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CHARACTERISATION OF RESPONSE TO ANTIEPILEPTIC DRUGS

Ghazi Ahmed Bamagous
MD, MSc

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Epilepsy Unit, Section of Clinical Pharmacology & Stroke Medicine,
Division of Cardiovascular & Medical Sciences, Department of Medicine
& Therapeutics, Glasgow, Western Infirmary

Abstract

This study aimed to construct a database of 1500 newly diagnosed patients with epilepsy referred to the epilepsy unit at the Western Infirmary in Glasgow between 1982 and 2005. These patients commenced their first ever epilepsy treatment at the unit. The database included demographic, clinical and investigational information together with a detailed account of every drug regimen applied starting from the first AED prescribed until the last follow up appointment. Using this database, I was able to identify the efficacy and tolerability of different AEDs in relation to various demographic, clinical and pharmacological characteristics. This analysis provides a better understanding of the natural history of treated epilepsy, an informational aid for the future prescription choice of drug and/or drug combination according to different patient characteristics and facilitates the study of patients with intractable seizures from a pharmacological point of view.

Summary

It has been almost two decades since the introduction of the second generation AEDs. Most of these drugs have been studied in head to head comparisons either with placebo or with first generation agents. A limited number of studies has examined the efficacy and tolerability of newer AEDs either among other modern drugs or in comparison with older generation AEDs. It seems appropriate after two decades of their introduction to investigate how these drugs have influenced the outcome of epilepsy and to compare them against first generation AEDs as groups regarding their efficacy and tolerability. As this is a retrospective study, it focuses more on groups of AEDs with regard to specific populations rather than investigation and comparison of the response among individual drugs that usually need a properly designed prospective study in order to obtain accurate results and appropriate analysis.

The population of this study was 1098 newly diagnosed patients referred to the Epilepsy Unit of the Western Infirmary Hospital, Glasgow, Scotland between 1982 and 2005 and followed up until the end of March 2008. The ultimate outcomes of epilepsy along with the efficacy of each AED/s combination were collected. Efficacy was calculated based on the percentage of patients who achieved a period of at least 12 months seizure freedom on a particular AED regimen among all the patients on that drug. Tolerability of AEDs was reported using withdrawal of treatment due to side effects as an indicator. With regard to the generations of AEDs, total cumulative efficacy and tolerability were also calculated. All these parameters were analysed in relation to various demographic, pharmacological and clinical aspects.

Regarding various age groups of recruited patients in this study, elderly patients with epilepsy ($\geq$ 65 years old) showed the highest remission rate in comparison to adolescents and adults. Also, total cumulative efficacy of first generation AEDs was found to be significantly better than newer agents in elderly patients; elderly patients also tolerated older AEDs better than modern drugs. Adults patients showed a lower total efficacy of established drugs than newer agents with small difference in terms of tolerability. On the other hand, adolescents patients had a higher efficacy of first generation AEDs than second generation agents with also minimal difference regarding the tolerability profiles.

Gender analysis showed a higher remission rate in male patients with epilepsy compared to females. Efficacy of the commonly prescribed AEDs and both generations of AEDs were

also higher in males than females. In terms of tolerability profiles, males were found to tolerate some AEDs better than females. Better tolerability to both generations of AEDs was observed in males in comparison to females. Treatment with AEDs acting primarily by potentiation of GABA inhibitory effect was found to be significantly more efficacious in male patients with idiopathic generalised epilepsy than females.

Based on epilepsy classification, idiopathic generalised epilepsy (IGE) patients had a higher remission rate compared to those with focal epilepsy. First generation AEDs had a higher response in IGE patients with slightly better tolerability than modern drugs. AEDs acting mainly by potentiation of GABA inhibitory effect were more efficacious in these patients than sodium channels blocking AEDs. Sodium valproate was associated with the highest efficacy and tolerability in patients with idiopathic generalised epilepsy. In contrast, lamotrigine was the AED with the highest efficacy and tolerability among patients with focal epilepsy. Second generation drugs were slightly more efficacious than older AEDs with minimal difference in terms of tolerability. In terms of mechanisms of action, only minimal difference was observed between AEDs acting by sodium channels blockage and potentiation of GABA inhibitory effect with regard to remission rate among focal epilepsy patients.

50% of the study population achieved seizure freedom while on the first AED treatment regimen with a dramatic decline in subsequent schedules. Most of patients with seizure freedom used moderate doses of AEDs even lower than the recommended defined daily dose in some cases. Similarly, the majority of patients who withdrew from AEDs due to side effects were taking moderate doses of these agents (even lower than the recommended daily defined dose) rather than high doses. Various patterns of response to AEDs have been noticed in this study; this might be due to the interaction of several factors such as epilepsy syndromes, genetics, and brain adaptation to AEDs.

Analysis of the annual outcome of epilepsy according to years of referral demonstrated a modest improvement in the ultimate outcome of epilepsy accompanied by the longer duration of follow up of patients. More second generation AEDs have been identified and applied in the last two decades which is assumed to contribute to the improvement in the epilepsy outcome. Failure of treatment regimen due to poor tolerability was associated with a better prognosis of epilepsy than failure due to lack of efficacy of that particular regimen. Since a decline in remission with further AED treatment regimens was noted after failure of the first AED, it can be assumed that failure of two treatment regimens due to

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1. Brodie, M., Bamagous, G., Kwan, P. Improved outcomes in newly diagnosed epilepsy. (in preparation).

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Author's declaration

I hereby declare that this thesis submitted in fulfilment for the degree of Doctor of Philosophy represents my own work, except where specifically stated in the acknowledgements and in the text of this thesis. This thesis has not been submitted before neither to this institution or any other institution for any degree.

Ghazi Ahmed Bamagous

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Abbreviations

AEDs: Antiepileptic drugs

AZM: Acetazolamide

Brain CT scan: Brain Computed Tomography scan

CBZ: Carbamazepine

CLB: Clobazam

CNS: Central Nervous System

CPS: Complex Partial seizures

CZP: Clonazepam

EEG: Electroencephalography

ESM: Ethosuximide

FBM: Felbamate

IGE: Idiopathic Generalised Epilepsy

ILAE: International League Against Epilepsy

GABA: Gamma Amino Butyric Acid

GBP: Gabapentin

GTCS: Generalised Tonic Clonic Seizures

LTG: Lamotrigine

LEV: Levetiracetam

MDR: Multidrug resistance

MES test: Maximal electroshock test

MRI: Magnetic Resonance Imaging

OXC: Oxcarbazepine

PB: Phenobarbital

PHT: Phenytoin

PGB: Pregabalin

PGP: P-glycoprotein

REM: Remacemide

SANAD study: study of Standard And New Antiepileptic Drugs

scPTZ test: subcutaneous pentylenetetrazol test

SPECT: single photon emission computed tomography

SPS: Simple Partial Seizures

SV2A: Synaptic Vesicle protein 2A

TGB: Tiagabine

TPM: Topiramate

VDCCs: Voltage Dependant Calcium Channels

VPA: Sodium valproate

VGB: Vigabatrin

ZNS: Zonisamide

Chapter 1. Introduction

1.1. Epilepsy

1.1.1. Introduction

Epilepsy is characterised by the presence of recurrent seizures. A seizure can be defined as "an episodic disturbance of movement, feeling, or consciousness caused by sudden synchronous, inappropriate, and excessive electrical discharges in the cerebral cortex" (Brodie and French, 2000). Epileptic convulsions are expected to have negative consequences on the patient's psychological and social life such as relationships, education and employment. Uncontrolled seizures are associated with physical and psychosocial morbidity, dependent behavior, poor quality of life and an increased risk of sudden unexpected death. Therefore, it is often recommended to begin treatment of epilepsy with antiepileptic drugs (AEDs) as soon as the patient has reported more than one documented or witnessed seizure bearing in mind that the goal of treatment should be to maintain as normal a life style through complete seizure control with no or minimal side effects (Brodie, 2005).

The process of epileptogenesis starts when a normal brain experiences an injury e.g. trauma, infection, ischemia or the presence of a malformation or mass lesion. Based on the patient's age and genetic background, some acute damage takes place with subsequent progressive damage. Although the brain tries to repair itself, after a latent period of time (might reach up to years), a condition of hyperexcitability develops and seizures begin (Dichter, 2009).

In the Greek language, epilepsy is derived from *epilamvanein* or *Epilepsia*, which means 'to be seized', 'to be taken hold' or 'to be attacked'. Such terms reflect an outlook of the period that considered this disease was the result of possession by evil spirits (Fong and Fong, 2001).

1.1.2. History of epilepsy

Epilepsy is thought to be one of the oldest recorded diseases that appeared in humans as it was reported in the earliest medical documents. This explains the attitudes of early civilisations, with the lack of understanding of its pathophysiology combined with the strange movements exerted by patients, that the concept of epilepsy was linked to legends and myths.

The earliest record of epilepsy was in ancient Indian medicine 4500-1500 B.C. In Ayurvedic literature of Charaka Samhita (literature of traditional medicine in India), epilepsy was described as "apasmara" which means "loss of consciousness".

All aspects of epilepsy were discussed in that record including symptomatology, aetiology, diagnosis and treatment (Pierce, 2002).

Around 3000 years ago, the ancient Babylonians posited some suggestions regarding the causes and symptoms of epilepsy. Ancient Greeks linked epilepsy to offending the moon goddess Selene and proposed a certain technique to cure it. Probably, the Greek physician Hippocrates, the Father of Medicine in 400 B.C., was the first to discuss epilepsy using scientific explanations as he connected this disease to the brain. During the Renaissance, a different view emerged on the causes of epilepsy in contrast to demonic possession. Some thought these patients were prophets while others believed they were extraordinary as some celebrated individuals in the Roman Empire had epilepsy such as Julius Caesar and Petrarch. From the late 1600s on, epilepsy was thought to be a contagious disease and therefore, its patients were confined to mental hospitals and separated from the other patients. The beginning of an enlightened approach towards epilepsy as a medical condition was between 1859 and 1906 and it was guided by three English neurologists; John Hughlings Jackson, Russell Reynolds and Sir William Richard Gowers. According to Jackson's definition "a seizure is an occasional, an excessive, and a disorderly discharge of nerve tissue on muscles". Also, he stated that seizures could alter consciousness, sensation and behaviour (Schachter, 2004).

Subsequently, further scientific discoveries on the brain and pathophysiology of epilepsy have taken place that enabled a better understanding of epilepsy and was accompanied by the introduction of pharmacological intervention in the treatment of epilepsy.

1.1.3. Epidemiology of epilepsy

Epilepsy is considered to be the most common neurological disease with an incidence rate of 50-70 cases per 100,000 persons per year in most developed countries and a prevalence of 5 - 10 cases per 1,000 in a typical European population excluding cases of single seizures and febrile convulsions in children (Brodie et al., 1997).

The incidence of epilepsy tends to be higher in developing countries than developed ones based on a recent study (Kotsopoulos et al., 2002), the estimated median incidence of epilepsy is 43.4/100,000 in the developed countries compared to 68.7/100,000 in the developing countries. Age specific incidence of epilepsy is characterised by a "U-shaped curve" in which the incidence is high in childhood and the elderly after the age of 55 in the industrialised nations. The developing countries have a different pattern of age specific incidence where higher incidence rates are observed in children and young adults compared to the elderly (Mac et al., 2007). First life time seizure has an incidence of 52 - 59 per 100,000 in the age group 40 - 59 years; these figures reach 127 per 100,000 in those who are 60 years and older (Hauser, 1997). The high incidence rate of epilepsy in the elderly might be due to the high rate of developing risk factors related to epilepsy in this age group. Vascular diseases (cerebral infarction and haematoma) tend to be the commonest cause of epilepsy (Loiseau et al., 1990). Other causes include brain tumours, metabolic disorders and degenerative diseases e.g. Alzheimer's disease. In other cases, the cause is unidentified (cryptogenic epilepsy).

With regard to gender, there is a broad agreement worldwide that females have a lower incidence rate of epilepsy compared to males; 46.2 and 50.7/100,000 respectively (Kotsopoulos et al., 2002). This gender difference can be explained by the fact that men have a greater exposure to risk factors of epilepsy such as head injuries, stroke and CNS infection, even alcohol-related seizures are more common in males.

Among developing countries that have a higher incidence of epilepsy compared to developed ones, Latin America and several African countries proved to have a particular high incidence of epilepsy, possibly due to certain parasitic infections with brain involvement, perinatal brain damage or hereditary factors (Senanayake and Roman, 1993).

Among all seizure types, partial seizures - with or without secondary generalisation (localisation-related epilepsies) - constitute the major type of seizures in all age groups (Sander et al., 1990).

The prevalence of active epilepsy in the developed world ranges between 4 and 10 per 1000 of the population (Jallon, 1997a). On the other hand, incidence of active epilepsy varies in developing countries, with ranges from 17 - 57/ 1000 in South America, 5.2 - 43/ 1000 in African countries and from 1.5 - 14 in Asia (Mac et al., 2007).

An estimate of people with active epilepsy in Europe is approximately 3.1 million (based on a prevalence of 6/1000), excluding Russia, Belarus and Ukraine (due to sparse information on the epidemiology of epilepsy in a large population) while the expected number of new cases per year in Europe based on an age-specific rate is 311,000 (Forsgren et al., 2005).

1.1.4. Classification of seizures and epilepsy syndromes

Determining an accurate classification of seizures for a particular patient is considered a crucial factor in the selection of the most appropriate AED to be applied and to provide prognostic information on that particular type of epilepsy. The most commonly used classification in clinical practice is that established by the International League Against Epilepsy (ILAE) to classify epileptic seizures (Commission, 1981) and epilepsy syndromes (Commission, 1989).

Based on the ILAE classification of epileptic seizures (Commission, 1981), these are divided into three groups based on clinical findings and electroencephalograph (EEG) readings: general, partial (localisation-related) and unclassified seizures. Generalised seizures are characterised by the involvement of the whole cerebral hemispheres from the onset. Partial seizures are localised to specific foci in the brain responsible for the electrical discharge. Generalised seizures are further subdivided into tonic-clonic, absence, myoclonic, atonic, tonic and clonic seizures. On the other hand, partial seizures have two subtypes: simple partial seizures in which the consciousness is preserved and complex partial seizures that are accompanied by impairment of consciousness. Sometimes, seizures may start as partial due to a discharge from a focus in the brain then spread to involve the whole cerebral hemisphere resulting in secondary generalisation of the seizures (Table 1).

Seizures type	Description

I. Partial seizures (with localised onset)	Simple partial seizures (consciousness preserved)
	
	    a. with motor symptoms
	    b. with somatosensory or special sensory symptoms
	    c. with autonomic symptoms
	    d. with psychic symptoms

	Complex partial seizures (consciousness impaired)
	
	    a. simple partial seizures onset followed by impaired consciousness
	    b. impaired consciousness at onset

	Partial seizures with secondary generalized seizures
II. Generalised seizures	Absence seizures (whether typical or atypical)
	Myoclonic seizures
	Clonic seizures
	Tonic seizures
	Tonic-clonic seizures
	Atonic seizures
III. Unclassified seizures	Includes all seizures unclassified due to inadequate or incomplete data e.g. some neonatal seizures presented as rhythmic eye movements or chewing

Table 1. International classification of epileptic seizures (Commission, 1981).

ILAE suggested in 1989 a new classification taking into consideration more factors than the 1981 classification. These factors include seizure type, EEG, prognosis, pathophysiological and aetiological data (Commission, 1989). This new classification has retained the main three types of seizures; generalised, partial and unclassified. But based on the cause, each type is further subdivided into idiopathic, symptomatic or cryptogenic epilepsy. Idiopathic epilepsy refers to syndromes assumed to be of genetic origin while symptomatic epilepsy is the result of a disorder in the central nervous system. Cryptogenic epilepsy is reserved for those syndromes with an underlying but unidentified focal abnormality (Table 2).

Seizures type	Description

I. Focal (localisation-related or partial)	Idiopathic epilepsy with age related onset
	   a. Benign rolandic epilepsy
	   b. Childhood epilepsy with occipital paroxysms
	   c. Primary reading epilepsy

	Symptomatic epilepsy
	Cryptogenic epilepsy

II. Generalised	Idiopathic epilepsy with age related onset
	   a. Benign neonatal familial convulsions
	   b. Benign neonatal non-familial convulsions
	   c. Benign myoclonic epilepsy in infancy
	   d. Juvenile absence epilepsy
	   e. Juvenile myoclonic epilepsy
	   f. Epilepsy with generalized tonic-clonic seizures on awakening
	   g. Other idiopathic epilepsies

	Cryptogenic or symptomatic epilepsy
	   a. West syndrome (infantile spasms)
	   b. Lennox-Gastaut syndrome (childhood epileptic encephalopathy)
	   c. Epilepsy with myoclonic-astatic seizures
	   d. Epilepsy with myoclonic absence seizures

	Symptomatic epilepsy
	   a. Non-specific syndromes e.g. early myoclonic encephalopathy
	   b. Specific syndromes i.e. epileptic seizures as a complication of a disease e.g. phenylketonuria.

III. Undetermined epilepsies whether focal or generalised	With both generalised and focal features
	   a. Neonatal seizures
	   b. Severe myoclonic epilepsy in infancy
	   c. Epilepsy with continuous spike waves during slow-wave sleep
	   d. Acquired epileptic aphasia
	   e. Other undetermined epilepsies not defined above

	Without unequivocal generalised or focal features
IV. Special syndromes	Febrile convulsions e.g. febrile convulsions, seizures due t o stress or alcohol or sleep deprivation.
	Isolated, apparently unprovoked seizures

Table 2. International classification of epilepsies and epileptic syndromes (Commission, 1989).

With regard to the aetiology of epilepsy, a wide range of causes of epilepsy has been identified in the brains of these patients. These include: cerebrovascular disease (ischaemia and haemorrhage), trauma, neoplasm, cerebral infection, degenerative disorders

and congenital abnormalities. In around half of the patients, the aetiology of epilepsy could not be identified (Forsgren et al., 2005).

Although these two classifications are still used today, it has been now more than two decades since their establishment by ILAE and this has led some specialists in epilepsy to look for an updated version of seizures classification as many of the observations regarding this disease have either been changed or discovered since those early days (Engel, 2001).

1.1.5. Diagnosis of epilepsy

Several conditions can mimic epileptic seizures (Table 3) such as syncopal attacks that are commonly misdiagnosed as epileptic seizures (Smith et al., 1999). Also, pseudoseizures or non-epileptic psychogenic seizures that occur in 10 - 45% of patients with apparently refractory epilepsy (Devinsky, 1999) are difficult to diagnose as non-epileptic attacks often coexist with epilepsy or may develop as a substitute for seizures once the epilepsy is controlled (Kuyk et al., 1997). Proper diagnosis of epilepsy is an essential element for the definition of the likely prognosis and selection of the most appropriate treatment. Diagnosis of epilepsy can be divided into two stages: clinical evaluation and investigations.

It is rare for the patient to have a seizure at the time of a medical examination. In addition, in some seizure types, the patient might lose consciousness and be unable to provide a full description of the seizure experienced. Therefore, a detailed history needs to be obtained from the patient and witnesses of seizures as well. Trevavathan showed that a proper detailed history taken from patients led to the correct diagnosis of epilepsy in 96% of cases even before performing any investigations (Trevathan, 2003). One important aspect in this regard is to distinguish whether the episode occurred was an epileptic or non-epileptic seizure, as the list of differential diagnosis of seizure is long (Table 3). A physical and neurological examination is usually performed to detect any neurological deficit that corresponds to an underlying pathology in the brain. At the other extreme, around one-quarter of epilepsy patients in some developed world clinics have been shown not to have the disease (Simkiss, 2001), and inadequate history taking and a failure to recognise a differential diagnosis were some of the important reasons identified.

Investigations of epilepsy are used to support the clinical diagnosis, to aid in the identification of seizure classification and to detect any underlying brain abnormalities.

Electroencephalography (EEG) is an important tool for the diagnosis of epilepsy because of its ability to identify epileptiform EEG activity in order to determine seizure classification. Since specific EEG patterns can reflect specific epileptic syndromes and also because some of the clinical manifestations e.g. aura can be explained through an EEG reading by the localisation and lateralisation of epileptogenic EEG foci (Oguni, 2004). It is based on the recording of electrical discharge generated in the brain that in the case of epilepsy would be excessive and sometimes characteristic.

Magnetic Resonance Imaging (MRI) is another essential tool in the diagnosis of epilepsy that was first employed in clinical practice in 1984. It is considered the most sensitive and specific structural neuroimaging procedure for epilepsy (Bergen et al., 1989). It is used to detect the underlying brain lesion that might be responsible for seizure development. The most common abnormalities that can be identified by MRI include: hippocampal sclerosis, malformations of cortical development, vascular malformations, tumours and acquired cortical damage (Duncan, 1997). MRI is particularly useful in symptomatic epilepsy and complex partial seizures (Oguni, 2004). In certain situations, the use of Computed Tomography (CT) scan is preferred to MRI in cases where patients have metal aneurysm clips, cardiac pacemakers, severe claustrophobia, acute intracranial haematomas and skull fractures. Various other techniques used in the functional imaging of the brain have been developed and are being applied in the evaluation of epilepsy. Such techniques include: functional MRI, magnetoencephalography, magnetic resonance spectroscopy, single photon emission computed tomography and positron emission tomography (Duncan, 1997).

Disorder	Description
Neurological disorders	Transient ischemic attack
	Transient global amnesia
	Migraine
	Narcolepsy
	Panic attacks
Cardiac disorders	Vasovagal syncope
	Reflex anoxic seizure
	Sick sinus syndrome
	Arrythmias
	Hypotension
Endocrine/ metabolic disorders	Hypoglycaemia
	Hyopnatremia
	Hypkalemia
Paroxysmal movement disorders	Acute dystonic reactions
	Hemifacial spasm
	Non-epileptic myoclonus
Sleep disorders	Obstructive sleep apnea
	Hypnic jerks
	Benign neonatal sleep myoclonus
	Rapid eye movement sleep disorder
	Parasomnias
	Cataplexy
Psychological	Non-epileptic psychogenic seizures

Table 3. Common differential diagnoses in epilepsy (Benbadis, 2009;Brodie et al., 2005).

Serious consequences can result from epilepsy misdiagnosis. These include inappropriate treatment supplied to patients who are deprived of the correct management (Petkar et al., 2005). Other consequences include the psychological impact related to the diagnosis of epilepsy, socio-economic disadvantages affecting car driving, education, employment and

insurance. Additional problems include harmful consequences related to AEDs such as serious side effects and risk of teratogenicity in women of childbearing age (Chowdhury et al., 2008;Smith et al., 1999).

1.1.6. Measuring the outcome of epilepsy

Outcomes research is a comprehensive approach used to evaluate the medical care offered to patients based on a variety of data sources and measurement methods. In the field of epilepsy, there are several measures that can be used for different purposes. These tools include the measurement of: seizure frequency and seizure severity, impact on physical and psychosocial function, the consequences of pharmacotherapy, the results of surgical therapy and the composite effect of epilepsy and treatment expressed as quality of life (QOL) (Baker et al., 1998).

Measuring outcome in epilepsy and determining the effect of an AED have proved to be difficult and elusive. This is due to several factors such as the unpredictable nature of the disease and the lack of clear recommendations for the minimum standards to be used to measure epilepsy outcomes during the conduct of randomised controlled trials. Baker and colleagues reported that in 44 randomised controlled trials of AEDs, a total of 54 different measures were used (Baker et al., 2000). As a result, the opportunity to make meaningful comparisons between these studies will be minimised without the ability to establish any useful conclusions about the effects of these AEDs.

Sometimes, even in the presence of a clear and accurate measure of outcome, its application in the real world would be difficult as in the case of using seizure frequency as an indicator of the outcome of epilepsy. The Commission on Outcome Measurement in Epilepsy (COME) report suggested that seizure frequency is the most sensitive measure for the assessment of efficacy amongst AEDs and recommended its use whenever possible (Baker et al., 1998). But, the reliance of investigators on seizure records compiled by patients themselves might lead to inaccurate results because some patients may not recognise genuine seizures events and others may have ulterior motives for censoring their disclosure, especially given the potential impact on employment and driving. In other cases, long intervals between clinic appointments might result in lapses in the recording of seizures. Engel's score is one of the widely used measures to quantify seizure frequency (Engel et al., 1993). It is mainly used to assess the surgical (and sometimes pharmacological) intervention to treat patients with epilepsy (Table 4).

Rating	Description
Class I	**Free of disabling seizures**
A	Completely seizure free since surgery
B	Non-disabling simple partial seizures only since surgery
C	Some disabling seizures after surgery, but free of disabling seizures for at least 2 years
D	Generalised convulsions with AED discontinuation only
Class II	**Rare disabling seizures ("almost seizure free")**
A	Initially free of disabling seizures but has rare seizures now
B	Rare disabling seizures since surgery
C	More than rare disabling seizures since surgery, but rare seizures for the last 2 years
D	Nocturnal seizures only
Class III	**Worthwhile improvement**
A	Worthwhile seizure reduction
B	Prolonged seizure free intervals amounting to greater than half the followed up period, but not < 2 years
Class IV	**No worthwhile improvement**
A	Significant seizure reduction
B	No appreciable change
C	Seizure worse

Table 4. Engel's score used for classification of postoperative outcome.

Other than seizure frequency, seizure severity is another measure of the outcome in epilepsy that is now considered an important additional aspect of epilepsy (Mattson and Cramer, 1993). Seizure severity represents any change in the severity of habitual seizures, possibly independent of seizure frequency such as more rapid recovery from seizures or fewer falls or injuries (ODonoghue et al., 1996). But similar to seizure frequency, measuring seizure severity is also associated with difficulty as the physician and the patient

can judge it differently. To quantify seizure severity, three scales have been developed (Table 5):

1. **The Veterans Administration Seizure Frequency and Severity Rating Scale.**

   This was the first scale designed to quantify seizure frequency and severity in clinical trials. It can be used for various types of seizure and represents an interview based assessment relying on the important factors frequently reported by patients that determine severity of their seizures such as sleep deprivation, warning/aura and missed doses of AEDs (Cramer et al., 1983).

2. **The Liverpool Seizure Severity Scale.**

   This is a patient filled questionnaire composed of 16 questions distributed into two categories; the first category is composed of 10 questions related to ictal and post-ictal phenomena, while the second category is composed of 6 questions concerned with the predictability of seizures. In this scale, seizures are either classified as major or minor seizures on a 5-point scale. Their definition is left to patients and does not necessary employ major seizures for Generalised Tonic Clonic Seizures (GTCS) and minor ones for Complex Partial Seizures (CPS). Such a decision is difficult to make by some patients. A newer version of this scale has been developed (Baker et al., 1991).

3. **The National Hospital Seizure Severity Scale (NHS3)** (formerly known as the Chalfont Seizure Severity Scale)**.**

   NHS3 is performed through interviewing the patients and witnesses to the seizures. It is mainly designed to score the seizures according to interference with patient function. It can be used for various types of seizures (ODonoghue et al., 1996).

Item	VA	L	N
Seizure type	+	+	+
Seizure duration	-	+	+
Post-ictal events and duration	-	+	+
Automatisms	+	+	-
Seizure clusters	+	-	+
Cyclic and diurnal patterns	+	-	+
Ability to predict seizures	+	+	+
Stopping seizures	-	-	+
Tongue biting and incontinence	-	+	+
Other injuries	-	+	+
Remediable precipitating factors	+	-	-
Drug levels and compliance	+	-	-
Functional impairment	+	+	+

Table 5. Comparison of the Veterans Administration (VA), Liverpool (L) and NHS3 (N) seizure severity scales (Baker et al., 1998).

As a part of the evaluation of medical care provided for patients with epilepsy, an evaluation of the AED therapy offered to these patients needs to be considered. The most important clinical characteristic of any drug is its effectiveness in the treatment of the disease. Effectiveness of a drug is a measure that includes both its efficacy and tolerability (Chadwick et al., 1998).

Achieving complete seizure control is the main target of AED treatment and is considered as the main indicator of treatment success. The probability of achieving complete seizure freedom varies depending on the efficacy of AED applied. Efficacy of AEDs can be defined as "the reduction in seizure frequency and/or severity directly attributable to treatment" (Chadwick et al., 1998). According to this definition, seizure frequency in which seizures can be simply counted over a defined period of time and seizure severity represent the most reliable measures to assess the efficacy of a particular AED. A variety

of other alternative measures might be considered in the assessment of AED efficacy such as the percentage reductions in seizure frequency or time required to develop the first seizure after starting treatment or percentage of patients with seizure freedom (length of seizure freedom period should be defined).

Use of greater than or less than 50% reduction in seizure frequency is not a preferred measure due to the chance of missing important differences between treatments by relying on an arbitrary cut-point of 50%. A more informative and less misleading alternative would be to select multiple categories of seizure frequency such as 0 - 20%, 21 - 40%, 41 - 60% etc. "Time to first seizure recurrence" has the capability of dealing with heterogeneous seizure counts and low seizure frequencies. It has several variants such as time to first seizure after the first 6 weeks post randomisation (thus seizures taking place during this 6 week period of dose adjustment will be ignored), time to first tonic-clonic seizure, time to nth seizure recurrence, time to first seizure after commencing therapy, time to discontinuation of medication, and time to 6-months or 12-months seizure freedom. When the period of follow up is the same for all patients included in a particular study and none are lost to follow up, then percentage of patients with seizure freedom is a good measure with the necessity to define the length of seizure freedom period (Baker et al., 1998). The proportion of patients achieving a pre-defined duration of seizure freedom is the clinically most meaningful endpoint and is recommended for trials conducted in newly diagnosed or previously untreated epilepsy (Perucca, 1997). The seizure severity measures discussed earlier can also be applied to evaluate the efficacy of AED therapy (Table 6).

The other important aspect in the effectiveness of any drug is its tolerability. Tolerability is a factor directly related to the side effects exerted by the drug. It is assessed based on the incidence, severity and impact of side effects of a particular agent on the patients. The main difficulty associated with the evaluation of side effects is that it is often based on spontaneous reporting by the patients. Although spontaneous reporting highlights the clinically relevant effects, it is accompanied by variability in the accuracy of detection of side effects (Mattson and Cramer, 1993). Further problems include the difficulty to assess the severity of these side effects quantitatively and to differentiate the side effects of an added AED from those resulting from concomitant medications or drug interactions (Cereghino, 1992). In addition, most clinical trials have allowed a limited flexibility for dose adjustment or dosage escalation (Perucca, 1996). Other less common methods of assessing side effects include physical examination and laboratory tests. Adverse effects have been shown to be the most common cause of AED withdrawal in many trials

(Fakhoury et al., 2004;Reunanen et al., 1996). Discontinuation of a certain drug due to intolerable adverse reactions is the most important measure in this regard, although the potential for precipitating idiosyncratic reactions should not be understated (Chadwick et al., 1998).

Study type	Efficacy endpoint
Short-term studies	- Retention of patients in the trial over time. - Time to nth seizure. - Absolute and percent change in seizure frequency over time. - Proportion of patients achieving 50%, 75% and 100% reduction in seizure frequency.
Long-term studies	- Retention of patients in the trial over time. - Absolute and percent change in seizure frequency over time. - Proportion of patients maintaining 50%, 75% and 100% reduction in seizure frequency over time. - Proportion of patients achieving 6, 12, 24 or 36 months remission rates.

Table 6. Commonly used efficacy endpoints in antiepileptic drug trials (Perucca, 1997).

For the purposes of this project, efficacy of AED is measured based on the percentage of patients achieving seizure freedom for a minimum period of 12 months at last recorded follow up. Several studies suggest that seizure freedom is the only outcome with a significant impact on quality of life. On the other hand, discontinuation of a drug because of side effects is applied as a measure for the assessment of AED tolerability. In terms of the outcome of epilepsy, this project will consider it as the final response on the maximum tolerated dose of the last AED/ AED combination prescribed to each patient in this study on the last follow up appointment.

1.1.7. Natural history of epilepsy

Newly diagnosed patients with epilepsy can be broadly categorised in three groups of treatment outcome based clinical characteristics (Figure 1). These include:

1. Excellent prognosis with or without treatment. This group of patients represent around 30%. These patients enter long term remission probably even without AED treatment. If treated, they will achieve seizure freedom usually on the first or second treatment regimen. Usually, moderate doses of AEDs are sufficient for remission, treatment can be successfully withdrawn after a period of seizure freedom (Shafer et al., 1988). Epilepsy syndromes that belong to this group include benign neonatal seizures, benign rolandic epilepsy and childhood absence epilepsy.

2. Remission with treatment only. Around 30% of epilepsy patients will need to continue on AED treatment in order to remain in a state of complete seizure control. They may need multiple trials of AEDs/ combinations to find the right treatment for the individual patients. Withdrawal of treatment after a period of seizure freedom will usually be accompanied by higher chances of recurrence. The majority of localisation related epilepsy and juvenile myoclonic epilepsy are examples of this group (Kwan and Sander, 2004).

3. Continuing seizures despite treatment. The remainder (around 40%) consists of patients who continue to have seizures with variable degrees of frequency and severity despite the application of multiple treatment regimens (monotherapy or combined therapy). These patients can be considered as having intractable seizures or refractory epilepsy. Conditions in this category include epilepsy with mesial temporal sclerosis, cortical dysplasia and gross structural brain lesions (Kwan and Brodie, 2006).

Another categorisation of the natural history of epilepsy has been applied taking into consideration the outcome of epilepsy in relation to various epilepsy syndromes. This classification is composed of four groups (Sander, 2003). In contrast to the three groups proposed by Kwan and Sander (2004), Sander's classification (2003) has one further group added to represent patients with excellent prognosis in whom seizures are self-limiting and very benign and patients usually do not require AED treatment as

spontaneous remission is the rule. This classification has taken into account the natural history of both treated and untreated epilepsy although limited information is available about the natural history of untreated epilepsy (Sander, 1995;Sander, 1993).
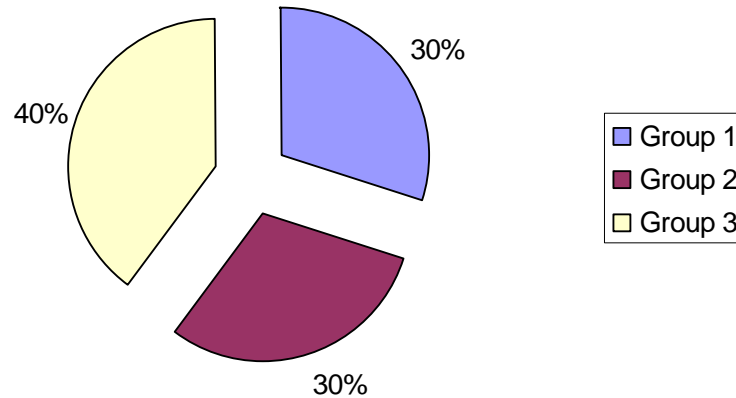
Figure 1. Natural history of epilepsy (Kwan and Sander, 2004).
Group 1: Excellent prognosis with or without treatment, Group 2: Remission with treatment only, Group 3: continuing seizures despite treatment.

1.2. Treatment of epilepsy

Options used in the treatment of epilepsy are in fact very limited. Furthermore, the use of some of these options is still a controversial issue. Antiepileptic drugs (AEDs) are the mainstay of epilepsy management. Around 60 - 70% of epileptic patients with seizures can be treated successfully with AED therapy (Kwan and Brodie, 2000a).

1.2.1. History of AED development

Seeking a treatment for epilepsy began as early as the discovery of the disease itself. Primitive procedures, materials and herbs have been employed since ancient times. In

1857, Sir Charles Locock advocated the use of potassium bromide for the treatment of epilepsy citing a German report and making bromide the first drug to be used against this disease (Pearce, 2002). But unfortunately, the side effects associated with bromide have limited its efficacy.

The beginning of modern pharmacotherapy of epilepsy was in 1912 when the anti-convulsant properties of phenobarbital were discovered accidentally by Hauptmann (1881-1948) when studying the anxiolytic effects of various drugs used to sedate a ward of noisy psychiatric patients and those with epilepsy during the night (Pearce, 2002). Therefore, phenobarbital is considered as the oldest among all the antiepileptic drugs available today (Hauptmann, 1912). It was initially synthesised in 1904 by a German chemist Fischer and was known to possess sedative and hypnotic properties but it was only in 1912 that its anticonvulsant effects were discovered.

In 1908, phenytoin (sodium diphenyl hydantoinate) was synthesised and in 1938, it was applied in clinical practice following the studies of Merritt and Putnam who showed favourable anticonvulsant efficacy of this agent against various seizure types without the sedative effect associated with phenobarbital (Merritt and Putnam, 1984).

Carbamazepine was synthesised in 1953 by Schindler at the Geigy laboratories in Switzerland (Schmutz, 1985). Initially in 1962, it was marketed to treat trigeminal neuralgia, and then in 1963, it was applied clinically to treat epilepsy in the United Kingdom (UK).

Sodium valproate was first synthesised in 1882 by Burton and for many decades was used as a solvent for organic compounds in research laboratories (Burton, 1882). Its anticonvulsant properties were discovered accidentally in 1963 by Pierre Eymard (Meunier et al., 1963).

Almost a century of AED research, development and practice has followed and there are now more than 15 AEDs available for the treatment of seizure disorders. AEDs introduced in the market during this period showed a variable extent of efficacy toward epilepsy syndromes and seizure types. They also displayed variable degrees of tolerability.

1.2.2. Generations of AEDs

AEDs can be classified on a chronological basis e.g. date of discovery or date of approval for clinical practice. Also, as there are several mechanisms of action by which AEDs exert their anticonvulsion activity, other classifications may depend on the primary mechanism. When classifying AEDs based on their dates of approval for clinical practice, these dates will vary between different countries. Also, certain AEDs are not licensed in particular countries. With reference to AED approval in the UK, phenobarbital was the first AED licensed officially for clinical practice in patients with epilepsy in 1912. Approval of other AEDs continued in the following years until the present. The period between 1979 and 1989 showed a hiatus in AED development resulting in a distinct separation of AEDs into two groups (generations); older or established (first generation) AEDs which represent AEDs introduced on or before 1979 and newer or modern (second generation) AEDs which were introduced on or after 1989. Table 7 shows AEDs introduced in the market in a chronological order according to their dates of license in the UK. Established agents comprise phenobarbital, phenytoin, primidone, ethosuximide, carbamazepine, clonazepam, clobazam and sodium valproate. On the other hand, vigabatrin was the first modern AED and has been followed by lamotrigine, gabapentin, felbamate, topiramate, tiagabine, oxcarbazepine, levetiracetam, pregabalin and zonisamide.

Many agents of the first and second generations are still being used to this day, while others are either not commonly prescribed or have been discontinued because of their serious side effects.

AED	UK approval date
Established (Older) AEDs	
Phenobarbital	1912
Phenytoin	1938
Primidone	1952
Ethosuximide	1955
Carbamazepine	1965
Sodium valproate	1973
Clonazepam	1974
Clobazam	1979
Modern (newer) AEDs	
Vigabatrin	1989
Lamotrigine	1991
Gabapentin	1993
Topiramate	1995
Tiagabine	1998
Oxcarbazepine	2000
Levetiracetam	2000
Pregabalin	2004
Zonisamide	2005

Table 7. Dates of AED licences in the UK.

Although several first generation AEDs are still used in clinical practice, these agents have some disadvantages that include a narrow therapeutic index, suboptimal response rates, non-linear pharmacokinetics, significant adverse effects and drug-drug interactions (Battino et al., 2000).

On the other hand, AED therapy using first generation agents has the advantage of being applied clinically for almost a century (since 1912). Such a long interval has enabled these agents to be studied extensively in terms of spectrum of efficacy against several seizure types, side effects, idiosyncratic reactions, drug-drug interactions, pharmacokinetic profiles

and the underlying mechanisms of action. This has led to the fact that consequences of treatment using these agents are known and predictable in many cases compared to second generation AEDs that have only been approved for clinical practice in the last two decades. Some characteristics of these agents are still under investigation e.g. mechanism of action, risk of teratogenicity and effects on bone health (LaRoche, 2007).

Most of the newer AEDs have multiple mechanisms of action compared to the established agents that usually have a single predominant mechanism of action, this has enabled the second generation drugs to be applied against several seizure types (Table 9). In terms of tolerability, the newer AEDs tend to have fewer side effects and fewer drug-drug interactions compared with the established drugs (Brodie et al., 1995;Dam et al., 1989;Meador et al., 1999;Perucca, 2001a). In addition, hepatic enzyme induction is a common characteristic of first generation agents e.g. carbamazepine, phenobarbital and phenytoin (Radtke, 2001;Radulovic et al., 1994), while it was found that most second generation agents lack this effect. The broader spectrum of anticonvulsant activity of second generation AEDs (lamotrigine, topiramate and zonisamide) in comparison to the first generation agents (sodium valproate) is a crucial issue as well (Beran et al., 1998;Biton et al., 1999;Kyllerman and Ben Menachem, 1998).

As a result of these issues, modern AEDs have been widely accepted by clinicians and prescribed to patients. It was found that 20% of the total prescriptions in 2002 were for newer AEDs and that these newer agents accounted for 69% of the total AED expenditure in the UK (£99m of £142m) (NICE, 2004). Modern AEDs are significantly more expensive than their established counterparts and it remains to be seen whether the expected novel characteristics of the newer AEDs justify their increase in costs (Chadwick, 1998;Perucca, 2002).

With the introduction of second generation AEDs, the number of AEDs available for treatment of epilepsy has almost trebled (Perucca, 2001a). But, although the availability of newer AEDs has widened the options for physicians to treat epilepsy, it has become more complicated to choose the most suitable agent to treat certain seizure types or specific epilepsy syndromes. However, despite the availability of wide range of AEDs these days, further newer agents are needed preferably working by unique modes of action (Brodie, 2001). It is hoped that these future agents (1) are safe, (2) can prevent epilepsy and its progression, (3) can reverse and treat pharmacoresistant epilepsy, and (4) can prevent epilepsy in patients at risk (Schmidt, 2002). These advances need to be coupled with better

understanding of the pathophysiology of seizures and the biological basis of pharmacoresistance in order to improve the outcome of epilepsy.

Since the beginning of development of second generation AEDs, their comparison with the first generation drugs has become an essential clinical issue. Such comparisons can include several factors such as efficacy, tolerability, mechanism of action, cost and ease of use. Some of these factors favour older agents while others are on the side of newer drugs. Clinicians usually make the decision to select the most appropriate AED of either first or second generation according to each patient situation. e.g. phenytoin is the most commonly prescribed medication against seizure in the United States (LaRoche, 2007). Therefore, after two decades of application of second generation AEDs, it is appropriate to examine the clinical impact of these agents on seizure control, tolerability and the overall outcome of epilepsy in comparison to first generation agents.

