Long-term efficacy and tolerability of antiepileptic drugs in newly diagnosed epilepsy patients

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Summary

Epilepsy is the most common serious chronic neurological disorder, affecting 65 million people worldwide. Antiepileptic drugs (AEDs) constitute the main treatment for epilepsy. The introduction of 14 new AEDs over the last three decades has expanded treatment options and increased the expectations about efficacy and tolerability. However, little is known about the effectiveness of new AEDs in routine clinical practice. It is also unclear whether the treatment outcomes in epilepsy have improved in recent decades as a consequence of the availability of an increasing number of AEDs. The present work attempts to provide a comprehensive evaluation of efficacy, tolerability, and retention rate of AED treatments in everyday clinical setting. This thesis is divided into six chapters, three general chapters and three result chapters (Chapter 3, 4, and 5).

Chapter 1 sorts out the background of epilepsy, pharmacological management, and adverse drug reactions. The new classification of seizures and epilepsies, AED therapy, and guidelines for initiation, selection and dosing of AEDs are described. Followed by discussion of clinically relevant adverse effects of AEDs.

Chapter 2 describes the study population and definition of outcome measures. Data collection and statistical analysis were presented as well. The data of this study were extracted retrospectively by reviewing the patients' medical records. The patients were first diagnosed with epilepsy and prescribed AED treatment at the Glasgow Epilepsy Unit between Jul 1982 and Oct 2012; then they were prospectively followed up until 30 Apr 2016 with at least one year follow-up after starting AEDs therapy. The study cohort included 1,528 patients aged 18 to 93 years (median 37), 849 (56%) were men, and 1,290 (84%) had focal epilepsy.

Chapter 3 evaluates efficacy of AEDs and the changes in treatment outcomes of epilepsy over the past 30 years. This was achieved by comparing the results of current analysis to the results of three analyses conducted in 1999, 2003, and 2008 on same expanding cohort (n=470, 890, and 1,098 respectively) from the Epilepsy Unit in Glasgow. The overall efficacy rate of AEDs in this study was 62% (n=941/1,528); this was comparable to what was observed in the previous analysis of 17 years ago on the same expanding cohort in which 64% (n=301/470) of newly diagnosed epilepsy patients achieved seizure-free. Likewise, the efficacy rates of

different established and new AEDs were comparable. Therefore, this provides a strong evidence that treatment outcomes in epilepsy have not improved in recent decades despite the availability of increasing number of AEDs. However, the results indicated that the use of new AEDs has increased, 41% of patients continued to take the new AEDs as a monotherapy in the current study, compared to 26% in 1999. This most likely due to their advantages in terms of tolerability. This analysis also found that family history of epilepsy, more than ten pre-treatment seizures, psychiatric conditions, alcohol and recreational drugs abuse, and failure to response to two or more AEDs were significantly associated with poor seizure outcomes.

In Chapter 4, the rate and predictors of intolerable adverse effects of AEDs were assessed. This study showed that 28% (n=815/2,911) of total AEDs prescriptions were discontinued because of poor tolerability. In which the most frequent problem was tiredness (5.2%, n=152/2,911) followed by poor coordination and rash, with a 2.9% (n=86) incidence for each. Among 17 different AEDs, lamotrigine was associated with the best tolerability whether it was used as monotherapy (19%, n=109/575) or as part of polytherapy (9%, n=35/387). While topiramate was associated with the highest rate of adverse effects (39%, n=32/81) among monotherapies, and retigabine had the highest rate of adverse effects (42%, n=8/19) among AEDs used as part of polytherapy. Moreover, each AED demonstrated a distinct tolerability profile; the main intolerable adverse reaction associated with lamotrigine and carbamazepine was skin rash while valproate was poorly tolerated most frequently due to tremor and weight gain. Furthermore, levetiracetam was poorly tolerated commonly due to psychiatric and behavioural side effects whereas cognitive dysfunction was the most common reason for topiramate intolerability. Beside individual AED, poor tolerability was related to patient's susceptibility and number of co-prescribed AEDs. Prior intolerable AEDs schedule was associated with high probability to experience intolerable adverse effects at subsequent AED schedule. Likewise, female, focal epilepsy, more than ten pre-treatment seizures, and psychiatric comorbidity were significantly associated with higher rates of adverse effects. However, older AEDs usage was not significantly associated with poorer tolerability. These may present novel findings from this study as very few studies have evaluated the predictors for poor tolerability particularly non-AEDs variables.

In Chapter 5, a survival analysis was performed to identify retention rates (time to discontinuation) of lamotrigine, valproate, carbamazepine, and levetiracetam monotherapies. Lamotrigine showed the highest retention rate, with median duration of therapy of 84 months. This was significantly higher than the retention times of valproate (42 months), carbamazepine (36 months), and levetiracetam (36 months); there was no significant difference in retention rates of other AEDs. However, within six months of therapy initiation, lamotrigine and carbamazepine demonstrated the highest discontinuation rates, most probably due to rash. Few observational studies have investigated the long-term retention rates of AEDs in the UK. Therefore, the current research may present novel findings in term of population as well.

In Chapter 6, study strengths and limitations are presented. Clinical implications and the future directions of research in epilepsy are described as well.

Table of Contents

List of Tables

List of Figures

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Author's Declaration

I declare that this represents my own work. I was responsible for obtaining the ethical approvals; extracting and analysing the data; interpretation of the results; and writing-up this thesis. The work represented in my thesis has not been previously submitted for any degree to the University of Glasgow or any other institutions.

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Bshra Ali A Alsfouk

Abbreviations

AEDs	Antiepileptic drugs
AEP	Adverse events profile
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
BZD	Benzodiazepine
CBZ	Carbamazepine
CI	Confidence interval
CLB	Clobazam
CNS	Central nervous system
CT	Computed tomography
CVD	Cerebrovascular disease
CZP	Clonazepam
DRESS	Drug-related rash with eosinophilia and systemic symptoms
EEG	Electroencephalography
ESL	Eslicarbazepine acetate
ESM	Ethosuximide
FBM	Felbamate
GABA	Gamma amino butyric acid
GBP	Gabapentin
GTCs	Generalised tonic clonic seizures
ILAE	International League Against Epilepsy
IQ	Intelligence quotient
IQR	Interquartile range
LCM	Lacosamide
LEV	Levetiracetam
LTG	Lamotrigine
MRI	Magnetic resonance imaging
NEAD	Neurodevelopmental Effects of Antiepileptic Drugs
NMDA	*N*-methyl- D-aspartate
OR	Odds ratio
OXC	Oxcarbazepine
PB	Phenobarbital
PER	Perampanel
PGB	Pregabalin
PHT	Phenytoin
PRM	Primidone
RCTs	Randomised Controlled Trials
RTG	Retigabine
SANAD	Study of Standard And New Antiepileptic Drugs
SD	Standard deviation
SJS	Stevens–Johnson syndrome
SV2A	Synaptic vesicle protein 2A
TEN	Toxic epidermal necrolysis
TGB	Tiagabine
TPM	Topiramate
VGB	Vigabatrin
VPA	Valproate
WHO	World Health Organisation
X^2	Chi-square
ZNS	Zonisamide

Chapter 1. Introduction

1.1 Epilepsy

Epilepsy is the most common serious chronic disorder of the brain, affecting 65 million people worldwide (Moshe et al., 2015). It entails a significant economic burden, which has been estimated to constitute more than €20 billion per year in Europe alone (International League Against Epilepsy/International Bureau for Epilepsy/World Health Organization Global Campaign Against Epilepsy, 2010). Furthermore, epilepsy is associated with increased mortality; in a 40-year population-based study, overall mortality rate in people with epilepsy who had been followed up since childhood was 24%, which was three times higher than the expected mortality rate in the general population, with more than half of the fatalities being epilepsy-related, including sudden, unexpected death, which constituted a third of all of the deaths (Sillanpää and Shinnar 2010). Moreover, epilepsy has a substantial impact on a person's life, affecting both their physical and psychosocial well-being. Depression, cognitive difficulties, the unpredictability of seizures, and social stigma and isolation due to factors such as unemployment, driving restrictions, and low rates of marriage, are major concerns for people with epilepsy. Together with the burden of the adverse effects of antiepileptic drug (AED) treatments, these concerns have a significant influence on the quality of life of people with epilepsy (Baker et al., 1997, Luoni et al., 2011, Quintas et al., 2012). The goal of treatment, therefore, should be to maintain a normal life with complete seizure control, with no, or minimal, adverse drug effects.

1.1.1 Prevalence

Active epilepsy has a prevalence of approximately six per 1,000 of the population worldwide (Fiest et al., 2017). However, the prevalence of epilepsy is higher in low-income countries than in developed countries, which may be due to differences in epilepsy risk factors, such as infections and poor neonatal care (Moshe et al., 2015). One meta-analysis estimated that in high-income countries, the annual incidence of epilepsy is 45 per 100,000 of the population [interquartile range (IQR 30–67)], and 82 per 100,000 of the population (IQR 28–240) in low- and middle-income countries (Ngugi et al., 2011).

In Scotland, there are 54,000 individuals with active epilepsy, with new annual diagnoses of between 2,000 and 3,500 cases (Scottish Intercollegiate Guidelines Network, 2015).

1.1.2 Definition and classification

Epilepsy is a tendency of the brain to produce unprovoked seizures, which are transient signs and/or symptoms that occur due to abnormal excessive, or synchronous, neuronal brain activity (Fisher et al., 2005). In practice, epilepsy can be diagnosed if:

1. At least two unprovoked (or reflex) seizures occur more than 24 hours apart;

2. A single unprovoked (or reflex) seizure and a probability of a second seizure comparable to the recurrence risk after two unprovoked seizures; for instance, one unprovoked seizure after a brain insult such as a stroke or trauma; or

3. Diagnosis of an epilepsy syndrome occurs (Fisher et al., 2014).

Clearly, epilepsy is not a uniform disorder, and it involves various seizure types and syndromes. Several attempts have been made by the International League Against Epilepsy (ILAE) to classify the seizure types and of epilepsies (Commission of ILAE, 1981, Commission of ILAE, 1989). However, this section discusses the most recent classification guidelines (Fisher et al., 2017, Scheffer et al., 2017), in which the new classifications include three categories: seizure type, epilepsy type, and epilepsy syndrome. Aetiology should be considered at each stage, since it influences the treatments substantially. However, when a patient presents with seizures, the first step in making a diagnosis of epilepsy is to confirm that the event is an epileptic seizure based on clinical evaluation (history and seizure description from the patient and witnesses of seizures), and investigations [Electroencephalography (EEG), Magnetic Resonance Imaging (MRI)].

Seizures can be categorised as focal, generalised, or unknown onset, and each seizure type includes the subgroups of motor, and non-motor, while focal seizures

also include the subgroups of retained, or impaired awareness. Figure 1-1 demonstrates detail about new classification of seizure types (Fisher et al., 2017).

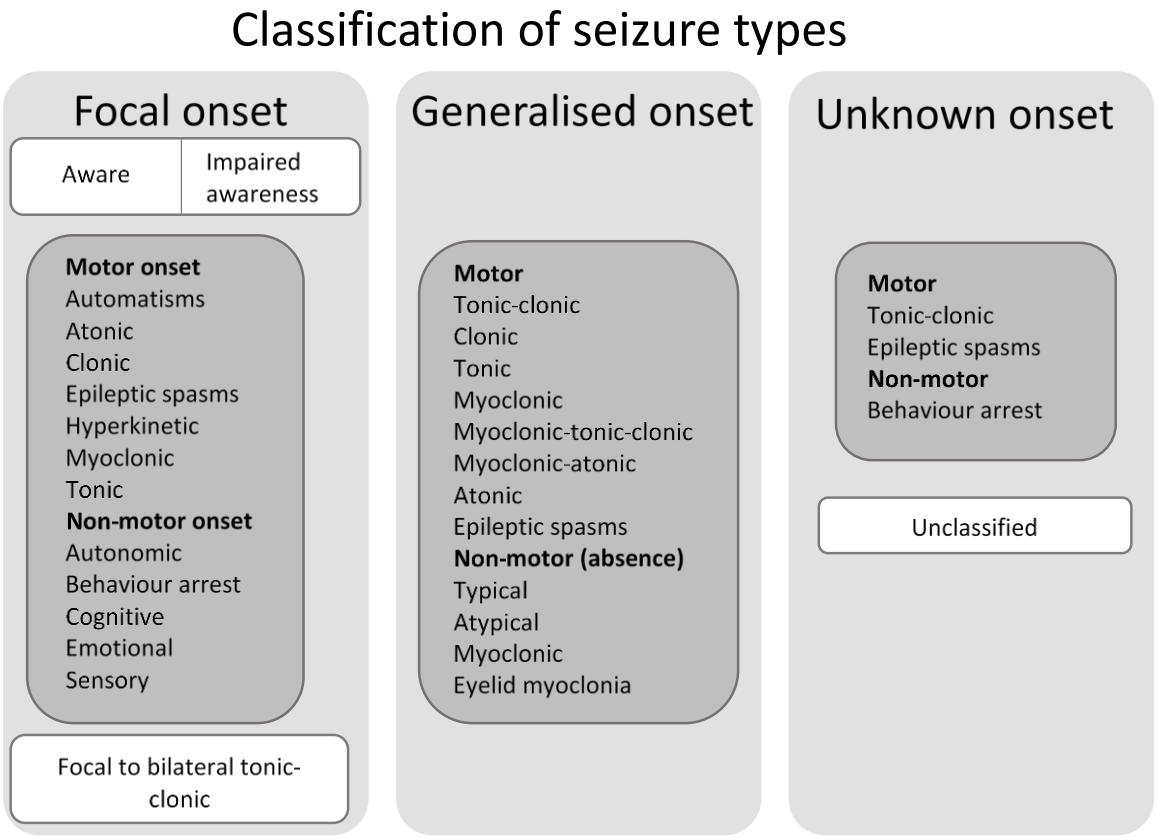


Figure 1-1. The new classification of seizures types proposed by International League Against Epilepsy (ILAE) (Fisher et al., 2017)

The diagnosis of epilepsy depends on clinical characteristics supported by the results of an EEG. As demonstrated in Figure 1-2, generalised epilepsies with absence, myoclonic, atonic, tonic, and tonic-clonic seizures are usually characterised in the EEG by generalised spike-wave activity, together with supporting information including a family history of epilepsy or myoclonic jerks which are particularly important in the case of a normal EEG. Focal epilepsies with focal motor, or non-motor seizures; focal with retained, or impaired awareness; and focal to bilateral tonic-clonic seizures are typically characterised by focal epileptiform discharges in the EEG. In combined generalised and focal epilepsies, both types of seizures occur, and the EEG may show both generalised spike-wave and focal epileptiform discharges. Dravet syndrome and Lennox-Gastaut syndrome are common examples in which both generalised and focal seizures occur. If there

is insufficient information to determine the epilepsy type, it can be denoted as ‘unknown’ (Scheffer et al., 2017).

The third stage is the diagnosis of an epilepsy syndrome. Generally, epilepsy syndromes include a set of characteristic seizure types, and EEG and neuroimaging findings appear together. They are typically age-dependent, include seizure triggers, and coexist with particular comorbidities, such as intellectual disabilities. Common syndromes of idiopathic generalised epilepsies are childhood absence epilepsy, juvenile myoclonic epilepsy (JME), and generalised tonic-clonic seizures (GTCs) (Scheffer et al., 2017).

A wide range of epilepsy aetiology exists, such as structural, genetic, and metabolic pathology, and it is important to determine the aetiology early, following the first seizures. Structural aetiology can be determined on the basis of neuroimaging investigations, such as MRI. Common structural abnormalities that may cause epilepsy are stroke, trauma, tumour, and genetic (such as cortical malformation), or infection. Known or presumed genetic defects can either directly cause epilepsy as a result of a rare single gene mutation, or indirectly as a result of the interaction of multiple genes, with or without environmental contributions in which gene defect has a significant effect in causing the epilepsy. The epilepsy can be classified as ‘unknown aetiology’ if the cause has not yet been determined. It can also be classified into more than one aetiological group if there are more than one causes of the epilepsy (Scheffer et al., 2017).

The identification of seizure types and syndromes is essential for the prognosis and selection of treatment. AEDs constitute the main treatment for epilepsy, while other intervention options include surgical treatment, neurostimulation, and ketogenic diet.

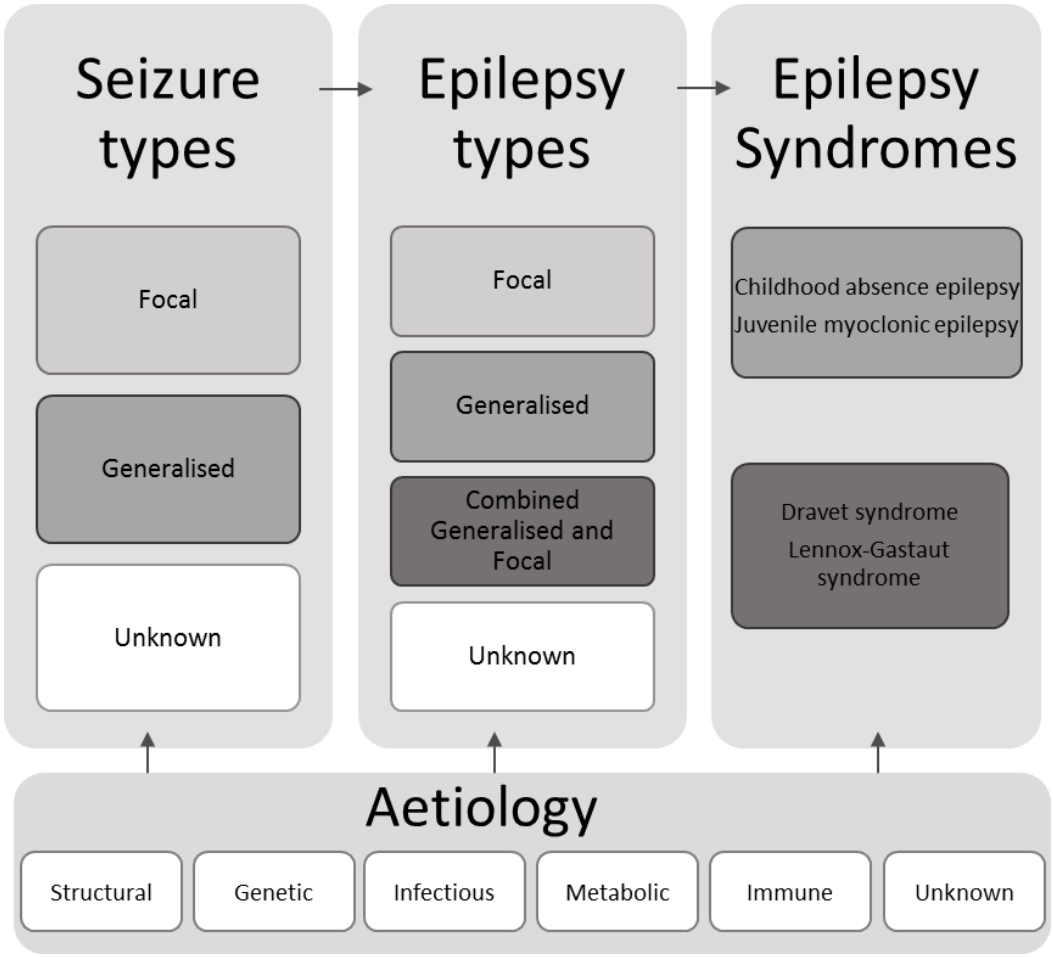


Figure 1-2. The new classification of epilepsy proposed by International League Against Epilepsy (ILAE) (Scheffer et al., 2017)
It includes three stages: seizure types, epilepsy types, and epilepsy syndromes. Aetiology should be considered at each stage as it substantially influences the treatments. The classification of seizure types by ILAE illustrated in Figure 1-1. However, there is no formal classification of epilepsy syndromes by ILAE; the illustrated are some examples of established syndromes.

1.2 Pharmacological treatment

Epilepsy in 60 to 70% of newly diagnosed patients is controlled with an appropriate AED treatment. Moreover, 50% of controlled patients response successfully to the initial monotherapy and usually on modest doses (Kwan and Brodie, 2000, Mohanraj and Brodie, 2005, Brodie et al., 2012).

There are currently 22 AEDs licensed in the UK as monotherapy, or as an adjunct for adult epilepsy patients (Table 1-1). They can be divided into established (old), and new AEDs on a chronological basis. Old generation AEDs were introduced to clinical practice before 1989, and include phenobarbital (PB), phenytoin (PHT), primidone (PRM), ethosuximide (ESM), carbamazepine (CBZ), sodium valproate (VPA), clonazepam (CZP), and clobazam (CLB).

The remaining AEDs are generally regarded as new drugs. These include vigabatrin (VGB), lamotrigine (LTG), gabapentin (GBP), topiramate (TPM), tiagabine (TGB), oxcarbazepine (OXC), levetiracetam (LEV), pregabalin (PGB), zonisamide (ZNS), lacosamide (LCM), eslicarbazepine acetate (ESL), retigabine (RTG), perampanel (PER), and brivaracetam.

In addition to stiripentol and rufinamide, the use of which is restricted to adjunct therapy for Dravet syndrome and Lennox-Gastaut syndrome in infants and children, respectively. Felbamate (FBM), which causes serious adverse reactions, and is therefore not licensed in the UK.

Table 1-1. Established and new antiepileptic drugs licensed as monotherapy or adjunct therapy for epilepsy in adults in the United Kingdom

Antiepileptic drugs	Year of introduction
Established drugs	
Phenobarbital	1912
Phenytoin	1938
Primidone	1952
Ethosuximide	1955
Carbamazepine	1965
Sodium valproate	1967
Clonazepam*	1969
Clobazam*	1974
New drugs	
Vigabatrin*	1989
Lamotrigine	1991
Gabapentin	1993
Topiramate	1995
Tiagabine*	1998
Oxcarbazepine	2000
Levetiracetam	2000
Pregabalin*	2005
Zonisamide	2006
Lacosamide	2008
Eslicarbazepine acetate	2009
Retigabine*†	2011
Perampanel*	2012
Brivaracetam*	2016

*Approved only as adjunct therapy. † Withdrawn in June 2017. Data sourced from (Loscher and Schmidt, 2011, Baulac et al., 2017, Brodie, 2017a, Trinka et al., 2017).

AEDs can also be classified based on their primary mechanism of action, as discussed in the following section.

1.2.1 Mechanisms of action

There are four main mechanisms by which most AEDs act: blockade of voltage gated sodium channels, blockade of voltage gated calcium channels, potentiation of gamma aminobutyric acid (GABA) inhibitory effect, and inhibition of the glutamate excitatory mechanism. Other mechanisms include: potentiation of potassium channels, and modulation of synaptic vesicle proteins.

Voltage gated sodium channels control the action potential by controlling the passage of sodium ions across the neuronal membrane. PHT, CBZ, LTG, and OXC act mainly through blocking the fast-inactivated state of the sodium channel, while LCM and ESL acetate block the slow-inactivated state of the sodium channel. Meanwhile, VPA, FBM, TPM, and ZNS have an effect on the sodium channels as part of their multiple mechanisms. Sodium channel blockers act during high frequency repetitive action potentials without affecting physiological neuronal activity, when they are administered at therapeutic concentration. They prevent repetitive action potentials in both the epileptic focus, and the spreading of seizure activity (Lason et al., 2011, Baulac et al., 2017).

Voltage dependent calcium channels include two main subtypes: high voltage calcium channels, and low voltage calcium channels (T-type). High voltage calcium channels control the neurotransmitter release from the presynaptic nerve terminals by controlling calcium influx across the neuronal membrane. GBP and PGB act mainly by blocking the high voltage calcium channels by binding to their $\alpha_2\delta$ subunit. TPM has also an effect on these channels. The low-voltage calcium channel (T-type) plays an essential role in the mechanism of the thalamo-cortical oscillatory activity, and the generation of spike-wave discharges; it plays a pathological role in the absence seizure. ESM acts mainly through the blocking of this channel; VPA and ZNS also have an effect on this T-type calcium channel (Lason et al., 2011).

The GABA is the most important inhibitory neurotransmitter in the brain, and there are three types of GABA receptors (A, B, and C). The GABA-A receptor is responsible for the generation of fast inhibitory postsynaptic potentials, and therefore for controlling seizure activity. They are ligand-gated chloride channels, and the stimulation of GABA-A receptors increases the entrance of chloride ions,

thus increasing the hyperpolarisation of the neuronal membrane. GABA-A receptor agonists often increase the seizure threshold in the epileptogenic brain, but not in the normal brain, and inhibit the spread of seizure activity. After GABA is released to the synapse, it is taken back into presynaptic neuronal cells and into glia cells, where it is metabolised to succinic semialdehyde by GABA aminotransferase. The antiepileptic activity of PB and BZD is mainly to activate the GABA-A receptors, while VGB and TGB potentiate GABA by inhibiting GABA aminotransferase, and GABA reuptake into the presynaptic membrane, respectively. VPA also enhances the inhibitory effect of GABA as part of its multiple mechanisms (Lason et al., 2011).

Glutamate is the main excitatory neurotransmitter in the central nervous system (CNS). It stimulates several receptors, such as *N*-methyl- D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), and kainate receptors. The complex of these receptors is comprised of an ion channel that controls the calcium and sodium ions influx, and potassium ions efflux, and therefore neuronal depolarisation. Several binding sites have been recognised on the NMDA receptor, such as the glycine site, where antagonism could demonstrate an anti-convulsive action. LCM and FBM show antagonistic activity towards the glycine-binding site on NMDA receptors. PER is a selective AMPA receptor antagonist, while TPM has an inhibitory effect on kainate receptors. PB also inhibits AMPA receptors, though this effect plays a minor role in its mechanisms of action.

The muscarine sensitive Kv7 (KCNQ) type potassium channels are responsible for controlling neuronal excitability and repetitive firing. The neuronal depolarisation induced by excitatory stimuli activates Kv7 potassium channels as a compensatory action, leading to the repolarisation of the neuronal membrane, with subsequent firing suppression that limits seizure activity. RTG is a first-in-class potassium channel opener (Lason et al., 2011).

The synaptic vesicle protein 2A is a commonly distributed CNS protein that modulates the exocytosis of neurotransmitters, particularly glutamate. LEV and brivaracetam bind selectively to the synaptic vesicle protein 2A (Gao and Li, 2016).

Figure 1-3, the mechanisms of action of different AEDs. The availability of more than 20 AEDs for treating epilepsy have increased the treatment options, however, there are key decisions to be considered in treating epilepsy, including the time at which AED treatment should be commenced, and which drug should be selected for the first-line therapy. The following sections discuss the initiation and selection of AED treatment.

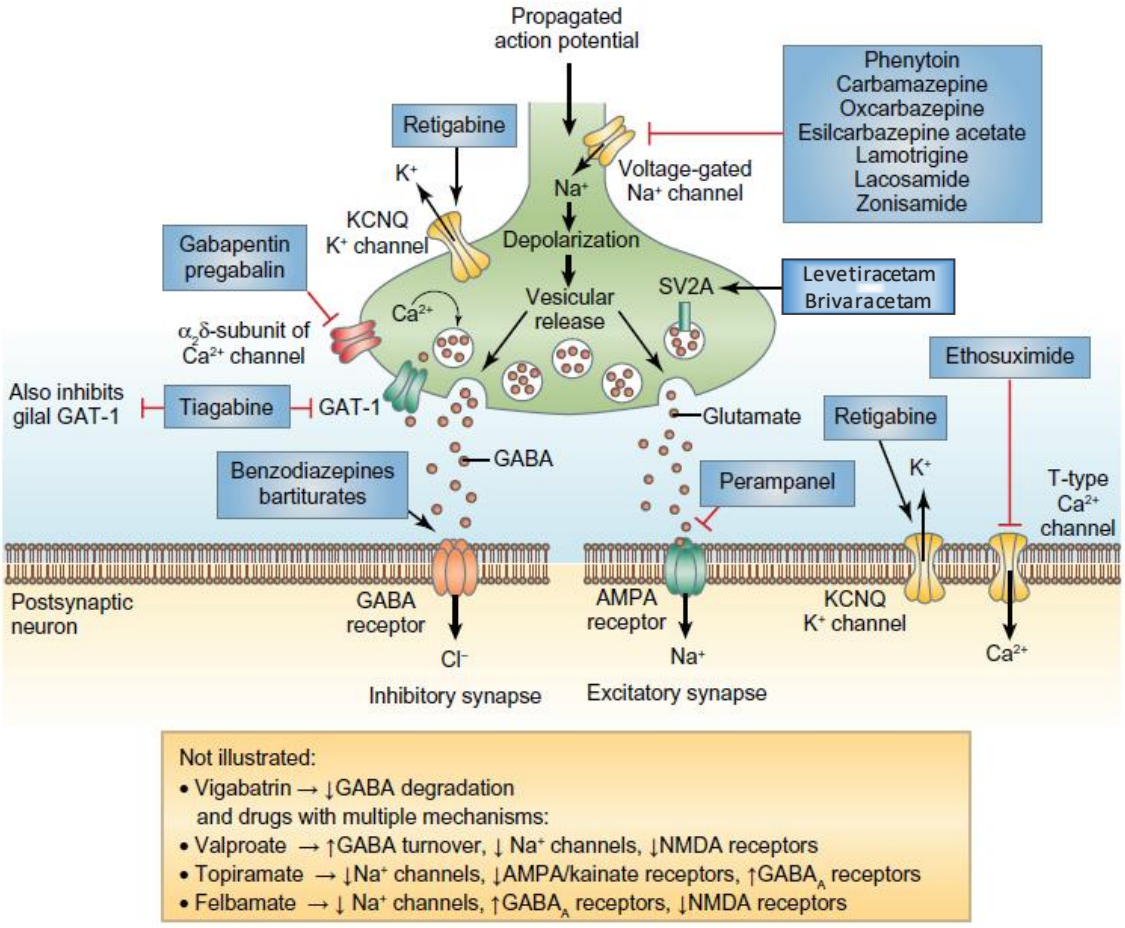


Figure 1-3. Mechanisms of action of different antiepileptic drugs that act on excitatory and inhibitory neurotransmitter systems
Key: AMPA: α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid, GABA, γ-aminobutyric acid: GAT-1, sodium- and chloride-depended GABA transporter 1: SV2A: synaptic vesicle glycoprotein 2A, NMDA: *N*-methyl-D-aspartate. Reproduced with permission from Dove Medical Press Ltd and (Shih et al., 2013).

1.2.2 Commencing antiepileptic drug treatment

The decision to initiate AED treatment is often based on the chance of seizure recurrence, the consequences of seizure recurrence on a patient's life, and the benefits and adverse effects of AED treatment. The decision of whether or not to commence treatment should be taken by an epilepsy specialist following a full

discussion with the patient and their family concerning the risks and benefits of both courses of action. Generally, AED treatment is recommended after two or more unprovoked seizures occurring more than 24 hours apart. However, treatment can be indicated after a single seizure in patients at high risk of recurrence. For instance, in the presence of a brain insult (like stroke, head trauma, or brain tumour), an abnormal EEG, a strong family history of epilepsy, or in the case of the diagnosis of an epilepsy syndrome with a high chance of seizure recurrence, such as JME (Stephen and Brodie, 2009, Perucca and Tomson, 2011, National Institute for Health and Care Excellence, 2012, Scottish Intercollegiate Guidelines Network, 2015).

1.2.3 Initial drug selection

A number of evidence-based guidelines for the selection of AED therapy are available, such as that produced by the National Institute for Health and Care Excellence in the UK (NICE, 2012), and the Scottish Intercollegiate Guidelines Network (SIGN, 2015). The selected AED should be effective for the given seizure type, or syndrome. Other characteristics, such as age, sex, and comorbidities, should also be taken into account, together with a consideration of other important aspects of AEDs, including safety; tolerability; pharmacokinetic properties and potential for drug interactions; dosing constraints, such as slow titration, frequency, and formulations; and cost (Perucca and Tomson, 2011, Moshe et al., 2015).

As shown in Table 1-2, AEDs possess different efficacy spectrums in relation to different seizure types and syndromes. Many established and new AEDs are currently licensed as monotherapy for epilepsy in adults. However, to date, no robust efficacy evidence exists supporting the use of a particular AED in relation to a specific seizure type (Perucca and Tomson, 2011). In focal epilepsy, LTG was found to be more effective than CBZ, GBP, TPM, and OXC in SANAD (Standard And New Antiepileptic Drugs) trial (Marson et al., 2007a). However, LTG was found to be superior to CBZ in the preceding trial largely due to fewer patients experiencing adverse effects, open-label design may have contributed to this difference, added to the use of immediate-release (rather than controlled-release CBZ) in some patients. Moreover, there was no significant difference in efficacy between LTG and CBZ in the per-protocol analysis in that trial. Other trials assessing efficacy of

newer drugs LEV, ZNS, LCM, and ESL acetate versus sustained-release CBZ showed that most of adults with newly diagnosed epilepsy respond to a modest dose of any first-line AED (Brodie et al., 2007, Baulac et al., 2012, Baulac et al., 2017, Trinka et al., 2017). Furthermore, LTG demonstrated a superior efficacy over PGB in one trial (Kwan et al., 2011). Few trials conducted in patients with generalised and unclassified epilepsies; in SANAD trial, VPA was more effective than LTG and TPM (Marson et al., 2007b). Altogether, the findings of these trials demonstrated that none of the newer AEDs were more effective than standard drugs for patients with newly diagnosed epilepsy.

Table 1-2. Efficacy spectrum of antiepileptic drugs against common seizure types in adults

		Idiopathic generalised seizures		
	Focal-onset seizures	Tonic-clonic	Absence	Myoclonic
Phenobarbital	+	+	0	0
Phenytoin	+	+	Aggravate	Aggravate
Ethosuximide	0	0	+	?+
Carbamazepine	+	+	Aggravate	Aggravate
Valproate	+	+	+	+
Benzodiazepines	+	+	?	+
Vigabatrin	+	?+	0	Aggravate
Lamotrigine	+	+	+	+ *
Gabapentin	+	?+	0	Aggravate
Topiramate	+	+	?	?+
Tiagabine	+	?+	Aggravate	Aggravate
Oxcarbazepine	+	+	Aggravate	Aggravate
Levetiracetam	+	+	?+	+
Pregabalin	+	?+	0	Aggravate
Zonisamide	+	?	?+	?+
Lacosamide	+	?	?	?
Eslicarbazepine acetate	+	?	Aggravate	Aggravate
Retigabine	+	?	?	?
Perampanel	+	?	?	?
Brivaracetam	+	?	?	?

Key: +; effective, 0; not effective, ?+; possible efficacy, ?; efficacy not documented.
*occasionally can aggravate. Data obtained from (Stephen and Brodie, 2009, Perucca and Tomson, 2011, Moshe et al., 2015, Gao and Li, 2016).

However, while randomised controlled trails (RCTs) can assess a drug's efficacy, they do not typically capture the other important factors affecting the selection of AEDs. These additional factors include teratogenic effects, rare idiosyncratic

reactions, chronic adverse effects, and enzyme-induction effects and the potential for drug interactions. Indeed, all of the available guidelines highlight the need to consider individual patient characteristics, such as childbearing potential, old age, and comorbidities, when selecting an AED (Perucca and Tomson, 2011). For instance, VPA is a potent teratogen, and should therefore be avoided in adolescent and young women (Tomson et al., 2015), whereas LTG and LEV are reasonable alternatives (Perucca and Tomson, 2011). Furthermore, CBZ is associated with poor tolerability in the elderly, while LTG, GBP, LEV appear to be more suitable (Werhahn, 2009).

Overall, the selection of the initial AED is largely based on its efficacy and tolerability, and on patient characteristics. While standard AEDs, such as CBZ and VPA, remain valuable first-line treatments, some new AEDs, such as LTG and LEV, are increasingly utilised as initial monotherapy, primarily because of their enhanced safety, tolerability, and drug interaction profiles.

1.2.4 Dosing guidelines

AED treatment is usually commenced with a low dose, and is up-titrated slowly in order to minimise neurotoxicity and the risk of cutaneous adverse reactions, unless there is an urgent need for anti-seizure effects. It is also generally recommended that the lowest effective dose should be maintained. The maintenance dosage should also consider the patient's characteristics, for instance, the elderly may require lower dosages, together with the patient's susceptibility to potential adverse effects, and the risk of seizure recurrence (Perucca and Tomson, 2011). The optimal starting dose, target maintenance dose, and dosing frequency vary with the type of AED as shown in Table 1-3.

Controlled-release CBZ is preferable over immediate-release formulation, as the former possesses a better tolerability (i.e. lower CNS toxicity). However, for other AEDs, there is no evidence that modified-release formulations are superior (Perucca and Tomson, 2011).

Generally, the dose adjustment of some AEDs is necessary if a potentially interacting drug is added or removed. The pharmacokinetics of AEDs, and potential drug interactions, are discussed in detail later in this chapter.

Table 1-3. Dosing guidelines for antiepileptic drugs in adults

	Starting dose	Commonest dose	Maintenance range	Dosing frequency
Phenobarbital	60	120	60-240	OD-BD
Phenytoin	100-200	300	100-600	OD-BD
Ethosuximide	500	1000	500-2000	OD-BD
Carbamazepine	200	600	400-2000	BD-QDS
Valproate	500	1000	500-3000	OD-BD
Clonazepam	0.5-1	4	2-8	OD-BD
Clobazam	10	20	10-60	OD-BD
Vigabatrin	500-1000	3000	2000-4000	OD-BD
Lamotrigine	25	200-400	100-800	OD-BD
Gabapentin	300-400	1800	900-4800	TDS
Topiramate	25-50	200-400	100-800	BD
Tiagabine	4-10	40	20-60	BD-QDS
Oxcarbazepine	150-600	900-1800	600-2400	BD
Levetiracetam	500-1000	1000-2000	1000-4000	BD
Pregabalin	75-150	300	150-600	BD-TDS
Zonisamide	50-100	300	100-500	BD
Lacosamide	100	200	100-600	BD
Eslicarbazepine acetate	400	800	800-1600	OD
Retigabine	150-300	900	600-1200	TDS
Perampanel	2	6-8	4-12	OD
Brivaracetam	50	100	50-200	BD

Doses in mg/day. Key: OD; once daily, BD; twice daily, TDS; three times daily, QDS; four times daily. Data obtained from (Perucca and Tomson, 2011, Brodie, 2017b).

1.3 Tolerability

1.3.1 Importance

The poor tolerability of AEDs is a major reason for treatment failure, because it leads to the early discontinuation of AEDs in approximately 20% of patients (Kwan and Brodie, 2000), prevents the administration of a therapeutic dosage (Perucca and Gilliam, 2012), and has a negative impact on patient adherence to medication (Eatock and Baker, 2007, Faught, 2012). The concerns relating to adverse effects remain significant for patients when taking a medication, and the adverse drug reactions experienced by patients with epilepsy, whether actual or perceived, increases the probability of non-adherence. A study examining the reasons for non-adherence in 131 patients who missed taking their AEDs revealed that the fear of adverse drug reactions (27%) was the third most frequent reason for non-

adherence, preceded only by forgetfulness (54%), and being seizure-free for a period of time (49%) (Tang et al., 2013).

In addition, the adverse drug reactions of AEDs represent a significant burden on the cost of healthcare and society. The total cost of the frequent adverse effects of AEDs has been estimated at approximately €21,000 per patient per year [confidence interval (CI) 15,000-27,200], which includes the cost to healthcare, the patients and their family in terms of informal care, together with other costs such as productivity loss (De Kinderen et al., 2014).

Moreover, adverse drug effect is considered as one of the strongest predictors of impaired health-related quality of life in people with epilepsy (Baker et al., 1997, Perucca et al., 2009, Kwon and Park, 2011, Luoni et al., 2011). In a study of controlled (1-year seizure-free) patients on monotherapy, depressive symptoms, and the adverse effects of AEDs were the strongest negative determinants of their quality of life (Kwon and Park, 2011). Moreover, an Italian multicentre study of 933 individuals with pharmacoresistant epilepsy demonstrated that adverse effects were by far the most important predictor of quality of life, with or without the symptoms of depression. The study also revealed that epilepsy-related factors, such as seizure frequency, tonic–clonic seizures, age of epilepsy onset, and epilepsy duration, together with the number of AEDs prescribed, had no significant predictive value on the quality of life. The authors of this study concluded that when seizure freedom is not achievable, managing depression, and reducing adverse drug effects can be far more valuable than interventions intended to reduce the frequency of seizures (Luoni et al., 2011).

1.3.2 Assessment and prevalence of adverse effects

A number of standardised methods exist for screening the adverse effects of AEDs in adults and children. The adverse event profile (AEP) method (Table 1-4) is one example of a self-completed screening measure of a patient's perception of the adverse effects of AEDs (Baker et al., 1994). The accurate usage of these validated screening approaches can allow better quantification, and the reduction of the burden of AEDs' adverse effects, together with the identification of the populations at a high risk of the adverse effects of AEDs (Perucca and Gilliam, 2012).

However, these screening measures, which include checklists and questionnaires, tend to overestimate the prevalence of side effects. In contrast, relying on the spontaneous reporting of adverse effects, and on unstructured interviews, results in an underestimation, since the patients may forget about problems that occurred between visits, are unable to describe problems, or employ inappropriate terminology, such as stating that they experienced dizziness when they were actually feeling lightheaded, or stating that they experienced speech problems when in fact they were mentally confused (Cramer, 2012, Perucca and Gilliam, 2012). In a multicentre study of 809 patients with pharmacoresistant epilepsy, the rate of adverse effects was almost three times greater when identified by a questionnaire (AEP 93%) than that detected by an unstructured interview (35%) (Canevini et al., 2010). Overall, the prevalence of the adverse effects of AEDs has been reported as being between 10 and 40% if tolerability was assessed by spontaneous reporting, and between 59 and 96% when it was detected via systematic screening methods (Perucca et al., 2009, Kwon and Park, 2011, Luoni et al., 2011).

The frequency of patient-perceived adverse effects (as AEP) correlates with seizure control; it is highest in patients with pharmacoresistant epilepsy (mean AEP score 42.7) (Luoni et al., 2011), intermediate in mixed populations (AEP 38.8) (Perucca et al., 2009), and lowest in well-controlled patients (AEP 27.3) (Kwon and Park, 2011). Other risk factors for AEPs are polytherapy, psychiatric comorbidity, being of the female gender, and being either a child, or elderly (Perucca and Gilliam, 2012).

In short, every method of tolerability assessment possesses limitations, and the prevalence of adverse effects varies greatly among studies, lies between 10 to 90% or higher, depending on the assessment method, seizure control, and other factors.

Table 1-4. 19-item Adverse Event Profile (AEP) screening method also known as Liverpool AEP

During the last four weeks have you had any of the problems listed below? For each item, if has always or often been a problem ring ④. If has sometimes been a problem ring ③ and so on. Please be sure to answer every item.				
	Always or often a problem	Sometimes a problem	Rarely a problem	Never a problem
1-unsteadiness	4	3	2	1
2-tirdedness	4	3	2	1
3-restlessness	4	3	2	1
4-feelings of anger or aggression to others	4	3	2	1
5-nervousness and/or agitation	4	3	2	1
6-headache	4	3	2	1
7-hair loss	4	3	2	1
8-problems with skin (like acne, rash)	4	3	2	1
9-double or blurred vision	4	3	2	1
10-upset stomach	4	3	2	1
11-difficultiy in concentrating	4	3	2	1
12-trouble with mouth or gums	4	3	2	1
13-shaky hands	4	3	2	1
14- weight gain	4	3	2	1
15-dizziness	4	3	2	1
16-sleepiness	4	3	2	1
17-depression	4	3	2	1
18-memory problems	4	3	2	1
19-disturbed sleep	4	3	2	1

This is a patient-completed questionnaire for assessing the frequency of the most frequent adverse effects of antiepileptic drugs during the last four weeks. Ratings can be added to obtain a total score of 19-76, higher scores indicating a greater burden of adverse effects. Obtained from (Baker et al., 1994).

1.4 Definition and classification of adverse drug reactions of antiepileptic drugs

World Health Organisation (WHO) defines an adverse drug reaction as “a response to a drug that is noxious and unintended and occurs at doses normally used in man for therapy, diagnosis, and prophylaxis” (WHO, 1972, pp. 9). While a more precise definition was proposed by Edwards and Aronson (2000, pp. 1255), as follows: “an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future

administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product".

According to the European Pharmacovigilance Legislation, the definition of the term 'adverse reaction' should be amended in order to ensure that it covers noxious and unintended effects resulting not only from the authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse and abuse of the medicinal product (Legislation, 2010).

The term 'adverse effect' appears to be more suitable than 'toxic effect', or 'side effect', since 'toxic effect' implies that it is limited to an event that appeared at a high dosage in the form of an exaggeration of the therapeutic effect desired. In contrast, the term 'side effect' may be dose-related or not, but includes both desirable and undesirable events occurring in the form of different mechanism from the pharmacological action for which the drug was being administered. Meanwhile, the term 'adverse effect' is precise, and implies all of the unwanted effects, regardless of their mechanism (Edwards and Aronson, 2000).

The terms 'adverse effect' and 'adverse reaction' are interchangeable, however it is important to distinguish between 'adverse effect' and the term 'adverse event'. An 'adverse effect' is an unpleasant effect that can be attributed to the medication, directly or indirectly, while an 'adverse event' is an undesirable experience appearing during treatment that is not necessarily caused by the medication (Perucca and Gilliam, 2012).

Different classifications of adverse drug reactions exist, based on their severity, frequency, symptoms, pathophysiological mechanisms, and the body organ affected. The adverse drug reactions of AEDs are divided into five categories, according to the revised version of the WHO classification: Type A (related to pharmacological characteristics of drug), Type B (idiosyncratic), Type C (chronic), Type D (delayed), and Type E (resulting from drug interactions) (Perucca and Gilliam, 2012). Table 1-5 compares these five categories, and the following section discusses the clinically relevant adverse effects of each type. In addition, the rate of adverse effects, underlying mechanisms, risk factors, offender AEDs, and prevention and management are described

Table 1-5. Classification of the adverse drug reactions of antiepileptic drugs

	Features	Examples	Prevention	Management
Type A	• Common (1 to 10%), or very common (>10%); • Related to a pharmacological action of the drug; • Dose-dependent; • Predictable; • Reversible; • Low mortality.	• Tiredness; • Dizziness; • Cognitive impairment; • Depression; • Gastrointestinal side effects.	• Select a suitable antiepileptic drug based on tolerability profile and patients' characteristics; • Start at low dose and up-titrate slowly; • Maintain at the lowest effective dose.	• Reduce dose or discontinue medication; • Modify dosing scheme or drug formulation;
Type B	• Rare (<0.1%)*; • Known as idiosyncratic; • Related to the patient's susceptibility such as genetic; • Dose independent†; • Unpredictable; • Reversible; • High mortality.	• Maculopapular rash; • Steven-Johnson syndrome; • Aplastic anaemia; • Hepatotoxic effects; • Pancreatitis.	• Avoid (or use very cautiously) particular antiepileptic drugs in high-risk patients; • Start lamotrigine at low dose and up-titrate slowly.	• Withdraw medication; • Avoid medication with a similar adverse effects profile in future.
Type C	• Common; • Related to cumulative dose; • Chronic; • Commonly reversible.	• Weight gain; • Folate deficiency; • Visual field loss; • Gingival hypertrophy.	• Select a suitable antiepileptic drug based on the tolerability profile and patients' characteristics.	• Replacement therapy (e.g. folic acid); • Withdraw medication.

Table 1-5. Classification of the adverse drug reactions of antiepileptic drugs

	Features	Examples	Prevention	Management
Type D	• Uncommon (0.1 to 1%); • Related to prenatal exposure to the medication (i.e. teratogenesis) or carcinogenesis; • Commonly dose-dependent; • Delayed; • Irreversible.	• Birth defects; • Neurodevelopmental delay in the offspring; • Pseudolymphoma.	• Avoid valproate, phenobarbital, and polytherapy in women of childbearing potential, if possible; • Use low-risk monotherapies at the lowest effective dose before pregnancy; • Avoid discontinuation during pregnancy.	-
Type E	• Common; • Adverse drug interactions; • Predictable; • Reversible.	• Increased risk of cutaneous reactions after adding lamotrigine to valproate; • Decreased efficacy of warfarin after adding carbamazepine.	• Avoid polytherapy if possible; • Select concomitant drugs with low potential for adverse drug interactions.	• Dose adjustment.

*Except maculopapular rash that can affect 5-17% of patients started phenobarbital, phenytoin, carbamazepine, and lamotrigine. †Except LTG-induced cutaneous reactions that correlate to starting dose and titration rate. Data obtained from (Edwards and Aronson, 2000, Perucca and Gilliam, 2012).

1.4.1 Type A reactions

Type A effects can be attributed to the drug's main mechanism of action, and are often predictable, thus the patient can be counselled regarding possible symptoms. The effects are generally present on the introduction of the drug or dose escalating, and diminish over time or after dosage reduction (Perucca and Gilliam, 2012).

CNS effects represent most of type A reactions of AEDs and can be further categorised into four groups; sedative effects, coordination disturbances, cognitive dysfunction, and psychiatric adverse effects.

1.4.1.1 Sedative effects

The sedative effects of AEDs range from mild tiredness or drowsiness to profound lethargy (Perucca and Gilliam, 2012). They are the most commonly reported adverse effects of AEDs and are shared by most, if not all, AEDs (Marson et al., 2007b, Perucca and Gilliam, 2012). They are also the most common reason for the treatment failure of AEDs, except for LTG, in which a rash is the most frequent reason (Marson et al., 2007a). Sedative effects are more common and severe in the first-generation AEDs, PB, PRM, and benzodiazepines (BZD) (Kennedy and Lhatoo, 2008). All new AEDs also possess sedative properties, except for LTG which rarely causes sedation (Zaccara et al., 2008, Brodie, 2017b).

1.4.1.2 Coordination disturbances

Coordination difficulties include dizziness, imbalance, unsteadiness, ataxia, gait difficulties, vertigo, nystagmus, tremor, and diplopia (Perucca and Gilliam, 2012).

All old AEDs, particularly CBZ, PHT, PRM, and BZD, are associated with a considerable risk of poor coordination (Kennedy and Lhatoo, 2008). However, these adverse effects also appear with new AEDs, although the risk appears to be lowest with LEV (Kennedy and Lhatoo, 2008, Zaccara et al., 2008, Brodie, 2017b).

In a meta-analysis of placebo-controlled studies of eight AEDs (GBP, LTG, LEV, OXC, PGB, TGB, TPM, and ZNS), all new AEDs except LEV have adverse coordination effects (but no meta-analysis could be performed with OXC and TGB)

(Zaccara et al., 2008). In another meta-analysis of the aforementioned eight AEDs, the risk of poor coordination related to the treatment was three times higher, compared with a placebo. A particular high risk was recorded with OXC, LTG, TPM, and PGB, whereas the risk was not significant for LEV and GBP (Sirven et al., 2007).

