al., 2015). Recent study by Schmid et al. (2016) demonstrated that overnight switching from OXC to ESL was safe and successful with regard to efficacy concerning the acute and immediate effects on tolerability and seizure issues. Other major finding is the absence of seizure related or other problems during the transition in any of our patients which give added value to the publication by Schmid et al. (2016). Furthermore, we did not find any specific concerns, why transition from OXC to ESL should be done necessarily in an inpatient setting as

TABLE 2 The effect of transition from oxcarbazepine to eslicarbazepine acetate on seizure frequency in 3 month follow-up

Patient	Baseline SF (previous month)	1st month SF	2nd month SF	3rd month SF	Outcome
1–11	Seizure free	No seizures	No seizures	No seizures	Still seizure free
12	1 SGS, 31 SPS, 4 CPS	30 SPS, 3 CPS	32 SPS, 4 CPS	31 SPS, 6 CPS	No significant change in SF
13	Infrequent seizures[a]	No seizures	No seizures	No seizures	No significant change in SF
14	1 SGS, 5 CPS	2 CPS	No seizures	1 CPS	50% reduction in seizure frequency
15	1 SPS, 2 CPS	2 SPS, 2 CPS	1 SPS, 3 CPS	1 SPS, 2 CPS	No significant change in SF
16	83 SPS, 8 CPS	84 SPS, 8 CPS	83 SPS, 8 CPS	83 SPS, 8 CPS	No change in SF
17	5 CPS	4 CPS	5 CPS	6 CPS	No change in SF, seizure duration shortened
18	1 CPS	No seizures	1 CPS	No seizures	30% reduction in seizure frequency
19	Infrequent seizures[b]	No seizures	No seizures	No seizures	No significant change in SF
20	5 SPS, 8 CPS	5 SPS, 8 CPS	8 SPS, 11 CPS	7 SPS, 8 CPS	No change in SF, CPS seizure duration shortened
21	1 SGS, 3 SPS, 1 CPS	1 SGS, 3 SPS, 3 CPS	2 SPS, 2 CPS	1 SGS, 3 SPS, 1 CPS	No significant change in SF
22	2 SGS, 7 CPS	3 SGS, 8 CPS	2 SGS, 11 CPS	3 SGS, 6 CPS	No significant change in SF
23	1 SGS, 4CPS	1 CPS	4 CPS	2 SGS, 4 CPS	No significant change in SF

CPS, complex partial seizure; SF, seizure frequency; SGS, secondary generalized tonic-clonic seizure; SPS, simple partial seizure.
[a]1 SGS during previous year.
[b]1 CPS during previous year.

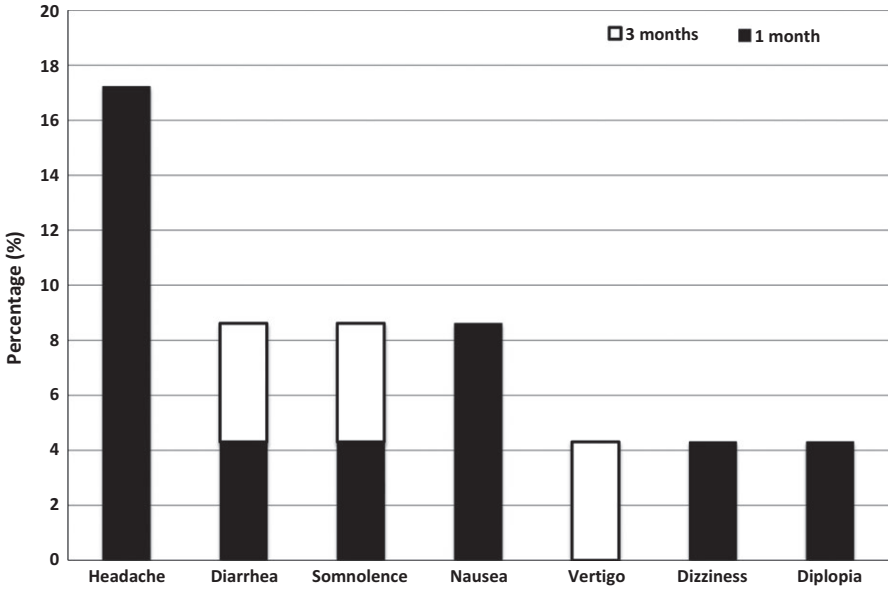

FIGURE 3 Duration of eslicarbazepine acetate-related adverse events

done earlier in our center. Transition from OXC to ESL can be safely done in an outpatient setting.

There were slight differences how the prompt switch from OXC to ESL was conducted in our center in comparison to the previous study by Schmid et al. (2016). In that study the last intake of OXC was the evening dose followed by first intake of ESL in the evening of next day, whereas in our center the last intake of OXC was the morning dose followed by the first intake of ESL already in the evening of the same day. There were no differences between these two studies on how the initiation of ESL was performed in terms of target dosing as both studies aspired to use a ratio of 1:1 of OXC and ESL.

Considering the limitations, this was retrospective uncontrolled follow-up study and the relative number of our patient is not high. However, when considering the results and conclusions emerging from our study the number of patients is justified as its' present form. The main conclusion is that such OXC-related neurological side-effects that appear after ingestion of the morning dose of OXC disappear in the vast majority (over 90%) of the patients when substituted with ESL, whereas if these symptoms exist either after evening dose or without diurnal variation the substitution is less helpful. This association is so strong that the current number of patients is sufficient to provide the conclusion.

In conclusion, our findings support the notion that patients currently receiving OXC and experiencing intolerable AEs benefit from switching to ESL in order to maintain seizure control and improve AED tolerability. This is particularly true if these AEs are most evident following morning dosing. Our data also suggest that transition from OXC to ESL can be performed safely in an outpatient setting instead of overnight hospitalization for cost effectiveness and patient comfort.

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CONFLICT OF INTEREST

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