1.2.3. Animal seizure models

During the process of developing second generation AEDs, two tests are commonly applied to evaluate the anticonvulsant activity of this new agent, the Maximal Electroshock (MES) test and the subcutaneous pentylenetetrazol (scPTZ) test. The MES test is a model of seizure spread; capable of identifying drugs with activity against partial and generalised tonic clonic seizures e.g. MES test gives positive results when applied on carbamazepine that is effective against tonic and/or clonic seizures (Table 8). In contrast, the scPTZ test is a model of seizure threshold that can predict agents effective against generalised absence and myoclonic seizures e.g. scPTZ is positive with ethosuximide that is used against absence seizures (Table 8) (Rho and Sankar, 1999). To identify activity against complex partial seizures, the kindling model in rodents that have many behavioural similarities with complete partial seizures in humans may be the model of choice e.g. phenytoin that is effective against partial seizures is positive in the electrical kindling test (Table 8). In the kindling process, the rat amygdale is subjected to a repeated sub-convulsive electrical stimulus that induces electrographic seizures or after discharges and with each further stimulus the seizure peak grows longer spreading to wide areas of the brain until complete (full blown) seizures are elicited (Racine, 1972).

The only exception is phenobarbital that is active against scPTZ in rodents but ineffective against absence seizures in humans. If the AED has multiple mechanisms of action such as

sodium valproate, it will be more likely to have a wide range of anticonvulsant applications and display activity in several anticonvulsant models (White et al., 1995).

Experimental model	Generalised seizures		Partial seizures	AEDs
	Tonic and/or clonic	Absence		
MES (tonic extension)	+			CBZ, PHT, VPA, PB
ScPTZ (clonic seizures)		+		VPA, ESM, PB, BZD
Electrical kindling (focal seizures)			+	CBZ, PHT, VPA, PB, BZD

Table 8. Correlation between experimental animal models and clinical applications of established AEDs.

1.2.4. Mechanisms of anticonvulsion activity

With regard to the mechanisms of action of AEDs, multiple mechanisms have been identified to play a role in the anticonvulsion activity exerted by these drugs. The four main mechanisms by which most of the established as well as the modern AEDs act are: blockade of voltage gated sodium channels, blockade of voltage gated calcium channels, potentiation of GABA (gamma aminobutyric acid) inhibitory effect and inhibition of the glutamate excitatory mechanism (Kwan et al., 2001;Rogawski and Loscher, 2004). Other mechanisms include: potentiation of potassium channels and inhibition of carbonic anhydrase.

1.2.4.1. Blockade of voltage gated sodium channels

Sodium channels control the passage of sodium ions across the cell membrane, an essential step in the action potential. They play a central role in the generation and transmission of action potentials in the excitable membranes of heart, muscle and nerve, leading to muscular contraction and neuronal discharge.

The major component of sodium channels is the single large α subunit. It has two main functions; it represents the channel gate for regulating sodium passage and acts as the ion conducting pore. Other components of sodium channels are one or two smaller β subunits that do not participate in the functional role of these channels (Catterall, 1992). Sodium channels are voltage gated channels i.e. certain changes in the membrane potentials will trigger these channels to open or close.

These channels are closed at resting membrane potential; once depolarization of the neuron takes place (after reaching the action potential threshold) a conformational change in these channels occurs converting them from the inactivated closed (resting) non-conducting state to the activated, opened conducting state. This permits sodium ion influx across the channel pore, followed by a return to the inactivated state when all these channels will be closed. Eventually repolarisation brings these channels to the resting membrane state making them ready for a new depolarisation action. These three stages only last for a few milliseconds. It is necessary for neurons to have states of such very short duration in order to fire high frequency trains of action potentials, a requirement of a normally functioning brain and for convulsion development as well (Rogawski and Loscher, 2004).

As these channels control the action potentials by controlling passage of sodium ions across the neuronal membranes, blockage of these channels by certain AEDs will lead to blocking of action potentials and consequently, prevention of neuronal high frequency repetitive spike firing that takes place during the spread of seizure activity without interfering with normal neuronal activity. Therefore, seizure control will be achieved. AEDs acting by blocking of sodium channels are found to share some characteristics. These agents are effective against partial and generalised tonic-clonic seizures in humans and inhibit sustained repetitive firing of action potentials. Inhibition of sodium channels by these agents tends to be voltage and activity dependent that might be responsible for their clinical efficacy (Ragsdale and Avoli, 1998). Further evidence for the role of sodium channels in epilepsy, is shown by a number of epilepsy syndromes that have been linked to genetic defects in genes encoding certain subunits of sodium channels such as generalised epilepsy with febrile seizures plus and benign familial neonatal infantile seizures (Baulac et al., 2001;Berkovic et al., 2004).

1.2.4.2. Blockade of voltage gated calcium channels

Voltage Dependant Calcium Channels (VDCCs) play an essential role in translating electrical signals into biochemical events that eventually lead to cell excitability, hormone and transmitter release, muscle contraction and gene expression. They play this role by controlling the action potential through regulating the passage of calcium ions across the excitable membranes (Van Petegem et al., 2004).

VDCCs can be classified into two major subtypes: High Voltage Activated calcium channels (HVA) that include P/Q, N, L and R-VDCCs and Low Voltage Activated calcium channels (LVA) that are T-VDCCs. This classification is based on the biophysical and pharmacological properties of these channels.

HVA channels are responsible for calcium flux across the cell membrane and neurotransmitter release from the presynaptic nerve terminals that make them important targets for AEDs. This type of channel (as their name indicates) requires a strong membrane depolarisation for opening the gates. On the other hand, by participating in bursts and intrinsic oscillations, LVA channels can control neuronal firing.

Structurally, VDCCs are composed of three subunits, $\alpha1$ that is the ion channel pore with gating properties, $\alpha2/\delta$ and β subunits which are responsible for cell surface expression and channel kinetics. They are found in a 1:1:1 stoichiometry. $\alpha1$ subunits are encoded by 10 genes, 3 genes encode $\alpha2/\delta$ subunits while 4 genes encode β subunits. It is highly significant that these subunits have diverse genetic compositions, since it is the nature of these gene products that determines the biophysical and pharmacological properties of VDCCs (Catterall, 2000). Distribution of VDCCs varies in discrete brain regions and even within the individual neurons (Elliott et al., 1995). In addition, a new subunit of VDCCs has been found in the brain with $\gamma2$, $\gamma3$ and $\gamma4$ subunits (Letts et al., 1998).

VDCCs have been linked to epilepsy since it was documented more than twenty years ago that an elevation of calcium ion influx with a subsequent reduction in extracellular free calcium ions stimulates seizure activity in the brain. Such evidence has been provided (in part) by studies employing the kindling animal seizure model. Therefore, blocking these channels represents a target for several antiepileptic drugs.

1.2.4.3. Potentiation of GABA

GABA (gamma-aminobutyric acid) is the major inhibitory neurotransmitter in the brain. It is formed from glutamic acid with the aid of Glutamic Acid Decarboxylase (GAD) and metabolised to succinic semialdehyde by the action of GABA transaminase (GABA–T). GABA acts as an inhibitory neurotransmitter, so once it binds to its own receptor, it inhibits the signals transmission across the neuronal membrane limiting the spread of action potentials across the brain and controlling seizure propagation. After GABA is released from the presynaptic terminal into the synapse, using a specific sodium/chloride voltage dependent reuptake system, around 80% of the released GABA is taken back into the presynaptic terminal. The remaining proportion is metabolised to succinic semialdehyde by GABA–T (Treiman, 2001).

Potentiation of GABA inhibitory effect constitutes the mechanism by which several antiepileptic drugs work as they cause an increase in GABA concentration in the brain limiting the spread of convulsant activity across the neuronal network and controlling seizure development.

There are three types of GABA receptors: GABA-A, GABA-B and GABA-C receptors. GABA-A and GABA-C receptors are ligand gated ion channels while GABA-B receptors are G protein coupled receptors.

GABA-A receptors constitute the target at which multiple antiepileptic drugs act; they are mainly located on the postsynaptic terminals (Fritschy et al., 1999). The GABA-A receptor is composed of five subunits that together form the pore; once GABA-A receptors on the postsynaptic neuron have been occupied, chloride ions enter through these pores. Consequently, hyperpolarisation of these neurons takes place with a decrease in the rate of neuronal firing. The greater the frequency of chloride channel opening, the greater is the reduction in the rate of neuronal firing (Sieghart et al., 1999). Bromide, the first historical AED increases the sensitivity of GABA-A receptors to GABA, resulting in an increase in GABA-A receptor mediated inhibition (Akaike et al., 1989).

GABA-B receptors are found on pre and postsynaptic GABAergic terminals. Those located on the presynaptic terminals (autoreceptors) regulate the release of GABA; once they have been stimulated they cause a decrease in the release of GABA (either through opening of potassium channels or inhibition of calcium influx or both). Therefore,

antagonising these receptors can represent a target for anticonvulsant activity (Figure 2) (Bonanno and Raiteri, 1993).
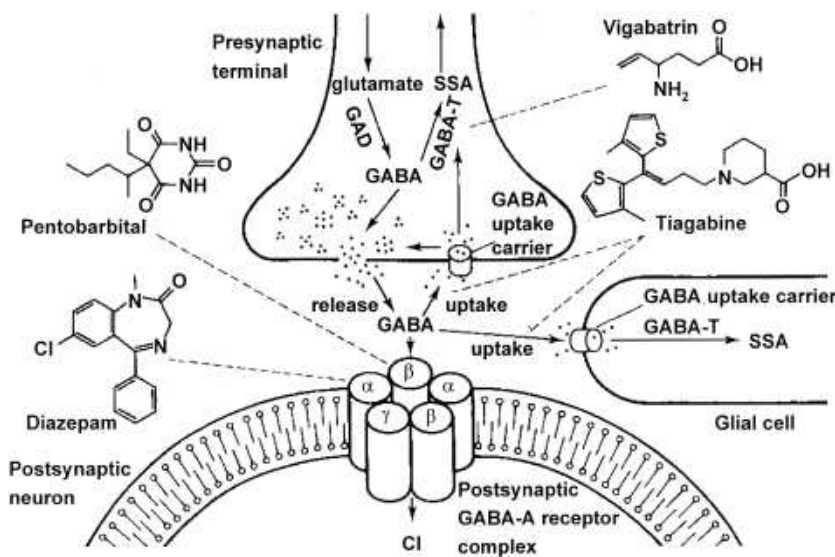
Figure 2. GABAergic synapse (Suzdak and Jansen, 1995).

1.2.4.4. Inhibition of glutamate excitatory mechanism

Glutamate gated cation channels are responsible for the bulk of fast excitatory neurotransmission in the central nervous system. Their subtypes include NMDA (N-methyl-D-aspartate) and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) receptors, the blockage of which can lead to seizure control. Another subtype of glutamate receptors comprises kainite receptors. Kainate receptors (GluR5) play a role in postsynaptic excitation, control of presynaptic glutamate release from excitatory afferents and suppression of GABA release (Rogawski et al., 2003) that also makes them a potential target for AEDs.

A relationship has been established between NMDA receptors and seizures development. The NMDA receptor operated complex is composed of an ion channel responsible for influx of calcium and sodium ions and efflux of potassium ions. Various binding sites have been identified on this complex, where antagonism could show anti-convulsant activity (Davies, 1995). Some AEDs have been found to be capable of reducing NMDA evoked depolarisations e.g. carbamazepine (at certain concentrations) and felbamate. NMDA receptors have multiple recognition sites for glutamate, glycine, polyamine, ions and use dependant channel blockers. Occupation of glycine and glutamate sites by an agonist is an essential requirement for NMDA channel opening and neuronal depolarisation (Monaghan et al., 1989).

Although AMPA receptors are considered to have a potential role in seizure control, no currently marketed AEDs have a major effect at these receptors.

1.2.4.5. Potentiation of potassium channels

Potassium (K^+) channels possess a regulatory role in the development of seizure activity for three reasons. Blockade of potassium channels is accompanied by the development of epileptic activity (Pena and Alavez-Perez, 2006;Wickenden et al., 2000). Also, benign familial neonatal convulsions (BFNC) a genetic disorder, is a generalised epilepsy syndrome that was found to be associated with a defect in the genes encoding voltage dependant potassium channels (Singh et al., 1998). Finally, potassium channels blockers provoke the development of animal seizure models (Bagetta et al., 1992).

K^+ channels are composed of four alpha subunits; auxillary beta subunits are present in some potassium channels. S4 is considered to be the voltage sensor segment while S5 and S6 constitute the channel pore. There are different types of voltage gated potassium channels, these include: A-type channels which rapidly activate and deactivate, delayed rectifier channels that open on depolarisation and inward rectifying channels that are blocked on depolarisation under the effect of internal ions. Several types of inward rectifying channels exist, such as ATP sensitive channels.

The M-type is a specific form of potassium channel; these channels are slowly activated by depolarisation while muscarinic stimulation causes their inhibition. The M-current plays a role in controlling neuronal excitability and firing properties. In the case of neuronal depolarisation evoked by excitatory stimuli, activation of M type K^+ current takes place

leading to repolarisation of the neuronal membrane with subsequent firing suppression limiting seizure propagation. Therefore, suppression of M-current is considered a mechanism that can lead to convulsions.

It has been found that the M-current in the neurons is subserved by KCNQ2 and KCNQ3 potassium channel subunits (Wang et al., 1998) and consequently, dysfunction of these subunits results in epileptic disorders.

1.2.4.6. Inhibition of carbonic anhydrase

Carbonic anhydrase catalyses the chemical reaction of CO_2 and H_2O to form carbonic acid. Brain carbonic anhydrase regulates (with the aid of Na/K ATPase anion exchanger) the exchange of extracellular chloride ions for intracellular bicarbonate ions ($HCO3^-$) (Woodbury et al., 1984). Carbonic anhydrase II represents 97% of brain carbonic anhydrase activity that makes it the major brain isozyme. The anticonvulsant effect of carbonic anhydrase inhibition is confirmed as acetazolamide is an AED that is a carbonic acid inhibitor.

Inhibition or deficiency of carbonic anhydrase will lead to an accumulation of carbon dioxide (CO_2) in the brain with a subsequent anticonvulsant effect. Deficiency of carbonic anhydrase II is accompanied by reduced susceptibility (more resistant) to flurothyl and scPTZ induced seizures (Velisek et al., 1993). CO_2 accumulation leads to a drop in pH level that acts to antagonise NMDA receptors. Severe systemic acidosis in mice with carbonic anhydrase II deficiency leads to a decrease in NMDA receptor function and consequently anticonvulsant activity (Velisek and Veliskova, 1994).

1.2.5. Mechanisms of action of commonly prescribed AEDs

1.2.5.1. Phenobarbital

In 1912, phenobarbital was licensed in the UK making it the oldest AED available today. Phenobarbital belongs to the barbiturates group that includes: phenobarbital, mephobarbital, metharbital and primidone. Despite its side effects that include cognitive (behavioural) changes, it is still used in clinical practice especially in the developing world as it is inexpensive and easy to use (Brodie and Kwan, 2004). Beside its application as an

anticonvulsive drug, phenobarbital can also be used as an anaesthetic and sedative-hypnotic agent.

Phenobarbital's mechanism of anticonvulsant activity is through augmenting the inhibitory effect of GABA (Macdonald and Barker, 1979); it binds to a specific binding site of chloride channels in GABA-A receptors present on postsynaptic terminals. This binding increases the mean opening time of chloride channels without interfering with the frequency of opening (Twyman et al., 1989). The net result is increased stimulation of the inhibitory effect of the GABA system leading to a decrease in the rate of neuronal firing with subsequent control of seizures.

Other less important mechanisms include a slight inhibitory effect on high voltage activated calcium channels (Ffrenchmullen et al., 1993).   At high concentrations, phenobarbital is also capable of inhibiting high frequency repetitive firing of action potentials, compatible with actions on voltage gated sodium channels (Mclean and Macdonald, 1988).

1.2.5.2. Phenytoin

Phenytoin is the longest established AED that is capable of inhibiting abnormal brain activity characteristic of seizures with a non-sedative effect (without affecting normal brain activity). As a result of this unique property, phenytoin has been extensively studied since its availability in 1938 in the UK.

In terms of its mechanism of action, phenytoin's inhibition of sodium channels is strongly related to the voltage of membrane potentials.

This was confirmed when phenytoin was found to be a weak blocker of hyperpolarised sodium channels (more negative than – 80 mV) with gradual elevation in blocking capability occurring at progressively more depolarised potentials (from –80mV to –30mV). Another important characteristic of phenytoin is its inhibition of high frequency repetitive firing of action potentials rather than slow or individual firing (without affecting spontaneous neuronal activity) (Matsuki et al., 1984). Also, inhibition by phenytoin is time dependant, as the time required to recover from depolarisations is prolonged (Macdonald, 1989).   In addition to a delayed recovery from suppression of sodium

channels, blockade by phenytoin is also slow in onset, stable and tight (Kuo and Bean, 1994).

These properties of phenytoin explain the reason of its selective control of seizures without producing sedation. Phenytoin is a weak blocker of sodium channels in the resting state (during normal brain activity) while seizures (abnormal brain activity) are characterised by high frequency trains of depolarisations, on a background of prolonged depolarisation episodes, a condition which favours phenytoin's mechanism of blocking sodium channels (Remy et al., 2003). Phenytoin's block of sodium channels is also use dependent, so that blockade accumulates with prolonged or repetitive activation. This is because phenytoin binds preferentially to the sodium channels in an inactivated state (Rogawski and Loscher, 2004).

A mutation of the gene encoding the $\beta 1$ subunit of sodium channels linked to an inherited epilepsy syndrome results in reduction in both sensitivity of these mutant channels toward the inhibitory effects exerted by phenytoin and frequency dependant inhibition by phenytoin. These effects are due to changes in the gating properties of these mutant channels (Lucas et al., 2005).

It has been proposed that phenytoin, carbamazepine and lamotrigine bind to a common binding site on sodium channels that does not exist in the resting state as the affinity of these drugs for binding is much higher in the inactivated state than the resting state (Kuo, 1998).

Also, Granger and colleagues showed that phenytoin enhances the effect of GABA at the α1β2γ2 subtype of GABA-A receptors (Granger et al., 1995).

On seizure development, there is elevation of potassium concentration extracellularly leading to depolarisation. This is accompanied by a decrease in extracellular calcium concentration due to calcium influx through the opened voltage operated calcium channels into the neuron. Increased calcium concentration intracellularly enhances excitatory neurotransmission.   Phenytoin's ability to block calcium entry results in limiting neurotransmission excitation and subsequently, seizure control (Pincus and Lee, 1973). Voltage and use-dependant inhibition of potassium channels by phenytoin has also been reported (Nobile and Vercellino, 1997).

1.2.5.3. Ethosuximide

Although ethosuximide was introduced in the UK in 1955, its mechanism was not documented until 1989. This process was elucidated as inhibition of voltage dependent T-type (low threshold) calcium channels at therapeutic levels in the thalamic neurons. Initially, this mechanism of action was identified theoretically based on the observation that methyl-phenylsuccinimide (an active metabolite of a related compound) also blocks T-type calcium channels and no inhibition was observed when using the inactive analogue succinimide (Coulter et al., 1990). Although several studies using therapeutically relevant concentrations showed a contradictory view of ethosuximide mechanism regarding blockage of T-VDCCs, Gomora et al. were able to show that ethosuximide and methyl-phenyl suximide (the active metabolite of a related compound methsuximide) were capable of blocking T-VDCC currents with a higher affinity for inactivated channels (Gomora et al., 2001). Furthermore, analogues of ethosuximide without anticonvulsive property were found to be poor blockers of calcium channels. The blockage was found to be voltage dependent at therapeutic concentrations (Coulter et al., 1989).

Absence seizures are characterised by the presence of 3Hz spike wave rhythms. As T-type calcium currents in thalamocortical neurons have an activity of low frequency (around 3Hz), it is believed that this is the reason why absence seizures can be affected by ethosuximide (Davies, 1995).

In addition, ethosuximide may lead to a slight reduction in persistent sodium currents, that are slowly inactivating and with relatively small depolarising potential (Niespodziany et al., 2004).

1.2.5.4. Carbamazepine

Carbamazepine was licensed in the UK in 1965. It is an iminostilbene derivative of tricyclic anti-depressants and among antiepileptic drugs, it is one of the most widely prescribed agents. Since carbamazepine and phenytoin have similar characteristics in their structures and mechanisms of action regarding blocking of voltage gated sodium channels with some differences, the spectrum of activity of these two agents is also very similar (Rogawski and Porter, 1990).

At therapeutic concentrations, carbamazepine or its metabolite 10,11-epoxycarbamazepine inhibit the high frequency firings of action potentials (repetitive action potentials) rather than low or individual polarisations. It inhibits sodium currents in a voltage and use (frequency) dependant manner (Kuo et al., 1997) and sodium channel inhibition by carbamazepine might also be considered time dependant as it can shift the current voltage dependence toward hyperpolarisation direction delaying the recovery of sodium channels from inactivation (Reckziegel et al., 1999). Carbamazepine tends to bind to sodium channels in the inactivated state that results in blockade accumulation with prolonged or repetitive activation (Rogawski and Loscher, 2004).

Although carbamazepine and phenytoin have a similar mechanism of action, the patients' response to these two agents is not same. There might be some molecular basis for the observation that some patients respond better to phenytoin while others find carbamazepine more effective in treating their seizures. Carbamazepine has a 3-fold lower affinity for depolarised sodium channels with a five times faster binding rate compared with phenytoin (Kuo et al., 1997).

Therefore, it would be more appropriate to use carbamazepine rather than phenytoin in treating patients with seizures of relatively short rather than prolonged depolarisations shifts.

Carbamazepine can at certain concentrations reduce NMDA (NMDA subtype of the glutamate receptor) evoked depolarisations while at higher concentrations, the effect is to potentiate depolarisations (Lancaster and Davies, 1992) and reduce presynaptic glutamate release. Carbamazepine is also able to potentiate GABA inhibitory effect at α1β2γ2 subtype of GABA-A receptors (Granger et al., 1995).

Carbamazepine has the capability to enhance the activity of glutamate transporters. Glutamate transporters help in the regulation of glutamate neurotransmission and GABA mediated inhibitory neurotransmission. Dysfunction of these transporters is associated with seizure development in rats. Carbamazepine potentiates the activity of glutamate transporter type 3 (the major glutamate transporter) (Lee et al., 2005).

1.2.5.5. Sodium Valproate

Valproic acid (a branched fatty acid) was one of the first drugs to be used in the treatment of epilepsy. It has been in clinical practice since 1962 and it has been licensed in the UK since 1973.

Sodium valproate (the sodium salt of valproic acid) has multiple mechanisms of action that can explain its wide range of clinical applications in epilepsy. It enhances GABA inhibitory effect by increasing the turnover of the GABA transporter (Whitlow et al., 2003) and elevating the synthesis of GABA through the stimulation of glutamic acid decarboxylase. Cunningham and colleagues identified a potentiating role of sodium valproate on postsynaptic GABA-A receptors (Cunningham et al., 2003). Sodium valproate can reduce the excitatory synaptic activity as increases in the frequency and amplitude of spontaneous excitatory postsynaptic currents are reduced resulting in suppression of epileptiform activity (Martin and Pozo, 2004).

Sodium valproate is also able to suppress persistent sodium currents (Taverna et al., 1998). Inhibition of NMDA evoked depolarisations by sodium valproate has been observed (Zeise et al., 1991) and at high concentrations, sodium valproate is able to reduce T-type calcium currents. Potassium conductance can also be activated by sodium valproate leading to potassium efflux and hyperpolarisation (Franceschetti et al., 1986).

1.2.5.6. Benzodiazepines

This group of drugs has four major pharmacological effects: sedative-hypnotic, muscle relaxant, anxiolytic and anticonvulsant properties. The benzodiazepine group includes about 50 agents, only four of which can be used as AEDs: diazepam, lorazepam, clonazepam and clobazam. Structurally, all benzodiazepines are 1,4-benzodiazepines with the exception of clobazam that is 1,5-benzodiazepine (the numbers represent nitrogen atom locations on the diazepine ring) (Nakajima, 2001). The chemical structure of clobazam was designed to be different from other benzodiazepines in order to exert different pharmacological properties. The most widely prescribed benzodiazepines agents used as AEDs are clonazepam and clobazam. Clonazepam was introduced in the UK in 1974 while clobazam was licensed in the UK in 1979 initially as an anxiolytic agent.

Clobazam's mechanism of action is by augmenting GABA-A receptors inhibitory effect on neurotransmission, thereby increasing the frequency of chloride channel opening that eventually results in a decrease in neuronal firing (Nakamura et al., 1996).

Clobazam (1,5-benzodiazepine) has an anticonvulsant action different from other benzodiazepines (1,4-benzodiazepines) as it inhibits the appearance of generalised tonic clonic seizures on which clonazepam (1,4-benzodiazepine) has no effect. This might be explained by the difference in chemical structure (Miura et al., 2002).

Benzodiazepines at high concentrations (in status epilepticus) can inhibit voltage gated sodium channels (Mclean and Macdonald, 1988) and to a lesser extent calcium channels (Skerritt et al., 1984).

1.2.5.7. Vigabatrin

Vigabatrin (gamma-vinyl GABA) is a structural analogue of GABA. Vigabatrin is present in two forms: an S (+) enantiomer that is the active form and an R (-) enantiomer that is inactive (Haegele and Schechter, 1986). Vigabatrin was the first of the modern AEDs to be licensed in the UK in 1989.

Vigabatrin increases the concentration of GABA at the synapse and postsynaptic GABA receptors. It achieves this through the irreversible inhibition of GABA transaminase (GABA-T), which converts GABA into succinic semialdehyde, the rate-limiting enzyme responsible for the metabolism of GABA (Jung et al., 1977). This results in an increase in synaptic and terminal GABA levels in the brain. In cortical astrocytes, vigabatrin is also able to reduce GABA uptake (Sills et al., 1999). These effects will eventually lead to those neurons involved in seizure activity being inhibited.

1.2.5.8. Lamotrigine

Initially, there was a mistaken belief that inhibition of folic acid had anticonvulsant activity. Therefore, lamotrigine was designed to act as a folic acid inhibitor. In the UK, it was approved for clinical practice in 1991.

In the beginning, the similarity in the range of anticonvulsant activity of lamotrigine to that of phenytoin and carbamazepine raised the suggestion of the possible role of sodium channel inhibition in the mechanism of action of this agent. It is now documented that

lamotrigine has a complex mechanism of action including blockade of sodium channels. Lamotrigine causes a reduction in the excitation of sodium channels in a voltage and use (frequency) dependant manner (Zona and Avoli, 1997). Lamotrigine binding to sodium channels tends to be slow in onset, tight and slow in recovery from blockade (unbinding) (Kuo and Lu, 1997).

Another mechanism by which this drug exerts its anticonvulsant activity is through the enhancement of potassium mediated hyperpolarising conductance in the neurons leading to inhibition of epileptiform discharges (Zona et al., 2002). Lamotrigine results in the reduction in both peak amplitude and time to peak A-type potassium currents in the hippocampal neurons (Huang et al., 2004).

Also, lamotrigine inhibits glutamate release and presynaptic calcium influx (Wang et al., 2001). The effect on calcium channels is restricted to high voltage activated types (Stefani et al., 1996). Both lamotrigine and levetiracetam act as antagonists of calcium channels preventing the elevation of intracellular calcium concentration, a process that results in an epileptiform activity (Pisani et al., 2004).

1.2.5.9. Gabapentin

Gabapentin (1-aminoethyl cyclohexane acetic acid) was synthesised to act as a GABA mimetic agent facilitating GABA inhibition but its mechanism of action appeared to be different from what was expected. It received approval for use in the UK in 1993. Gabapentin's mechanism of action has long been a mystery and represents one of the most intriguing stories to emerge in the understanding of VDCCs.

Various studies initially showed that gabapentin does not act on GABA-A or GABA-B receptors and does not elevate GABA levels in nerve terminals (White, 1997). Also it does not act on glutamate, glycine or NMDA receptors. Additionally, its mechanism of action does not affect sodium channels.

Eventually, it was shown that gabapentin exerts its anticonvulsant activity through inhibition of HVA calcium currents in a concentration dependent manner with L-type calcium channels as the predominant type involved (Stefani et al., 1998). Gabapentin binds (in high affinity) and blocks the $\alpha2\delta$ subunit of VDCCs (Gee et al., 1996), making gabapentin the first ligand for this auxiliary subunit. This binding is subtype specific with

a higher affinity to α2δ-1 than α2δ-2 subunits. The third type of subunits (α2δ-3) does not bind to gabapentin (Marais et al., 2001).

Some studies have suggested that inhibition of VDCCs by gabapentin might be indirectly due to activation of GABA-B receptors (Mintz and Bean, 1993). Although Ng and colleagues (2001) showed that gabapentin is an agonist at GABA-B gb1a-gb2 heterodimer coupled to inwardly rectifying potassium conductance (Ng et al., 2001), several studies have disputed this theory. There is still a possibility that gabapentin is involved in the activation of GABA-B receptors (Bonhaus et al., 2002) with a more predominant effect on presynaptic GABA-B heterorecptors (Parker et al., 2004). Also, gabapentin has been shown to be capable of increasing GABA level in human brain tissues resected during epilepsy surgery while this effect was not observed in normal brain tissues (Errante et al., 2002).

Gabapentin can also inhibit presynaptic glutamic excitatory neurotransmission with a postsynaptic enhancement of NMDA receptor transmission (Shimoyama et al., 2000). In addition, it has the capability to enhance NMDA currents selectively in GABAergic neurons of the spinal dorsal horn (Gu and Huang, 2002).

1.2.5.10. Topiramate

Topiramate (a sulfamate substituted monosaccharide) is considered to be an AED with a wide range of anticonvulsant activity. It was licensed in the UK since 1995.

Topiramate has multiple mechanisms of action. It can inhibit L-type calcium channels of the high voltage activated currents controlling neuronal depolarisation with subsequent anticonvulsant activity (Zhang et al., 2000).

Also, topiramate enhances GABA mediated chloride flux by increasing the opening and burst frequency of GABA-A receptor channels (Browm et al., 1993;White et al., 1997). Beside its action on GABA-A receptors, Kim and colleagues have suggested that topiramate can selectively inhibit pre/postsynaptic GABA-B receptors in the interneurons, an action that eventually results in elevation of GABA release (Kim et al., 2005).

Voltage gated sodium channels can also be blocked by topiramate through the inhibition of sustained repetitive firing in neurons (Taverna et al., 1999). In addition, it can also positively modulate potassium channels (Herrero et al., 2002).

At glutamate receptors, topiramate is capable of blocking kainate–induced excitatory conductance reducing neuronal excitability (Gibbs et al., 2000); this blockade is specific to kainite receptors containing GluR5 subunits. Topiramate can also block AMPA receptors but to a lesser extent (Gryder and Rogawski, 2003). It has the capability to reduce the levels of glutamate and aspartate release (Kanda et al., 1996) and to inhibit carbonic anhydrase isozymes II and IV more potently than other isozymes (Dodgson et al., 2000). Reduction of glutamate levels by topiramate has anticonvulsive consequences as AMPA receptors activation by glutamate will result in an inhibitory effect on inwardly rectifying potassium channels with a subsequent potentiation on neuronal excitability (Schroder et al., 2002).

1.2.5.11. Tiagabine

Tiagabine is an antiepileptic drug that has a clearly defined mechanism of action. It is a derivative of nipecotic acid and was licensed in the UK in 1998.

Tiagabine acts as a selective inhibitor of the reuptake of GABA at the synapse by irreversible binding to the transporter isoform-1 (carrier protein) i.e. GAT-1 responsible for GABA reuptake into the presynaptic terminal (Braestrup et al., 1990). As a result the concentration of GABA increases at the postsynaptic GABA receptor complex exhibiting its inhibitory effect on seizure development.

1.2.5.12. Levetiracetam

Levetiracetam [(S)-[alpha]-ethyl-2-oxo-1-pyrrolidine acetamide] was approved in the UK in 2000. Chemically, it is not related to any other antiepileptic drugs but structurally, it is similar to piracetam which is a nootropic drug used against myoclonus and to enhance the memory.

Levetiracetam is considered to be exceptional among other AEDs because of unique properties. For instance, it is inactive against acute seizure models usually used to test the antiepileptic activity of AEDs i.e. MES and scPTZ tests (Klitgaard et al., 1998), it can counteract the development of amygdala electrical kindling even after termination of drug dosing (Loscher et al., 1998) and in rats, it has the capability to inhibit neuronal hypersynchronisation when epileptiform activity is evoked (Niespodziany et al., 2003). Also its main mechanism of action does not include any of the usual known targets of AEDs (LaRoche and Helmers, 2004).

Although its exact mechanism of action was not yet been identified, it is believed that levetiracetam has a unique stereo-selective binding site in the brain. This binding site may be involved in an interaction with the GABA system in the brain since levetiracetam causes a significant increase in GABA aminotransferase activity and a marked decrease in glutamic acid decarboxylase GAD activity (Loscher et al., 1996). Further attempts were made to characterise this binding site and eventually it was classified as an integral membrane protein enriched in the synaptic vesicles and called synaptic vesicle protein 2A (SV2A). Levetiracetam derivatives are unable to bind to neurons lacking SV2A on their membranes which indicate the essential role of these binding sites in binding to levetiracetam. Other isoforms (SV2B and SV2C) do not seem to exhibit any binding to levetiracetam (Lynch et al., 2004).

Another mechanism of this agent is its minor inhibitory effect on high voltage activated calcium channels (Niespodziany et al., 2001), predominantly N-type channels (Lukyanetz et al., 2002).

Levetiracetam has an indirect effect on GABA-A receptors through the occlusion of the inhibitory action of GABA-A receptors antagonists (mainly bicuculline) that are usually responsible for neuronal epileptiform excitability in the hippocampus (Poulain and Margineanu, 2002).

A view different from that commonly accepted regarding potassium channels and epilepsy was suggested by (Madeja et al., 2003). It concluded that levetiracetam application resulted in a reduction of delayed rectifier potassium current and repetitive action potential generation in the hippocampal neurons that eventually leads to anticonvulsant activity. This conclusion was explained by levetiracetam interference with the duration of action potential through the reduction of delayed rectifier potassium current, an action that ultimately resulted in a decrease in amplitude and/or decrease of frequency of discharge.

1.2.5.13. Oxcarbazepine

Oxcarbazepine (10-keto-carbamazepine) is an analogue of carbamazepine. It was introduced in the UK in 2000. Oxcarbazepine was designed to have the same efficacy of carbamazepine with fewer side effects. Chemically, a keto group was added to oxcarbazepine at the position 10 of the azepine ring. This keto ring is reduced to a

monohydroxy derivative (MHD) that is responsible for the anticonvulsant activity of the drug.

The difference in the chemical structure between oxcarbazepine and carbamazepine due to the presence of the keto group has lead to differences in the metabolic pathways and properties of each drug e.g. side effects and enzyme induction. Unlike carbamazepine, oxcarbazepine is not metabolised to an epoxide metabolite responsible for the toxic effects of carbamazepine (Faigle and Menge, 1990). Instead, oxcarbazepine is metabolised to a monohydroxy derivative responsible for its pharmacological effects.

Oxcarbazepine acts by blocking voltage sensitive sodium channels inhibiting repetitive neuronal firings and stabilising hyperexcited membranes (Mclean et al., 1994). Another mechanism is through the inhibition of voltage activated calcium currents, an effect observed in cortical and striatal neurons (Stefani et al., 1997). An inhibitory effect of oxcarbazepine on excitatory glutamate release was also noted (Calabresi et al., 1995).

Hippocampal dopamine and serotonin have been found to have anticonvulsant properties against limbic seizures through stimulation of D2 and 5-HT1A receptors (Clinckers et al., 2004). Oxcarbazepine and its metabolite 10,11-dihydro-10-hydroxycarbamazepine (MHD) promote the release of hippocampal dopamine and serotonin (Clinckers et al., 2005) which might contribute at least partly to the anticonvulsant effects of oxcarbazepine.

1.2.5.14. Pregabalin

Pregabalin was licensed in 2004. Pregabalin (S-(+)-3-isobutylgaba) is a lipophilic structural analogue of GABA, it is substituted at the 3 position so that it can traverse the blood brain barrier.

Although it is an analogue of GABA, pregabalin is inactive at GABA receptors. Similar to gabapentin, it binds with high affinity to voltage gated calcium channels subunit $\alpha2\delta$ (Ben Menachem, 2004). This binding is restricted to the $\alpha2\delta$ type 1 subunit of voltage gated calcium channels (Bian et al., 2006). This results in a reduction in calcium influx at nerve terminals and a reduction in the release of several neurotransmitters including glutamate, noradrenaline and substance P (Fink et al., 2002), which might be the reason for its anticonvulsant activity.

Although, pregabalin does not act directly on postsynaptic GABA receptors, it causes a small inhibition of synaptic vesicle exocytosis in GABAergic and glutamatergic neurons (Micheva et al., 2006). Although this effect seems to counterintuitive for an AED, the existence of depolarising GABA responses in certain excitatory neurons has been reported; these were suggested to be capable of initiating epileptic discharges (Cohen et al., 2002). Therefore, inhibition of synaptic vesicle exocytosis of GABA will result in an anti-convulsant activity.

In addition, a recent study suggested a role for pregabalin in the activation of GABA-B receptors based on the finding that long-interval intracortical inhibition (a measure of human motor cortex excitability) mediated by GABA-B activation was increased following pregabalin administration (Lang et al., 2006).

Pregabalin activates ATP-sensitive potassium channels (K_{ATP}) in the differentiated hippocampal neuron derived H19-7 cells in a concentration dependant manner; this activation was associated with a significant increase in the mean open lifetime of these channels (Huang et al., 2006) which will hyperpolarise the cell membranes and aid in seizure control.

1.2.5.15. Zonisamide

Zonisamide (1, 2-benzisoxazole-3-methanesulfon-amide) is structurally a derivative of sulfonamide. It was developed and licensed in Japan in 1989 while in the UK, it was licensed in 2005.

Probably, zonisamide is the AED with the highest multiple known mechanisms of action. These mechanisms include: reduction of sustained repetitive firing of neurons through blockage of voltage dependant sodium channels (Rock et al., 1989), reduction of voltage dependant T-type calcium currents (Suzuki et al., 1992), facilitation of dopaminergic (Okada et al., 1995) and serotonergic (Okada et al., 1999) neurotransmission, potentiation of GABA release as it reacts with the GABA receptor complex (Mimaki et al., 1990) and weak inhibition of carbonic anhydrase (Masuda and Karasawa, 1993). Rather than a weak inhibitor, De Simone and colleagues showed that zonisamide is in fact an effective inhibitor of carbonic anhydrase isozymes II in the cytosole and isozymes V in the mitochondria (De Simone et al., 2005). However, other investigators suggested that inhibition of carbonic anhydrase does not participate in the anticonvulsant properties of

zonisamide (Masuda et al., 1994). Also, it can lead to blockage of potassium evoked glutamate response (Okada et al., 1998). Zonisamide was found to be able to offer protection of neurons against free radicals damage through scavenging of these free radicals (Mori et al., 1998).

AED	Main mechanism of action	Other mechanisms
Established AEDs		
Phenobarbital	Potentiation of GABA inhibition	Inhibition of glutamate excitatory mechanism
Phenytoin	Blockade of voltage gated sodium channels	
Ethosuximide	Blockade of LVA (T-type) calcium channels	
Carbamazepine	Blockade of voltage gated sodium channels	
Valproic acid	Potentiation of GABA inhibition	Blockade of voltage gated sodium channels and LVA (T-type) calcium channels
Clobazam	Potentiation of GABA inhibition	
Modern AEDs		
Vigabatrin	Potentiation of GABA inhibition	
Lamotrigine	Blockade of voltage gated sodium channels	Blockade of HVA calcium channels
Gabapentin	Blockade of HVA calcium channels	
Topiramate	Equal multiple mechanisms of action: blockade of voltage gated sodium channels, HVA calcium channels, potentiation of GABA inhibition and inhibition of glutamate excitatory mechanism	
Tiagabine	Potentiation of GABA inhibition	
Oxcarbazepine	Blockade of voltage gated sodium channels	Blockade of calcium and potassium channels
Levetiracetam	Equal multiple mechanisms of action: binding to SV2A receptors and blockade of HVA calcium channels.	
Pregabalin	Blockade of HVA calcium channels	
Zonisamide	Equal multiple mechanisms of action: Blockade of voltage gated sodium channels, LVA (T-type) calcium channels and potentiation of GABA inhibition.	

Table 9. The mechanisms of action of AEDs.

(HVA = high voltage activated, LVA = low voltage activated, SV2A: synaptic vesicle protein 2A; (Ben Menachem, 2004;Kwan et al., 2001;Lynch et al., 2004;Rogawski and Loscher, 2004;White et al., 2007).

1.2.6. Future directions of AEDs

Advanced molecular biology techniques have enabled investigators to define the mechanism of action of several AEDs, to understand the process of epileptogenesis and to discover the link between targets for AEDs and epilepsy. Nevertheless, it seems that much remains to be discovered in the continuous process for developing new novel AEDs. Some of the future promising directions include:

1.2.6.1. Future mechanisms of AEDs

Inhibition of sodium channels has proven to be a very effective target for controlling seizures. As several isoforms of sodium channels with different functions exist throughout the brain, development of blockers against these specific sodium channels isoforms might improve the pharmacological outcome of epilepsy.

Serotonergic receptors are believed to be potential targets for future AEDs. Elevation of extracellular concentration of serotonin (5-HT) is accompanied by inhibition of limbic and generalised seizures while its depletion will lower seizure threshold. This was confirmed by the discovery of anticonvulsant activity in a 5-HT2B/2C receptor agonist (Isaac, 2005). Such findings indicate that serotonin receptors will play a role in the design of future AEDs.

H-channels are hyperpolarization activated cation channels constituted by a depolarising, non-activating, mixed Na-K current. They control neuronal excitation and inhibition in neuronal and cardiac tissues. These channels represent a new potential target for AEDs as recent evidence has established the effects of their modulation on neuronal excitability and consequently a net antiepileptic effect (Chen et al., 2002). For example, after febrile convulsions, an inhibition of H-channels in the limbic system has minimized hyperexcitability generated by the post inhibitory rebound firing in principal cells (Chen et al., 2001). Experiments have also showed that certain manipulations could either increase e.g. febrile convulsions or decrease e.g. diabetic neuropathy neuronal activity of H-channels and that the recurrent burst firing has been stopped by changing the activity of these channels (Soltesz et al., 1991).

Therefore, it is possible that decreasing H-channels activity in epileptic cortical structures may lead to antiepileptic activity making the inhibitors of these channels potential future AEDs.