1.4.1.3 Cognitive dysfunction

The adverse cognition effects of AEDs primarily include psychomotor dysfunction, concentrating difficulty, and memory problems (Perucca and Meador, 2005). The rate of negative cognitive effects in AEDs is estimated at approximately 13-15%, although it varies greatly among AEDs (Arif et al., 2009, Javed et al., 2015). Among the older AEDs, PB, PRM, and BDZ possess more negative effects on cognition than VPA and CBZ. However, neither VPA nor CBZ are completely free of adverse cognitive effects. New AEDs are generally less likely to have adverse effects on cognition, and the only new AEDs known to cause substantial cognitive dysfunction are TPM and ZNS, both of which have a negative impact on cognition, and a specific effect on verbal function, language, and memory. However, LTG, GBP, and LEV are less likely to interfere with the cognitive processes, even among patients on polypharmacy (Perucca and Meador, 2005, Arif et al., 2009, Perucca and Gilliam, 2012, Javed et al., 2015).

The risk of cognitive dysfunction is increased in polytherapy, and higher AEDs doses (Perucca and Meador, 2005). Other non-AED factors can also contribute to a high rate of these effects, including epilepsy aetiology and duration; seizure type, frequency, and severity; postictal states; comorbidity; and psychosocial factors (Perucca and Gilliam, 2012). Patients with an intellectual disability are less likely to report cognitive adverse effects, while patients with depression are more likely to do so (Javed et al., 2015).

1.4.1.4 Psychiatric effects

Approximately 15 to 20% of epilepsy patients who take AEDs report adverse psychiatric effects. These effects include behavioural or personality changes, such as irritability, hyperactivity, agitation, and aggressiveness; mood disorders; and psychoses (Perucca and Gilliam, 2012). Behavioural problems are the most commonly reported psychiatric adverse effects of AEDs, while psychosis is a relatively rare (Schmitz, 2006). AEDs can induce psychiatric changes via two

mechanisms: GABAergic effects in depression, and forced normalisation, i.e. seizure control, in psychosis (Schmitz, 2006).

Not all AEDs have the same psychiatric effects; of the established AEDs, a high risk of negative psychotropic effects is associated with PB, PRM, ESM, and BZD, while among the new AEDs, VGB, TPM, TGB, LEV, ZNS, FBM, and PER are associated with a high risk of negative psychiatric effects. In contrast, several AEDs have positive psychotropic properties, and are commonly utilised in psychiatric disorders, including CBZ, VPA, LTG, and GBP (Schmitz, 2006, Weintraub et al., 2007, Brodie, 2017b).

A history of psychiatric disorders is an important risk factor for experiencing adverse psychiatric effects with AEDs. The risk of negative psychiatric effects with AEDs seems to also be related to the severity of the epilepsy, polypharmacy, fast up titration, and high doses of medication (Mula et al., 2003a, Schmitz, 2006, Perucca and Gilliam, 2012). Moreover, psychiatric comorbidity has been shown to deteriorate common AED-related adverse effects (Kanner et al., 2012).

In summary, the Type A reactions of AEDs are the most frequently reported adverse effects, and are associated with the use of all AEDs at different rates, being typically more common and severe with first-generation agents. Table 1-6 is an attempt to summarise the CNS adverse effects of AEDs that represent the majority of type A reactions.

Table 1-6. Central nervous system effects of antiepileptic drugs

	Sedative effects	Coordination disturbances	Cognitive dysfunction	Psychiatric effects
Phenobarbital	++	+	++	++
Phenytoin	+	++	++	0
Ethosuximide	+	+	0	++
Carbamazepine	+	++	+	Protective
Valproate	+	+	+	Protective
Clonazepam	++	++	++	++
Clobazam	+	++	+	++
Vigabatrin	+	+	0	++
Lamotrigine	0	+	0	Protective
Gabapentin	+	+	0	Protective
Topiramate	+	+	++	++
Tiagabine	+	++	++	++
Oxcarbazepine	+	++	+	0
Levetiracetam	+	+	0	++
Pregabalin	+	+	0	0
Zonisamide	+	+	++	++
Lacosamide	+	+	0	0
Eslicarbazepine acetate	+	+	0	0
Retigabine	+	+	0	+
Perampanel	+	+	0	++
Brivaracetam	+	+	0	+

Key: 0; no effect, +; mild effect, ++; marked effect. This table based on information obtained from (Sirven et al., 2007, Weintraub et al., 2007, Kennedy and Lhatoo, 2008, Zaccara et al., 2008, Arif et al., 2009, Javed et al., 2015, Brodie, 2017b).

1.4.2 Type B reactions

Usually known as idiosyncratic, these reactions cannot be attributed to the main mechanism of action of the medication. Type B effects are often unpredictable, and are related to individual vulnerabilities, such as genetic, immunological, or other mechanisms. Most of these adverse drug reactions occur irrespective of the dosage, while others such as LTG-induced skin rash, are correlated with the starting dose and titration rate (Zaccara et al., 2007, Perucca and Gilliam, 2012).

Type B reactions account for up to 10% of all adverse reactions of AEDs. Apart from maculopapular rash, idiosyncratic reactions are rare but include the most life-threatening effects of AEDs. They are reversible on discontinuation, but delayed identification and intervention can lead to a high morbidity, and even to mortality (Zaccara et al., 2007).

Idiosyncratic reactions often occur within the first few weeks or months of treatment, and are more frequent with the established AEDs (Brodie, 2017b). The mechanisms underlying these effects include immune-mediated hypersensitivity reactions, direct cellular damage by the drug or its active metabolites, and, less commonly, the off-target interaction of the drug or its active metabolites with atypical system (Zaccara et al., 2007).

The most common Type B effects of AEDs include cutaneous, haematological, hepatic or pancreatic reactions, or other reactions.

1.4.2.1 Cutaneous reactions

Immune-mediated skin hypersensitivity reactions are the most common idiosyncratic reactions of AEDs. These reactions often consist of maculopapular rash that can affect 5 to 17% of patients who are started on CBZ, PHT, PB, and LTG. However, these AEDs are also associated with a risk of potentially life-threatening Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug-related rash with eosinophilia and systemic symptoms (DRESS), affecting 1 to 10 per 10,000 new users (Zaccara et al., 2007, Perucca and Gilliam, 2012).

Genetic predisposition plays an important role in AED-induced idiosyncratic skin reactions. A strong association has been found between the genetic marker HLA-B*1502 and CBZ-induced SJS in Han Chinese patients (Chung et al., 2004), while the genetic marker HLA-A*3101 has been found to be associated with CBZ-induced skin reactions in European patients (McCormack et al., 2011).

Other risk factors for these reactions are young or old age, a history of drug-induced skin reactions, a high start dose and fast up titration, concomitant infectious disease or immune system disorders, and particular concurrent medications (Zaccara et al., 2007, Perucca and Gilliam, 2012).

1.4.2.2 Haematological reactions

The most serious blood dyscrasia is aplastic anaemia (in which bone marrow fails to produce enough blood cells of all three cell types), and the AED most strongly associated with this reaction is FBM. The incidence of FBM-induced aplastic anaemia is 127 cases in one million per year, compared with two cases in one

million per year in the general population (Zaccara et al., 2007). Other AEDs can also cause aplastic anaemia. In a case-control study, 9.2% of 173 patients with aplastic anaemia were taking AEDs, with most taking CBZ, VPA, or PHT, although FBM was excluded. While 0.8% of the 497 control patients were taking these medications, which means that AEDs exposure was associated with a nine-fold increase in the risk of aplastic anaemia (Handoko et al., 2006).

AEDs can also cause agranulocytosis (lowered white blood cell particularly neutrophils), with CBZ associated with the highest risk. In a population-based study, CBZ was observed to be associated with an increased risk of developing this condition; the OR (odds ratio) was 10.96 (95% CI 1.17–102.64) (Ibanez et al., 2005). PHT was also associated with an increased risk, and rare cases have also been reported with other AEDs (Ibanez et al., 2005, Zaccara et al., 2007).

1.4.2.3 Hepatic or pancreatic reactions

The liver is the main organ responsible for drug metabolism, and is therefore prone to drug toxicity. Hepatotoxicity can be part of DRESS, especially with aromatic AEDs such as PB, PHT, CBZ, LTG or it can present separately. Isolated hepatotoxicity can be caused by immune-mediated mechanisms, or by direct cytotoxic damage, as in VPA-induced liver toxicity (Zaccara et al., 2007).

In a population-based study in Untied State, AEDs were found to be the fourth most frequent medications to cause acute drug-iduced hepatotoxicity leading to liver transplantation, preceded only by paracetamol, isoniazid, and propylthiouracil (Russo et al., 2004).

VPA and FBM are associated with the highest risk of acute hepatotoxicity. The risk of fatal liver damage with VPA is one in 10,000 to 49,000 for the general population, and one in 500 for the highest risk group (paediatric < 2 years old, inborn metabolic conditions, and polypharmacy) (Pellock et al., 2006). However, the rate of fatal hepatotoxicity induced by VPA seems to have declined recently, perhaps because a better awareness of the condition has engendered an avoidance of VPA in the patients with a high risk, and the immediate withdrawal of the drug when the initial symptoms present (Zaccara et al., 2007). The risk of fatal liver damage with FBM is one in 26,000 to 34,000, while occasional cases of

hepatotoxicity have been reported with CBZ, PHT, and LTG (Perucca and Gilliam, 2012).

Pancreatitis is another rare, but serious, effect of VPA, with an incidence rate of 1:40,000 in adults. An age of < 20 years, polypharmacy, haemodialysis, and chronic encephalopathy appear to be risk factors for pancreatitis induced by VPA (Zaccara et al., 2007, Perucca and Gilliam, 2012). Rare cases of pancreatitis have also been reported with other AEDs (Zaccara et al., 2007).

1.4.2.4 Other reactions

There are a number of other idiosyncratic reactions related to AEDs, such as CNS reactions, systemic lupus erythematosus, and ocular reactions.

Encephalopathy caused by VPA, which may range from confusion to lethargy and coma; PHT-induced dyskinesia (abnormal involuntary muscle movement); and non-epileptic myoclonus induced by PGB and GBP are examples of unusual idiosyncratic CNS effects of AEDs (Zaccara et al., 2007).

Systemic lupus erythematosus has been reported with a number of AEDs, including CBZ, and with less incidence, VPA, PHT, ESM, and LTG (Zaccara et al., 2007).

In rare cases, TPM can cause a number of ocular adverse reactions, such as acute angle-closure glaucoma, of which 81 cases were reported up to 2002. Blurry vision is the usual symptom of this condition, and such reactions are reversible on immediate discontinuation of TPM. The sulfonamide part of TPM appears to be responsible for this reaction (Fraunfelder et al., 2004).

In summary, the Type B reactions of AEDs are arguably the most concerning adverse effects associated with AED use. Apart from mild skin rash, these idiosyncratic reactions are often rare, but life threatening, and are reported more often with the old AEDs. Table 1-7 demonstrates some serious idiosyncratic reactions associated with individual AED

Table 1-7. A selection of serious idiosyncratic reactions associated with some antiepileptic drugs

	SJS/TEN/ DRESS	Aplastic anaemia	Agranulocytosis	Hepatotoxicity	Pancreatitis	SLE	Other
Phenobarbital	++	+	+	+	0	+	
Phenytoin	++	+	+	+	0	+	
Ethosuximide	+	+	+	+	0	+	
Carbamazepine	++	+	++	+	0	+	
Valproate	+	0	0	++	++	+	Thrombocytopenia, hyperammonemia
Lamotrigine	++		+	+	0	0	Aseptic meningitis
Felbamate	+	++	++	++	+	+	
Topiramate	+	0	0	0	0	0	Angle closure glaucoma, oligohidrosis, hyperthermia
Tiagabine	+	0	0	0	0	0	Stupor, non-convulsive status epilepticus
Oxcarbazepine	+	+	+	0	0	0	
Levetiracetam	0	0	0	0	0	0	Thrombocytopenia
Zonisamide	+	0	+	0	0	0	Hyperthermia, oligohydrosis
Eslicarbazepine acetate	+	0	0	0	0	0	

Key: 0: no reported cases, +: occasional reported cases, ++: high risk. SJS: Stevens–Johnson syndrome, TEN: toxic epidermal necrolysis, DRESS: drug-related rash with eosinophilia and systemic symptoms, SLE: systemic lupus erythematosus. This table based on data obtained from (Ibanez et al., 2005, Handoko et al., 2006, Pellock et al., 2006, Zaccara et al., 2007, Perucca and Gilliam, 2012, Brodie, 2017b)

1.4.3 Type C effects

Type C reactions are chronic effects that result from cumulative drug use. These effects progress slowly and complete manifestation appears after a long-term exposure of between a few months and several years. Although most of these effects disappear following the discontinuation of AEDs, others can be irreversible (Perucca and Meador, 2005).

The known long-term effects of the enzyme induction of some AEDs, particularly old generation AEDs, can cause a number of chronic reactions, such as osteoporosis and osteomalacia, sexual dysfunction, and increased cardiovascular risk (Brodie, 2017b). But for other chronic effects, the underlying mechanisms are not fully understood, as in gingival hyperplasia, induced by PHT (Perucca and Meador, 2005).

Type C effects of AEDs include changes in bodyweight, abnormalities in bone health, reproductive disorders, visual field loss, cosmetic side effects, renal and electrolytes disturbances, and atherosclerosis and cardiovascular risks.

1.4.3.1 Changes in bodyweight

This is a classic Type C effect, which can increase morbidity, impair self-esteem, and lead to a poor adherence to AEDs, or to the discontinuation of treatment (Perucca and Gilliam, 2012). AEDs have different effects on bodyweight, some of which are associated with weight gain, and some with weight loss, while others have a neutral effect on bodyweight (Figure 1-4).

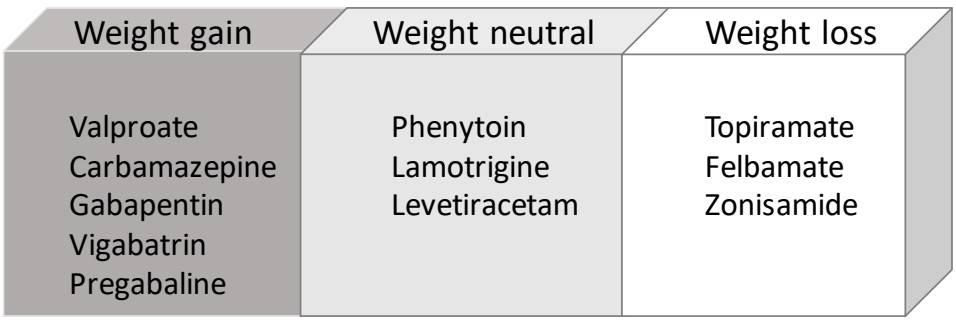


Figure 1-4. The effect of some antiepileptic drugs on body weight

Weight gain is a common adverse cosmetic effect associated with a number of AEDs. The underlying mechanisms are poorly understood, and vary among different AEDs. Several mechanisms have been suggested: first, a competition between the binding of AEDs and long chain fatty acids increases the availability of fatty acids, which consequently stimulates insulin production. Hyperinsulinemia causes a decrease in blood glucose level, which consequently stimulates eating, and increases hunger through its effect on the hypothalamus. Another possible explanation is that AEDs enhance GABA-neurotransmitters that increase appetite and decrease energy expenditure. Furthermore, abnormal thirst associated with some AED therapy may increase the intake of energy-rich beverages, and therefore increase weight gain (Jallon and Picard, 2001).

The AEDs associated with weigh gain are VPA, GBP, VGB, PGB, and to a lesser extent, CBZ (Ben-Menachem, 2007).

An increase in body weight can disturb general health, with a possible increase in the risk of cardiovascular diseases, Type 2 diabetes mellitus, hyperlipidaemia, and some cancers (Ben-Menachem, 2007, Perucca and Gilliam, 2012). Of note is the fact that enzyme-inducing AEDs have been found to increase the risk of cardiovascular disease independently of weight gain (Perucca and Gilliam, 2012, Brodie, 2017b). In addition to weight gain, VPA can cause several endocrine dysfunctions in women, such as hyperandrogenism, polycystic ovary symptoms, and menstrual disorders. It has been proposed that obesity-induced insulin resistance, and hyperinsulinemia, underlie these endocrine disorders (Ben-Menachem, 2007).

The AEDs associated with weight loss are TPM, FBM, and ZNS (Ben-Menachem, 2007). Although possibly helpful in obese or overweight patients, weight loss can be a problem for nutritionally susceptible individuals (Perucca and Gilliam, 2012), therefore it is important to monitor the bodyweight of patients at every visit.

The AEDs that appear to be weight neutral are PHT, LTG, and LEV, based on clinical experience and clinical study (Ben-Menachem, 2007).

1.4.3.2 Abnormalities in bone health

Epilepsy patients treated with AEDs are at increased risk of fracture and abnormalities in bone health (Pack, 2011). Consistent evidence has suggested that the enzyme-inducing AEDs, PHT, PB, and PRM, are highly associated with a lowered active vitamin D metabolite, and low bone mineral density, while studies have produced conflicting results for CBZ, VPA, and LTG. OXC is also an enzyme inducer at a high dose, and has been observed to reduce bone health in adults and children (Kim et al., 2007, Pack et al., 2008, Pack, 2011). It is therefore important to optimise calcium and vitamin D intake for all epilepsy patients treated with AEDs.

1.4.3.3 Reproductive dysfunction

There is a complex interaction between epilepsy, AEDs, and the reproductive system. Low fertility, and reproductive endocrine disorders in both men and women with epilepsy are more common than in the general population due to epilepsy per se, and to the use of AEDs (Isojarvi et al., 2005).

The enzyme-inducing AEDs, PB, PHT, and CBZ, increase serum sex hormone-binding globulin (SHBG) concentrations in both men and women with epilepsy. This increase gradually leads to decrease testosterone and oestradiol bioactivity, which consequently causes impotence in men, and menstrual disorders in women, and therefore decreased fertility (Isojarvi et al., 2005).

As previously described, VPA is known to cause reproductive endocrine dysfunction in women, which is usually associated with weight gain. In men, VPA also increases serum androgen levels. However, the clinical significance of endocrine changes in men is unknown. In low doses, OXC has no effect on the level of reproductive hormones in men, but it may have an effect in high doses, and may increase SHBG levels (Rattya et al., 2001).

LTG has demonstrated better outcomes than enzyme-inducing AEDs with regards to sexual function and reproductive hormone levels in men. The hormonal effects of other new AEDs have not been studied (Isojarvi et al., 2005).

1.4.3.4 Visual field loss with vigabatrin

VGB was approved in 1989 in the UK as adjuvant therapy for adult patients with focal epilepsy. Nine years later, the first cases of VGB-induced irreversible bilateral concentric visual field defects were noted (Eke et al., 1997).

This defect is a common chronic side effect. A systematic review of 32 studies revealed that 44% (n=738/1678) of patients experienced visual field loss following exposure to VGB therapy, with a relative risk of 4 (95% CI 2.9–5.5) (Maguire et al., 2010). This study concluded that the prevalence of this defect was lower in children compared to adult (34% vs. 52%), suggesting that risk factors include older age and cumulative doses of VGB.

Interestingly, many affected patients are unaware of this visual defect, as they simply adjust their head to compensate for any restriction in vision (Brodie, 2017b). Nevertheless, this adverse effect has substantially limited the use of VGB, which should therefore be reserved as last option for refractory epilepsy patients, and regular visual field examinations may be required (Maguire et al., 2010).

1.4.3.5 Cosmetic adverse effects

AEDs can cause several cosmetically undesirable effects, such as bodyweight changes, hair problems, acne, oligohydrosis, blue skin discoloration, and gingival enlargement. These adverse effects are common, accounting for 42% of reported adverse effects of AEDs, and impose a negative impact on drug adherence and the economic burden, the estimated annual cost of which per patient is €2,800 (De Kinderen et al., 2014, Chen et al., 2015). Being of the female gender, and possessing a history of previous cosmetic adverse effect seem to be risk factors for this category of adverse effects (Chen et al., 2015). Changes in bodyweight was described previously, therefore this section focuses on hair- and skin-related cosmetic adverse effects.

VPA can cause alopecia, or hair changes such as hair thinning or change of colour, in 8 to 12% of patients. VPA-induced alopecia is typically mild and transient, and hair regrowth can occur without ceasing the use of VPA, although the hair can grow back curly. The hair-related problems induced by VPA are reversible on drug discontinuation (Tisdale and Miller, 2010, Gaitatzis and Sander, 2013). The

underlying mechanisms of VPA-induced alopecia remain unclear, although lowered zinc levels in hair and blood, and reduced biotindase activity induced by VPA may lead to hair loss. Meanwhile, biotin supplements have been found to ameliorate VPA-induced alopecia (Chen et al., 2015). CBZ and LTG can also cause hair loss, typically 2 to 3 months after treatment initiation (Gaitatzis and Sander, 2013).

Additionally, VPA can cause hirsutism and acne in women, as consequences of hyperandrogenism, whereas PHT can cause hypertrichosis and acne in both sexes. Abnormal extra hair growth usually appears on the trunk and face, and can continue for a year or more after ceasing use of the medication (Gaitatzis and Sander, 2013). Both hirsutism and hypertrichosis are conditions of abnormal excess hair growth, but hirsutism presents only in women, due to hyperandrogenism, with the extra hair usually growing on the face and body in a 'male-like' pattern. While hypertrichosis can occur in both sexes, unrelated to androgen, hair can grow on any part of the body in excess to the amount that normally appears in individuals of the same sex, age, and race (Tisdale and Miller, 2010).

Oligohydrosis, or reduction in sweating, and hyperthermia can present in a small number of patients taking ZNS, and to a lesser extent TPM. This effect is reversible upon discontinuation of ZNS and TPM (Gaitatzis and Sander, 2013, Brodie, 2017b). Although the underlying mechanism of oligohyrosis is not fully understood, the effect of carbonic anhydrase inhibition induced by ZNS and TPM on sweat glands may be involved. Hyperthermia resulting from oligohydrosis occurs mainly in children in hot climates, and it is therefore important to ensure that the children remain cool and well hydrated during the summer months (Low et al., 2004).

A blue discolouration of the skin, nails, lips, mucous membrane, and most importantly, the retina, can be produced by chronic use of RTG (Figure 1-5), the manufacturer of which consequently discontinued production in June 2017. This effect is dose- and time-related, and is probably reversible following the withdrawal of RTG. It may result from the accumulation of RTG's dimers, and/or its *N*-acetyl metabolite, in the tissues (Brodie, 2017b).

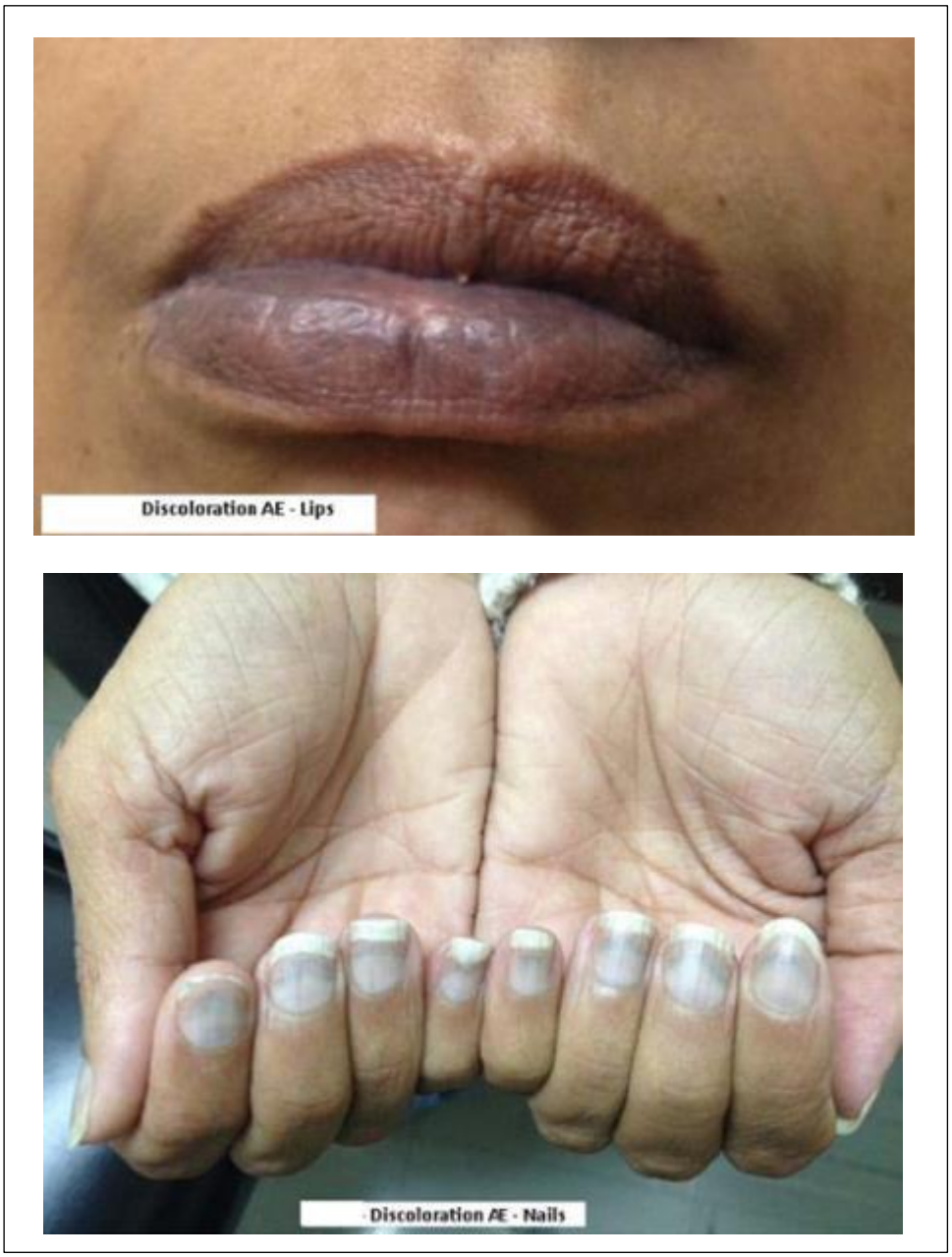


Figure 1-5. Blue discolouration adverse effect induced by retigabine (Food and Drug Adminstration, 2013)

Gum hyperplasia is a commonly reported chronic side effect of PHT (Figure 1-6). Approximately 40 to 50% of patients taking PHT experience gingival as early as 3 months after treatment introduction. The underlie mechanism is multifactorial, and is not fully understood. Low serum folate is substantially associated with the severity and early onset of PTH-induced gum hyperplasia. PHT may also stimulate inflammation in patients with chronic gingivitis, leading to an abnormal excess of fibroblast proliferation and collagen deposition in the gingiva. Genetic predisposition is likely to be involved, since the growth of fibroblast is sensitive

to PHT in these individuals. The severity of the gingival enlargement of PHT has been found to be dose-dependent, although the data concerning this correlation is contradictory. The rate of this effect appears to be greater in children, and is similar in both genders. Poor dental care is a risk factor for gum hyperplasia in patients taking PHT, therefore it is important to maintain good oral hygiene. Additionally, long-term use of PHT may result in facial coarsening due to generalised skull thickening; this chronic dysmorphic change related to PHT appears to persist after its withdrawal (Gaitatzis and Sander, 2013, Chen et al., 2015).

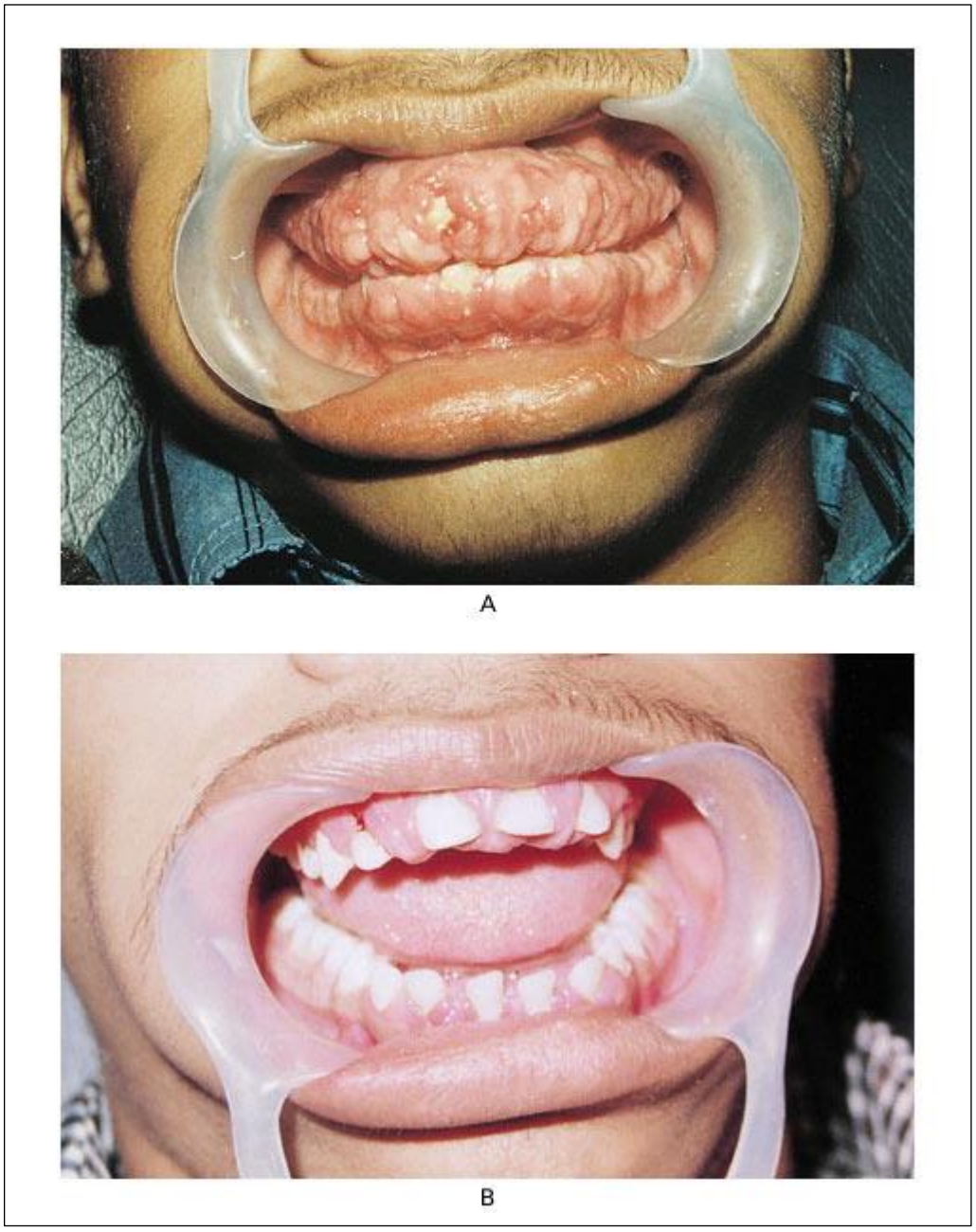


Figure 1-6. Gingival hyperplasia induced by phenytoin (A)
Improvement after 3 months of phenytoin discontinuation (B). Reproduced with permission from (Sharma and Dasroy 2000), Copyright Massachusetts Medical Society.

1.4.3.6 Renal and electrolytes disturbances

Renal calculi can occur as a result of TPM and ZNS chronic therapy in approximately 1 to 2% of patients (Wroe, 2007, Gaitatzis and Sander, 2013), probably due to the drugs' inhibitory effects on carbonic anhydrase, and their potential for mild metabolic acidosis (Gaitatzis and Sander, 2013, Brodie, 2017b). However, the evidence is insufficient to conclude whether the combination therapy of TPM with ZNS increases the risk of kidney stones. Personal or family history of renal stones appears to increase the risk of developing kidney calculi induced by ZNS, and adequate hydration can minimise the risk of stone formation (Wroe, 2007).

Dose-dependent hyponatremia (sodium <135 mg/l) can occur with OXC, CBZ, and ESL acetate (Gaitatzis and Sander, 2013). This adverse effect is more common and severe with OXC than with CBZ (30% vs. 13.5% of patients, respectively) (Dong et al., 2005). Old age is a risk factor for hyponatremia (Dong et al., 2005), and concomitant diuretic and selective serotonin reuptake inhibitors can deteriorate AED-induced hyponatremia (Gaitatzis and Sander, 2013, Brodie, 2017b), since they have similar effects. The majority of patients with mild hyponatremia (sodium 125-135 mg/l) remain asymptomatic, and often require no intervention, but the dose should be reduced when the serum sodium level falls below this level (Brodie, 2017b).

Some bladder symptoms, such as hesitation, dysuria, and less often, urinary retention, have been documented with RTG use (Brickel et al., 2012).

1.4.3.7 Atherosclerosis and cardiovascular risks

The chronic use of enzyme-inducing AEDs can cause metabolic changes, and increase the risk of atherosclerosis in epilepsy patients at any age. The underlying mechanisms include the stimulation of cytochrome P450, which plays a significant role in cholesterol synthesis, as well as an increase in homocysteine (Belcastro et al., 2010, Chuang et al., 2012, Gaitatzis and Sander, 2013). VPA can cause metabolic dysfunctions including hyperinsulinemia, dyslipidaemia, hyperhomocysteinemia, obesity, and hypertension (Chuang et al., 2012). The lipid abnormalities induced by AEDs are hypertriglyceridemia, low high-density lipoprotein-cholesterol, and occasionally high total cholesterol. Switching to LTG

or LEV treatments can reverse, or ameliorate, the metabolic dysfunctions induced by VPA and enzyme-inducing AEDs (Belcastro et al., 2010, Chuang et al., 2012).

Hyperhomocysteinemia is a contributor to atherosclerosis, and can increase the risk of cardiovascular and cerebrovascular diseases, and even brain atrophy and dementia. Hyperhomocysteinemia is often associated with low folate levels, and has consistently been reported in the chronic use of VPA and enzyme inducer AEDs including OXC and TPM, which are considered weak enzyme inducers. The risk of atherosclerosis is associated with the duration of AED therapy. In contrast, the chronic use of LTG therapy is not associated with hyperhomocysteinemia, or an increased risk of atherosclerosis (Belcastro et al., 2010, Chuang et al., 2012).

1.4.4 Type D effects

This category includes carcinogenic and teratogenic effects, which are delayed and irreversible (Perucca and Gilliam, 2012).

Adverse drug effects on the foetus can present as foetal loss, intrauterine growth retardation, congenital malformations, impaired postnatal development, and behavioural problems (Tomson and Battino, 2012).

1.4.4.1 Carcinogenic effects

PHT and PB have consistently demonstrated carcinogenic effects in animals, however, to date, there is no clear evidence of the carcinogenic effect of AEDs in humans (Gaitatzis and Sander, 2013).

In rare cases, PHT can cause pseudolymphoma, a benign condition that mimics clinically and histologically malignant lymphoma, and which disappears on treatment discontinuation. Misdiagnosis is not uncommon, and can lead to unnecessary chemotherapy. Occasional cases of pseudolymphoma have also been documented with other AEDs (Perucca and Gilliam, 2012).

1.4.4.2 Major congenital malformations

Prenatal exposure to AEDs, particularly in the first trimester, is associated with a greater risk of major congenital malformations; the risk is approximately three

times that in the children of healthy women (Perucca and Gilliam, 2012, Tomson and Battino, 2012).

However, the magnitude of the risk differs for each AED, Figure 1-7 shows the rates of major congenital malformations for different monotherapies from different American and European pregnancy registries. The rates are greatest for VPA, ranging from 4.7 to 9.7%, while PB is also associated with a high risk of birth defects of up to 7.4%. However, the risk is smaller for PHT (2.9 to 6.7%), and CBZ (2.6 to 5.6%). Among the newer AEDs, LTG is the only agent for which sufficient exposed cases have been enrolled in pregnancy registries in order to allow a firm conclusion, demonstrating that LTG is associated with a low risk of teratogenicity (1.9 to 3.4%). The number of pregnant women on LEV, OXC, and TPM, have been too low to permit reasonable conclusions, nevertheless the current evidence suggests that LEV and OXC are associated with a low risk of teratogenicity, but that TPM is a potential teratogen (up to 7.7%) (Hernandez-Diaz et al., 2012, Tomson and Battino, 2012, Tomson et al., 2015).

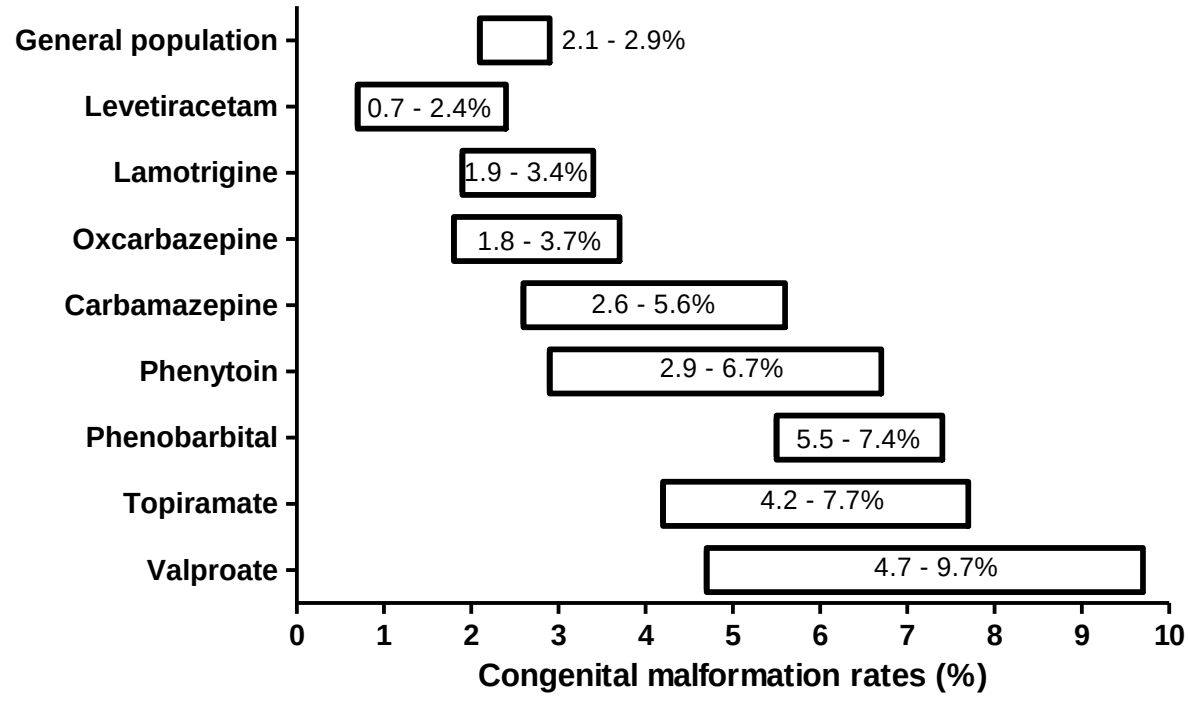


Figure 1-7. Major congenital malformation rates of different monotherapies from different European and American pregnancy registries (Tomson et al., 2015)

The specific malformations vary for each AED. VPA has been found to increase the risk of several birth defects, including neuronal tube defects, cardiac defects, oral clefts, hypospadias, which is the unusual location of the urinary opening in males, polydactyly, which is extra fingers or toes, and craniosynostosis, or abnormal skull growth. Meanwhile, PB is associated with cardiac defects and oral defects; PHT with digit hypoplasia, or underdevelopment of fingers and toes; TPM and LTG with oral clefts; and CBZ with neuronal tube defects (Hernandez-Diaz et al., 2012, Tomson and Battino, 2012).

Certain factors appear to increase the AED-related risk of major congenital malformations. Polytherapy of AEDs is consistently associated with higher rates than monotherapy, however, the risk depends on the involvement of specific AEDs in combination, rather than only the number of AEDs taken, with rates often increasing in polytherapy that includes VPA (Tomson and Battino, 2012). Risk of birth defects is also consistently correlated with the dose of VPA; generally, a higher risk has been found at a daily dosage (>600-1500 mg). Likewise, the risk has been found to be dose related for CBZ (>400-1000 mg), and LTG (>200-400 mg) in some registries (Tomson et al., 2015). Furthermore, it has been found that malformation in a previous child is associated with a high risk of having further children with birth defects; this may support the hypothesis that genetic factors may influence the AED-related risk of teratogenicity (Campbell et al., 2013).

With regard to the potential mechanism of malformations, enzyme-inducing AEDs decrease serum and red blood cell folic acid levels by increasing the folic acid metabolism. While VPA-induced teratogenicity is not fully understood, it perhaps interferes with angiogenesis in uterus. Additionally, VPA appears to interfere with the folate metabolism by inhibiting glutamate formyl transferase, and reducing folinic acid production. Folic acid is critical for the biosynthesis of DNA and RNA. In women with epilepsy, low serum and red blood cell folate levels are associated with an increased incidence of spontaneous abortion and malformation (Morrell, 2002). Folate supplementation is often recommended in order to reduce the risk of birth defects, such as neural tube defects, however there is no evidence of a reduction in the teratogenicity risk associated with VPA exposure (Tomson et al., 2015).

1.4.4.3 Neurodevelopmental delay in offspring

Increasing evidence has suggested an association between prenatal exposure to AEDs and an increased risk of neurodevelopmental impairment in the child. The prospective "Neurodevelopmental Effects of Antiepileptic Drugs" (NEAD) study compared the cognitive outcomes at age six of children exposed to VPA, CBZ, LTG, and PHT monotherapy. It suggests that the intelligence quotient (IQ) was 8 to 11 points lower in children exposed to VPA, compared with children exposed to other AEDs. These IQ reductions were sufficient to affect education and occupational outcomes in later life. Memory and verbal abilities were also lower in the VPA-exposed group than in other AED exposure. The cognitive impairment was dose-dependent for VPA (Meador et al., 2013); however, this study did not include an unexposed control group.

Similarly, a recent Cochrane Review of 22 prospective cohort studies, and six registry-based studies, revealed a significant reduction of cognitive function in VPA-exposed children, compared with the children of mothers without epilepsy, the children of mothers with untreated epilepsy, and the children of mothers treated with other AEDs, such as CBZ, LTG, and PHT. Furthermore, dose dependence for VPA was reported in six studies included in the review, and an increased cognitive impairment was associated with children exposed to a dosage >800-1000mg/day. No convincing evidence of dose dependence exists for other AEDs (Bromley et al., 2014).

Aforementioned review also concluded that insufficient data exist concerning the newer AEDs. For instance, there has been no systematic review regarding the effect of prenatal exposure to TPM on the cognitive development of exposed children (Bromley et al., 2014). The only study evaluating the effects of LEV concerned the development of exposed children at age three, and indicated that the LEV-exposed children did not differ from the unexposed control children, but achieved higher scores in language and motor development than the VPA-exposed children (Shallcross et al., 2014). However, there was a low and varied age at assessment in this study, and fewer children were exposed to VPA than to LEV (44 vs. 131).

1.4.4.4 Adverse behavioural effects in offspring

It has been suggested that the maternal use of AEDs during pregnancy affects the behaviour of the exposed child. The aforementioned prospective NEAD study also examined the effects of foetal exposure to the AEDs CBZ, LTG, PHT, and VPA on adaptive and emotional/behavioural functioning in 195 six-year-old children. The adjusted mean scores for the four AED groups were in the low average to, average range for the parent ratings of adaptive functioning, and for the parent and teacher ratings of emotional/behavioural functioning. The VPA-exposed children possessed significantly lower adaptive functioning than the LTG and PHT exposed groups. These effects were dose-dependent for VPA and PHT. Furthermore, the VPA-exposed children were also recorded by their parents as possessing significantly more atypical behaviours and inattention than those in the LTG and PHT groups. Based on the parent and teacher ratings of attention span and hyperactivity, the children of mothers who took VPA during their pregnancy were at a significantly greater risk of a diagnosis of attention-deficit/hyperactivity disorder (ADHD) (Cohen et al., 2013).

It has been found that the maternal use of VPA during pregnancy is associated with a significantly increased risk of autism spectrum disorders, and childhood autism in exposed children. After adjusting for maternal epilepsy, the children who were exposed to VPA in utero were at a 1.7-fold risk of autism spectrum, and a 2.9-fold risk of childhood autism, compared with children not exposed to VPA (Christensen et al., 2013).

VPA is associated with the greatest teratogenicity risk, including postnatal adverse cognitive and behavioural effects. Consequently, the Medicines and Healthcare Products Regulation Agency (2015) in the UK stated that “in girls and women of childbearing potential, VPA should be initiated and supervised by a specialist and only when other medications have not been tolerated or have been found to be ineffective”. A number of recommendations have been proposed for the use of VPA in female patients of childbearing age (Tomson et al., 2015):

1. Avoid VPA in young women whenever possible;

2. Share the decision to choose VPA with patients;

3. Risks and benefits of VPA and alternatives should be assessed by an epilepsy specialist;

4. VPA should not be prescribed as a first-line therapy for focal epilepsy;

5. VPA may be prescribed as a first-line therapy for some idiopathic generalised syndromes associated with tonic–clonic seizures;

6. VPA may be considered in women with significant intellectual or physical disabilities, who are unlikely to become pregnant; and

7. Girls and young women who are currently on VPA therapy require regular follow-up in order to review the treatment.

Since these adverse effects are dose-dependent, the key recommendation is to use the lowest effective dose of VPA before pregnancy (Tomson et al., 2015).

1.4.5 Type E effects

Type E adverse drug interactions constitute a clinically important aspect of AEDs, since many AEDs have a narrow therapeutic range (minor alterations in pharmacokinetics causes toxicity or low efficacy), and some AEDs such as PHT, CBZ, and VPA exhibit non-linear pharmacokinetics. Furthermore, many AEDs induce or inhibit drug-metabolising enzyme activities, and most AEDs are metabolised by the same enzymes. Moreover, intractable epilepsy patients usually require two or more co-prescribed AEDs that may interact with one other. AEDs can also interact with other concomitant medications (Perucca and Gilliam, 2012).

These involve pharmacokinetic or pharmacodynamic drug interactions. Pharmacokinetic interactions may change the absorption, distribution, or metabolism, while pharmacodynamic interactions can be synergistic or antagonistic therapeutic effects (Zaccara and Perucca, 2014).

1.4.5.1 Pharmacokinetic drug interactions

Pharmacokinetic interactions are more frequent with old AEDs, since they can affect the activity of drug-metabolising enzymes. CBZ, PHT, PB, and PRM are

strong enzyme inducers, and thus decrease the serum levels and efficacy of several drug classes, including oral contraceptives, calcium antagonists, oral anticoagulants, antibiotics, steroids, immunosuppressants, antineoplastic drugs, antidepressants, and other AEDs (Johannessen and Landmark, 2010, Perucca and Gilliam, 2012, Zaccara and Perucca, 2014).

In contrast, enzyme inhibition decreases the metabolic elimination of the substrates, and thus increases serum levels that may lead to toxic effects. Enzyme inhibition results most commonly from the use of VPA. Two important interactions include the inhibition of PB and LTG by VPA. VPA can increase PB concentration by 57 to 81%. The serum concentrations of LTG are also increased two- to three fold by VPA, which has major clinical significance. LTG should be introduced at much smaller doses, and up-titrated slower in patients with concomitant VPA, in order to reduce the risk of skin rash. The maintenance dosage of LTG is smaller when it is combined with VPA. There is also an increased risk of the CNS adverse effects of LTG if VPA is added, and thus the LTG dosage should be reduced by 50% when the VPA dosage reaches 500mg/day; the LTG dose should be also adjusted when VPA is discontinued (Johannessen and Landmark, 2010, Perucca and Gilliam, 2012, Zaccara and Perucca, 2014).

Despite the improved pharmacokinetic profiles of new AEDs, they are not completely free from clinically relevant interactions. LTG, OXC, ESL acetate, TPM (at dose >200mg/day), and PER (at dose 12mg/day) can reduce the serum concentration of some oral contraceptives. OXC, which is a weak enzyme inducer, can also decrease the serum concentration of some calcium channel blockers, such as felodipine (Johannessen and Landmark, 2010, Plosker, 2012, Zaccara and Perucca, 2014).

Because most AEDs are substrates of drug-metabolising enzymes, they are susceptible to enzyme induction and inhibition. For instance, the serum concentration of CBZ can be increased by some antibiotics, such as erythromycin, and the serum concentration of LTG can be reduced by contraceptives containing oestrogen (Zaccara and Perucca, 2014).

GBP and PGB have no clinically relevant drug interactions, as they neither affect nor are metabolised by the hepatic cytochrome P system (Johannessen and Landmark, 2010, Zaccara and Perucca, 2014).

1.4.5.2 Pharmacodynamic drug interactions

The combination of two or more AEDs may cause shared interactions on the site of action, which may consequently affect their efficacy and tolerability. However, some of these interactions can have potentially favourable effects, and the best established pharmacodynamic interaction is that occurring between VPA and LTG. Several studies have suggested a synergistic therapeutic effect of the combination of these two AEDs on the seizure control of different seizure types, since doses of VPA and LTG in combination are lower than their doses when they were used alone, or are combined with other AEDs (Stephen et al., 2012). However, as previously mentioned, this combination requires dosage adjustments due to the significant pharmacokinetic interactions between VPA and LTG. Other possibly beneficial pharmacodynamic interactions have been indicated between VPA and ESM on absence seizures, and between VPA and CBZ on focal seizures (Zaccara and Perucca, 2014). These observations may suggest that additive or synergistic efficacy is included in combinations of AEDs with different mechanisms of action.

In contrast, adverse pharmacodynamic drug interactions may result from the co-prescribing of AEDs possessing the same main mechanism of action. In experimental and clinical studies, the combinations of sodium channel blocking AEDs have been shown to potentiate their individual neurotoxic effects. Indeed, combinations of CBZ with different sodium channel blocking AEDs, such as OXC, ESL acetate, LTG, and LCM, are associated with increased neurotoxicity (Zaccara and Perucca, 2014).

1.5 Safety profile of individual antiepileptic drugs

The safety profiles of 21 AEDs are summarised in chronological order in Table 1-8, excluding PRM, stiripentol, rufinamide, and FBM. PRM is a prodrug of PB and has similar tolerability profiles; the use of stiripentol and rufinamide is limited to children with Dravet syndrome and Lennox-Gastaut syndrome, respectively; and FBM is not licensed in the UK.

Table 1-8. Safety profile of antiepileptic drugs

	Type A	Type B	Type C	Type D	Type E
Phenobarbital	Sedation, dizziness, cognitive impairment, depression, irritability, aggression, distractibility.	Skin rash, SJS, TEN, DRESS, hepatotoxicity, blood dyscrasias.	Frozen shoulder, decreased bone mineral density, folate deficiency, decreased libido.	Birth defects.	Pharmacokinetic: It is an enzyme inducer and can reduce the serum levels of concurrent drugs. Its metabolism is susceptible to enzyme inhibition. Pharmacodynamic: Concomitant CNS depressing agents (e.g. alcohol) can potentiate adverse effects.
Phenytoin	Fatigue, nystagmus, ataxia, diplopia, dysarthria, drowsiness.	Skin rash, SJS, hepatotoxicity, aplastic anaemia, SLE.	Hirsutism, gingival hypertrophy, acne, facial coarsening, osteopenia, folate deficiency, peripheral neuropathy, cerebellar atrophy.	Pseudo-lymphoma, birth defects (low risk).	Pharmacokinetic: It has non-linear pharmacokinetic and its use needs phenytoin assay. It is an enzyme inducer, and can reduce the serum levels of concurrent drugs. Its metabolism is susceptible to enzyme induction and inhibition. Pharmacodynamic: Concomitant CNS depressing agents (e.g. alcohol) can potentiate adverse effects.
Ethosuximide	Nausea, abdominal discomfort, vomiting, diarrhoea, drowsiness, dizziness, ataxia, headache, hiccoughs, psychosis, irritability, aggression, euphoria.	Skin rash, SJS, aplastic anaemia, SLE, agranulocytosis, hepatotoxicity.	-	Unknown.	Pharmacokinetic: Its metabolism is susceptible to enzyme induction and inhibition.

Table 1-8. Safety profile of antiepileptic drugs

	Type A	Type B	Type C	Type D	Type E
Carbamazepine	Drowsiness, dizziness, unsteadiness, vertigo, ataxia, diplopia.	Skin rash, SJS, TEN, agranulocytosis, aplastic anaemia, dyskinesia.	Decreased bone mineral density, folate deficiency, weight gain, hyponatremia.	Birth defects (low risk).	Pharmacokinetic: It is an enzyme inducer, and can reduce the serum levels of concurrent drugs. Its metabolism is susceptible to enzyme induction and inhibition. Pharmacodynamic: Concomitant sodium-channel blocking AEDs increase CNS toxicity.
Valproate	Tremor, drowsiness, tiredness, nausea, abdominal discomfort, vomiting.	Hepatotoxicity, pancreatitis, thrombocytopenia, aplastic anaemia, hyperammonemia, encephalopathy.	Weight gain, alopecia, polycystic ovary syndrome, decreased bone mineral density.	Birth defects (high risk), neurodevelop-menal delay and behavioural disorders in the offspring.	Pharmacokinetic: It is an enzyme inhibitor, and can increase the toxicity of concomitant drugs. Its metabolism is susceptible to enzyme induction and inhibition.
Benzodiazepines	Fatigue, tiredness, drowsiness, lethargy, dizziness, ataxia, cognitive impairment, hyperactivity, irritability, aggression, depression.	-	-	Unknown.	Pharmacokinetic: Their metabolism is susceptible to enzyme induction and inhibition. Pharmacodynamic: Concomitant CNS depressing agents (e.g. alcohol) can potentiate adverse effects.

Table 1-8. Safety profile of antiepileptic drugs

	Type A	Type B	Type C	Type D	Type E
Vigabatrin	Drowsiness, fatigue, dizziness, ataxia, agitation, depression, psychosis, agitation, confusion.	-	Visual field loss, weight gain.	Unknown.	Pharmacokinetic: It can reduce the serum levels of phenytoin.
Lamotrigine	Dizziness, ataxia, tremor, diplopia, insomnia, headache, nausea, vomiting.	Skin rash, SJS, TEN, aseptic meningitis, agranulocytosis, hepatotoxicity.	Nothing major reported to date.	Birth defects (low risk).	Pharmacokinetic: It can decrease the serum levels of levonorgestrel. Its metabolism is susceptible to enzyme induction and inhibition. Pharmacodynamic: Concomitant valproate and sodium-channel blocking AEDs can increase CNS toxicity.
Gabapentin	Drowsiness, fatigue, dizziness, vertigo, ataxia, nystagmus, diplopia, nausea, hyperactivity, irritability, aggression.	Nothing major reported to date	Weight gain	Not a teratogen	No important drug interactions.
Topiramate	Cognitive impairment, concentration/attention difficulties, speech problems, drowsiness, fatigue, dizziness, depression, aggression, psychosis, anorexia, paraesthesiae, headache, ataxia.	Angle closure glaucoma, oligohidrosis, hypertermia.	Weight loss, nephrolithiasis , glaucoma.	Birth defects	Pharmacokinetic: At doses >200 mg/day, it can decrease the serum levels of serum levels of ethynylestradiol. Its metabolism is susceptible to enzyme induction.

Table 1-8. Safety profile of antiepileptic drugs

	Type A	Type B	Type C	Type D	Type E
Tiagabine	Dizziness, unsteadiness, nausea, asthenia, nervousness, light-headedness, ataxia, tremor, somnolence, irritability, aggression, depression, psychosis.	Stupor, non-convulsive status epilepticus.	Nothing major.	Unknown (probably not a teratogen).	Pharmacokinetic: Its metabolism is susceptible to enzyme induction.
Oxcarbazepine	Drowsiness, dizziness, unsteadiness, ataxia, blurred vision, diplopia, nausea, vomiting, headache.	Skin rash, including severe mucocutaneous reactions (SJS, TEN), aplastic anaemia, granulocytosis.	Hyponatremia.	Birth defects (probably low risk; limited evidence).	Pharmacokinetic: It can increase serum phenytoin levels. It is a weak enzyme inducer, and can decrease the serum levels of oral contraceptives and calcium antagonist (felodipine). Its metabolism is susceptible to enzyme induction. Pharmacodynamic: Concomitant sodium-channel blocking AEDs can increase CNS toxicity.
Levetiracetam	Drowsiness, fatigue, dizziness, ataxia, irritability, aggression, depression, psychosis, headache, nausea, vomiting.	Thrombocytopenia.	Nothing major reported to date.	Not a teratogen (limited evidence).	Enzyme-inducing AEDs can moderately decrease its serum concentrations.

Table 1-8. Safety profile of antiepileptic drugs

	Type A	Type B	Type C	Type D	Type E
Pregabalin	Dizziness, vertigo, abnormal coordination, ataxia, blurred vision, diplopia, drowsiness, fatigue, oedema, headache, tremor, constipation.	No major reaction.	Weight gain, gynaecomastia, erectile dysfunction.	Unknown (probably not a teratogen).	No important drug interaction.
Zonisamide	Drowsiness, fatigue, dizziness, concentration/attention difficulties, irritability, agitation, depression, psychosis, anorexia, nausea, vomiting, anorexia.	Oligohidrosis, hyperthermia, skin rash, including severe mucocutaneous reactions.	Weight loss, nephrolithiasis.	Unknown (no evidence that it is a teratogen).	Pharmacokinetic: Its metabolism is susceptible to enzyme induction.
Lacosamide	Dizziness, unsteadiness, vertigo, ataxia, blurred vision, diplopia, nausea, vomiting, headache, tremor.	Skin rash.	Unknown.	Unknown (no evidence that it is a teratogen).	Pharmacokinetic: Its metabolism may be susceptible to enzyme induction. Pharmacodynamic: Concomitant sodium-channel blocking AEDs can increase CNS toxicity.
Eslicarbazepine acetate	Dizziness, vertigo, abnormal coordination, blurred vision, diplopia, nausea, vomiting, headache, drowsiness, fatigue, tremor.	Skin rash, DRESS.	Hyponatremia.	Unknown.	Pharmacokinetic: It is a weak enzyme inducer, and may reduce the serum levels of certain concurrent drugs. Its metabolism may be susceptible to enzyme induction. Pharmacodynamic: Concomitant sodium-channel blocking AEDs may increase CNS toxicity.

Table 1-8. Safety profile of antiepileptic drugs

	Type A	Type B	Type C	Type D	Type E
Retigabine	Drowsiness, fatigue, dizziness, vertigo, blurred vision, diplopia, confusion.	Unknown.	Weight gain, blue discolouration in skin and retina, urinary hesitancy/ retention.	Unknown.	No important drug interaction to date.
Perampanel	Dizziness, somnolence, fatigue, irritability, nausea, falls, anger, hostility, aggression.	-	Weight gain.	Unknown.	At dose 12mg/day, it can reduce the serum concentration of levonorgestrel. Its metabolism may be susceptible to enzyme induction.
Brivaracetam	Dizziness, fatigue, somnolence, nausea, vomiting, depression, insomnia, irritability, anxiety.	-	-	Unknown.	No important drug interaction to date.

Key: SJS: Stevens–Johnson syndrome, TEN: toxic epidermal necrolysis, DRESS: drug-related rash with eosinophilia and systemic symptoms, SLE: systemic lupus erythematosus. This table is based on data obtained from the supplementary appendix of (Perucca and Gilliam, 2012), and from (Brodie, 2017b). Additional information was sourced from other references mentioned in section 1.4. Only important adverse effects listed above, not comprehensive safety profile, considered important by the preceding authors, based on their frequency or severity.

1.6 Summary of the literature review, and rationale for the present study

Epilepsy is the most common chronic neurological disorder. Many established and new AEDs are available, however it is unclear whether the treatment outcomes in epilepsy have changed over the last three decades as a result of the introduction of the 14 new AEDs. Data concerning their safety and efficacy can be obtained primarily from RCTs, however these trials do not capture other important factors such as teratogenic effects, rare idiosyncratic reactions, chronic adverse effects, enzyme-induction effects, and the potential for drug interactions, therefore further data regarding their long-term effectiveness and tolerability in everyday clinical practice are required. There is also limited evidence concerning certain predictors of efficacy and tolerability. This thesis therefore seeks to fill the gaps in knowledge listed below.

1.7 Aims of the thesis

This thesis attempts to evaluate the long-term effectiveness of AEDs in routine clinical practice. The following are the three core aims of this thesis.

1. Evaluate the efficacy of AEDs on basis of seizure control at last follow-up. Determinants of pharmacoresistant epilepsy and changes in pharmacological outcomes over the last few decades are also studied.

2. Study the rate and predictors of intolerable adverse effects of AEDs.

3. Compare the retention rates of LTG, VPA, CBZ, and LEV as monotherapy.

1.7.1 Methodologies for answering abovementioned research questions

- Retrospective observational study. This was the methodology of the current study. This method has several advantages such as low cost, relatively rapid, can include large number of patients, accurate, good to moderate validity, and allows for historical comparisons or trend analysis. The following are potential different methodologies that can be used to address these research questions.

- Prospective observational study using standardised tools for screening some outcomes. For instant, use adverse event profile (AEP) for measuring adverse effects, use Morisky questionnaire to evaluate drug adherence, and use neurological disorder depression inventory for epilepsy for psychiatric screening. The accurate usage of these validated screening approaches can allow better quantification of the outcomes and identification of the populations at a high risk. However, these screening measures, which include checklists and questionnaires, tend to overestimate the prevalence of measured outcome.

- Randomised controlled trial (RCT). Randomisation and control group can overcome the selection bias and confounding issues of observational studies, respectively. Indeed, RCT is the gold standard for comparing drug effectiveness. However, RCTs have some limitations as discussed in the next section.

While comparative RCTs provide evidence of drugs efficacy, observational studies provide insight into their effectiveness in real-life. Clinical trials include a selection of patients who are often young, more intractable, and without comorbidities or concomitant medications, therefore they do not adequately represent the population of epilepsy patients. Whereas real-world studies provided bridge from the results of RCTs to daily clinical practice by including special populations such as elderly, pregnancy, children, and patients with psychiatric comorbidity and intellectual disability, who are often excluded from RCTs (French, 2012, Perucca and Gilliam, 2012).

RCTs are often include small sample size and short duration (often 12 weeks) while epilepsy is a chronic condition and requires a lifelong treatment. Therefore, RCTs not only provide little information about long-term efficacy, they cannot detect the rare and chronic adverse drug reactions (Mohanraj and Brodie, 2003). For instance, FBM-induced aplastic anaemia and VGB-induced visual-field defects were identified during post-marketing phase (Perucca and Gilliam, 2012), and RTG was recently withdrawn from the market because of blue discolouration chronic side effect (Brodie, 2017b). Furthermore, the risk of teratogenicity is generally identified from real-world studies (Perucca and Gilliam, 2012).

Observational studies better reflecting the daily clinical setting where the dose of drug is individualised for each patient based on drug tolerability and efficacy, whereas RCTs usually use fixed doses and rapid titration protocol. Does-related side effects such as tiredness and poor coordination can abate with dose reduction. However, in trials with a rigid dose schedule, does reduction may not be allowable and thus the patients may discontinue drug and not gain efficacy from the drug. These neurotoxic adverse effects along with systemic adverse effects, including gastrointestinal upsets, may also resolve with time. The development of tolerance to initial adverse effects may allow higher doses to be used later (Mohanraj and Brodie, 2003).

Additionally, in observational studies, other non-AED variables influencing the treatment outcomes can be evaluated. For instance, the effect of gender, age, epilepsy type, number and duration of pre-treatment seizures, psychiatric comorbidity, alcohol and recreational drug abuse, and number of prior unsuccessful AEDs can be assessed.

Chapter 2. Methods

In order to achieve the aim and objectives set out in the previous chapter, a large-scale observational study was conducted utilising a paper-based database and pre-specified statistical analysis plan, as explained in the following section.

2.1 Study design

This study was a retrospective single centre clinic-based observational cohort study of patients with new-onset epilepsy from a tertiary care hospital.

2.2 Study population

The presented research involved a cohort of 1,528 consecutive unselected adult patients, who had been first diagnosed with epilepsy and prescribed AED treatment at Glasgow Epilepsy Unit. The patients were referred between 1 July 1982 and 31 Oct 2012. The patients were prospectively managed and followed up until 30 April 2016, or death, with at least a one-year follow-up after initiation of AED treatment. The study cohort included most of patients investigated in three previous analyses in 1999, 2003, and 2008 (Kwan and Brodie, 2000, Mohanraj and Brodie, 2005, Brodie et al., 2012).

2.2.1 Glasgow Epilepsy Unit

The Epilepsy Unit at the Western Infirmary and subsequently at the West Glasgow Ambulatory Care Hospital (WGACH) provides a specialist clinical service for patients with suspected and established seizure disorders, conducts research related to aetiology and pharmacological management of epilepsy, and trains a range of health professionals.

Clinical services for people with epilepsy were set up in 1982. Subsequently data has been collected from every patient using a “pink folder” system including a standard data collection form and investigative protocol. All subsequent information has been collected prospectively. A dedicated telephone line was made available to patients, families, and their primary care physician to facilitate optimal management. Patient data were included in a computer database and in pink folders which were stored in metal cabinets. The appropriate pink folders accompanied the team to every clinic and were available when patients, relatives and general practitioners phoned the Epilepsy Unit. Over the next 34 years, each

new patient was registered in the database and a folder developed for storage. There are currently 8068 pink folders in the system (Brodie, 2017a).

Once the decision was taken to focus the outcome programme on adolescents and adult patients with newly diagnosed epilepsy, a letter was sent to all general practitioners in the West of Scotland offering to review suitable patients reporting a first seizure or with likely untreated epilepsy within a few weeks of referral. A direct line to the Epilepsy Unit office was set up to expedite the review of urgent cases. Most of these patients were sent home with no investigations or follow up arranged. Hence, a direct referral arrangement was established with the Epilepsy Unit, which initially bypassed the patient's general practitioner. Lastly, the epilepsy nurse specialists reviewed patients admitted to the emergency and general medical wards with untreated seizures or epilepsy. Appropriate investigations were arranged and rapid referral to Epilepsy clinic was organised as appropriate. All clinical information available from these patients was included in the database (Brodie, 2017a).

More than 90% of patients are referred from general practitioners with the majority of the reminder being tertiary referrals from other hospital across the West of Scotland. Most of the patients live in Glasgow but 20% travel to the clinic from outside the city. These largely originated from Lanarkshire, Argyll & Clyde, and Ayrshire & Arran.

The epilepsy service is manned by medical and nursing staff from the division of Cardiovascular and Medical Sciences at Western Infirmary and subsequently at WGACH. The director of the Epilepsy unit is Professor Martin Brodie. Dr John Paul Leach is a consultant neurologist and neurophysiologist. Dr Linda Stephen organises patient services and the epilepsy Unit. In addition to other medical and nursing staff.

2.2.2 Inclusion and exclusion criteria

Patient inclusion criteria:

- Age 18 years or above at treatment initiation;

- Referred to the Seizure Clinics between 1 Jul 1982 and 31 Oct 2012;
- New-onset of seizure;
- Confirmed diagnosis of epilepsy based on clinical evaluation (history and seizure description from the patient and witnesses of seizures), and investigations (EEG and MRI);
- Started first-ever AED at the Glasgow Epilepsy Unit between 1 Jul 1982 and 31 Oct 2012; and
- Followed-up for at least one year after treatment commencement.

Patient exclusion criteria:

- Patients younger than 18 years old at treatment commencement;
- Started AED therapy before 1 Jul 1982 or after 31 Oct 2012;
- Previously treated with AEDs;
- Psychogenic non-epileptic seizures
- Most of the seizure were secondary due to reactional drug or alcohol abuse;
- Patients with less than one years' follow-up after treatment initiation, including patients with immediate seizure control on treatment, who did not complete one year of follow-up at 30 Apr 2016, and deceased patients with a period of treatment less than one year; and
- Persistent poor adherence to AED treatments unrelated to drug efficacy or tolerability.

2.2.3 Patient flow chart

As shown in Figure 2-1, of the 3,356 patients screened, 1,528 were eligible to include in this study based on the inclusion and exclusion criteria described in the previous section.

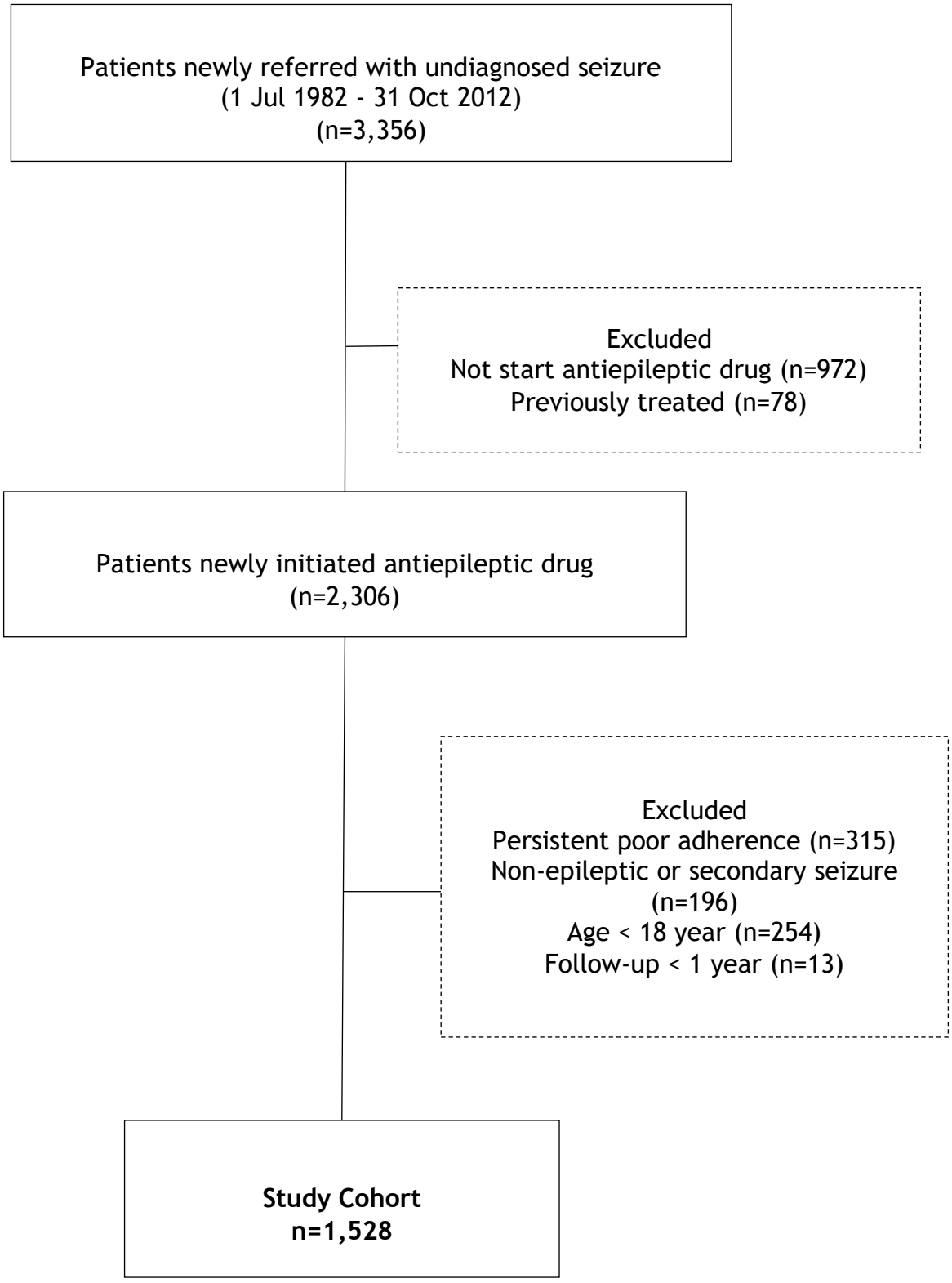


Figure 2-1. Flow chart for patients' inclusion

At the first clinical visit, general physical and neurological examinations were performed. Additionally, clinicians used a predesigned questionnaire (Appendix) to collect demographic and clinical information from the patient and witnesses. Several investigations were performed [EEG, and brain imaging i.e. computed tomography (CT) scan and MRI] that might support the diagnosis and classification of the epilepsy, and to screen for underlying structural abnormalities, which subsequently helped in selecting the appropriate AED.

2.3 Seizure and epilepsy classification

Seizure and epilepsy types were classified according to the guidelines of the ILAE published in 1981 and 1989 (Commission of ILAE, 1981, Commission of ILAE, 1989). The most recent guideline for epilepsy classification published in 2017 (Fisher et al., 2017, Scheffer et al., 2017) was explained in Chapter 1; however, it was not applied to the classification of the current cohort.

In this study, epilepsy was classified as either generalised or focal based on the seizure types and the assumed cause. Several important factors were also considered including the results of the EEG, CT, and MRI investigations, the patient's age, and any family history of epilepsy.

Generalised epilepsy was assumed to have a genetic origin and included primary GTCs, myoclonic jerks, absence seizures, and syndromes such as juvenile absence epilepsy and juvenile myoclonic epilepsy.

Focal epilepsy, with or without secondary generalisation, was further subdivided into symptomatic or cryptogenic epilepsy. Symptomatic epilepsy was identified by the presence of epileptogenic lesions in the brain (evident on a CT or MRI scan), such as trauma, tumour, infection, cerebrovascular disease, mesial temporal sclerosis, and cortical dysplasia. Cryptogenic epilepsy was identified when an underlying brain lesion was presumed but not confirmed through clinical information or investigations.

Once an epilepsy diagnosis was confirmed, an appropriate AED was initiated.

2.4 Treatment approach

Treatment selection was based on efficacy of AED for the given seizure type or syndrome, the patients' characteristics (i.e. age, gender, comorbidities, and concomitant drugs), and on the AEDs' pharmacokinetics and tolerability profiles (Stephen and Brodie, 2009, Perucca and Tomson, 2011). In practice, the AED was usually initiated after two or more unprovoked seizures had occurred more than 24 hours apart; however, patients who had experienced one seizure with evidence of an epileptogenic lesion in the brain that increased the probability of further seizures could be offered an AED therapy (Brodie et al., 2012, Fisher et al., 2014).

Patients were subsequently evaluated at the epilepsy clinic every four to six weeks for the first six months and at least every four months thereafter. If medical attention was necessary between scheduled appointments, the patients or their primary care physicians could call the epilepsy unit by using a dedicated telephone line. At each follow-up visit, clinical information and the response to antiepileptic-drug therapy were recorded (Appendix). Compliance was monitored at the clinic as well. Drug doses were adjusted as clinical circumstances dictated, with particular attention paid to efficacy and tolerability.

Initial monotherapy was prescribed for all the patients included in the study. Then, where necessary, treatment regimens were modified based on response to treatment (i.e. efficacy and tolerability). Modification of treatment schedules included dose adjustment, replacement of ongoing AED, or the addition of a combined therapy. Generally, if the initial AED was poorly tolerated at a low dose, or failed to improve seizure control, it was replaced with an alternative. If the first AED was tolerated and significantly improved seizure control, but did not completely provide seizure freedom, combination therapies were usually recommended (Brodie et al., 2012).

Adherence to the medication was evaluated by directly questioning the patient in each visit and measuring drug levels in the blood whenever possible. Patients with persistent poor adherence to AEDs were excluded from this study. While patients with intermittent poor adherence who missed the medication occasionally were included and the reasons for the poor concordance were reported.

This approach to data collection provides benefits like highly accuracy and good validity to detect and quantify diagnoses that medically confirmed by general physical and neurological examinations, and laboratory investigations. These included adverse effects like weight gain, coordination abnormality specially tremor, skin reactions, haematological and hepatic side effects, and eye field examination. On the other hand, some symptoms were mainly recoded based on patient reports including seizure and some adverse effects like psychiatric disorders.

2.5 Definitions

2.5.1 Outcome measures

This research was carried out to assess the long-term efficacy, tolerability, and effectiveness of AEDs. The efficacy of the AED treatment was evaluated on the basis of achieving a seizure-free status. Studies have indicated that absolute seizure freedom, usually 12 months, is the only relevant outcome resulting in a significant improvement on quality of life compared to reduced seizure frequency and severity (Kwan et al., 2010). Therefore, seizure-free status in the current study was defined as a minimum of one-year without a seizure at last follow-up, or no seizure reported at last follow-up, and there was at least one year between the last follow-up date and the date on which data was extracted (data extraction was completed on 30 Apr 2016). In many countries, including the UK, one-year seizure freedom is required to reinstate a driving licence. Therefore, there was consensus that the seizure-free duration assigned should be at least one year (Kwan et al., 2010). Seizure-free status included freedom from all seizures, including auras. The Epilepsy Clinic usually discharges seizure-free patients to primary care, requiring re-referral in the case of relapse, poor tolerability, or for a pregnancy consultation, etc. General practitioners and all patients are aware of this arrangement, also they could call the Epilepsy Unit if necessary. Therefore, it was assumed that the patients remained seizure-free if they were not referred back to the Epilepsy Clinic.

Withdrawal of a drug because of intolerable or life threatening adverse drug reactions is the most significant outcome measure for side effects (Mohanraj and Brodie, 2003). Therefore, modification of the AED schedule due to intolerable

adverse effects was the outcome measure for poor tolerability in this study. In this context, modifications in the AED regimen primarily involved withdrawal of the offending AED, or a reduction in the dose and requiring of an adjunct AED to control seizures in some cases. This is because an intolerable adverse effect could cause treatment failure, either alone or in combination with poor seizure control. In this retrospective analysis, only intolerable adverse effects that contributed to treatment failure were explored. Thus, the prevalence of adverse effects of continued AEDs was not measured. This was because of the study design and the limited availability of data.

Efficacy and tolerability integrate to form effectiveness and thus cannot be reasonably separated. The most relevant outcome measure to evaluate both these factors is the survival analysis, which reports the retention of patients on a specific treatment programme over a period of time (Mohanraj and Brodie, 2003). In addition, this approach shows the time to discontinuation of treatment due to any cause; thus, enabling the investigation of different reasons for treatment failure (Cramer, 2012). Therefore, in the present study, the retention rates for the most common monotherapies (LTG, VPA, CBZ, and LEV) were compared to evaluate their long-term effectiveness in routine clinical practice. Retention time was calculated in months from the start date of each AED to either the discontinuance date for the treatment, or the final follow-up date for continued therapy.

2.5.2 Predictors

A number of potential factors that influence the treatment outcomes (efficacy, tolerability, and effectiveness) were evaluated including factors related to patient and drug. Patient-related factors were gender, age at treatment initiation, epilepsy type and aetiology, family history of epilepsy, febrile convulsion, birth trauma, head injury, cerebrovascular disease, number and duration of pre-treatment seizures, learning disability, psychiatric comorbidity, and alcohol and recreational drug abuse. While pharmacological factors were individual AED, number of prior unsuccessful AEDs schedule, number of co-prescribed AEDs, AED generation, and dosage. However, the influence of EEG results (normal, abnormal, epileptiform, not available) on treatment outcome was not evaluated, this

variable probably correlates to other variables such as epilepsy type and aetiology, and family history of epilepsy.

The following are descriptions of some factors.

- **Family history of epilepsy:** Family history of epilepsy in a first-degree relative (i.e. parent, child, full-sibling). This also includes a family history of any seizures, regardless of cause.

- **Birth trauma**: Including documented birth trauma or any other birth difficulty resulting in an abnormality identified on brain imaging.

- **Learning disability:** Including mild, moderate, and severe cases. Patients with Down's syndrome were considered to have a learning disability. In these cases, a history was taken from care providers or parents at the follow-up stage.

- **Head injury**: Including a skull fracture, head trauma with abnormality identified on a CT/MRI scan, or any severe head trauma that led to loss of consciousness or required investigation/hospitalisation. Not including minor head injury.

- **Cerebrovascular disease**: Including stroke, transient ischaemic attack, or small vessel ischaemic change, as identified on brain imaging.

- **Psychiatric comorbidity:** Including depression, anxiety, panic attacks/agoraphobia, suicidal attempts/thoughts, psychoses/schizophrenia, behavioural disorders (personality problems/antisocial), or anorexia. In addition to ongoing or past prescription of antipsychiatry medications.

- **Pre-treatment seizure count**: The numbers of GTCs and focal (with or without impaired awareness, and auras) seizures were counted. More than one seizure within 24 hours was considered as one seizure. For myoclonic jerks and absence seizures, the number of days with seizures was counted.

- **Alcohol abuse:** Including alcoholism syndrome, frequent excess intake of alcohol, or chronic alcohol problems that resulted in hepatic problems or required medical intervention. This does not include occasionally drinking to excess.

- **Recreational drug abuse**: Including smoke, inhalation, ingestion, or injection of illicit drugs; e.g. benzodiazepines, cannabis, cocaine, opioids, and amphetamines.

2.5.3 Drug regimen

Each AED used was expressed as AED regimen. The first AED regimen was always monotherapy while the subsequent regimens could be an alternative monotherapy or polytherapy combined the previous AED(s) and the add-on AED. Polytherapy could be a combined of 2 to 5 AEDs. Number of prior unsuccessful AED regimens ranged from 0 to 13th schedules.

2.5.4 Drug dosage

Medication dosage was recorded as daily dosage in milligrams based on what dose the patient was administered at the last follow-up or at what dosage the patient discontinued treatment.

To evaluate the dosage of different AEDs, drug doses were categorised into low, moderate, and high doses based on the interquartile range (IQR) of each drug used in the presented cohort. Low doses were smaller than the IQR, moderate doses were within the IQR, and high doses were greater than the IQR. Generally, the IQR describes the middle 50% of values when ordered from smallest to largest, and therefore represents the average (common) dose interval.

In this analysis, only the dosage for the most commonly used monotherapies (LTG, VPA, LEV, and CBZ) were included. The common doses (IQRs) of these drugs in the current study were comparable to the commonest doses according to other references as shown in Table 2-1.

Table 2-1. Dosages that considered as "common dosages" in the present study and according to other references

	Interquartile range in current study	Commonest dose (Brodie, 2017b)	Usual Dose (BNF NICE, 2016)	Defined Daily Dose (WHO, 2015)
Lamotrigine	150-350	200-400	100-200	300
Valproate	1000-1700	1000	1000-2000	1500
Carbamazepine	400-800	600	800-1200	1000
Levetiracetam	1000-2000	1000-2000	Max 3000	1500

Doses in mg/ day

2.5.5 Generations of antiepileptic drugs

In this study, AEDs were divided into first and new generation on a chronological basis. AEDs introduced into clinical practice before 1989 were considered first generation drugs. This group includes PB, PHT, ESM, CBZ, VPA, CZP, and CLB. The remaining AEDs were regarded as new drugs.

2.6 Adverse effects assessment

Only one adverse effect of one offender AED was assigned for each case of treatment failure due to intolerable side effect.

- If more than one intolerable adverse effect caused the treatment failure, the severest and/or the adverse effect closest to the date of discontinuation/dose reduction was indicated as the reason for treatment discontinuation.

- If a combination of two AEDs or more caused the adverse effect, the AED that was discontinued or reduced was indicated as the offender AED.

Adverse effects were categorised into groups including tiredness, poor coordination, skin rash, gastrointestinal side effect, tremor, mood disorder, headache, weight gain, aggression, cognitive dysfunction, insomnia, irritability, paraesthesia, anorexia/weight loss, psychotic effect, sexual dysfunction, hyponatremia, and other. This categorisation based on the importance and

frequency of adverse effect, and on the classifications used in other clinical studies (Baker et al., 1994, Mohanraj and Brodie, 2005, Marson et al., 2007a, Marson et al., 2007b). Table 2-2 shows some details of categorisation of intolerable adverse effects.

Several criteria were considered to establish a causality of adverse effects (Edwards and Aronson, 2000):

- Reasonable time relation between the use of AED (introduction or does elevation) and the incidence of adverse effect;

- Concomitant disease or drugs cannot explain the adverse effect;

- The pattern of the adverse effect may fit the known pharmacology or allergy pattern of AEDs;

- Reversibility of adverse effects after drug discontinuation or dose reduction; and

- The background frequency of the event and how often it is associated with drugs were considered. For instance, headache is relatively common, so its association with a medicine may be by chance. In contrast, rash has a low background incidence and is often associated with particular AED, therefore it is more likely to be an adverse drug reaction.

Table 2-2. Categorisation of intolerable adverse effects

Category	Include
Tiredness	Drowsiness, sleepiness, sedation, lethargy, and fatigue
Poor coordination	Blurred/doulbe vision, diplopia, dizziness, unsteadiness, vertigo, imbalance, ataxia, gait difficulties, nystagmus, and staggering
Skin rash	
Gastrointestinal side effect	Nausea, vomiting, diarrhoea, constipation, stomach cramps, and heartburn.
Tremor	
Mood disorder	Depression, low mood, mood swings, emotional lability, and suicidal thoughts/attempts
Headache	
Weight gain	
Aggression	Impulsiveness, anger, agitation
Cognitive dysfunction	Word finding difficulties, poor concentration, and poor memory
Insomnia	Sleep difficulties and sleep disturbance
Irritability	
Paraesthesia	
Anorexia/ weight loss	
Hair loss	
Psychosis effect	Visual hallucination, delusion, paranoia, and confusion
Sexual dysfunction	
hyponatremia	
Other	

This categorisation based on the importance and frequency of adverse effect, and on the classifications used in other clinical studies (Baker et al., 1994, Mohanraj and Brodie, 2005, Marson et al., 2007a, Marson et al., 2007b).

2.7 Data extraction and management

I was based at the Epilepsy Unit between 1 Jul 2015 and 30 Apr 2016 to extract data from patients' paper-based medical records. Each clinical record was assigned a unique identification (ID) number (Epilepsy Research Unit number). During the data collection phase, the ID numbers were only known to the research team. Access to the data was restricted to the team and movement of the data out of the Research Unit was limited. Physical and IT security was also applied to maintain confidentiality. This included storing the paper folders in a locked filing cabinet and saving the electronic data on a password-protected computer.

During the study, I reviewed 1,528 eligible clinical records and created an electronic database, entering the extracted data into a pre-designed template. Microsoft Excel 2016 software was used to construct and store the electronic database.

Several details were extracted for each eligible patient, including the patient's demographic information, medical history, risk factors for epilepsy, seizure information, investigations, antiepileptic drug treatment details, and pharmacological outcomes. Table 2-3 shows more details of extracted data for each included patient.

After the data collection, the dataset itself was unlinked anonymised (the IDs were removed) prior to conducting the analyses. The data collection and dataset contained no potential identifiers or personal information (only the patient's year of birth).

Table 2-3. Extracted information for each eligible patients

Demographic information
- Gender
- Year of birth

Referral details
- Date of referral
- Source of referral
- Date of the last follow-up

Risk factors
- Family history of epilepsy (first degree relative)
- History of febrile convulsion
- Birth trauma
- Head injury
- Smoke, alcohol, and drugs abuse

Seizure details
- First seizure's date and type
- Subsequent seizures' date, type and frequency at each visit
- Classification of seizure type, epilepsy, and aetiology
- Investigations' date and results (EEG, CT, and MRI)

Medical history
- Other medical conditions including surgical procedures and onset date
- Other medications and commence date

Antiepileptic drugs
- Name and commence date
- Daily dosage at last follow-up or at discontinuation
- Plasma concentration of antiepileptic drugs and measurement date
- Adherence to medication, reason for poor adherence
- Adverse effects:
  - Symptoms
  - Onset or reported date
  - Dose at adverse effect and date of this dose
  - Intervention (antiepileptic drug discontinuation, dose reduction, or other)
- Treatment outcomes
  - Continuation or discontinuation of antiepileptic drugs
  - Date of discontinuation
  - Reason for discontinuation (lack of efficacy, poor tolerability, or both lack of efficacy and poor tolerability)

Seizure outcomes at last follow-up
- Controlled or uncontrolled seizure
- Date of last seizure
- Continued antiepileptic drug (s) regimen and daily doses
- Off medication patient, date and reason for discontinuation

2.9 Ethical considerations

This study was carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo [1975], Venice [1983], Hong Kong [1989], South Africa [1996], Edinburgh [2000], Seoul [2008], and Fortaleza [2013]).

This study was approved by the Yorkshire and the Humber – Bradford Leeds Research Ethics Committee (REC reference: 16/YH/0513), and by the NHS Greater Glasgow & Clyde Health Board (Research and Development reference: GN16NE639).

My right of access to conduct research in the NHS Greater Glasgow & Clyde region was obtained from the Research and Development Office, West Glasgow-ACH.

2.10 Statistical analyses

2.10.1 Statistical packages used

Microsoft Excel 2016, Minitab 17 Statistical Software, IBM SPSS statistics 22.0, and Graphpad Prism 5 were used for data analyses.

2.10.2 Summary of statistics

Categorical data was summarised using counts and percentage. Whereas continuous data was summarised using median, IQR, and range.

2.10.3 Comparison of categorical data

A chi-square (X^2) test and test for two proportions were carried out to assess the associations of the categorical data. The chi-square (X^2) test for trend was performed to evaluate the linear relationship between the ordered variables and the treatment outcomes. When previous analyses included expected counts of less than five, the Fisher's exact test was applied. To address the issue of multiple comparisons, and to avoid a type I error, the p-value for significance was modified based on the Bonferroni correction (0.05/number of comparisons).

2.10.4 Comparison of continuous data

The Mann-Whitney test and Kruskal-Wallis test were applied for a comparison of the non-parametric continuous data. The normality of the continuous data was tested visually (Normal Q-Q plot and histogram) and statistically (Shapiro-Wilk test). An attempt was made to transform the non-normally distributed variables ($p<0.05$) into normal ones using a natural logarithm and log base 10.

2.10.5 Regression

Univariate and multivariate regression analyses were used to evaluate and adjust the effect of the potential factors on treatment outcomes. The dependent variable was binary in efficacy and tolerability studies and thus logistic regression was used. However, the dependent variable was continuous in retention rate study and, therefore, Cox regression was used. The independent variables were a mix of binary, categorical with more than two groups, and continuous variables. Each covariate was entered into a univariate analysis, covariate that predicted the outcome significantly ($P<0.05$) in univariate analysis were subsequently entered into a multivariate analysis. If two variables were significantly correlated to each other, one (the weakest) should be excluded from multiple model as these variables had independent association with outcome due to their relationships with each other. No correction was made for multiple testing in regression analysis (i.e. significant at $P<0.05$).

2.10.6 Survival analysis

A Kaplan-Meier survival analysis was performed to estimate the cumulative probability of retention on treatments. A Cox regression model was applied to evaluate the effect of covariates and to compare the retention rates of different treatments before and after adjustment for significant covariates.

All statistical tests were 2-sided, p-value was significant at 0.05, and a 95% confidence interval was used, except in X^2 pairwise comparisons, where corrections were applied.

2.10.7 Missing data

There were very few missing values. Missing data was treated as a separate group for categorical variables (not available, NA), and kept as missing data for continuous variables. Analyses then were run as if all complete cases.

Chapter 3. The long-term efficacy of antiepileptic drugs

3.1 Introduction

Approximately 50% of newly diagnosed epilepsy patients are controlled on an appropriate AED, either immediately or after one to two years of trying different treatment schedules, however around 25-30% of this population continue to be pharmacoresistant from outset. The remainder of population show a relapsing/remitting pattern with some of these eventually developing refractory epilepsy (Brodie et al., 2012). It remains unclear why and how some patients become refractory, while others with an apparently identical form of epilepsy achieve complete seizure control on AED therapy. A number of clinical and pharmacological factors have been demonstrated as being correlated or predictive of seizure outcomes (Mohanraj and Brodie, 2013). A lack of early response to AEDs is frequently regarded as a strong predictor of pharmacoresistant epilepsy (Kwan and Brodie, 2000, Brodie et al., 2013). However, limited or inconsistent evidence exists about other factors that may predict seizure outcomes (Mohanraj and Brodie, 2013). Some patients with intractable epilepsy may benefit from non-pharmacological treatment, particularly epilepsy surgery. Studies have demonstrated that epilepsy surgery in certain types of refractory epilepsy, specifically temporal lobe epilepsy, provides significantly better outcomes than continued manipulation of AEDs therapy (Wiebe et al., 2001). Therefore, the early prediction of treatment outcomes is necessary for selecting the appropriate clinical management at appropriate stage such as considering more aggressive pharmacotherapy or early referral for surgery (Hitiris et al., 2007, Kwan et al., 2010).

Over the last three decades, the introduction of 14 new antiepileptic drugs (Figure 3-1), some with novel mechanisms of action, has expanded treatment choices and increased expectations about efficacy and tolerability (Loscher and Schmidt, 2011, Brodie, 2017a). However, it is unclear whether treatment outcomes have changed in recent decades as a consequence of the availability of an increasing number of AEDs as adjunct therapy, or as initial monotherapy.

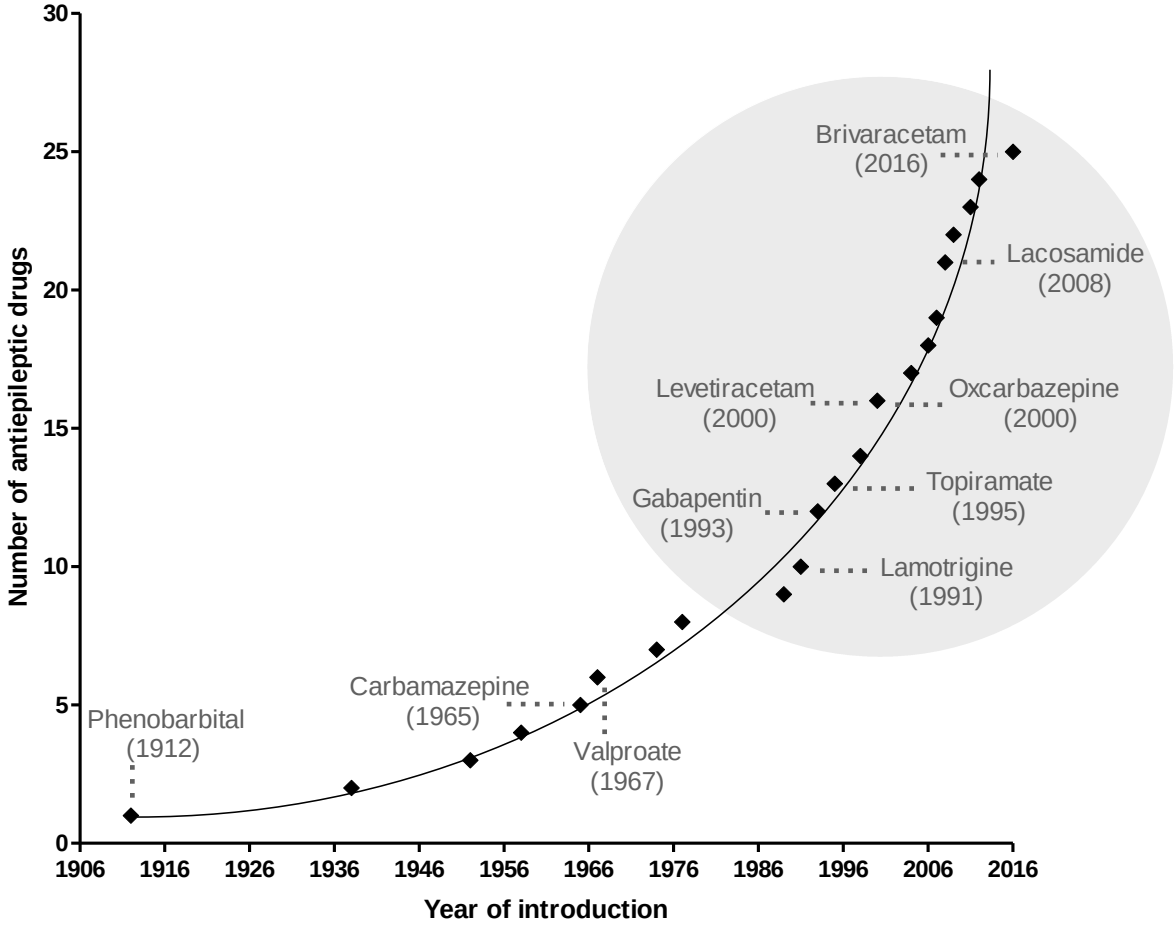


Figure 3-1. Development of antiepileptic drugs since 1912 [modified from (Loscher and Schmidt, 2011)]
Circled in grey are new generation drugs

This chapter evaluates efficacy of AEDs based on seizure control at last follow-up. Clinical and pharmacological determinants for pharmacoresistant epilepsy was identified. As well as, the changes treatment outcomes of epilepsy over the past 30 years was studied. This was achieved by comparing the results of current analysis to the results of three analyses conducted in 1999, 2003, and 2008 on same expanding cohort (n=525, 890, and 1098, respectively) (Kwan and Brodie, 2000, Mohanraj and Brodie, 2005, Bamagous, 2010, Brodie et al., 2012) from the Epilepsy Unit in Glasgow.

3.2 Methods

The patients were divided into controlled and uncontrolled groups based on their seizure outcomes at their final clinic visit. The ‘controlled’ group was constituted

of patients who had been seizure-free for at least 12 months. These patients had attained a seizure-free state either immediately after AED initiation (i.e. they had experienced no seizure on treatment) or they had attained a delayed seizure-free state after experiencing seizures on AED therapy, prior to their ultimate seizure control. Delayed seizure control was commonly achieved following the commencement of a new AED regimen, a new dosage, improved adherence to AEDs, or an adjustment of seizure triggers, such as excessive alcohol intake, stress, and sleep deprivation.

Meanwhile, the patients who had not achieved seizure control were categorised into drug resistant, relapsed, or undefined, based on their response to the trials of AED schedules. The consensus definition of drug resistant epilepsy by the ILAE was adopted (Kwan et al., 2010). The patients were regarded as being drug resistant if they failed to achieve 12-month seizure freedom on their most recent two appropriate, adequate, and tolerated AED schedules. Relapsed patients were considered to be those who had successfully attained initial seizure freedom for at least 12 months, on one of their most recent two appropriate, adequate, and tolerated AED regimens, but had subsequently relapsed prior to the end of the study. In this study, the category of 'undefined drug responsiveness' was applied to uncontrolled patients who could not be classified as being either drug resistant or relapsed. Uncontrolled patients included those who preferred to continue with their AED schedules unchanged, because they accepted the improvement of their seizures, especially if their GTCs had been abolished, and their focal seizures were reduced.

Dosage of AEDs was reported as daily dose in milligrams based on what dose the patient was taken at the last follow-up. Drug doses were categorised into low, moderate, and high doses based on the interquartile range (IQR) of each drug used in the presented cohort. Low doses were smaller than the IQR, moderate doses were within the IQR, and high doses were greater than the IQR. Only the dosage for the most commonly used monotherapies (LTG, VPA, LEV, and CBZ) were included. IQR in mg/day for LTG=150-350, VPA=1000-1700, CBZ=400-800, and LEV=1000-2000.

Univariate and multivariate logistic regression analysis were applied to assess seizure determinants. A chi-square (X^2) test was used to compare the proportions

of controlled patients, while a Mann-Whitney was performed to compare the dosages of successful and unsuccessful AEDs regimens.

3.3 Results

3.3.1 Patient demographics

Table 3-1 summarises the clinical characteristics of the 1,528 patients involved in the study. All the patients were adults, aged 18 to 93 years (median=37) at the initiation of their treatment, and there was a slight predominance of male patients (56%). The patients were referred to the seizure clinic between 1 July, 1982, and 30 October, 2012, and were prospectively followed until 30 April, 2016, with an average 5-year follow-up duration (range= 1-28) following the commencement of AED therapy. As expected from epidemiological studies on adult populations, focal seizures were more frequently represented in the cohort of this study (84%). Furthermore, 28% of patients possessed a psychiatric comorbidity at the baseline, or during follow-up. The cohort of this study included 10% deceased patients.