1.2.6.2. Future concepts of AEDs

A clear distinction should be made between anti-epileptogenesis (suppression of progressive development of epilepsy) and anti-convulsion (suppression of seizures). Almost all AEDs used today are anticonvulsants and they attract almost all the attention in laboratory studies and clinical trials. Although some of the anti-convulsant agents (AEDs) have been noted to possess some anti-epileptogenesis activity in selected experimental models (Loscher et al., 1998;Pitkanen, 2002), a limited number of clinical trials has addressed this issue. It seems that anti-epileptogenesis deserves more attention as its role should not be ignored in preventing early development of epilepsy particularly when studies on this issue are encouraging (Silver et al., 1991;Stasheff et al., 1989).

1.2.7. Clinical trials of AEDs

Clinical trials of antiepileptic compounds are essential to assess the efficacy and, perhaps more importantly, the safety of these novel agents before their application in clinical practice in epilepsy patients. For modern AEDs, these are basic requirements for regulatory approval. Some clinical trials are primarily designed to meet the demands of regulatory agencies providing information of little relevance to clinical practice. For instance, to examine the effects of certain newer AEDs, "pseudo-placebo" controlled monotherapy trials are conducted in which the second generation drug is compared to a sub-optimal dose of comparator e.g. a first generation agent. As the comparison of this kind of studies is not clinically relevant, these trials do not provide data suitable for clinical guidance (Perucca and Tomson, 1999;Tomson, 2004). Another disadvantage shared by many clinical trials is their short duration that is not sufficient to examine AED efficacy and tolerability. Much of what we understand about the effectiveness of any given antiepileptic agent is actually gained through clinical experience in the post-marketing period. Instead of being concerned about short term efficacy and adverse effects seen in clinical trials, it is often only at the stage of clinical experience that drug-drug interactions, efficacy to reduce seizure frequency and/or severity and issues of long term safety become apparent (Brodie and Kwan, 2001). For instance, the correlation of felbamate with aplastic anaemia was only evident after administration in the clinical setting.

Therefore, if we are to take advantages of this unprecedented expansion in the pharmacological armamentarium and genuinely seek the most appropriate drug or combination of drugs for any given patient, then comparative long-term efficacy and tolerability studies are essential.

Some of the clinical trials performed on AEDs to investigate their efficacy and tolerability were conducted on first generation AEDs in comparison with either, other first generation agents or using a placebo, while other studies have made comparisons between second generation AEDs and either placebo or first generation AEDs (Kwan and Brodie, 2003). Unfortunately, a very limited number of studies has been performed to compare the efficacy and tolerability of modern AEDs (Brodie et al., 2002). Also, all these comparative studies examined certain specific drugs with little attention to the comparison between generations of AEDs as a whole.

Therefore, there is a need to compare different individual modern AEDs using a long period of follow up on patients with epilepsy with an emphasis on their efficacy against different seizure types and their adverse effects in every day clinical practice. In addition, a comparison between first and second generations AEDs as a whole in terms of efficacy and tolerability is required.

1.2.8. Indications of AEDs

Starting a patient on AED therapy is not an easy step. Such a decision is going to have a significant influence on the patient's life regarding side effects (along with their consequences), compliance (with the risk of relapse in case of poor compliance) and financial impact, bearing in mind that treatment might be life long. Therefore, this decision should be made only by a person qualified in this field and only when a definite diagnosis has been made using proper clinical evaluation and investigations.

Table 10 shows the therapeutic uses in epilepsy of both first and second generation AEDs. Second generation AEDs include more agents with broad spectrum of anticonvulsant activity against almost all seizure types compared to drugs of the first generation. Following the introduction of second generation AEDs, more agents are available for treating epilepsy, which has made the selection of the most appropriate agent for a particular patient with a particular seizure type by clinicians a more complicated issue.

1.2.9. Side effects of AEDs

Adverse drug reaction to any therapeutic intervention for any disease including epilepsy has been defined by the WHO (World Health Organization) as "a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function" (Edwards and Aronson, 2000;World Health Organization, 1972).

Epilepsy patients on treatment with AEDs are subject to side effects that can be considered as either biological or cognitive (behavioral). Biological side effects such as rash or hair loss can be detected by physical examination or using laboratory tests. They are divided into two types, acute and chronic organ effects. Acute reactions as in idiosyncratic reactions which are not predicted e.g. hepatitis, or chronic organ effects that take place as a result of cumulative toxicity e.g. gingival hyperplasia. Felbamate has been identified as the reason for fatal cases of aplastic anaemia and liver failure; this has restricted its use to a drug of last choice for refractory epilepsy (Pellock and Brodie, 1997). On the other hand, cognitive (behavioral) side effects such as depression and aggressiveness may not usually be evident to physicians on examination but reported by patients or families (Camfield and Camfield, 1994) (Table 11). Neurotoxic side effects (e.g. nausea, diplopia, dizziness, headache, fatigue, tiredness, ataxia) are considered as some of the common dose-related side effects (Brodie, 2001).

AED	Partial seizures	GTC seizures	Absence seizures	Myoclonic seizures	Infantile spasms
First generation					
Phenobarbital	+	+	-	-	-
Phenytoin	+	+	-	-	-
Ethosuximide	-	-	+	-	-
Carbamazepine	+	+	-	-	-
Sodium valproate	+	+	+	+	-
Benzodiazepines	+	+	+	+	-
Second generation					
Vigabatrin	+	+	-	-	+
Lamotrigine	+	+	+	(+/-)	-
Gabapentin	+	+	-	-	-
Topiramate	+	+	(+)	(+)	(+)
Tiagabine	+	+	-	-	-
Levetiracetam	+	(+)	(+)	(+)	-
Oxcarbazepine	+	+	-	-	-
Pregabalin	+	-	-	-	-
Zonisamide	+	+	(+)	(+)	(+)

Table 10. Indications for AEDs (arranged in chronological order).
GTC seizures: generalized tonic clonic seizures, +: Evidence of efficacy, (+): Less extensive
base of evidence, ⁻: Evidence of lack of efficacy or worsening; (Perucca, 2001a;Rogawski
and Loscher, 2004).

AED	Side effects
Phenobarbital	Fatigue, tiredness, depression, in children: insomnia, distractability, hyperkinesias, irritability
Phenytoin	Nystagmus, ataxia, acne, gum hypertrophy, coarse facies, hirsutism
Ethosuximide	Nausea
Carbamazepine	Diplopia, dizziness, headache, nausea, rash
Sodium valproate	Tremor, weight gain, hair fall
Benzodiazepines	Fatigue, drowsiness, sedation
Vigabatrin	Dizziness, headache, weight gain, agitation, depression
Lamotrigine	Diplopia, dizziness, headache, nausea, ataxia, tremor, insomnia, rash
Gabapentin	Dizziness, fatigue, somnolence, weight gain, ataxia, tremor
Topiramate	Dizziness, ataxia, fatigue, paraesthesia, somnolence, word finding difficulties, mental slowing, poor concentration
Tiagabine	Dizziness, somnolence, fatigue, headache, tremor, nervousness, impaired concentration, depression
Levetiracetam	Dizziness, fatigue, headache, somnolence, nervousness, depression, agitation
Oxcarbazepine	Fatigue, headache, dizziness, ataxia, sedation, nausea
Pregabalin	Dizziness, somnolence, headache, ataxia
Zonisamide	Fatigue, dizziness, ataxia, somnolence, impaired concentration, mental slowing, nausea, agitation

Table 11. Common side effects of the commonly prescribed AEDs
(Brodie and Dichter, 1997;Perucca, 2001a).

1.2.10. Hypothesis

With evidence to suggest that modern AEDs have multiple cellular effects at therapeutically relevant concentrations and that they are associated with fewer adverse effects, it is my hypothesis that the introduction of these agents has significantly improved the effectiveness of drug treatment in epilepsy, as assessed by long-term outcome. Almost one hundred years after the introduction of phenobarbital we have multiple treatment options for epilepsy and still no indication of how these might best be employed. This project builds on previous investigations at the Epilepsy Unit, Western Infirmary, Glasgow, but focuses specifically on the employment of antiepileptic agents in newly diagnosed epilepsy. I aimed to distinguish outcome on the basis of pharmacology and to assess the clinical impact of modern AEDs in relation to their more established compounds.

1.2.11. Research questions

On completion of data collection of this project, the database was applied to answer the following research questions of interest to the study. Further analyses were performed on the basis of initial results and findings of concern were pursued in detail.

1. To determine the annual outcome of epilepsy according to year of referral to the Epilepsy Unit during the study period.

2. To identify the impact on epilepsy outcome after the introduction of second generation AEDs.

3. To demonstrate the outcome of epilepsy in relation to several demographic (age and gender) , pharmacological and clinical aspects.

4. To investigate and compare the efficacy among: Individual AEDs, older AEDs, modern AEDs, generations of AEDs, gender, age groups, years of referral and epilepsy type.

5. To investigate and compare the tolerability among: Individual AEDs, established AEDs, modern AEDs, generations of AEDs, gender, age groups, years of referral and epilepsy type.

6. To define the term of refractory epilepsy giving the number of treatment regimens applied that need to be failed before a patient can be considered as having refractory epilepsy.

1.2.12. Pharmacogenetics of AEDs

Pharmacological intervention is considered as the main tool for the treatment of epilepsy. The response to AEDs has demonstrated a wide range of variation among these patients. Accordingly, individual variation in the response to these drugs among patients is becoming an important clinical issue. Hartl and Orel (1992) have shown that genetic factors play a major role in the variability of drug response (Hartl and Orel, 1992). The variability in drug response based on genetic basis is known as "pharmacogenetics" (Vogel, 1959). It ranges from resistance to treatment to adverse drug reactions and drug-drug interactions. Therefore, further research on pharmacogenetics can provide an opportunity to tailor drugs selection and dosage based on both clinical and genetic factors (Kruglyak, 1999).

At least 33 chromosome regions have been linked to epilepsy (Prasad et al., 1999). Several syndromes of idiopathic generalised epilepsy have been linked to genetic variation in ion channels. For instance, generalised epilepsy with febrile seizures plus (GEFS+) is linked to a variation in the sodium channel subunit (Ceulemans et al., 2004;Kamiya et al., 2004). Four groups of genes have been identified to play a major role in controlling epilepsy and its AED treatment response.

1. Genes responsible for characterisation of epilepsy subclass.

2. Genes that encode pharmacokinetic related proteins associated with AED efficacy.

3. Genes that are associated with AED toxicity.

4. Genes responsible for ion channel and AED receptors (Spear, 2001).

Therefore, any individual variation among these genes can influence the response to AED treatment (Clancy and Kass, 2003;Holmes, 2002;Ma et al., 2004;Ramachandran and Shorvon, 2003;Spear, 2001).

Pharmacogenetics can play a role in the pharmacodynamics of AEDs. AED targets such as ion channels and receptors might be altered by the changes in their genetic transcription. These changes can lead to variation in drug response or even drug non-responsiveness (Ramachandran and Shorvon, 2003). Sometimes, seizures can induce modifications in AED targets leading to a change in the sensitivity to these drugs (Remy and Beck, 2006).

In terms of the effects of pharmacogenetics on the pharmacokinetic properties of AEDs, a limited number of studies have explored the association between drug transporter protein gene polymorphisms and the response to AED treatment (Hung et al., 2005;Siddiqui et al., 2003;Tan et al., 2004). ABCB1 gene is responsible for encoding the efflux transporter, P-gp. P-gp is used in the transport of several AEDs (Potschka et al., 2002). Over expression of P-gp has been identified in the brain tissues of patients with refractory epilepsy that raised its likely role in the development of intractable seizures (Marchi et al., 2004). Therefore, variability in the expression of P-gp can result in individual variation in AED response.

1.2.13. Pharmaco-resistance to AEDs (refractory epilepsy)

Although, the majority of patients with epilepsy end up having well-controlled seizures, around 30% of epilepsy patients do not achieve remission despite using several options of AED/s combinations (Cockerell et al., 1995;Kwan and Brodie, 2000a). This leads to negative physical, psychological and social consequences in this group of patients associated with increased drug load and sudden unexpected death (Kwan and Brodie, 2002). In the presence of treatment options other than pharmacotherapy, particularly epilepsy surgery, there is no doubt that early identification of patients with refractory epilepsy will be accompanied by considerable saving of time, effort and economic costs through offering this alternative option to suitable patients. Certain epilepsy syndromes are known to have a low response rate to medical treatment but can be cured through surgical intervention (Engel and Shewmon, 1993). One of these is mesial temporal lobe epilepsy in which surgical treatment can offer a 70 – 80% chance of a cure (Wieser et al., 1993). According to a US study that investigated the total life time treatment cost in patients with epilepsy, this was $4272 US for a patient in remission while the treatment cost in a patient with refractory epilepsy was $138,602 US (Begley et al., 1994). Refractory epilepsy can be considered as the main reason for the continued search for new AEDs (Jallon, 1997b).

Obviously, not all patients with persistant seizures despite AED treatment can be labeled as having refractory epilepsy. In some cases, the epilepsy appears to be uncontrolled because it has not been adequately treated leading to a "pseudo-resistance" or false resistance to treatment (Perucca, 1998). Pseudo-resistance to AED treatment can be due to: poor compliance of the patients, inappropriate drug selection for a particular seizure type, inadequate dosage of drugs, inappropriate life style (e.g. high alcohol intake, sleep deprivation and exposure to excessive stress) and inappropriate assessment of response e.g. development of pseudoseizures (psychogenic seizures) as a substitute for epileptic seizures and being treated without effect with the eventual misdiagnosis of pharmacoresistant epilepsy.

As a self-explanatory term "pharmacoresistant epilepsy" might be defined as the persistence of seizures despite using the most appropriate AEDs and reaching the maximally tolerated doses of these drugs. Although, it seems a straight forward definition, it is associated with multiple uncertainties such as: individual differences, the tolerated dose for each drug adjusted for each patient, the number of drugs that needs to be prescribed before a patient can be considered as resistant to treatment and whether they should be on monotherapy or combined therapy.

Despite the usefulness of such a definition, we lack a consensus of how this concept can be applied in both daily clinical practice and in the research field (French, 2006). This is evident since "refractory epilepsy" or "pharmacoresistant epilepsy" has been given a variety of definitions by different investigators based on several factors e.g. seizure frequency, seizure severity, drug concentration and life style. Table 12 shows some of these definitions. In addition, other investigators have developed scoring systems to distribute patients in groups based on the presence of certain criteria. For instance, Perucca (1997) has graded patients with pharmacoresistant epilepsy into three grades taking into account the number of drugs that failed at maximally tolerated dosage and the probability of achieving seizure freedom consequently at each grade (Perucca, 1997). Instead of three grades, Schmidt (1986) has applied six grades for these patients in which the first four grades were related to pseudoresistant epilepsy while the fifth and sixth grades were linked to the number of drugs that failed (Schmidt, 1986). Alving (1995) added a seventh grade that represented the failure to achieve remission using AED combinations, an aspect that was not addressed in the previous two scoring systems (Alving, 1995).

Absence of a uniform definition of refractory epilepsy leads to significant differences in the outcome of clinical studies recruiting this group of patients because they would represent a mixture of underlying definitions of pharmacoresistant epilepsy (e.g. seizure type, severity and number of regimens applied). Such differences in outcome can even be observed in studies using the same AED e.g. a difference in responder rates to lamotrigine from 13% to 67% in two double blind add-on studies using comparable doses (Fitton and Goa, 1995;Goa et al., 1993). It will also lead to inaccurate selection of patients to be considered suitable candidates for surgery.

Reference	Definition
(Leppik, 1992)	Occurrence of seizures with an anti-convulsant drug concentration of at least 1 standard medication, the usually effective range at the time of the seizures.
(Schachter, 1993)	Inability to live a life-style consistent with personal capabilities because of seizures, adverse effects of anticonvulsants and/or psychosocial problems.
(Wolf, 1994)	Persistence of seizures even at the highest dosage of anti-convulsant drug tolerated without unacceptable adverse effects.
(Berg et al., 1996)	Uncontrolled seizures with an average frequency of at least 1 per month for at least 2 years despite trials of at least 3 anticonvulsants.

Table 12. Some definitions of pharmacoresistant epilepsy proposed by various investigators.

Once a unified definition of pharmacoresistant epilepsy has been achieved, it will be beneficial for people of various professions. These include: clinicians providing medical care for epilepsy patients, researchers interested in conducting clinical trials of AEDs and

comparing their results, epilepsy patients themselves and their caretakers, health administrators, legislators, insurers, educators, lawyers and employers.

Based on this essential need, a definition of drug resistant epilepsy has recently been proposed as "failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" (Kwan et al., 2009).

Intractability of seizures might be predicted by the presence of a number of factors. The predictors might be broadly divided into three groups; disease related, genetic and drug related factors. Disease related factors include early onset of seizures (Camfield et al., 1993;Casetta et al., 1999), the long duration between first seizure and onset of treatment, high frequency of seizures before starting treatment (Arts et al., 1999;Beghi and Tognoni, 1988), type of seizures and epilepsy syndrome (Aikia et al., 1999;Mattson et al., 1996), persistence of seizures despite continuing proper treatment, occurrence of status epilepticus, the number of frequently failed drugs at appropriate doses, family history of epilepsy (Berg et al., 2001;Elwes et al., 1984), presence and severity of brain damage and the presence of certain structural lesions in the brain such as cortical dysplasia and hippocampal sclerosis(Brorson and Wranne, 1987;Hauser et al., 1996). The relation between intractable seizures and some of these factors is still a controversial issue (Regesta and Tanganelli, 1999). The initial response to AED treatment can also be an important factor for predicting drug resistant epilepsy (Camfield and Camfield, 1996;Dlugos et al., 2001;Kwan and Brodie, 2000a) and patients with failure of two consecutive AED treatment regimens are unlikely to develop seizure freedom afterwards.

Regarding genetic predictors, two hypotheses have been proposed. One of the possible mechanisms underlying refractory epilepsy is the multi-drug transporter hypothesis. There are certain substances (transporters) present in the endothelial cells of the blood brain barrier; these play a major role in the outward efflux of many molecules including drugs which is considered as a defense mechanism to prevent drug accumulation within the brain. Consequently, these transporters lead to the regulation of the pharmacological behavior of many drugs through affecting their absorption, distribution and elimination. They are also involved in "multidrug resistance" (MDR) development that represents the failure of treatments in several diseases such as tumours, infections and epilepsy because of their role in limiting the ability of drugs to reach target tissues and expediting the elimination of these treatments (Loscher and Potschka, 2002). P-glycoprotein (PGP) is one

of these transporters; it is the encoded product of the human multi-drug resistance -1 (MDR-1) gene or ABCB1 gene. PGP is of particular importance due to the wide range of substrates it can act on including many drugs (Fromm, 2004).

There is accumulating evidence correlating the multi-drug transporter hypothesis to refractoriness of epilepsy, as first proposed by Tishler and colleagues (1995) who reported an over-expression of MDR-1 encoding the multidrug transporter PGP in humans in the majority of patients with drug resistant epilepsy when studying their brain tissues (Tishler et al., 1995).

Another hypothesis that has been raised as a possible mechanism contributing to drug resistant epilepsy is the drug target hypothesis in which certain changes are assumed to take place in one of the targets of AEDs such as ion channels, neurotransmitter receptors, transporters and enzymes involved in drug pharmacokinetics. Several studies have confirmed either loss or complete absence of anticonvulsant activity exerted by AEDs on certain drug targets in patients with refractory epilepsy. For, instance, Vreugdenhil and Wadman (1999) have reported a reduction by half of the carbamazepine response of sodium channels of CA1 neurons isolated from the epileptic focus of fully kindled rats compared with control rats (Vreugdenhil and Wadman, 1999). There are two points that need to be considered in this hypothesis, the limited ability to demonstrate it clinically in humans because patients responding to treatment do not generally undergo surgery making it difficult to obtain tissue samples. Also, since patients with refractory epilepsy do not respond to a wide range of AEDs acting through various mechanisms makes the drug target hypothesis of limited value to contribute to refractory epilepsy as it is usually based on one AED rather than multiple drugs.

In terms of drug related factors that might contribute to refractory epilepsy, development of tolerance to the antiepileptic activity of drugs is an important issue. In such situations, the anticonvulsant effect of AEDs will decrease following prolonged use (Bogg et al., 2000). The same pattern is observed with side effects of AEDs in which their severity has been shown to reduce after prolonged exposure to AEDs (Frey et al., 1986). Other factors are the ineffectiveness of the current mechanisms of antiepileptic action of the available AEDs to treat intractable seizures. In addition, several types of epilepsy such as temporal lobe epilepsy lead to physiological and morphological changes in the neural circuits of brain regions e.g. the hippocampus (Elger, 2003), lowering the sensitivity to AEDs as seen in

mesial temporal lobe epilepsy (the most common type of epilepsy treated surgically) in which the rate of treatment failure reaches 75% (Spencer, 2002).

Patients with pharmacoresistant epilepsy can be grouped into three patterns based on the timing of developing the intractable seizures. It might present initially (de novo) in some patients even before starting their AED treatment as evident in their poor response to the first AED prescribed; this group represents most patients with pharmacoresistant epilepsy as only few patients who fail on their first AED treatment will develop remission eventually (Kwan and Brodie, 2000a). In other cases, refractory epilepsy might develop later, a condition that might be due to progression of the disease or certain accompanying changes within the brain. A third group of patients with refractory epilepsy might show a fluctuating pattern of response to AED treatment ranging between periods of frequent seizures and intervals of complete seizure control.

In an attempt to correlate the patterns of drug resistant epilepsy discussed earlier in this section with the current understanding of mechanisms contributing to this refractoriness, the multi-drug transporter and drug-target hypotheses might be applied to explain at least partially, two patterns. The first pattern i.e. initial (de novo) AED resistance can be assumed to be either intrinsic or acquired. Acquired initial resistance, even before starting treatment and based on results from animal studies might be explained as frequent seizures before starting treatment that lead to over-expression or upregulation of multi-drug transporters and drug-target alterations in epileptogenic brain tissues, which consequently results in AED resistance. High seizure frequency before commencing treatment is one of the factors associated with intractability (Sillanpaa, 1993). In other cases, alterations of multi-drug transporters of drug-targets might be of an intrinsic nature due to genetic polymorphisms which will also leads to de novo AEDs resistance eventually.

The second pattern of AED resistance (i.e. recurrence of seizures after initial remission) occurs despite AED treatment and is due to alterations in drug-targets in the brain associated with progression of epilepsy, as has been shown by certain investigations (sensitive imaging techniques and histological examination) that recurrent seizures and a long duration of epilepsy are associated with changes in the brain such as volume reduction and neuronal loss in the hippocampus (Liu et al., 2001;Mathern et al., 2002). Recurrence of seizures will be followed by over-expression of multi-drug transporters leading to AED resistance.

Chapter 2: Methods

2.1. Study population

This is a large-scale retrospective observational study involving patients with newly diagnosed epilepsy. Patients were first diagnosed and commenced treatment with antiepileptic drugs (AEDs) at the Epilepsy Unit of the Western Infirmary Hospital, Glasgow, Scotland. They were seen between the period from July 1982 to December 2005. As the Unit is not only a tertiary referral service, patients are referred to the Unit either by general practitioners or accident and emergency department physicians.

It is essential for patients enrolled in this study to be diagnosed with epilepsy at the epilepsy unit by qualified doctors not by general practitioners or accidents and emergency physicians. This is due to:

- Epilepsy can be easily misdiagnosed as the differential diagnosis of seizures includes several conditions (Table 3).

- To ensure the correct diagnosis of epilepsy, it is advisable to allow a period of observation for further events instead of introducing treatment immediately after the first seizure.

- Patients with provoked seizures and those with widely separated seizures are not usually prescribed treatment, as avoidance of the precipitating factors can be sufficient.

- To create patient awareness regarding the implications and consequences of this diagnosis e.g. driving, employment and life style.

- Accepting the need for treatment obtained from qualified professional epilepsy staff is likely to maximise the compliance of patients with AED therapy.

- The choice of AED to be prescribed to these patients depends on several factors such as seizure type, number of seizures and the tolerability profile of that particular AED.

- Common side effects of AED treatment along with the risk of teratogenesis in females with childbearing age and advice on contraception should be provided to the patients.

Also, patients recruited should be started on their first ever AED treatment at the epilepsy unit. This is because epilepsy clinics accept both newly diagnosed patients and those with refractory epilepsy in which seizure freedom rate is usually low. Consequently, performing studies in populations including refractory epilepsy will yield results which do not reflect accurately findings in the general population. Therefore, using newly diagnosed epilepsy patients with their AED treatment first started at the Epilepsy Unit will be associated with more accurate findings and more reliable assessment of AEDs treatment.

2.2. Managing patients at the epilepsy unit

The Epilepsy Unit of the Western Infirmary Hospital, Glasgow provides clinical services for patients with established and suspected seizure disorders, conducts research related to aetiology and pharmacological intervention of epilepsy and trains a range of health professionals.

The outpatient service operates on Tuesday and Wednesday from 1.30 PM to 4.30 PM every week. The Tuesday clinic is confined to patients who have already embarked on their AED treatment, while the Wednesday clinic usually deals with patients following their first seizure, those with untreated epilepsy and those with whom the diagnosis of epilepsy has not yet been confirmed. It is managed by two epilepsy nurse specialists and at least two qualified doctors specialising in epilepsy. Also many patients are reviewed throughout the week in the Epilepsy Unit in particular urgent referrals of treated and untreated epilepsy. Usually, patients suspected of having epilepsy are referred to the first seizure clinic by general practitioners or accidents and emergency physicians.

In the clinic, a detailed history is obtained from the patient and witnesses. This includes demographic data, risk factors of epilepsy, medical conditions, regular medications and a detailed description and frequency of episodes that have already occurred.

This is followed by investigations i.e. electroencephalography (EEG) and brain imaging i.e. computed tomography (CT) scan and magnetic resonance imaging (MRI) that are carried out as clinically indicated in order to confirm the diagnosis of epilepsy and to help

in identifying the seizure type which will subsequently aid in the selection of AED appropriate for that specific seizure type. Some of these investigations are used to determine the presence of any brain lesion that could be the focus of seizures with the possibility of subsequent surgical intervention.

Once the diagnosis of epilepsy has been confirmed, treatment of these patients with the most appropriate AEDs commences.

2.3. Treatment schedules

Patients in whom the diagnosis of epilepsy has been confirmed start their first ever AED. The first treatment regimen is usually monotherapy. Subsequent appointments are arranged to follow up patients regarding their response to treatment. Treatment schedules are modified in the following circumstances:

- Persistence of seizures despite reaching the maximum tolerated dose and good patient compliance.

- Development of intolerable side effects.

- Risk of teratogenic effects in female patients of childbearing potential.

- Risk of toxicity identified by high serum anticonvulsant concentration.

Modification of treatment schedules is either by dosage adjustments, substitution of the current AED or offering combined therapy. These steps are followed until the final goal of complete seizure control is achieved. When poor compliance with epilepsy treatment is suspected, it can be assessed either by direct questioning and/or measurement of serum drug concentration in the blood (for certain AEDs). Measurement of serum anticonvulsant concentration can also be used as a guide to dosage adjustments and drug toxicity.

Carbamazepine and sodium valproate are prescribed either in the regular release form or a sustained release form that is usually associated with a lower risk of side effects and prolonged serum concentration. Sustained release forms are usually selected to minimise the frequency of drug administration and lower the risk of side effects with subsequent improvement in patient compliance. In this study, both regular release and sustained

release forms are considered as the original regular form since this project is mainly concerned with the pharmacodynamics of AEDs (the mechanisms by which these agents act) rather than their pharmacokinetics properties (the ways by which body systems handle the drug).

2.4. Filing system at the epilepsy unit

The patients' folders are kept in the epilepsy research unit in appropriate cabinets; these folders are arranged in chronological order starting from 1982, the year at which the Epilepsy Unit was established. Folders of deceased patients are kept in two separate cabinets. Access to folders of the Epilepsy Research Unit is only allowed to authorised unit staff. The patients' folders usually contain demographic data, details of each visit to the epilepsy clinic along with investigations carried out and details of treatment regimens.

Prior to each clinic, folders of appointed patients are collected from cabinets and transferred to the epilepsy clinic in the out patient department. After the clinic, these folders are taken back to the epilepsy research unit where all details and consultations between doctor and patient during the visit are typed by the administrative staff on a letter to the referring physician; eventually the letter is filed in the folder which is stored in the appropriate cabinet.

2.5. Data collection

Based on the inclusion criteria of this project, patients were identified, their case records were obtained and the required patient information extracted by detailed review of the case notes and recorded on a prepared worksheet using software Microsoft® Access 2000 (9.0.3821 SR-1).

As data collection for this study required a long time to be collated, there was a long interval between the data collection for the first patient in the study and that of the last patient. During this interval, changes in treatment details of patients could have taken place and even inclusion criteria could have changed. Therefore, to ensure the accuracy of data obtained, a second patient review was performed to pick up any such changes.

Ethical approval of such type of study was not required beside the measures taken to keep data collected as confidential as possible e.g. limited access to authorized staff and deleting

patients names from the database. In addition, data obtained from patients' records were recorded and stored in adherence with the Data Protection Act 1998.

Patient data were recorded according to the following categories:

- Demographic data: name, folder number, gender, date of birth, intellectual status, date of referral and date of last clinic visit.

- Clinical history: family history of epilepsy, birth injury, febrile seizures, other medical conditions, alcohol abuse, drug abuse and any neurological deficit with the cause.

- Investigations: findings from EEG, brain CT scan, brain MRI, any other imaging procedures and also the results of serum anticonvulsant concentrations obtained.

- Seizure details: seizure type, epilepsy type, syndrome (if known), date of first ever seizure and whether patient was seen after first seizure by medical staff.

- Treatment details (including each AED/ AED combination): starting date of treatment, starting dose, serum concentration on starting dose (if available), maximum dose, serum concentration on maximum dose (if available), side effects, maximum tolerated dose, response on maximum tolerated dose and any comments on that particular treatment regimen.

- Outcome: analysis of the outcome of epilepsy by the end of 2 years, 5 years, 10 years and 15 years of patient follow up. Each section includes: number of treatment regimens applied, current type of treatment (monotherapy or combined therapy), current AED/s, seizure status and any comments till that point of follow up.

There were two types of outcomes of epilepsy in this study. These were ultimate and partial outcomes. The ultimate outcome of epilepsy represents the final response on the maximum tolerated dose of the last AED/ AED combination prescribed to each patient in this study on the last follow up appointment. The ultimate outcome of epilepsy is categorised into three groups:

1. Patients in remission: these are the patients who had a seizure free period for at least the last 12 months of follow up (duration of remission recorded).

2. Relapsed patients: these are the patients who experienced ongoing uncontrolled seizures after at least a 12 months period of initial control. A seizure following a missed dose of treatment after a year of seizure freedom period was not considered as a relapse if control was established again.

3. Patients with refractory epilepsy: these represent the patients who have never been seizure free. Patients who developed complete seizure control following surgery were considered as refractory because this study is mainly targeted at outcome due to pharmacological intervention. By the time of database lock, every patient who had less than 12 months seizure freedom period was also considered as refractory since they had a period of treatment within the Unit of at least 12 months.

Partial outcome of epilepsy constitutes the response to each AED/ AED combination given to the patients using the maximum tolerated dose on the last follow up appointment on that particular agent (s).

Dynamic data as in this study requires a cut-off point to define the end of follow up of patients. All the information included in the database up to that point was analysed regardless of any future changes in these data sets after the end of data collection. It was decided to end following up the study population (lock database) on the first of April 2008; the last patient followed up at the last day of data collection (31st of March 2008) had a minimum period of 27 months (2 years and 3 months) of follow up.

Following up the patients for the purpose of this study started from the visit at which AED treatment was commenced. AED/AED combination and dose modifications prescribed on the last visit of a patient to the Unit were not included in the study due to the difficulty of assessing the efficacy and tolerability of these agents after the end of patient follow up.

Microsoft® Word 2000 (9.0.3821 SR-1) was applied for writing up this thesis and Microsoft® Excel 2000 (9.0.3821 SR-1) for constructing various figures and curves.

2.6. Seizure classification

Classification of seizure types and epilepsy syndromes was performed using guidelines of the International League Against Epilepsy ILAE (Commission, 1981; Commission, 1989). In this study, epilepsy will be broadly classified into two groups based on seizures types:

Focal (localisation related) epilepsy: this group is characterised by the presence of partial seizures (either simple or complex) with or without secondary generalisation. It can be further subdivided into:

- Symptomatic epilepsy in which there is an underlying pathology in the brain (evident by brain imaging techniques) that contributes to the development of seizures e.g. infections, tumours, cerebrovascular disease (cerebral infarction or cerebral hemorrhage), mesial temporal sclerosis and cortical dysplasia.

- Cryptogenic epilepsy in which it is assumed that there is an underlying brain lesion but it is unidentified.

Idiopathic generalised epilepsy: this group includes several subtypes such as primary generalised tonic clonic seizures, myoclonic jerks and absence seizures and syndromes e.g. benign neonatal familial convulsions, juvenile absence epilepsy and juvenile myoclonic epilepsy. Idiopathic epilepsy is presumed to posses a genetic origin.

2.7. Analysis of database

In order for the database to be able to answer the research questions of this study, the following calculations had to be performed:

2.7.1. Outcome of epilepsy

This section investigates the ultimate outcome of epilepsy in relation to several demographic, clinical and pharmacological aspects. As mentioned earlier in the section of data collection, the ultimate outcome of epilepsy represents the final response on the maximum tolerated dose of the last AED/ AED combination on the last follow up appointment. It is classified into three groups that include remission, refractory and relapsed.   Patients who relapsed and those who continued to have seizures despite

treatment were considered as non-responders, while patients with remission represented the responder group. The aspects investigated in relation to outcome of epilepsy were:

- Outcome by year of referral

- Outcome by age groups

- Outcome by gender

- Outcome by type of treatment regimen (monotherapy or combined therapy)

- Outcome by type of epilepsy

- Outcome by mechanism of action

- Outcome by generations of AED

For some of those aspects, the ultimate outcome of epilepsy was calculated based on the last treatment schedule e.g. outcome by mechanism of action of the last AED prescribed. In contrast, other aspects were analyzed in relation to the ultimate outcome of epilepsy using the first treatment regimen e.g. outcome by age groups.

2.7.2. Effectiveness of AEDs

Two parameters were considered, the efficacy and tolerability of AEDs. Both were also analysed in relation to several demographic, clinical and pharmacological aspects in order to investigate any significant influence of any of these aspects on the effectiveness of AEDs and consequently the ultimate outcome of epilepsy.

2.7.2.1. Efficacy of AEDs

Efficacy of AEDs in this project was measured based on the percentage of patients achieving seizure freedom for a minimum period of 12 months at last recorded follow up. It was calculated using the parameter "Response on maximum tolerated dose of that particular regimen" available in the therapy section of the database. This parameter was categorised as follows: seizure freedom (of at least 12 months on that particular AED/AED combination), ongoing seizures, discontinued due to side effects, relapsed (after a period of

at least 12 months of seizure freedom). Efficacy of each AED/AED combination represents the rate of patients who achieved seizure freedom among the total number of patients on that particular agent(s). Efficacy was calculated with regard to the following aspects:

- Efficacy among individual AEDs

- Efficacy among generations of AEDs

- Efficacy among gender

- Efficacy among combinations of AEDs

- Efficacy among epilepsy type

- Efficacy among age groups

2.7.2.2. Tolerability of AEDs

To demonstrate the tolerability of AEDs applied in this study, withdrawal due to side effects was employed as an indicator. All side effects attributable to AED/AED combination treatment were recorded in the database including idiosyncratic reactions bearing in mind that only side effects that remain were recorded while those that resolved after some time from starting treatment were ignored. AEDs tolerability was calculated as the rate of patients who discontinued a certain AED/ AED combination due to side effects among the total number of patients on that particular agent/ combination. The high percentage of withdrawal due to side effects among patients on a particular AED indicated a low tolerability profile for that agent and vice versa. Tolerability was calculated in relation to the following factors:

- Tolerability among individual AEDs

- Tolerability among generations of AEDs

- Tolerability among gender

- Tolerability among epilepsy type

- Tolerability among age groups

2.7.3. Potential applications of database

One of the main advantages of Microsoft Access software used for database construction is its ability to analyze the data included to answer questions of interest to this study. Further details on the benefits of this software are discussed in other sections of this chapter. In addition to defining the efficacy and tolerability of AEDs and examining the relationships of outcome of epilepsy with different demographic, pharmacological and clinical issues, this database can be employed for other applications such as:

- Demonstrating the response rate of a particular AED after failure of response to another AED working by the same primary mechanism of action.

- Identifying the response rate of the two generations of AEDs in patients with a particular type of epilepsy (localisation-related or idiopathic generalised).

- Identifying the response rate of different classes of AEDs (grouped according to the primary mechanism of action) in patients with a particular type of epilepsy.

- Defining the frequency of prescription and response rate of a particular AED combination in comparison with another combination.

2.8. Mechanism of action of AEDs

In this study, mechanisms of action of AEDs were analysed in relation to the ultimate outcome of epilepsy and effectiveness of these drugs.

AEDs prescribed were divided into groups based on the mechanism of action. As it is well known that most AEDs tend to have multiple mechanisms of action in order to exert their effects, this project focused on the primary mechanism of action of each drug. Agents with multiple mechanisms of action without an identifiable primary mechanism were included in one group. Those drugs that have never been applied in this study population or were prescribed rarely or those that have been withdrawn from the market for various reasons or unidentified AEDs (as in the case of clinical trials) were not considered in the classification. The main mechanism of action was defined based on the observations of

Kwan and colleagues that ranked all the mechanisms of action of each AED (Kwan et al., 2001).

2.9. Defining refractory epilepsy

Another aspect of this study is to define refractory epilepsy by identification of the number of treatment regimens needed to be deemed unsuccessful after which, the term of "refractory epilepsy" can be applied. Failure of AEDs was considered either due to poor tolerability or lack of efficacy. Initially, calculations were made based on 50% of WHO's defined daily dose of each AED (World Health Organization, 2008). Therefore, below that level, failure would be due to poor tolerability while above which, failure would be due to lack of efficacy. In order to detect any difference that might take place, this study also considered 25% and 75% of the daily defined dose. Table 13 demonstrates the doses of AEDs after manipulation into the three categories (25%, 50% and 75%). Again, patients with rarely prescribed AEDs or those with unidentified agents (in clinical trials) were excluded from this analysis.

Defining refractory epilepsy using the two types of treatment failures i.e. due to lack of efficacy and poor tolerability was performed through comparing the prognosis of epilepsy following each of these types of failures.

The aim of this analysis is to demonstrate the number of patients who might develop a state of seizure freedom after each failure of a treatment regimen due to the lack of efficacy. The lower the number of patients with seizure freedom indicates a more likely chance of having refractory epilepsy. This analysis included the first, second, third and forth treatment regimens. The prognosis of these regimens was demonstrated by comparison of both types of failures i.e. due to lack of efficacy or poor tolerability.

2.10. Statistical analysis

Analysis was undertaken in consultation with Professor John Norrie, Director of Robertson centre for Biostatistics, University of Glasgow. Univariate analysis employed Student's t-test for continuous or numerical data (Mann-Whitney test where data is not normally distributed) and Chi-square test for categorical data. Statistical significance was inferred, after appropriate correction for multiple comparisons, for p-value of less than 0.05. Multivariate analysis was performed under expert supervision.

AED	DDD (WHO)	25 % of DDD	50 % of DDD	75 % of DDD
CARBAMAZEPINE	1 g	250 mg or less	500 mg or less	750 mg or less
SODIUM VALPROATE	1.5 g	375 mg or less	750 mg or less	1125 mg or less
LAMOTRIGINE	0.3 g	75 mg or less	150 mg or less	225 mg or less
PHENYTOIN	0.3 g	75 mg or less	150 mg or less	225 mg or less
OXCARBAZEPINE	1 g	250 mg or less	500 mg or less	750 mg or less
TOPIRAMATE	0.3 g	75 mg or less	150 mg or less	225 mg or less
GABAPENTIN	1.8 g	450 mg or less	900 mg or less	1350 mg or less
LEVETIRACETAM	1.5 g	375 mg or less	750 mg or less	1125 mg or less
PREGABALIN	0.3 g	75 mg or less	150 mg or less	225 mg or less
ZONISAMIDE	0.2 g	50 mg or less	100 mg or less	150 mg or less
VIGABATRIN	2 g	500 mg or less	1 g or less	1500 mg or less
TIAGABINE	30mg	7.5 mg or less	15 mg or less	22.5 mg or less
PHENOBARBITAL	0.1 g	25 mg or less	50 mg or less	75 mg or less
PRIMIDONE	1.25 g	312.5 mg or less	625 mg or less	937.5 mg or less
CLOBAZAM	20 mg	5 mg or less	10 mg or less	15 mg or less
ACETAZOLAMIDE	0.75 g	187.5 mg or less	375 mg or less	562.5 mg or less

Table 13. Recommendations of the WHO for the daily defined dose (DDD) of AEDs along with 25%, 50% and 75% of the doses.

2.11. Limitations

This study includes the following limitations:

- As this study recruited all newly diagnosed patients who were referred to the Epilepsy Unit at the Western Infirmary, Glasgow and who started AED treatment between 1982 and 2005, there was no randomisation of the study population.

- Patients included in the study were prescribed different AEDs to manage a particular seizure type. This is due to the wide range of physicians in the Epilepsy Unit during the long period of study i.e. almost 26 years with different experiences and opinions in the diagnosis and management of this disease, and also due to the different criteria of the patients themselves.

- Using seizure frequency is not a hundred percent reliable as it depends on the patient's memory to record their seizures especially after a long period between clinic appointments that might reach up to 6 months. To make these recordings as accurate as possible, the patients were supplied with seizure description charts to record the number of seizures they develop along with the timing and description of these seizures. Also it is advised that patients bring a witness of the seizure with them to the clinic. Despite all these precautions, they are not successful at all times as the patients may forget to bring these charts at the clinic appointment or there was no witness when the seizure occurred.

- It is not appropriate to compare the annual outcome of epilepsy of seven years of using older AEDs (before the introduction of new AEDs i.e. 1982 - 1988) to that of 19 years (1989-2008) of using both older and modern AEDs since the Epilepsy Unit of Western Infirmary was established in 1982. However, the current project showed to be able to identify any changes that took place in the annual outcome of epilepsy before and after the introduction of second generation AEDs.

- The exclusion of patients with poor compliance in order to make the study as accurate as possible has taken away many patients, which indicates that poor compliance is a characteristic of the normal population and therefore, excluding these patients does not make the study population actually represent the general population.

2.12. Inclusion / exclusion criteria

2.12.1. Inclusion criteria

- Only patients with confirmed diagnosis of epilepsy were included in this project.

- This study included all newly diagnosed epilepsy patients.

- These patients first started treatment with AEDs and were followed up at the Epilepsy Unit of the Western Infirmary, Glasgow.

- Patients included in the study were those who were referred to the epilepsy clinic in the period from the 1st of July 1982 until the 30th December 2005.

- Patients recruited had their treatment started in the Epilepsy Unit within the period from the 1st July 1982 until the 5th April 2006.