Table 3-1. Demographic characteristics of 1,528 patients

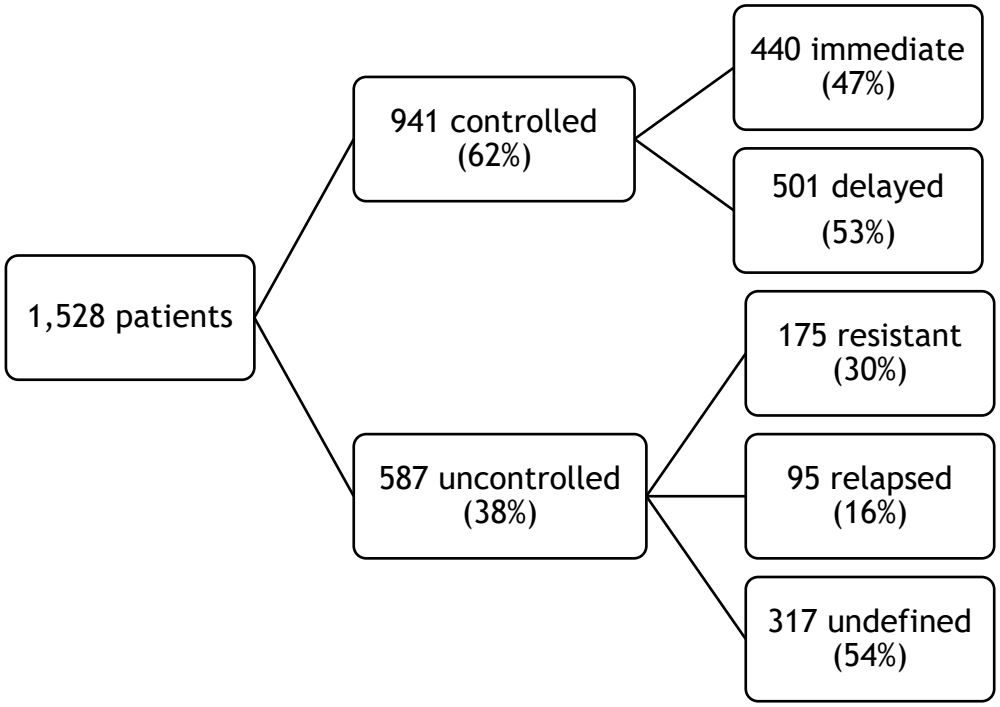
	n (%)
Gender	
Female	679 (44)
Male	849 (56)
Age at treatment initiation (Years), median (range)	37 (18-93)
Age at treatment initiation in years	
18-29	519 (34)
30-39	299 (20)
40-49	258(17)
50-59	179 (12)
60-69	134 (8)
70-93	139 (9)
Year of referral	Jul-1982 - Oct-2012
Duration of follow-up after treatment initiation (Years), median (range)	5 (1-28)
Epilepsy type	
Focal	1290 (84)
Generalised	238 (16)
Seizure aetiology	
Cryptogenic	776 (51)
Idiopathic	238 (16)
Symptomatic	514 (34)
Family history of epilepsy	246 (16)
Febrile convulsion	66 (4)
Birth trauma	14 (1)
Cerebral infection	18 (1)
Head injury	230 (15)
Cerebrovascular disease	192 (13)
Number of the pre-treatment seizure	
1	55 (4)
2	300 (20)
3-5	439 (29)
6-10	219 (14)
11-20	95 (6)
>20	420 (27)
Duration of the pre-treatment seizure (Months)	
<2	182 (12)
2-6	378 (25)
7-12	216 (14)
13-24	214 (14)
25- 60	279 (18)
>60	259 (17)
Learning disability	57 (4)
Psychiatric comorbidities	433 (28)
Alcohol abuse	329 (22)
Recreational drug abuse	175 (11)
Deceased patients	151 (10)

3.3.2 Seizure outcomes at the final follow-up

As demonstrated in Figure 3-2 by the final follow-up session, of the total 1,528 patients, 62% (n=941) were controlled, had been seizure-free for one year, while the remainder were uncontrolled. The mean duration of the seizure freedom of the controlled patients was 10 years (standard deviation [SD] =6). 47% (n=440) of the controlled patients achieved seizure freedom immediately following the commencement of their first AED. The remainder experienced a delay in achieving seizure freedom after commencing the new AED schedule, with the introduction of a new dosage, an improved drug adherence, or a modification to their lifestyle, such as a reduction in their alcohol intake, improved stress management, or control of other seizure triggers. Of the uncontrolled group, 30% were drug resistant (n=175), and 16% were relapsed (n=95), while the remainder were classified as 'undefined drug responsiveness'.

Table 3-2 shows the clinical characteristics of the 1,528 patients according to their seizure status at the final follow-up session (controlled and uncontrolled). Baseline characteristics such as gender, age, and epilepsy type and aetiology, were comparable between the controlled and uncontrolled groups. However, potential risk factors, such as a family history of epilepsy and head injury, were generally more frequent in the uncontrolled group.

At their final visit to the clinic, 55 patients (4%) withdrew their AEDs, preferring to remain off-medication. Their reasons behind this choice included the side effects and concern regarding side effects (33%, n=18), long-term seizure freedom (25%, n=14), treatment ineffectiveness (7%, n=4), concerns about teratogenicity (5%, n=3), and unknown reasons (30%, n=16). Another 30 patients changed to a different AED regimen at their final visit to the clinic, while the remainder continued with their current regimen (n=1443).



Definition adapted from (Kwan et al., 2010):

Controlled: seizure-free for at least 1 year at last follow-up
Uncontrolled: continued to have seizures at last follow-up
Immediate: achieved 1-year seizure-free immediately after starting antiepileptic drugs
Delayed: ultimately achieved 1-year seizure-free after experienced seizures on treatment
Resistant: failed to achieve any 1-year seizure-free on the last two proper antiepileptic drugs schedules
Relapsed: seizure reappeared and continued at last follow-up after initial 1-year seizure-free on one of the last two proper treatment regimens
Undefined: drug responsiveness neither classified as drug resistant nor relapsed

Figure 3-2. Seizure outcomes and drug responsiveness at last follow-up

Table 3-2. Clinical characteristics of 1,528 patients according to their seizure status (controlled/uncontrolled)

		Controlled (n=941)	Uncontrolled (n=587)	P-value (95% CI)
Gender	Female Male	412 (44) 529 (56)	267 (45) 320 (55)	0.515 (-0.068, 0.034)
Age at treatment initiation (Years), median (IQR)		38 (25,57)	37 (26,49)	0.039 (0,3)
Diagnosis	Focal Generalised	787 (84) 154 (16)	503 (86) 84 (14)	0.275 (-0.057, 0.016)
Seizure aetiology	Cryptogenic Idiopathic Symptomatic	459 (49) 154 (16) 328 (35)	317 (54) 84 (14) 186 (32)	0.135
Family history of epilepsy	Yes No	118 (13) 823 (87)	128 (22) 459 (78)	<0.000 (-0.132,-0.053)
Head injury	Yes No	112 (12) 829 (88)	118 (20) 469 (80)	<0.000 (-0.12, -0.043)
Number of pre-treatment seizure	1 2 3-5 6-10 11-20 >20	43 (5) 220 (23) 294 (31) 132 (14) 46 (5) 206 (22)	12 (2) 80 (14) 145 (25) 87 (15) 49 (8) 214 (36)	<0.000
Duration of pre-treatment seizure (Months)	<2 2-6 7-12 13-24 25-60 >60	120 (13) 238 (26) 142 (15) 127 (13) 164 (17) 150 (16)	62 (11) 140 (24) 74 (12) 87 (15) 115 (19) 109 (19)	0.286
Learning disability	Yes No	29 (3) 912 (97)	28 (5) 559 (95)	0.106
Psychiatric comorbidity	Yes No	195 (20) 746 (80)	238 (40) 349 (60)	<0.000 (-0.246,-0.15)
Alcohol abuse	Yes No	149 (16) 792 (84)	180 (31) 407 (69)	<0.000 (-0.192, -0.104)
Recreational drugs abuse	Yes No	59 (6) 882 (94)	116 (20) 471 (80)	<0.000 (-0.17, -0.099)
Number of prior antiepileptic drugs	0 1 2 3-13	665 (71) 182 (19) 54 (6) 40 (4)	220 (37) 155 (26) 82 (14) 130 (23)	<0.000

Data are presented in patient number (%). Statistical tests used were 2-proportions, X^2 and Mann Whitney tests.

3.3.3 Continued antiepileptic drugs

Of the 1,443 patients who continued to take AEDs at the last follow-up, 78% (n=1130) were on a monotherapy, while the remainder were on a combined therapy of 2, 3, 4, or 5 AEDs. The new AEDs were continued as a monotherapy by 44% (n=630) of patients.

63% (n=914) of continued AED schedules were successful, i.e. seizures were successfully controlled, while the remainder were unsuccessful regimens (37%, n=529). Table 3-3 shows the features of the 1,443 patients who continued on AED regimens at their final visit to the clinic, according to their seizure status in terms of whether it was controlled or uncontrolled. 89% (n=811) of the successful regimens constituted monotherapy, while only 11% (n=103) constituted polytherapy. The new AEDs were successful in 57% (n=459) of patients and the figure was slightly lower in the unsuccessful regimens, in which 54% (n=171) were on new AEDs.

Table 3-3. Features of continued antiepileptic drug regimens at last follow-up according to the seizure status (controlled/uncontrolled)

		Controlled (n=914)	Uncontrolled (n=529)	P-value (95% CI)
Number of taken antiepileptic drugs	Monotherapy Dual therapy Triple therapy or more	811 (89) 88 (10) 15 (1)	319 (60) 155 (30) 55 (10)	<0.000
		Controlled (n=811)	Uncontrolled (n=319)	
Drug generation of monotherapy	First generation New generation	352 (43) 459 (57)	148 (46) 171 (54)	0.363 (-0.094, 0.034)

Data are presented in patient number (%).2-proportions and X^2 tests were used.

3.3.4 Efficacy rates of individual antiepileptic drugs

As shown in Figure 3-3, efficacy rates of individual AEDs ranged from 55% with LCM, to 88% with GBP. However, few patients had continued to take these AEDs as a monotherapy by the final follow-up session (n=11, and 17, respectively). However, the efficacy rates of the most commonly used monotherapies (LTG, VPA, CBZ, and LEV) were more comparable (74, 70, 72, and 76%, respectively). Indeed, there was no significant difference in the efficacy rates of the different AEDs (p=0.256).

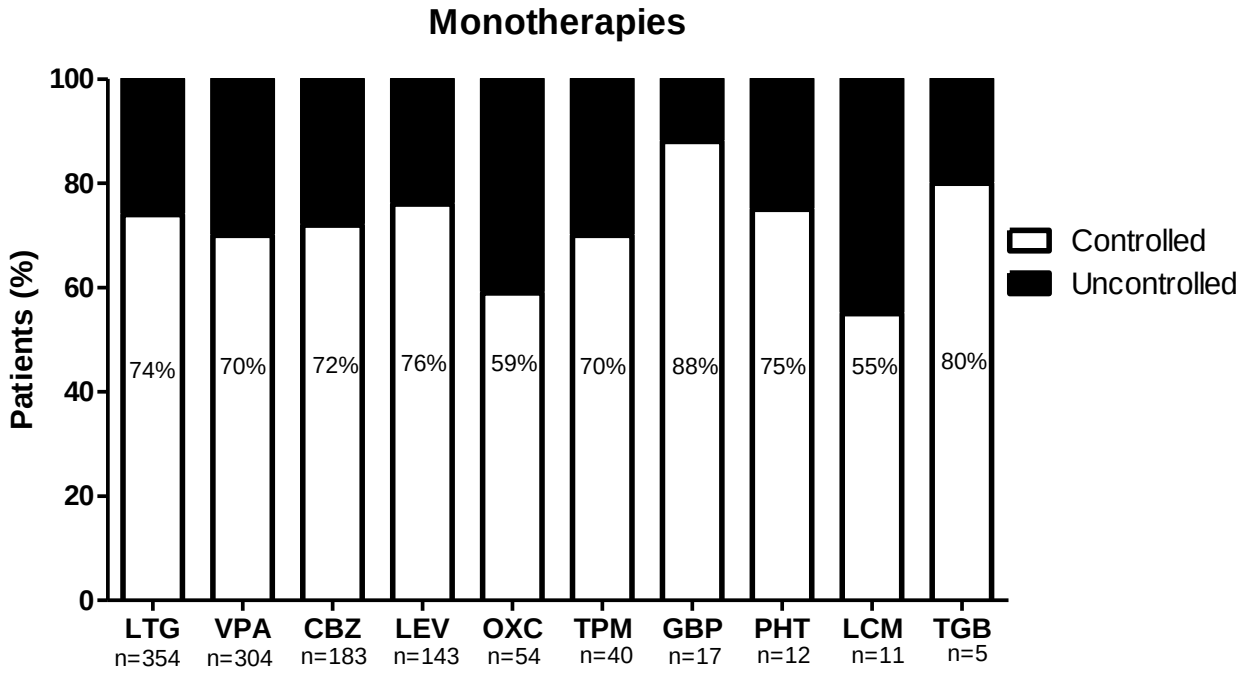


Figure 3-3. Efficacy rates of antiepileptic drugs that continued as monotherapy at the last follow-up
X^2 P-value was 0.256. Key: LTG: lamotrigine, VPA: valproate, CBZ: carbamazepine, LEV: levetiracetam, OXC: oxcarbazepine, TPM: topiramate, GPB: gabapentin, PHT: phenytoin, LCM: lacosamide, TGB: tiagabine.

In order to assess and overcome the potential effect of confounders on seizure outcome and efficacy rate of AEDs, several analyses were performed. First, a univariate regression analysis which shows that 9 determinants significantly influenced the seizure outcomes: patients' age, family history of epilepsy, head injury, number and duration of pre-treatment seizures, psychiatric conditions, alcohol and recreational drugs abuse, and number of prior AEDs. Head injury and pre-treatment seizure duration were excluded from the multivariate model

because they possessed strong correlations with other variables ($p<0.000$ for each comparison). After accounting for the significant variables in the adjusted model (multivariate), there was found to be no significant evidence of an association between age and seizure outcome. In this adjusted model, the odds of having uncontrolled seizures for an individual with family history of epilepsy, more than ten seizures before treatment, psychiatric comorbidity, alcohol abuse, or recreational drugs abuse, and more than two prior AEDs, were 1.8, 1.9, 1.7, 1.7, 2.4, and 4.5 times the odds for an individual without these risk factors, respectively. Table 3-4 shows the univariate and multivariate logistic regression analysis for risk factors of intractable seizure. These factors will be discussed further later in this chapter.

Then, the aforementioned significant determinants were assessed for individual AEDs (LTG, VPA, CBZ, LEV, OXC, and TPM) to examine their effect on the reported efficacy rates. As shown in Table 3-5 , age, family history, more than 10 /1-year pre-treatment seizures, and psychiatric comorbidities were comparable among monotherapies users. However, there were significant differences in rates of head injury, alcohol abuse, recreational drugs abuse, and more than two prior AEDs between treatments groups; and these may partially explain the reported efficacy rates. Patient taking VPA and CBZ had higher rate of head injury and alcohol abuse while OXC was more frequently used after trial of more than two AEDs. Table 3-6 demonstrates more details about pairwise comparisons of these factors among different treatment groups.

Table 3-4. Univariate and multivariate logistic regression analysis for predictors of uncontrolled seizure

	Univariate		Multivariate	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Female gender	1.067 (0.867, 1.313)	0.538		
Age (Years)	0.99 (0.984, 0.996)	**0.001**	0.997 (0.99, 1.004)	0.368
Focal epilepsy	1.172 (0.878, 1.564)	0.281		
Idiopathic seizure aetiology† Cryptogenic seizure†	1.218 (0.968, 1.533) 0.962 (0698, 1.326)	0.093 0.812		
Family history of epilepsy	1.945 (1.477, 2.561)	**<0.000**	1.796 (1.323, 2.439)	**<0.000**
Febrile convulsion	1.115 (0.675, 1.842)	0.67		
Birth trauma	0.265 (0.059, 1.187)	0.083		
Head injury*	1.862 (1.404, 2.47)	**<0.000**		
Cerebrovascular disease	0.932 (0.682, 1.275)	0.662		
More than 10 seizures before treatment	2.219 (1.786, 2.758)	**<0.000**	1.876 (1.475, 2.385)	**<0.000**
Seizures for >1 year before treatment*	1.278 (1.039, 1.571)	**0.02**		
Learning disability	1.575 (0.927, 2.676)	0.093		
Psychiatric comorbidity	2.609 (2.077, 3.277)	**<0.000**	1.753 (1.353, 2.263)	**<0.000**
Alcohol abuse	2.351 (1.835, 3.012)	**<0.000**	1.752 (1.317, 2.331)	**<0.000**
Recreational drug use	3.682 (2.64, 5.135)	**<0.000**	2.446 (1.667, 3.59)	**<0.000**
More than two prior antiepileptic drugs	5.094 (3.882, 6.684)	**<0.000**	4.491 (3.369, 5.987)	**<0.000**

†Symptomatic seizure aetiology was the reference group. *Head injury and pre-treatment seizure duration were excluded from multivariate model as they had strong correlations with other variables ($p<0.000$ for each comparison).

Table 3-5. Clinical characteristics of patients who continued monotherapy at last follow-up

	LTG	VPA	CBZ	LEV	OXC	TPM	P-value
Age (Years), median (range)	44 (18-87)	42 (18-89)	42 (18-93)	39 (18-83)	43 (18-82)	45 (19-77)	0.416
Family history of epilepsy	50 (14)	50 (16)	34 (19)	17 (12)	7 (13)	7 (18)	0.569
Head injury	32 (9)	46 (15)	36 (20)	15(10)	7 (13)	2 (5)	**0.005**
More than 10 pre-treatment seizure	109 (31)	99 (33)	55 (27)	37 (26)	19 (35)	16 (40)	0.530
More than 1 year pre-treatment seizure	165 (47)	157 (52)	90 (49)	71 (50)	25 (46)	21 (52)	0.844
Psychiatric comorbidity	81 (23)	85 (28)	41 (22)	38 (27)	12 (22)	12 (30)	0.568
Alcohol abuse	41 (12)	93 (31)	43 (23)	18 (13)	9 (17)	6 (15)	**<0.000**
Recreational drugs abuse	17 (5)	60 (20)	17 (9)	6 (4)	3 (5)	2 (5)	**<0.000**
Failure of two or more previous antiepileptic drugs	27 (8)	20 (7)	14 (8)	13 (9)	12 (22)	5 (12)	**0.031**
Total	354	304	183	143	54	40	

Data are presented in patient number (%). Kruskal–Wallis test, X^2/ Fisher's exact test were used. Key: LTG: lamotrigine, VPA: valproate, CBZ: carbamazepine, LEV: levetiracetam, OXC: oxcarbazepine, TPM: topiramate. Because of small sample sizes, other antiepileptic drug were not included.

Table 3-6. Pairwise comparisons of clinical characteristics of monotherapy users

	VPA N=304	CBZ N=183	LEV N=143	OXC N=54	TPM N=40
Head injury	**15%**	**20%**	**10%**	**13%**	**5%**
LTG (9%), n= 354	**0.017**	**0.001**	0.627	0.415	0.557
VPA		0.205	0.158	0.665	0.092
CBZ			**0.019**	0.217	**0.034**
LEV				0.637	0.371
OXC					0.293
Alcohol abuse	**31%**	**23%**	**13%**	**17%**	**15%**
LTG (12%), n= 354	**<0.000**	**0.001**	0.757	0.34	0.562
VPA		0.084	**<0.000**	**0.015**	**0.012**
CBZ			**0.009**	0.252	0.188
LEV				0.48	0.701
OXC					0.826
Recreational drug abuse	**20%**	**9%**	**4%**	**5%**	**5%**
LTG (5%) n=354	**<0.000**	0.065	0.765	0.738	1
VPA		**0.001**	**<0.000**	**0.011**	**0.026**
CBZ			0.061	0.578	0.538
LEV				0.708	0.687
OXC					1
≥2 prior antiepileptics	**7%**	**8%**	**9%**	**22%**	**12%**
LTG (8%) n=354	0.601	0.992	0.778	**0.012**	0.368
VPA		0.659	0.368	**0.007**	0.275
CBZ			0.643	**0.015**	0.385
LEV				**0.033**	0.554
OXC					0.207

Data are p-values of X^2/ Fisher's exact test. Key: LTG: lamotrigine, VPA: valproate, CBZ: carbamazepine, LEV: levetiracetam, OXC: oxcarbazepine, TPM: topiramate.

3.3.5 Efficacy rates of combined antiepileptic drugs therapies

Efficacy rates of AEDs polytherapies that continued at the last follow-up are shown in Table 3-7. Dual therapies of VPA/LTG, LTG/LEV, and LEV/LCM were the most frequently employed regimens (n=71, 25, and 15, respectively). Among these dual therapies (Figure 3-4), the efficacy was the highest with the LTG/LEV combination, in which 48% of patients achieved seizure-free status, and lowest with the VPA/LTG combination, in which 38% of patients achieved seizure-free status, however this difference was not significant (p=0.682).

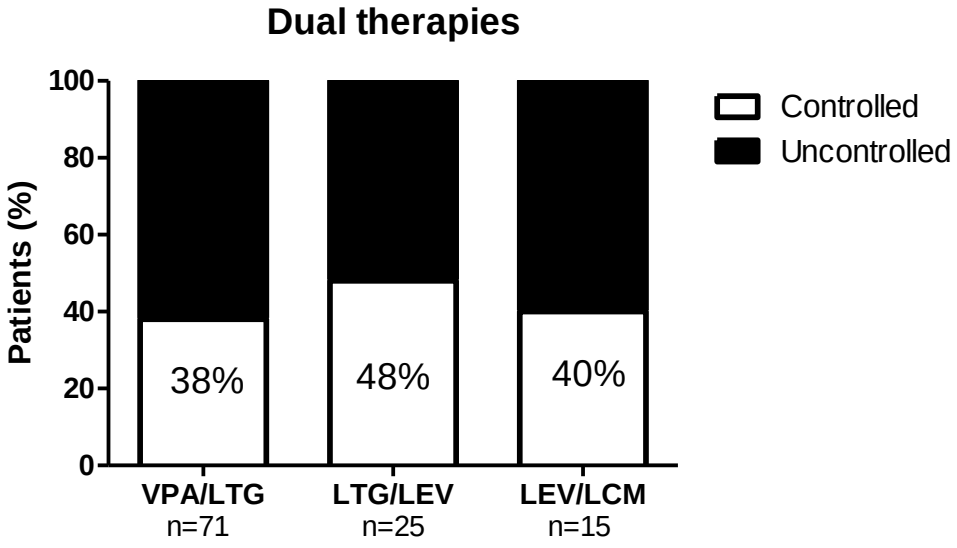


Figure 3-4. Efficacy rates of the most commonly used dual therapies that continued at the last follow -up
X^2 P-value was 0.682. Key: VPA: valproate, LTG: lamotrigine, LEV: levetiracetam, LCM: lacosamide.

Table 3-7. Efficacy rates of ploytherapies that continued at the last follow-up (n=313)

	Controlled (n=103)	Uncontrolled (n=210)
Dual therapies		
VPA/LTG (n=71)	27 (38)	44 (62)
LTG/LEV (n=25)	12 (48)	13 (52)
LEV/LCM (n=15)	6 (40)	9 (60)
VPA/LEV (n=9)	5 (56)	4 (44)
CBZ/LEV (n=7)	3 (43)	4 (57)
Others (n=116)	35	81
Triple therapies		
VPA/LTG/LEV (n=8)	3 (38)	5 (63)
VPA/LTG/TPM (n=4)	1 (25)	3 (74)
VPA/LTG/ZNS (n=4)	1 (25)	3 (75)
Others (n=41)	9	32
Quadruple therapies		
VPA/LTG/LEV/TPM (n=1)	1 (100)	0
Others (n=12)	0	11 (92)
5 AEDs		
VPA/LTG/LEV/TPM/CLB (n=1)	0	1 (100)

Data are presented in patient number (%). Key: VPA: valproate, LTG: lamotrigine, LEV: levetiracetam, LCM: lacosamide, CBZ: carbamazepine, TPM: topiramate, ZNS: zonisamide, CLB: clobazam.

3.3.6 Drug dosage

The median (IQR) dosage of controlled therapy in mg/day was 200 (150, 200) for LTG, 500 (400, 600) for CBZ, 1000 (1000, 1500) for VPA, and 1000 (1000, 1000) for LEV as a monotherapy. A comparison of the median doses between the controlled group and uncontrolled group for each AED is shown in Figure 3-5. A Mann-Whitney test revealed that the median dosage in the uncontrolled group was significantly higher than that in the controlled group, for each of the AEDs. In addition, the IQR was wider in the uncontrolled group for each drug, compared to the controlled group.

Table 3-8 shows daily dosages of dual therapy of VPA/LTG, LTG/LEV, and LEV/LCM. A similar general pattern of high medians and wider intervals in the uncontrolled group was also evident in the case of dual therapy. As expected, the median daily dosage of LTG was lower in the VPA combination than in the LEV combination (150 vs 400mg). Likewise, the dosage of LEV was lower in combination with LTG than its dosage in combination with LCM (1000 vs 2000mg).

Figure 3-5. Comparison between doses of controlled and uncontrolled groups for each antiepileptic drug
Mann Witney test was used. Key: **P≤0.01, ***P≤0.001

Table 3-8. Dosages (mg/day) of the most commonly used polytherapies

Combination	Controlled	Uncontrolled
Valproate Lamotrigine	1000 (500,1500) 150 (50, 200)	1500 (1000, 1500) 150 (100, 225)
Lamotrigine Levetiracetam	400 (300, 600) 1000 (1000, 3000)	400 (300, 600) 2000 (1000, 3000)
Levetiracetam Lacosamide	2000 (1375, 2125) 175 (50, 225)	2000 (2000, 2500) 500 (400, 550)

Doses are presented in median (IQR).

3.3.7 Clinical and pharmacological determinants of seizure outcomes

In this section, the effect of the determinants of seizure outcomes will be examined and quantified in more detail. These include factors demonstrating a significant association in univariate regression analysis, i.e. patient's age, family history of epilepsy, head injury, number and duration of pre-treatment seizures, psychiatric conditions, and alcohol and recreational drug abuse, in addition to pharmacological determinants including the number of prior AED regimens, the number of AEDs taken, and drug generation..

Overall, the patients' age at treatment initiation demonstrated a positive linear association with the efficacy outcomes (p=0.001). However, an interesting pattern was observed with regard to age. The efficacy rate was 61% in patients aged 18 to 29 years, and this was followed by a reduction in efficacy rate, reaching a minimum in patients aged 40 to 49 years (52%), after which the efficacy rate showed a gradual increase to a maximum rate in patients aged 70 to 93 years (81%). As shown in Table 3-9 and Figure 3-6 patients with a family history of epilepsy, head injury, psychiatric conditions, alcohol abuse, and recreational drug abuse demonstrated lower seizure control compared with patients without these risk factors. Furthermore, the rate of seizure control decreased as the number and duration of pre-treatment seizures increased.

With regard to pharmacological factors, the number of prior and co-prescribed AEDs demonstrated a negative linear correlation with seizure control (both p<0.000). The rate of seizure control was highest in patients receiving their first AEDs schedules (75%), and then gradually decreased in subsequent schedules until

almost no patients achieved complete seizure control on their eighth regimen onwards. Similarly, more patients (72%) were controlled by monotherapy compared to dual therapy (36%), or by treatment with three or more AEDs (25%, 8%, respectively). However, the seizure outcome was similar in patients treated with older AEDs (70%) compared to the patients treated with new AEDs (73%), p=0.363. Table 3-10 and Figure 3-7 demonstrate the effect of the pharmacological factors on seizure outcomes.

Table 3-9. Potential patient-related factors on seizure outcome

		Controlled	P-value (95% CI)
Age group (Years)	18-29 (n=519) 30-39 (n=299) 40-49 (n=258) 50-59 (n=179) 60-69 (n=134) 70-93 (n=139)	318 (61) 176 (59) 134 (52) 106 (59) 95 (71) 112 (81)	0.001
Family history of epilepsy	Yes (n=246) No (n=1282)	118 (48) 823 (64)	<0.000 (-0.23, -0.094)
Head injury	Yes (n=230) No (n=1298)	112 (49) 829 (64)	<0.000 (-0.221, -0.082)
Number of pre-treatment seizure	1 (n=55) 2 (n=300) 3-5 (n=439) 6-10 (n=219) 11-20 (n=95) >20 (420)	43 (78) 220 (73) 294 (67) 132 (60) 46 (48) 206 (49)	<0.000
Duration of pre-treatment seizure	<2 (n=182) 2-6 (n=378) 7-12 (n=216) 13-24 (n=214) 25-60 (n=279) >60 (n=259)	120 (66) 238 (63) 142 (66) 127 (59) 164 (59) 150 (58)	0.058
Psychiatric comorbidity	Yes (n=433) No (n=1095)	195 (45) 746 (68)	<0.000 (-0.285, -0.176)
Alcohol abuse	Yes (n=329) No (n=1199)	149 (45) 792 (66)	<0.000 (-0.268, -0.148)
Recreational drugs abuse	Yes (n=175) No (n=1353)	59 (34) 882 (65)	<0.000 (-0.389, -0.24)

Data are presented in patient number (%). 2-proportions test and X^2 for trends test were used.

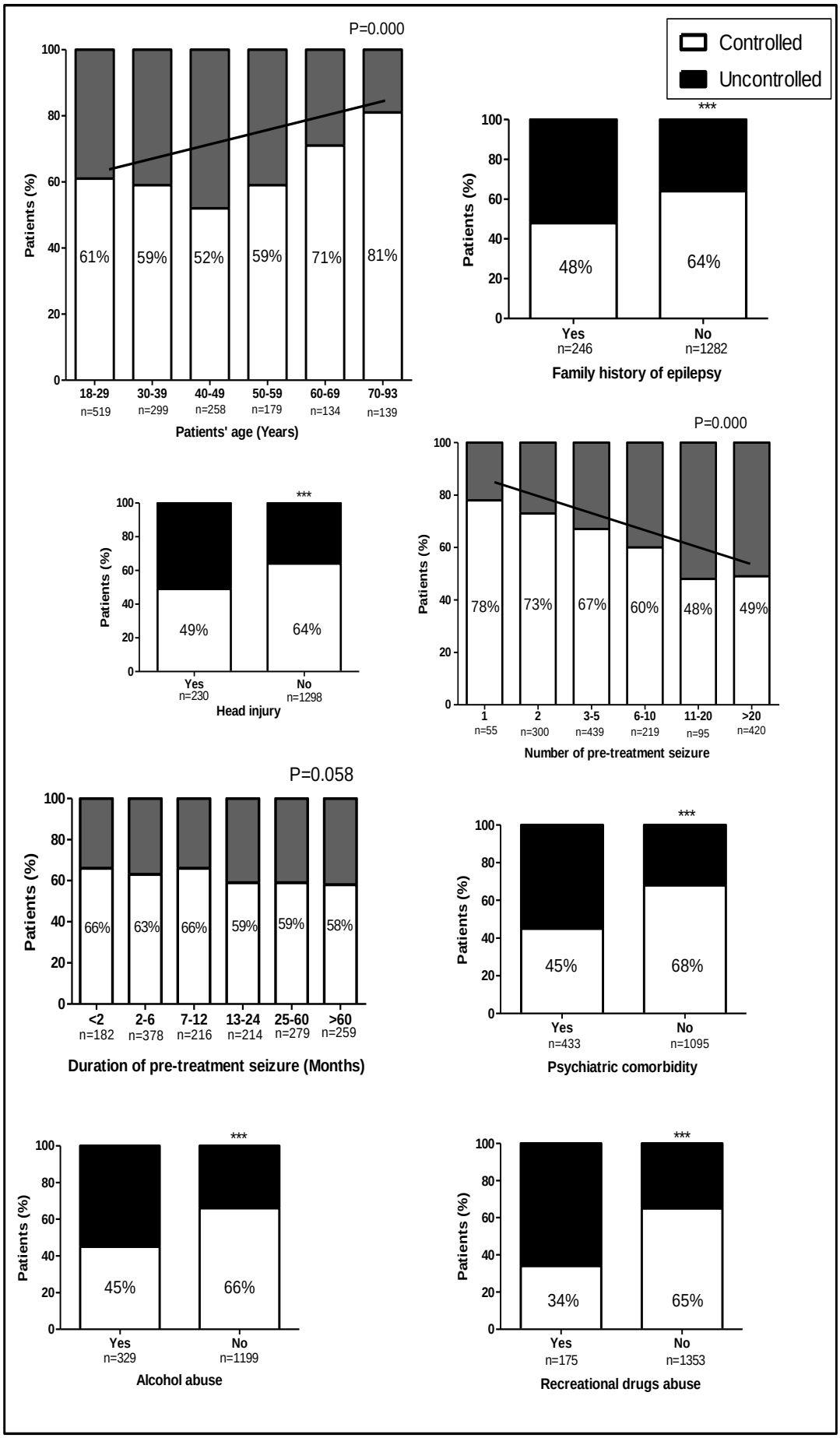


Figure 3-6. Potential clinical determinants of seizure outcomes
X^2 and X^2 for trends were used. Key: ***P≤0.001

Table 3-10. Potential pharmacological factors on seizure outcome

		Controlled	P-value (95% CI)
Number of prior antiepileptic drugs	0 (n=885) 1(n=337) 2 (n=136) 3 (n=68) 4 (n=43) 5 (n=20) 6 (n=16) 7 (n=4) 8 (n=11) 9 (n=2) 10 (n=2) 11 (n=1) 12 (n=2) 13 (n=1)	665 (75) 182 (54) 54 (40) 22 (32) 7 (16) 7 (35) 3 (19) 0 1 (9) 0 0 0 0 0	<0.000
Number of taken antiepileptic drugs	Monotherapy (n=1130) Dual therapy (n=234) Triple therapy (n=57) Quadruple therapy (n=12) 5 antiepileptics (n=1)	811 (72) 88 (36) 14 (25) 1 (8) 0	<0.000
Drug generation of monotherapy	First generation (n=500) New generation (n=630)	352 (70) 459 (73)	0.363 (-0.077, 0.028)

Data are presented in patient number (%). Statistical tests included X^2, 2-proportions, and X^2 for trends.

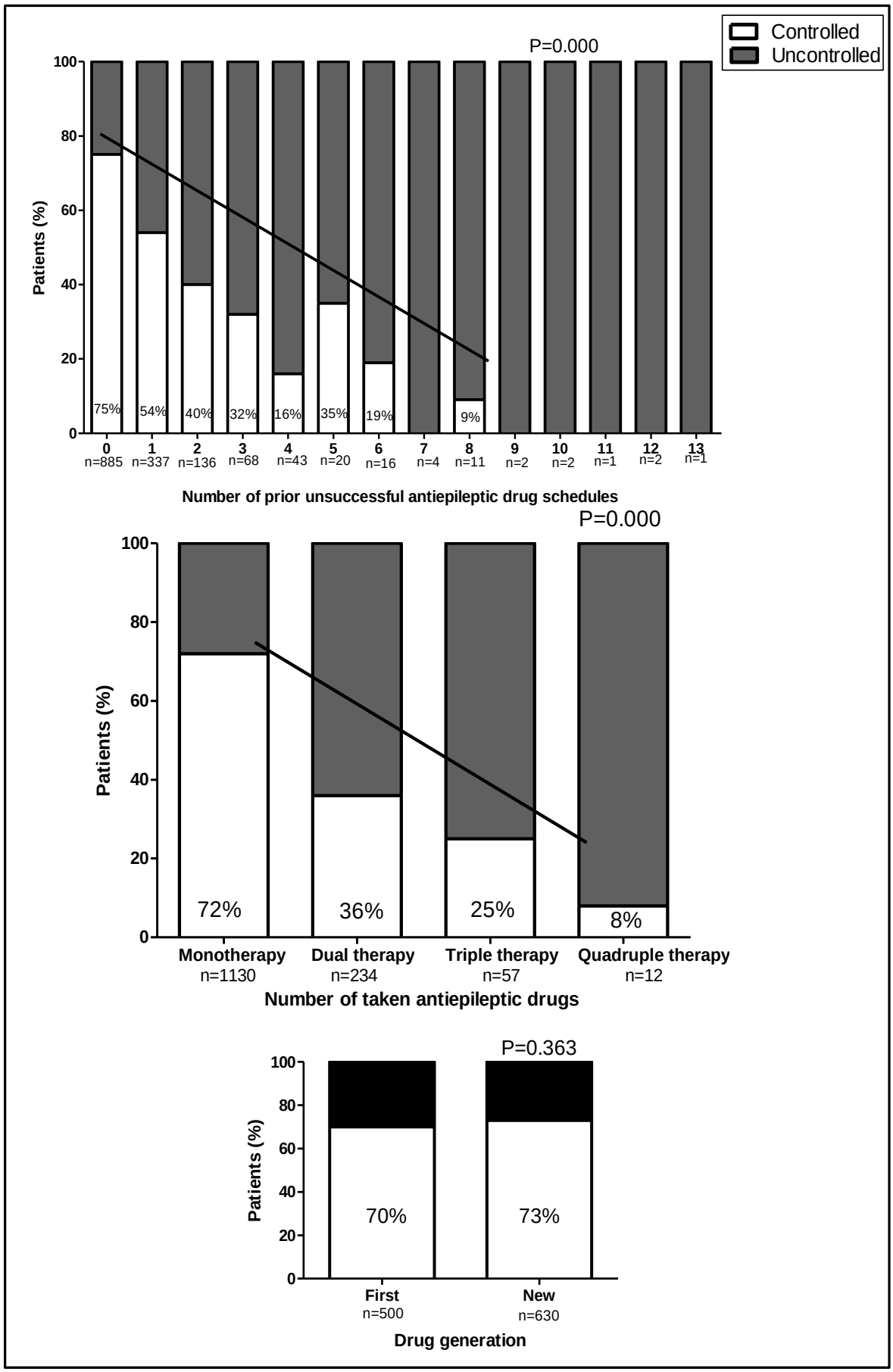


Figure 3-7. Potential pharmacological determinants of seizure outcomes
X^2 and X^2 for trends were used.

3.3.8 Comparison of treatment outcomes in the analyses of the Glasgow expanding cohort

Table 3-11 summarises the baseline characteristics of the current and previous analyses on one expanding cohort. The previous three analyses were undertaken in 1999, 2003, and 2008 (n=525, 890, and 1098, respectively) (Kwan and Brodie, 2000, Mohanraj and Brodie, 2006, Brodie et al., 2012) at Epilepsy Unit in Glasgow. The first analysis included few patients (10%) who had previously been treated with antiepileptic drugs, while the subsequent three analyses included only patients with new-onset seizures. The current analysis included only adult patients aged 18 to 93 years, while the other analyses included adults and adolescents, aged 9 to 93 years. As expected, the prescription of new agents as monotherapy increased from 26% in 1999, to 41% in 2016. Similarly, the use of combined therapy increased from 13% in 1999 and 17% in 2008 to 20% in 2016. Furthermore, the use of new agents as combined therapy in the form of a combination of new agents only, or together with standard drugs, increased from 5 and 11.5% in 2008, to 6.5 and 13% in 2016, respectively.

Table 3-12 and Figure 3-8 show the changes in pharmacological outcomes in newly diagnosed epilepsy over a period between 1999 and 2016. Seizure remission rates were similar in 1999 (64%) and 2016 (62%), although the rate changed between these dates, decreasing to 59% in 2003, and increasing to 68% in 2008. Furthermore, there was gradual increase in seizure control on polytherapy, with 3% in 1999, 5% in 2003, 6% in 2008, and 7% in 2016. In contrast, fewer patients were controlled on standard monotherapy, with (23%) in 2016 compared to 31% in 2008. Finally, more seizure control was achieved on a combination of new agents (2.5%) in 2016 compared to 1% in 2008.

With regard to treatment tolerability, 21% of the initial AEDs were discontinued in 1999, due to their side effects. The figure was lower in 2003, 2008, and 2016, in which 11, 14, and 13% of patients respectively discontinued their first AEDs due to intolerable side effects.

Table 3-11. Comparison of baseline characteristics of the current and previous analyses of Glasgow expanding cohort

Year of analysis	1999	2003	2008	2016
Total number of patients	525*	780	1,098	1,528
Year of referral	1982-1997	1982-2001	1982-2005	1982-2012
Age in years as median (range)	27 (9-93)	31 (9-93)	32 (9-93)	37 (18-93)
Male n (%)	157 (47)	405 (52)	575 (52)	849 (56)
Current treatment n (%)				
No treatment	44 (8)			55 (4)
Monotherapy	423 (81)		913 (83)	1130 (74)
Standard drugs	289 (55)		457 (42)	500 (33)
Valproate	125 (24)			304 (20)
Carbamazepine	155 (29)			183 (12)
Phenytoin	8 (2)			12 (1)
Ethosuximide	1			1
Clobazam	0			0
New drugs	134 (26)		456 (41)	630 (41)
Lamotrigine	99 (19)			354 (23)
Levetiracetam	0			143 (9)
Oxcarbazepine	7 (1)			54 (4)
Topiramate	3			40 (2)
Gabapentine	15 (3)			15
Lacosamide	0			11
Tiagabine	9 (2)			4
Pregabalin	0			2
Eslicarbazepine	0			2
Vigabatrin	1			1
Zonisamide	0			1
Polytherapy	70 (13)		185 (17)	313 (20)
Standard drugs			4 (0.5)	7 (0.5)
New drugs			54 (5)	104 (6.5)
Combination of standard and new drugs			127 (11.5)	202 (13)

*470 newly diagnosed,

Table 3-12. Comparison of pharmacological outcomes of the current and previous analyses of newly diagnosed epilepsy cohort in Glasgow

Year of analysis	1999	2003	2008	2016
Total number of patients	470	780	1,098	1,528*
Seizure control	301 (64)	462 (59)	750 (68)	941 (62)
Successful monotherapy	287 (61)	420 (54)	680 (62)	811 (53)
Standard drugs			345 (31)	352 (23)
Valproate				212 (14)
Carbamazepine				131 (9)
Phenytoin				
New drugs			335 (30)	459 (30)
Lamotrigine				262 (17)
Levetiracetam				109 (7)
Oxcarbazepine				32 (2)
Topiramate				28 (2)
Other				28 (2)
Successful polytherapy	14 (3)	42 (5)	70 (6)	103 (7)
Standard drugs			1	1
New drugs			15 (1)	34 (2.5)
Combination of standard and new drugs			54 (5)	68 (4.5)
Pharmacoresistant†		276 (36)	272 (25)	175 (11)
Withdrawal of initial monotherapy due to poor tolerability	98 (21)	90 (11)	157 (14)	206 (13)

Data are number of patients (%). *only 1443 continued to take antiepileptic drugs at last follow-up. †Pharmacoresistant was defined in 2003 and 2008 analyses for patients who never achieved seizure-free for any 12 months, and in 2016 as failure to achieve any 12-month seizure-free on the last two proper drug schedules.

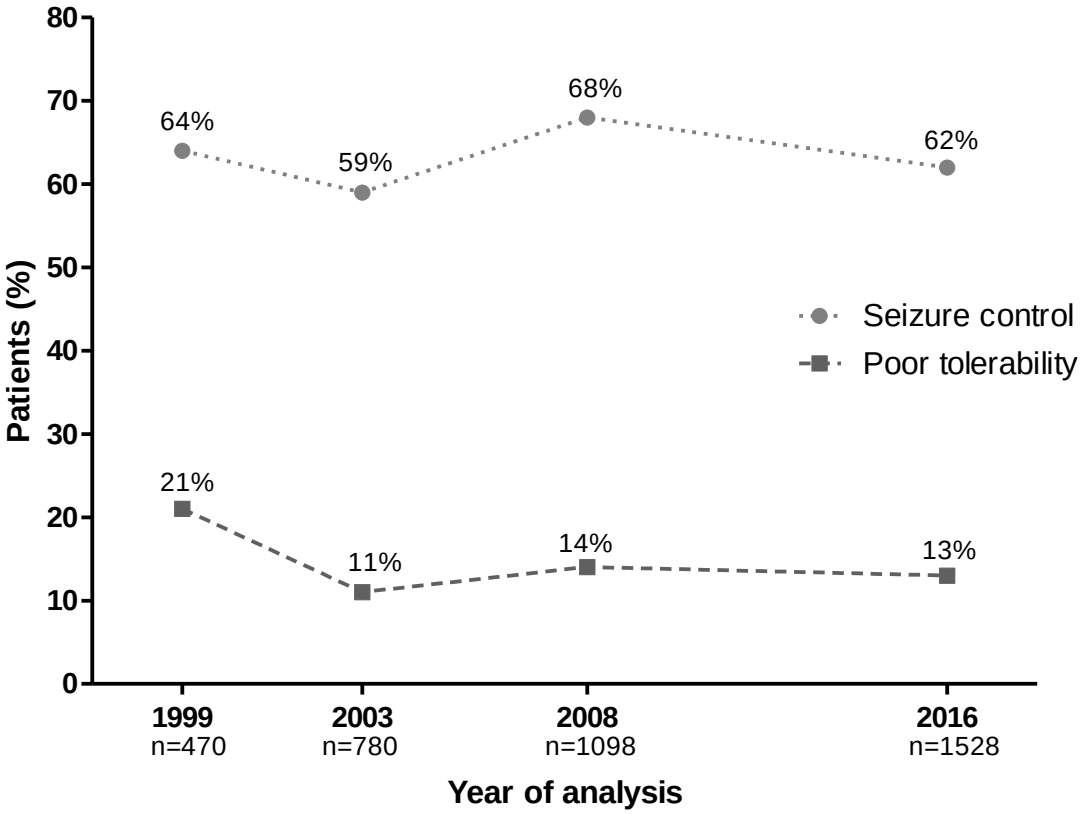


Figure 3-8. Changes in pharmacological outcomes between 1999 1nd 2016 in the Glasgow cohort of newly diagnosed epilepsy

3.4 Discussion

This section compares the current pharmacological outcomes to those of 17, 13, and eight years ago in an expanding cohort of newly diagnosed epilepsy patients. The study concerned evaluated whether the outcomes in the treatment of epilepsy were enhanced as a result of the introduction of a number of modern AEDs with different modes of action, and also assessed the clinical and pharmacological factors involved in seizure outcomes.

This observational study shows no evidence that treatment outcomes have improved in recent decades. Indeed, the seizure remission rate reported in this study (62%) was lower than that observed in the previous two analyses, with (64%) in 1999, and (68%) in 2008, despite an increase in the use of new AEDs as monotherapy, from 26% in 1999, to 41% in 2016, and as adjunct therapy, from 11.5% in 2008, to 13% in 2016. Several factors may have contributed to this low rate of seizure remission. First, the longer period of follow-up of this study may

have increased the possibility of detecting fluctuations in seizure control, and occasional seizure recurrence, among patients who were regarded as being seizure-free in previous studies. Furthermore, children and adolescents younger than 18 years, in whom seizure control was observed to be relatively high (Bamagous, 2010), were excluded from this study.

The findings of this study lend support to the concern that the efficacy of AEDs has not enhanced, despite the introduction of 14 new AEDs since the early 1990s, some of which include novel mechanisms of action (Loscher and Schmidt, 2011). The seizure remission rate in newly diagnosed epilepsy patients was estimated to be 70% in 1979 (Annegers et al., 1979). The figure was similar in the subsequent observational studies of newly diagnosed epilepsy in 2001 (Lindsten et al., 2001) and 2012 (Brodie et al., 2012), in which seizure-free rates were observed in 68% of patients in both studies.

The reason for this failure of the new AEDs is most likely due to preclinical approaches in the discovery and development of AEDs. The typical animal models utilised in the development of almost all AEDs have not succeeded in discovering AEDs with better efficacy in pharmacoresistant patients. A further reason is that almost all available AEDs are anti-seizure, temporarily supressing symptoms of epilepsy, and are not anti-eplieptogenic, nor they possess disease-modifying effects (Bialer and White, 2010). The clinical development of new AEDs may also contribute to this failure, to a lesser extent, as follows: the first problem is the clinical testing of a new drug in refractory patients with continuously AED-resistant seizures, who are unable to achieve seizure freedom to any significant degree, based on their treatment history. A further issue is the design of the current regulatory trials, in terms of them including intentionally fewer efficacious placebo controls and non-inferiority models, which do not determine whether the new drug is superior in efficacy to a standard treatment, prior to its approval (Loscher and Schmidt, 2011). In order to improve the discovery of AEDs, models for AED-resistant seizures are required, and anti-epileptogenic drugs should be developed that interrupt, or reverse, the underlying disease, instead of only symptomatically supressing seizures. In order to overcome the clinical problems, study populations should include patients with less resistant seizures, and the use of comparative effectiveness research of the new AEDs versus standard treatment, prior to approval (Loscher and Schmidt, 2011, Brodie, 2017a).

Although no enhancement was evident in the overall rate of seizure control in this study, several important changes in pharmacological treatments should be noted. The use of modern AEDs had increased: 41% of patients continued to take the new AEDs as a monotherapy in 2016, compared to 26% in 1999. A surveillance study conducted in 2011 showed that approximately 30% of epilepsy patients in Europe received the new AEDs (Cramer et al., 2011). This may imply that the prescription of modern AEDs has continually increased over the time, probably due to their favourable safety and tolerability, which makes them widely used AEDs. The use of combination therapy had also increased in this study. Due to the availability of many new AEDs as adjunct therapy alongside existing AEDs, the add-on strategy may have been preferred over alternative monotherapy approaches. Moreover, this analysis revealed that seizure remission achieved on polytherapy gradually increased as a result of the introduction of several new AEDs with different mechanisms of action. This increase in successful AED polytherapy may be due to a relapse of seizures in patients received monotherapy in the previous analyses, in whom combination therapy was required.

The results of this study demonstrated that the efficacy rates of different AEDs as a monotherapy were comparable. It should be noted that the cohort involved in this study constituted a combination of generalised and focal epilepsies, and that the evaluation of drug efficacy relating to a particular seizure type, or epilepsy syndrome, is outside the scope of this analysis. Moreover, no important differences were demonstrated in the efficacy rates of established and new AEDs. This is consistent with the findings of earlier comparative monotherapy trials, in which none of the new AEDs were found to be superior in efficacy to standard AEDs (i.e. VPA and CBZ) in new-onset generalised and focal epilepsy (Brodie et al., 2007, Marson et al., 2007b, Marson et al., 2007a, Baulac et al., 2012, Baulac et al., 2017, Trinka et al., 2017). However, LTG was shown to be less efficacious than VPA in generalised epilepsy, and GBP was less efficacious than CBZ in focal epilepsy. Subsequent large-scale observational studies were unable to produce convincing evidence that any modern AEDs are more efficacious than standard AEDs for newly diagnosed epilepsies (Loscher and Schmidt, 2011). However, there is no doubt that some of modern AEDs possess advantages in terms of safety and tolerability, which makes them common first-line treatments. For example, LEV and GBP have a lower risk of hypersensitivity reactions, and potential drug

interactions mediated by enzyme induction, than CBZ and PHT (Perucca and Gilliam, 2012). Additionally, the potential risk of teratogenicity in the use of LTG and LEV is lower than in VPA, and similar to that in CBZ (Tomson and Battino, 2012). Finally, LEV, GBP, and LTG appear to possess a better tolerability than CBZ in the elderly (Werhahn, 2009). Therefore, the tolerability aspect of AEDs is the single most important factor in drug selection, and this aspect will be discussed in later chapters.

Likewise, no significant difference existed in the efficacy rates of the most common AED combined therapies in this analysis. In some studies, the VPA/LTG combination has been observed to produce the highest remission rate among polytherapies (Mohanraj and Brodie, 2005), however the results of this study did not confirm this observation. Indeed, the remission rate was lower in this particular combination than in other common dual therapies studied in this analysis. Stephen et al. (2012) found that VPA/LTG dual therapy was the most common successful combination therapy. Doses of both LTG and VPA as a combination were lower than their doses when they were combined with other AEDs, indicating a possible synergistic effect. However, it should be pointed out that VPA inhibits LTG metabolism, therefore dosage reduction of LTG is generally required in this combination (Zaccara and Perucca, 2014). Moreover, the finding that VPA/LTG dual therapy was the most common successful polytherapy perhaps because it was the highest prescribed combination, though, the remission rates of common combination therapies, and the unsuccessful combined therapies, were not evaluated in Stephen et al. (2012) study.

The dosage involved in the uncontrolled group was higher than that in the controlled group in monotherapy and polytherapy. This may be because patients with intractable seizures require higher dosages. Moreover, consistent with other studies (Mohanraj and Brodie, 2005), the controlled patients commonly achieved seizure freedom on moderate doses (median LTG 200mg, CBZ 500mg, VPA and LEV 1000mg). Furthermore, doses of AEDs in combination therapy were generally higher than their dosages in monotherapy, except for LTG and VPA where they recombine, due to the aforementioned pharmacokinetic interaction and pssible synergism, respectively. The general high dosages in combination possibly because those patients who required polytherapy were more refractory than those on

monotherapy, and consequently required larger doses, although the dosage of AED monotherapy is usually reduced before an extra AED is added.

The univariate regression analysis demonstrates that poor seizure control was associated with the patients' age, family history of epilepsy, head injury, number and duration of pre-treatment seizures, psychiatric conditions, alcohol and recreational drugs abuse, and number of prior AEDs. The factors not associated with uncontrolled seizures included the patients' gender, epilepsy classification and aetiology, febrile convulsion, birth trauma, cerebrovascular disease, and learning disability.

Increased age at treatment initiation showed a significant association with better seizure control in univariate analysis, however the effect was small (OD 0.99, p=0.001) and not significant in the adjusted analysis. Inconsistent evidence existed with regards to age as a prognostic factor; the studies included patients of all ages did not demonstrate a correlation of age at onset with seizure outcome (Hitiris et al., 2007, Shen et al., 2016, Jiang et al., 2017). However, studies of the elderly (age >65 years at epilepsy onset) have indicated better treatment outcomes than for young patients (Stephen et al., 2006, Werhahn, 2009). Seizure aetiology may explain the better outcome in this group of patients. The most common aetiologies of epilepsy in the elderly are stroke and neurodegenerative diseases (Werhahn, 2009). Moreover, genetic involvement and lesional epileptogenicity that negatively influence the epilepsy prognosis and treatment response are lower in the elderly (Stephen et al., 2006). The findings of this study support this hypothesis, as the oldest patients (over 60 years) possessed the highest rate of seizure control.

A family history of epilepsy appeared to be a risk factor for poor seizure control in the adult cohort. Indeed, growing evidence exists for the contribution of genetic factors, and therefore of family history in the pathogenesis of epilepsy, and to a smaller degree in drug response (Reid et al., 2010). Similarly, a history of head injury was associated with uncontrolled seizure in this study, possibly due to brain damage (Mohanraj and Brodie, 2013). In line with other studies (Kwan and Brodie, 2000, MacDonald et al., 2000, Schiller and Najjar, 2008, Shen et al., 2016, Jiang et al., 2017), an increased number of pre-treatment seizures and duration was associated with worse outcomes in this study. Those experiencing more than 10

seizures and/ or one year before commencing AED therapy were more likely to be uncontrolled. A high frequency and duration of seizures have been demonstrated to produce structural changes in the brain, and consequently drug resistance. However, this may only be the case for patients with specific seizure types, i.e. focal seizures with impaired awareness (MacDonald et al., 2000, Mohanraj and Brodie, 2013).

Alcohol and recreational drugs abuse were associated with poor seizure control in this study. Ethanol can often provoke seizures as result of withdrawal phenomenon, since ethanol is a well-known sedative agent (Brust, 2008). Those admitting to the intermittent use of illegal recreational drugs in this study were two to three times more likely to be uncontrolled. Several reasons exist for the association between recreational drug abuse and intractable seizures. First, most illicit substances per se are psychostimulants, can reduce the seizure threshold, and have pharmacokinetics and pharmacodynamics potential interaction with AEDs. Furthermore, other seizure-provoking factors, such as alcohol abuse, head trauma, and other medical and psychiatric conditions, often coexist with illicit drug abuse. Finally, people exhibiting this behaviour are less likely to adhere to prescribed medications such as AEDs (Smith and McBride, 1999). Although particular illegal drugs, specifically cannabis, are beneficial to seizures, irregular and inappropriate use often results in uncontrolled seizures. The prevalence of this behaviour has been observed to be higher among epilepsy patients than in the general population (Smith and McBride, 1999). In this study, 11% of patients admitted to using illicit substances at some point during the follow-up period. However, there was no accurate tool to assess this activity, and it was possibly underestimated due to its dependency on self-reporting.

Psychiatric disorders, particularly depression, are common in people with epilepsy (Boylan et al., 2004, Guo et al., 2015). The pathogenesis shared by epilepsy and depression includes abnormalities in brain structure, function, and neurotransmitters secretion, such as serotonin. Moreover, psychiatric problems are very common, and under-recognised, in patients with refractory epilepsy (Boylan et al., 2004, Guo et al., 2015). Boylan et al. (2004) examined 122 epilepsy patients with intractable seizures and found that 54% of patients had depression, with only 17% of them being managed with antidepressants, while 37% were undiagnosed. In this current study, patients with psychiatric comorbidity were

associated with poor seizure control. Several assumptions can be proposed as an explanation for poor seizure control among psychiatric patients. First, some antidepressants can decrease the seizure threshold (Mohanraj and Brodie, 2013). Furthermore, depression and anxiety have been demonstrated to reduce adherence to AEDs therapy (Guo et al., 2015). Finally, neurobiological abnormality involved in psychiatric disorders interacts with those producing seizure, and therefore increases brain abnormality and the probability of pharmacoresistant epilepsy. The latter fact explains both pharmacological and post-surgical poor outcomes in epilepsy patients with psychiatric comorbidities (Hitiris et al., 2007). However, it should be noted that data regarding psychiatric disorders was not collected systemically, using validated tools, in this study.

The regression analysis of this study demonstrated that the failure of the first two AEDs schedules was the strongest covariate correlated with intractable seizures; patients with this covariate were four to five times more likely to be uncontrolled. Moreover, the majority (93%) of the controlled patients achieved seizure freedom on their first or second regimens. This finding lends further support to the ILAE definition of pharmacoresistant epilepsy, which recommends that patients who fail to attain a 12-month seizure remission on two tolerated and appropriate AED regimens should be reviewed by a specialist for a confirmation of their diagnosis, and for surgery consideration (Kwan et al., 2010). Indeed, early response to the AEDs has been regarded as the single most important predictor of the long-term prognosis (Kwan and Brodie, 2000, Schiller and Najjar, 2008, Brodie et al., 2013). In a prospective clinic-based study of 478 epilepsy patients, the seizure-free rates declined from 62% for the first AED, to 42% after one, 17% after two to five, and 0% after six to seven previous AEDs that failed due to their ineffectiveness (Schiller and Najjar, 2008).

However, other studies have appeared more optimistic, suggesting that pharmacological manipulation is still worthwhile in refractory patients. In a study of 155 refractory patients who tried 265 new drug introductions, 16% of drug additions resulted in a seizure remission of 12 months, and 28% of patients attained seizure remission by changing their medication (Luciano and Shorvon, 2007). A further study of 246 adult patients who fulfilled the ILAE's definition of drug-resistant epilepsy demonstrated that a high proportion of these patients (around 5% per year) achieved a seizure-free status of 12 months (Callaghan et

al., 2011). Although these studies apparently lend hope to refractory patients, the risk of subsequent relapse is high (71% at 5 years) (Schiller, 2009, Callaghan et al., 2011, Brodie et al., 2012).

Seizure relapse is not uncommon in patients who initially respond well to AEDs. In this study 16% (n=95) of uncontrolled patients initially entered a 12-month remission. Other studies have shown that 40% of patients had a seizure relapse five years after achieving seizure freedom; history of AED usage, and epilepsy duration were predictors for these seizure relapses (Schiller, 2009). This further evidence the fact that the available AEDs are anti-seizure, and not anti-epileptogenic.

Although seizure types and aetiology have been proposed as prognostic factors, this could not be confirmed by the results of this study. Several studies have observed better seizure outcomes in patients with idiopathic epilepsy than with symptomatic or cryptogenic epilepsy (Kwan and Brodie, 2000, Luciano and Shorvon, 2007). However, MacDonald et al. (2000) have concluded that the effect of the seizure type and aetiology is unimportant in determining long-term seizure remission, compared to other significant predictive factors, such as the number of early seizures.

In summary, although the introduction of several new AEDs has expanded treatment options, the results of this study suggested that treatment outcomes have not improved. Future research should therefore focus on novel treatments, such as gene therapy, that are able to modify epilepsy, instead of merely supressing the seizures. Although this new generation of AEDs has failed to provide more efficacious treatment options, the findings of this study indicated that their use has increased, most likely due to their advantages in terms of safety and tolerability. Favourable pharmacokinetic profiles, improved tolerability, and lower risk of hypersensitivity reactions, drug interactions, and teratogenicity have made many new AEDs being widely medication, and some as a first-line therapy. Therefore, tolerability of AEDs is invaluable in assisting in the drug selection. The next two chapters will focus on tolerability of AEDs.

Chapter 4. Intolerable adverse effects of antiepileptic drugs

4.1 Introduction

Adverse effects are a major reason for treatment failure, because they lead to early discontinuation of AEDs in 20% of patients (Kwan and Brodie, 2000), have a negative impact on patient adherence to medications (Eatock and Baker, 2007), and may prevent the administration of a therapeutic dosage (Perucca and Gilliam, 2012). In addition, they have a significant influence on the costs of healthcare (De Kinderen et al., 2014), and have emerged as one of the strongest predictors of health-related impaired quality of life (Perucca et al., 2009, Kwon and Park, 2011, Luoni et al., 2011).

Regulatory clinical trials and subsequent observational studies have focused on the efficacy of AED therapy rather than its safety and tolerability. However, if the patients cannot tolerate the treatment, efficacy becomes irrelevant (Brodie, 2017b). Because efficacy rates do not demonstrate substantial differences across AEDs that are effective against a specific seizure type, whereas adverse effect profiles differ greatly from drug to drug, tolerability is often the single most important consideration affecting AED selection (Perucca and Meador, 2005).

Adverse effects can be categorised as early and late appearing. Early appearing side effects are usually identified during regulatory clinical trials, while late appearing effects are generally detected during post-marketing surveillance. Thus, the adverse events reported in clinical trials are biased towards the inclusion of early problems, to which patients commonly develop tolerance. Further problem is the regulatory needs to evaluate AEDs as add-on to an existing schedule, versus placebo. Thus, adverse effect results are mixed-up by the concomitant AEDs (Cramer, 2012).

Long-term observational studies better reflect clinical practice, but few existing studies have examined which variables other than AEDs influence adverse effect reporting (Perucca and Gilliam, 2012). Definition and quantification of adverse effects of AEDs, and identification of population at high risk can help in reducing burden of adverse effects by optimising treatment, and eventually resulting in enhanced quality of life.

4.2 Methods

The primary endpoint for this analysis was the intolerable adverse effects of AEDs. In this context, an intolerable adverse effect was defined as that which caused drug withdrawal and an alternative AED was needed, or dose reduction and an add-on AED was required. The intolerable adverse effect could cause treatment failure alone or in combination with poor seizure control.

Adverse drug reactions were categorised into groups including tiredness, poor coordination, skin rash, gastrointestinal side effect, tremor, mood disorder, headache, weight gain, aggression, cognitive dysfunction, insomnia, irritability, paraesthesia, anorexia/weight loss, psychotic effect, sexual dysfunction, hyponatremia, and other. This categorisation based on the importance and frequency of adverse effect, and on the classifications used in other clinical studies (Baker et al., 1994, Mohanraj and Brodie, 2005, Marson et al., 2007a, Marson et al., 2007b). The details of these categories are explained in Chapter 2.

To compare the rates of adverse drug reactions between AEDs, a series of Chi-square (X^2) analyses was performed. The rate of adverse drug reactions from one AED was compared with that of another AED in a two-by-two comparison. When X^2 analyses included expected counts less than five, the Fisher's exact test was applied. To address the issue of multiple comparisons and to avoid a type I error, the P-value for significance was modified based on the Bonferroni correction (0.05/number of comparisons). Univariate and multivariate logistic regression analyses were used to evaluate the effect of the potential factors on tolerability outcome. Chi-square and two proportional statistical tests were used to compare other categorical data, if one variable was ordered, a chi-square test for trend was performed.

4.3 Results

A total of 2,911 AED regimens were tried during the follow-up period (Figure 4-1). Of these 2,911 regimens, approximately 50% (n=1,443) were continued by the patients when they were assessed during their final visit, while the remaining regimens were discontinued at any given time during the follow-up period. The continued AED schedules and the seizure outcomes were discussed in the previous

section. For each discontinued drug, the reasons for discontinuation were recorded and categorised into four groups: poor seizure control, poor drug tolerability, both ineffective and intolerance, or other reasons. Other reasons for AED discontinuation (n=100) included a long-term seizure-free period (n=34), regulatory reasons (such as trial halted) (n=32), patient preference (such as fear of side effects) (n=23), or teratogenicity concerns (n=11). The preceding group was excluded from subsequent analyses. The poor seizure control resulted in treatment failure in 553 attempts, and details of the AED regimens are shown in Table 4-1. Treatment failure due to poor tolerability or both ineffective and intolerance will be discussed in the following section (Table 4-2).

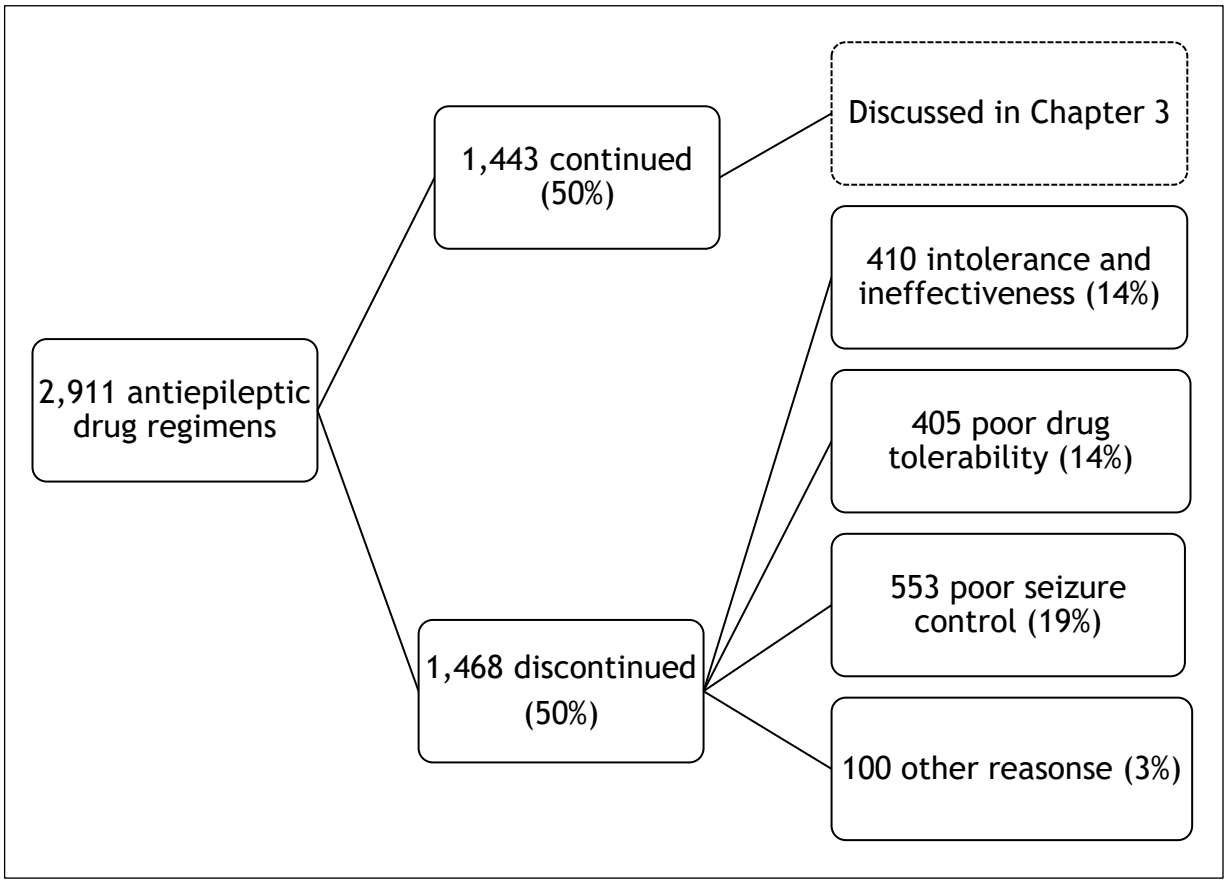


Figure 4-1. Response to each antiepileptic drug schedule tried during the follow-up
Other reasons for antiepileptic drugs discontinuation (n=100) included a long-term seizure-free period (n=34), regulatory reasons (n=32), patient preference (n=23), or teratogenicity concerns (n=11).

Table 4-1. Discontinued antiepileptic drug regimens due to poor seizure control (n=553)

Monotherapy		Dual therapy		Triple therapy		Quadruple therapy	
VPA	108	VPA/LTG	21	CBZ/LEV/TPM	4	VPA/TPM/PGB/CLB	1
LTG	99	LTG/LEV	17	VPA/LTG/TPM	3	VPA/LTG/TPM/RTG	1
CBZ	61	VPA/LEV	10	Other	39	Other	2
LEV	41	CBZ/LTG	6				
OXC	14	LTG/PGB	5				
GBP	8	CBZ/GBP	5				
TPM	8	Other	58				
Other	19						
Total	360		143		46		4

Data are presented in number of cases. Key: VPA: valproate, LTG: lamotrigine, CBZ: carbamazepine, LEV: levetiracetam, OXC: oxcarbazepine, GPB: gabapentin, TPM: topiramate, PGB: pregabaline, CLB: clobazam, RTG: retigabine.

Table 4-2. Discontinued antiepileptic drug regimens due to intolerable adverse effects (n=815)

Monotherapy		Dual therapy		Triple therapy		Quadruple therapy	
VPA	143	VPA/LTG	47	VPA/LTG/LEV	4	VPA/LTG/LEV/TPM	3
LTG	109	VPA/LEV	16	VPA/LEV/ESL	3	Other	6
CBZ	106	LTG/LEV	13	Other	55		
LEV	61	LTG/TPM	12				
OXC	43	CBZ/LTG	9				
TPM	32	VPA/TPM	7				
GPB	10	Other	102				
LCM	8						
FBM	6						
TGB	6						
PHT	6						
other	8						
Total	538		206		62		9

Data are presented in number of cases Key: Key: VPA: valproate, LTG: lamotrigine, CBZ: carbamazepine, LEV: levetiracetam, OXC: oxcarbazepine, TPM: topiramate, GPB: gabapentin, LCM: lacosamide, FBM: felbamate, TGB: tiagabine, PHT: phenytoin, ESL: eslicabazepine acetate.

4.3.1 Rate of adverse drug reactions

Of the total 2,911 treatment schedules, 815 (28%) failed due to intolerable adverse effects, either alone (n=405) or in combination with the lack of efficacy (n=410). Among 1,528 initial monotherapies, 206 (13%) were stopped due to adverse drug reactions.

Tiredness was the most frequent intolerable side effect of AED usage. The overall incidence of tiredness was 5.2% (n=152/2,911), which represented 19% (n=152/815) of treatment failure due to adverse drug reactions. Poor coordination and skin rash were the second most common adverse drug reactions, with a 2.9% (n=86) incidence for each. Poor coordination and rash each alone accounted for 11% of the total intolerable adverse effects. Incidence of gastrointestinal side effects and tremor was 2.7% (n=80) and 2.2% (n=63), respectively. The incidence of psychiatric and behavioural side effects including mood changes, aggression and irritability was 3% (n=91), and accounted for 11% of overall AED intolerability. Table 4-3 shows the frequent intolerable adverse drug reactions associated with AEDs use.

Table 4-3. Intolerable adverse effects associated with antiepileptic drug use

	Overall n (%), [incidence]	Monotherapy	Polytherapy
Tiredness	152 (19), [5.2]	92 (17)	60 (22)
Poor coordination	86 (11), [2.9]	50 (10)	36 (13)
Skin rash	86 (11), [2.9]	80 (15)	6 (2)
Gastrointestinal side effect	80 (10), [2.7]	57 (11)	23 (8)
Tremor	63 (8), [2.2]	43 (8)	20 (7)
Mood change	44 (5), [1.5]	22 (4)	22 (8)
Headache	43 (5), [1.5]	32 (6)	11 (4)
Weight gain	38 (5), [1.3]	29 (5)	9 (3)
Aggression	33 (4), [1.1]	18 (3)	15 (5)
Cognitive dysfunction	24 (3), [0.8]	10 (2)	14 (5)
Insomnia	20 (2), [0.7]	16 (3)	4 (2)
Irritability	14 (2), [0.5]	11 (2)	3 (1)
Paraesthesia	12 (1), [0.4]	8 (1)	4 (2)
Anorexia/ weight loss	11 (1), [0.4]	7 (1)	4 (2)
Hair loss	8 (1), [0.3]	5 (1)	3 (1)
Psychosis effect	8 (1), [0.3]	5 (1)	3 (1)
Sexual dysfunction	8 (1), [0.3]	8 (1)	0
hyponatremia	7 (1), [0.3]	4 (1)	3 (1)
Other	78 (9), [28]	41 (8)	37 (13)
Total cases	815	538	277

Data are presented in number of cases (% of total number of cases), [incidence=case number/total number of attempts*100]. Total number of attempts was 2,911.

4.3.2 Comparison of tolerability of antiepileptic drugs

The tolerability rates of 17 different AEDs were compared when AEDs were used as monotherapy or as part of polytherapy. As shown in pairwise comparisons in Table 4-4, Figure 4-2, Table 4-5, and Figure 4-3, LTG was associated with the lowest adverse effects rate whether it was used as monotherapy (19%, n=109/575) or as part of polytherapy (9%, n=35/387). However, TPM was associated with the highest rate of adverse effects (39%, n=32/81) among monotherapies, while RTG had the highest rate of adverse effects (42%, n=8/19) among AEDs used as part of polytherapies.

In order to asses and overcome the potential effect of confounders on tolerability rate of AEDs, several analyses were performed. First, a univariate regression analysis which shows that six factors were significantly influenced the tolerability; gender, epilepsy type and aetiology, number of pre-treatment seizure, psychiatric comorbidity, and number of prior and concomitant AEDs. Seizure aetiology and number of prior AEDs were excluded from the multivariate model because they interacted with other variables. After accounting for the significant variables in the adjusted model (multivariate), there was found to be no significant evidence of an association between seizure type and tolerability. Table 4-6 shows univariate and multivariate logistic regression analysis for predictors of tolerability. These factors will be discussed further later in this chapter.

Then, the aforementioned significant factors were assessed for individual AEDs (LTG, VPA, CBZ, LEV, OXC, and TPM) to examine their effect on the reported tolerability rates. As shown in Table 4-7, psychiatric comorbidity rate was comparable among monotherapies users. However, differences were observed in gender, epilepsy type, pre-treatment seizure number, and number of prior AEDs. VPA was the least AED tried by female patients (30%), while LTG (61%) and LEV (57%) were the most frequent AEDs used by those patients. Likewise, VPA was the least AED tried by patients with focal epilepsies (80%), the figure was the highest in CBZ and OXC groups (both 90%). Patients with more than 10 seizures before treatment tried LTG (33%) less frequently than other treatment groups. Patients tried OXC (19%) after failure of two previous AEDs more frequently than patients tried other AEDs. Table 4-8 demonstrates more details about pairwise comparisons of these factors among different treatment groups.

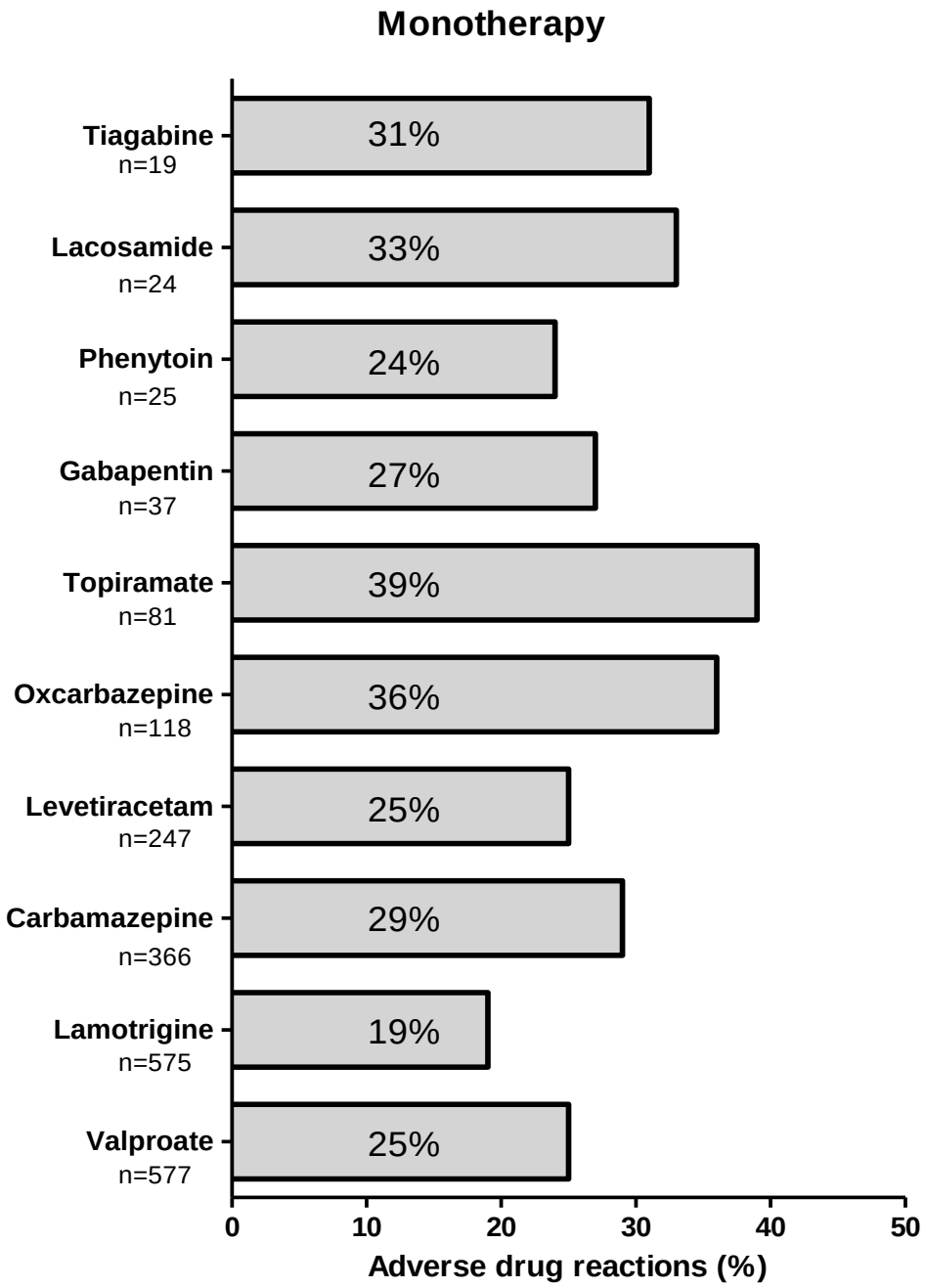


Figure 4-2. Comparison of tolerability of antiepileptic drugs used as monotherapy
Pairwise comparison shown in Table 4-4.

Table 4-4. Pairwise comparison of tolerability of antiepileptic drugs used as monotherapy

	LTG (19%) n=575	CBZ (29%) n=366	LEV (25%) n=247	OXC (36%) n=118	TPM (39%) n=81	GPB (27%) n=37	PHT (24%) n=25	LCM (33%) n=24	TGB (31%) n=19
VPA (25%) n=577	0.017	0.157	0.979	0.009	0.005	0.76	0.929	0.344	0.59
LTG		**<0.000**	0.062	**<0.000**	**<0.000**	0.229	0.602	0.11	0.231
CBZ			0.24	0.126	0.063	0.804	0.595	0.648	0.807
LEV				0.02	0.01	0.76	0.939	0.354	0.583
OXC					0.661	0.292	0.234	0.772	0.682
TPM						0.183	0.158	0.584	0.518
GBP							0.789	0.599	0.722
PHT								0.47	0.577
LCM									0.903

Data are P-value of X^2/ Fisher's exact test, Significance at $p < 0.001$ (Bonferroni correction=0.05/45). n=number of total attempts (% of intolerable adverse reactions). Key: VPA: valproate, LTG: lamotrigine, CBZ: carbamazepine, LEV: levetiracetam, OXC: oxcarbazepine, TPM: topiramate, GPB: gabapentin, PHT: phenytoin, LCM: lacosamide, TGB: tiagabine. Eslicabazepine acetate, pregabaline, zonisamide, vigabatrin, clobazam, retigabine, and perampanel were excluded from pairwise comparison because the results were inaccurate for small samples.

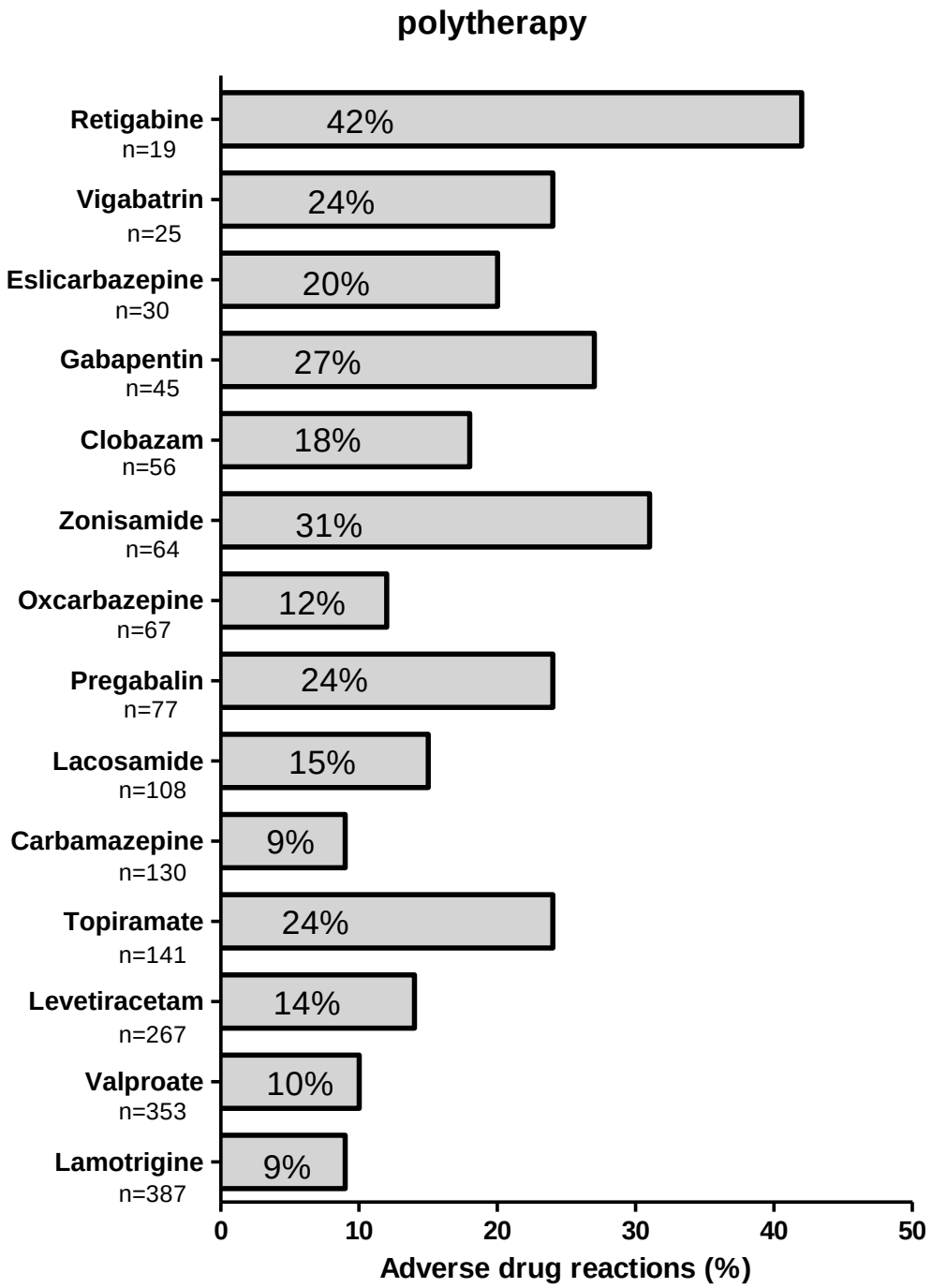


Figure 4-3. Comparison of tolerability of antiepileptic drugs used as part of polytherapy
Pairwise comparison shown in Table 4-5.

Table 4-5. Pairwise comparison of tolerability of antiepileptic drugs used as polytherapy

	VPA (10%) n=353	LEV (14%) n=267	TPM (24%) n=141	CBZ (9%) n=130	LCM (15%) n=108	PGB (24%) n=77	OXC (12%) n=67	ZNS (31%) n=64	CLB (18%) n=56	GBP (27%) n=45	ESL (20%) n=30	VGB (24%) n=25	RTG (42%) n=19
LTG (9%) n=387	0.691	**<0.000**	**<0.000**	0.91	0.066	**<0.000**	0.411	**<0.000**	0.034	0.001	0.055	0.025	**<0.000**
VPA		0.001	**<0.000**	0.695	0.13	0.001	0.564	**<0.000**	0.065	0.001	0.11	0.037	**<0.000**
LEV			0.236	0.006	0.326	0.409	0.169	0.033	0.829	0.242	0.906	0.598	0.034
TPM				**<0.000**	0.066	0.903	0.041	0.287	0.334	0.731	0.624	0.99	0.103
CBZ					0.125	0.003	0.44	**<0.000**	0.063	0.003	0.094	0.034	0.001
LCM						0.141	0.588	0.01	0.616	0.092	0.094	0.034	0.01
PGB							0.071	0.295	0.441	0.685	0.704	0.949	0.1
OXC								0.007	0.355	0.048	0.353	0.193	0.006
ZNS									0.088	0.604	0.256	0.499	0.38
CLB										0.288	0.809	0.544	0.059
GBP											0.508	0.807	0.23
ESL												0.721	0.098
VGB													0.202

Data are P-value of X^2/ Fisher's exact test, Significance at $p < 0.0005$ (Bonferroni correction=0.05/91). n=number of total attempts (% of intolerable adverse reactions). Key: LTG: lamotrigine, VPA: valproate, LEV: levetiracetam, TPM: topiramate, CBZ: carbamazepine, LCM: lacosamide, PGB: pregabaline, OXC: oxcarbazepine, ZNS: zonisamide, CLB: clobazam, GPB: gabapentin, ESL: eslicabazepine acetate, VGB: vigabatrin, RTG: retigabine. Phenytoin, tiagabine, and perampanel were excluded from pairwise comparison because the results were inaccurate for small samples.

Table 4-6. Univariate and multivariate logistic regression analysis for predictors of adverse effects

	Univariate		Multivariate	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Female gender	1.528 (1.299, 1.798)	**<0.000**	1.485 (1.259, 1.754)	**<0.000**
Age (Years)	1.004 (0.999, 1.009)	0.133		
Focal epilepsy	1.4 (1.093, 1.794)	**0.008**	1.265 (0.981, 1.631)	0.087
Seizure aetiology*		**0.017**		
Family history of epilepsy	1.147 (0.933, 1.41)	0.192		
Febrile convulsion	1.064 (0.729, 1.552)	0.749		
Birth trauma	1.549 (0.675, 3.554)	0.302		
Head injury	0.911 (0.731, 1.137)	0.411		
Cerebrovascular disease	1.209 (0.951, 1.537)	0.121		
More than 10 seizures before treatment	1.608 (1.365, 1.893)	**<0.000**	1.488 (1.259, 1.758)	**<0.000**
Seizures for >1 year before treatment	1.08 (0.918, 1.269)	0.353		
Learning disability	0.617 (0.361, 1.054)	0.077		
Psychiatric comorbidity	1.388 (1.174, 1.641)	**<0.000**	1.215 (1.022, 1.444)	**0.027**
Alcohol abuse	0.881 (0.727, 1.067)	0.194		
Recreational drug use	1.099 (0.87, 1.388)	0.429		
Number of prior antiepileptic drugs*	1.118 (1.1071, 1.168)	**<0.000**		
Monotherapy	0.642 (0.539, 0.766)	**<0.000**	0.686 (0.577, 0.827)	**<0.000**

*excluded from multivariate analysis because they interacted with other variables.

Table 4-7. Clinical characteristics of patients starting different antiepileptic drugs as monotherapy

	VPA n=577	LTG n=575	CBZ n=366	LEV n=247	OXC n=118	TPM n=81	X^2-P-value
Female gender	176 (30)	353 (61)	155 (42)	141 (57)	48 (41)	42 (52)	**<0.000**
Focal epilepsy	460 (80)	490 (85)	328 (90)	210 (85)	106 (90)	67 (83)	**0.001**
Seizure aetiology							
Cryptogenic	299 (52)	286 (50)	187 (51)	122 (49)	62 (53)	45 (56)	
Idiopathic	117 (20)	85 (15)	38 (10)	37 (15)	12 (10)	14 (17)	
symptomatic	161 (28)	204 (35)	141 (39)	88 (64)	44 (37)	22 (27)	
More than 10 pre-treatment seizure	226 (39)	192 (33)	130 (35)	84 (34)	53 (45)	37 (46)	**0.045**
Psychiatric comorbidity	188 (33)	167 (29)	101 (38)	82 (33)	36 (31)	26 32)	0.527
Failure of two or more previous antiepileptic drugs	44 (8)	50 (9)	39 (11)	21 (9)	23 (19)	10 (12)	**0.003**

Data are presented in patients number (%). Key: VPA: valproate, LTG: lamotrigine, CBZ: carbamazepine, LEV: levetiracetam, OXC: oxcarbazepine, TPM: topiramate. Because of small sample sizes, other antiepileptic drugs were not included in this sub-analysis.

Table 4-8. Pairwise comparisons of clinical characteristics of different treatment groups

	VPA n=577	CBZ n=366	LEV n=247	OXC n=118	TPM n=81
Female	**30%**	**42%**	**57%**	**41%**	**52%**
LTG 61%, n=575	**<0.000**	**<0.000**	0.25	**<0.000**	0.107
VPA		**<0.000**	**<0.000**	**0.038**	**<0.000**
CBZ			**<0.000**	0.748	0.121
LEV				**0.003**	0.412
OXC					0.147
Focal	**80%**	**90%**	**85%**	**90%**	**83%**
LTG 85%, n=575	**0.014**	**0.043**	0.942	0.143	0.574
VPA		**<0.000**	0.06	**0.002**	0.508
CBZ			0.098	0.947	0.125
LEV				0.18	0.629
OXC					0.158
>10 pre-treatment seizure	**39%**	**35%**	**34%**	**45%**	**46%**
LTG 33%, n=575	**0.041**	0.504	0.864	**0.021**	**0.036**
VPA		0.258	0.156	0.251	0.269
CBZ			0.7	0.072	0.094
LEV				**0.047**	0.064
OXC					0.915
Failure of two previous antiepileptic drugs	**8%**	**11%**	**9%**	**19%**	**12%**
LTG 9%, n=575	0.507	0.326	0.928	**0.005**	0.389
VPA		0.121	0.675	**0.002**	0.248
CBZ			0.369	**0.027**	0.672
LEV				**0.007**	0.344
OXC					0.166

Data are p-values of X^2 test. Key: VPA: valproate, LTG: lamotrigine, CBZ: carbamazepine, LEV: levetiracetam, OXC: oxcarbazepine, TPM: topiramate. Because of small sample sizes, other antiepileptic drugs were not included in this sub-analysis.

4.3.3 Tolerability profiles of individual antiepileptic drugs

Table 4-9 shows the adverse drug reactions reported for individual AEDs. The main adverse reaction associated with LTG was skin rash which caused 28% of poor tolerated cases, this was the case with CBZ (28%) and PHT (50%) as well. VPA poorly tolerated most frequently due to tremor and weight gain, which scored 27 and 18% respectively. Whereas LEV poorly tolerated commonly due to psychiatric and behavioural side effects including mood disorder, aggression, and irritability, which accounted for 41% (n=46/112) of the overall intolerability of LEV. Cognitive

dysfunction was most commonly associated with TPM with 6.4% incidence. The incidence of hyponatremia was 2.7% with OXC therapy, and much lower for CBZ (0.4%). Headaches were frequently associated with LCM (2.3%), while CLB was the most common AED cause the tiredness in this cohort with 10.5% incidence. ESL acetate was the most AED associated with gastrointestinal adverse effects with 8.1% (n=3) incidence, while PER was the drug most associated with poor coordination (15.4%, n=2); though, the cases number were few.

Table 4-9. Intolerable adverse effects of individual antiepileptic drugs used as monotherapy or as part of polytherapy

	n (%), [incidence]					
	LTG n=962	VPA n=930	LEV n=514	CBZ n=496	TPM n=222	OXC n=185
Tiredness	15 (10), [1.6]	28 (16), [3]	26 (23), [5]	31 (26), [6]	10 (15), [4.5]	15 (29), [8.1]
Poor coordination	17 (12), [1.8]	8 (5), [1]	4 (4), [1]	20 (17), [4]	1 (2)	12 (24), [6.5]
Skin rash	40 (28), [4.2]	1 (1)		33 (28), [6.6]		6 (12), [3.2]
GI side effect	12 (8), [1.2]	24 (14), [3]	8 (7), [2]	8 (7), [2]		6 (12), [3]
Tremor	10 (7), [1]	48 (27), [5.2]		2 (2)		
Mood disorder	1 (1), [0.1]	3 (2)	22 (20), [4]	1 (1)	7 (11), [3]	1 (2), [1]
Headache	15 (10), [1.6]	3 (2)	10 (9), [1.9]	8 (7), [1.6]	1 (2)	1 (2), [1]
Weight gain		32 (18), [3.4]	1 (1)			
Aggression	3 (2), [0.3]	1 (1)	18 (16), [4]	1 (1)	4 (6), [2]	
Cognitive dysfunction	1 (1), [0.1]	1 (1)		1 (1)	14 (21), [6.4]	1 (2), [1]
Insomnia	8 (6), [0.8]	1 (1)	7 (6), [1]			1 (2), [1]
Irritability	3 (2), [0.3]	1 (1)	6 (5), [1]		2 (3), [1]	
Paraesthesia			1 (1)		10 (15), [4.5]	
Anorexia/ weight loss					10 (15), [4.5]	
Hair loss		7 (4), [1]		1 (1)		
Psychosis effect	4 (3), [0.4]					
Sexual dysfunction		1 (1)		5 (4), [1]		1 (2), [1]
Hyponatremia				2 (2), [0.4]		5 (10), [2.7]
Other	14	18	9	4	7	2
Total cases	143	177	112	117	66	51

Table 4-9. Intolerable adverse effects of individual antiepileptic drugs used as monotherapy or as part of polytherapy

	n (%), [incidence]					
	LCM n=132	GBP n=82	PGB n=81	ZNS n=68	CLB n=57	PHT n=38
Tiredness	4 (17), [3]	4 (18), [5]	2 (10), [2]	6 (29), [8.8]	6 (60), [10.5]	
Poor coordination	4 (17), [3]	6 (27), [7.3]	3 (15), [4]	1 (5), [1]		
Skin rash	1 (4), [1]		1 (5), [1]			3 (50), [7.9]
GI side effect	2 (8), [2]	6 (27), [7.3]	2 (10), [2]	1 (5), [1]	1 (10), [2]	2 (33), [5.3]
Tremor	1 (4), [1]		2 (10), [2]			
Mood disorder	2 (8), [2]		1 (5), [1]	3 (14), [4]		
Headache	3 (13), [2.3]			1 (5), [1]		1 (17), [3]
Weight gain		2 (9), [2]	2 (10), [2]			
Aggression				1 (5), [1]	1 (10), [2]	
Cognitive dysfunction	1 (4), [1]	1 (5), [1]	1 (5), [1]	2 (10), [3]		
Insomnia			1 (5), [1]	1 (5), [1]		
Paraesthesia	1 (4), [1]					
Anorexia/ weight loss				1 (5), [1]		
Psychosis effect	1 (4), [1]		1 (5), [1]	1 (5), [1]		
Sexual dysfunction		1 (5), [1]				
Other	4	1	4	1	2	
Total cases	24	22	20	21	10	6

Table 4-9. Intolerable adverse effects of individual antiepileptic drugs used as monotherapy or as part of polytherapy

	n (%), [incidence]					
	ESL n=37	TGB n=27	VGB n=27	RTG n=19	PER n=13	
Tiredness	1 (13), [3]		2 (29), [7]	1 (13), [5]		
Poor coordination	3 (38), [8]	3 (38), [11]		1 (13), [5]	2 (50), [15.4]	
Skin rash	1 (13), [2.7]					
GI side effect	3 (38), [8.1]			1 (13), [5]	1 (25), [8]	
Mood disorder		1 (13), [4]		1 (13), [5]		
Weight gain			1 (14), [4]			
Aggression		1 (13), [4]	2 (29), [7]		1 (25), [8]	
Cognitive dysfunction		1 (13), [4]				
Paraesthesia				1 (13), [5]		
Other		2	2	3		
Total cases	8	8	7	8	4	

Data are presented in number of cases (% of total number of cases), [incidence=case number/total number of attempts*100], n=number of total attempts.). Key: LTG: lamotrigine, VPA: valproate, LEV: levetiracetam, CBZ: carbamazepine, TPM: topiramate, OXC: oxcarbazepine, LCM: lacosamide, GPB: gabapentin, PGB: pregabaline, ZNS: zonisamide, CLB: clobazam, PHT: phenytoin, ESL: eslicabazepine acetate, TGB: tiagabine, VGB: vigabatrin, RTG: retigabine, PER: perampanel, GI: gastrointestinal.

4.3.4 Adverse drug reactions with particular combination therapies

The combination therapy of VPA with LTG was the most commonly used combination in this cohort (n=136). Followed by the combination of LTG with LEV (n=55), then VPA with LEV (n=37). The rate of adverse drug reactions was 35% (n=24/136) with VPA/LTG, 24% (n=13/55) with LTG/LEV, and 43% (16/37) with VPA/LEV (Figure 4-4). However, these differences did not reach a statistical significance (p=0.132). Tremor was the most common side effect reported for the VPA/LTG combination, which rated a 28% of poor tolerability. Tiredness was the most frequent reaction reported for both LTG/LEV and VPA/LEV. The details about other adverse drug reactions are shown in Table 4-10.

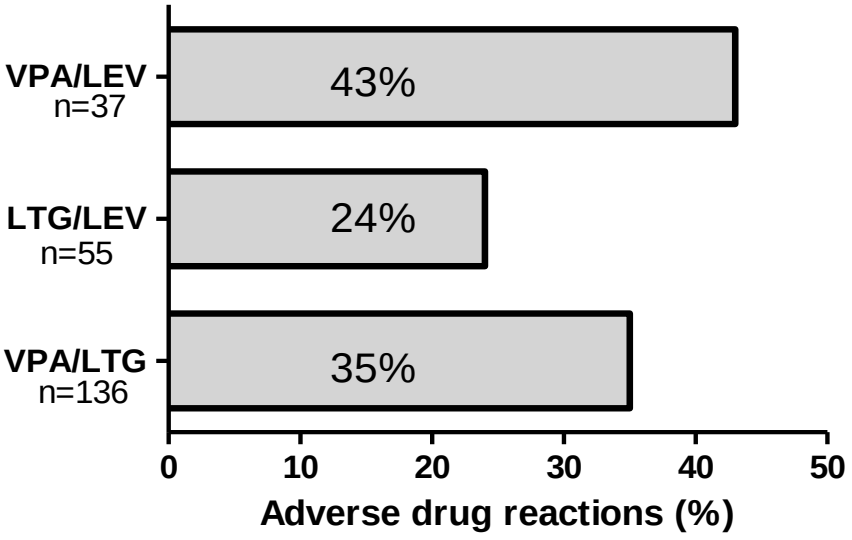


Figure 4-4. Tolerability of the most commonly used combination therapies
X^2 p-value=0.132. Key: VPA: valproate, LTG: lamotrigine, LEV: levetiracetam.

Table 4-10. Adverse effects of particular antiepileptic drug combinations

	VPA/LTG	LTG/LEV	VPA/LEV
Tremor	13 (28)		2 (13)
Poor coordination	6 (13)		
Tiredness	6 (13)	6 (46)	5 (31)
Weight gain	4 (8)		1 (6)
Skin rash	3 (6)		
Gastrointestinal side effect	2 (4)	2 (15)	2 (12)
Headache	2 (4)	2 (15)	1 (6)
Cognitive dysfunction	1 (2)		
Hair loss	1 (2)		
Psychosis effect	1 (2)		
Insomnia	1 (2)		1 (6)
Aggression			1 (6)
Mood disorder		2 (15)	3 (19)
Other	7 (15)	1 (8)	
Total	47	13	16

Data are presented in number of cases (%). Key: VPA: valproate, LTG: lamotrigine, LEV: levetiracetam.

4.3.5 Potential predictors for adverse drug reactions

The following section will more closely examine and quantify the effect of several potential predictors that demonstrated a significant correlation with poor tolerability in the univariate regression analysis (Table 4-6). These included patient-related factors (gender, epilepsy diagnosis, seizure aetiology, psychiatric comorbidity, and number of pre-treatment seizure) and pharmacological factors (number of prior AEDs, number of concomitant AEDs, and drug generation).

Female sex was significantly associated with higher levels of poor tolerability (28%, n=189/679) than the male patients (21%, n=177/849). The adverse drug reactions rate was also significantly higher in patients with focal epilepsy (25%, n=322/1290) compared to patients with generalised epilepsy (18%, n=44/238). Likewise, cryptogenic (26%) and symptomatic (24%) seizure aetiology had higher instances of poor tolerability than idiopathic seizure (18%). Patients with psychiatric comorbidity presented higher levels of poor tolerability (29%, n=125/433) than patients with no psychiatric problems (22%, n=241/1095), p=0.005 (95% CI 0.139, 0.258). Finally, number of pre-treatment seizures had a linear positive correlation with poor tolerability (p=0.001). Table 4-11 and Figure 4-5 summarise the influence of patient-related factors on tolerability of AEDs.