2.12.2. Exclusion criteria

- Patients with significant exposure to AEDs (other than rescue medication) prior to referral to the Epilepsy Unit were excluded.

- Newly diagnosed patients who were started on AEDs at the unit before July 1982 or after 5th April 2006 were not included in the study.

- Patients known to be persistently non-compliant with treatment were excluded from the study.

- Exclusion criteria included patients with pseudoseizures and those with dubious diagnosis.

- Patients who were immediate responders on the last treatment regimen (monotherapy or polypharmacy) but the database was locked before completion of the 12 months period of seizure freedom were excluded form the study.

- Deceased patients with a period of treatment less than 12 months.

- Patients who moved to another area during the period of follow up or were referred to another hospital for ease of transport (according to their wishes) were excluded because of the difficulty to assess their response to treatment once they are away if they have not been seen regularly in the clinic especially in case of seizures recurrence.

2.13. Database construction

Databases are created to be useful; they enable us to store, retrieve, analyse and summarise data. Subsequently, results of any query can be obtained and presented. As mentioned earlier, the database applied in this study was built using Microsoft Access software, which employs relational databases in which the data stored are related and can be brought together whenever needed. There are four main components of the Access databases:

1. Tables: these are considered to be the building blocks of databases; they are used to store data and subsequently are employed for extraction of information required to achieve data analysis. Therefore, caution should be taken when constructing these tables in order to ensure ease of data entry and accuracy of data analysis afterwards. All databases either contain one or more tables.

2. Queries: the main benefits of using databases are the capability of answering questions and performing tasks on request, a function of the queries section. Queries can retrieve essential data from multiple tables and analyse them based on the design of a query in order to answer the question raised.

3. Forms: these are used to control data entry and data views. Sometimes, the tables used are large, thereby making it difficult to detect a small piece of information, therefore, using forms will allow the study to focus on what is really needed when entering or viewing data e.g. instead of showing the data obtained from all patients in one table, the forms section of the software can be used to show the required data of each patient individually. Privacy can also be ensured when designing forms by selecting which fields can be viewed by other users.

4. Reports: these are used to summarise and print data of the database.

All the data obtained in this study were distributed into six different tables:

1. "Demography" table: this table was designed to collect demographic data of the patients, clinical history, investigations and relapse details (Table 14).

2. "Outcome" table: in which details were collected regarding the progress of patient treatment after 2, 5, 10 and 15 years of follow up. This information includes: number of treatment regimens applied, current type of treatment (monotherapy or combined therapy), current AED/ AED combination used and seizure status (Table 15).

3. "Therapy" table: this table is concerned with all the details of each AED/ AED combination prescribed. These details include: type of treatment (monotherapy or combined therapy), date of starting treatment, AED/ AED combination applied, starting dose, serum concentration after starting dose, maximum dose, serum concentration after maximum dose, side effects, response on maximum tolerated dose and any comments on that particular treatment regimen. These details were collected in each treatment regimen applied to the patients. The maximum number of regimens applied in this study was nine (Table 16).

4. "Last regimen" table: that includes details on the last AED/ AED combination applied to the whole study population along with the generation to which they belong and the ultimate outcome of epilepsy (Table 17).

5. "Daily defined doses" table: this table contains all the required information on the doses of AEDs applied by all the recruited patients in all treatment regimens. In those patients with ongoing seizures, failure of treatment was categorised into either, a lack of efficacy or poor tolerability. These calculations were performed at 25%, 50% and 75% of the daily defined doses based of the WHO recommendations (Table 18).

6. "Length to seizure freedom" table: this table in only concerned with patients who achieved complete seizure control as an ultimate outcome of epilepsy by the end of study. It includes details on the duration (in months) required by this group of patients to reach seizure freedom. These include: date of starting treatment, date of starting seizure freedom, the period (in months) required to reach seizure freedom, date of last visit, the period (in months) between starting seizure freedom and last

clinic visit and responder classification (immediate or delayed responders) (Table 19).

Demographic data	Name
	File number
	Date of birth
	Gender
	Intellectual status
	Referral date
	Date of last visit

History	Alcohol abuse
	Drug abuse
	Birth injury
	Family history of epilepsy
	Febrile seizures
	Other medical problems
	Neurological deficit & cause

Investigations	Electroencephalography (EEG)
	Magnetic resonance imaging (MRI)
	Brain computed tomography (Brain CT scan)
	Other Imaging

Seizure details	Date of first seizure
	Epilepsy classification
	Epilepsy syndrome
	Seizure type
	Multiple seizure types
	Seizure free period
	Date of starting reseizure (if relapsed)
	Action before relapse
	Action after relapse
	Remission again?

Table 14. Data collected in the "demography table" of the database.

General information		Unit number
		Referral date
		Date of starting treatment
		Date of last visit
		Months required to reach first seizure freedom period
		Months required to reach second seizure freedom period
		Months required to reach third seizure freedom period
		Months required to reach forth seizure freedom period
		Months required to reach fifth seizure freedom period
Outcome	Outcome at 2 years	Number of regimens applied
		Current regimen type (monotherapy or combined therapy)
		AED/ AEDs combination
		Seizure status
	Outcome at 5 years	Number of regimens applied
		Current regimen type (monotherapy or combined therapy)
		AED/ AEDs combination
		Seizure status
	Outcome at 10 years	Number of regimens applied
		Current regimen type (monotherapy or combined therapy)
		AED/ AEDs combination
		Seizure status
	Outcome at 15 years	Number of regimens applied
		Current regimen type (monotherapy or combined therapy)
		AED/ AEDs combination
		Seizure status

Table 15. Data collected in the "outcome table" of the database.

General information	Unit number
	Outcome
	Number of regimens applied
	Type of treatment among all regimens applied (monotherapy or polypharmacy)
Treatment regimen (starting from first until ninth regimen)	Existing AED/ AEDs combination
	New AED/ AEDs combination
	Type of treatment (monotherapy or polypharmacy)
	Date of starting new treatment
	Starting dose
	Serum level (on starting dose)
	Maximum dose
	Serum level (on maximum dose)
	Maximum tolerated dose
	Response on maximum tolerated dose
	Side effects

Table 16. Data collected in the "therapy table" of the database.

General information	Unit number
	Outcome
	Number of regimens
Last treatment regimen details	Last regimen type
	Last regimen AED/s combination
	Generation of last regimen AED/s combination

Table 17. Date collected in the "last regimen table" of the database.

General information	Unit number
	Outcome
Treatment regimen (starting from first until ninth regimen)	AED
	Maximum tolerated dose
	Response on maximum tolerated dose
	Type of treatment failure on 25% of DDD (LOE or PT)
	Type of treatment failure on 25% of DDD (LOE or PT)
	Type of treatment failure on 25% of DDD (LOE or PT)

Table 18. Data collected in the "daily defined doses (%) table" of the database; DDD: daily defined dose, LOE: lack of efficacy, PT: poor tolerability.

General information	Unit number
	Date of birth
	Sex
	Age
	Responders classification
Details on length to seizure freedom	Date of starting treatment
	Date of last visit
	Comments on patients details on last clinic visit
	Period (in months) between starting seizure freedom and last clinic visit
	Date of starting seizure freedom
	Months required until starting seizure freedom

Table 19. Data collected in the "length to seizure freedom table" of the database.

Chapter 3: Results

3.1. General Overview

3.1.1. Demography

Among 1502 patients referred to the Epilepsy Unit during the period from July 1982 till December 2005, 1098 patients (73%) met the inclusion criteria and were recruited in the study. The remaining 404 (27%) were excluded mainly due to either poor compliance (n = 107) or because treatment was started before referral to the unit (n = 95) or there was not enough details in the case records on the treatment given to patients (n = 68). Patients recruited had a minimum period of follow up of two years and 26 years as the maximum (median 8 years, IQR 5 to 12). The ages of study population were between 9 and 93 years old when started their treatment at the Unit (median 32 years, IQR was from 20 to 51). 575 of the study population were males (52 %) and 523 were females (48 %).

3.1.2. AED regimens

Based on the regimens of AEDs taken by the patients of study population, Table 20 and Flow Chart 1 were constructed showing the flow of patients throughout the study from one regimen to the next according to their response to that regimen (percentage outcome on each regimen). In table 20, (n) represents number of patients with ongoing seizures or relapses who went on to treatment with a new regimen after failure of the previous regimen either due to lack of efficacy or poor tolerability, except in the first regimen in which (n) represents the total number of patients recruited in the study. For a number of reasons, some patients who were not controlled on a particular regimen did not proceed to a further treatment option. Therefore, the number of patients who started a new regimen was always lower than those who did not respond to AED/ AED combination treatment on the previous regimen. Table 20 also demonstrates the percentage developing seizure freedom on each particular treatment regimen; patients in their first ever AED treatment had the highest rate of achieving complete seizure control compared to the subsequent schedules. Information on patients on monotherapy and polypharmacy (combined therapy) along with their response in each treatment regimen is shown in the flow chart (Flow Chart 1).

Regimen	n	Responders (%)	Non-responders
First	1098	544 (50%)	554
Second	398	146 (37%)	252
Third	168	41 (24%)	127
Fourth	68	11 (16%)	57
Fifth	32	4 (13%)	28
Sixth	16	2 (13%)	14
Seventh	9	2 (22%)	7
Eighth	3	0	3
Ninth	2	0	2

Table 20. Flow of patients throughout the study regarding treatment regimens applied along with rates of seizure freedom in each regimen.
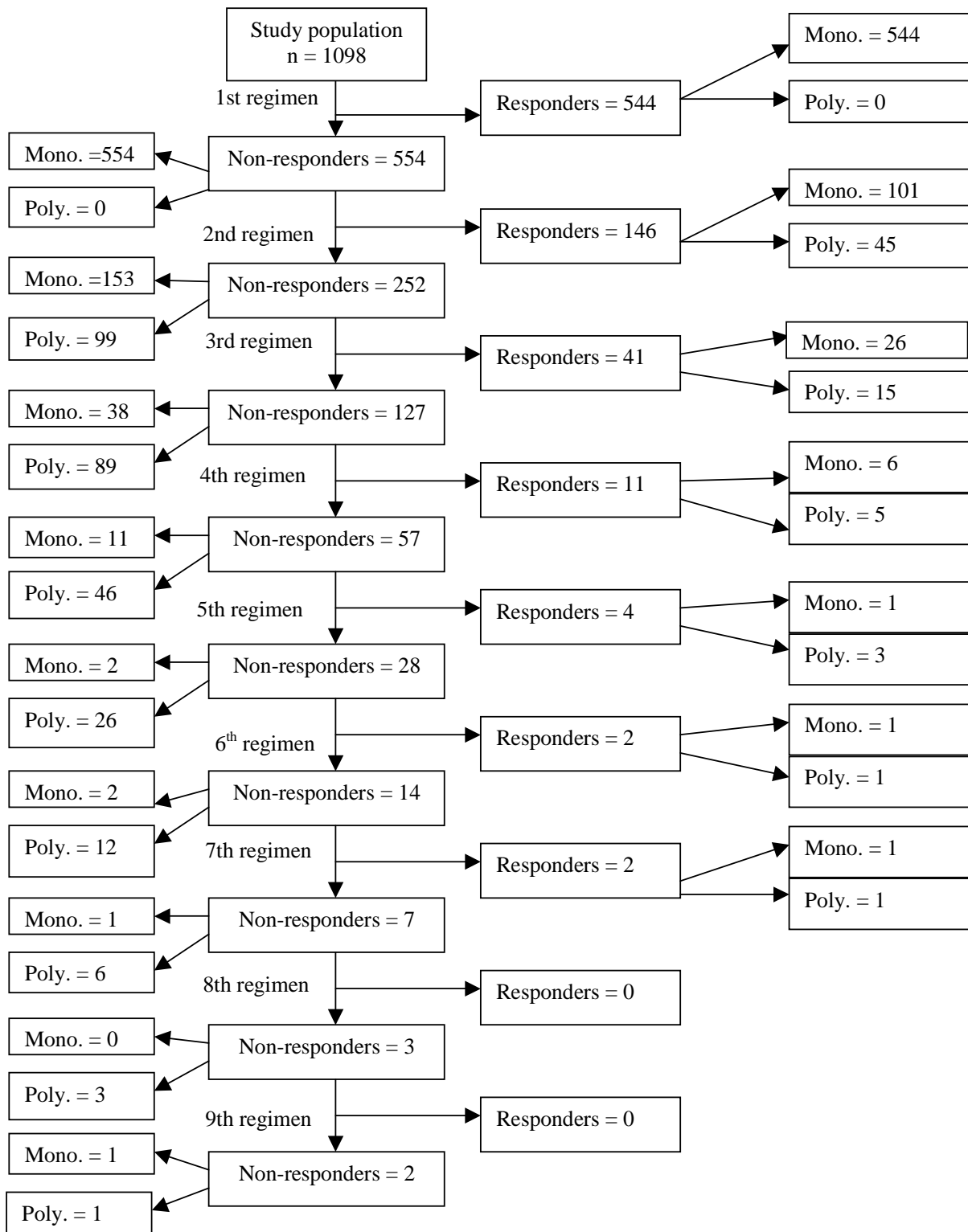
Flow Chart 1. Patients' response to AEDs treatment regimens including monotherapy (mono) and polypharmacy (poly).

The chance to develop complete seizure freedom on the first ever treatment with AEDs was also the highest when I compared the rates of response to AEDs based on outcome of each individual regimen independent of other regimens i.e. those patients who continued with their particular AED treatment regimen until either reaching complete seizure control or continuing seizures that necessitated moving to the subsequent regimen (Table 21 and Figure 2). The highest response in the first regimen was followed by a gradual reduction in response rate with the subsequent treatment regimens.

Regimens	n	Responders (%)	Non-responders
Patients in first regimen only	700	544 (78%)	156
Patients in second regimen only	230	146 (63%)	84
Patients in third regimen only	100	41 (41%)	59
Patients in fourth regimen only	36	11 (31%)	25
Patients in fifth regimen only	16	4 (25%)	12
Patients in sixth regimen only	7	2 (29%)	5
Patients in seventh regimen only	6	2 (33%)	4
Patients in eighth regimen only	1	0	1
Patients in ninth regimen only	2	0	2
Total	**1098**	**750**	**348**

Table 21. Response of patients to each treatment regimen individually.
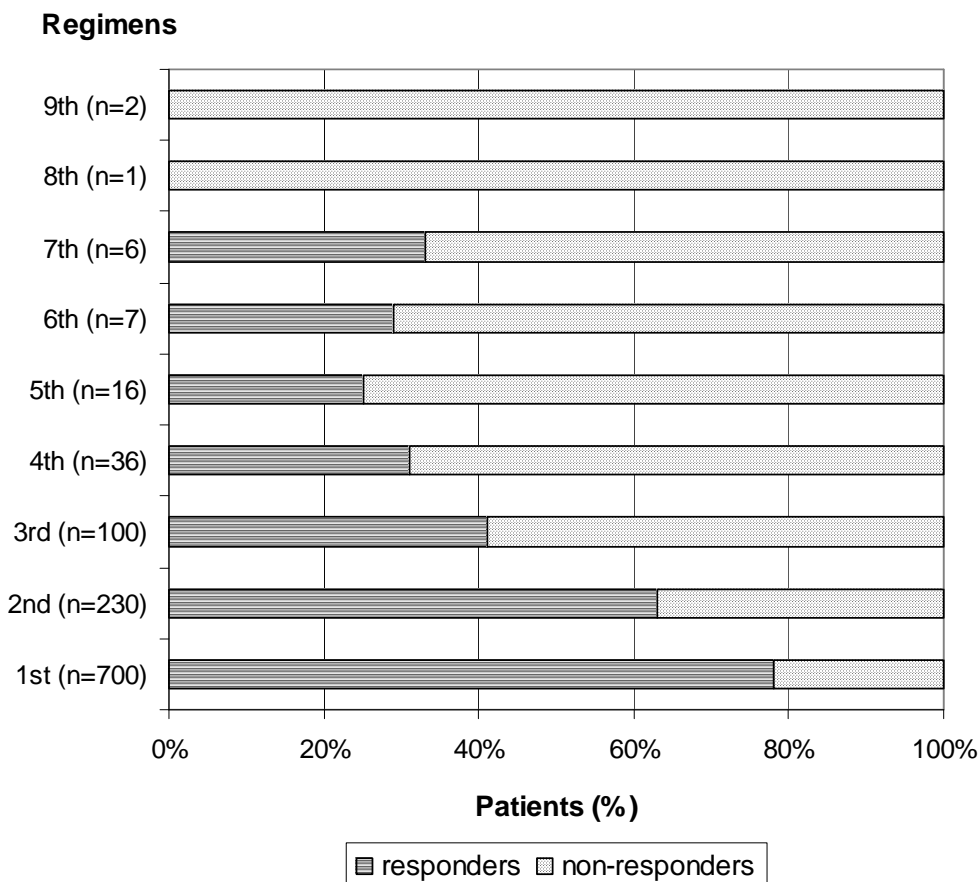
Regimens

Figure 3. Response of patients to each treatment regimen individually.

3.1.3. The first AED

Of the 1098 patients recruited, 544 (50%) reached a state of seizure freedom on the first ever AED applied. In the first ever AED treatment, drugs with the highest prescription rate were lamotrigine (n = 372) followed by sodium valproate (n = 274) and carbamazepine (n = 224) with similar rates of response (53%, 53% and 51%, respectively); there was insignificant difference between these three drugs in terms of efficacy. Among these three agents, side effects leading to withdrawal of treatment were marginally more frequent with carbamazepine (13%) compared to sodium valproate (12%) and lamotrigine (10%), but statistical analysis did not show any significant difference regarding tolerability between these drugs.

	CBZ	VPA	LTG	Others	Total
n	224	274	372	228	1098
Responders on first regimen (%)	115 (51%)	146 (53%)	196 (53%)	87(38%)	544
Withdrawal rate due to side effects on first regimen (%)	29 (13%)	34 (12%)	39 (10%)	55(24%)	157

Table 22. Response to treatment with AEDs in the first regimen.

3.1.4. Patterns of response

Based on the response to AEDs of patients in this study, the analysis demonstrated three different patterns of response.

1. Patients who managed to achieve complete seizure control by the end of study after having continuous ongoing seizures. They constituted 66% of the total study population (728). This group of patients had been prescribed either single AED treatment regimen or tried multiple regimens with either monotherapy or combined therapy until remission was obtained.

2. Patients with intractable (continuing) seizures despite the application of multiple AED regimens as monotherapy or combined therapy. These patients were never able to achieve seizure freedom. They were 272 (25%).

3. Patients with fluctuation of response to AED treatment. Sometimes, they have a period of seizure freedom that might reach up to 12 months or even longer then suddenly develop relapse with reappearance of seizures that last for a period of

time, eventually, they either become seizure free again or continue with seizures. The situation will be different in other patients who have a period of ongoing seizures that might last up to several years despite using multiple treatment regimens and then develop a state of seizure freedom that lasts for at least 12 months period. They either continue seizure free or relapse. In some cases, the patients might have multiple relapses after multiple periods of seizure freedom states. These patients constituted 98 (9%) of the total study population.

3.1.5. Immediate responders

Among patients who responded to the first AED treatment (544), a group developed seizure freedom immediately after starting treatment. This group constituted 24% (261 patients) of the whole study population. As mentioned earlier in section 3.1.3, lamotrigine, sodium valproate and carbamazepine were prescribed more frequently in comparison to other agents (Figure 4). The response rate of these three drugs in the immediate responders showed lamotrigine to be associated with the highest efficacy (33%) followed by sodium valproate (28%) and carbamazepine (22%) with a significant difference noted (p-value = 0.02).

Among immediate responders with idiopathic generalised epilepsy (n = 74), sodium valproate was associated with the highest response rate (41%) followed by lamotrigine (35%) and carbamazepine (9%) (p-value < 0.001). In terms of immediate responders with focal epilepsy (n = 187), lamotrigine had the highest efficacy (32%) followed by carbamazepine (27%) and sodium valproate (22%) without any significant difference (p-value = 0.1). Males had a higher immediate response rate than females on sodium valproate and carbamazepine while females demonstrated a higher response than males which treated with lamotrigine (Table 23).

This group of patients was maintained on relatively moderate doses of AEDs. Ages of these patients were between 10 and 93 years with a median of 32. This group of patients had a median period of follow up 8 years.

	LTG	VPA	CBZ	Others	Total
Immediate responders on first regimen (%)	86 (33%)	72 (28%)	58 (22%)	45	261
Idiopathic	26 (35%)	30 (41%)	7 (9%)	11	74
Focal	60 (32%)	42 (22%)	51 (27%)	34	187
Male / Female	34 / 52	54 / 18	35 / 23	29 / 16	152 / 109
Dosing median (mg/day)	150 (25–200)	1000 (300–1500)	400 (100–1000)	-	-
Median age (range) on starting treatment (years)	32 (10 – 93)				
Median period (range) of follow up (years)	8 (2 – 25)				

Table 23. Characteristics of immediate responders (n = 261).
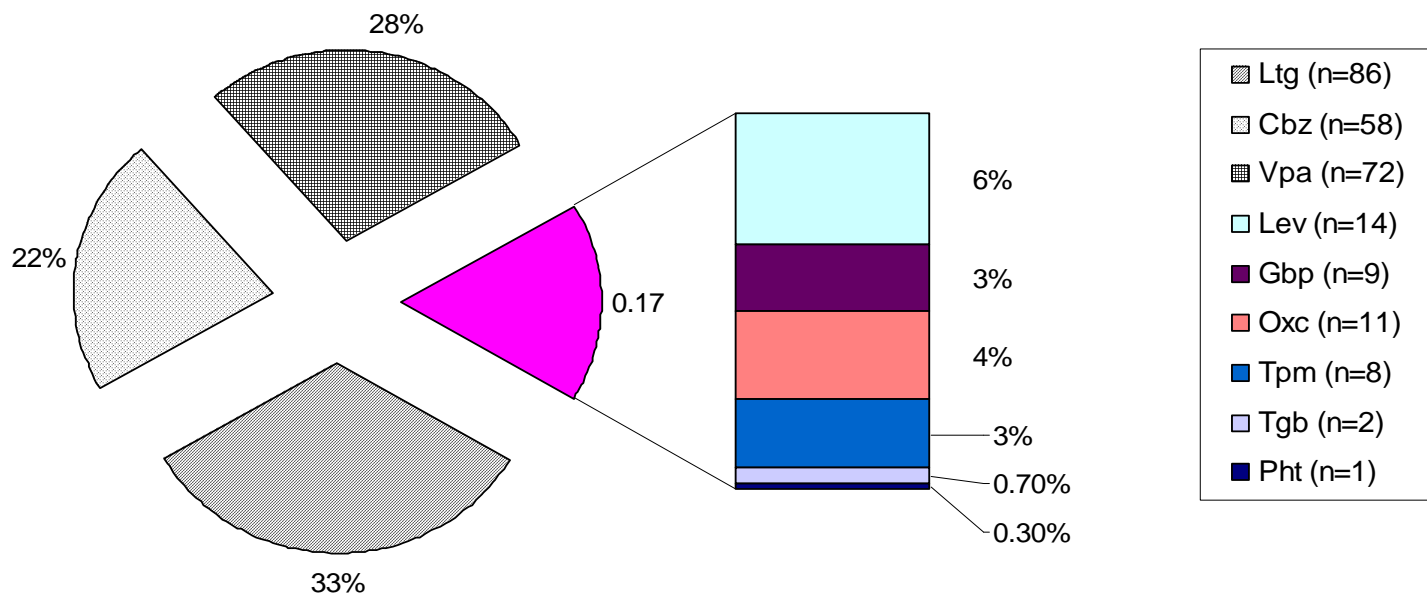
Figure 4. AEDs taken by immediate responders (n = 261).

3.2. Factors with potential to influence the outcome of epilepsy

The number of patients who achieved complete seizure freedom (responders) by the end of study was 750 (68%) while the non-responders (relapsed patients and those with refractory seizures) were 348 (32 %) (Table 24).

	The study population (n= 1098)	Responders (n= 750)	Non-responders (n= 348)
Demographic description			
Male / Female	575 / 523	411 / 339	164 / 184
Median age on starting treatment (years)	32 (range 9 - 93)	32 (range 9 - 93)	33 (range 12 – 81)
Median period of follow up (years)	8 (range 2 – 26)	8 (range 2 - 26)	8 (range 2 - 24)
Epilepsy classification			
Idiopathic	251	182	69
Cryptogenic	400	286	114
Symptomatic	447	282	165
Treatment details			
Median number of regimens	1 (range 1 – 9)	1 (range 1 – 7)	2 (range 1 – 9)
Monotherapy / Polypharmacy	913 / 185	680 / 70	233 / 115

Table 24. Comparison between responder and non-responder patients regarding several aspects.

The outcome of epilepsy was analysed in relation to two categories of factors: pharmacological and non-pharmacological.

3.2.1. Non-pharmacological factors

3.2.1.1. Gender

Among all male patients of the study population (575), 411 (71%) developed complete seizure freedom by the end of study. The figure was lower in females in whom responders to AEDs were 339 (65%) against 184 (35%) non-responders (Figure 5). In terms of statistical analysis, a significant difference was noticed between males and females regarding the outcome of epilepsy (p-value = 0.018).
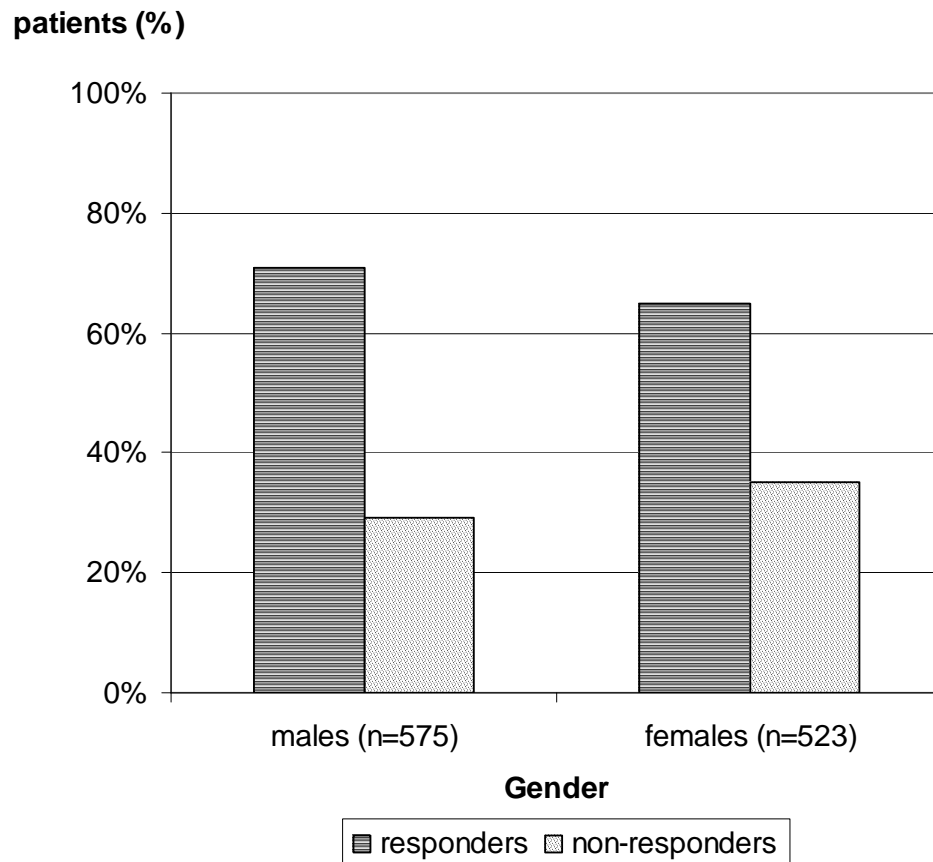
patients (%)

Figure 5. Outcome of epilepsy vs. gender.

3.2.1.2. Age groups

Dividing the study population according to the age of patients on starting treatment with AEDs resulted in eight groups. The response rate to AED treatment was relatively high in patients aged less than 20 years old (72%); this was followed by a gradual decline in response rate until it reaches the minimum in patients with age between 40 and 49 years (52%), after which, the response rate shows a gradual elevation again until it reaches the highest rate in patients with age 80 years or older (96%) (Table 25 and Figure 6).

Age group (years)	N	Responders (%)	Non-responders (%)
< 20	241	173 (72 %)	68 (28 %)
20 – 29	243	169 (70 %)	74 (30 %)
30 – 39	176	112 (64 %)	64 (36 %)
40 – 49	144	75 (52 %)	69 (48 %)
50 – 59	118	77 (65 %)	41 (35 %)
60 – 69	86	63 (73 %)	23 (27 %)
70 – 79	67	59 (88 %)	8 (12 %)
≥ 80	23	22 (96 %)	1 (4 %)
Total	**1098**	**750**	**348**

Table 25. Outcome of epilepsy vs. age groups of patients.
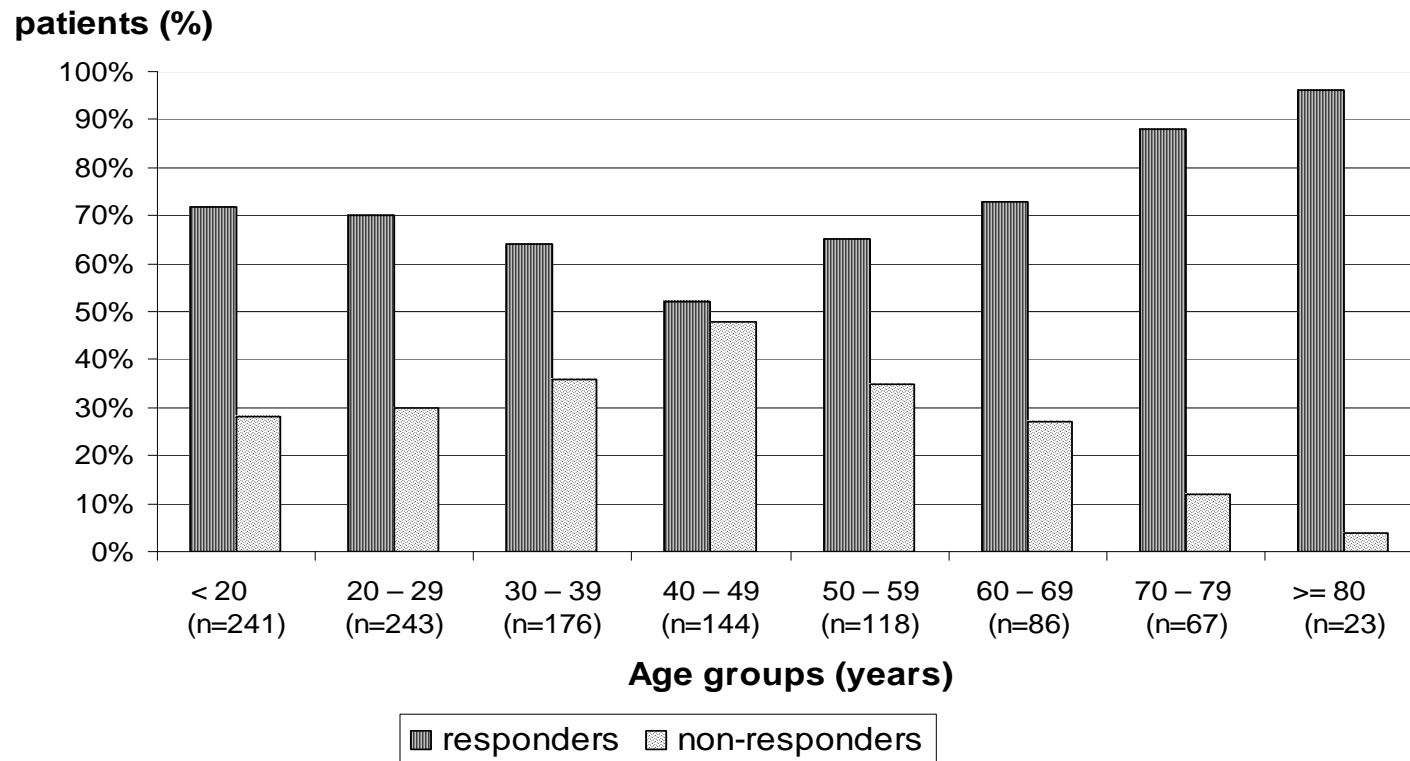
patients (%)

Figure 6. Outcome of epilepsy vs. age groups of patients.

In the group of patients ($\geq$ 65 years old), there were 122 patients aged between 65 and 93 years old. Among these, 106 patients developed complete seizure freedom (87%) by the end of study while 16 did not. Out of the responders (106), 75 patients (61%) achieved seizure freedom state while on the first AED treatment regimen. In terms of epilepsy classification, 118 (97%) of this age group patients had focal epilepsy compared to 4 patients (3%) with idiopathic generalised epilepsy. Responders to monotherapy were 101 (95%) compared to only 5 patients (5%) who developed complete seizure control on combined therapy.

3.2.1.3. Years of referral

By distributing the patients included in this study according to their years of referral to the Epilepsy Unit, 24 groups of patients were developed, representing the period from 1982 until 2005 (Table 26). In general, the number of patients referred to the unit showed a pattern of gradual elevation from 1982 (4 patients) until 2005 (77 patients). Obviously, the duration of follow up is decreased as the years of referral become more recent. In terms of the percentage achieving a complete seizure control, this ranged between 59% and 90% except for those years characterized by very low numbers of patients referred.

Year of referral	N	Responders (%)	Non-responders
1982	4	4 (100 %)	0
1983	2	2 (100 %)	0
1984	6	4 (67 %)	2
1985	14	9 (64 %)	5
1986	11	7 (64 %)	4
1987	2	2 (100 %)	0
1988	10	9 (90 %)	1
1989	14	11 (79 %)	3
1990	31	22 (71 %)	9
1991	24	19 (79 %)	5
1992	30	21 (70 %)	9
1993	30	24 (80 %)	6
1994	51	32 (63 %)	19
1995	69	46 (67 %)	23
1996	73	50 (68 %)	23
1997	46	32 (70 %)	14
1998	58	34 (59 %)	24
1999	66	48 (73 %)	18
2000	87	67 (77 %)	20
2001	89	59 (66 %)	30
2002	83	58 (70 %)	25
2003	122	84 (69 %)	38
2004	99	63 (64 %)	36
2005	77	43 (56 %)	34
Total	**1098**	**750 (68 %)**	**348**

Table 26. Outcome of epilepsy vs. years of patients' referral.

The whole study population was subsequently divided based on years of referral into three groups with similar numbers of patients. The first group comprised patients referred to the Epilepsy Unit in the period from 1982 to 1996, the second group had patients referred

between 1997 and 2001. Those patients referred between 2002 and 2005 represented the third group (Table 27 and Figure 7).

Period of referral	n	Responders (%)	Non-responders
1982 - 1996	371	262 (71 %)	109
1997 - 2001	346	240 (69 %)	106
2002 - 2005	381	248 (65 %)	133
Total	**1098**	**750**	**348**

Table 27. Outcome of epilepsy vs. periods of referral.
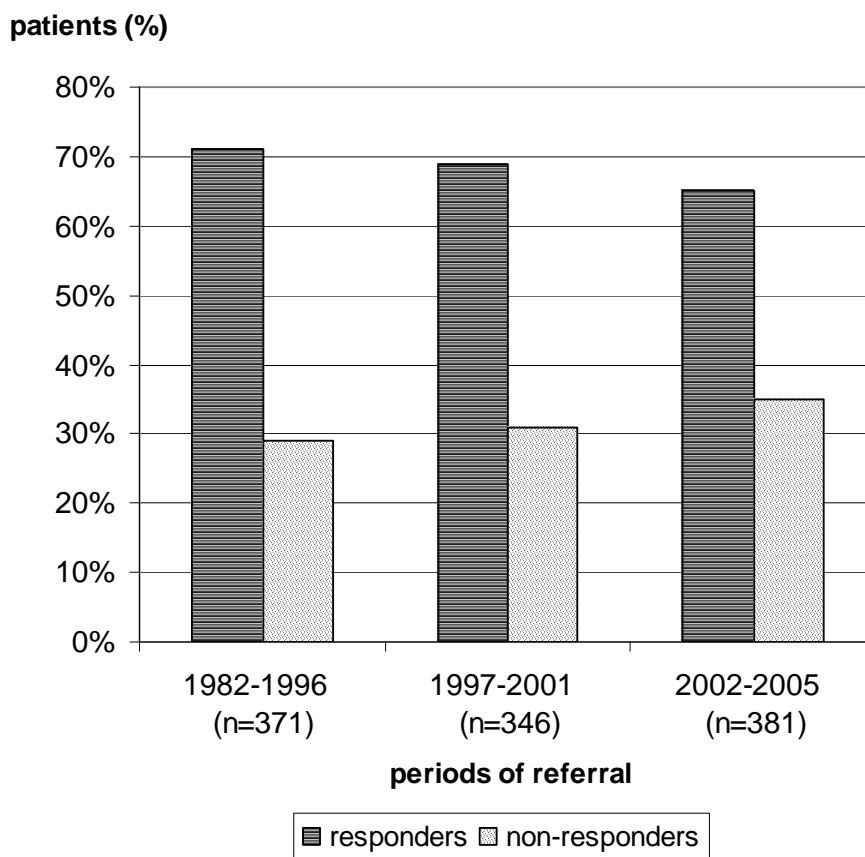
Figure 7. Outcome of epilepsy vs. periods of referral.

The group with the most recent range of referral years had the lowest remission rate (65%) compared to the group that constituted the oldest range of years of referral (Table 27 and Figure 7). There was insignificant difference between the three groups regarding remission rate (p-value = 0.2).

3.2.1.4. Type of epilepsy

Based on the aetiology of epilepsy, patients were divided into two groups i.e. idiopathic and focal epilepsy. Focal (localization related) epilepsy was further subdivided into cryptogenic and symptomatic epilepsy. Patients with symptomatic epilepsy had the lowest rate of developing complete seizure freedom after treatment with AEDs (63%). Rate of achieving complete seizure control was similar in the other two groups i.e. idiopathic and cryptogenic epilepsy (73% and 72 % respectively) and higher than symptomatic epilepsy. There was a statistically significant difference between these three groups in terms of achieving seizure freedom (p-value = 0.008). By distributing the patients into the two major groups i.e. idiopathic and focal epilepsy, focal epilepsy showed a lower response rate to AEDs (67%) compared to idiopathic epilepsy (73%). Insignificant statistical difference was detected between these two major groups of epilepsy regarding developing complete seizure control state (p-value = 0.1).

3.2.2. Pharmacological factors

3.2.2.1. Type of treatment with AEDs

With regard to type of treatment with AEDs i.e. monotherapy or polypharmacy (combined therapy), 50% of responders to AEDs were on monotherapy in the first treatment regimen. There was a gradual decline in the rate of developing seizure freedom in the subsequent treatment schedules (Table 28). Statistical analysis showed a significant difference between these groups of treatment regimens with regard to developing seizure freedom (p-value = 0.03).

Treatment regimens	N	Responders on monotherapy (%)	Non-responders on monotherapy
First	1098	544 (50%)	554
Second	254	101 (40%)	153
Third	64	26 (41%)	38
Fourth	17	6 (35%)	11
Fifth	3	1 (33%)	2
Sixth	3	1 (33%)	2
Seventh	2	1 (50%)	1
Eighth	0	0	0
Ninth	1	0	1

Table 28. Response to sequential monotherapies.

Patients on polypharmacy had a similar pattern of response with a 31% response rate in the second regimen followed by a dramatic reduction until the last regimen (Table 29). A statistical difference was noticed between these schedules of combined therapy and rate of seizure freedom (p-value = 0.0006). This might indicate that in some patients, treatment with polypharmacy was better than sequential monotherapy.

Treatment regimens	N	Responders on polypharmacy (%)	Non-responders on polypharmacy
First	-	-	-
Second	144	45 (31%)	99
Third	104	15 (14%)	89
Fourth	51	5 (10%)	46
Fifth	29	3 (10%)	26
Sixth	13	1 (8%)	12
Seventh	7	1 (14%)	6
Eighth	3	0	3
Ninth	1	0	1

Table 29. Response to sequential polypharmacies.

3.2.2.2. Mechanism of action of AEDs

In an attempt to detect any possible correlation that might exist between the rate of developing seizure freedom in epilepsy patients and the mechanisms of actions by which AEDs work, AEDs applied by patients in this study in their last monotherapy regimen were initially divided into five groups based on their primary mechanisms of action i.e. blockade of sodium channels, blockade of calcium channels, potentiation of potassium channels, potentiation of GABA inhibitory mechanism and inhibition of glutamate excitatory mechanism. Subsequently, based on the number of patients taking each AED in their last monotherapy regimen of the study, these groups were reduced to two: blockade of sodium channels and potentiation of GABA inhibitory mechanism. Other mechanisms were not included in the analysis as they were represented by a small number of patients taking AEDs working primarily by other mechanisms of action. AEDs with primary action on sodium channels include carbamazepine, phenytoin, lamotrigine and oxcarbazepine. On the other hand, AEDs that act mainly through the potentiation of GABA inhibitory effect are clobazam, phenobarbital, tiagabine, sodium valproate and vigabatrin.

74% of patients developed seizure freedom while being on AEDs acting mainly by blockade of sodium channels against 76% for those on drugs mainly acting by potentiation of GABA inhibitory mechanism without any statistical significant difference between them with regard to the ultimate outcome of epilepsy (p-value = 0.4) (Fig 8).

patients (%)
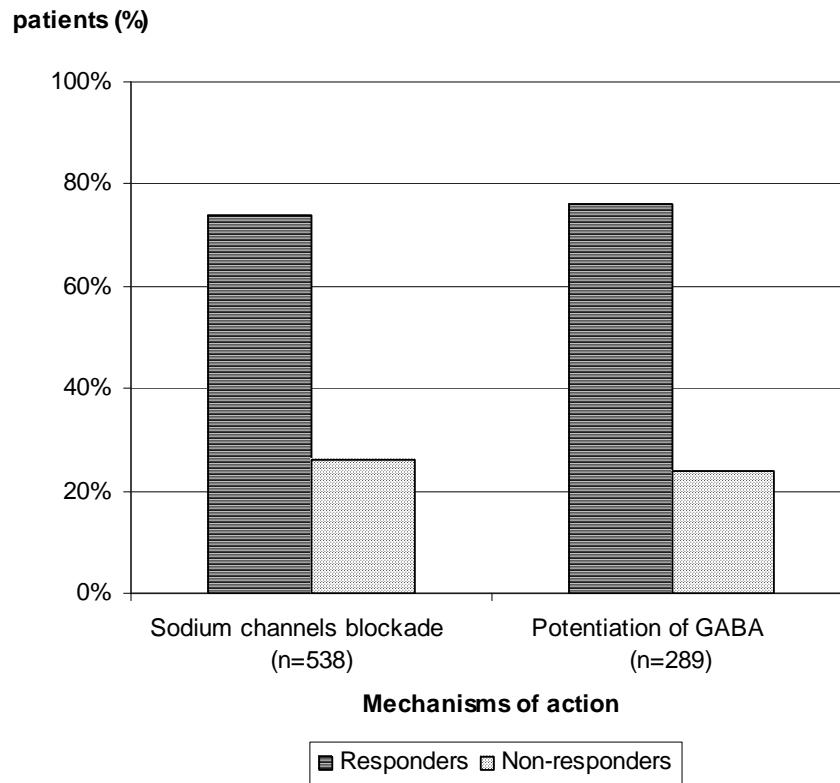
Figure 8. Outcome of epilepsy vs. mechanisms of action of AEDs.

It is believed that AEDs working by the same primary mechanism of action will lead to the same drug response regardless of the number of times they have been prescribed to a particular patient i.e. changing the AED but the main mechanism of action remains the same. The following analysis was performed on AEDs working by blockade of sodium channels as the main mechanism of action (carbamazepine, lamotrigine, oxcarbazepine and phenytoin) using treatment regimen failure on 50% of the daily-defined dose due to lack of efficacy as an indicator. There were 31 attempts to use sodium channels blockers after failure initially using another agents working primarily by the same mechanism of action. Out of these 31 attempts, seizure freedom was achieved in 12 cases while 15 cases failed that regimen again due to lack of efficacy. The remaining 4 cases had failure of treatment due to poor tolerability. AEDs acting primarily by potentiation of GABA (sodium valproate, vigabatrin, tiagabine, phenobarbital and clobazam) were used 10 times after they

have been applied initially with unsuccessful results. Out of these, seizure freedom was achieved in 6 cases while the regimen failed due to lack of efficacy in 4 cases.

3.2.2.3. Generations of AEDs

Among the total study population of this project (n =1098), 913 patients were taking AED monotherapy at the last clinic visit and out of these, 680 patients (61.9%) reached a state of complete seizure control. In order to detect any significant correlation between generations of AEDs and the ultimate outcome of epilepsy, these monotherapy patients were divided in two groups according to the generation of AEDs they were using on their last visit and then were subsequently further categorized in two further subgroups based on the outcome of epilepsy. The remission rates of patients on first and second generations AEDs were found to be exactly the same i.e. 31% of the population in each subgroup.

185 patients were on combined therapy (polypharmacy) on their last clinic appointment. Out of these, 70 patients (6.4%) achieved seizure freedom. In order to demonstrate any significant difference between first and second generations AEDs in terms of the outcome of epilepsy, patients on combined therapy were divided in three groups based on generations of AEDs included in each combination of AEDs i.e. a combination of first generation drugs, a combination of second generation drugs and a combination of both first and second generations AEDs. Analysis showed a response rate of 25% among those patients who had a combination of first generation drugs in their last visit to the epilepsy clinic (n = 4). In those patients with a combination of second generation agents, the response rate was 28% (n = 54) while those with a combination of both generations had the highest remission rate of 43% (n = 127) (Flow Chart 2). Unfortunately, the low number of patients on combination of first generation agents (n = 4) has limited the ability to compare with the other two groups. This kind of analysis was not possible in patients in their first treatment regimen as all epilepsy patients on their first treatment regimen are prescribed AED treatment on monotherapy basis.

Adding responder patients on monotherapy on the last clinic visit with those responders on combined therapy resulting in a total remission rate of 750 patients (68.3%) in this study.
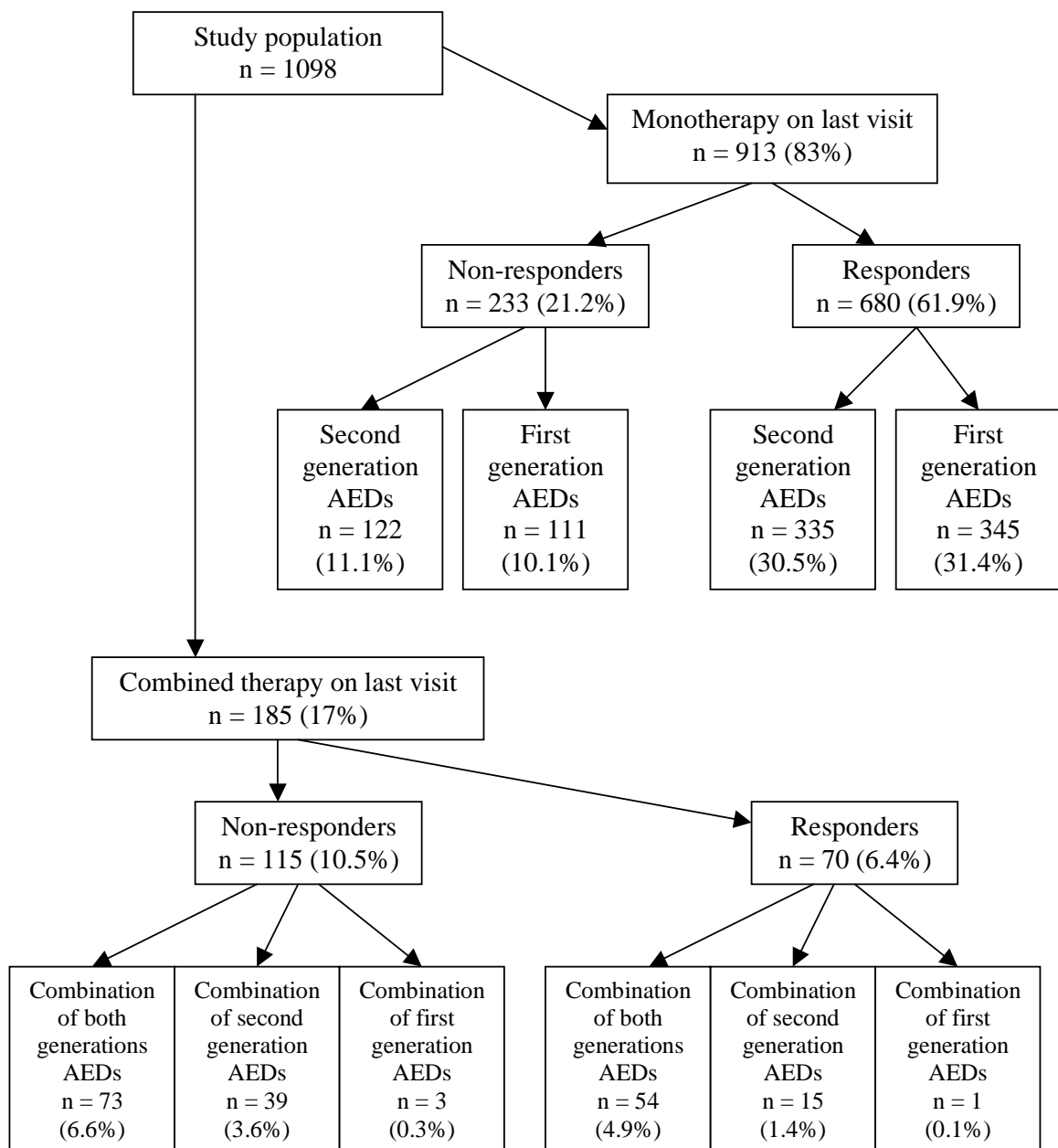
Flow Chart 2. Response rate to type of treatment at the last clinic visit among the two generations of AEDs.

3.3. Factors with potential to influence the effectiveness of AEDs

This section examines any potential correlation between the response (efficacy and tolerability) of individual AEDs included in the study in relation to various pharmacological and non-pharmacological issues.

3.3.1. Effectiveness among individual AEDs and generations

Among all the patients recruited to this study, 750 developed complete seizure freedom. Of these, 680 (62%) had remission using a single AED treatment (monotherapy). In total, there were 1442 attempts to use AEDs as monotherapy in patients in this study, of which 680 were successful. Among individual AEDs, agents with the highest prescription rate were identified and their efficacy calculated. These included (in descending order of efficacy): levetiracetam (65%), topiramate (53%), carbamazepine (50%), sodium valproate (49%), lamotrigine (49%) and oxcarbazepine (43%). The remaining AEDs were taken by only a small number of patients. Among these agents, a significant statistical difference was observed in terms of their efficacy to eliminate seizures (p-value < 0.001) (Table 30 and Figure 9). Focusing on the three most commonly prescribed agents, these included lamotrigine, sodium valproate and carbamazepine.

By dividing AEDs applied in this study into two groups based on their generation, first and second generation AEDs showed almost the same total cumulative efficacy (49% and 50%, respectively) excluding unknown AEDs (in clinical trials) and rarely prescribed agents. Statistically, results showed insignificant difference between the first and second generations AEDs in terms of total cumulative efficacy (p-value = 0.6) (Table 30 and Figure 10).

AED	Regimens									Total	Efficacy
	1	2	3	4	5	6	7	8	9		
CBZ	115 (224)	21 (47)	3 (11)	2 (2)	0	0	0	0	0	141 (284)	50 %
VPA	146 (274)	47 (115)	3 (12)	1 (3)	0 (1)	1 (1)	0	0	0	198 (406)	49 %
PHT	4 (7)	1 (4)	0 (1)	0	0	0	0	0	0	5 (12)	42 %
LTG	196 (372)	21 (59)	8 (18)	0 (6)	1 (1)	0	0	0	0 (1)	226 (457)	49 %
GBP	14 (19)	1 (6)	1 (2)	0	0	0 (1)	0	0	0	16 (28)	57 %
LEV	26 (42)	0 (1)	6 (7)	0	0	0	1 (1)	0	0	33 (51)	65 %
TPM	24 (42)	4 (10)	2 (5)	1 (2)	0	0	0	0	0	31 (59)	53 %
OXC	13 (31)	6 (12)	3 (8)	2 (4)	0	0	0 (1)	0	0	24 (56)	43 %
TGB	5 (14)	0	0	0	0	0	0	0	0	5 (14)	36 %
VGB	0	0	0	0	0 (1)	0	0	0	0	0 (1)	0
ZNS	0	0	0	0	0	0 (1)	0	0	0	0 (1)	0
Others	1 (73)	0	0	0	0	0	0	0	0	1 (73)	1 %
Total of responders on monotherapy	544	101	26	6	1	1	1	0	0	680	-
Total of non-responders on monotherapy	554	153	38	11	2	2	1	0	1	-	-
n	1098	254	64	17	3	3	2	0	1	-	-

Table 30. Efficacy of AEDs in patients on monotherapy.

Shaded rows represent first generation AEDs.

In terms of the tolerability profile of AEDs, lamotrigine demonstrated the best tolerability with the lowest rate of withdrawal due to side effects of 11%, it was followed by carbamazepine and sodium valproate (13%), levetiracetam (14%) while topiramate and oxcarbazepine showed the worst tolerability profile with a rate of withdrawal of 20%

excluding AEDs taken by a small number of patients (Table 31 and Figure 9). There was not any significant difference between these AEDs and tolerability profile (p-value = 0.2).

In order to detect any difference in the tolerability profile of AEDs among the two generations of these agents, the total cumulative tolerability of AEDs of each generation was calculated. First and second generations had the same overall tolerability (13%) - excluding unknown AEDs (in clinical trials) and rarely prescribed agents - without any significant difference between them (Table 31 and Figure 10).

AED	Regimens									Total	Rate of withdrawal
	1	2	3	4	5	6	7	8	9		
CBZ	29 (224)	8 (47)	1 (11)	0 (2)	0	0	0	0	0	38 (284)	13%
VPA	34 (274)	17 (115)	1 (12)	0 (3)	0 (1)	0 (1)	0	0	0	52 (406)	13%
PHT	1 (7)	1 (4)	0 (1)	0	0	0	0	0	0	2 (12)	17 %
LTG	39 (372)	10 (59)	0 (18)	0 (6)	0 (1)	0	0	0	0 (1)	49 (457)	11%
GBP	2 (19)	2 (6)	0 (2)	0	0	0 (1)	0	0	0	4 (28)	14 %
LEV	6 (42)	1 (1)	0 (7)	0	0	0	0 (1)	0	0	7 (51)	14 %
TPM	9 (42)	2 (10)	0 (5)	1 (2)	0	0	0	0	0	12 (59)	20 %
OXC	9 (31)	1 (12)	1 (8)	0 (4)	0	0	0 (1)	0	0	11 (56)	20 %
TGB	3 (14)	0	0	0	0	0	0	0	0	3 (14)	21 %
VGB	0	0	0	0	1 (1)	0	0	0	0	1 (1)	100 %
ZNS	0	0	0	0	0	1 (1)	0	0	0	1 (1)	100 %
Others	25 (73)	0	0	0	0	0	0	0	0	25 (73)	34 %

Table 31. Withdrawal rate of AEDs due to side effects in patients on monotherapy.
Shaded rows represent first generation AEDs.

Patients (%)
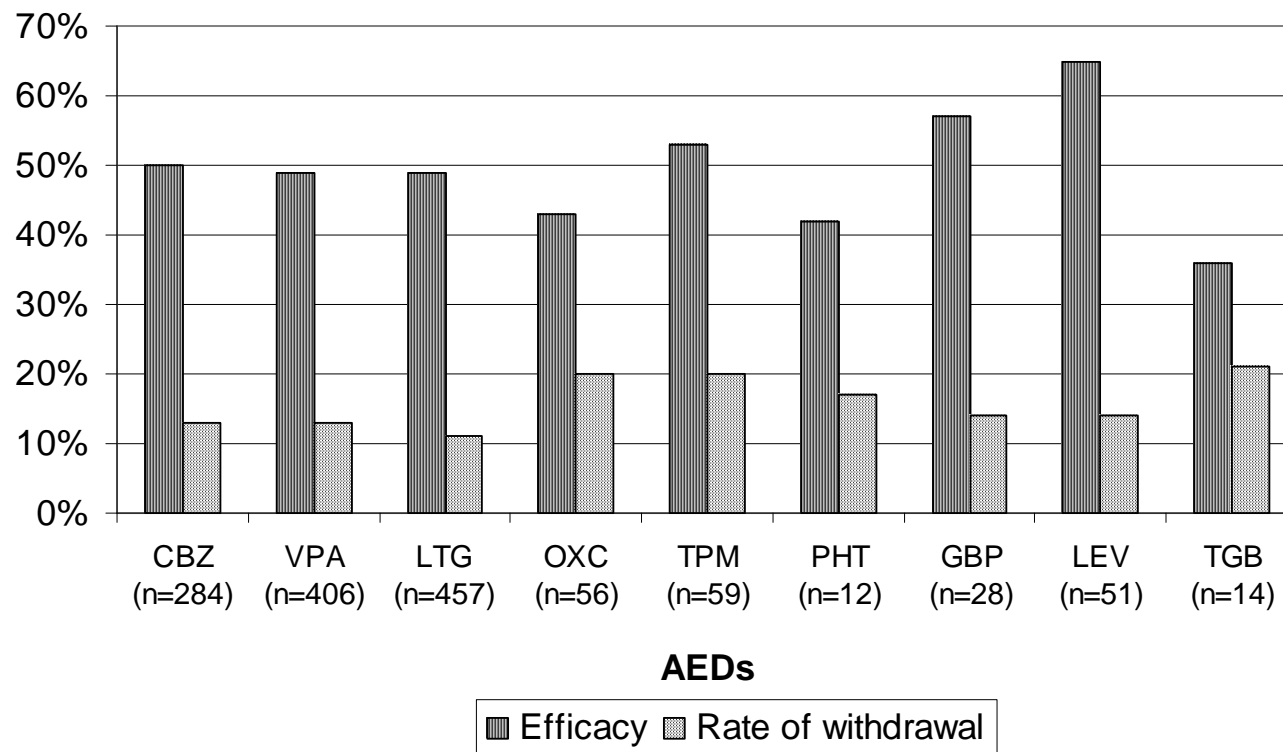
Figure 9. Effectiveness of AEDs
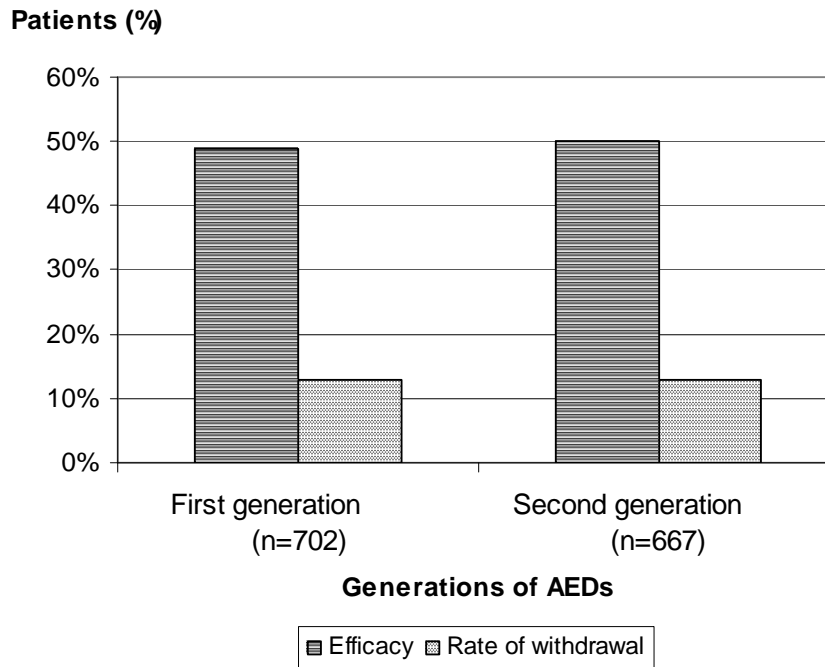
Patients (%)

Figure 10. Effectiveness of AEDs among generations.

3.3.2. Efficacy among AED combinations

In the 1098 patients of this study, 356 attempts at AED combinations utilizing various agents were made. Out of these, 70 attempts were successful in bringing patients into a state of complete seizure freedom, 6.4% of the whole study population. Most of the combinations (311) comprised two AEDs. There were 311 attempts at double therapy and 67 of these were successful (6.1% of the total study population). 37 attempts used combinations of three agents with two successful attempts, a remission rate of 0.2%. Quadruple therapy comprising 4 agents was attempted on 8 occassions and one was successful (remission rate of 0.1%) (Appendix 1).

In terms of specific AED combinations, the combination with the highest prescription rate was valproate and lamotrigine (81 patients) with an efficacy of 40%, this was followed by lamotrigine and levetiracetam combination with a prescription rate of 27 patients and efficacy of 11%, then lamotrigine and topiramate combination (23 patients) with an efficacy of 26% (Table 32).

AED Combinations	n	Responders (%)
Duo therapy		
VPA + LTG	81	32 (40%)
LEV + 1AED	64	13 (20%)
TPM + 1AED	46	11 (24%)
CBZ + 1 AED	50	7 (14%)
Other duo therapies	70	4 (6%)
Triple therapy		
CBZ + GBP + TPM	5	1 (20%)
VPA + TPM + LEV	1	1 (100%)
Other triple therapy	31	0
Quadruple therapy		
VPA + LTG + TPM + LEV	2	1 (50%)
Other quadruple therapy	6	0
Total	**356**	**70**

Table 32. Efficacy among AEDs combinations.

3.3.3. Effectiveness among age groups

For all AEDs (monotherapy) applied in the first treatment regimen among various age groups of patients recruited in the study, there were minimal differences in the efficacy in age groups less than 60 years. After 60 years, there is a pattern of gradual elevation of the efficacy profile of AEDs as patients' age increases until it reaches the maximum in patients with ages of 80 years or older. In terms of tolerability of AEDs in the first treatment regimen, similar values were noticed among all age groups, ranging from 9% to 17%. It was difficult to calculate the efficacy in the subsequent treatment regimens, as the timing of starting these regimens varied among patients (Table 33 and Figure 11). Insignificant statistical differences were noted in terms of efficacy and tolerability of AEDs regarding various age groups (p-value = 0.1 and 0.6, respectively).

Age groups (years)	n	Efficacy (%)	Rate of withdrawal (%)
< 20	241	119 (49%)	31 (13%)
20 – 29	243	123 (51%)	38 (16%)
30 – 39	176	82 (47%)	28 (16%)
40 – 49	144	66 (46%)	13 (9%)
50 – 59	118	53 (45%)	18 (15%)
60 – 69	86	42 (49%)	15 (17%)
70 – 79	67	43 (64%)	10 (15%)
≥ 80	23	16 (70%)	4 (17%)
Total	**1098**	**544**	**157**

Table 33. Effectiveness of AEDs among age groups of patients in the first treatment regimen.
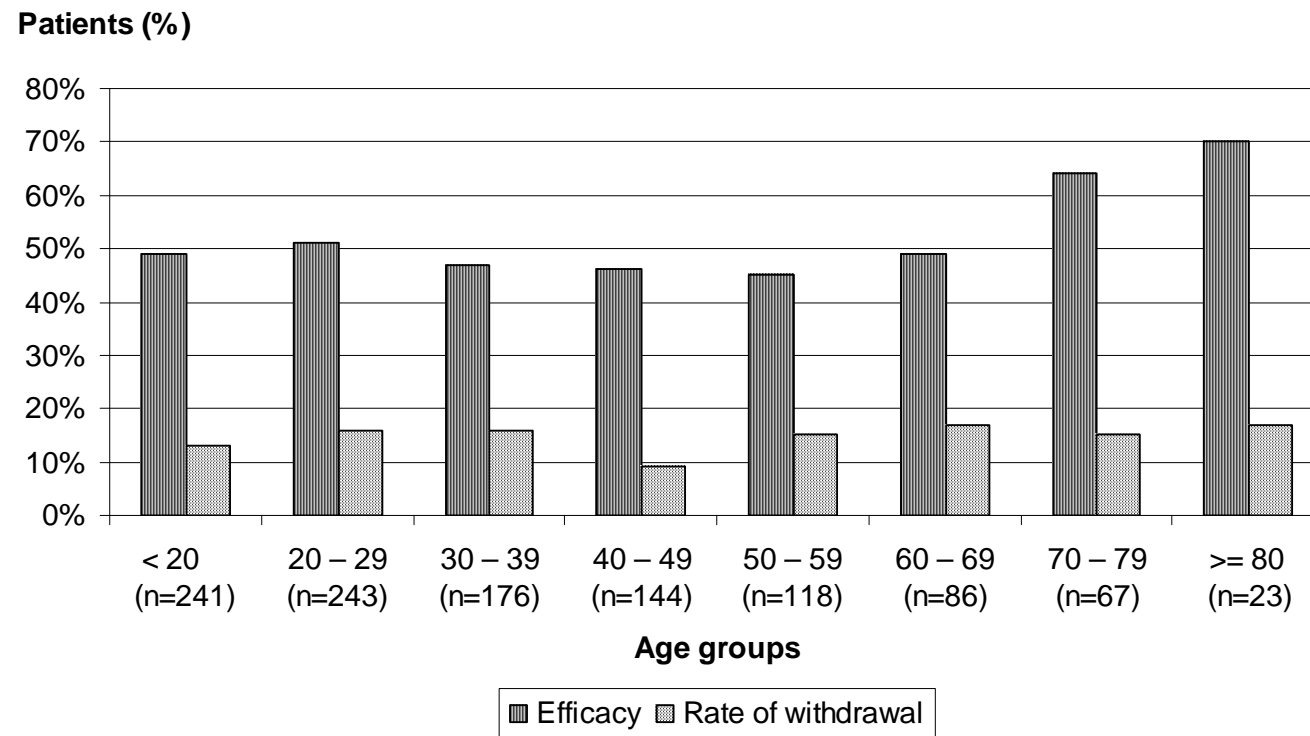
Patients (%)

Figure 11. Effectiveness of AEDs among age groups of patients in the first treatment regimen.

Out of the group of patients aged over 64 years (n = 122), 101 patients developed complete seizure freedom while on monotherapy compared to 5 patients on combined therapy. Among patients on monotherapy, carbamazepine (n = 40), sodium valproate (n = 35) and lamotrigine (n = 48) were the highest prescribed AEDs. Among these three agents, sodium valproate was the drug with the highest efficacy (77%) compared to carbamazepine (75%) and lamotrigine (69%) (Table 34). Statistical significant difference in efficacy could not be identified for these drugs (p-value = 0.6). Also in this group of patients, it was shown that first generation AEDs were more efficacious (77%) than second generation agents (56%) with a significant statistical difference (p-value = 0.007) (Table 34).

With respect to the tolerability profile of AEDs in elderly patients and among the three most commonly prescribed agents i.e. sodium valproate, carbamazepine and lamotrigine, sodium valproate was the best tolerated drug with the lowest rate of withdrawal due to side effects (9%) followed by carbamazepine and lamotrigine (both 13%) (Table 35) without any significant difference (p-value = 0.8). A small difference in rate of withdrawal due to side effects between the first and second generations of AEDs was observed (13% and 15%, respectively) without any significant difference (p-value = 0.7) (Table 35).

AED	Regimens									Total	Efficacy
	1	2	3	4	5	6	7	8	9		
CBZ	24 (33)	5 (6)	0	1 (1)	0	0	0	0	0	30 (40)	75 %
VPA	18 (24)	8 (10)	1 (1)	0	0	0	0	0	0	27 (35)	77 %
PHT	2 (2)	0	0	0	0	0	0	0	0	2 (2)	100 %
LTG	24 (39)	8 (8)	1 (1)	0	0	0	0	0	0	33 (48)	69 %
GBP	1 (1)	0	1 (1)	0	0	0	0	0	0	2 (2)	100 %
LEV	2 (3)	0	0	0	0	0	0	0	0	2 (3)	67 %
TPM	2 (4)	0	0	0	0	0	0	0	0	2 (4)	50 %
OXC	2 (9)	0 (1)	1 (1)	0	0	0	0	0	0	3 (11)	27 %
Others	0 (7)	0	0	0	0	0	0	0	0	0 (7)	0 %
Total of responders on monotherapy	75	21	4	1	0	0	0	0	0	101	-
Total of non-responders on monotherapy	47	4	0	0	0	0	0	0	0	-	-
n	122	25	4	1	0	0	0	0	0	-	-

Table 34. Efficacy of AEDs in elderly patients (≥ 65 years old) on monotherapy.

Shaded rows represent first generation AEDs.

AED	Regimens									Total	Rate of withdrawal
	1	2	3	4	5	6	7	8	9		
CBZ	5 (33)	0 (6)	0	0 (1)	0	0	0	0	0	5 (40)	13%
VPA	3 (24)	0 (10)	0 (1)	0	0	0	0	0	0	3 (35)	9%
PHT	0 (2)	0	0	0	0	0	0	0	0	2 (2)	100 %
LTG	6 (39)	0 (8)	0 (1)	0	0	0	0	0	0 (1)	6 (48)	13%
GBP	0 (1)	0	0 (1)	0	0	0	0	0	0	0 (2)	0 %
LEV	0 (3)	0	0	0	0	0	0	0	0	0 (3)	0 %
TPM	2 (4)	0	0	0	0	0	0	0	0	2 (4)	50 %
OXC	3 (9)	0 (1)	0 (1)	0	0	0	0	0	0	3 (11)	27 %
Others	0 (7)	0	0	0	0	0	0	0	0	0 (7)	0 %

Table 35. Withdrawal rate of AEDs due to side effects in elderly patients (≥ 65 years old) on monotherapy.
Shaded rows represent first generation AEDs.

3.3.4. Effectiveness among gender

Efficacy of all AEDs given as monotherapy was examined in relation to gender. In most AEDs used, the efficacy in males was found to be higher than in females although there was variability regarding the rate of AED prescription i.e. carbamazepine, sodium valproate, phenytoin and tiagabine showed a higher prescription rate in males in comparison to lamotrigine, topiramate, gabapentin and levetiracetam in which the females had a higher prescription rate. Males and females had the same prescription rate for oxcarbazepine (Table 36 and Figure 12). Among the three most commonly prescribed AEDs i.e. carbamazepine, sodium valproate and lamotrigine, sodium valproate showed a statistically significant gender-related difference of efficacy (p-value = 0.006). Calculations of the total cumulative efficacy of AEDs in this study in males and females showed a higher total efficacy in males (55%) in comparison to females (44%) with a significant statistical difference (p-value < 0.001).

In case of tolerability profiles, male patients tolerated AEDs better than females. For instance, out of 164 attempts of carbamazepine application in males, the rate of withdrawal due to side effects was 10% compared to 18% with females in which there were 120 attempts. Rate of sodium valproate prescription was higher than for carbamazepine, it was applied in 243 male patients with a withdrawal rate due to side effects of 9%. Similar to carbamazepine, female patients on sodium valproate (n = 163) had a higher rate of withdrawal than males i.e. 18%. The same pattern was noticed with lamotrigine in which males had a rate of withdrawal due to side effects of 8% (n = 166) compared to 12% in case of females (n = 291) (Table 37 and Figure 13). Carbamazepine and sodium valproate showed statistically significant gender differences in tolerability (p-value = 0.03 and 0.006, respectively). Based on cumulative tolerability males tolerated AEDs (9%) better than females (17%) with a statistically significant difference (p-value < 0.001).

Regimen	Gender	CBZ	VPA	LTG	OXC	TPM	PHT	GBP	LEV	TGB	VGB	ZNS
1st	N	224	274	372	31	42	7	19	42	14	0	0
	Males	70 (135)	102 (178)	81 (143)	9 (15)	16 (23)	2 (5)	4 (7)	17 (23)	4 (8)	0	0
	Females	45 (89)	44 (96)	115 (229)	4 (16)	8 (19)	2 (2)	10 (12)	9 (19)	1 (6)	0	0
2nd	N	47	115	59	12	10	4	6	1	0	0	0
	Males	13 (27)	26 (60)	10 (18)	4 (7)	1 (1)	1 (2)	0	0	0	0	0
	Females	8 (20)	21 (55)	11 (41)	2 (5)	3 (9)	0 (2)	1 (6)	0 (1)	0	0	0
3rd	N	11	12	18	8	5	1	2	7	0	0	0
	Males	0 (2)	3 (4)	1 (4)	3 (4)	2 (3)	0	0	1 (1)	0	0	0
	Females	3 (9)	0 (8)	7 (14)	0 (4)	0 (2)	0 (1)	1 (2)	5 (6)	0	0	0
4th	N	2	3	6	4	2	0	0	0	0	0	0
	Males	0	1 (1)	0 (1)	0 (1)	0	0	0	0	0	0	0
	Females	2 (2)	0 (2)	0 (5)	2 (3)	1 (2)	0	0	0	0	0	0
5th	N	0	1	1	0	0	0	0	0	0	1	0
	Males	0	0	0	0	0	0	0	0	0	0	0
	Females	0	0 (1)	1 (1)	0	0	0	0	0	0	0 (1)	0
6th	N	0	1	0	0	0	0	1	0	0	0	1
	Males	0	0	0	0	0	0	0	0	0	0	0 (1)
	Females	0	1 (1)	0	0	0	0	0 (1)	0	0	0	0
7th	N	0	0	0	1	0	0	0	1	0	0	0
	Males	0	0	0	0 (1)	0	0	0	1 (1)	0	0	0
	Females	0	0	0	0	0	0	0	0	0	0	0
8th	N	0	0	0	0	0	0	0	0	0	0	0
	Males	0	0	0	0	0	0	0	0	0	0	0
	Females	0	0	0	0	0	0	0	0	0	0	0
9th	N	0	0	1	0	0	0	0	0	0	0	0
	Males	0	0	0	0	0	0	0	0	0	0	0
	Females	0	0	0 (1)	0	0	0	0	0	0	0	0
Total	Males (Efficacy)	83 (164) 51%	132 (243) 54%	92 (166) 55%	16 (28) 57%	19 (27) 70%	3 (7) 43%	4 (7) 57%	19 (25) 76%	4 (8) 50%	0	0 (1) 0%
	Females (Efficacy)	58 (120) 48%	66 (163) 40%	134 (291) 46%	8 (28) 29%	12 (32) 38%	2 (5) 40%	12 (21) 57%	14 (26) 54%	1 (6) 17%	0 (1) 0%	0

Table 36. Differences between gender in efficacy of all AEDs in all regimens.

Patients (%)
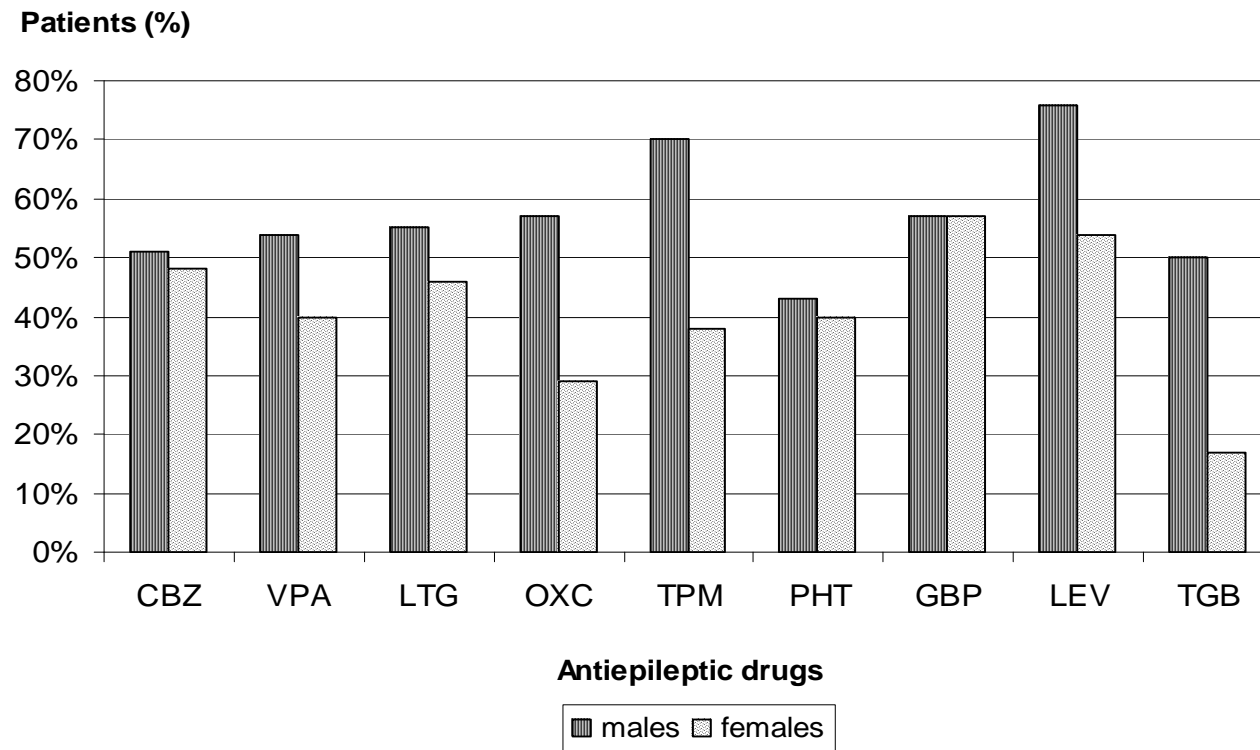
Figure 12. Efficacy of AEDs vs. gender.

Regimen	Gender	CBZ	VPA	LTG	OXC	TPM	PHT	GBP	LEV	TGB	VGB	ZNS
1st	N	224	274	372	31	42	7	19	42	14	0	0
	Males	13 (135)	16 (178)	12 (143)	2 (15)	3 (23)	1 (5)	1 (7)	2 (23)	1 (8)	0	0
	Females	16 (89)	18 (96)	27 (229)	7 (16)	6 (19)	0 (2)	1 (12)	4 (19)	2 (6)	0	0
2nd	N	47	115	59	12	10	4	6	1	0	0	0
	Males	3 (27)	6 (60)	2 (18)	0 (7)	0 (1)	0 (2)	0	0	0	0	0
	Females	5 (20)	11 (55)	8 (41)	1 (5)	2 (9)	1 (2)	2 (6)	1 (1)	0	0	0
3rd	N	11	12	18	8	5	1	2	7	0	0	0
	Males	0 (2)	0 (4)	0 (4)	0 (4)	0 (3)	0	0	0 (1)	0	0	0
	Females	1 (9)	1 (8)	0 (14)	1 (4)	0 (2)	0 (1)	0 (2)	0 (6)	0	0	0
4th	N	2	3	6	4	2	0	0	0	0	0	0
	Males	0	0 (1)	0 (1)	0 (1)	0	0	0	0	0	0	0
	Females	0 (2)	0 (2)	0 (5)	0 (3)	1 (2)	0	0	0	0	0	0
5th	N	0	1	1	0	0	0	0	0	0	1	0
	Males	0	0	0	0	0	0	0	0	0	0	0
	Females	0	0 (1)	0 (1)	0	0	0	0	0	0	1 (1)	0
6th	N	0	1	0	0	0	0	1	0	0	0	1
	Males	0	0	0	0	0	0	0	0	0	0	1 (1)
	Females	0	0 (1)	0	0	0	0	0 (1)	0	0	0	0
7th	N	0	0	0	1	0	0	0	1	0	0	0
	Males	0	0	0	0 (1)	0	0	0	0 (1)	0	0	0
	Females	0	0	0	0	0	0	0	0	0	0	0
8th	N	0	0	0	0	0	0	0	0	0	0	0
	Males	0	0	0	0	0	0	0	0	0	0	0
	Females	0	0	0	0	0	0	0	0	0	0	0
9th	N	0	0	1	0	0	0	0	0	0	0	0
	Males	0	0	0	0	0	0	0	0	0	0	0
	Females	0	0	0 (1)	0	0	0	0	0	0	0	0
Total	Males (Tolerability)	16 (164) 10%	22 (243) 9%	14 (166) 8%	2 (28) 7%	3 (27) 11%	1 (7) 14%	1 (7) 14%	2 (25) 8%	1 (8) 13%	0	1 (1) 100%
	Females (Tolerability)	22 (120) 18%	30 (163) 18%	35 (291) 12%	9 (28) 32%	9 (32) 28%	1 (5) 20%	3 (21) 14%	5 (26) 19%	2 (6) 33%	1 (1) 100%	0

Table 37. Differences between gender in tolerability of all AEDs in all regimens.
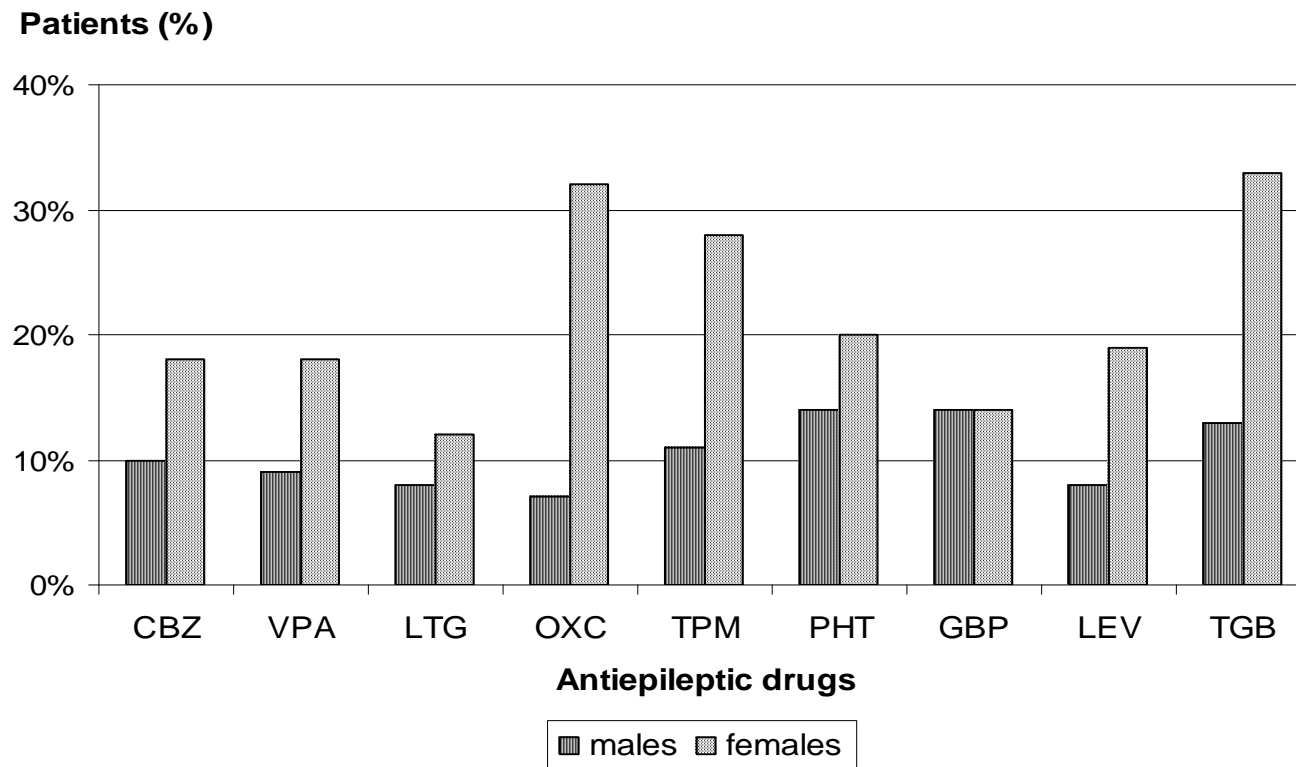
Patients (%)

Figure 13. Tolerability of AEDs vs. gender.

3.3.5. Effectiveness in idiopathic generalised epilepsy

Patients recruited with idiopathic generalised epilepsy were 251, 182 of these became seizure free by the end of study while the remaining (69 patients) did not (Table 24). 164 patients achieved remission while being on monotherapy and 18 were on polypharmacy.

Analyzing the effectiveness of AEDs among patients with idiopathic generalised epilepsy, first generation AEDs showed a total cumulative efficacy of 58% in comparison to second generation agents that had a total efficacy of 48% excluding unknown AEDs (in clinical trials) and rarely prescribed agents. Insignificant statistical difference existed between first and second generation AEDs in terms of the total efficacy (p-value = 0.07). With respect to individual drugs, sodium valproate was the AED with the highest prescription and response rate as well among all first and second generations agents (59%) excluding AEDs applied by a small number of patients (Table 38 and Figure 14). Statistical investigation among the two commonly prescribed agents in this group of patients i.e. sodium valproate and lamotrigine showed a significant difference (p-value = 0.03).

In patients with idiopathic generalised epilepsy, sodium valproate also demonstrated the best tolerability profile with the lowest rate of drug withdrawal due to side effects (9%) compared to 13% in case of lamotrigine without any significant statistical difference between them (p-value = 0.3). In addition, first generation AEDs had a total cumulative tolerability profile slightly better than second generation AEDs with a rate of withdrawal due to side effects of 10% compared to 15% in case of modern agents with a non-significant difference (p-value = 0.2) (Table 39 and Figure 14).