With regard to pharmacological factors, the number of the prior unsuccessful AED schedules and co-prescribed AEDs showed a linear positive relationship with poor tolerability (both p<0.000). However, the adverse drug reactions rate was not different in patients treated with older AEDs compared to the patients treated with new AEDs (p=0.377). Table 4-12 and Figure 4-6 present the effect of the pharmacological factors on drug tolerability.

As shown in Figure 4-7, patient groups who had an intolerable adverse effect at one AEDs schedule were more likely to experience intolerable adverse effects at subsequent AED schedule.

Table 4-11. Potential patient-related factors on tolerability of antiepileptic drug used as first attempt (n=1,528)

		Intolerable adverse effects (n=366)	P-value (95% CI)
Gender	Female (n=679) Male (n=849)	189 (28) 177 (21)	0.001 (0.026, 0.113)
Epilepsy type	Focal (n=1290) Generalised (n=238)	322 (25) 44 (18)	0.032 (0.01,0.119)
Seizure aetiology	Cryptogenic (n=776) Idiopathic (n=238) Symptomatic (n=514)	199 (26) 44 (18) 123 (24)	<0.000
Number of pre-treatment seizure	1 (n=55) 2 (n=300) 3-5 (n=439) 6-10 (n=219) 11-20 (n=95) >20 (n=420)	10 (18) 62 (21) 98 (22) 44 (20) 31 (33) 121 (29)	0.001
Psychiatric comorbidity	Yes (n=433) No (n=1095)	125 (29) 241 (22)	0.005 (0.139,0.258)

Data are presented in number of cases (%). X^2, 2-proportions test and X^2 for trend were used.

Table 4-12. Potential pharmacological factors on tolerability of all antiepileptic drugs regimens tried during follow-up (n=2,911)

		Intolerable adverse effects (n=815)	P-value (95% CI)
Number of prior antiepileptic drugs	0 (n=1,528) 1 (n=643) 2 (n=306) 3 (n=170) 4 (n=102) 5 (n=59) >5 (n=103)	366 (24) 192 (30) 98 (32) 62 (36) 39 (38) 20 (34) 38 (37)	<0.000
Number of co-prescribed antiepileptic drugs	Monotherapy (n=2113) Dual therapy (n=605) Triple therapy (n=167) Quadruple therapy (n=25) 5 antiepileptics (n=1)	538 (25) 206 (34) 62 (37) 9 (36) 0	<0.000
		Intolerable adverse effects (n=538)	
Drug generation of monotherapies	First generation (n=969) New generation (n=1144)	255 (26) 283 (25)	0.377 (-0.02,0.054)

Data are presented in number of cases (%). 2-proportion and X^2 for trend tests were used.

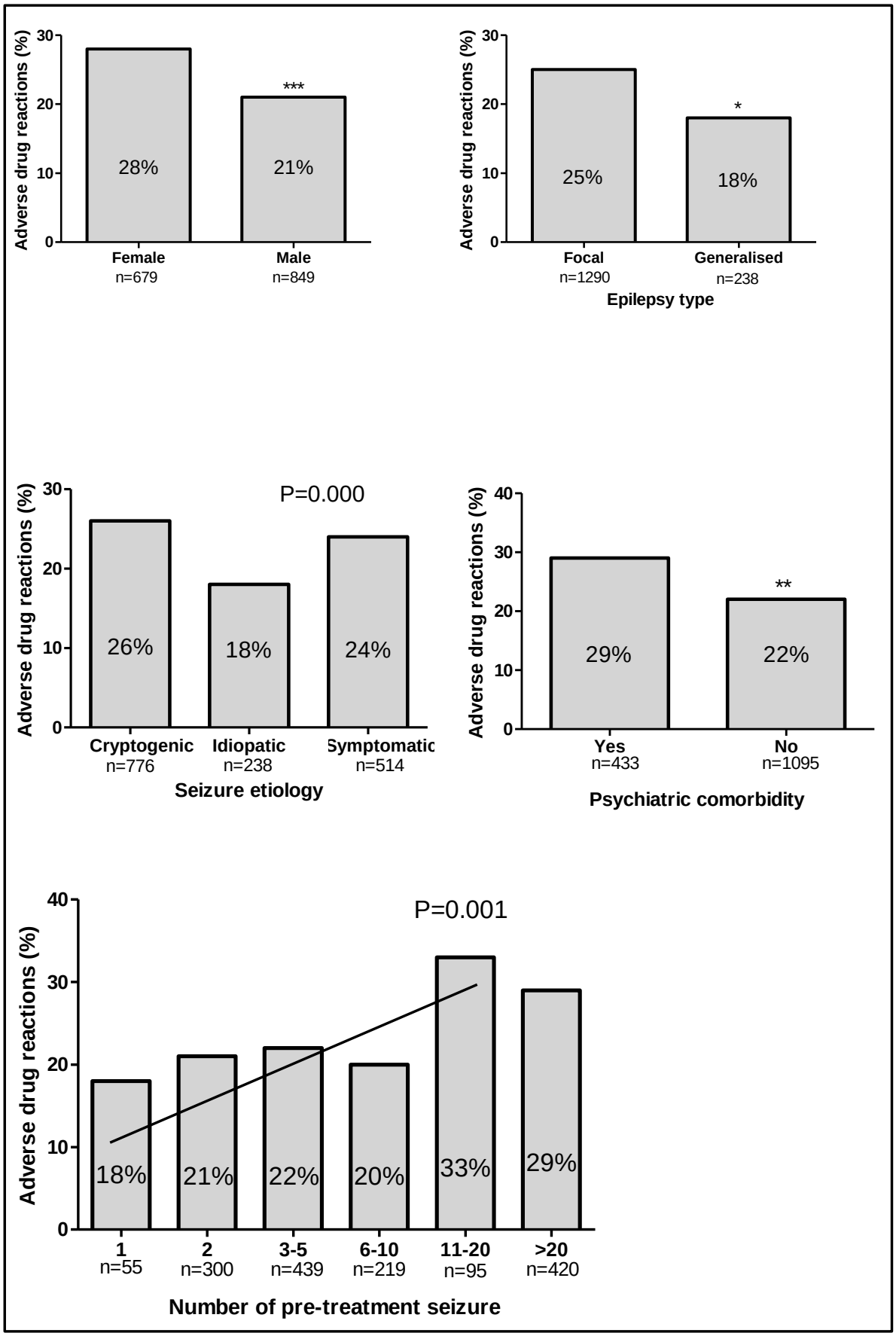


Figure 4-5. Potential patient-related factors on tolerability
X^2 and X^2 for trend tests were used. Key: *P<0.05, **P<0.01, ***P<0.001, ns: not significant.

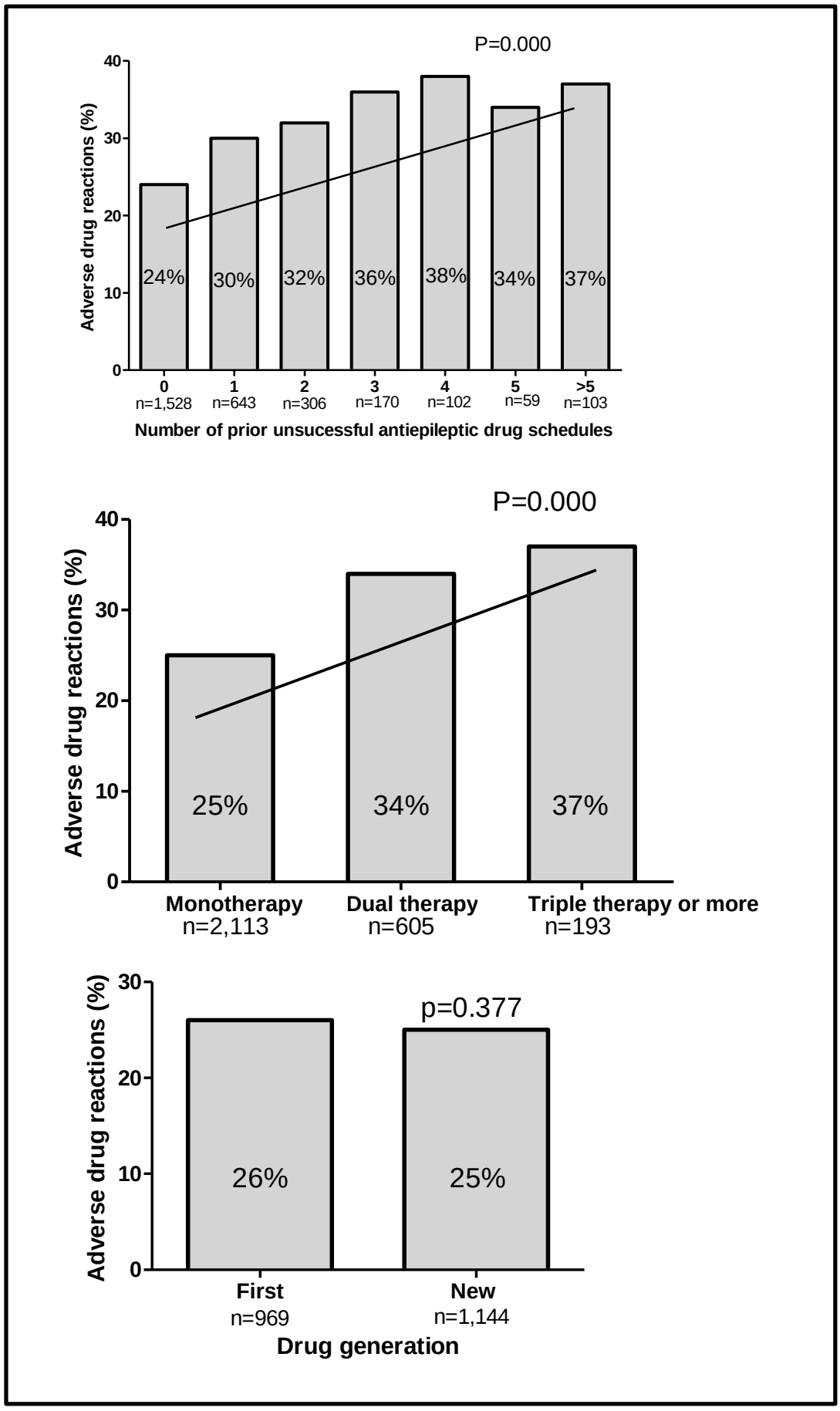


Figure 4-6. Potential pharmacological factors on tolerability
X^2 and X^2 for trend tests were used.

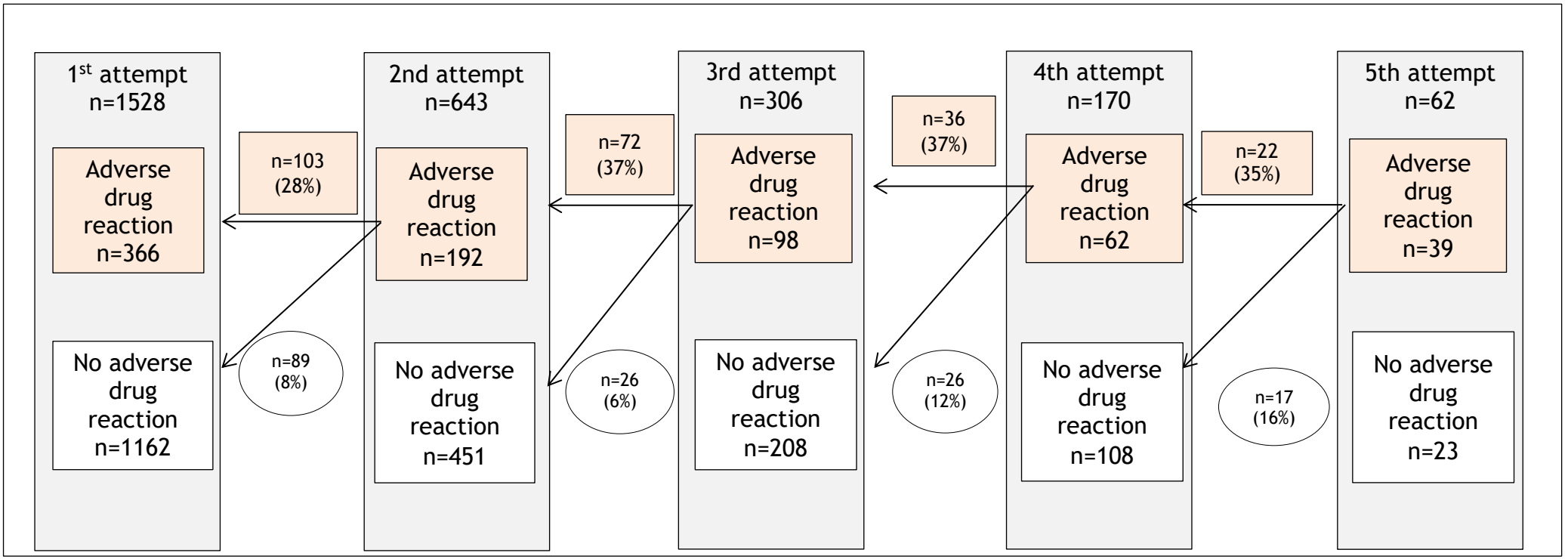


Figure 4-7 Tolerability of the previous antiepileptic drug schedules as a predictor for tolerability of the subsequent schedules
Patients who experienced adverse drug reactions on one AED schedule were significantly more likely to experience adverse drug reactions on the successive schedule, compared to those with no reported adverse drug reactions. 2-proportions test p-value (confidence interval) were <0.000 (0.156, 0.253) for (28 vs 8%), <0.000 (0.245, 0.389) for (37 vs 6%), <0.000 (0.137, 0.348) for (37 vs 12%), and 0.005 (0.06, 0.355) for (35 vs 16%).

4.3.6 Adherence and adverse drug reactions

14% of the patients (n=315/2306) were excluded from this study because of persistent poor adherence to their AED therapy. In the study cohort, the overall intermittent poor adherence rate was 13% of the total regimens tried (n=371/2911).

The rate of this erratic poor adherence was 11% in the regimens discontinued due to poor tolerability (n=86/815), 17% (n=180/1081) in ineffective regimens, and 10% (n=90/9014) in successful regimens (Figure 4-8). Poor adherence was significantly higher in ineffective regimens than successful regimens ($p<0.000$, 95% CI 0.026, 0.088) and regimens with poor tolerability ($p<0.000$, 95% CI 0.03, 0.092). However, there was no significant difference between the successful regimens and poorly tolerated regimens ($p=0.588$).

Erratic poor concordance was higher for monotherapies (14%, n=293/2113) than polytherapies (10%, n=78/798).

In 102 cases, patients admitted to occasionally missing an AED dose, and the reasons for this were recorded. The primary reason was forgetfulness (42%) followed by alcohol intake (24%) (as some patients believed that AEDs interact with alcohol), then side effects (21%) (including fear of side effects and discomfort after taking the medication). All reasons recorded from the patients are presented in Figure 4-9. Social problems including homelessness, prison, and stress while other reasons given were misunderstanding the dosage, seizure-free achievement, and inability to swallow the tablet.

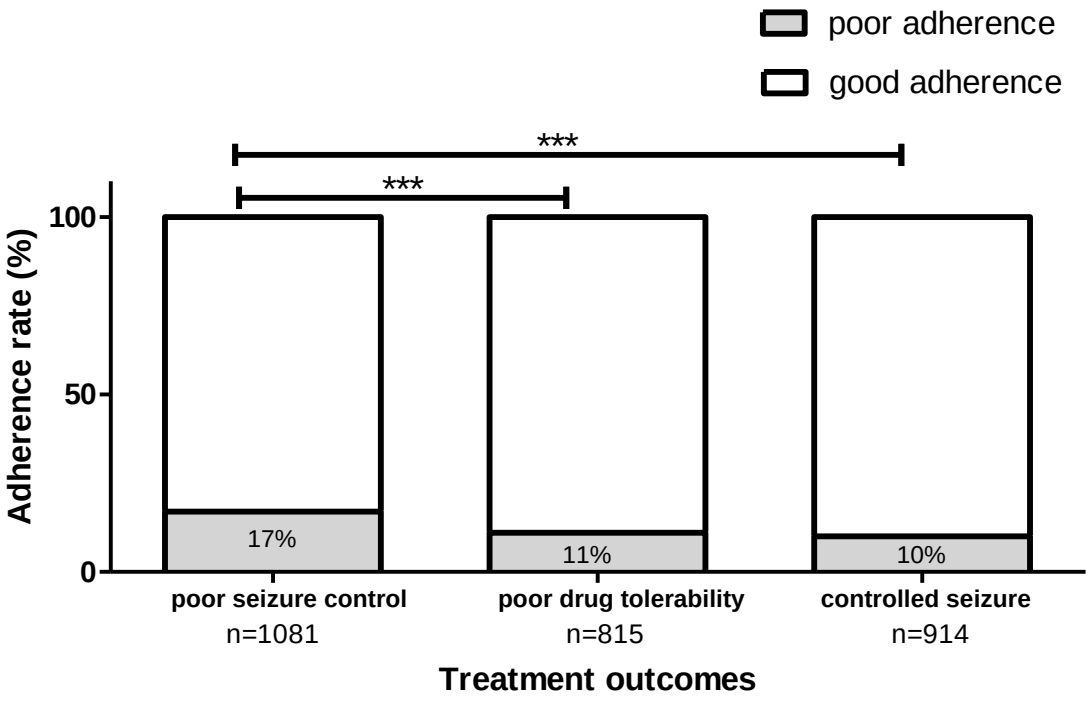


Figure 4-8. Poor adherence effect on treatment outcomes
Test for 2 proportions was used. Key: ***P<0.001

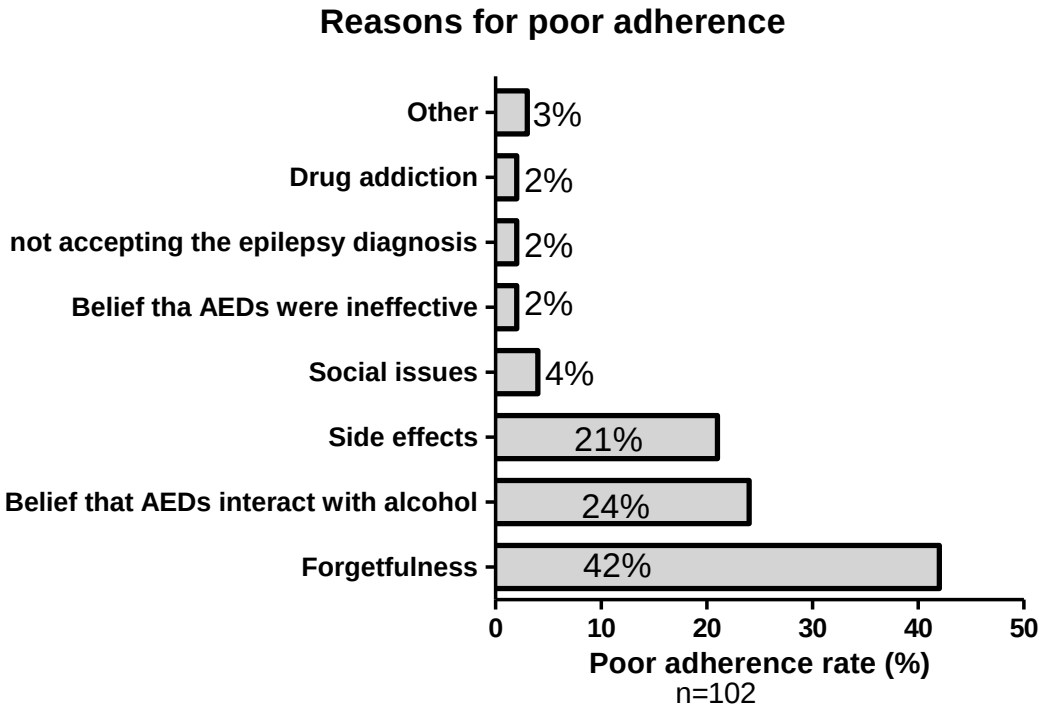


Figure 4-9. The reasons for poor adherence in 102 epilepsy patients who admitted missed antiepileptic drugs (AEDs) doses
Social problems including homelessness, prison, and stress while other reasons given were misunderstanding the dosage, seizure-free achievement, and inability to swallow the tablet.

4.4 Discussion

Patient tolerability of AEDs is integral to successful treatment. There are currently 24 AEDs available for treating epilepsy, many of which have similar efficacy but differ in their tolerability profiles (Perucca and Meador, 2005, Brodie, 2017b). Clinical studies are intended to focus more on the efficacy of the drug than its tolerability. Furthermore, they concentrate on early adverse events than late appearing reactions, although patients usually adjust to these early problems (Cramer, 2012). Understanding the long-term tolerability of AEDs, and the risk factors involved, will provide valuable knowledge for tailoring treatment choices to individual patient characteristics and enhancing treatment effectiveness.

In this large study of newly diagnosed epilepsy patients, who began treatment with AEDs at Glasgow Epilepsy Unit and were followed up for up to 32 years, the primary objective was to evaluate the long-term adverse drug reactions profiles of different AEDs and to assess the effect of the other variables.

One of the main findings of the research is that the rate of intolerable adverse effects of AEDs therapy was 28%. 13% of patients stopped their initial AED treatment as a result of adverse drug reactions. This result is comparable to a previous study conducted on a similar cohort in 2010, in which 14% of the patients discontinued their initial AED due to adverse drug reactions (Bamagous, 2010). However, the figure is different from the findings of two earlier studies of similar cohorts conducted in 2000 (Kwan and Brodie, 2000) and 2005 (Mohanraj and Brodie, 2005), in which 21 and 11% of the patients, respectively, stopped their first monotherapy because of intolerable adverse drug reactions. The results of these studies are shown in Table 4-13. The differences in the findings may reflect the differences in study time, study period, sample size, and AEDs used. Extra new agents were included in the current study, as several new AEDs have been approved since the previous research conducted in 2005, and some new agents have become more popular. The findings of the current study are also comparable to an unblended randomised controlled trial conducted in the UK, which evaluated the effectiveness of five AEDs (CBZ, GBP, LTG, OXC, and TPM) in 1712 patients. The results of the study indicated that 12.3% (n=212) of patients stopped the initial AEDs due to adverse drug reactions (Marson et al., 2007a).

Table 4-13. Initial treatment discontinuation due to drug intolerance in the current and previous analyses on Glasgow cohort

	Patients (n)	Rate of discontinuation
(Kwan and Brodie, 2000)	470	21% (n=98)
(Mohanraj and Brodie, 2005)	780	11% (n=90)
(Bamagous, 2010)	1098	14% (n=157)
Current analysis in 2016	1,528	13% (n=206)

However, the outcomes of the current study differ greatly from studies conducted in other countries. This dissimilarity reflects the variations in the nature of study populations, healthcare systems, AEDs used, treatment approaches, and study period and design. In a 10-year study conducted in Italy, the medical records of 747 patients (aged 11m-94y) were identified by general practitioners between 2000 and 2008; only 2.7% (n=20) of patients stopped their first AED as a result of adverse events (Giussani et al., 2017). Moreover, the rate of adverse drug reactions varied from study-to-study. In a retrospective study conducted in China of 784 patients followed up for 7 years, the overall discontinuation rate as a result of the adverse effects of six AEDs (CBZ, VPA, TPM, OXC, LTG, and LEV) was 7.10% (n=56) (Zhu et al., 2015). While another Chinese study of 654 patients followed up for 3 years found that 19.3% (n=126) of patients discontinued their AED (CBZ, VPA, LTG, TPM, or OXC) due to the adverse effects encountered (Zeng et al., 2015). Although there was little variation in the populations and other parameters of the two studies, they showed a large difference in the rate of adverse drug reactions.

A novel finding from the present study was the examination of the adverse drug reactions in all regimens used during follow-up. This enabled evaluation of poor tolerability in initial AED monotherapies, as well as successive AED regimens. Therefore, the tolerability of newer agents used as adjunct therapy was well evaluated. This method also allowed evaluation of poor tolerability in polytherapies. Furthermore, the study assessed treatment failure due to drug intolerance alone and in combination with poor drug efficacy; the latter is a common occurrence in epilepsy patients.

In the present retrospective analysis, only intolerable adverse effects that contributed to treatment failure were explored. Thus, the prevalence of adverse

drug reactions of continued AEDs was not measured. This is because of the study design and limited available data. The prevalence of adverse drug reactions of continued AEDs has greatly varied in many studies, depending on the assessment tools and study populations (Perucca and Gilliam, 2012). Overall, the rate of adverse effects has been reported as between 10 and 40% if tolerability was estimated by unstructured interviews or spontaneous reporting, and between 59 and 96% when adverse effects were estimated by screening methods (Perucca et al., 2009, Kwon and Park, 2011, Luoni et al., 2011, Perucca and Gilliam, 2012). The prevalence of adverse drug reactions associated with seizure control was highest in those with pharmacoresistant epilepsy, intermediate in mixed populations, and lowest in seizure-free patients (Table 4-14).

Table 4-14. Adverse Event Profile (AEP) scores among different seizure control populations [modified from (Perucca and Gilliam, 2012)]

	Patients (n)	Seizure outcome	Antiepileptic regimen	AEP score	Version of the AEP
(Kwon and Park, 2011)	150	All controlled (1-year seizure-free)	All on monotherapy	27.3 (8.2)	19-item
(Martins et al., 2011)	100	38% controlled (1-year seizure-free)	29% on monotherapy	37.6 (13.3)	19-item
(Perucca et al., 2009)	200	29% controlled (6m-seizure-free)	50% on monotherapy	38.8 (11.8)	19-item
(Luoni et al., 2011)	809	All uncontrolled	22% on monotherapy	42.7 (11.4)	21-item

AEP: adverse event profile. AEP score in mean (SD).

In the cohort for this study, a sedative effect was the most common adverse effect leading to treatment failure. It accounted for approximately 20% of the total intolerability of AEDs. Almost all AEDs were associated with tiredness but at different rates. The figure was the highest with CLB, followed by ZNS and OXC, and lowest with LTG. This is not an unprecedented result. In a SANAD study of CBZ, LTG, OXC, TPM, and GBP, sedative effects such as tiredness/ drowsiness/ fatigue/ lethargy were the most common reported adverse drug reactions, although they did not seem specific to any individual drug (Marson et al., 2007a). Moreover, in a meta-analysis of placebo-controlled studies of eight new AEDs

(GBP, LTG, LEV, OXC, PGB, TGB, TPM, and ZNS), all AEDs except LTG (although no meta-analysis could be performed with OXC and TGB) had sedative properties (Zaccara et al., 2008). As with other benzodiazepines, sedation appears to be the most common adverse effect of CLB (Kennedy and Lhatoo, 2008, Brodie, 2017b). However, CLB (1.5-Benzodiazepin) is less likely to cause sedation than clonazepam (1.4-Benzodiazepine) because of the difference in their chemical structures. Therefore, CLB was preferred over clonazepam in the Glasgow Epilepsy Unit.

Poor coordination was the second most frequent adverse effect reported in this cohort, and was associated with the majority of AEDs. It presented highest with PER, followed by TGB, GBP, and OXC, and lowest with LEV and VPA. A community-based population study of 346 patients in the Netherlands in which adverse effects were assessed by questionnaire showed that CNS-related complaints such as fatigue and dizziness yielded the highest prevalence of adverse effects (Carpay et al., 2005). Furthermore, in the aforementioned meta-analysis conducted by Zaccara et al. (2008), all AEDs except LEV were significantly associated with poor coordination side effects such as dizziness, ataxia, and diplopia. In randomised clinical trials, PER had a strong negative impact on patient balance, including dizziness and falls (Steinhoff et al., 2013), and the intolerable side effects of PER in a recent German study of 214 patients are predominantly reported as dizziness (Pensel et al., 2016).

In this study, the overall rash rate was 2,9%, and it was the most frequent reaction that caused discontinuation of LTG, CBZ, and PHT treatments. The highest rash incidence occurred with PHT, followed by CBZ, LTG, OXC, and then ESL acetate. The incidence of rash reported in this cohort is in line with other studies. The incidence of skin reactions in 753 Polish patients who were exposed to 18 different AEDs was 7.2% (n=54). 92.5% of the reactions occurred with LTG (n=27), CBZ (n=20), or OXC (n=3) (Bosak et al., 2016). In a large Chinese study of 3793 patients, 3.61% (n=137/3793) of patients experienced a skin reaction with one out of 11 different AEDs, most notably with CBZ (3.8%), LTG (11.11%), and OXC (8.92%) (Wang et al., 2012). In another Chinese study, of six AEDs used as monotherapies for 789 patients, the most common adverse effect related to treatment withdrawal was the appearance of a rash with 3.7% (n=29) incidence and this accounted for 52% of treatment discontinuation due to adverse effects (n=29/56). Of all terminated cases, LTG demonstrated the highest rate (8.69%, n=10/115) of

discontinuation due to rash, followed by OXC (7.53%, n=7/93), and CBZ (4.14%) (Zhu et al., 2015). It has been observed that AEDs with aromatic ring structures associated with the highest rate of rash (Wang et al., 2012). Furthermore, Handoko et al. (2008) showed that cutaneous adverse reactions appeared twice as frequently with aromatic AEDs than with non-aromatic AEDs. The outcome of the current study supports this hypothesis, in which higher rash cases were observed in patients treated with aromatic AEDs (such as PHT, CBZ, LTG, and OXC) and lower rates with nonaromatic AEDs (such as VPA and LEV).

In the present study, a pairwise comparison of the tolerability rates of 17 different AEDs revealed that LTG had the best tolerability whether it was used as monotherapy or as part of polytherapy, while TPM and RTG were associated with highest rate of adverse effects when they were used as monotherapy and as part of polytherapy, respectively. Indeed, LTG has consistently demonstrated a better tolerability profile than most other AEDs in several studies, and TPM has shown inferior tolerability (Marson et al., 2007a, Marson et al., 2007b, Bamagous, 2010, Zeng et al., 2015, Zhu et al., 2015). Another study evaluated the rate of discontinuation due to adverse effects in new agents, including LEV (n=196), LTG (n=251), OXC (n=97), TPM (n=156), and ZNS (n=128). LTG showed the best tolerability rate (19%, n=47), followed by OXC (24%, n=23), ZNS (30%, n=38), and then LEV (37%, n=72). While TPM demonstrated the poorest tolerability rate (40%, n=61) (Chung et al., 2007). Most studies that have compared the tolerability of AEDs have focused on drugs used as monotherapy. Thus, newer agents which are used as adjunct therapies, such as RTG, have not been studied extensively. In the present study, RTG was associated with the highest rate of reported adverse effects. Although no specific adverse effect contributed to the high rate of RTG discontinuation in the population of this study, concerns about the blue discolouration effect substantially limited its use. At the final follow-up (data extraction end date was April 2016), only two patients continued to use RTG. As a consequent of its chronic adverse effects, it was regarded as the last choice of drug for refractory seizures (Brodie, 2017b). Therefore, the patients with the most intractable epilepsy were used RTG, which may have contributed to the poor outcome in this analysis. It is important to note that the results from these multiple comparisons should be interpreted with caution because of the

unavoidable selection bias of this study as the case with all observational studies. This selection bias and the efforts made to address it are explained in Chapter 6.

One of the main results of this research is that each AED had its own distinct tolerability profile which allow tailoring treatment selection efficiently. The adverse effects profiles of the most widely used AEDs (LTG, VPA, CBZ, and LEV) are discussed in Chapter 5 of this thesis. In this study, TPM was one of the most widely prescribe AEDs. Cognitive dysfunction was reported in 6.4% of the patients, which represented the most common reason (20%) for TPM intolerability. Cognitive dysfunction included word finding difficulties, poor concentration, and poor memory. In fact, there is consistent evidence of TPM's negative effect on cognition and verbal function. In a recent, large retrospective study (n=2,860) that compared the cognitive side effects of 18 different AEDs, intolerable cognitive side effects most commonly occurred with TPM as adjunct therapy (22.8% of 281 patients) and as monotherapy (18.5% of 54 patients). The most frequent specific cognitive side effect associated with TPM was psychomotor/cognitive slowing (13.7%) (Javed et al., 2015). Beside tiredness, parathesia, and anorexia/weight loss, TPM was also associated with psychiatric and behavioural disorders in approximately 5% of patients in the current study. In another prospective study, psychiatric comorbidity occurred in 103 (23.9%) patients with PTM; this included aggressive behaviour, irritability and/or anxiety (Mula et al., 2003b).

It is worthy of note that in this study, hyponatremia incidence was higher in OXC therapy than CBZ and this is consistent with other studies. Dong et al. (2005) found that the frequency of hyponatremia (Na<134 mEq/L) was 29.9% among OXC-treated patients and 13.5% among CBZ-treated patients ($p < 0.0001$) (Dong et al., 2005).

As with individual AEDs, tiredness was the most common adverse effect of the combination therapies. However, tremor was the most common side effect of the VPA/LTG combination, and resulted in 38% intolerability. The well-known pharmacodynamic and pharmacokinetic interactions can be proposed as the explanation for the marked tremor seen in some patients taking VPA and LTG in combination. Most tolerability studies have evaluated the rate of adverse effects in monotherapy and compared it to the overall rate in polytherapy. However, very few studies evaluate the adverse effects with specific AED combinations. Kowski

et al. (2016) investigated the adverse effects of dual AED therapy and found that the most commonly reported specific adverse effects were sleepiness, difficulty concentrating, and memory problems. Furthermore, the AED combination LTG/LEV was commonly associated with blurred vision, while hair loss was commonly reported with LTG/VPA and LEV/VPA combination therapies (Kowski et al., 2016).

One of the most important findings of this study is that among the many variables investigated, female sex, focal seizure, number of pre-treatment seizure, psychiatric comorbidities, number of prior AEDs, and polytherapy were by far the most important determinants of poor AED tolerability. This result is similar to those found in a Brazilian study of 100 patients, in which higher AEP (Adverse Events Profile) scores were significantly associated with the female gender ($P<0.001$) (Martins et al., 2011). Similarly, a case-control analysis of 418 patients pooled from two large prospective studies on newly diagnosed epilepsy found that female gender was associated with higher AEP scores (Perucca et al., 2011). This could be explained by the compelling evidence that pharmacokinetic and pharmacodynamic drug properties are influenced by gender, leading to a higher incidence of adverse effects in females than in males across a variety of drug classes, including AEDs (Schwartz, 2007). An additional explanation may be an interaction between female gender and mood dysfunction (Kimiskidis et al., 2007), as more women in our study presented with psychiatric comorbidities than men (34 vs 24%, $p<0.001$). Moreover, another study found that female gender predicted adverse effect reporting independently of drug exposure or mood dysfunction (Perucca et al., 2011). However, the author concluded that additional research are needed to determine potential mechanisms and whether this association is limited to women with seizures. Furthermore, a large study ($n=3,793$) conducted on Chinese epileptic patients showed that females had a higher risk of skin reactions compared to males (Wang et al., 2012), although once again the author recommended a further study to discern the underlying mechanisms.

In the participants of this study, focal epilepsy was associated with a higher rate of adverse effects than idiopathic generalised epilepsy. Prior studies have described similar figures, with higher rates of adverse effects occurring with symptomatic epilepsy compared to other epilepsy types (Perucca et al., 2011).

This could be because symptomatic focal epilepsy has been found to be less tractable epilepsy (Kwan and Brodie, 2000); therefore, patients with pharmacoresistant epilepsy require higher AED loads and polytherapy, which may increase the AED toxicity burden. However, in this analysis, there was no significant difference in seizure outcomes among different seizure types. An additional explanation is due to difference in AED selection for different epilepsy subtypes, as AEDs have different tolerability profiles that could contribute to different rates of adverse effects in different seizure types. Although another study found that overall AEP scores were similar in patients with symptomatic focal epilepsy and idiopathic generalised epilepsy and were not helpful in differentiating adverse effects in these two groups (Martins et al., 2011). However, the latter study assessed the adverse effects using an AEP instrument, which has potential limitations because of its subjectivity, lack of a physical evaluation to medically confirm some side effects such as weight changes, ataxia, nystagmus, speech and coordination abnormalities, and lack of objective examination of systemic involvement such as haematological and hepatic side effects. Furthermore, the AEP instrument could cause over-reporting because of the direct approach of the questionnaire. In fact, the author of the study acknowledged some limitations of their research, such as the tertiary care feature of their institute, as well as the large number of pharmacoresistant epilepsy patients in their sample.

In the current study, adverse effect rates were significantly higher in patients with psychiatric comorbidities compared to patients without psychiatric disorders. This is not an unprecedented finding (Weintraub et al., 2007, Perucca et al., 2011). 28% of patients in this study had psychiatric comorbidity at baseline or during follow-up. It is well-known that psychiatric disorders, particularly depression, are more common in the epilepsy population (Hitiris et al., 2007, Lin et al., 2012, Chowdhury and Brodie, 2016). Indeed, there is a complex interrelationship between adverse drug effects and psychiatric disorders. Firstly, psychiatric and behavioural symptoms are a common adverse effect of many AEDs (Weintraub et al., 2007, Lin et al., 2012). In this study, psychiatric side effects accounted for 11% of overall AED intolerability. Furthermore, patients with psychiatric disorders (depression and/or anxiety) are more likely to report adverse effects of AEDs (Kwon and Park, 2011, Kanner et al., 2012). Finally, patients with psychiatric

comorbidities are less tractable (Hitiris et al., 2007); consequently, they may need aggressive treatments (i.e., polytherapy/high AED doses) that increase the adverse effect burden of AEDs. It should be noted that the data on psychiatric comorbidities in this study was not collected systemically using validated instruments.

Number of pre-treatment seizure and number of prior AEDs appeared to be correlated positively with high rate of adverse drug reactions in this cohort. In fact, it has been showed that the rate of seizure-free decreases with high pre-treatment seizure and high prior AEDs, and the probability of developing a refractory epilepsy increases (Kwan and Brodie, 2000, Brodie et al., 2013). The patients with pharmacoresistant epilepsy may require higher AED loads and polytherapy, and consequently, associate with higher adverse drug reactions rate. These two particular factors were discussed in previous chapter.

The rate of adverse drug reactions related to the number of concomitant AEDs was lowest with monotherapy, intermediate with dual therapy, and highest with triple therapy or more in this analysis. The observation that polytherapy caused more side effects than monotherapy is consistent with the findings of several other studies (Carpay et al., 2005, Martins et al., 2011, Andrew et al., 2012). Andrew et al. (2012) found that patients undertaking polytherapy reported significantly higher adverse effect rates (AEP 46, n=325) than patients on monotherapy (AEP 42, n=186), patients were on numerous combinations typically including at least one new AED (the most common AEDs were, CBZ/LTG/LEV/VPA). Similarly, Martins et al. (2011) showed that polytherapy with three or more AEDs was significantly associated with higher rates of side effects than monotherapy, the most common AEDs-induced adverse effects were CBZ, VPA, PB, LTG, TPM, PHT, CLB. In contrast, a cohort study of 809 refractory epilepsy patients failed to show any significant difference in adverse effects between monotherapy and polytherapy patients, leading the authors to conclude that, “adverse effects are determined more by individual susceptibility, type of AEDs used and physicians’ skills than number of co-prescribed AEDs” (Canevini et al., 2010, page.797). However, the latter study was a cross-sectional survey on pharmacoresistant epilepsy patients, thus the issues of high drug toxicity caused by overtreatment in refractory patients, along with the subjectivity/ overestimation of AEP instrument use, may limit the generalisation of the results to newly diagnosed epilepsy.

It is also worth noting that in this study the rate and nature of safety profiles varied among individual AEDs. However, the generation of individual AED did not appear to influence the rate of adverse drug reactions: new agents did not consistently present better tolerability than the established AEDs. For example, VPA, an old generation drug, demonstrated a lower adverse effect rate than the newer agents TPM or OXC. Thus, the findings of this study do not support the assumption of inferior tolerability of standard AEDs. This is inconsistent with the results of a study that extensively reviewed the prevalence of systemic and neurological reactions reported in clinical trials of AED monotherapy, which demonstrated unidirectional higher prevalence of selected adverse effects with standard AEDs compared with new agents (Cramer, 2012). However, this report was limited to data from clinical trials of monotherapies. Such trials are sufficient to evaluate the efficacy of a drug, but inadequate to assess the tolerability of the medication. It should be noted that VPA and CBZ are the most common first-line monotherapy, while most newer AEDs like TPM and OXC are used after failure to response to initial therapy. This may contribute to the poor outcomes found with new agents in the current study as severity of seizure may differ across patients groups taking standard and new agents.

In addition to the main evaluation of AED tolerability, this analysis also studied the correlation with poor adherence. Overall, 14% of patients were persistently non-adherent to their AEDs and another 13% were intermittently poor adherent. Several studies have measured drug adherence in adult epilepsy patients and found the rates to be between 50-79% (Faught, 2012, Ferrari et al., 2013). It should be noted that the data on medication adherence used in the present research was not collected systemically using a validated instrument. Instead, the patients were asked directly and/or their blood drug levels were measured. This may have led to underestimation of poor adherence in the population. In this study, erratic poor adherence was associated more with treatment failure due to poor seizure control than due to side effects. However, side effects, including fear of side effect and discomfort after taking medication, was one of the most frequently reported reasons for poor adherence. It is well known that side effects cause drug poor adherence (Eatock and Baker, 2007). With regard to efficacy, results of this study demonstrated a negative correlation between seizure frequency and adherence. Of course, drugs do not work in patients who do not

take them; however, patients seem to adhere to the effective drugs (i.e. stop their seizures) (Faught, 2012). Indeed, with poor adherence it is unclear whether patients are not adherent to the drugs because they do not prevent their seizures, or drugs do not work because the patients do not take them correctly. Patients in this study reported different reasons for missing doses; forgetfulness was the primary factor, followed by alcohol intake, as some patients assumed that AEDs interact with alcohol. This is consistent with another study that evaluated the adherence in 131 patients in China using a self-report instrument, in which 4.6, 70.2, and 25.2% of patients reported high, medium, and low adherence, respectively, and the frequent reasons given for non-adherence were forgetfulness (54.2%), being seizure-free for a long period (48.9%), and fear of adverse drug effects (27.5%) (Tang et al., 2013). The relationship between the number of daily drug doses and adherence has been extensively investigated; available evidence suggests that taking a drug less frequently is a substantial aid to adherence (Eatock and Baker, 2007, Faught, 2012). However, the findings of this study contradict this fact: poor adherence was associated more with monotherapy than polytherapy. Nevertheless, this should be interpreted with caution for several reasons. Firstly, the number of co-prescribed AEDs was assessed rather than dosing frequency, and the data on adherence was limited to the patients with intermittent poor adherence, as patients with persistent poor adherence were excluded. In addition, the use of suboptimal assessment tools, long-term follow-up, and the large number of patients may have contributed to weakening the accuracy of drug adherence assessment. Taken together, erratic poor adherence to AEDs was relatively infrequent in this study but influenced seizure control substantially and side effects of AEDs was one of the most frequently reported reasons for this behaviour.

In summary, this analysis showed that the incidence of adverse effects with AEDs was 28%, of which tiredness was the most frequent problem. Each AED had its own distinct tolerability profile which provides the opportunity of tailoring drug choice more effectively. LTG was the best tolerated AED, while TPM was associated with the highest rate of adverse effect among monotherapies and RTG had the highest rate of adverse effects among AEDs used as polytherapy. Poor tolerability was higher in females and in patients with focal epilepsy, psychiatric comorbidities and those established on AED polytherapy. Additionally, number of pre-treatment

seizure and number of prior AEDs appeared to be correlated positively with high rate of adverse drug reactions. Prior intolerable AEDs schedule was also associated with high probability to experience intolerable adverse effects at subsequent AED schedule.

Chapter 5. Comparative retention rates of the most commonly used antiepileptic drugs

5.1 Introduction

In the previous two parts of this thesis, the efficacy and tolerability of AEDs were discussed separately. Despite the valuable knowledge each section has provided, the effectiveness of comprehensive long-term treatments has not yet assessed sufficiently. Determining retention rates is one approach to evaluating both the efficacy and tolerability of a drug (Mohanraj and Brodie, 2003). This survival analysis is often employed as an assessment of short-term and long-term effectiveness because it considers time to treatment modification for any reason (Cramer, 2012).

Because epilepsy is a chronic neurological condition, its management commonly requires lifelong intervention. Apart from the small number of patients who undergo successful epilepsy surgery, the majority of patients rely on pharmacological management to control seizures. The pharmacological treatment of epilepsy often involves exposure to a number of AEDs and requires long-term adherence and commitment from patients (Kwan and Brodie, 2000, Chung et al., 2007, Ferrari et al., 2013). Drug selection is based on seizure type, patient characteristics such as age, gender and comorbidities, and the tolerability profiles of the AEDs (French et al., 2004, Chung et al., 2007). Providing information about the long-term retention times of AEDs and the most common reasons for discontinuation can be invaluable in helping to choose the most appropriate drug for each individual patient and minimising the probability of exposure to ineffective and/or poorly tolerated AEDs.

LTG, VPA, CBZ, and LEV are the most commonly prescribed AEDs for epilepsy patients, particularly as initial monotherapies (Gamble et al., 2006, Hu et al., 2011, Glauser et al., 2013, Brodie, 2017b). Both the efficacy and tolerability of these drugs have been investigated (Brodie et al., 1995, Steinhoff et al., 2005, Brodie et al., 2007, Hu et al., 2011). However, their long-term retention times as monotherapies in a large sample of patients with new onset epilepsy have not been studied extensively. The cohort for this study was made up of patients with new onset seizure; thus, the majority of the drug exposures of these AEDs were tried as a first or second treatment attempt.

This section presents a comprehensive comparison between the retention rates of the most common monotherapies, LTG, VPA, CBZ, and LEV, in order to provide insight into how they differ in their efficacy, tolerability, treatment duration, and reasons for discontinuation in everyday clinical practice.

5.2 Methods

Retention of patients on a specific drug over a period of time is the best outcome measure that represents its effectiveness. The effectiveness of an AED is a function of its efficacy and tolerability, and thus cannot be sensibly separated (Mohanraj and Brodie, 2003).

In this study, the retention time of an AED was defined as the time between starting monotherapy and withdrawal or addition of another agent. This was calculated in months from the start date of each specific AED administered as monotherapy to either the discontinuance date for the treatment or the last follow-up date for continued therapy. Continuity was defined as patients treated currently with the same AED monotherapy from treatment beginning until the final follow-up. Discontinuation was defined for patients who stopped their AED monotherapy (or required alternative monotherapy or add-on therapy) at any time during the follow-up period. The reason for treatment discontinuation was documented based on patients' main complaint, whether this was drug intolerance, ineffectiveness, both, or other causes.

Dosage of AEDs was reported as daily dose in milligrams based on what dose the patient was taken at the last follow-up or at what dosage the patient discontinued treatment. Drug doses were categorised into low, moderate, and high doses based on the interquartile range (IQR) of each drug used in the presented cohort. Low doses were smaller than the IQR, moderate doses were within the IQR, and high doses were greater than the IQR. IQR in mg/day for LTG=150-350, VPA=1000-1700, CBZ=400-800, and LEV=1000-2000.

A chi-square test was used to compare the proportions of continued AEDs; the significance p-value was set at $p<0.008$ (based on Bonferroni correction=0.05/6). A Kaplan-Meier survival analysis was applied to estimate the cumulative probability of retention on treatments. While a Cox regression model was

implemented to evaluate and adjust for potential covariates. Finally, a two proportional statistical test was used to compare the other categorical data, and a Mann-Whitney test and a Kruskal-Wallis test were used to compare the non-parametric continuous data.

5.3 Results

5.3.1 Treatment response and antiepileptic drug use

Figure 5-1 summarises patient responses to the AEDs tried during the follow-up period. Of the total 1,765 data points, 56% (n=989) of the AED therapies were continued at the final clinic visit, while 41% (n=723) were discontinued during the follow-up period. Overall, the main reason for discontinuation of the AEDs was poor seizure control (18%, n=318), followed by poor drug tolerability (12%, n=211), and then both ineffectiveness and intolerance (11%, n=194). A small group of patients (3%, n=53) discontinued the treatment for other reasons, such as long-term seizure-free periods, clinical trial regulations, patient preference, or concerns about teratogenicity. As the results from this group could be misleading (Mohanraj and Brodie, 2003), this cohort was excluded from subsequent analyses, and the remaining 1,712 AEDs regimens were studied.

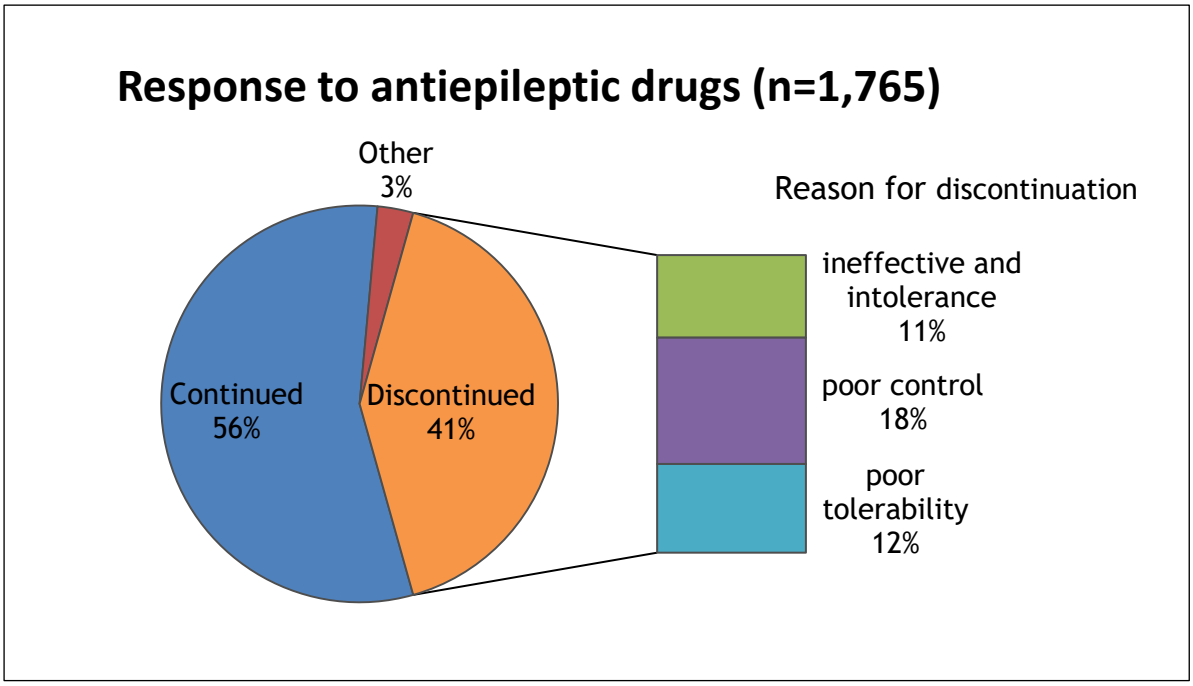


Figure 5-1. Treatment response during the follow-up period

The highest level of AED exposure was obtained from LTG, making up 33% (n=562) of the data, although VPA data followed closely at 32% (n=555). CBZ data represented 20% (n=350) and the least amount of data was collected from LEV exposures, at 15% (n=245). As mentioned previously, these four drugs are the most commonly medications prescribed as initial monotherapies for newly diagnosed epilepsy patients. Therefore, in this study, the majority of the AED exposures were tried as a first treatment (74%, n= 1,270).

5.3.2 Potential effect of covariate on treatment outcomes

A number of analyses were performed to evaluate and adjust the potential effect of covariates on treatment continuation and retention rates of AEDs. First, Cox regression analysis that shows that five covariates were significantly ($P<0.05$) influenced the treatment continuation in the univariate model: epilepsy type and aetiology, CVD, number of pre-treatment seizures, and psychiatric condition. However, gender factor appeared marginally significant ($p=0.058$). Seizure aetiology was excluded from the multivariate model because it significantly correlated to epilepsy type ($p<0.000$). After accounting for the significant variables in the adjusted model (multivariate), there was no significant evidence of an association between epilepsy type and treatment continuation. Table 5-1 demonstrates the univariate and multivariate Cox regression analysis for predicators of treatment discontinuation.

Then, the potential covariates were assessed for individual AEDs (LTG, VPA, CBZ, and LEV) to examine their effect on the reported retention rates. As shown in Table 5-2, CVD, number of pre-treatment seizure, psychiatric disorder and number of prior AEDS were comparable among treatment groups. However, female gender was significantly higher ($p<0.000$) in LTG group (62%) and LEV (57%) than CBZ (42%) and VPA (42%). Similarly, patients with focal epilepsies were significantly ($p=0.031$) higher in LTG treatment (85%) than VPA (80%), and marginal significant ($p=0.05$) in CBZ (89%) than LTG (85%).

Table 5-1. Univariate and multivariate Cox regression analysis for predictors of treatment discontinuation

	Univariate		Multivariate	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Female gender	1.151 (0.995, 1.331)	0.058		
Age (Years)	1.003 (0.999, 1.007)	0.179		
Focal epilepsy	1.303 (1.057, 1.607)	**0.013**	1.184 (0.957, 1.464)	0.121
Seizure aetiology*		**0.047**		
Family history of epilepsy	1.002 (0.832, 1.208)	0.982		
Febrile convulsion	1.059 (0.757, 1.48)	0.739		
Birth trauma	0.933 (0.848, 1.0.26)	0.15		
Head injury	1.150 (0.951, 1.39)	0.15		
Cerebrovascular disease	1.245 (1.006, 1.539)	**0.044**	1.241 (1.002, 1.536)	**0.048**
More than 10 seizures before treatment	1.396 (1.205, 1.617)	**<0.000**	1.348 (1.162, 1.564)	**<0.000**
Seizures for >1 year before treatment	1.041 (0.9, 1.204)	0.539		
Learning disability	1.143 (0.915, 1.428)	0.238		
Psychiatric comorbidity	1.311 (1.129, 1.523)	**<0.000**	1.256 (1.079, 1.462)	**0.003**
Alcohol abuse	1.152 (0.977, 1.359)	0.093		
Recreational drug use	1.103 (0.903, 1.347)	0.336		
Number of prior antiepileptic drugs*	1.066 (0.989, 1.151)	0.096		

*excluding form multivariate model as they interacted with other variables.

Table 5-2. Clinical characteristics of patients starting different antiepileptic drugs

	LTG N=562	VPA N=555	CBZ N=350	LEV N=245	X^2-P-value
Female gender	346 (62)	159 (29)	147 (42)	140 (57)	**0.000***
Focal epilepsy	478 (85)	445 (80)	313 (89)	208 (85)	**0.002†**
Seizure aetiology					
Cryptogenic	277 (49)	287 (52)	175 (50)	120 (49)	
Idiopathic	84 (15)	110 (20)	37 (11)	37 (15)	
symptomatic	201 (36)	158 (28)	138 (39)	88 (36)	
Cerebrovascular disease	73 (13)	74(13)	40 (11)	42 (17)	0.255
More than 10 pre-treatment seizure	186 (33)	217 (39)	123 (35)	83 (34)	0.185
Psychiatric comorbidity	164 (29)	181 (33)	96 (27)	82 (33)	0.24
More than two prior unsuccessful antiepileptic drug schedules	47 (8)	39 (7)	29 (8)	21 (9)	0.854

Data are presented in patients number (%). Key: LTG: lamotrigine, VPA: valproate, CBZ: carbamazepine, LEV: levetiracetam. *p<0.000 for all comparisons except for LTG vs. LEV p=0.241. †only significant for LTG vs. VPA (p=0.031), but p=0.05 for LTG vs. CBZ and p=0.097 for VPA vs. CBZ.

5.3.3 Retention on treatment

The cohort of this study was followed up for up to 32 years. Based on treatment continuation at the last follow-up, LTG demonstrated the highest retention rate of 63% (n=354/562). This was significantly higher than the retention rates of VPA (55%, n=304/555) and CBZ (52%, n=183/350). However, there was no significant difference in the retention rates of the other AEDs. Figure 5-2 and Table 5-3 present the details of the retention rates (in percentages) of the different AEDs and the pairwise comparisons using the Chi-square test and the significance p-value was set at p<0.008 (based on Bonferroni correction). Because this analysis does not take into account the duration of therapy (it only compares the proportions of continued AEDs), survival analysis was performed.

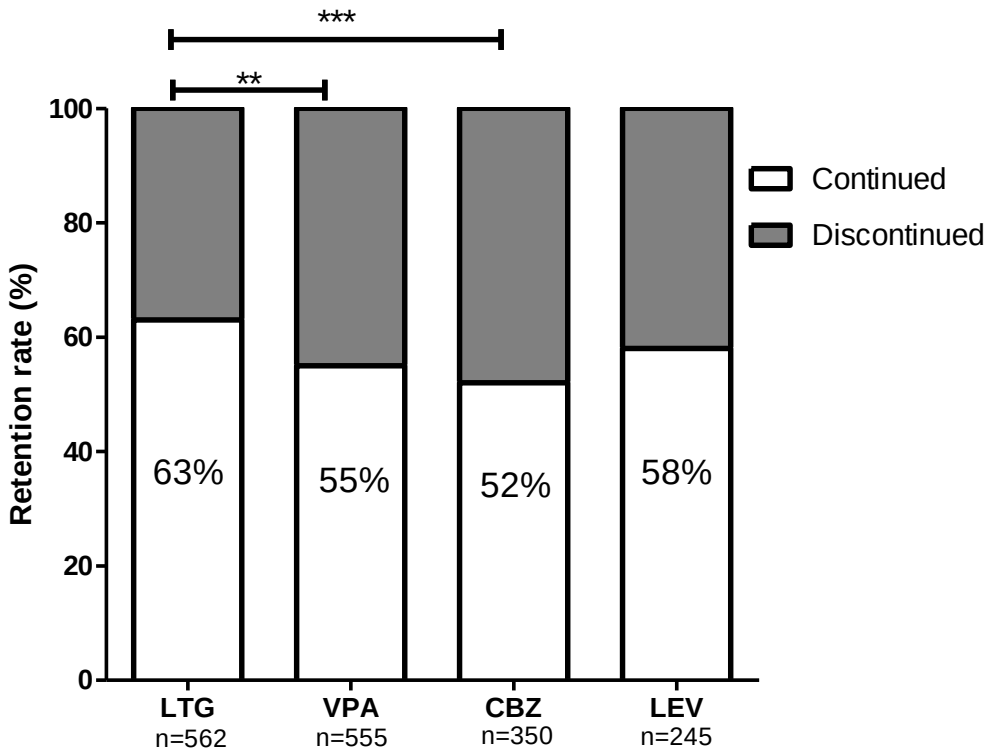


Figure 5-2. Overall retention rate of different antiepileptic drugs at last follow-up
Key: **P≤0.01, ***P≤0.001, LTG: lamotrigine, VPA: valproate, CBZ: carbamazepine, LEV: levetiracetam. X^2 test was used.

Table 5-3. Multiple comparison of retention rate of different antiepileptic drugs

LTG vs. CBZ	**0.001**
LTG vs. VPA	**0.005**
LTG vs. LEV	0.215
CBZ vs. VPA	0.465
CBZ vs. LEV	0.142
VPA vs. LEV	0.345

Data are p-value of X^2 test. Significant at P<0.008 (Bonferroni correction). Key: LTG: lamotrigine, VPA: valproate, CBZ: carbamazepine, LEV: levetiracetam, vs.: versus.

In the survival analyses, a Kaplan-Meier method was carried out to estimate the retention times of the different AEDs (Figure 5-3 and Table 5-4), and Cox regression model was employed to compare the retention rates of different AEDs before and after adjustment for potential covariates. As demonstrated in Table 5-5, the adjusted and unadjusted retention rates were similar. Consistent with the previous analysis (Chi-square), LTG achieved the highest retention rate, with an average therapy duration of 84 months. This was significantly higher than the retention rates of VPA (42 months), CBZ (36 months), and LEV (36 months). There was no significant difference in retention rates of other AEDs.

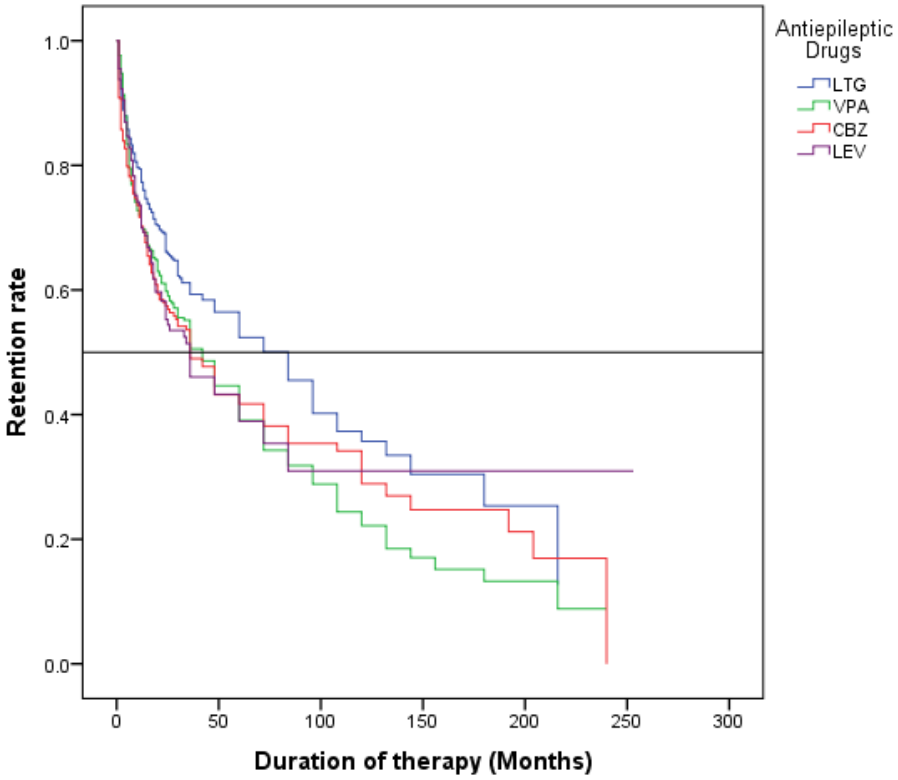


Figure 5-3. Retention rate of different antiepileptic drugs estimated by Kaplan-Meier analysis
Median retention time in months was 84 for LTG, 42 for VPA, and 36 for CBZ and LEV. Key: LTG: lamotrigine, VPA: valproate, CBZ: carbamazepine, LEV: levetiracetam.

Table 5-4. Retention time of different antiepileptic drugs estimated by Kaplan-Meier survival analysis

	Retention time (Months)	Log Rank P-value
Lamotrigine	84 (64.404, 103.595)	0.007
Valproate	42 (34.231, 49.769)	
Carbamazepine	36 (25.861, 46.139)	
Levetiracetam	36 (19.508, 52.492)	

Data are presented in median (95% confidence interval).

Table 5-5. Comparative retention rate of different antiepileptic drugs estimated by Cox regression analysis before and after adjustment for covariates

	Unadjusted		Adjusted	
	Hazard ration (95% CI)	P-value	Hazard ration (95% CI)	P-value
LTG vs. LEV	0.763 (0.602, 0.968)	**0.026**	0.769 (0.606, 0.975)	**0.03**
LTG vs. CBZ	0.754 (0.615, 1.213)	**0.007**	0.768 (0.626, 0.943)	**0.012**
LTG vs VPA	0.756 (0.629, 0.909)	**0.003**	0.772 (0.642, 0.929)	**0.006**
CBZ vs. LEV	1.013 (0.791, 1.297)	0.921	1 (0.780, 1.283)	0.998
VPA vs. LEV	1.01 (0.802, 1.271)	0.936	0.995 (0.79, 1.255)	0.969
CBZ vs VPA	1.003 (0.824, 1.22)	0.976	1.005 (0.824, 1.225)	0.961

Key: LTG: lamotrigine, VPA: valproate, CBZ: carbamazepine, LEV: levetiracetam. The hazard of treatment discontinuation on LEV, CBZ, and VPA was approximately 24% higher than the hazard on LTG before and after adjustment for covariates. The covariates included in the model were gender, cerebrovascular diseases, psychiatric comorbidity, focal epilepsy and more than 10 seizures before treatment.

Because length of exposure to treatment was different for different subject, the person-months statistic was applied (Table 5-6).

Table 5-6. Person-months of follow-up / drug exposure

Lamotrigine	Valproate	Carbamazepine	Levetiracetam
7 cases per 1000 person-months	10 cases per 1000 person-months	10 cases per 1000 person-months	11 cases per 1000 person-months

Data are number of incident cases (discontinued) divided by the amount of person-months at risk.

Results showed a rapid discontinuation rate during the first two years of treatment, as expected. Thus, the data was further stratified at every two months during the initial two years of therapy. As presented in Figure 5-4 , CBZ showed the highest discontinuation rate at most assessment points, while there was an overlap between the discontinuation of VPA and LEV at several assessment points. At six months of treatment initiation onwards, LTG demonstrated the lowest discontinuation rate. However, before six months (i.e. at two and four months), LTG had a higher discontinuation rate than VPA and LEV.

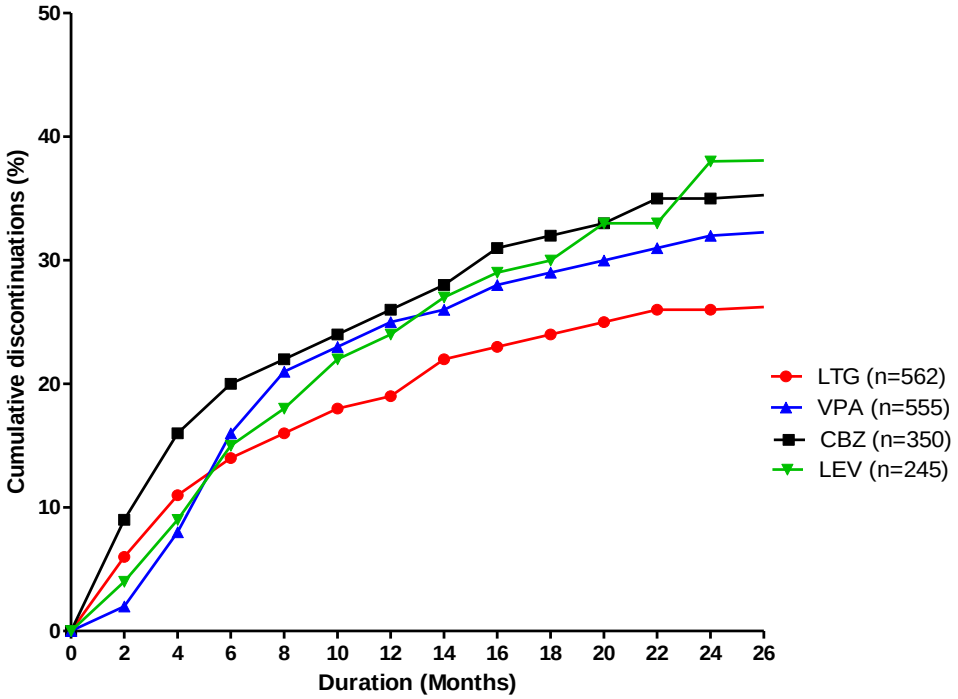


Figure 5-4. Short-term discontinuation rate of different antiepileptics over the first two years of treatment
Key: LTG: lamotrigine, VPA: valproate, CBZ: carbamazepine, LEV: levetiracetam.

5.3.4 Reasons for antiepileptic drug discontinuation

As shown in Figure 5-5, poor seizure control was the primary reason for the discontinuation of LTG, VPA, and LEV. Rates ranged from 40% for LEV to 47% for LTG. In the case of CBZ, poor drug tolerability was the main cause of discontinuation and accounted for 43% of discontinued cases.

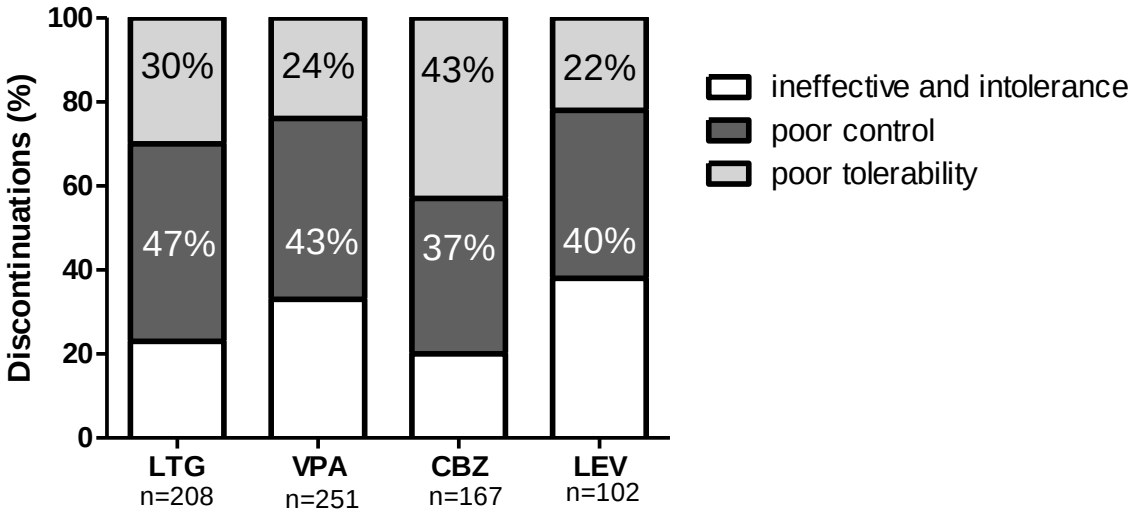


Figure 5-5. Reason for discontinuation with individual medication
Key: LTG: lamotrigine, VPA: valproate, CBZ: carbamazepine, LEV: levetiracetam.

Table 5-7 summarises the intolerable adverse effects of LTG, VPA, CBZ, and LEV as administered as monotherapies. Tiredness was the most common intolerable adverse effect reported and did not appear to be specific to any individual AED. Skin rash was the most frequent reaction that caused discontinuation of LTG and CBZ that accounted for 32 and 31% of total adverse drug reactions, respectively. Tremor and weight gain were the most intolerable effects reported for VPA therapy, accounting for 25 and 20% of VPA's poor tolerability, respectively. Psychiatric and behavioural disorders were the most common reported side effects with the LEV monotherapy, and represented 44% of LEV's poor tolerability. A total of 27 (11%) patients developed these psychiatric adverse effects with LEV including: 12 reported mood changes (5%), 11 reported aggression (4.5%), and 4 demonstrated irritability (1.5%). Gastrointestinal adverse effects were also common, particularly with VPA, accounting for 15% of its poor tolerability. Poor coordination was common with the Na-channel blocker AEDs (i.e. LTG and CBZ), and made up 12% of the intolerable effects for LTG and CBZ separately. While headaches represented 10% of the intolerable effects for each LTG and LEV, and insomnia was 6 and 10% of the intolerable effects in the same drugs, respectively.

Table 5-7. Intolerable adverse effects with the most commonly used antiepileptic drugs

	LTG	VPA	CBZ	LEV	Total
Tiredness	11 (10)	24 (17)	30 (28)	10 (17)	75 (18)
Skin rash	35 (32)	1 (1)	33 (31)	1 (2)	70 (17)
Tremor	5 (5)	36 (25)	2 (2)	0	43 (11)
Gastrointestinal side effect	8 (7)	22 (15)	8 (8)	4 (6)	42 (10)
Poor coordination	13 (12)	4 (3)	13 (12)	3 (5)	33 (8)
Weight gain	0	29 (20)	0	0	29 (7)
Headache	11 (10)	3 (2)	7 (7)	6 (10)	27 (6)
Aggression	3 (3)	1 (1)	1 (1)	11 (18)	16 (4)
Mood change	1 (1)	2 (1)	1 (1)	12 (20)	16 (4)
Insomnia	7 (6)	1 (1)	0	6 (10)	14 (3)
Irritability	3 (3)	1 (1)	0	4 (6)	8 (2)
Hair loss	0	5 (3)	0	0	5 (1)
Other	12 (11)	14 (10)	11 (10)	4 (6)	36 (9)
total	109	143	106	61	419

Data are presented in number of cases (%). Key: LTG: lamotrigine, VPA: valproate, CBZ: carbamazepine, LEV: levetiracetam.

5.3.5 Duration of therapy among different reasons for discontinuation

Kaplan-Meier and Cox regression analyses were performed to estimate and compare the cumulative probability of retention for AEDs stratified by the different reasons for discontinuation (Figure 5-6, and Table 5-8). Poor drug tolerability resulted in the lowest retention rates with average therapy duration of two months. This was significantly lower than time to discontinuation due to poor seizure control with or without adverse effects, which were nine and eighteen months respectively.

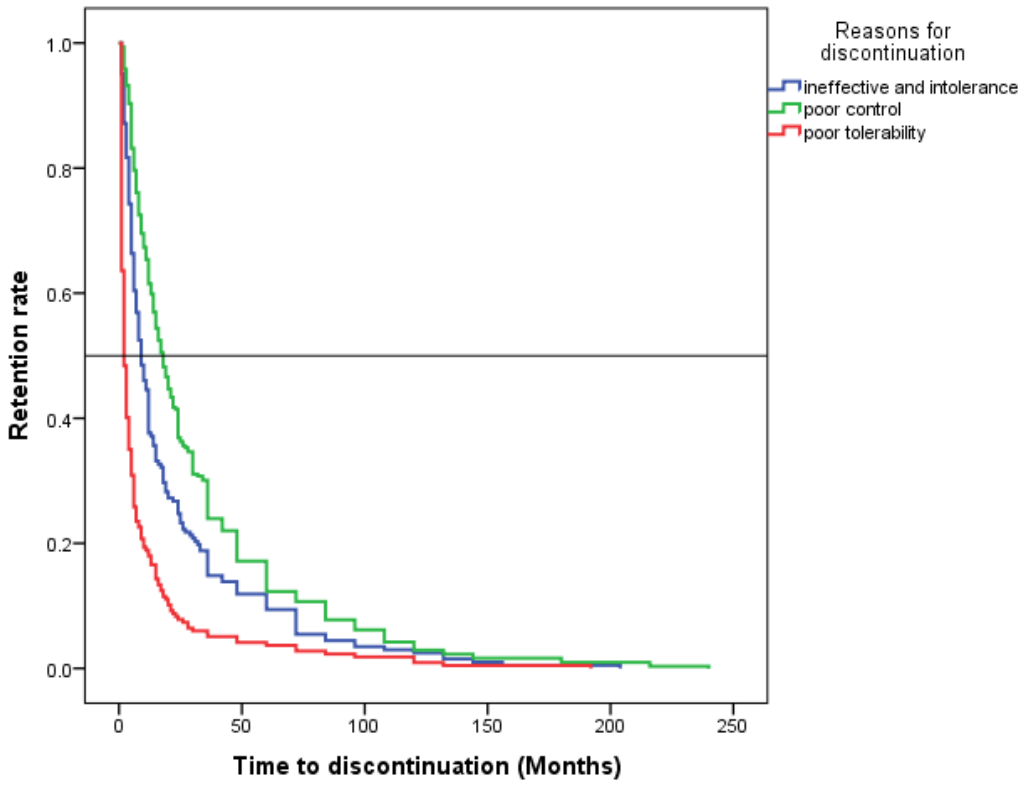


Figure 5-6. Retention rate among different reasons for discontinuation estimated by Kaplan-Meier analysis
Median retention time in months for poor tolerability, poor seizure control, and for ineffective and intolerance was 2, 9, and 18, respectively.

Table 5-8. Retention time for different reasons for discontinuation estimated by Kaplan-Meier survival analysis

	Retention time (Months)	Log Rank P-value
Ineffective and intolerance	9 (6.772, 11.228)	<0.000
Poor control	18 (15.282, 20.718)	
Poor tolerability	2 (1.434, 2.566)	

Data are presented in median (95% confidence interval).

Figure 5-7 demonstrates the cumulative discontinuation rate at every two months for the first two years of treatment, and the different causes of discontinuation. The majority (70%) of AEDs discontinued due to poor tolerability appeared within six months of treatment initiation. The figure was far lower for AEDs discontinued due to poor seizure control with (35%) or without (17%) intolerance.

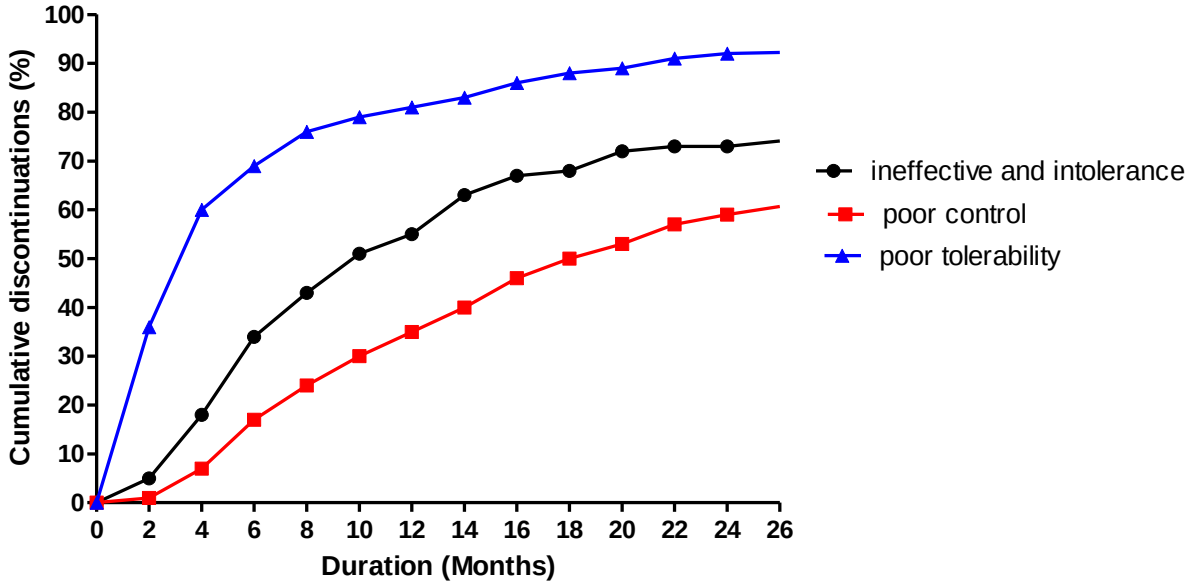


Figure 5-7. Discontinuation rate among different reasons for discontinuation

5.3.6 Dosage evaluation

The median (IQR) dose of continued therapy in mg/day was 200 (150, 300) for LTG, 600 (400, 700) for CBZ, and 1000 (1000, 1500) for VPA and LEV. A comparison of the median doses between the continued group and discontinued group for each AED is demonstrated in Table 5-9 and Figure 5-8. For LTG, VPA, and LEV, a Mann-Whitney test of the dosages showed significant differences between the continued and discontinued groups. For these AEDs, the median daily doses were higher in the discontinued group. However, the median dosage of the CBZ groups did not reveal a significant difference between them.

The dosage of the discontinued group for each treatment was further stratified by the cause of discontinuation (Table 5-10 and Figure 5-9). For each of the four AEDs there were significant differences ($p<0.000$, Kruskal Wallis test) between the three different groups that discontinued treatments for different reasons (poor

tolerability, poor seizure control, and ineffective and intolerance). The median dosage of the poor tolerability group was the lowest for each therapy, while the dosage of poor seizure control was the highest. Thus, the group that discontinued the therapy due to both ineffectiveness and intolerance had median dose in between the other two groups.

Table 5-9. Average dosage (mg/day) of continued and discontinued groups for each medication

	LTG	VPA	CBZ	LEV
Continued	200 (150-300)	1000 (1000-1500)	600 (400-700)	1000 (1000-1500)
Discontinued	300 (100-400)	1500 (1000-2000)	600 (400-800)	2000 (1000-2500)
Mann Whitney test p-value (95% CI)	0.022 (-99.98, -0.01)	<0.000 (-500,0.0)	0.9633 (-0.0, 0.0)	<0.000 (-1000,0.0)

Doses are presented in median (IQR). Key: LTG: lamotrigine, VPA: valproate, CBZ: carbamazepine, LEV: levetiracetam.

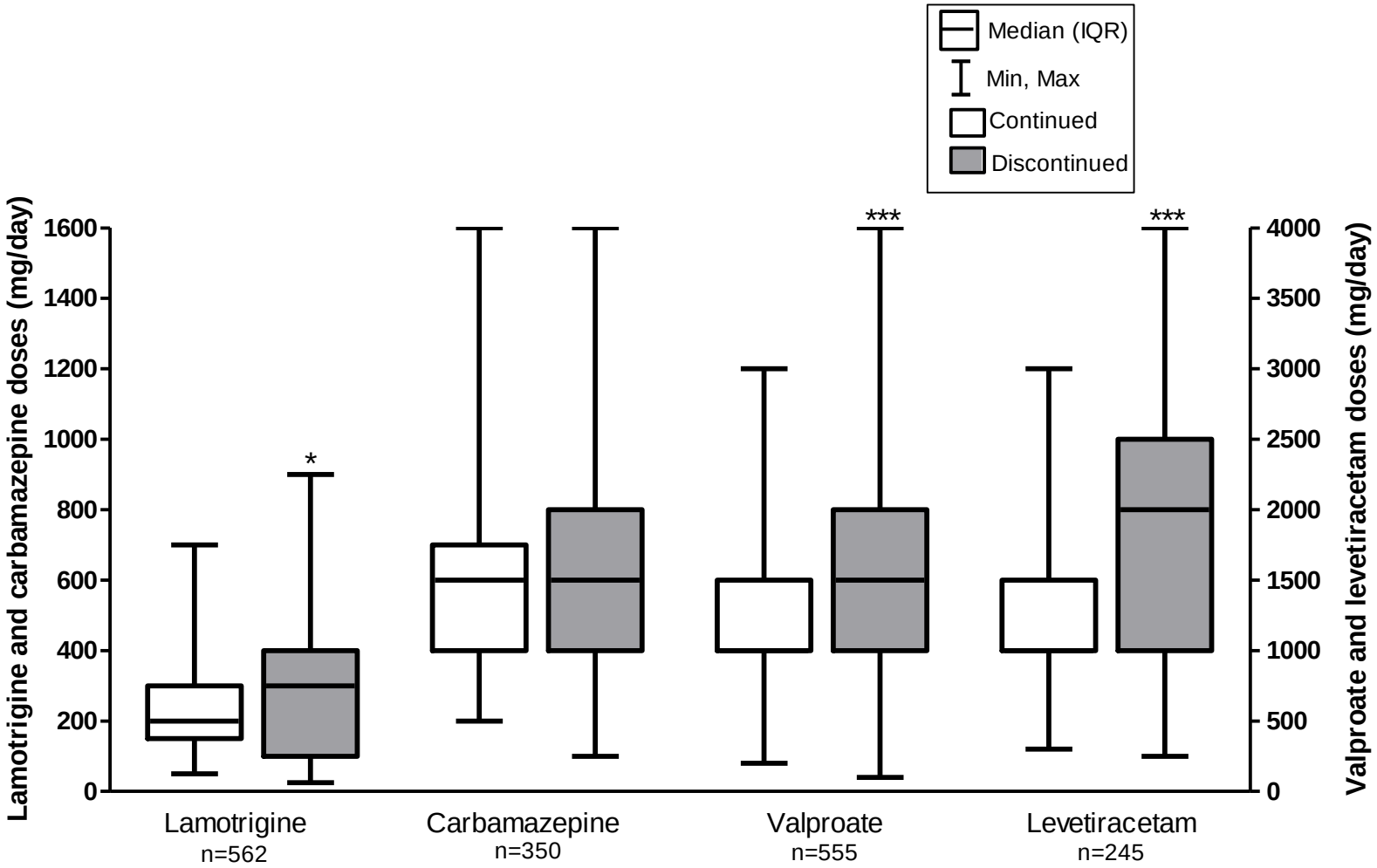


Figure 5-8. Comparison between the doses of continued and discontinued groups for individual medication
Key: *P<0.05, ***P≤0.001. Mann-Whitney test was used.

Table 5-10. Average dosage (mg/day) of discontinued group for each medication stratified by the discontinuation reasons

	LTG	VPA	CBZ	LEV
Ineffective and intolerance	200 (150-350)	1500 (1000-2000)	800 (400-1000)	1000 (1000-2500)
Poor control	400 (300-500)	2000 (1500-2000)	800 (600-1000)	2500 (2000-3000)
Poor tolerability	50 (25-150)	1000 (1000-1500)	400 (200-400)	1000 (875-1000)
Kruskal-Wallis test p-value	<0.000	<0.000	<0.000	<0.000

Doses are presented in median (IQR). Key: LTG: lamotrigine, VPA: valproate, CBZ: carbamazepine, LEV: levetiracetam.

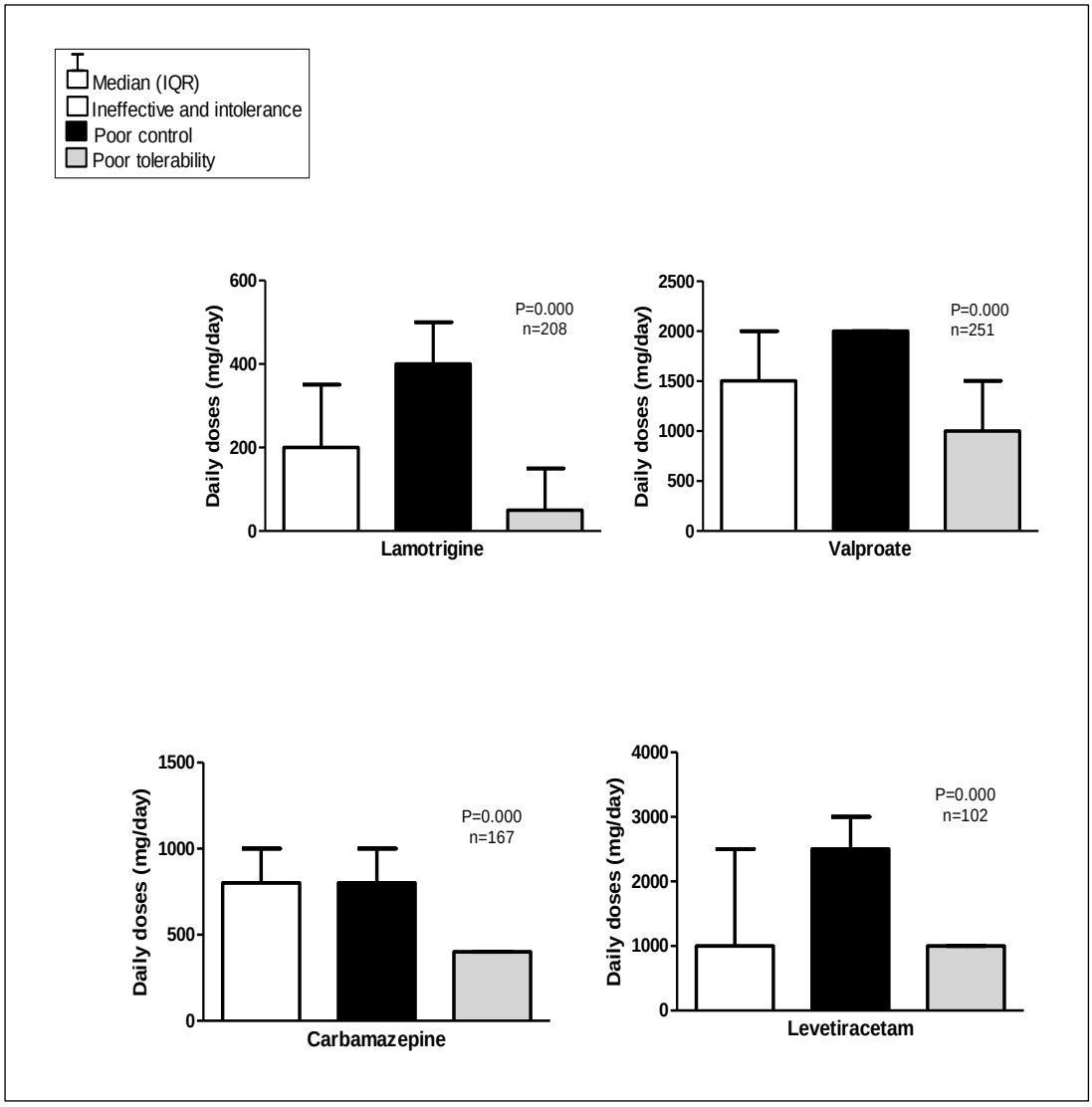


Figure 5-9. Comparison between doses of different reasons for discontinuation of discontinued group for individual medication
Kruskal-Wallis test was used.

5.3.7 Dose-response tolerability versus drug toxicity

The dosages of each discontinued AED were categorised into three levels (low, moderate, and high dose) based on the median and IQR doses for the individual medications. At low dose, the majority (69%) of discontinued drugs were stopped due to poor tolerability alone, and one quarter (25%) were discontinued due to poor tolerability with poor seizure control. At moderate dose, around one-third of treatments were discontinued due to intolerable adverse effects alone (31%), and another third were discontinued due to intolerable adverse effects with poor efficacy (33%). At high dose, one quarter of the therapies were discontinued due to drug poor tolerability with (23%) or without (3%) ineffectiveness. More details of the dosage levels and reasons for discontinuation are shown in Figure 5-10.

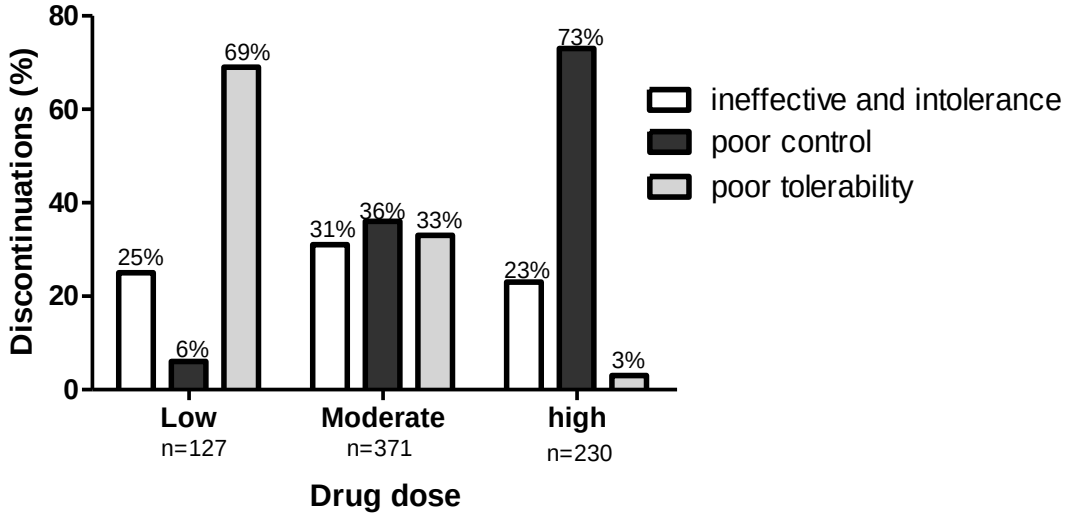


Figure 5-10. Dose-response tolerability and drug toxicity
Low, moderate and high doses were <, =, and > than Interquartile range (IQR), respectively. IQR in mg/day for lamotrigine=150-350, valproate=1000-1700, carbamazepine=400-800, and levetiracetam=1000-2000,

Table 5-11 shows the rate of intolerable adverse reactions at the different dosage levels (low, moderate, and high dose). Acute neurotoxicity symptoms resulted in 22% of treatment failures at low dose, 57% at moderate dose, and 21% at high dose. The majority (67%) of skin rash reactions caused treatment withdrawal at low drug dose while the remaining (33%) were on moderate dose. The Majority of chronic reactions were reported at moderate dose level (70%), and a further 23% at high dose. Psychiatric and behavioural disorders appeared frequently (63%) with the moderate dose, while 21% appeared at low dose and 16% at high dose. Similar

patterns were seen with GI side effects, headaches, and insomnia: around half of the cases were on a moderate dosage, and one quarter were on a low dose and one quarter were on a high dose.

Table 5-11. Adverse effects causing treatment discontinuation at different dose levels

	n	Low dose	Moderate dose	High dose
Acute neurotoxic symptoms (tiredness, poor coordination, tremor)	151	33 (22)	86 (57)	32 (21)
Skin rash	69	46 (67)	24 (33)	
Chronic reactions (weight gain, sexual dysfunction, hair loss, hyponatremia, muscle pain)	44	3 (7)	31 (70)	10 (23)
Psychiatric and behavioural side effects (aggression, mood change, irritability, psychosis, cognitive dysfunction)	43	9 (21)	27 (63)	7 (16)
Gastrointestinal side effects	42	11 (26)	27 (64)	4 (10)
headache	27	7 (26)	15 (56)	5 (18)
insomnia	14	2 (14)	10 (72)	2 (14)

Data are presented in case number (%), Low, moderate and high doses were <, =, and > than Interquartile range, respectively. IQR in mg/day for lamotrigine=150-350, valproate=1000-1700, carbamazepine=400-800, and levetiracetam=1000-2000.

5.3.8 Adverse effects causing treatment discontinuation at specific time periods

Table 5-12 presents the intolerable side effects reported at specific time periods. Within two weeks of treatment initiation, early appearing problems such as a skin rash and gastrointestinal problems were common. They remained common after two months, at which time acute neurotoxicity symptoms such as tiredness, poor coordination and insomnia were also reported commonly. Between two and six months of treatment, chronic effects such as weight gain, hair loss, sexual dysfunction and hyponatremia began to emerge, as well as frequent reports of side effects such as tremor, headaches, aggression and mood changes. In the time period between six months and two years of therapy, weight gain was a common compliant, along with tremor and tiredness. Between two and five years, frequently reported side effects were psychiatric and behavioural disorders, cognitive impairment, and sexual dysfunction. In long-term treatment (more than five years), tremor, poor coordination, and tiredness were reported frequently, along with cases of sexual dysfunction.

Table 5-12. Adverse effects causing treatment failure at specific time periods

	LTG (n=109)	VPA (n=143)	CBZ (n=106)	LEV (n=61)
<2 weeks	rash (15)	GI side effect (3)	rash (9)	aggression (2)
	GI side effect (2)	tiredness (2)	headache	headache
	poor coordination	rash	poor coordination	mood change
	irritability	tremor	GI side effect	tiredness
	headache		tiredness	
2 weeks-2 months	rash (14)	GI side effect (4)	rash (18)	tiredness (3)
	tiredness (5)	weight gain (2)	GI side effect (4)	aggression (2)
	Irritability (2)	tremor (2)	tiredness (4)	insomnia (2)
	insomnia (2)	mood change	headache (3)	GI side effect
	aggression	poor coordination	aggression	mood change
	headache	tiredness	mood change	irritability
	poor coordination		poor coordination	poor coordination
	muscle pain		sexual dysfunction	
2-6 months	skin rash (5)	weight gain (14)	poor coordination (4)	Aggression (3)
	GI side effect (3)	tremor (14)	tiredness (3)	irritability (3)
	insomnia (2)	tiredness (10)	skin rash (2)	mood change (2)
	psychosis	GI side effect (9)	sexual dysfunction (2)	insomnia (2)
	headache	hair loss (3)	hyponatremia	poor coordination
	poor coordination	headache (2)	GI side effect	tiredness
	tiredness	poor coordination	headache	skin rash
	aggression	aggression		paraesthesia
	muscle pain			
	irritability			
	mood change			
6 months -2 years	headache (8)	weight gain (9)	tiredness (12)	mood change (5)
	poor coordination (5)	tiredness (7)	skin rash (4)	headache (4)
	insomnia (2)	tremor (6)	poor coordination (2)	tiredness (4)
	tiredness (2)	GI side effect (4)	headache (2)	GI side effect (3)
	sweaty	hair loss (2)	GI side effect	aggression (3)

Table 5-12. Adverse effects causing treatment failure at specific time periods

	LTG (n=109)	VPA (n=143)	CBZ (n=106)	LEV (n=61)
6 months -2 years				
	tremor	insomnia	tremor	insomnia (2)
	aggression	headache		
	GI side effect	irritability		
	psychosis	gynaecomastia		
		teratogenicity		
		thrombocytopenia		
		poor coordination		
2-5 years	GI side effect (2)	tiredness (4)	tiredness (3)	mood change (2)
	tiredness (2)	weight gain (2)	poor coordination (3)	aggression
	tremor (2)	mood change	sexual dysfunction (2)	tiredness
	skin rash		tremor	poor coordination
	insomnia		GI side effect	
	cognitive dysfunction		cognitive dysfunction	
	Poor coordination			
>5 years	poor coordination	tremor (10)	tiredness (7)	headache
	tiredness	GI side effect (2)	poor coordination	
		tiredness		
		poor coordination		
		sexual dysfunction		

Data are presented in case number. Key: LTG: lamotrigine, VPA: valproate, CBZ: carbamazepine, LEV: levetiracetam. GI: gastrointestinal. Other less common side effects are not shown on this table.

5.4 Discussion

Retention on treatment is often used as a surrogate for effectiveness as it shows time to discontinuation of treatment for any reason. Therefore, it provides useful and practical knowledge for optimising treatment selection. While regulatory clinical trials provide evidence-based information for selecting AEDs, identifying the retention rates of treatments in real-world practice could provide a comprehensive insight into long-term effectiveness, efficacy, and tolerability (Chung et al., 2007). This large and long-term cohort study provides valuable

information on the outcomes of four common standard and new AEDs in a daily clinical setting.

This research investigated the long-term retention rates of LTG, VPA, CBZ, and LEV used as monotherapies in adult patients with new-onset seizures. Patients were treated and followed up for up to 32 years in the Glasgow Epilepsy Unit.

The primary finding of the study is that LTG showed a higher retention rate (at and after six months of treatment initiation) than VPA, CBZ and LEV, and there was no significant difference in the retention rates of other investigated AEDs. In earlier clinical trials, LTG exhibited a higher retention rate than CBZ. In a 48-week trial, 65% of patients treated with LTG (n=131) completed the study, compared to 51% of CBZ patients (n=129), and this difference was significant (p:0.018, HR:1.57, 95% CI: 1.07, 2.31) (Brodie et al., 1995). Steinhoff et al. (2005) found that the retention rate of LTG (92%, n=88) was higher than CBZ (81%, n=88) in patients with focal seizures, although the difference was not significant. Furthermore, a comprehensive review of five randomised control trials which compared LTG and CBZ determined that LTG was significantly better than CBZ regarding time to treatment discontinuation (HR 0.55, 95% CI 0.35, 0.84) (Gamble et al., 2006). Moreover, LTG demonstrated significantly superior outcome times to treatment failure than CBZ (HR 0.78, 95% CI 0.63-0.97) in the treatment of focal epilepsy (Marson et al., 2007a).

LTG also achieved higher retention rates than LEV. In a 26-week comparative study, the retention of LTG and LEV were 71.4, and 63.1% respectively, although this difference did not reach statistical significance (p: 0.07, HR 1.34, 95% CI 0.95, 1.88) (Rosenow et al., 2012). The authors of the study proposed that lack of retention in the LEV group was due to poor tolerability rather than poor efficacy, and adverse events leading to discontinuation were more frequent in the LEV arm (74.5%) than LTG (70.6%), yet once again the difference was not significant. These findings from CBZ and LEV trials are in line with the observations of the current investigation.

However, the results of the present study contrast with existing VPA trials, in which LTG has demonstrated a non-significantly lower retention in patients with generalised epilepsy. In a 24-week comparative study, Steinhoff et al. (2005)

found that the retention rate of LTG (88%, n=33) was lower than VPA (97%, n=30). However, during the early stages of LTG therapy, seizure-related discontinuation (first seizure under-treatment) caused by compulsory slow dose titration led to the low retention rate in the LTG group, which was acknowledged by the authors. Indeed, in the current study, LTG had a lower short-term retention rate (before six months of treatment initiation) to VPA. In another clinical trial with a longer follow-up (seven years), VPA achieved slightly and non-significantly better retention than LTG (HR 1.25, 95% CI 0.94, 1.68) (Marson et al., 2007b). However, the two preceding trials mentioned here were limited to patients with generalised epilepsy, whereas the cohort for this study was more heterogeneous, which may have contributed to inconsistent outcomes for the time to treatment failure in patients treated with VPA.

The subsequent observational studies with longer follow-up have confirmed that LTG has superior retention. Zeng et al. (2015) compared the long-term effectiveness of five monotherapies (CBZ, VPA, LTG, TPM, and OXC) in adult focal epilepsy patients. They demonstrated that LTG had the highest retention rate, significantly higher than VPA (HR 0.53, 95% CI 0.37, 0.74) and CBZ (HR 0.80, 95% CI 0.67, 0.96), and there was no significant difference in the retention rates of CBZ and VPA. Furthermore, Chung et al. (2007) observed the retention rates of five new medications (LEV, LTG, OXC, TPM, and ZNS) and showed that the retention rate was highest with LTG, which was significantly different from LEV ($P<0.0001$). Both these studies were relatively short-term, with three and two-year follow-ups, respectively. A ten-year follow-up, observational study performed by Hu et al. (2011) did not identify a significant difference in the retention rates of CBZ and VPA used as the initial monotherapies in patients with newly diagnosed focal seizures. These findings are consistent with the findings of the present study. However, a study conducted in China showed that CBZ exhibited the highest retention rate, followed by LEV, LTG, and then VPA. CBZ was significantly different from VPA ($p=0.008$) and LTG ($p=0.041$), and LEV significantly different from VPA ($p=0.021$) (Zhu et al., 2015). However, the authors of the former study explained the possible reasons for the poor outcomes with LTG. Firstly, the slow titration of the LTG dosage caused poor drug adherence, as some patients did not increase their drug dosage according to their clinicians' recommendations. Furthermore, the rash rate with LTG was high in their

institution (17.31%), therefore, they assumed that Chinese people exposed to LTG are more prone to rash and will more readily withdraw medications due to the appearance of a rash. However, the authors highlighted that this assumption needs further validation.