AED	Idiopathic epilepsy (n=164)									Total	Efficacy
	1	2	3	4	5	6	7	8	9		
CBZ	12 (26)	4 (6)	-	1 (1)	-	-	-	-	-	17 (33)	52%
VPA	55 (89)	15 (28)	0 (1)	0 (1)	-	-	-	-	-	70 (119)	59%
PHT	1 (1)	1 (1)	-	-	-	-	-	-	-	2 (2)	100%
LTG	49 (102)	3 (13)	2 (4)	-	-	-	-	-	-	54 (119)	45%
GBP	1 (1)	0 (1)	-	-	-	-	-	-	-	1 (2)	50%
LEV	4 (5)	0 (1)	4 (5)	-	-	-	-	-	-	8 (11)	73%
TPM	2 (4)	1 (4)	-	1 (1)	-	-	-	-	-	4 (9)	44%
OXC	6 (8)	0 (1)	1 (1)	-	-	-	-	-	-	7 (10)	70%
TGB	1 (6)	-	-	-	-	-	-	-	-	1 (6)	17%
Others	0 (9)	-	-	-	-	-	-	-	-	0 (9)	0
Total of responders	131	24	7	2	0	0	0	0	0	164	-
n	251	55	11	3	0	0	0	0	0	-	-

Table 38. Efficacy of AEDs used as monotherapy among patients with idiopathic generalised epilepsy.

AED	Idiopathic epilepsy (n=164)									Total	Rate of withdrawal
	1	2	3	4	5	6	7	8	9		
CBZ	4 (26)	1 (6)	0	0 (1)	0	0	0	0	0	5 (33)	15%
VPA	9 (89)	2 (28)	0 (1)	0 (1)	0	0	0	0	0	11 (119)	9%
PHT	0 (1)	0 (1)	0	0	0	0	0	0	0	0 (2)	0%
LTG	14 (102)	2 (13)	0 (4)	0	0	0	0	0	0	16 (119)	13%
GBP	0 (1)	0 (1)	0	0	0	0	0	0	0	0 (2)	0%
LEV	1 (5)	1 (1)	0 (5)	0	0	0	0	0	0	2 (11)	18%
TPM	2 (4)	1 (4)	0	0 (1)	0	0	0	0	0	3 (9)	33%
OXC	1 (8)	1 (1)	0 (1)	0	0	0	0	0	0	2 (10)	20%
TGB	1 (6)	0	0	0	0	0	0	0	0	1 (6)	17%
Others	0 (9)	-	-	-	-	-	-	-	-	0 (9)	0%

Table 39. Withdrawal rate due to side effects of AEDs used as monotherapy among patients with idiopathic generalised epilepsy.
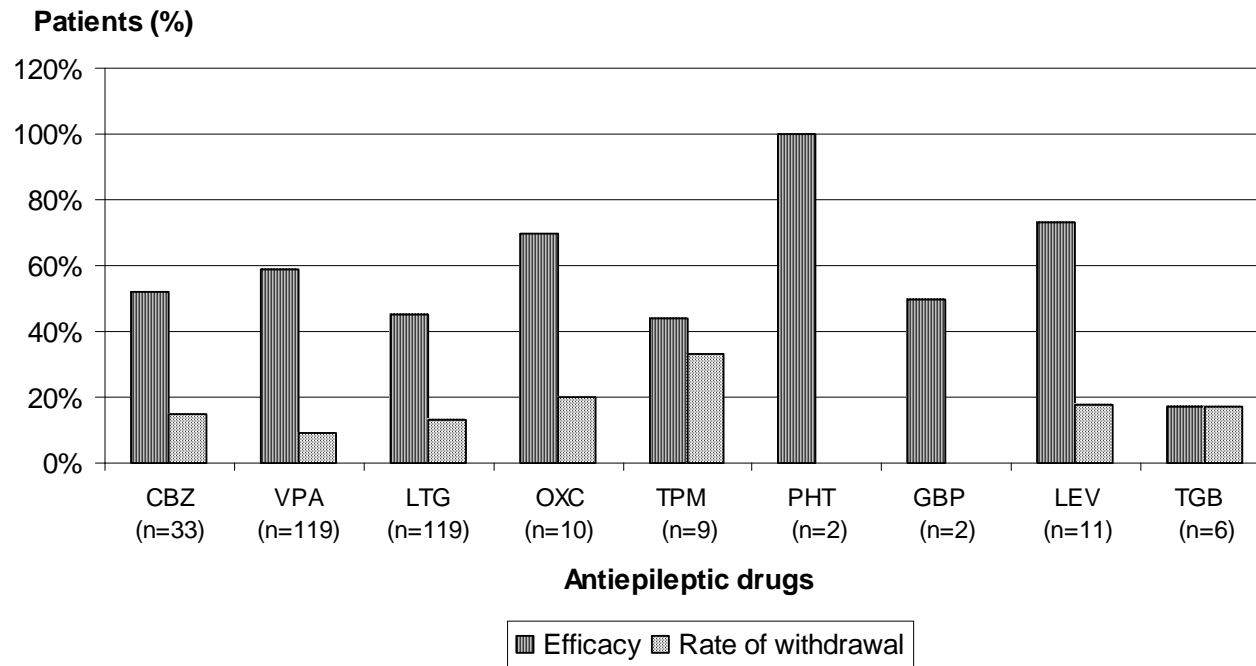
Figure 14. Effectiveness of AEDs among patients with idiopathic generalised epilepsy.

3.3.6. Effectiveness in focal epilepsy

There were 847 patients with focal epilepsy included in this study, 400 of whom had cryptogenic epilepsy (unknown aetiology) and 447 had symptomatic epilepsy with a defined aetiology.   Responders to AEDs among the two groups (cryptogenic and symptomatic epilepsy) comprised 568 patients, 279 did not achieve seizure freedom by the end of study (Table 24). Out of the 568, 516 patients achieved remission while being on monotherapy while the remaining (52) were on polypharmacy.

Table 40 shows that 47% of patients with focal epilepsy achieved remission using older AEDs compared to 51% who were prescribed second generation AEDs - excluding unknown AEDs (in clinical trials) and rarely prescribed agents - with a non significant difference (p-value = 0.1). Lamotrigine was the AED with the highest prescription and response rates (51%) among all other AEDs (first and second generations) followed by carbamazepine (49%) and sodium valproate (45%), excluding AEDs taken by a small number of patients.   Statistical analysis showed insignificant difference between these three agents in terms of efficacy (p-value = 0.2) (Table 40 and Figure 15).

The AED with the best tolerability profile was also lamotrigine with a rate of withdrawal due to side effects of 10% followed by carbamazepine (13%) and sodium valproate (14%) excluding AEDs taken by a small number of patients; there was insignificant difference between these drugs in terms of tolerability. A similar total cumulative tolerability profile was noted when the first and second generations of AEDs were compared (14% and 13% respectively) with an insignificant difference (p-value = 0.5) (Table 41 and Figure 15).

AED	Focal epilepsy (n=516)									Total	Efficacy
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**		
CBZ	103 (198)	17 (41)	3 (11)	1 (1)	-	-	-	-	-	**124 (251)**	**49%**
VPA	91 (185)	32 (87)	3 (11)	1 (2)	0 (1)	1 (1)	-	-	-	**128 (287)**	**45%**
PHT	3 (6)	0 (3)	0 (1)	-	-	-	-	-	-	**3 (10)**	**30%**
LTG	147 (270)	18 (46)	6 (14)	0 (6)	1 (1)	-	-	-	0 (1)	**172 (338)**	**51%**
GBP	13 (18)	1 (5)	1 (2)	-	-	0 (1)	-	-	-	**15 (26)**	**58%**
LEV	22 (37)	-	2 (2)	-	-	-	1 (1)	-	-	**25 (40)**	**63%**
TPM	22 (38)	3 (6)	2 (5)	0 (1)	-	-	-	-	-	**27 (50)**	**54%**
OXC	7 (23)	6 (11)	2 (7)	2 (4)	-	-	0 (1)	-	-	**17 (46)**	**37%**
TGB	4 (8)	-	-	-	-	-	-	-	-	**4 (8)**	**50%**
VGB	-	-	-	-	0 (1)	-	-	-	-	**0 (1)**	**0%**
ZNS	-	-	-	-	-	0 (1)	-	-	-	**0 (1)**	**0%**
Others	1 (64)	-	-	-	-	-	-	-	-	**1 (64)**	**2%**
Total of responders	413	77	19	4	1	1	1	0	0	**516**	**-**
n	847	199	53	14	3	3	2	0	1	**-**	**-**

Table 40. Efficacy of AEDs used as monotherapy among patients with focal epilepsy.

AED	Focal epilepsy (n=516)									Total	Rate of withdrawal
	1	2	3	4	5	6	7	8	9		
CBZ	25 (198)	7 (41)	1 (11)	0 (1)	0	0	0	0	0	33 (251)	13%
VPA	25 (185)	15 (87)	1 (11)	0 (2)	0 (1)	0 (1)	0	0	0	41 (287)	14%
PHT	1 (6)	1 (3)	0 (1)	0	0	0	0	0	0	2 (10)	20%
LTG	25 (270)	8 (46)	0 (14)	0 (6)	0 (1)	0	0	0	0 (1)	33 (338)	10%
GBP	2 (18)	2 (5)	0 (2)	0	0	0 (1)	0	0	0	4 (26)	15%
LEV	5 (37)	0	0 (2)	0	0	0	0 (1)	0	0	5 (40)	13%
TPM	7 (38)	1 (6)	0 (5)	1 (1)	0	0	0	0	0	9 (50)	18%
OXC	8 (23)	0 (11)	1 (7)	0 (4)	0	0	0 (1)	0	0	9 (46)	20%
TGB	2 (8)	0	0	0	0	0	0	0	0	2 (8)	25%
VGB	0	0	0	0	1 (1)	0	0	0	0	1 (1)	100%
ZNS	0	0	0	0	0	1 (1)	0	0	0	1 (1)	100%
Others	22 (64)	0	0	0	0	0	0	0	0	22 (64)	34%

Table 41. Withdrawal rate due to side effects of AEDs used as monotherapy among patients with focal epilepsy.
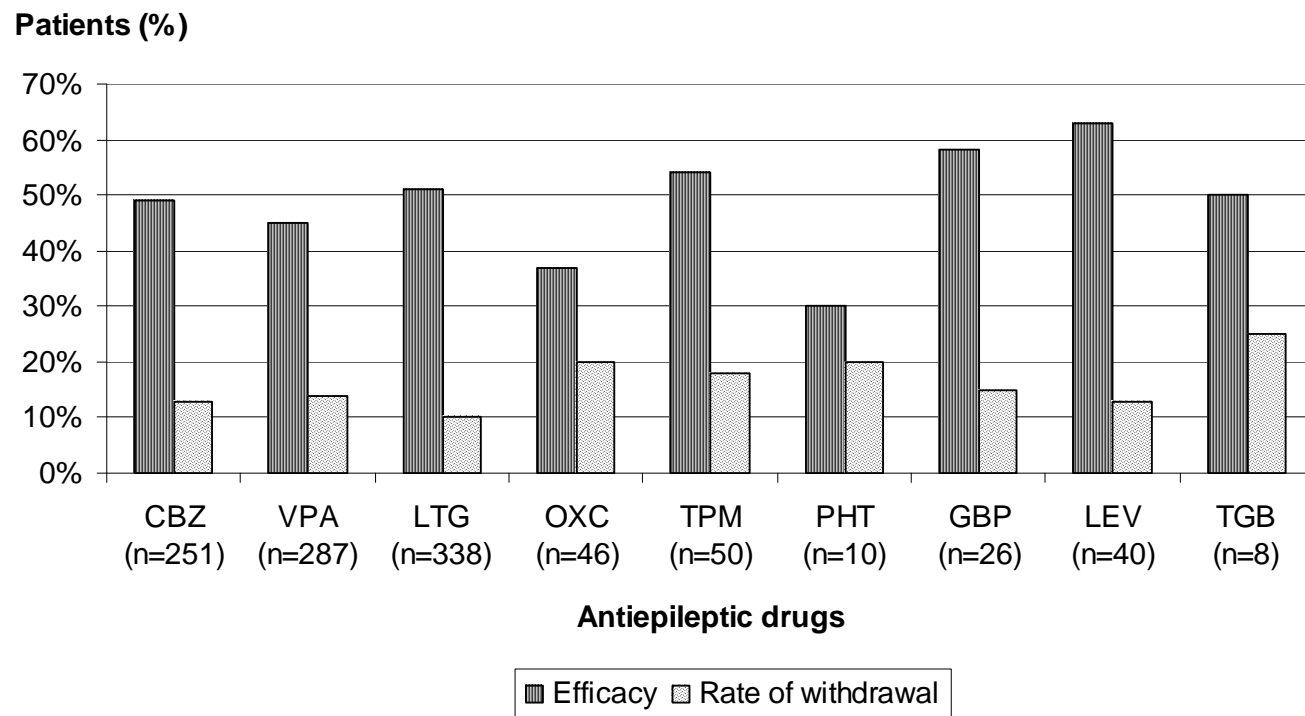
Patients (%)

Figure 15. Effectiveness of AEDs among patients with focal epilepsy.

3.3.7. Effectiveness among various treatment regimens (sequence of prescription)

Based on the calculations of individual AED efficacy and tolerability in various treatment regimens, it seems that the response to AEDs is a dynamic matter rather than constant because it varies based on the sequence of treatment regimen in which a particular AED has been applied. For instance, efficacy of carbamazepine when applied in the first treatment regimen (51%) was different from its efficacy in the remaining regimens (43%) (Table 42). The same issue was also noted for tolerability profiles e.g. tolerability to lamotrigine when prescribed in the first treatment regimen (10%) was different from its tolerability in the remaining regimens (12%) (Table 42). This variation in effectiveness of AEDs has been observed in most of the AEDs used in this study, the extent of variation tended to be bigger in case of efficacy in comparison with tolerability.

AED	Efficacy			Tolerability		
	First regimen	Remaining regimens	Total	First regimen	Remaining regimens	Total
CBZ	51%	43%	50%	13%	15%	13%
VPA	53%	39%	49%	12%	14%	13%
LTG	53%	35%	49%	10%	12%	11%
TPM	57%	41%	53%	21%	18%	20%
OXC	42%	44%	43%	29%	8%	20%
LEV	62%	78%	65%	14%	11%	14%

Table 42. A comparison of efficacy and tolerability of AEDs among various treatment regimens.

3.3.8. Effectiveness of AEDs among dose ranges

Recruited patients were categorized according to the last AED applied. AEDs with the highest prescription rate were selected which constituted six groups of patients using six AEDs; these included (in descending order) lamotrigine (n = 457), sodium valproate (n = 406), carbamazepine (n = 284), topiramate (n = 59), oxcarbazepine (n = 56) and levetiracetam (n = 51). In responders, doses were categorized. Eventually, efficacy (cumulative percentages of patients with seizure freedom) was calculated for all doses categories for all six AEDs. In terms of tolerability of these AEDs, the common side effects leading to withdrawal of these agents were identified (Table 43) along with the doses at which most of the patients discontinued these drugs.

AED	n	Common side effects
Lamotrigine	49 (457)	Rash (43%), GI disturbance (22%), Irritability (13%), Headache (11%), Tiredness (11%).
Sodium valproate	52 (406)	Weight gain (31%), Tiredness (27%), Tremor (23%), GI disturbance (17%).
Carbamazepine	38 (284)	Rash (55%), Tiredness (29%), GI disturbance (11%).
Topiramate	12 (59)	Paraesthesia (67%), GI disturbance (50%), Word finding difficulty (25%), Weight loss (25%).
Oxcarbazepine	11 (56)	Tiredness (45%), Rash (36%), GI disturbance (18%).
Levetiracetam	7 (51)	Behavioral problems (57%), Headache (29%), Tiredness (29%).

Table 43. Withdrawals from AEDs due to side effects along with the common side effects.

3.3.8.1. Lamotrigine

Of patients who achieved seizure freedom while on monotherapy with lamotrigine (n = 226), 94% developed remission while taking around two thirds or less (≤ 400 mg/day) of the maximum dose required for all the patients to reach a state of complete seizure control (≤ 600 mg/day). Among patients who discontinued lamotrigine due to side effects (n = 49), 94% of these patients were found to be taking a dose of ≤ 300 mg/day, the daily defined dose of lamotrigine based on WHO recommendations (Figure 16).

Figure 16. Seizure freedom achieved on lamotrigine (n=226) and its rate of withdrawal due to side effects (n=49) among various dose ranges.

3.3.8.2. Sodium Valproate

In case of sodium valproate, efficacy and tolerability followed an almost identical pattern in relation to dose ranges. 90% of the patients who developed complete seizure control on this drug (n =198) were taking around half or less (≤ 1500 mg/day) of the maximum dose required for all the patients on this drug to achieve remission (≤ 3000 mg/day). In terms of tolerability, 92% of patients who discontinued this AED due to side effects (n = 52) were also taking a dose of ≤ 1500 mg/day that is the recommended daily dose (Figure 17).

Figure 17. Seizure freedom achieved on sodium valproate (n=198) and its rate of withdrawal due to side effects (n=52) among various dose ranges.

3.3.8.3. Carbamazepine

Among patients who achieved remission while on monotherapy with carbamazepine (n = 141), 92% were taking half or less than the maximum dose needed for all the patients on this drug to obtain seizure control i.e. ≤ 800 mg/day. Among patients who withdrew from carbamazepine due to side effects (n = 38), 97% of these patients were on a dose of 600 mg/day or less which is around half of the WHO recommended daily defined dose (1000mg/day) (Figure 18).
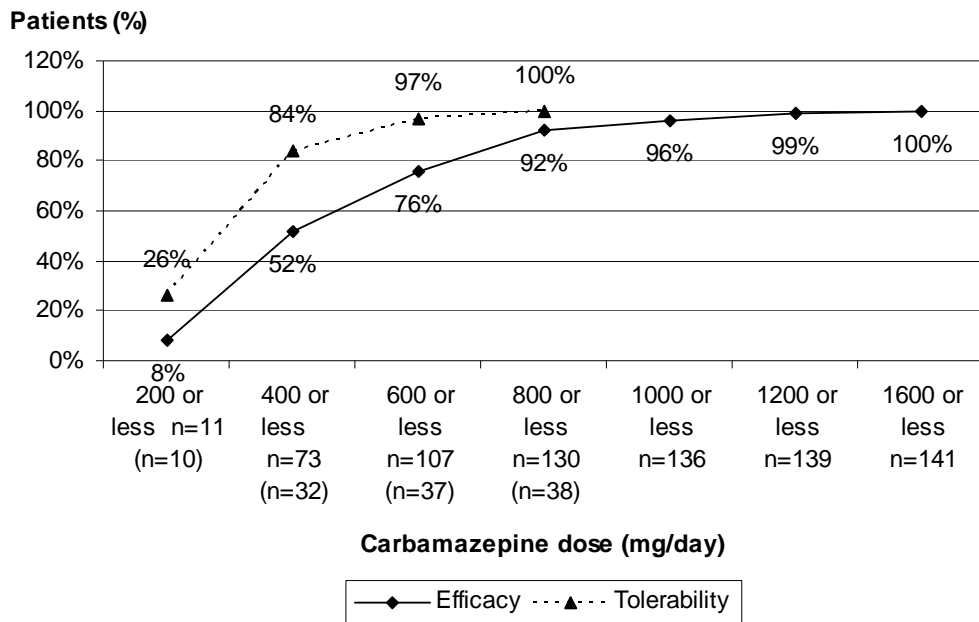
Figure 18. Seizure freedom achieved on carbamazepine (n=141) and its rate of withdrawal due to side effects (n=38) among various dose ranges.

3.3.8.4. Topiramate

In patients who achieved remission while on topiramate (n = 31), 600 mg/day was the maximum dose at which all responders had seizure freedom. 97% of this group of patients managed to obtain complete seizure control while on a dose as low as one third or less than that maximum dose i.e. ≤ 200 mg/day. All the patients (100%) who discontinued topiramate due to side effects (n = 12) were on a dose of ≤ 200 mg/day that is two thirds of the daily defined dose (300 mg/day) (Figure 19).
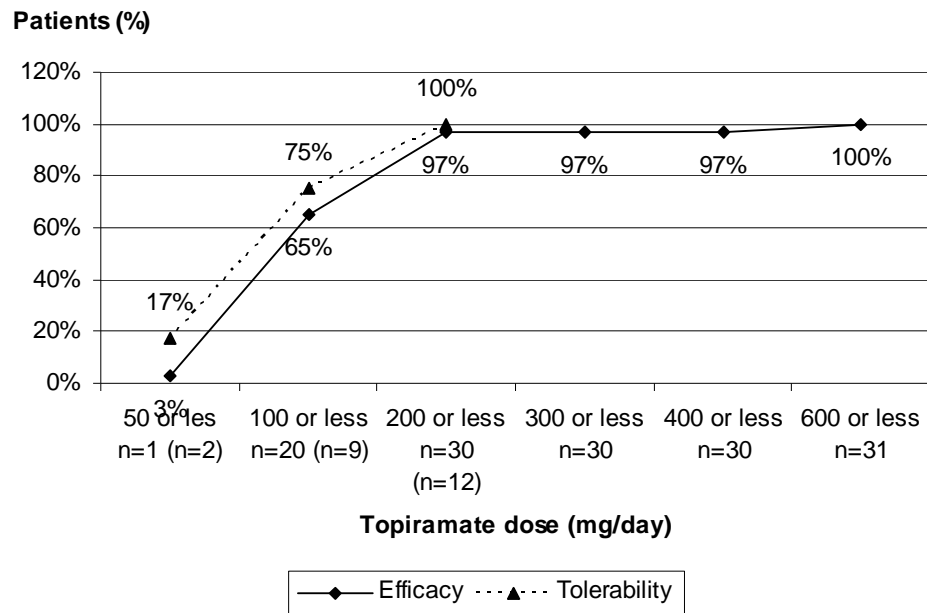
Patients (%)

Figure 19. Seizure freedom achieved on topiramate (n=31) and its rate of withdrawal due to side effects (n=12) among various dose ranges.

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3.3.8.5. Oxcarbazepine

The maximum dose of oxcarbazepine required for all patients to obtain remission was 1500 mg/day. 96% of these patients were able to achieve seizure freedom while being applying three fourths or lower than that maximum dose i.e. ≤ 1200 mg/day. In terms of tolerability of oxcarbazepine, 91% of patients who discontinued this agent (n = 11) were taking a dose of ≤ 900 mg/day that is slightly lower than the recommended daily defined dose (1000 mg/day) (Figure 20).
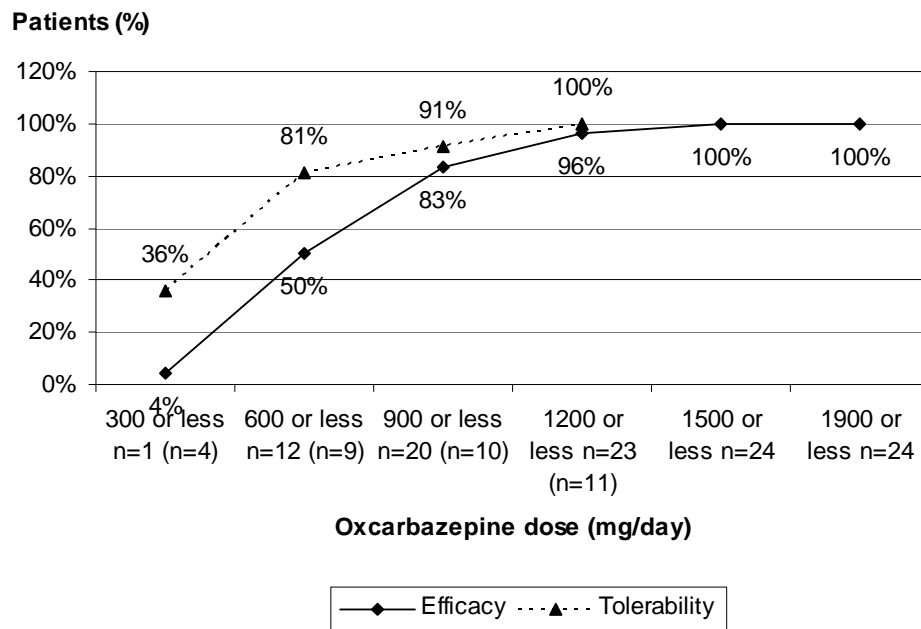
Figure 20. Seizure freedom achieved on oxcarbazepine (n=24) and its rate of withdrawal due to side effects (n=11) among various dose ranges.

3.3.8.6. Levetiracetam

Among patients who achieved remission while being on levetiracetam (n = 33), 91% of these patients were on a dose of ≤ 2000 mg/day that is two thirds of the maximum dose required for all patients on this drug to reach a state of complete seizure control. Among patients who discontinued levetiracetam due to side effects (n = 7), 86% were on a dose of ≤ 1000 mg/day which is two thirds of the recommended daily defined dose (1500 mg/day) (Figure 21).
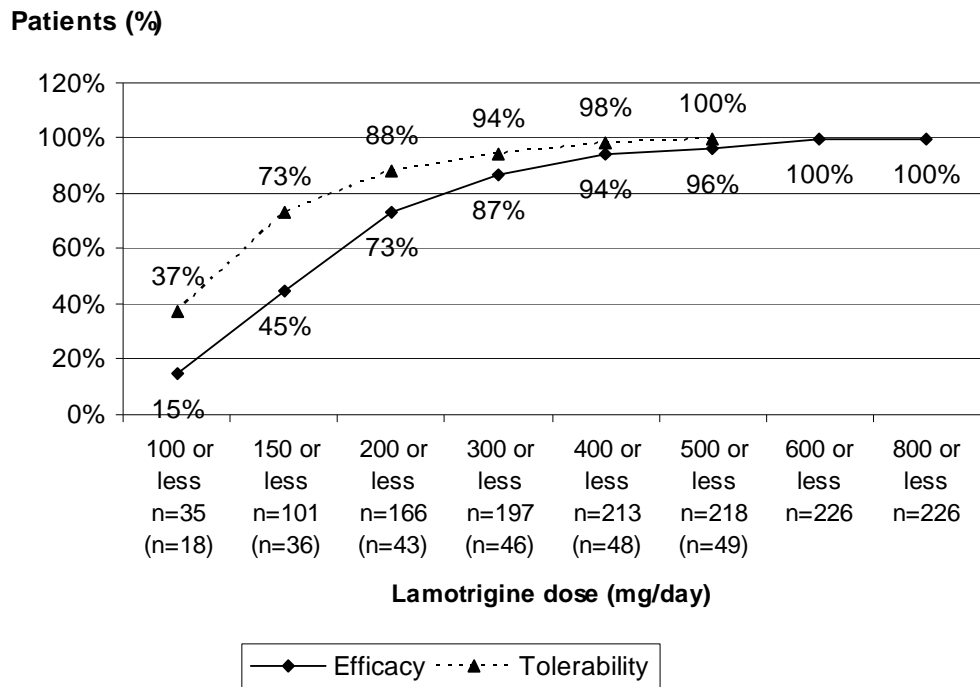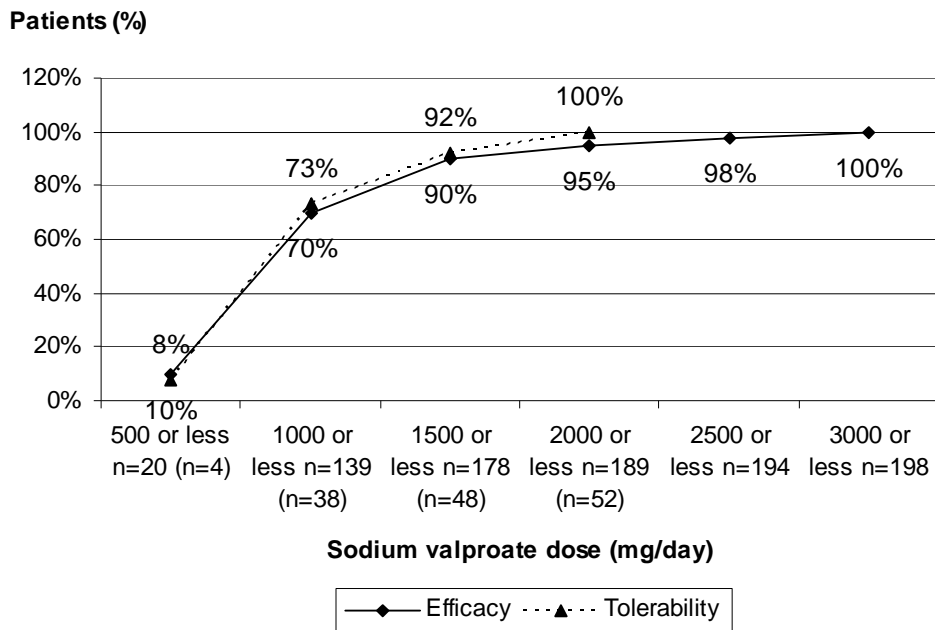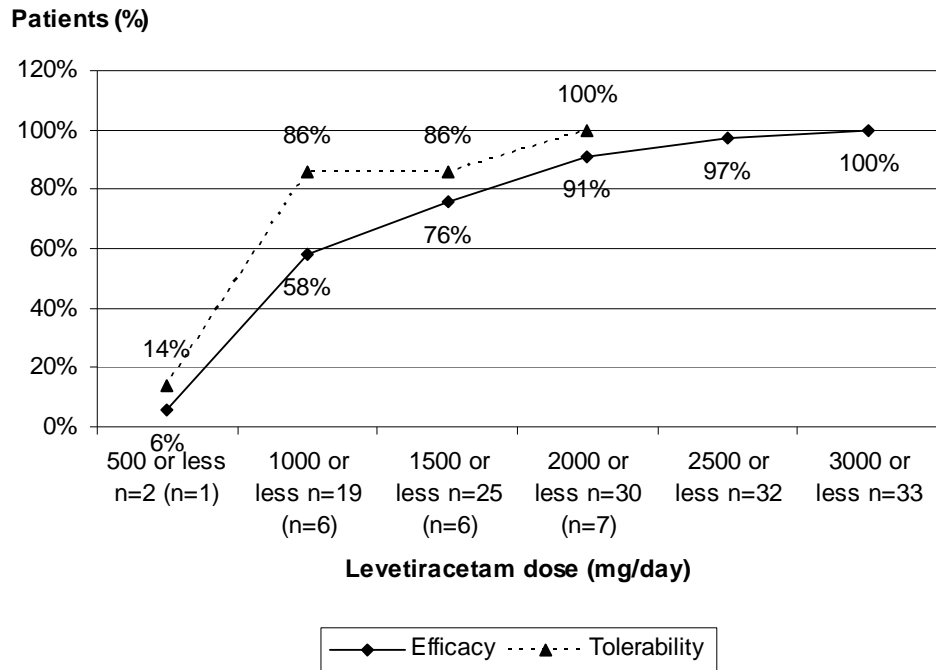

Figure 21. Seizure freedom achieved on levetiracetam (n=33) and its rate of withdrawal due to side effects (n=7) among various dose ranges.

3.4. Defining refractory epilepsy

This study used a cut off point as 50% of the daily defined dose to be the limit below which the failure of treatment will be due to poor tolerability while above that level, failure would be due to lack of efficacy of the drug.

After failure of the first treatment regimen with monotherapy due to lack of efficacy (n = 347), the number of responders among those who applied the second regimen (n = 223) constituted 31% (n = 69). Patients in whom treatment had failed in the first regimen due to poor tolerability were 135, 104 of whom were started on the second regimen with a response rate of 45% (n = 47) (Table 44 and Flow Chart 3).

In patients who failed of the first and second treatment regimens due to lack of efficacy and started on the third schedule (n = 70), the response rate was 19% (n = 13) compared 20% (n = 6) in those who failed the first regimen due to lack of efficacy and second due to poor tolerability and then were started on their third schedule (n = 30).

Failure of the first and second treatment regimens due to poor tolerability and starting on the third schedule (n = 12) was associated with a response rate of 25% (n = 3). In contrast, failure of the first regimen due to poor tolerability and the second due to lack of efficacy with starting the third schedule subsequently (n = 29) has resulted in a response rate of 41% (n = 12) (Table 44 and Flow Chart 3).

Unfortunately, the lower number of patients following the third treatment regimen has limited the capability to compare between the two different types of treatment failures.

First regimen n= 1098	LOE n= 347	Second regimen n= 223	RES n=69				
			LOE n= 107	Third regimen n= 70	RES n= 13		
					LOE n= 37	Forth regimen n=19	RES (n=2)
							LOE (n=10)
							PT (n=7)
					PT n= 20	Forth regimen n=12	RES (n=2)
							LOE (n=6)
							PT (n=4)
			PT n= 47	Third regimen n= 30	LOE n=18	Forth regimen n=8	RES (n=0)
							LOE (n=4)
							PT (n=4)
					PT n=6	Forth regimen n=3	RES (n=0)
							LOE (n=1)
							PT (n=2)
					RES n=6		
	PT n= 135	Second regimen n= 104	LOE n=41	Third regimen n=29	RES n=12		
					LOE n=11	Forth regimen n=6	RES (n=0)
							LOE (n=5)
							PT (n=1)
					PT n=6	Forth regimen n=4	RES (n=3)
							LOE (n=1)
							PT (n=0)
			PT n= 16	Third regimen n=12	LOE n=6	Forth regimen n=3	RES (n=1)
							LOE (n=1)
							PT (n=1)
					PT n=3	Forth regimen n=2	RES (n=0)
							LOE (n=1)
							PT (n=1)
					RES n=3		
			RES n=47				
	RES n= 544						

Table 44. Failure of treatment despite reaching 50% of the daily defined dose.
RES: responders, LOE: failure of treatment due to lack of efficacy, PT: failure of treatment due to poor tolerability.
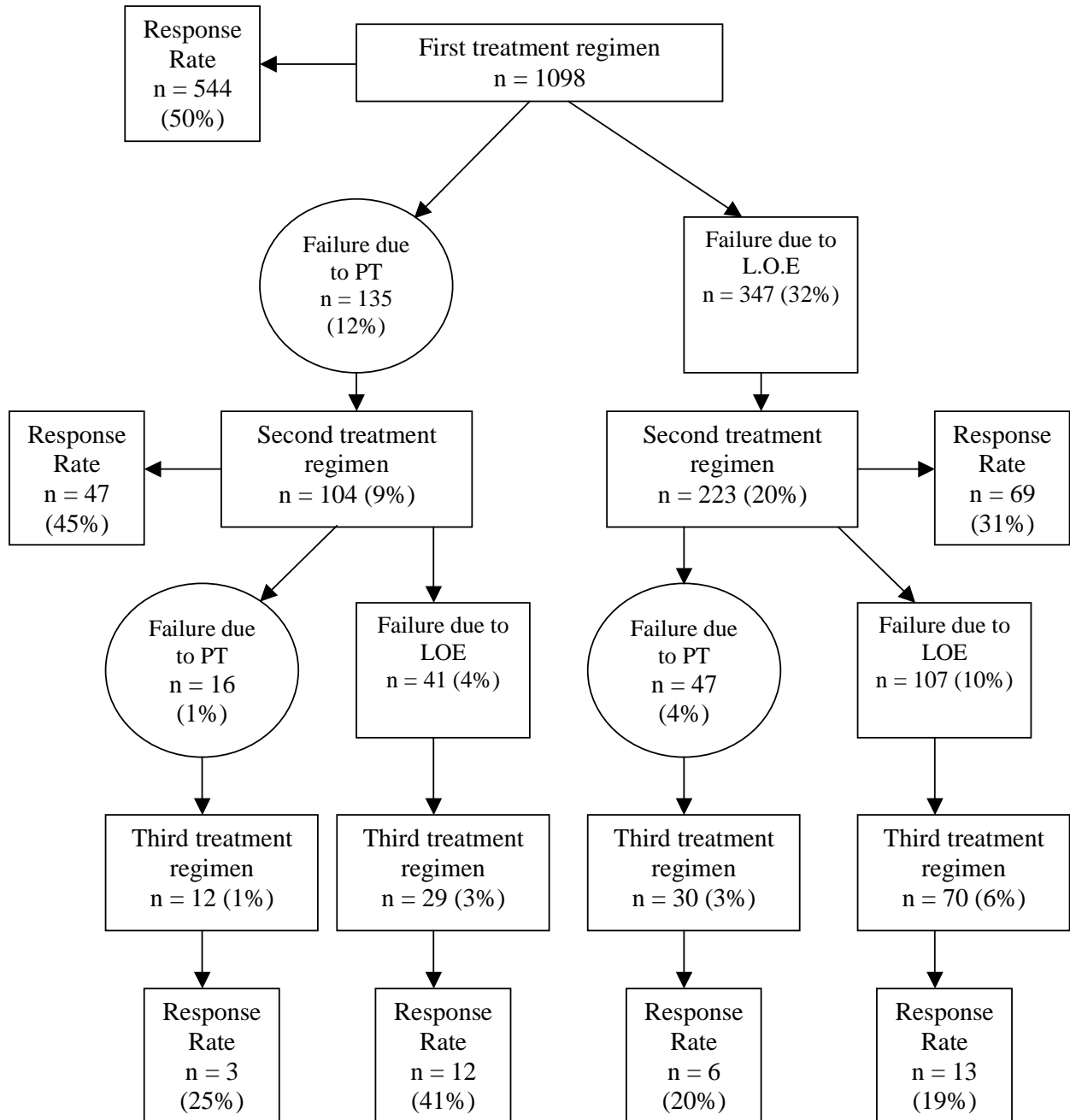
Flow Chart 3. Failures of treatment due to lack of efficacy (LOE) and poor tolerability (PT) based on 50% of the daily defined dose.

Changing the cut off point to 25% of the daily defined dose resulted in an increase in the number of patients with failure of treatment regimens due to lack of efficacy while failure due to poor tolerability became lower compared to the 50% daily dose threshold.

Analysis showed 41% of patients had failure of the first regimens due to lack of efficacy with a response rate in the second regimen of 34%, failure of the first regimen due to poor tolerability comprised 3% of the study population with a response rate in this group of patients of 50% (Table 45 and Flow Chart 4).

The response rate of patients who failed two regimens due to lack of efficacy was 25% compared to 0% (nil) in those who failed two regimens due to poor tolerability. There were no patients who developed seizure freedom after treatment failures in the first regimen due to lack of efficacy and second regimen due to poor tolerability while on the opposite i.e. failure of the first regimen due to poor tolerability and second schedule due to lack of efficacy was associated with a response rate of 33% (Table 45 and Flow Chart 4).

First regimen n= 1098	LOE n= 452	Second regimen n= 303	RES n=104				
			LOE n= 190	Third regimen n= 130	RES n= 32		
					LOE n= 88	Forth regimen n=46	RES (n=5)
							LOE (n=35)
							PT (n=6)
					PT n= 10	Forth regimen n=7	RES (n=2)
							LOE (n=3)
							PT (n=2)
			PT n= 9	Third regimen n= 4	LOE n=4	Forth regimen n=0	RES (n=0)
							LOE (n=0)
							PT (n=0)
					PT n=0	Forth regimen n=0	RES (n=0)
							LOE (n=0)
							PT (n=0)
					RES n=0		
	PT n= 30	Second regimen n= 24	LOE n=11	Third regimen n=6	RES n=2		
					LOE n=4	Forth regimen n=3	RES (n=1)
							LOE (n=2)
							PT (n=0)
					PT n=0	Forth regimen n=0	RES (n=0)
							LOE (n=0)
							PT (n=0)
			PT n= 1	Third regimen n=1	LOE n=1	Forth regimen n=1	RES (n=0)
							LOE (n=1)
							PT (n=0)
					PT n=0	Forth regimen n=0	RES (n=0)
							LOE (n=0)
							PT (n=0)
					RES n=0		
			RES n=12				
	RES n= 544						

Table 45. Failure of treatment despite reaching 25% of the daily defined dose.
RES: responders, LOE: failure of treatment due to lack of efficacy, PT: failure of treatment due to poor tolerability.
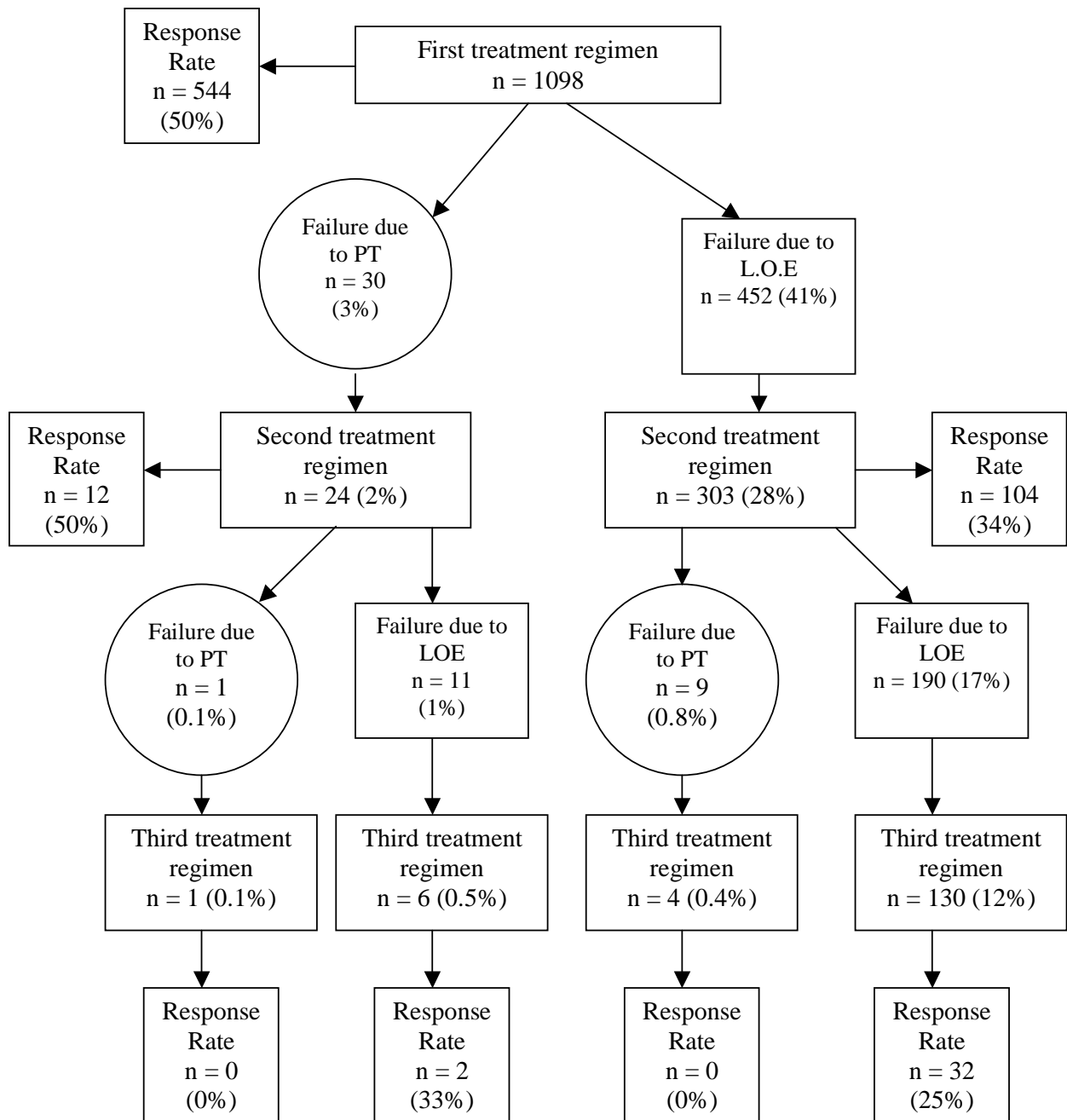
Flow Chart 4. Failures of treatment due to lack of efficacy (LOE) and poor tolerability (PT) based on 25% of the daily defined dose.