In the current analysis, there was high discontinuation of CBZ and LTG within six months of therapy start. The notable high initial discontinuation of CBZ and LTG may be due to skin rash, which led to 49% (n=34/69) and 37% (n=29/78) of discontinuation within six months for CBZ and LTG therapies, respectively. Moreover, in order to diminish the risk of rash, LTG was started at a low dose with a slow titration schedule. Consequently, due to the time taken to reach therapeutic maintenance dose, it may be difficult to control seizures during early stages of LTG therapy. This may indicate that the tolerability of CBZ and LTG should be carefully assessed in the first six months after commencement of therapy. Indeed, this investigation also concludes that after the hurdle initial six months of LTG therapy, the continuation rate was markedly high. However, the discontinuation rate of CBZ remained high for the first two years of therapy in this study. The primary reason for CBZ discontinuation was poor tolerability, while in all other AEDs ineffectiveness was the main reason for discontinuation, Poor tolerability resulted in early discontinuation compared to other reasons, which may explain the high withdrawal rate of CBZ compared to all other AEDs at most evaluation points during first two years of therapy. With VPA and LEV therapies, the nature of the most frequent adverse effects may explain the relatively high short-term retention rate. Tremor and weight gain were the most common intolerable adverse effects reported with VPA, while psychiatric and behavioural difficulties were most common with LEV therapy. These adverse effects were frequently reported during the periods of two-six months and six months-two years, and continued to appear after two years of therapy.

It is important to emphasise that a high retention rate does not necessarily indicate better efficacy, this assumption is in common with existing studies that evaluated retention rates of treatments (Zeng et al., 2015, Zhu et al., 2015). Many patients in this research continued treatment despite the lack of optimal efficacy, as shown in Chapter 3: 24-30% of patients continued with LTG, VPA, CBZ, and LEV although they were not completely effective.

To the best of our knowledge, this is the largest and longest observational cohort study of newly diagnosed epilepsy patients. The large number of patients included in this research and the long-term follow-up period has increased the possibility of finding clinically important differences between medications. Moreover, few studies have investigated the retention rates of standard and new AEDs, and these were limited to the Chinese population (Zeng et al., 2015, Zhu et al., 2015). Therefore, the current research may present novel findings in terms of population as well.

It may raise concern that prior exposure to AEDs would influence the retention rate. In fact, the efficacy of AEDs declines substantially after failure of the second AED regimen, and patients develop drug resistant epilepsy (Kwan and Brodie, 2000, Brodie et al., 2013). Therefore, the probability of treatment continuation might be lower with a drug tried after two prior medication trials compared to one tried as a first or second regimen (Chung et al., 2007). However, this potential bias is unlikely to affect the reported retention rate results in this study. Firstly, the regression analysis in this study revealed that a history of prior AED use did not influence the treatment continuation significantly ($p>0.05$). Moreover, there was no significant difference in number of prior AEDs between different treatment groups. The majority (92%) of the AEDs were used as a first or second regimen because these four AEDs (LTG, VPA, CBZ, and LEV) are the most common first-line and second-line monotherapies for epilepsy (Gamble et al., 2006, Hu et al., 2011, Glauser et al., 2013, Brodie, 2017b).

However, there was a significant ($P<0.05$) difference in gender and epilepsy type between treatment groups. More females tried LTG and LEV than CBZ and VPA; perhaps due to teratogenicity concerns. Studies showed that LTG and LEV safer in pregnancy than VPA and similar to CBZ (Perucca and Gilliam, 2012). Indeed, VPA should be avoided in childbearing women (Tomson et al., 2015). In this study, more patients with focal epilepsies tried LTG than VPA, because LTG was found to be less officious than VPA in generalised epilepsies (Marson et al., 2007b). This unavoidable selection bias may affect the reported retention rates in this study as discussed in Chapter 6.

Besides the comparison of retention rates, this study identified several further noteworthy findings. Overall, lack of efficacy was the primary reason for

treatment failure in the analysis, which accounted for 42% (n=309/728) of total treatment discontinuation. This was also the case with several other studies (Chung et al., 2007, Zhu et al., 2015). Similarly, lack of efficacy was the main cause of treatment discontinuation with individual AEDs in this investigation, except for CBZ.

Poor tolerability was the primary reason for treatment discontinuation with CBZ therapy. This may indicate inferior tolerability of CBZ compared to LTG, VPA and LEV. In fact, CBZ has demonstrated lower tolerability than LTG, VPA and LEV in several studies. Brodie et al. (1995) found that more patients on CBZ (27%, n=129) than LTG (15%, n=131) withdrew due to adverse events. Likewise, unacceptable adverse events occurred more frequently with CBZ (74%, n=88) compared to LTG (43%, n=88) in another study (Steinhoff et al., 2005). Moreover, the SANAD study indicated that adverse events leading to discontinuation were more frequent with CBZ (13%, n=50/378) than LTG (8%, n=30/378), and compared with CBZ, LTG achieved 10–11% less treatment withdrawal for adverse events and was statistically different at all time points between one and six years (Marson et al., 2007a). In addition, Mohanraj and Brodie (2005) demonstrated that adverse effects leading to withdrawal were significantly higher with CBZ (16%, n=45/268) than VPA (7%, n=17/198) or LTG (7%, n=15/198). Furthermore, Zeng et al. (2015) showed that adverse effects leading to treatment failure were more common with CBZ (25.5%, n=32/125) than VPA (23.8%, n=36/151) and LTG (11.1%, n=15/135). Brodie et al. (2007) found that more CBZ treated patients discontinued treatment because of adverse effects (19.2%, n=56/291) than LEV (14.4%, n=41/285), although this difference was not significant. Finally, Zhu et al. (2015) demonstrated that CBZ and LTG were most frequently associated with treatment failure as a result of unacceptable adverse effects (23.7 and 23.3%, respectively), while LEV (9.1%) was the least likely to result in treatment failure; although none of the differences between the AEDs with regard to treatment failure were statistically significant. These observations are keeping with the findings of the current study. However, in another study conducted by Hu et al. (2011), patients were less likely to discontinue treatment of CBZ than VPA. Yet this difference only occurred during the time period from the first six months to two years of treatment initiation, and the overall discontinuation due to adverse effects in the two groups were comparable.

Cutaneous reactions were the most frequent adverse effect reported for CBZ and LTG in the cohort for the present study. However, the incidence was higher with CBZ (9.4%, n=33/350) than LTG (6.2%, n=35/562), although the difference was not statistically significant (p=0.086). This result is consistent with the findings from studies conducted in the UK. Brodie et al. (1995) showed that 9% of patients treated with LTG developed rash necessitating drug withdrawal compared with 13% receiving CBZ. Marson et al. (2007a) demonstrated that CBZ (7%, n=378) exhibited a higher rash rate than LTG (3%, n=378). In contrast, Wang et al. (2012) from China found that more patients experienced rash following LTG treatment (11.1%, n=139) than CBZ therapy (3.8%, n=1172). Similarly, LTG (8.7%, n=115) was associated with a higher rate of skin reactions than CBZ (4.1%, n=193) in another Chinese study (Zhu et al., 2015). Genetic factors play a role in the development of AED-induced cutaneous reactions (Zaccara et al., 2007, Franciotta et al., 2009). This may explain the discrepancy in findings from different populations, in addition to the differences in dosing guidelines for treatment commencement and titration that affect rash appearance, particularly for LTG.

In VPA monotherapy, tremor and weight gain were the most frequent adverse effects that led to treatment discontinuation in this research. The incident rate of intolerable tremor was 6.5% (n=36/555) of VPA patients. VPA-induced essential tremor has been observed in 6-45% of patients in different studies (Perucca, 2002, Hamed and Abdellah, 2017). A potential reason for this wide range may be the use varied VPA dosage, as well as the use of different methods to assess tremor across studies. Furthermore, different VPA formulations have been found to influence the rate of tremor. Controlled-release VPA may have less tremorigenic activity compared to conventional VPA, as the latter exhibits higher peak-trough variation (Rinnerthaler et al., 2005). The appearance of tremor is dose-dependent, but the mechanism is not known. In general, VPA enhances γ-amino butyric acid (GABA) and inhibits *N*-methyl-D-aspartate (NMDA) in a dose-related manner. VPA also affects several other central neurotransmitters such as dopamine, epinephrine, and norepinephrine. These effects involved in the mechanism of VPA as anticonvulsant and the latter effect may be related to a number of CNS adverse effects of VPA including tremor (Hamed and Abdellah, 2017).

Weight gain has been identified as another common adverse effect of VPA therapy in several studies (Corman et al., 1997, Jallon and Picard, 2001, Biton, 2003, Ben-

Menachem, 2007). In the current study, the rate of unacceptable weight gain was 5% (n=29/555) in VPA recipients. This is keeping with other published data. In SANAD trial, the weight gain was observed in 4% of patients randomised to VPA (n=238) (Marson et al., 2007b). However, the rate in the present study was slightly lower than the rate reported in one observational study in which weight gain that led to discontinuation of therapy was observed in 9% (n=5/55) of patients treated with VPA (Corman et al., 1997). In fact, the rate of weight gain reported as an adverse event with VPA used in clinical trials not designed to assess the incident of this adverse effect was relatively low (3%), but the figure was far higher in studies intended to evaluate weight gain (up to 70%) (Biton, 2003). The mechanism of VPA-associated bodyweight gain is not yet clear. One possible mechanism is involvement of eating stimulation and increasing hunger through an effect on the hypothalamus as a result of decreased blood glucose levels (Jallon and Picard, 2001). Weight gain can pose a health hazard (possible increase in the risk of diabetes mellitus and/or heart disease) and lead to poor adherence with therapies (Biton, 2003, Ben-Menachem, 2007). The risk factors for VPA-associated bodyweight gain are not entirely clear (Jallon and Picard, 2001, Biton, 2003).

With the LEV monotherapy tried in this study, psychiatric disorders including mood changes, aggression and irritability were the most common reported adverse effects (11%). Other studies showed similar figures. A prospective study of 517 adult patients treated with LEV found that 10% of the patients developed a psychiatric adverse effect, and aggression (3.5%) was the most frequently presented psychiatric condition (Mula et al., 2003b). Furthermore, a retrospective observational study that compared the psychiatric and behavioural side effects of nine new AEDs in 1394 adults found that LEV exhibited the highest rate of psychiatric and behavioural adverse effects, which contributed to 8.8% (n=521) of the treatment failures for that therapy (Weintraub et al., 2007). Another study demonstrated a higher rate, in which 20% (n=38/196) of patients reported behavioural problems or irritability with LEV, but it did not review the patients' past psychiatric history, and it was not clear whether this could have contributed to the results (Chung et al., 2007). In the present study, in which patients were treated in the Glasgow Epilepsy Unit, LEV therapy was avoided for patients with current or previous psychiatric conditions whenever possible. The effect of psychiatric coexistence was examined and is shown in Table 5-13. In general, past

psychiatric history has been regarded as the most important determinant for the probability of a patient experiencing psychiatric effects with AED use, including LEV therapy (Mula et al., 2003b, Weintraub et al., 2007). Furthermore, psychiatric adverse effects occurred similarly in AEDs (including LEV) used as monotherapies and as polytherapies (Weintraub et al., 2007), and LTG co-medication was protective (Mula et al., 2003b). It should be highlighted that the data used in this study on psychiatric conditions were not collected systematically using a validated tool. In addition, other comorbidities (other than epilepsy and psychiatric conditions) and co-prescribed medications (other than AEDs) were not taken into account, which may have influenced LEV-associated psychiatric adverse effects. Nevertheless, the rate of psychiatric adverse effects in the LEV monotherapy was similar in patients with and without psychiatric comorbidities Table 5-13, which suggests that the differences were most likely due to LEV use and not due to other variables.

Table 5-13. Levetiracetam-related psychiatric and behavioural adverse effects in patients with and without pre-treatment psychiatric history

Pre-treatment psychiatric comorbidities	Psychiatric and behavioural adverse effect	P-value (95% CI) of 2-Proportion test
No (n=186)	17 (9)	0.142 (-0.026, 0.182)
Yes (n=59)	10 (17)	

Data are presented in case number (%).

It is important to note that, in the current study, treatment discontinuation due to intolerable adverse effects was commonly limited to the early period after treatment initiation, while the time of therapy discontinuation due to poor seizure control with or without intolerable adverse effects was later. The median number of months to failure for intolerable adverse effects was two, and for poor seizure control with or without intolerable adverse effects was nine and eighteen respectively. Moreover, the majority (70%) of treatment failures caused by unacceptable side effects appeared within six months of therapy commencement. Zhu et al. (2015) found that the most frequent time to discontinuation was within one month of treatment introduction, and the main cause of discontinuation during this early period was the adverse effects associated with the medication. This was followed by inadequate seizure control during the next few months. The average number of months to discontinuation for unacceptable adverse effects

was 1.89, and was 15.4 for inadequate seizure control. Similarly, in SANAD studies, the median number of months to treatment failure due to unacceptable adverse events was three, and was eight for inadequate seizure control (Marson et al., 2007a, Marson et al., 2007b). These findings are consistent with the observations of the present analysis. These characterisations of treatment stages may indicate that adverse effect should be thoroughly assessed soon after the introduction of an AED.

The types of adverse effects were also varied between the different treatments stages. In the earliest phase, within two months of treatment commencement, skin rash, gastrointestinal disorders and acute neurotoxicity symptoms (such as sedation, poor balance and sleep difficulties) were predominate. In the later phase, six months and onwards, chronic reactions such as weight gain, hair loss and hyponatremia started to appear, in addition to psychiatric and cognitive disorders. In the latter stage, early appearing problems such as sedation and tremor where also reported, which may have been caused by dose elevation.

AED dosage had a substantial effect on treatment outcomes during the three treatment characterisations in this research. The dosage at which the treatment was discontinued was the lowest for poor tolerability, intermediate for both ineffectiveness and intolerance, and highest for poor seizure control. This is in line with other studies (Marson et al., 2007a, Marson et al., 2007b). Treatment failure due to poor tolerability alone frequently occurred early and at low dose (in some cases the doses were sub-therapeutic) in the current study, although it could also be caused by high starting dose and/or rapid titration. The intermediate stage, in which treatment failure was frequently due to both inadequate seizure control and unacceptable side effects, was also associated with intermediate dosage. This stage is interesting because treatment failure may have been caused by drug toxicity in some patients, as the dose was increased aggressively in an attempt to achieve seizure freedom; in other patients, it may have been caused by drug intolerance that prevented the usage of a fully effective dosage. Therefore, it is important to differentiate between dose-response drug tolerability and drug-toxicity to avoid poisoning the patients with inadequate seizure control. In fact, at low dose, the majority (94%) of treatment failure was due to unacceptable side effects with or without poor seizure control, and this may represent true drug intolerance. This dose-response drug intolerance may be

unavoidable in most cases, although a low starting dose and slow titration schedule can minimise it. At high dose, one quarter of treatment discontinuation was due to intolerable adverse effects with or without inadequate seizure control, and this may represent drug toxicity as the patients initially tolerated the low and moderate dosages.

In this study, the median dose of continued therapy was 200 mg/day for LTG, 600mg/day for CBZ, and 1000mg/day for VPA and LEV. These doses can be considered as moderate dosages. Few studies have investigated the doses of successful and unsuccessful AEDs, which may be an additional novelty of this research. Mohanraj and Brodie (2005) showed that the majority of patients with new-onset seizures respond to moderate doses of AEDs, but the doses of unsuccessful AEDs were not evaluated. In the present analysis, continued therapy does not necessarily mean successful treatment (i.e. seizure-free achievement). Moreover, the results show that the continued dosage was lower than the discontinued dosage for each AED. Furthermore, the interquartile range doses (mg/day) were wider for discontinued therapies than continued therapies for each drug, especially LEV, which was 1000-1500 for the continued group while 1000-2500 for the discontinued. However, Chung et al. (2007) demonstrated that the dosages of the continuing groups were higher and with a wider range than those of the discontinued groups for new AEDs (LEV, LTG, OXC, TPM, and ZNS), which contradicts the observations of this study. However, the preceding research (Zeng et al., 2015) differed to the current study in several aspects: their clinic had a larger refractory epilepsy population, and AEDs were frequently prescribed as the third, fourth and fifth treatment approach. Whereas the cohort for the present study was newly diagnosed epilepsy patients, and the AEDs were generally used as a first or second choice. In addition to this variation in the intractability of study populations, the number of concurrent AEDs used was also different. The current analysis focused on monotherapy, while their patients were taking AEDs as monotherapy or as adjunct therapy. Consequently, the doses of AEDs drugs were different.

In conclusion, evaluating retention rates of the most commonly used established and modern AEDs can provide valuable insight into their long-term effectiveness in routine clinical setting. This study found highest retention rate with LTG after six months of treatment initiation, which was significantly higher than VPA, CBZ,

and LEV. Beside ineffectiveness, other main reasons for discontinuation were rash with LTG and CBZ, tremor and weight gain with VPA, and psychiatric and behavioural adverse effects with LEV.

Chapter 6. Conclusion and future directions

6.1 Overview of study presented

The present study provides a comprehensive evaluation of clinical effectiveness of different standard new AEDs. The treatment efficacy (1-year seizure –free), poor tolerability (adverse effects leading to treatment failure), and retention rate (time to discontinuation) were measured in a real-world practice and therefore can largely present the clinical effectiveness (Figure 6-1).

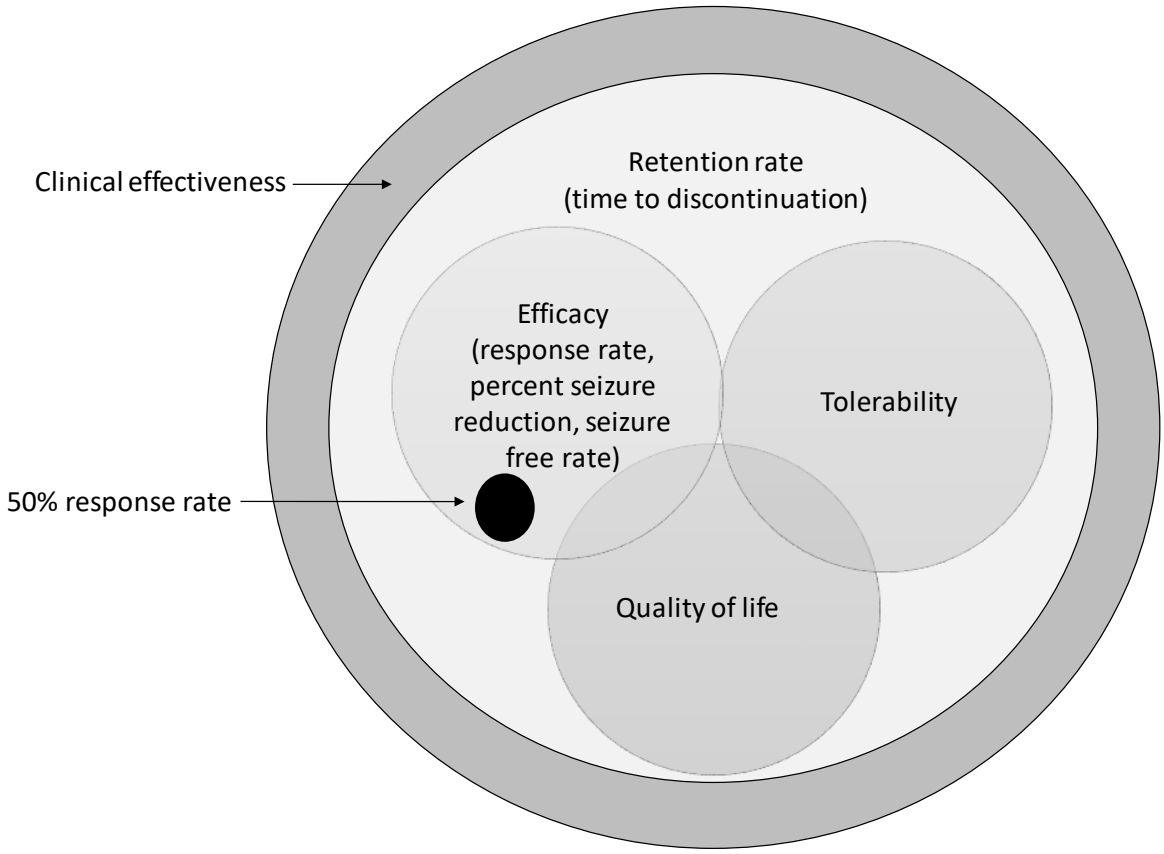


Figure 6-1. Measuring different treatment outcomes of antiepileptic drugs [modified from (Lee, 2014)]
Clinical effectiveness evaluation should include comprehensive measures of efficacy, tolerability and quality of life in a setting relevant to real-life, and retention rate is very similar to this concept. This study assessed the efficacy (1-year seizure-free) and intolerable adverse effects of 17 antiepileptic drugs. As well as the retention rates of the most common four monotherapies was compared and therefore can largely present the clinical effectiveness

This study provides some novel and strong aspects. This study included a large number of patients (n=1,528) with newly diagnosed epilepsy who were followed-up for up to 32 years. During this period, 14 new AEDs has been introduced to

clinical use some with novel mechanism of actions. Additionally, a number of previous analyses were performed on same expanding cohort at different points during this period. Therefore, this study provides a strong evidence that treatment outcomes in epilepsy have not improved despite the availability of increasing number of AEDs. This study has extensively evaluated the clinical and pharmacological predictors for poor tolerability. This may present novel findings as few observational studies have evaluated the predictors for poor tolerability particularly non-AEDs variables. This study compared the long-term retention rates of the most widely used AEDs in a large number of patients from everyday clinical practice. Moreover, few observational studies have investigated the retention rates of standard and new AEDs, and these were limited to the Chinese population (Zeng et al., 2015, Zhu et al., 2015). Therefore, the current research may present novel findings in terms of population as well.

This research concluded that treatment failure could be categorised into three distinct types based on time to discontinuation, reasons of discontinuation, and dosage at which AEDs were discontinued. As shown in Table 6-1, early treatment failure at which treatments were largely failed within 2 months, mainly due to intolerable adverse effect, and at low dose (< IQR). Cutaneous adverse reactions were frequent in that phase. This type of adverse effects may represent the drug intolerability and may be difficult to avoid, although low starting dose and slow titration can minimise it. Late treatment failure (median time to discontinuation 18 months) was mainly due to poor seizure control and at high dose (>IQR). The intermediate stage was an overlap between two previous phases. This stage is interesting because treatment failure may have been caused by drug toxicity in some patients, as the dose was increased aggressively in an attempt to achieve seizure freedom; in other patients, it may have been caused by drug intolerance that prevented the usage of a fully effective dosage. Therefore, it is important to differentiate between dose-response drug tolerability and drug-toxicity to avoid poisoning the patients with inadequate seizure control. More strengths of this study are discussed in the next section.

Table 6-1. Three distinct types of treatment failure of antiepileptic drugs concluded from the current study

Predominant reasons for discontinuation	• Intolerable adverse effects	• Both	• Poor seizure control
Type of treatment failure	• Early	• Intermediate	• Late
Time to discontinuation (median)	• 2 months	• 9 months	• 18 months
Percentage of treatment failure	• 28%	• 28%	• 44%
Predominant dosage	• Low dose (<IQR)	• Moderate (within IQR)	• High (>IQR)
Predominant adverse effects	• Rash	• Neurotoxicity/ chronic adverse effects	• Neurotoxicity/ chronic adverse effects
Type of adverse effects	• Tolerability	• Both	• Drug toxicity
Management	• Mainly unavoidable • Low start dose/ slow titration	• Important to differentiate between dose-response adverse effect and drug toxicity	• Avoid pushing dose aggressively in uncontrolled patients • Minimise number of concomitant drugs

IQR: interquartile range

6.2 Study strengths

To the best of my knowledge, this is the largest and longest observational study of newly diagnosed epilepsy patients. The large number of patients included in this study and the long-term follow-up period have increased the possibility of finding clinically important differences between medications. This as well allow assessment of rare and late appearing side effects of drugs.

More recent, longer duration, larger sample size, and higher rate new drug use represent the advantages of the current analysis over the previous analyses on the same expanding cohort. Extra new agents were included in the current study as several new AEDs have been approved since the previous research conducted in 2005 and some new agents have become more popular. This particular analysis has allowed the evaluation of changes in treatment outcome of epilepsy over the

last three decades as a result of availability of an increasing number of AEDs by comparing the results of the current analysis to previous analyses.

Furthermore, this analysis has provided a comprehensive assessment of tolerability aspect of AED treatments. The tolerability of 17 standard and new AEDs was studied and this covers almost all AEDs used in UK for adult epilepsy patients. The examination of the adverse effects in all regimens used during follow-up represent a uniqueness as this enabled investigation of poor tolerability in initial AED monotherapies, as well as successive AED regimens. Therefore, the tolerability of newer agents used as adjunct therapy was well evaluated. This method also allowed investigation of poor tolerability in polytherapies. Furthermore, the study assessed treatment failure due to drug intolerance alone and in combination with poor drug efficacy; the latter is a common occurrence in epilepsy patients.

6.3 Study Limitations

Although this is the largest observational study of newly diagnosed epilepsy patients, there were small sample sizes in some subgroup analyses. The following part explain other caveats of the current study.

6.3.1 Generalisability

It should be acknowledged that this study has its restrictions such as the tertiary care character of the Epilepsy Unit, as well as being on a single centre. Thus, the results may not be generalisable to the entire population but may reflect treatment outcomes in the institutions with similar patient demographics.

Although excluding patients with persistent poor drug adherence may provide accurate evaluation of AEDs efficacy, the employment of intention-to-treat principle was impossible. Patients younger than 18 years were excluding as well, as their seizure types/ syndromes along with treatment response may be different from adults. Therefore, findings of this study may not reflect complete scenario sufficiently.

The findings of this study can be therefore generalised to epilepsy centres for adult patients with newly diagnosed epilepsy including both focal and generalised

epilepsies in the UK. Different health care systems are used outside the UK which can affect the treatment outcomes. This study included a tertiary care clinic from specialists, their patients may have more severe epilepsy than primary clinics. On the other hand, this is an out-patient clinic and these patients may be less intractable than patients admitted to hospital or emergency for severe seizures like status epilepticus. Additionally, this study included patients from one clinic in West of Glasgow which had been managed by few neurologists, this may limit the generalisability.

6.3.2 Assessment of seizure outcomes

There are a number of caveats in regards with evaluation of efficacy of AEDs in this study. First, the efficacy evaluation based on seizure outcomes at last clinic visit but many patients particularly seizure-free were discharged from the Epilepsy Clinic to primary care. Nevertheless, patients usually re-refer in case of relapse, poor tolerability, or for a pregnancy consultation, etc. General practitioners and all patients are aware of this arrangement; they also could phone the Epilepsy Unit if necessary. Therefore, it was assumed that the patients remained seizure-free if they were not referred back to the Epilepsy Clinic. This limitation is difficult to overcome but a potential statistical analysis, i.e. sensitivity analysis, could be performed to test the robustness of the results. Generally, sensitivity analysis is a process of recalculating outcomes under alternative assumptions that differ from those used in the primary analysis to test the robustness of the results of a study in the presence of uncertainty. Sensitivity analysis can be performed for different reasons, including Good Clinical Practice (GCP) violations, protocol violations, ambiguous/missing data. This analysis has not performed in the current analysis to test the result of the assumption that the discharged controlled patients remained seizure-free if they do not come back to the Epilepsy Unit. The sensitivity analysis could be performed under alternative assumption, for example, the discharged patients did not remain controlled. Then the results of this sensitivity analysis could be compared to results of primary analysis to check robustness.

Further issue is that a complete seizure control (i.e. seizure-free for at least 12 months) was the only outcome measure for AEDs efficacy in the current study. A reduction in seizure frequency / severity and an improvement in post-ictal

recovery have not been measured. Although these improvement may increase seizure acceptance by some patients, several studies have indicated that complete seizure freedom is a major determinant of quality of life, independent from seizure severity or frequency, due to the psychological impact of the unpredictability of seizures (Kwan et al., 2010).

Seizures were counted based on patients' seizure diaries in each clinic visit, however, studies have shown that seizure diaries are unreliable. Scalp electrodes and electronic devices are recommended instead to detect and count seizures prospectively (Jory et al., 2016).

6.3.3 Assessment of adverse drug reactions

Generally, there are several challenges regarding assessment of adverse drug reactions of AEDs. The following section will discuss these difficulties and how they have been overcome in the current study. Attribution of causality of adverse drug reactions can be challenging particularly when managing individual patients (Edwards and Aronson, 2000). It is important to distinction between the terms adverse effect and adverse event. An adverse effect is an unpleasant reaction that can be attributed to the medication. An adverse event is an unpleasant reaction appearing during treatment but not necessary caused by the medication (Perucca and Gilliam, 2012). In RCTs or case-control studies, the causality of suspected adverse drug reactions can be estimated by comparison with a control group; but this is impossible for the observational studies of patients from routine clinical practice. Therefore, in this study, several criteria were considered to establish a certain causality of adverse effects, whenever possible. First, reasonable time relation between the use of AEDs (introduction or does elevation) and the incidence of adverse effect. Furthermore, concomitant disease or drugs cannot explain the adverse effect. Additionally, the pattern of the adverse effect may fit the known pharmacology or sensitivity pattern of AEDs. Moreover, reversibility of adverse effects after drug discontinuation. Finally, the background frequency of the event and how often it is associated with drugs were considered. For instance, headache is relatively common, so its association with a medicine may be by chance. In contrast, rash has a low background incidence and is often associated with particular AED, therefore it is more likely to be an adverse drug reaction.

Further common issue associated with the tolerability evaluation is the methodology used to detect and quantify adverse effect as the rate of side effects tends to be underestimated or overestimated by relying on spontaneous reporting or checklists, respectively (Perucca and Gilliam, 2012). In the current study, however, the tolerability was assessed prospectively in each clinic visit by structured interview focused on common concerns of each particular AEDs. Moreover, only intolerable adverse effects were evaluated using a definitive outcome measure i.e. withdrawal of a drug (or failure of therapy). Nevertheless, it should be pointed out that drug withdraw due to side effect is often based on clinical benefit-risk judgment (Edwards and Aronson, 2000), considering the severity of reaction and the efficacy of drug (i.e. seizure control). Therefore, adverse effect that caused dosage reduction and addition of AED was regarded as intolerable adverse effect in this study.

Side effects of AEDs were recorded based on patient complaints and clinical judgments by epilepsy specialists. Most of these symptoms were not standardised or validated. This is most likely due to the fact that no universally-recognised method of capturing these patient-reported outcomes, and that the difficulties inherent in capturing and analysing indices of quality of life and more subjective adverse effects has been discussed in the literature (Gilliam, 2002). Furthermore, there is no need for routine screening for adverse effects with blood and urine tests, or AEDs blood level, etc., in clinical practice. Camfield and Camfield (2006) showed that these tests have little value in preventing, detecting, or reducing side effects. Moreover, this is a pragmatic study and recorded those problems which the patients felt were important to them. Setting thresholds would be complicated and might arguably detract from the value of the information (for example, a 5kg weight gain would be more of a problem to a 60 kg teenager than to a 100 kg adult). Studies have shown that patient concerns about adverse effects of AEDs, whether actual or perceived, has negative impacts on adherence to medication and quality of life (Eatock and Baker, 2007).

To make the analysis clear and straightforward, a single side effect of a single offender AED was assigned for each intolerable adverse effect case in this study. However, this ideal situation is not always the case in real world in which more than one intolerable of one or more AED(s), in polytherapy, could cause treatment failure. For example, in an instance of tremor with a VPA/LTG combination that

results from the pharmacodynamics and pharmacokinetic interaction, both AEDs contribute to this side effect. However, in this study, only the discontinued AED was indicated as a culprit one.

6.3.4 Potential confounding factors

There is an unavoidable selection bias in observational studies of patients from everyday clinical practice because of absence of randomisation. The selection of AED for each patient is based on seizure type and patients' characteristics such as age, gender and comorbidities (French et al., 2004). For an instance, VPA is a potent teratogenic agent and therefore is recommended to be avoided in girls and young women (Tomson et al., 2015). On the other hand, LTG and LEV are associated with low risk of teratogenicity (Tomson and Battino, 2012). Likewise, LTG has showed less efficacious than VPA in generalised and unclassifiable epilepsy (Marson et al., 2007b). Consequently, in the current study, female patients used LTG and LEV significantly higher than VPA and CBZ; and patients with focal epilepsies used LTG significantly higher than VPA. Other potential confounders were number of concurrent AEDs and previous unsuccessful AED schedules. Therefore, dissimilar seizure severity between patient groups of AEDs used as first line monotherapy and AEDs used as adjunct therapy for intractable seizure.

Several attempts have been made to minimise the risk of bias or confounding in this study. First, restricted patient selection was applied so all groups had the same value for the confounder. For instances, restricting this study to adult patients with newly diagnosed epilepsy, comparison of efficacy and tolerability of AEDs monotherapy was separated than AEDs polytherapy, and the comparative retention rates analysis was restricted to four AEDs (LTG, VPA, CBZ, and LEV) monotherapy that frequently used as first-line therapy. In addition, to show the extent of the balance between treatment groups for the confounder, the baseline characteristics were compared for different treatment groups. Moreover, the effect of the confounder was quantified and adjusted, whenever possible, in regression statistical analyses.

6.4 Clinical implications

This study identified some characteristics of patients likely to be pharmacoresistant. Failure to response to two or more AEDs was the strongest predictor for intractable seizures which lends further support to the ILAE definition of pharmacoresistant epilepsy, which recommends that a specialist should review these patients for confirmation of diagnosis of seizure/ syndrome and consideration of epilepsy surgery.

This study also identified the patients at high risk of adverse drug effects. It is important to recognise these patients in order to avoid specific AEDs, counsel them and their families about the possible adverse effects, to use a careful titration scheme, and to make sure that the patients are seen frequently. When recognised at an early stage, adverse effects are mild and reversible in most cases.

This research showed that there were distinct tolerability profiles for each AED which may affect each patient on different way depending on several of factors such as age, gender, lifestyle, type of occupation and comorbidity. Tolerability, also, related to patients' susceptibility. Therefore, patients more likely to experience specific adverse effect based on their intolerability history or comorbidity should rationally avoid AEDs with potential risk of that particular adverse effect. For instance, AEDs with potential risk of rash such as LTG and CBZ should be avoided in patients who have a history of cutaneous adverse drug reactions. LEV and GBP have a lower risk of hypersensitivity. Similarly, AEDs that known to cause or worse psychiatric disorders such as LEV, PER and TPM should be avoided in patients with psychiatric comorbidity. VPA should be avoided in women with childbearing potential due to its teratogenicity, and LTG and LEV seems safer alternatives. Finally, LEV, GBP, and LTG appear to have better tolerability and have lower potential of drug interactions than CBZ in the elderly with concomitant medications. In short, tolerability offers the opportunity for patients-tailored AEDs to optimise efficacy, minimise adverse effects, and eventually improve patients' quality of life.

Intolerable adverse effects were mainly appeared early after treatment initiation that may indicate that tolerability should be thoroughly assessed soon after the introduction of an AED. Especially for LTG in which continuation rate after the

hurdle initial six months was markedly high. The strategy of "start low and go slow" may be helpful. Although most of the observed intolerability occurred at low dose, some intolerable adverse effects cases were on moderate or high dose. It is important, thus, to differentiate between dose-response tolerability and drug toxicity to avoid poison uncontrolled patients, avoid pushing dose aggressively and minimise number of concurrent AEDs.

Psychiatric comorbidity seems to be a predictor for poor seizure control and poor tolerability. Therefore, assessment and management of psychiatric disorder may help in management of epilepsy and enhance quality of life. As expected, poor adherence was associated with poor seizure control. Assessment and management of poor drug adherence may be required before alteration of AEDs schedule/ dose. As forgetfulness was the most common reason for that behaviour, a simple intervention like a reminder (e.g. phone alarm) or pill organiser may be helpful. Furthermore, particular groups of patients have been shown to be more likely to be poorly drug adherent (such as patients with psychiatric comorbidity and alcohol or drug abuse). Thus, prescribing measurable AEDs in blood may be suitable for those patients in order to assess adherence regularly.

6.5 Future directions of research

The results of the present study provide further evidence that current AEDs are seizure suppress but not anti-epileptogenic thus, researchers should focus on novel treatments that can modify the development or progression of the epilepsy. The following section outline the directions of future research in epilepsy.

6.5.1 Anti-epileptogenesis

Epileptogenesis is the gradual processes that lead to development of chronic epilepsy after a brain injury. As shown in Figure 6-2, novel approaches may produce anti-epileptogenic effect (prevent epilepsy development after an epileptogenic insult), disease-modifying effect (reduce seizure frequency / severity, or alter disease natural history), neurodegeneration inhibition, or prevent behavioural and cognitive alterations associated with epilepsy. Results from studies on neuroprotective, anti-inflammatory and neuro-modulatory agents suggest that these approaches are realistic. However, many other pathological

changes occur simultaneously during the epileptogenic process, therefore, targeting only single process probably impossible to prevent epileptogenesis. Instead, combinations of agents that target various epileptogenic processes should be taken after brain injuries (Loscher, 2012).

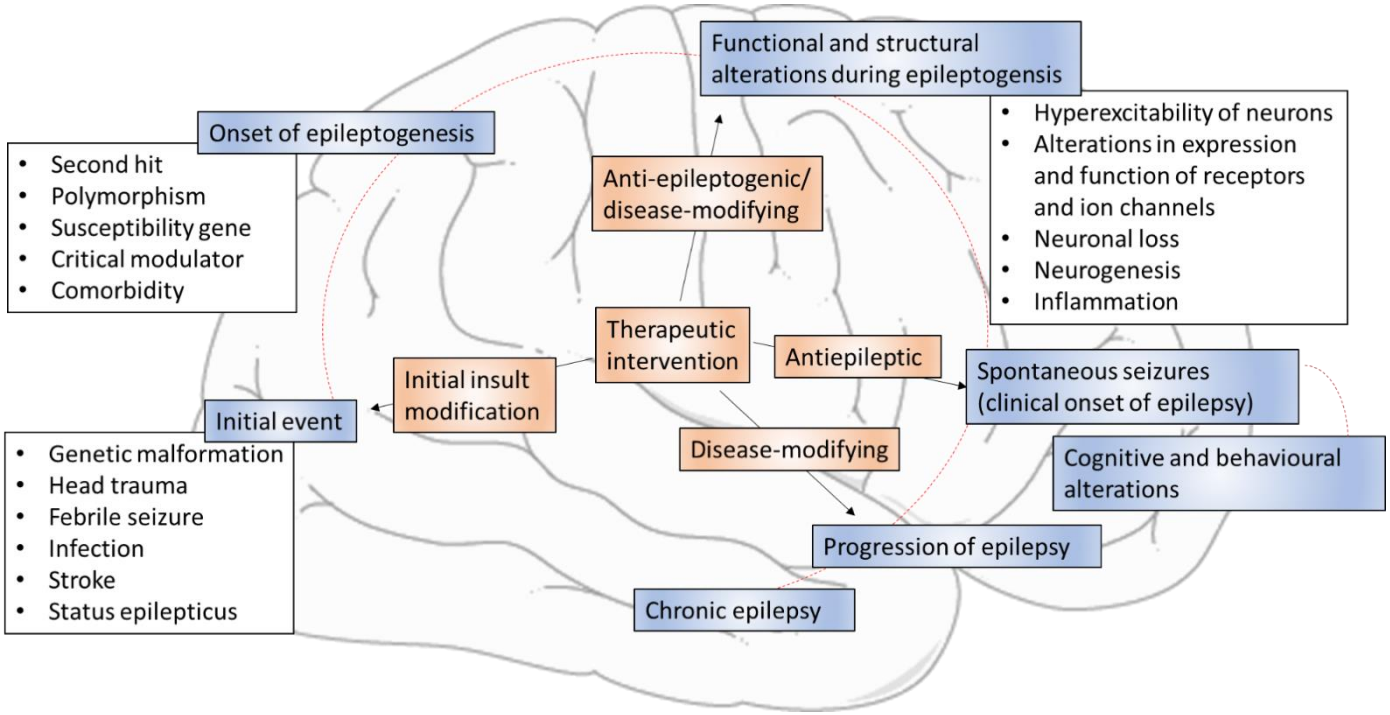


Figure 6-2. Strategies for antiepileptigenesis [modified from (Loscher, 2012)]
Novel approaches may produce anti-epileptogenic effect (prevent epilepsy development after an epileptogenic insult), disease-modifying effect (alter disease natural history, or reduce seizure frequency / severity), neurodegeneration inhibition, or prevent behavioural and cognitive alterations associated with epilepsy.

6.5.2 Gene and cell therapy for epilepsy

Gene therapy is a technique used to introduce a functional copy of a gene in place of defective copy in order to restore normal function (Riban et al., 2009).

Epilepsy is the most challenging and may be not the most suitable target for development of gene therapy for several reasons. First, only minority of epilepsy syndromes are pure monogenic forms, the majority of epilepsy disorders are complex conditions involving several genetic and environmental factors. Additionally, it is difficult to identify the link between the gene mutation and the hyper-excitability phenotype (specific seizure) as a result of the compensatory mechanisms that occur in the brain. Finally, because of the technical limitations, it is difficult to achieve widespread gene transfer for a disease like epilepsy that often involves a large area of the brain (Riban et al., 2009).

Nevertheless, this approach may represent an alternative therapy for pharmacoresistant patients, and focal epilepsies with epileptogenic lesion seem to be the best candidate epilepsy forms for gene therapy (Simonato, 2014).

Gene therapy has been used to provide anti-epileptogenic, anti-seizure, and disease-modifying effects (Figure 6-2). Results from animal studies have shown that several candidate genes such as brain-derived neurotrophic factor (BDNF) and fibroblast growth factor 2 (FGF-2) produced anti-epileptogenic effects. While galanin or neuropeptide Y provided anti-seizure effects (Simonato, 2014).

Viral and non-viral (cell transplantation) approaches can be used to delivery of gene to the brain. Recombinant adeno-associated viral (rAAV) vectors, which are safe and stable persistence in neurons, have shown a promise for gene therapy of neurological disorders in clinical trials (Riban et al., 2009).

Before starting studies in human, more research are required to evaluate the safety and therapeutic benefit of gene therapy in chronic models of epileptogenesis (Riban et al., 2009, Simonato, 2014).

6.5.3 Pharmacogenomics and precision medicine in epilepsy

Genetic factors contribute to the high variability in the response to AED treatment across patients (Franco and Perucca, 2015). Many genetic markers have been studied to identify predictors of efficacy and adverse effects of AED therapy. Variation in ABCB1 gene was associated with refractory epilepsy in some studies, this gene encoding drug transporter protein that extrudes AEDs from the seizure focus. Furthermore, there is an established evidence that variation in CYP2C9 gene is associated with PHT-induced neurotoxicity. Moreover, there is a strong association between HLA-B*15:02 allele and CBZ-induced Stevens-Johnson syndrome in patients from Han Chinese origin (Balestrini and Sisodiya, 2017), and genetic testing is recommended for those patients (Franco and Perucca, 2015).

However, the value of genetic testing in guiding AED treatment in other situations remains limited. As most genetic markers identified to date have limited sensitivity and specificity (Franco and Perucca, 2015). Furthermore, responsiveness to AED therapy is a complex outcome that based on an interaction of several genetic and environmental factors (Mohanraj and Brodie, 2013). Moreover, the biology of almost all epilepsy syndromes is largely unknown (Balestrini and Sisodiya, 2017). But in future, the use of genetic testing to guide epilepsy treatment is likely to increase because of greater understanding of the function of epilepsy genes, this will also allow the application of precision medicine (Franco and Perucca, 2015).

Precision medicine treatments represent a growing area of interest, focussing on reversing the pathophysiological effects of specific gene mutations. A current established example of the application of the precision medicine concept in epilepsy is in the management of GLUT-1 deficiency syndrome, a genetic metabolic encephalopathy due to mutations in the SLC2A1 gene, which encodes the glucose type I transporter (GLUT-1), resulting in impaired transport of glucose across the blood-brain barrier. The gold standard treatment is the ketogenic diet for treating the symptoms of neuroglycopenia. A second example, with less robust evidence, is the use of quinidine in KCNT1-related epilepsies, (Balestrini and Sisodiya, 2017).

6.5.4 Detecting seizures

The unpredictability of epileptic seizures is disabling for patients. If a seizure can be reliably detected then the patient or carer could be alerted, and therefore, injury and death could be prevented. Seizure detection theories based on detecting physiological changes that occur before and during a seizure such as changes of movements and heart rate. Electronic devices, scalp electrodes, and alert dogs are studied to detect and count seizures. A new example of using electronic devices for seizure detection is EpiWatch, an app designed for use on an Apple Watch with its paired iPhone. The development of seizure detection devices can offer a practical benefit for the management of epilepsy, however, these devices are at a relatively early stage of development (Jory et al., 2016).

6.5.5 Biomarkers for pharmacoresistant epilepsy

Early identification of patients likely to be drug resistant allows earlier specialist intervention. To date, early prediction of pahrmacoresistant patients is mainly based on clinical characteristics such as the numbers of pre-treatment seizures and the early response to antiepileptic drugs (Mohanraj and Brodie, 2013). However, these manifestations are subjective and poorly defined. Therefore, objective and definite biomarkers are in need. Several studies have showed that microRNAs were differentially expressed in epilepsy; microRNAs may be involved in epilepsy by regulating inflammatory response, neuronal apoptosis and transcription factors involved in differentiation. In a preliminary study, several circulating microRNAs showed a diagnostic value in drug resistant epilepsy as they were deferentially expressed between drug resistant patients and drug responsive patients (Wang et al., 2015).

6.6 Conclusion

Despite the availability of many AEDs, this research concluded that seizure control rates have not improved over the last three decades. Probably because the current AEDs are anti-seizure and not anti-epilepsy. Future research should therefore focus on novel treatments that can interfere or reverse the development and progression of epilepsy, such as anti-epileptogenic agents and gene therapy. Although the new generation of AEDs has failed to provide more efficacious treatment options, the findings of this study indicated that their use has

increased, most likely due to their enhanced tolerability. Indeed, some new AEDs such as LTG showed high tolerability rate in this study, however, the results did not demonstrate a unidirectional better tolerability with new agents over established AEDs. Nevertheless, each AED has shown a distinct adverse effects profile that may influence each individual patient differently. Therefore, tolerability of AEDs provides the opportunity of tailoring AED selection more effectively to optimise efficacy and minimise adverse effects in the individual patients and eventually resulting in enhanced quality of life. This research also has identified the patients more likely to experience poor seizure control and poor drug tolerability; psychiatric comorbidity and previous unsuccessful AEDs schedules were associated with poor treatment outcomes. Early identification of these patients allowing interventions by specialists such as early referral of intractable patients for epilepsy surgery and carful use of pharmacotherapy in patients at high risk of adverse drug reactions. This study also concluded that LTG demonstrated better outcomes in terms of retention rate and therefore clinical effectiveness, most probably due to its superior tolerability which may explain why it was the most frequent prescribed AED in this cohort.

Appendix

CASE REPORT FORM

BASELINE INFORMATION

PID: _____ Date of Birth (dd/mm/yyyy): ____/____/_____ Gender (M/F): _____

Seizure Details

Seizure Classification(s): _____

Seizure Syndrome (generalised/focal): _____

First Referral Date (dd/mm/yyyy): ____/____/_____

First Seizure Date (dd/mm/yyyy): ____/____/_____

Total Number of **Pre-treatment** Seizures: _____

Number of **Pre-treatment** Seizures **within the last 12 months**: _____

Longest Pre-treatment Inter-Seizure Interval **within the last 12 months** (days): _____

History of Provoked Seizure before the First Unprovoked Seizure? (Y/N): _____

If 'Y', Provoking Factor: _____ Number of Provoked Seizure: _____

Aetiological/Risk Factors

Aetiological/Risk Factors	Ever had the condition? (Y/N/Unknown)	Onset/Record Date (dd/mm/yyyy)	Details
Alcohol Abuse			
Neoplasm			
Arteriosclerosis			
Trauma			
Infection			
Drugs Abuse			
Metabolic			
Cerebral Atrophy			
Cortical Dysgenesis			
Birth trauma			
Febrile Convulsion			
Family History of Seizures			

Other Medical Details

Smoking (Y/N/Ex): _____

Other Medical Condition/Family History	First Onset/Record Date (dd/mm/yyyy)

Other Medications	Commence Date (dd/mm/yyyy)	Daily Dose (mg)

CT/MRI/EEG Details (most significant result)

	Date (dd/mm/yyyy)	Details
CT		
MRI		
EEG		

FOLLOW-UP INFORMATION (complete for each contact, start with the initial visit)

Follow-up Number: ____ Date (dd/mm/yyyy): ____/____/_____

Contact type (mark 'Y' for the appropriate type):

Epilepsy Clinic ____ Emergency & Accident ____

Phone ____ Letter/Email ____

Height (meter): _____ Weight (kg): _____

Date of the **Most Recent** Seizure (dd/mm/yyyy): ____/____/_____

Number of Seizures Since Last Contact (or **within the last 3 months for the initial visit**):

Tonic-Clonic _____ Simple Partial _____

Absence _____ Complex Partial _____

Myoclonic _____ Secondary Generalised _____

Tonic _____ Unclassifiable _____

Akinetic _____

Total _____

AED Therapy (leave blank if the patient had not commenced treatment at the visit):

AED	Start/Last Dose Change Date (dd/mm/yyyy)	Initial (if newly commenced) /Daily Dose (mg)	Titration Pattern (if newly commenced) (mg/days)

New Adverse Effect(s) Since Last Contact:

Onset/Report Date (dd/mm/yyyy)	Adverse Effect	Culprit AED

Other New Medical Condition(s) Since Last Contact:

New Medical Condition	Onset/Report Date (dd/mm/yyyy)

Other Medication(s) Newly Commenced Since Last Contact:

New Medication	Onset/Report Date (dd/mm/yyyy)	Daily Dose (mg)

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