When the cut off point was moved to 75% of the daily defined dose, there was a wider dose range of poor tolerability and consequently higher number of patients with failure of treatment due to poor tolerability. On the other hand, number of patients with failure of treatment due to lack of efficacy was lower than that in case when cut off is 50% of the daily defined dose.

After failure of the first treatment schedule due to lack of efficacy (21%), the response rate in the second schedule was 29% compared to 42% response rate in the second regimen in case of failure of the first schedule due to poor tolerability (23%) (Table 46 and Flow Chart 5).

 Patients with failure of two treatment regimens due to lack of efficacy had a response rate of 13% in comparison to 39% response rate in case of patients with failure of two schedules due to poor tolerability. In case of failure of the first regimen due to lack of efficacy and second schedule due to poor tolerability, the response rate was 12% while it was 33% in the opposite sequence i.e. failure of the first regimen due to poor tolerability and second schedule due to lack of efficacy (Table 46 and Flow Chart 5).

First regimen		Second regimen		Third regimen		Forth regimen	
First regimen n= 1098	LOE n= 232	Second regimen n= 156	RES n=45				
			LOE n= 58	Third regimen n= 38	RES n= 5		
					LOE n= 15	Forth regimen n=8	RES (n=1)
							LOE (n=5)
							PT (n=2)
					PT n= 18	Forth regimen n=10	RES (n=2)
							LOE (n=4)
							PT (n=4)
			PT n= 53	Third regimen n= 34	LOE n=15	Forth regimen n=7	RES (n=0)
							LOE (n=0)
							PT (n=7)
					PT n=15	Forth regimen n=8	RES (n=0)
							LOE (n=3)
							PT (n=5)
					RES n=4		
	PT n= 250	Second regimen n= 171	LOE n=43	Third regimen n=33	RES n=13		
					LOE n=7	Forth regimen n=6	RES (n=0)
							LOE (n=4)
							PT (n=2)
					PT n=13	Forth regimen n=6	RES (n=2)
							LOE (n=1)
							PT (n=3)
			PT n= 57	Third regimen n=36	LOE n=10	Forth regimen n=4	RES (n=1)
							LOE (n=1)
							PT (n=2)
					PT n=14	Forth regimen n=8	RES (n=2)
							LOE (n=2)
							PT (n=4)
					RES n=12		
			RES n=71				
	RES n= 544						

Table 46. Failure of treatment despite reaching 75% of the daily defined dose.
RES: responders,   LOE: failure of treatment due to lack of efficacy, PT: failure of treatment due to poor tolerability.

Response
Rate
n = 544
(50%)

First treatment regimen
n = 1098

Failure due
to PT
n = 250
(23%)

Failure due to
L.O.E
n = 232 (21%)

Response
Rate
n = 71
(42%)

Second treatment
regimen
n = 171 (16%)

Second treatment
regimen
n = 156 (14%)

Response
Rate
n = 45
(29%)

Failure due
to PT
n = 57
(5%)

Failure due to
LOE
n = 43
(4%)

Failure due
to PT
n = 53
(5%)

Failure due to
LOE
n = 58 (5%)

Third treatment
regimen
n = 36 (3%)

Third treatment
regimen
n = 33 (3%)

Third treatment
regimen
n = 34 (3%)

Third treatment
regimen
n = 38 (3%)

Response
Rate
n = 12
(33%)

Response
Rate
n = 13
(39%)

Response
Rate
n = 4
(12%)

Response
Rate
n = 5
(13%)
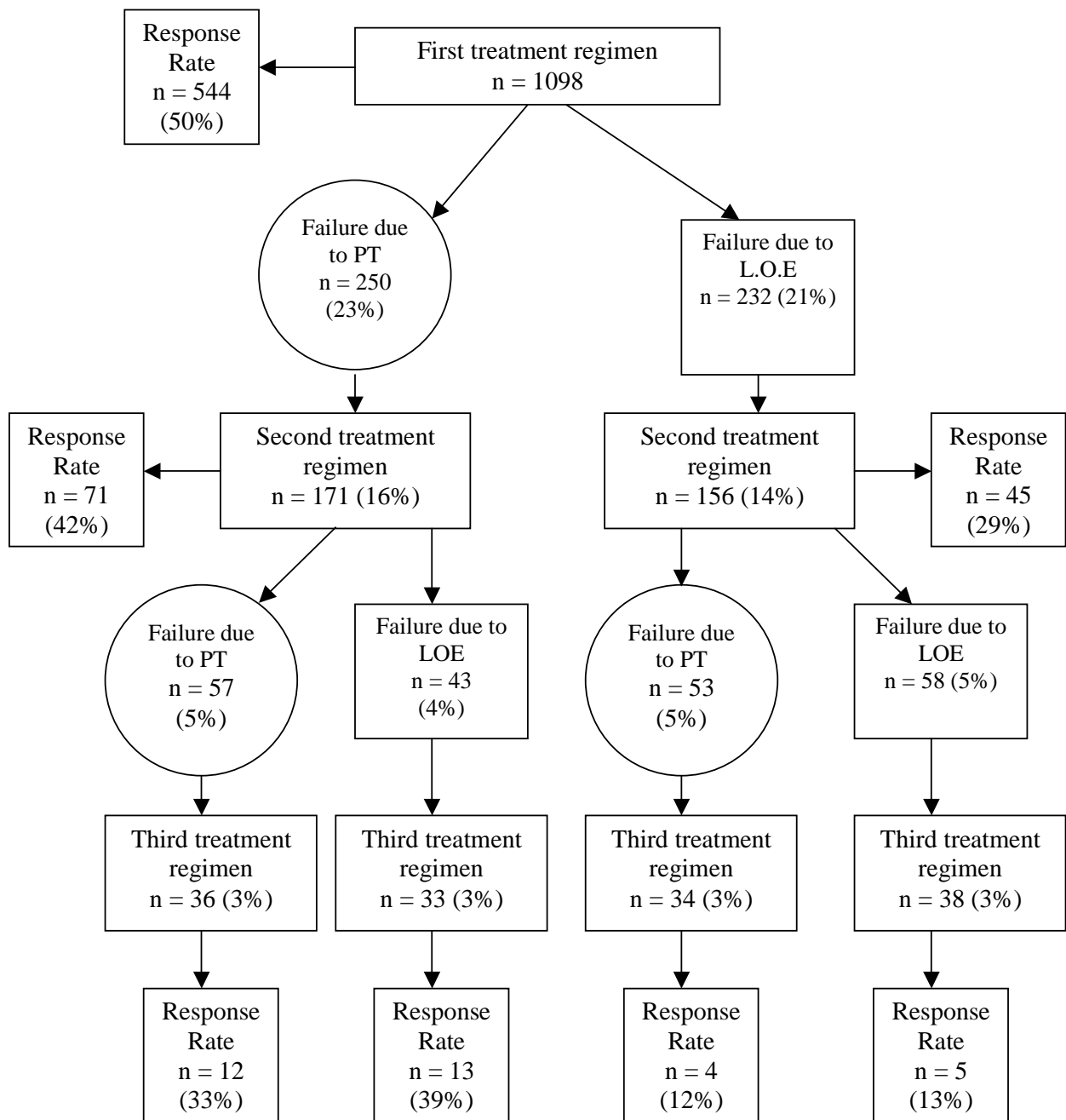
Flow Chart 5. Failures of treatment due to lack of efficacy (LOE) and poor tolerability (PT) based on 75% of the daily defined dose

Chapter 4. Discussion

In this chapter, discussion focused initially on special populations i.e. age groups, gender, idiopathic generalised epilepsy and focal epilepsy, followed by consideration of the whole study population with regard to the ultimate outcome of epilepsy, AED response, dosage, mechanism of action, generations of AEDs and definition of drug resistant epilepsy.

4.1. Age groups

Calculation of the remission rate among various age groups of patients recruited in this study was performed at the end of the study based on age on starting AED treatment.

Patients in the age group less than 20 years had a high remission rate followed by a gradual decline till it reached the minimum at age group (40-49). After the age of 50, there was an elevation of response rate as the age of epilepsy patients increases till it reached the highest in patients ≥ 80 years old. Therefore, epilepsy patients in age groups older than 50 years tended to have a higher rate of seizure freedom compared to adults with age groups between 20 and 49 years old. Similar results were noticed by Brodie and Kwan who reported a dramatic elevation in the remission rate after the age of 50 years (Figure 22) (Brodie and Kwan, 2005).

In order to be able to compare these results with other relevant studies, patients of this investigation have been redistributed into three major groups based on their age; adolescents (< 20 years old) with median follow up of 9 years, adults (between 20 and 64 years old with median follow up of 8 years) and elderly patients (≥ 65 years old with median follow up of 9 years) (Table 47).

Patients groups	Age (years)	n	Median follow up (years)	Responders (%)	Non-responders (%)
Adolescents	< 20	241	9	173 (72 %)	68 (28 %)
Adults	20 - 64	735	8	471 (64%)	264 (36%)
Elderly	≥ 65	122	9	106 (87%)	16 (13%)
Total		**1098**		**750**	**348**

Table 47. Outcome of epilepsy among the three major age groups.

Findings in table 47 are consistent with those of Mohanraj and Brodie from the same Epilepsy Unit but on a smaller population with shorter duration of follow up; patients were diagnosed with epilepsy and started their first ever AED treatment between July 1982 and May 2001 (Mohanraj and Brodie, 2006). They observed the same pattern of remission rate that is initially high in adolescents group of patients, with a drop in adults' age group then an elevation again in elderly patients to reach its highest rate (Figure 23).
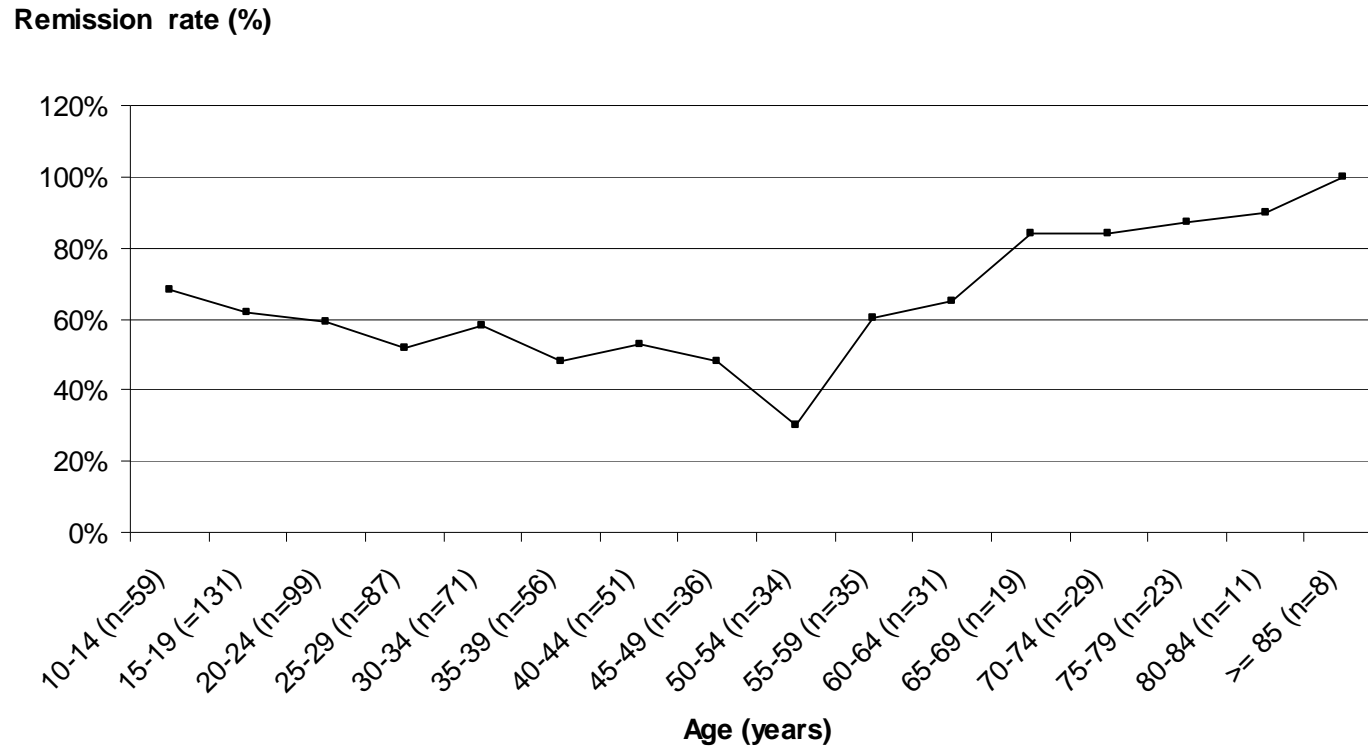
Remission rate (%)

Figure 22. Remission rates among age groups (Brodie and Kwan, 2005).

Responders (%)
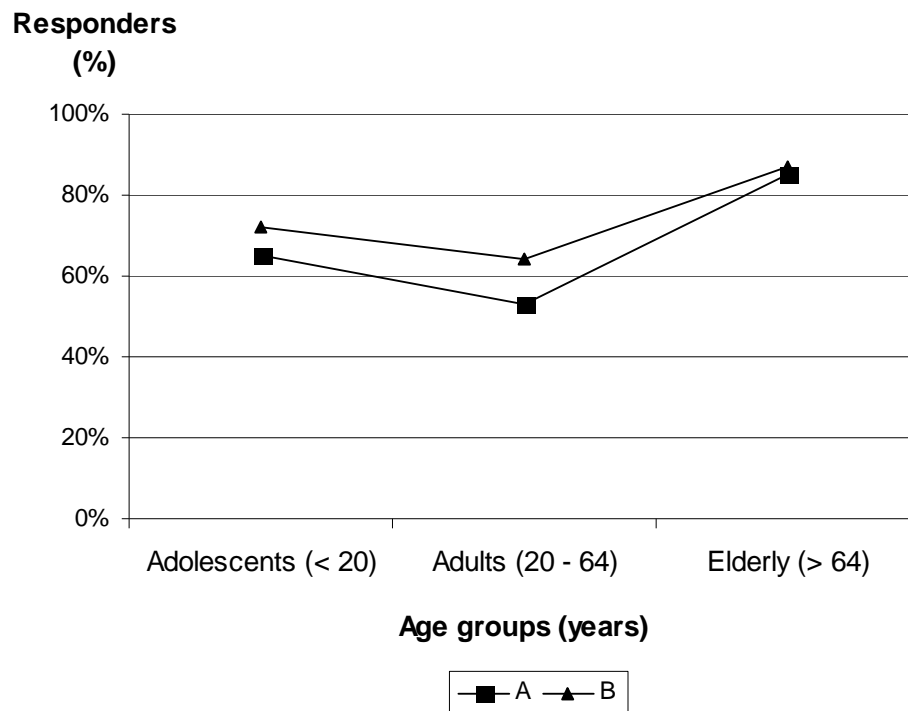
Figure 23. A comparison of remission rates between A (Mohanraj and Brodie, 2006) and B (this study).

The higher response rate in elderly patients might be explained by the low epileptogenicity of underlying cerebral lesions in these patients and the low risk of genetic predisposition for recurrent seizure activity or better compliance. Unfortunately, few randomized clinical trials are available to evaluate the efficacy and tolerability of individual AEDs in elderly patients with newly diagnosed epilepsy although it is an age group with amongst the highest incidence of epilepsy (Stephen and Brodie, 2000).

When calculating the efficacy and tolerability of AEDs among age groups, only the first treatment regimen was employed because of the difficulty of performing these calculations in the subsequent regimens due to individual differences of starting each regimen among

patients. Also, as adolescent patients move toward adulthood and adults become elderly, this leads to overlapping results.

In the first treatment regimen of this study among the three age groups, adolescents and adults had similar total cumulative efficacy of drugs (49% and 48%, respectively) while - as in the case of the ultimate outcome of epilepsy - elderly patients with epilepsy showed the highest total cumulative efficacy of AEDs in the first schedule (61%) (Table 48). The variation in efficacy between these three age groups resulted in a significant statistical difference (p-value = 0.01). Minimal differences were observed in total cumulative tolerability of AEDs among the three age groups. Elderly patients showed a slightly lower tolerability (higher rate of withdrawal due to side effects) compared to the other two groups with insignificant difference (p-value = 0.7).

The highest total cumulative efficacy of AEDs in elderly patients may be due to the same factors assumed to be responsible for the higher remission rate observed by the end of study in this group. These factors include better compliance, the low risk of genetic predisposition for recurrent seizures and the low epileptogenecity of underlying cerebral lesions.

Patients groups	Age (years)	n	Efficacy in first regimen (%)	Tolerability in first regimen (%)
Adolescents	< 20	241	119 (49%)	31 (13%)
Adults	20 – 64	735	350 (48%)	106 (14%)
Elderly	≥ 65	122	75 (61%)	19 (16%)
Total		**1098**	**544**	**157**

Table 48. Effectiveness of all AEDs in the first regimen among the three major age groups.

Stephen and colleagues - defining remission as developing a minimum period of seizure freedom of at least 12 months - showed total cumulative efficacy of AEDs of 63% in the first AED treatment regimen in elderly patients with newly diagnosed focal epilepsy referred between 1982 and 2003, a value exactly the same as in this report (63%) (Stephen et al., 2006). They also showed a total cumulative tolerability of 12% in the first schedule compared to 16% in this study. AEDs with the highest prescription rate were the same in both studies; these included carbamazepine, sodium valproate and lamotrigine (Table 49) (Stephen et al., 2006). Based on the findings of Stephen et al., there was a total remission rate of 79% by the end of study, 93% of these had seizure freedom while on monotherapy and 7% on polypharmacy. This analysis showed a remission rate of 87% by the end of study, 96% of these patients developed seizure freedom on monotherapy and 4% on combined therapy.

The higher total remission rate of this study (around 26 years of follow up) compared to Stephen and colleagues (2006) observations (with follow up of 24 years approximately) might indicate that the longer duration of patients follow up with consecutive AED treatment regimens will be associated with the higher chances of developing seizure freedom eventually even in terms of individual AEDs (Table 49).

AED	A	B
Carbamazepine		
N	39	33
Efficacy (%)	26 (67%)	24 (73%)
Tolerability (%)	5 (13%)	5 (15%)
Sodium valproate		
N	23	23
Efficacy (%)	15 (65%)	17 (74%)
Tolerability (%)	2 (9%)	3 (13%)
Lamotrigine		
N	35	30
Efficacy (%)	22 (63%)	20 (67%)
Tolerability (%)	6 (17%)	5 (17%)

Table 49. Effectiveness of the three commonly prescribed AEDs in the first regimen in elderly patients with focal epilepsy, comparison between A (Stephen et al., 2006) and B (this study).

Among adolescent patients of this study with age less than 20 years old (n = 241), remission rate at the end of study was 72% with a seizure freedom rate of 49% following the first treatment regimen. Carbamazepine, sodium valproate and lamotrigine constituted the drugs with the highest prescription rate in the first regimen (40, 63 and 101, respectively). Efficacy among these three agents was 58% for carbamazepine followed by sodium valproate (54%) and lamotrigine (50%) without any significant difference (p-value = 0.6). Carbamazepine also showed the best tolerability profile in the first regimen with the lowest withdrawal rate due to side effects of (8%) followed by sodium valproate (11%) and lamotrigine (12%) but without any statistical difference between them (p-value = 0.7).

Adult patients in the age group between 20 and 64 years old (n = 735) had 64% as a total remission rate over the course of the study and 48% after the first treatment regimen. In the first regimen, AEDs with the highest prescription rate were lamotrigine (n =232), sodium

valproate (n =187) and carbamazepine (n =151) with lamotrigine as the most efficacious agent (53%) and also best tolerability (9%). There was insignificant difference observed between these three AEDs in terms of efficacy (p-value = 0.3) and tolerability (p-value = 0.2).

Elderly patients $\geq$ 65 years old (n = 122) had a seizure freedom rate of 87% at the end of study and 61% following the first treatment regimen. During the first regimen, AEDs with the highest prescription rate were lamotrigine (n = 39) followed by carbamazepine (n = 33) and sodium valproate (n = 24). Sodium valproate had the highest efficacy (75%) followed by carbamazepine (73%) and lamotrigine (62%) with insignificant statistical difference (p-value = 0.4), while sodium valproate was also the best tolerated (13%) followed by carbamazepine (15%) and lamotrigine (18%) without any statistical difference (p-value = 0.9). Similar effects were observed by Morgan and colleagues who noted an increased rate of continuation on sodium valproate treatment in the first regimen associated with increasing age i.e. from 71% in those under 5 years of age to 84% in cases of $\geq$ 75 years old (Morgan et al., 2004).

Elderly patients tend to be more susceptible to side effects of AEDs compared to younger populations (Arroyo and Kramer, 2001). In the current investigation, elderly patients had the highest rate of AED withdrawal due to side effects compared to adults and adolescents (Table 48) particularly in the case of second generation AEDs (Table 50). This increased susceptibility to development of side effects in elderly patients might be due to the lower performance of various body systems and the physiological changes that are characteristics of this age group. Lamotrigine has significantly better tolerability compared with carbamazepine but with similar efficacy (time to first seizure) (Brodie et al., 1999). Lamotrigine is better tolerated in terms of withdrawal due to side effects compared with gabapentin and carbamazepine without significant difference in rates of seizure freedom during the first 12 months of treatment (Rowan et al., 2005). This was not the case in our study in which lamotrigine and carbamazepine showed a similar tolerability profile (15%) (Table 50), while in terms of efficacy, carbamazepine was more superior (73%) to lamotrigine (62%) in patients with aged $\geq$ 65 years old (Table 51).

There was a noticeable variation between the age groups in the efficacy of first and second generations on AEDs in the first treatment regimen (Table 51). Adolescents patients with epilepsy in this study showed a higher total cumulative efficacy of first generation agents i.e. carbamazepine, sodium valproate and phenytoin (55%) compared to second generation

drugs (lamotrigine, gabapentin, levetiracetam, topiramate, oxcarbazepine and tiagabine) (48%) with insignificant statistical difference (p-value = 0.2). The opposite was the case in adult patients in whom the total cumulative efficacy of older drugs (48%) was lower than the newer drugs (55%) associated with insignificant statistical difference (p-value = 0.05). There was a big variation between the total cumulative efficacy of the two generations drugs in elderly patients. The efficacy of first generation AEDs (75%) was much higher than second generation drugs (55%) with a significant statistical difference noticed (p-value = 0.03).

Tolerability of different generations of AEDs among age groups in the first treatment schedule was also analyzed in this study with small differences observed between the first and second generations drugs in the adolescent (3% variation with p-value = 0.3) and adult groups (1% variation and p-value = 0.4). Again, the elderly patients in this study showed a relatively bigger difference between the total cumulative tolerability of the two generations AEDs in comparison to other age groups. This group of patients tolerated older drugs with a cumulative rate of withdrawal due to side effects of 14% compared with newer drugs in which the cumulative rate of withdrawal due to side effects was 20% (Table 50) lacking any significant statistical difference (p-value = 0.3).

Among elderly patients on monotherapy in the last treatment regimen (n = 113), those with focal epilepsy comprised 109 patients. Remission rate of elderly patients with focal epilepsy on sodium channels blocking AEDs was 89% compared to 90% in those on AEDs working mainly by potentiation of GABA inhibitory effect with insignificant difference noticed (p-value = 0.8). Only 4 elderly patients with idiopathic generalised epilepsy were identified limiting the ability to perform an accurate analysis with regard to the correlation between the ultimate outcome of epilepsy and the mechanism of action of AEDs on the last treatment schedule.

AED	Adolescents (< 20 years) (n=241)	Adults (20 – 64) (n=735)	Elderly (> 64 years) (n=122)
CBZ	3 (8%) (40)	21 (14%) (151)	5 (15%) (33)
VPA	7 (11%) (63)	24 (13%) (187)	3 (13%) (24)
PHT	0 (0)	1 (20%) (5)	0 (2)
LTG	12 (12%) (101)	20 (9%) (232)	6 (15%) (39)
GBP	0 (3)	2 (13%) (15)	0 (1)
LEV	1 (17%) (6)	5 (15%) (33)	0 (3)
TPM	3 (50%) (6)	4 (13%) (32)	2 (50%) (4)
OXC	1 (20%) (5)	5 (29%) (17)	3 (33%) (9)
TGB	0 (6)	3 (38%) (8)	0 (0)
Generation of AEDs			
First	10%	13%	14%
Second	13%	12%	20%

Table 50. Tolerability (%) of individual and generations of AEDs among various age groups in the first treatment regimen (monotherapy).

AED	Adolescents (< 20 years) (n=241)	Adults (20 – 64) (n=735)	Elderly (> 64 years) (n=122)
CBZ	23 (58%) (40)	68 (45%) (151)	24 (73%) (33)
VPA	34 (54%) (63)	94 (50%) (187)	18 (75%) (24)
PHT	0 (0)	2 (40%) (5)	2 (100%) (2)
LTG	50 (50%) (101)	122 (53%) (232)	24 (62%) (39)
GBP	1 (33%) (3)	12 (80%) (15)	1 (100%) (1)
LEV	3 (50%) (6)	21 (64%) (33)	2 (67%) (3)
TPM	3 (50%) (6)	19 (59%) (32)	2 (50%) (4)
OXC	3 (60%) (5)	8 (47%) (17)	2 (22%) (9)
TGB	1 (17%) (6)	4 (50%) (8)	0 (0)
Generation of AEDs			
First	55%	48%	75%
Second	48%	55%	55%

Table 51. Efficacy (%) of individual and generations of AEDs among various age groups in the first treatment regimen (monotherapy).

To sum up, among the three age groups of epilepsy patients i.e. adolescents, adults and elderly, elderly patients had the highest remission rate by the end of study and also the highest total cumulative efficacy of AEDs in the first schedule. A longer duration of follow up of epilepsy patients with various AED treatment regimens was associated with a higher chance of developing remission eventually.

The total cumulative efficacy of the two generations of AEDs demonstrated a higher efficacy of the first generation AEDs compared to second generation agents (p-value = 0.2) among adolescents patients. Adult patients with epilepsy had an opposite pattern with a lower efficacy of older drugs than newer agents (p-value = 0.05). Among elderly group of patients, first generation agents were significantly more efficacious than newer drugs (p-value = 0.03). In terms of total cumulative tolerability, minimal differences were noticed between the two generations of AEDs in case of adolescents and adults patients. Elderly patients had a bigger difference between the two generations of AEDs in favour of older drugs with insignificant difference.

4.2. Gender

According to (Kotsopoulos et al., 2002), epilepsy is more common in males than females probably as a result of the more likely exposure to risk factors of epilepsy in males than females e.g. head trauma and CNS infections. Following treatment, my study was able to detect a statistical significant difference in the outcome of epilepsy between males and females (p-value = 0.018). Male patients with epilepsy showed a rate of complete seizure freedom of 71% compared to female patients who had a lower rate of developing remission (65%). This might be because epilepsy tends to raise more medical issues in females than males with a consequent withdrawal of AEDs treatment in females (Morrell, 1996). Some of these issues include: cosmetic reasons as some AEDs can lead to weight gain, risk of teratogenecity in pregnant and child bearing age women, disturbances in bone health, fertility, menstruation and ovulation and failure of hormonal contraception.

For most of the AEDs prescribed in this study i.e. carbamazepine, sodium valproate, lamotrigine, oxcarbazepine, topiramate, phenytoin, levetiracetam and tiagabine, the efficacy of drugs was higher in males than females except for gabapentin where efficacy was similar. Carbamazepine, sodium valproate, lamotrigine were the AEDs with the highest prescription rate; among these, sodium valproate exhibited a significant statistical difference of efficacy between males and females patients (p-value = 0.006) (Table 52).

The total cumulative efficacy of all AEDs prescribed in this study in males (55%) was also higher than that in females (44%) with a significant statistical difference (p-value < 0.001). With regard to generations of AEDs, males showed a higher significant efficacy than females to both first (p-value = 0.02) and second generation AEDs (p-value < 0.001) (Table 53).

	Efficacy		Tolerability	
	males	females	males	females
Carbamazepine	51%	48%	10%	18%
	(n=164)	(n=120)	(n=164)	(n=120)
Sodium valproate	54%	40%	9%	18%
	(n=243)	(n=163)	(n=243)	(n=163)
Lamotrigine	55%	46%	8%	12%
	(n=166)	(n=291)	(n=166)	(n=291)

Table 52. Gender differences of efficacy and tolerability among the three commonly prescribed AEDs.

Gender	Efficacy among first generation AEDs (%)	Efficacy among second generation AEDs (%)
Males	53%	59%
Females	44%	45%

Table 53. Gender differences of efficacy among generations of AEDs.

Tolerability profile of AEDs used in this study indicated a better tolerability in males than females for most of the drugs prescribed i.e. carbamazepine, sodium valproate, lamotrigine, oxcarbazepine, topiramate, phenytoin, levetiracetam and tiagabine. Also, as for efficacy, gabapentin was the only drug with the same tolerability in males and females. Lower body weight of females may be the reason that makes males more readily tolerate these drugs than females as lower body weight leads to a high serum concentration more rapidly which will consequently raise the risk of developing side effects in females. Among the three commonly prescribed agents i.e. carbamazepine, sodium valproate and lamotrigine, tolerability differences between males and females were statistically significant for carbamazepine (p-value = 0.03) and sodium valproate (p-value = 0.006) (Table 52). Male patients with epilepsy tolerated AEDs better with a lower rate of side effects (9%) than females (17%) with a significant statistical difference (p-value < 0.001). Gender differences in tolerability among generations of AEDs showed that male patients tolerated drugs better than females for both first (p-value = 0.001) and second generation agents (p-value = 0.01) (Table 54).

Gender	Tolerability among first generation AEDs (%)	Tolerability among second generation AEDs (%)
Males	9%	9%
Females	18%	16%

Table 54. Gender differences of tolerability among generations of AEDs.

Although insignificant difference in the efficacy of lamotrigine by gender in patients with partial seizures has been reported (Glaxo, 1996), this study was able to demonstrate a significant difference (p-value = 0.03) between gender in patients with partial seizures on lamotrigine where 58% of male patients on this drug developed complete seizure control compared to 46% of females. The application of a different measure of efficacy of drugs i.e. 50% or more reduction in seizure frequency and median seizure reduction might be in part the reason behind the observed differences between the two studies. The same

scenario was also noticed by (Pledger et al., 1995) when topiramate was applied as add-on therapy in patients with partial-onset seizures; an insignificant difference was observed between males and females in terms of efficacy of the drug. When this project focused only on patients with partial seizures on topiramate, a statistical significant difference was demonstrated in the efficacy between males (70%) and females (41%) (p-value = 0.04) taking into consideration that this analysis was performed only on monotherapy.

In terms of AEDs prescription rate for older compared to newer drugs, Falip et al., found that 8% of men and 21% of women were treated with second generation AEDs as monotherapy (n= 496) (Falip et al., 2005). This study also demonstrated that females had a higher rate of second generation AEDs prescription (62%) than males (41%) in the first treatment schedule. Morgan and colleagues observed a significantly higher prescription rate for lamotrigine in females (57%) in comparison with males (23%) (Morgan et al., 2004). Increased rate of second generation AEDs prescription in females may be explained by the more frequent side effects of older agents in females such as teratogenicity, interference with contraception and weight gain. This analysis was only performed on the first treatment regimen because there is an overlap with first generation drugs as these drugs might be used in the second treatment regimen in case of failure of achieving complete seizure freedom in the first regimen in some patients.

When analyzed in terms of generations of AEDs, male patients with epilepsy in this study showed a lower total cumulative efficacy with first generation AEDs i.e. carbamazepine, sodium valproate and phenytoin (55%) compared with second generation agents i.e. lamotrigine, oxcarbazepine, topiramate, gabapentin, levetiracetam, tiagabine, vigabatrin and zonisamide (60%) with insignificant statistical difference (p-value = 0.2). The analysis showed almost the same difference between the two generations of drugs whether conducted in the first treatment schedule (p-value = 0.2) or on the total attempts of using these drugs at the end of study (p-value = 0.1) (Table 55). In contrast, female patients had the same total cumulative efficacy in the two generations (49%) in the first treatment regimen and similar findings were noted in terms of the total attempts at AEDs prescribtion (Table 55).

	Generation of AEDs	First treatment regimen	Total regimens
Efficacy in males	First	55%	53%
	Second	60%	59%
Efficacy in females	First	49%	44%
	Second	49%	45%

Table 55. Efficacy of first and second generation AEDs according to gender.

Only a minimal difference was observed in male patients between the total cumulative tolerability of older AEDs (9%) and newer drugs (10%) in the first treatment regimen. In the case of the total attempts of AEDs application, the total cumulative tolerability was exactly the same (9%) for the two generations of AEDs in males (Table 56). Similarly, total cumulative tolerability of the two generations of AEDs among females showed a very small difference (2%) in the first treatment regimen and in the total attempts of AEDs application (Table 56).

	Generation of AEDs	First treatment regimen	Total regimens
Tolerability in males	First	9%	9%
	Second	10%	9%
Tolerability in females	First	18%	18%
	Second	16%	16%

Table 56. Tolerability of first and second generation AEDs according to gender.

Among patients with idiopathic generalised epilepsy, male patients on monotherapy in the last treatment schedule showed a higher remission rate (79%) with AEDs acting primarily by blockage of sodium channels than females (69%) with insignificant difference (p-value = 0.2). In case of AEDs working mainly by potentiation of GABA inhibitory effect as monotherapy in the last regimen, males also demonstrated a higher remission rate (90%) compared to females (69%) with a significant statistical difference observed (p-value = 0.01). This difference might be because sodium valproate which is the AED with the highest prescription rate and highest efficacy against IGE patients belongs to this group. It is more commonly used by males than females because of its side effects are related more to females, such as the risk of teratogenicity in women of childbearing age and weight gain.

Among patients with focal epilepsy on monotherapy in the last AED regimen, remission rate was similar for male and female patients (75% and 73%, respectively) on AEDs acting mainly by blockage of sodium channels (p-value = 0.6). Also similar values were observed for males (70%) and females (74%) regarding the remission rate on AEDs acting primarily by potentiation of GABA inhibitory effect applied in the last regimen as monotherapy (p-value = 0.6).

In summary, this study demonstrated a highly significant difference for remission rate in male patients with epilepsy than in females following AEDs treatment. Efficacy analysis of the commonly prescribed AEDs demonstrated that sodium valproate had a significantly higher efficacy in males than females; also the total cumulative efficacy of all AEDs was significantly higher in males than females. The efficacy of first and second generation AEDs were also shown to be significantly higher in male patients than in females. Among the three commonly prescribed AEDs, carbamazepine and sodium valproate showed a significant difference between males and females in favour of males regarding tolerability. In terms of the total cumulative tolerability profiles, male patients with epilepsy were found to tolerate AEDs significantly better than females. Also males had a better tolerability to both first and second generations of AEDs than females. Second generation AEDs were found to be more frequently prescribed to female patients with epilepsy compared to males.

Among male patients, the total cumulative efficacy was lower with older drugs than newer agents with a very small difference in case of total cumulative tolerability. A minimal

difference was observed in the total cumulative efficacy and tolerability between first and second generation AEDs among female patients in this study.

The main mechanism of action of AEDs applied as monotherapy in the last treatment schedule in both types of epilepsy (idiopathic and focal) was associated with insignificant small differences except in IGE patients receiving AEDs acting primarily by potentiation of GABA inhibitory effect in which males had a significantly higher remission rate in comparison to females.

4.3. Idiopathic generalised epilepsy (IGE)

Among the total population of this study, 251 patients with idiopathic generalised epilepsy were identified with a total remission rate of 73% that is similar to findings of other investigators (Perucca, 2001b;Reutens and Berkovic, 1995) who showed the rate of developing complete seizure control in patients with IGE ranged from 80% to 90%. In terms of response to the first ever treatment with AEDs in idiopathic generalised epilepsy, Mohanraj and Brodie showed a similar rate (50%) compared to 52% in this project but with slightly lower total remission rate (64% versus 73%) (Mohanraj and Brodie, 2007). Patients with IGE tend to have a better prognosis possibly due to the presumed genetic origin of this type of epilepsy that is usually accompanied by an epileptogenic process remission either with AED treatment or even without treatment in some cases i.e. spontaneous remission (Kwan and Sander, 2004).

Idiopathic generalised epilepsy includes several syndromes; it is essential to use the most appropriate AED therapy for the treatment of IGE syndromes. Among older AEDs, sodium valproate is considered as the drug of choice for treatment of multiple IGE syndromes, it can be used in juvenile myoclonic epilepsy and absence seizures with a rate of seizure freedom of more than 80% (Bourgeois et al., 1987;Calleja et al., 2001;Covanis et al., 1982) while other agents such as carbamazepine and phenytoin were associated with poor outcome, exacerbation of seizures and subsequent categorization of these patients as having refractory epilepsy (Benbadis et al., 2003). For instance, carbamazepine was found to exacerbate absence seizures and juvenile myoclonic epilepsy in this group of patients (Thomas et al., 2006). Of the second generation agents, lamotrigine, levetiracetam, topiramate and zonisamide are becoming more known for efficacy against IGE (Karceski et al., 2005) but they are less commonly prescribed in this type of epilepsy, as they are not officially approved for use (Table 57). That explains the findings of this analysis in which

sodium valproate and lamotrigine were the drugs with the highest prescription rate in patients with idiopathic generalised epilepsy (n = 119 for each) with sodium valproate as the most efficacious AED (59%) compared to lamotrigine (45%) with a statistical significant difference between them (p-value = 0.03). Similar findings were reported by other investigators who showed sodium valproate to be the most effective drug against idiopathic generalised epilepsy (68%) followed by lamotrigine (45%) (Mohanraj and Brodie, 2005b). In addition, the Standard And New Antiepileptic Drugs (SANAD) study, found that sodium valproate is the most effective AED in this group of patients and recommended its remaining as the first line treatment for such patients (Marson et al., 2007b).

Epilepsy syndrome	First-line AEDs	Second-line AEDs
Childhood absence	Lamotrigine	Levetiracetam Topiramate
Juvenile absence	Lamotrigine	Levetiracetam Topiramate
Juvenile myoclonic epilepsy	Lamotrigine	Clobazam Levetiracetam Topiramate
Generalised tonic–clonic seizures only	Lamotrigine Topiramate	Levetiracetam

Table 57. NICE guidelines for newer AEDs treatment by idiopathic generalised epilepsy syndrome (NICE, 2004).

Unfortunately, data collection on patients with idiopathic generalised epilepsy in this study only focused on the major classification of epilepsy (i.e. idiopathic and focal) with their responses to AEDs treatment without looking for specific individual syndromes of each

subgroup. Therefore, detecting the details of AEDs applied in each syndrome cannot be performed in this analysis.

In terms of tolerability of AEDs applied in patients with idiopathic generalised epilepsy, sodium valproate was also the drug associated with the highest tolerability as its rate of withdrawal due to side effects was the lowest (9%) compared with 13% for lamotrigine with insignificant deference noted (p-value = 0.3). Also, a similar sequence was observed in another study that reported sodium valproate as the best tolerated drug (5%) followed by lamotrigine (6%) (Mohanraj and Brodie, 2005b), an observation also reported by the SANAD study (Marson et al., 2007b). Based on the findings of other investigators, sodium valproate had the highest rate of continuation on treatment in comparison to carbamazepine, lamotrigine and phenytoin (Morgan et al., 2004).

In order to detect any correlation between the generations of AEDs used in this study and patients with idiopathic generalised epilepsy, an analysis demonstrated a higher response rate to the first generation AEDs than second generation agents in this group of patients. The total cumulative efficacy in the older AEDs of this study (carbamazepine, sodium valproate and phenytoin) in the first treatment regimen was 59% compared to 50% in case of modern drugs (lamotrigine, gabapentin, levetiracetam, topiramate, oxcarbazepine and tiagabine) with insignificant difference noted (p-value = 0.1). The pattern was similar when the analysis was performed using the total attempts of AEDs applications at the end of study with 58% total cumulative efficacy in the older agents in comparison to 48% in case of newer AEDs lacking any significant statistical difference (p-value = 0.07) (Table 58). On the other hand, the difference observed between the first and second generation AEDs in terms of the total cumulative tolerability was smaller than that noticed in case of efficacy. Total cumulative tolerability of the first generation drugs was 11% compared to 15% in the newer agents in the first treatment schedule with insignificant difference (p-value = 0.3). Regarding the total attempts of AEDs applications, total cumulative tolerability was 10% in older drugs compared to 15% in newer agents also lacking any statistical significant difference (p-value = 0.2) (Table 58).

Among idiopathic generalised epilepsy patients on monotherapy in the last treatment schedule (n = 212), those on AEDs acting by sodium channels blockage (carbamazepine, phenytoin, lamotrigine and oxcarbazepine) as the primary mechanism of action (n = 110) had a remission rate of 73% in comparison to 82% for those on AEDs acting by potentiation of GABA inhibitory effect (clobazam, phenobarbital, tiagabine, sodium

valproate and vigabatrin). Insignificant statistical difference was noted between these two groups (p-value = 0.1).

	Generation of AEDs	First treatment regimen	Total regimens
Efficacy	First	59%	58%
	Second	50%	48%
Tolerability	First	11%	10%
	Second	15%	15%

Table 58. Total cumulative effectiveness of first and second generation AEDs among patients with idiopathic generalised epilepsy.

In summary, patients with idiopathic generalised epilepsy in this analysis demonstrated a high rate of developing complete seizure control. In terms of individual AEDs, sodium valproate and lamotrigine were the drugs with the highest prescription rate in this group of patients with sodium valproate as the drug with the highest efficacy and best tolerability. First generation AEDs showed a higher response rate in patients with IGE than modern drugs without any significant difference. In terms of tolerability, older AEDs showed a slightly better tolerability than newer drug with insignificant difference. Analysis of the mechanism of action of the last AED monotherapy applied to idiopathic generalised epilepsy patients demonstrated a higher response rate to AEDs acting by potentiation of GABA inhibitory effect than sodium channels blocking AEDs with insignificant difference.

4.4. Focal (localization-related) epilepsy

847 patients with focal epilepsy were recruited in this study, more than three times the number of patients with idiopathic generalised epilepsy (n = 251). Analysis in this study

demonstrated that a lower number of patients with focal (localization-related) epilepsy achieved remission using AEDs treatment (67%) than idiopathic generalised epilepsy patients (73%) with a non-significant difference between the two groups (p-value = 0.1), a finding also been reported by other studies (Aikia et al., 1999;Kwan and Brodie, 2000a;Mattson et al., 1996;Perucca, 2001b;Reutens and Berkovic, 1995). The same pattern of response according to type of epilepsy was reported by Kwan and Brodie who observed a lower remission rate for patients with focal epilepsy (60%) in comparison to 74% in case of idiopathic generalised epilepsy patients (Kwan and Brodie, 2000a). The 67% remission rate in focal epilepsy patients in this project was close to that reported by (Mohanraj and Brodie, 2005a) who showed a remission rate by 57% of patients with this type of epilepsy. The lower opportunity of developing complete seizure control in focal epilepsy in comparison to idiopathic generalised epilepsy might be due to the presence of underlying cerebral pathology such as gross structural brain lesion or congenital neurological deficit (Sander, 2003).

In terms of efficacy of AEDs, carbamazepine or lamotrigine are usually the treatments of choice to start with in case of epilepsy with localized onset in the brain (Marson et al., 2007a). According to Marson and colleagues (SANAD study) lamotrigine has efficacy similar to that of carbamazepine for the treatment of partial seizures while gabapentin and topiramate are inferior to carbamazepine in this group; these findings were obtained based on the efficacy measure "time to 12 months remission" (Marson et al., 2007a). In contrast, this analysis showed that among the three commonly prescribed AEDs, lamotrigine was the drug with both the highest prescription and highest response rate (51%) while carbamazepine had a remission rate of 49% followed by sodium valproate (45%) with non-significant difference (p-value = 0.2). Based on the findings of other investigators, there is a consensus based on 43 opinion leaders in the field of epilepsy that carbamazepine is the treatment of choice for simple partial, complex partial and secondary generalized seizures (Karceski et al., 2005). According to that analysis, three agents had the highest scores for the treatment of localization-related epilepsy; carbamazepine, lamotrigine and oxcarbazepine. A similar conclusion was reached from this analysis with respect to carbamazepine and lamotrigine but with sodium valproate instead of oxcarbazepine.

Focusing the analysis on the first treatment regimen for patients with focal epilepsy, carbamazepine, sodium valproate and lamotrigine were also the three most commonly prescribed AEDs. There were small differences in efficacy between these agents. Lamotrigine had the highest efficacy (54%) followed by carbamazepine (52%) and sodium

valproate (49%) (p-value = 0.5). Another study found a similar pattern of response of these three drugs in the first treatment schedule in patients with focal epilepsy reporting that these three agents were the more commonly prescribed and that lamotrigine was more likely to provide seizure control (63%) followed by carbamazepine (45%) and sodium valproate (42%) (Mohanraj and Brodie, 2005b).

Lamotrigine was also according to our analysis the best tolerated AED with a rate of withdrawal due to side effects of 10% followed by carbamazepine and sodium valproate (13% and 14%, respectively) (p-value = 0.2). These findings are consistent with (Marson et al., 2007a) in which lamotrigine was the agent with the least number of patients reporting side effects.

It seems there is not a big difference between the efficacy of the first and second generation AEDs when applied in the treatment of patients with localization-related epilepsy. Findings for both two generations were identified and compared (Table 59) showing a slightly lower total cumulative efficacy of older AEDs than modern agents, this difference (4%) is same whether in the first regimen or total attempts of AEDs applications at the end of study in patients with focal epilepsy (p-value = 0.2 and 0.1, respectively). For tolerability of AEDs in patients with focal epilepsy, both generations had similar values whether in the first treatment schedule or total attempts of using these agents (p-value = 0.7 and 0.5, respectively) (Table 59).

	Generation of AEDs	First treatment regimen	Total attempts
Efficacy	First	51%	47%
	Second	55%	51%
Tolerability	First	13%	14%
	Second	12%	13%

Table 59. Total cumulative effectiveness of first and second generation AEDs among patients with focal epilepsy.

701 patients with focal epilepsy on monotherapy in the last treatment regimen were identified. Among these, 428 were found to be taking sodium channels blocking agents (carbamazepine, phenytoin, lamotrigine and oxcarbazepine) as AEDs compared to 185 patients on AEDs acting primarily by potentiation of GABA inhibitory effect (clobazam, phenobarbital, tiagabine, sodium valproate and vigabatrin). Remission rate was similar in the two groups (74% and 71%, respectively) with insignificant difference noted (p-value = 0.5).

To sum up, in contrast to patients with idiopathic generalised epilepsy, focal epilepsy patients demonstrated a lower remission rate. The three commonly prescribed AEDs in patients with focal epilepsy were lamotrigine, carbamazepine and sodium valproate. Among these, lamotrigine was the drug with the highest prescription rate, highest efficacy and best tolerability profile. Second generation AEDs demonstrated a slightly higher efficacy than first generation agents with insignificant difference while in terms of tolerability, similar values were noticed for older and newer AEDs. Minor differences were observed in the remission rate among the primary mechanisms of action of AEDs applied in the last treatment regimen as monotherapy (sodium channels blockage and potentiation of GABA inhibitory effect) in patients with focal epilepsy.

4.5. Improved outcome of epilepsy

Total remission rate of patients recruited in this study was 68.3%. This value was attributable to 61.9% seizure freedom in patients while on monotherapy at their last clinic visit and 6.4% in those on combined therapy (polypharmacy).

To detect any improvement in the outcome of epilepsy, it was essential to compare the findings of this current study with another one preferably with the same conditions. Fortunately, a study has been conducted previously at the same department (the Epilepsy Unit of the Western Infirmary); it was similar to this study but with shorter duration of patient follow up and smaller study population and was conducted on the newly diagnosed patients from 1982 until 1997 with 470 patients recruited (Kwan and Brodie, 2000a). In contrast, this current investigation followed 1098 newly diagnosed epilepsy patients referred to the Unit between 1982 and 2005.

The comparison demonstrated around 4% elevation in the total remission rate; this value was obtained through an increase in remission using treatment with monotherapy (around 1% compared with the first cohort) and treatment with polypharmacy (around 3% from the first cohort) (Table 60).

Recruitment	n	Monotherapy	Combined therapy	Total Remission rate
1982 – 1997	470	61 %	3.0 %	64.0 %
1982 – 2005	1098	61.9 %	6.4 %	68.3 %

Table 60. Seizure freedom rates in an expanded cohort of patients with newly diagnosed epilepsy.

When the study population of Kwan and Brodie (2000) (n = 470) was followed up for a longer duration until 2008 instead of 1997 i.e. 26 years of follow up (11 years longer), 417 patients were found to be still under active follow up. Analysis to 2008 demonstrated the total remission rate was increased by around 6% (around 3% remission on monotherapy and 3% on combined therapy (Table 61).

This finding suggested an elevation in the rate of achieving seizure freedom as the period of patients follow up was increased. An eleven years longer duration of follow up of patients referred between 1982 and 1997 resulted in around 6% increase in the chance of achieving seizure freedom state in these patients (Figure 24). Analysis of the outcome of epilepsy based on years of referral (Table 27) indicates a decline in remission rate in the recent years where duration of patient follow up is short compared to the high rate of complete seizure control in patients referred to the Epilepsy Unit with long duration of follow up. Camfield and Camfield have also reported that the longer the period of follow up of patients, the greater the proportion of those who develop complete seizure control subsequently (Camfield and Camfield, 1996).

Recruitment	Date of analysis	n	Monotherapy	Combined therapy	Total Remission rate
1982 – 1997	1997	470	61 %	3.0 %	64.0 %
1982 – 1997	2008	417	64.5 %	6 %	70.5 %

Table 61. Recalculation of seizure freedom rates of data of (Kwan and Brodie, 2000a) study based on analysis performed on 2008 (after 26 years of follow up) compared with initial analysis on 1997.

Responders
(%)
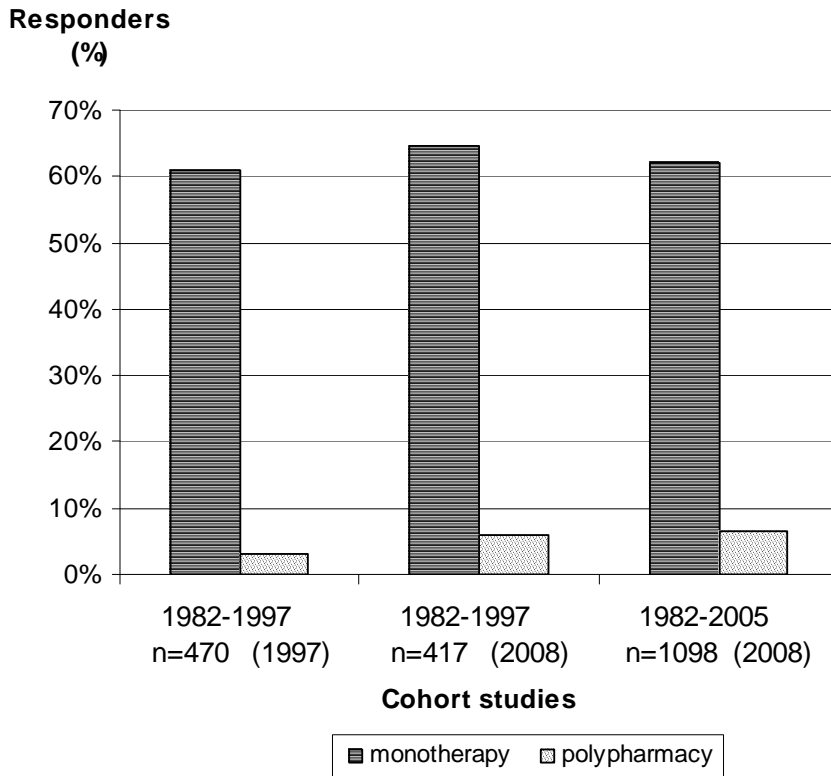
Figure 24. Seizure freedom on AEDs treatment (monotherapy and combined therapy) of this study compared to Kwan and Brodie (Kwan and Brodie, 2000a).

This improvement in the outcome of epilepsy was related to the longer duration of follow up of these patients. The development and introduction of new AEDs for epilepsy is a continuous process and as time passes, more new agents are available in the market for clinical practice. Therefore, the improvement in the outcome of epilepsy following longer duration of patients' follow up might be linked to the increasing options of second generation AEDs available to treat this disease.

There is an increasing rate of prescription of second generation AEDs as these agents are becoming more widely accepted and prescribed by clinicians in the last decade (NICE, 2004). To identify the AEDs that those 417 patients who continued treatment after 1997, a further analysis was performed on patients referred to the epilepsy unit after 1997 i.e. from 1998 until 2005 (n = 681) as treatment would be expected to be similar to those 417 patients referred before 1998 in terms of choice of AEDs selection. This analysis

demonstrated that the rate of second generation AEDs prescription in patients on monotherapy referred after 1997 was 60% compared to 40% in case of first generation agents. On the other hand, these figures were completely opposite for patients referred before 1998 in which the rate of second generation AEDs prescription (34%) was lower than first generation agents (66%) (Table 62).

Dividing the study population into three groups based on years of referral with the first group representing the population of Kwan and Brodie (2000) with referral period between 1982 and 1997 while the other two groups represent the more recent years of referral to the Epilepsy Unit, (Figure 25) demonstrates a gap between the first group and the other two groups. According to this analysis, patients of the two more recent groups needed a shorter duration of treatment to achieve seizure freedom compared with the first group keeping in mind that during the period of referral of the two recent groups (1998 – 2005) more options of second generation AEDs were available.

	Drug use before 1998 (A; n = 470)	Drug use before 1998 (B; n = 417)	Drug use after 1997 onwards (B; n = 681)
Monotherapy	423	349	564
Older AEDs (%)	289 (68%)	232 (66%)	224 (40%)
Newer AEDs (%)	134 (32%)	117 (34%)	340 (60%)

Table 62. A comparison of monotherapy drug use on the last clinic visit of patients commenced on treatment before 1998 and after 1997 onwards with seizure freedom rates, A (Kwan and Brodie, 2000a) and B (this study).

Another way of determining the rate of second generation AED prescription since their introduction was by identifying these agents during the three periods of referral adjusted to make the number of patients in each group as equal as possible. This analysis showed a gradual elevation in the rate of prescription of modern drugs over the years of referral at

the expense of old drugs; 28% in patients referred to the Epilepsy Unit between 1982 and 1996, and 38% between 1997 and 2001. In the most recent group (referred between 2002 and 2005), the prescription rate of second generation agents reached 59%. Increasing the rate of newer drugs prescription was associated with a gradual elevation in the response rate. This was accompanied by a gradual reduction in the prescription rate of first generation AEDs from 58% in the earliest referral group, then 39% in the next group and 27% in the most recent group of referral. Accordingly, a gradual reduction in response rate of these older agents was noticed (Table 63).
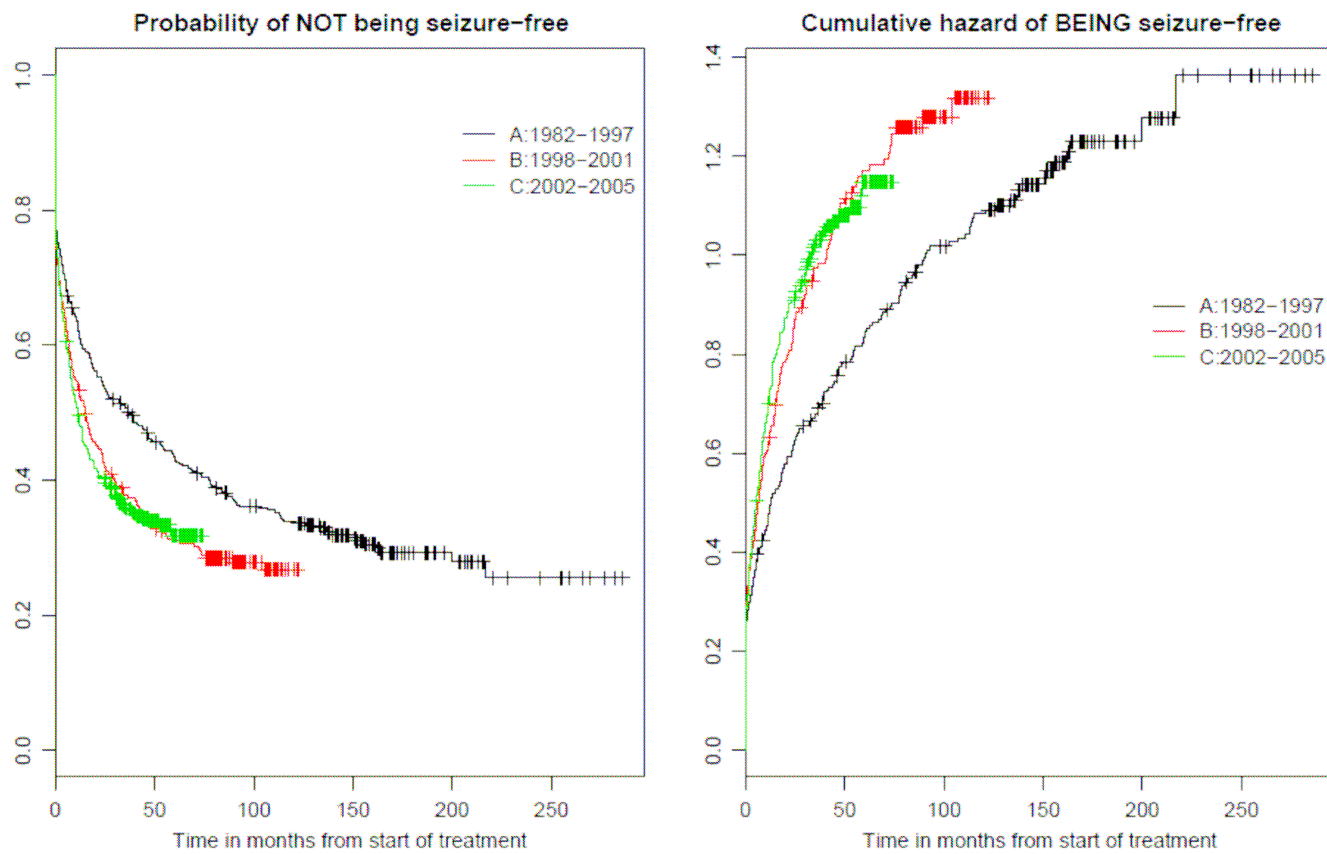
Figure 25. Outcome of epilepsy by duration of treatment during three periods of referral to the epilepsy unit.

	Generation of AEDs	n (%)	Responders
(1982 – 1996) **(n = 371)**	First	216 (58%)	165 (76%)
	Second	103 (28%)	82 (80%)
(1997 – 2001) **(n = 346)**	First	136 (39%)	99 (73%)
	Second	131 (38%)	102 (78%)
(2002 – 2005) **(n = 381)**	First	104 (27%)	81 (78%)
	Second	223 (59%)	151 (68%)

Table 63. A comparison between the rate of first and second generations AEDs prescription on the last clinic visit and their response rates according to the periods of referral in patients on monotherapy.

When the second generation AEDs started to be prescribed clinically, most were usually given to epilepsy patients as add-on medications (polypharmacy). Table 64 shows the type of treatment (monotherapy or polypharmacy) given to patients on their last clinic visit among the three periods of referral. It demonstrates the highest rate of combined therapy prescription in the second group of years of referral (1997 - 2001) 23% compared to the first (1982 - 1996) 14% and third group (2002 - 2005) 14%. In the first period of referral, rate of combined therapy prescription was low as the second generation AEDs were just entering the market with limited clinical trial data and lack of awareness of their effectiveness by the clinicians. The higher prescription of combined therapy in the second group compared with the first period may be because second generation drugs had been shown to have good efficacy with lower side effects profiles that made them more widely accepted and prescribed by physicians. Similar to the first period of referral, the third group was characterised by a lower polypharmacy prescription rate in comparison to the second period possibly because further research had shown similar efficacy of second generation AEDs compared to first generation agents minimizing their prescriptions as

add-on therapy. Remission rate was also the highest in the second group (16%) compared to the first (6%) and third group (6%) (Table 64 and Figure 26).

Period of referral	n	Monotherapy on last regimen	Responders on monotherapy	Polypharmacy on last regimen	Responders on polypharmacy
1982 - 1996	371	319 (86%)	247 (94%)	52 (14%)	15 (6%)
1997 - 2001	346	267 (77%)	201 (84%)	79 (23%)	39 (16%)
2002 - 2005	381	327 (86%)	232 (94%)	54 (14%)	16 (6%)
Total	1098	913	680	185	70

Table 64. Type of treatment on last regimen (monotherapy or polypharmacy) with response rate during periods of referral.
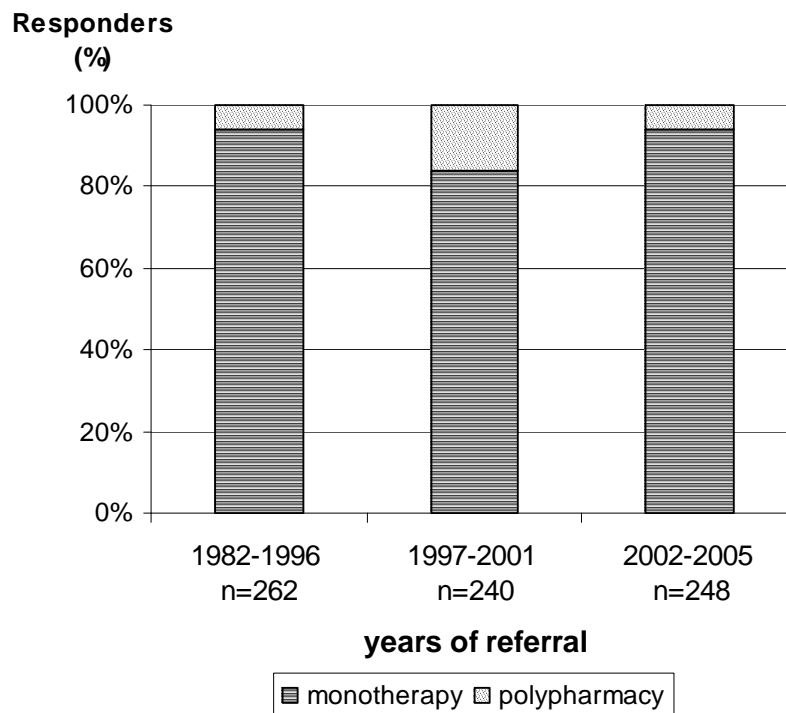

Figure 26. Type of treatment on last regimen (monotherapy or polypharmacy) during year of referral in seizure freedom patients.

Therefore, it might be concluded that the longer duration of follow up of epilepsy patients is associated with more opportunities to select one of the wide range of second generation AEDs (with variable mechanisms of actions) with a consequent better chances of achieving seizure control in these patients.

Another element associated with increasing the duration of follow up is the number of treatment regimens applied. Patients who fail to show complete seizure control on a certain treatment regimen (whether monotherapy or polypharmacy) will eventually be moved to another regimen either through substitution or combining with another AED.

The chance of achieving seizure freedom is highest with the first treatment schedule and declines with subsequent regimens whether the AED treatment is applied as monotherapy or combined therapy. Based on this study, complete seizure control was achieved progressively until the seventh treatment schedule (Table 65). Patients who developed complete seizure freedom on the first treatment regimen constituted 50% of the whole study population compared to 13% in case of responders to the second treatment schedule (whether monotherapy or polypharmacy). On the other hand, patients with remission on all subsequent regimens together (i.e. third, fourth, fifth, sixth and seventh treatment schedules) constituted only 5% of the whole study population (Figure 27). Therefore, responders on the first two regimens contributed to 63% of the remission rate of the whole study population. Failure to achieve remission on the first two treatment regimens was associated with a low chance of achieving seizure freedom on the subsequent schedules (Figure 28). These findings support other studies that suggested the definition of refractory epilepsy should follow the failure of two appropriately selected and adequately tried AEDs based on their observations of remission rate of 47% following the first treatment regimen, 13% following the second and only 4% on the subsequent regimens (Arts et al., 2004; Kwan and Brodie, 2000a). The hope for achieving a state of complete seizure control is always there although small as in the work of Sillanpaa who demonstrated that remission of seizures can be achieved after a period of as long as 30 - 35 years after the diagnosis (Sillanpaa, 1993). By modification of AED therapy demonstrated a remission rate of 3% of the patients each year after a 20 year history of intractable seizures (Callaghan et al., 2007) using the available second generation AEDs during the study period i.e. 2000 – 2003 compared to the more commonly prescribed first generation drugs before 2000. Considering a particular patient as drug resistant does not necessarily imply that the patient will never achieve complete seizure control after further AED therapy manipulation

(Callaghan et al., 2007;Luciano and Shorvon, 2007;Schiller and Najjar, 2008). This is because drug responsiveness in epilepsy should be considered as a dynamic process.
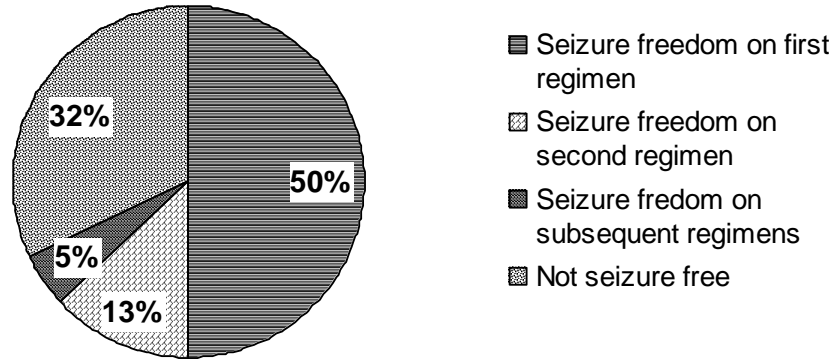
Figure 27. Outcome of newly diagnosed epilepsy patients.

There may be other factors not related to drugs that participated in the improvement of outcome of epilepsy after long duration of follow up such as improvement of patients' awareness of this disease and the necessity to take treatment in order to avoid its negative consequences. Health education programs could have played a major role in this regard. In some patients, the improvement may be part of the natural history of the disorder.

Treatment regimens	Type of treatment	Number of patients	Responders (%)
First	Monotherapy	1098	544 (50%)
Second	Monotherapy	254	101 (40%)
	Polypharmacy	144	45 (31%)
	Total	398	146 (37%)
Third	Monotherapy	64	26 (41%)
	Polypharmacy	104	15 (14%)
	Total	168	41 (24%)
Fourth	Monotherapy	17	6 (35%)
	Polypharmacy	51	5 (10%)
	Total	68	11 (16%)
Fifth	Monotherapy	3	1 (33%)
	Polypharmacy	29	3 (10%)
	Total	32	4 (13%)
Sixth	Monotherapy	3	1 (33%)
	Polypharmacy	13	1 (8%)
	Total	16	2 (13%)
Seventh	Monotherapy	2	1 (50%)
	Polypharmacy	7	1 (14%)
	Total	9	2 (22%)
Eighth	Monotherapy	0	0
	Polypharmacy	3	0
	Total	3	0
Ninth	Monotherapy	1	0
	Polypharmacy	1	0
	Total	2	0

Table 65. Remission rate of both both monotherapy and polypharmacy in all treatment regimens.

Figure 28. Outcome of epilepsy by number of regimens taken.

The concept of "adequately tried AEDs" is an important factor in the definition of refractory epilepsy as failure of a certain treatment schedule may not be only due to lack of efficacy of that particular AED/s combination against a certain seizure type, but also could be due to the development of intolerable side effects making the AED/s combination poorly tolerated and subsequently withdrawn.
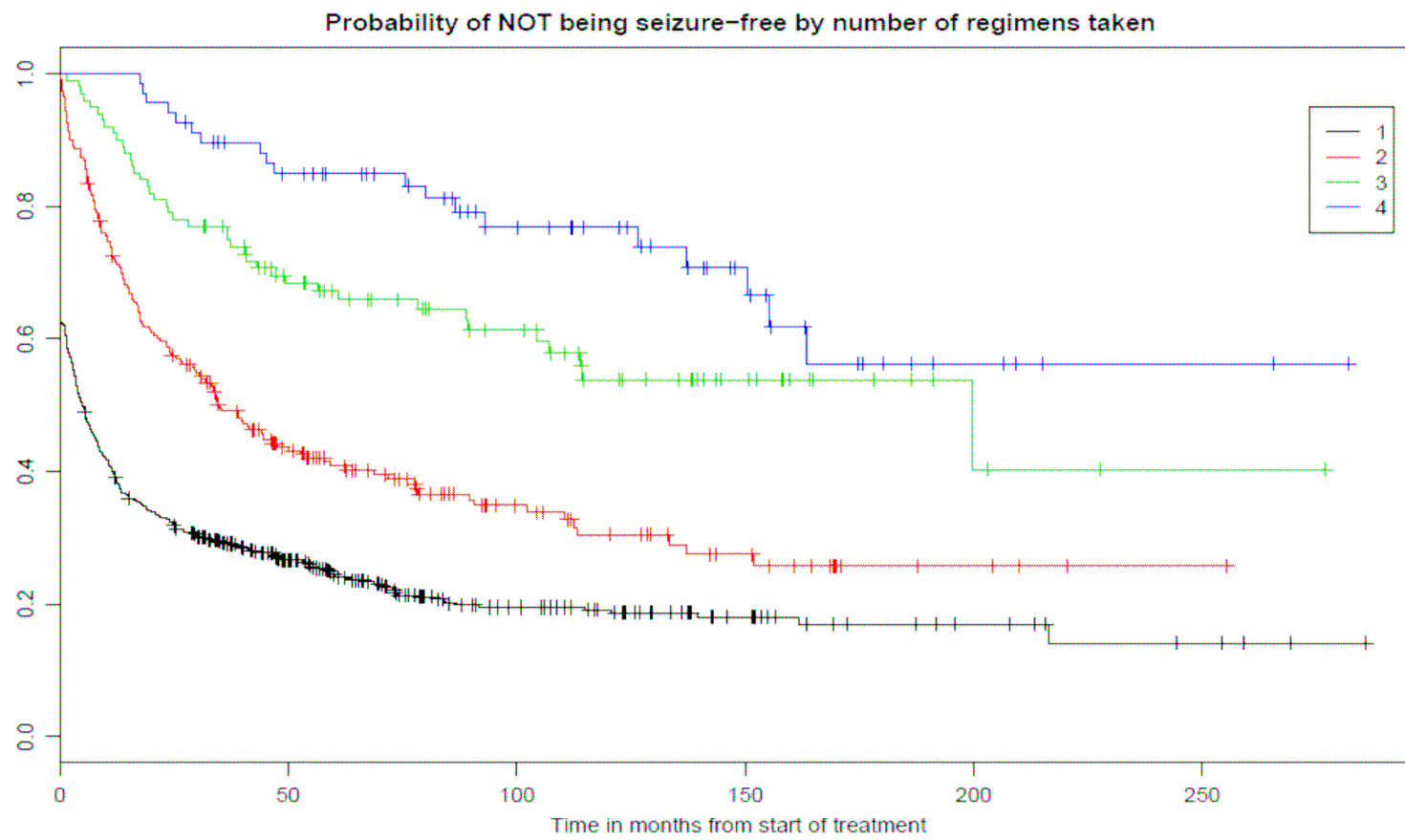
The rate of development of complete seizure control following failure of a particular regimen due to poor tolerability tends to be higher than remission after failure due to lack of efficacy. This finding was observed after failure of the first and also second schedule. The small number of patients in the subsequent schedules limited the ability to analyze their rates of seizure freedom. This pattern of remission was observed in almost all three levels of cut off points of the recommended daily defined doses of AEDs applied as monotherapy (Table 66). Statistical analysis of the remission rate following failure of the first treatment regimen demonstrated a significant difference between the three cut off levels (25%, 50% and 75%) in term of types of treatment failure i.e. failure due to lack of efficacy and failure due to poor tolerability (p-value = 0.01). These observations are in agreement with the findings of Kwan and Brodie who reported that seizure freedom on the second regimen following failure of treatment due to poor tolerability tends to be higher than that failure due to lack of efficacy (Figure 29) (Kwan and Brodie, 2000b). The small number of patients with remission following failure of two treatment regimens has limited the ability to perform a statistical analysis. The higher remission rate following failure of a previous regimen due to poor tolerability supports the idea that treatment failure because of poor tolerability does not represent refractory epilepsy because the development of intolerable side effects shortly after the prescription made withdrawal of that particular drug an essential step. This is consistent with Kwan and colleagues who reported that a pharmacological intervention can only be considered if it was "appropriate" for the patient epilepsy and seizure type and applied "adequately" in terms of strength/ dosage for a sufficient length of time (Kwan et al., 2009).

Instead of the three levels of cut off points of the recommended daily defined doses of AEDs, using simple calculations of patients who failed treatment with the first schedule due to ongoing seizures (regardless of the dosing) or withdrawal of treatment due to side effects, the remission rate on subsequent schedules was 10% (n = 109). This value is almost identical to Kwan and Brodie who showed a value of remission rate of 11% on subsequent regimens in this group of patients(Kwan and Brodie, 2000a).

Percentage of DDD	Type of failure	Remission following one regimen failure	Remission following two regimens failure
25%	LOE	34%	25%
	PT	50%	0%
50%	LOE	31%	19%
	PT	45%	25%
75%	LOE	29%	13%
	PT	42%	33%

Table 66. Remission rates following the two types of treatment failure (lack of efficacy (LOE) and poor tolerability (PT)) based on 25%, 50% and 75% of the daily defined dose (DDD) in epilepsy patients on monotherapy.
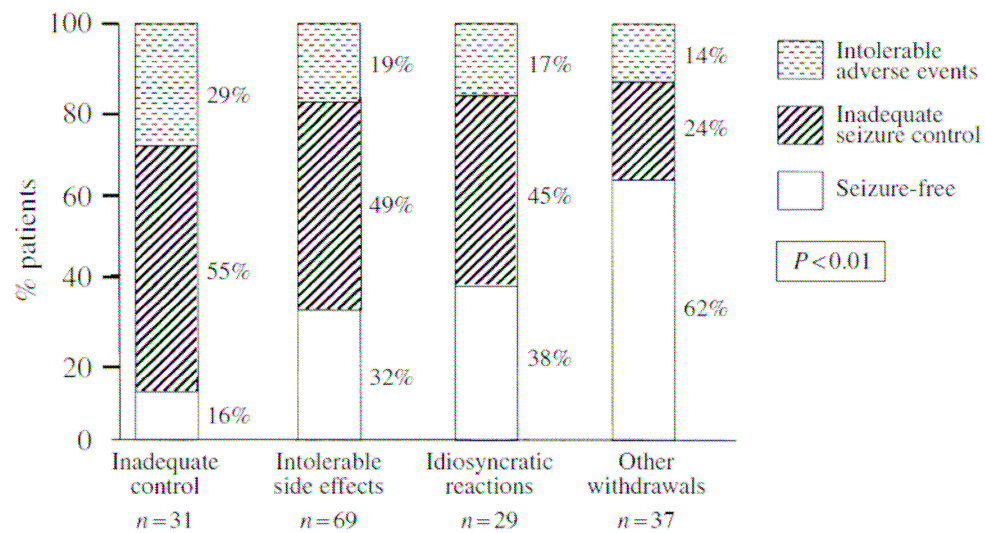

Figure 29. Response to the second antiepileptic drug according to reason for failure of the first drug (Kwan and Brodie, 2000b).

Based on findings of this study and other related ones, longer duration of follow up of epilepsy patients appears to be associated with a modest improvement in the ultimate outcome as it will be accompanied by the application of more regimens most of which will include second generation AEDs. Therefore, it appears that the availability of wide range of these agents with variable mechanisms of action has contributed to this outcome improvement. In addition, improvement of patients' awareness about epilepsy could have contributed to the improvement of outcome.

The modest improvement in the outcome of epilepsy was in patients with complete seizure control. It is also possible that there might be an improvement in patients with ongoing seizures. This improvement might take the form of reduced seizure frequency and/or seizure severity but unfortunately this study was not able to show this due to lack of required data. Again, there is a chance that such improvement might be at least partially attributable to second generation AEDs.

Failure of two consecutive schedules was associated with a lower chance to develop seizure freedom subsequently. Thus, development of refractory epilepsy is more likely to take place following failure of the first two treatment regimens. Failure of these two regimens is more likely to be due to lack of efficacy rather than poor tolerability.

4.6. AEDs response and doses

The response to individual AEDs does not seem to be constant but varies according to sequence of prescription e.g. efficacy of carbamazepine when applied as a first treatment schedule differs from when given in any other regimens. This variability is observed not only for efficacy of AEDs but also for tolerability. Compared with variability in efficacy, differences in tolerability profiles of AEDs between first regimen and other regimens were smaller. This phenomenon was observed for most of the AEDs applied in this study as monotherapy. Bogg and colleagues have linked the reduction in the sensitivity to AEDs with the prolonged application of these agents (Bogg et al., 2000), perhaps due to overlapping effects of other previous AEDs already applied or prolonged exposure to these agents that results in brain morphological or physiological changes leading to alteration in the response to these drugs. This has also been shown by Frey and colleagues who showed a reduced severity of side effects of AEDs following prolonged use of these drugs (Frey et al., 1986). Based on these observations, it might be concluded that the response to the first AED prescribed is the corner stone for determining the ultimate outcome of epilepsy.

Consequently, failure to respond to the first AED therapy is associated with a poor prognosis of epilepsy in the future while patients with a good response on the first regimen are more likely to develop complete seizure control eventually, an observation that was also reported by other investigators (Kwan and Brodie, 2000a). In this study, patients who responded to the first AED therapy comprised 50% of the total number who achieved remission by the end of this investigation in comparison to the subsequent treatment regimens that showed a continuous reduction in the remission rate. These findings are similar to those of Kwan and Brodie who observed a decline in the rate of developing complete seizure control following failure of the first treatment regimen (Figure 30) (Kwan and Brodie, 2000b). Ma and colleagues also observed that majority of epilepsy patients achieved seizure freedom while on the first treatment regimen (Ma et al., 2009). Among patients with partial epilepsy, the rate of complete seizure control after failure of the first regimen was found to be around 14% in patients on monotherapy (Kwan and Brodie, 2000a;Schmidt, 1986;Schmidt and Richter, 1986) and between 3% and 11% in case of combined therapy (Kwan and Brodie, 2000a;Mattson et al., 1985). The current investigation demonstrated a rate of remission after failure of the first regimen of 9% in patients on monotherapy and 5% in case of combined therapy among patients with partial seizures.

It may be that the response to first drug is important because the brain has never been exposed to these agents before maximising effects on brain targets without the chance to develop drug tolerance through brain target modifications that may alter the brain response. This might be the reason for variation in response to the same drug in two different patients according to its sequence of prescription. Individual differences can also be an important factor in this regard as there might be some degree of cellular differences in the brain among patients that control the response to AEDs.
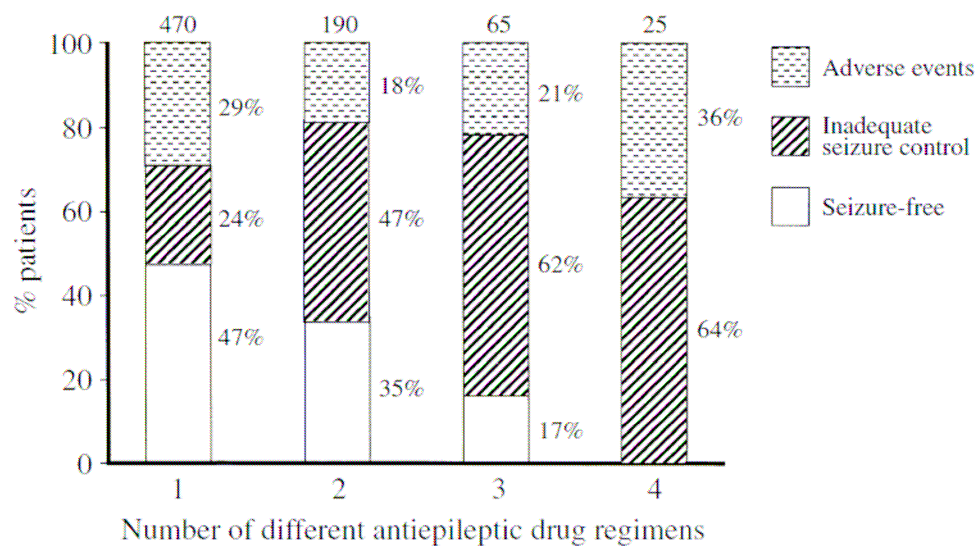
Figure 30. Remission rate of epilepsy following failure of the first regimen (Kwan and Brodie, 2000b).

Based on the results obtained in this study and according to the recommendations of the World Health Organization (WHO), it was observed that seizure freedom state was reached using a relatively moderate dose of the six commonly prescribed AEDs i.e. lamotrigine, sodium valproate, carbamazepine, topiramate, oxcarbazepine and levetiracetam in majority of the responder patients without the need to reach high dose concentrations (Table 67). Even in case of carbamazepine and topiramate, most of the patients who achieved complete seizure control (92% and 97%, respectively) were found to be taking lower than the daily defined dose recommended by WHO (Table 67). A similar pattern was observed in case of tolerability profiles of these six commonly applied agents. It was observed that the majority of patients who discontinued these drugs due to side effects were receiving doses lower than the recommended daily defined doses rather than high doses (Table 67). Therefore, it can be concluded that the response to initial doses of AEDs can be assumed as an indicator of the overall response at least in the commonly prescribed AEDs.

These findings are in agreement with other researchers who reported a high proportion of patients with complete seizure control while on moderate doses of AEDs without developing intolerable side effects (Kwan and Brodie, 2001;Ma et al., 2009;Ryvlin, 2005).

Adjusting AEDs dose within the low to moderate range without reaching the high concentrations will lower the risk of developing side effects. In addition, this will lead to saving time required in the treatment of patients as the opportunity to move to another treatment regimen (by substitution or combination) will be more rapid. Another advantage is lowering the cost and various other resources needed to provide medical care for patients with epilepsy. Improvement of the patients' compliance is a likely consequence of restriction of AEDs dose to low and moderate ranges as the patients do not need to persist on a particular AED treatment without improvement of seizures. In addition, there might be a risk of developing tolerance to a particular AED or other future drugs as remaining on the same agent for a long period of time may result in morphological and physiological changes in the brain (Bogg et al., 2000). However, some investigators believe that seizures do not beget seizures except in rare cases with extremely prolonged seizures (Berg and Shinnar, 1997). It would be appropriate to establish a predefined period of time for the application of each AED with failure to obtain seizure freedom or at least 50% or 75% seizures reduction within this period necessitating introduction of a new AED treatment regimen either through substitution or combination.

AED	DDD	Dose required to reach a certain remission rate	Dose required for a certain withdrawal rate
Lamotrigine	300 mg/day	≤ 400 mg/day (94%)	≤ 300 mg/day (94%)
Sodium valproate	1500 mg/day	≤ 2000 mg/day (95%)	≤ 1500 mg/day (92%)
Carbamazepine	1000 mg/day	≤ 800 mg/day (92%)	≤ 600 mg/day (97%)
Topiramate	300 mg/day	≤ 200 mg/day (97%)	≤ 200 mg/day (100%)
Oxcarbazepine	1000 mg/day	≤ 1200 mg/day (96%)	≤ 900 mg/day (91%)
Levetiracetam	1500 mg/day	≤ 2000 mg/day (91%)	≤ 1000 mg/day (86%)

Table 67. Remission and withdrawal rates due to side effects among certain dose ranges.

As it has been discussed earlier, three different patterns of response were observed in the patients recruited to this study. These included patients who developed complete seizure freedom after a period of ongoing seizures (66%), those with intractable seizures despite various AED treatment regimens either as monotherapy or combined therapy (25%). The last group of patients consisted of those who had a fluctuation in response to AEDs with periods of remission and relapse (9%). With the exception of the third category of this study (patients with fluctuating response to AEDs), the other two groups (patients with remission and those with intractable seizures) were similar to those studied by Kwan and Sander who categorised the prognosis of epilepsy into three groups i.e. excellent prognosis with or without treatment (around 30%), good prognosis only with treatment (30% approximately) and poor prognosis with continuous seizures despite AEDs treatment (around 40%) (Kwan and Sander, 2004). When adding the percentages of the first two remission groups of Kwan and Sander together i.e. 60% approximately, these findings are

similar to those of the first group of this current investigation (remission after a period of ongoing seizures) i.e. 66% (Figure 31).
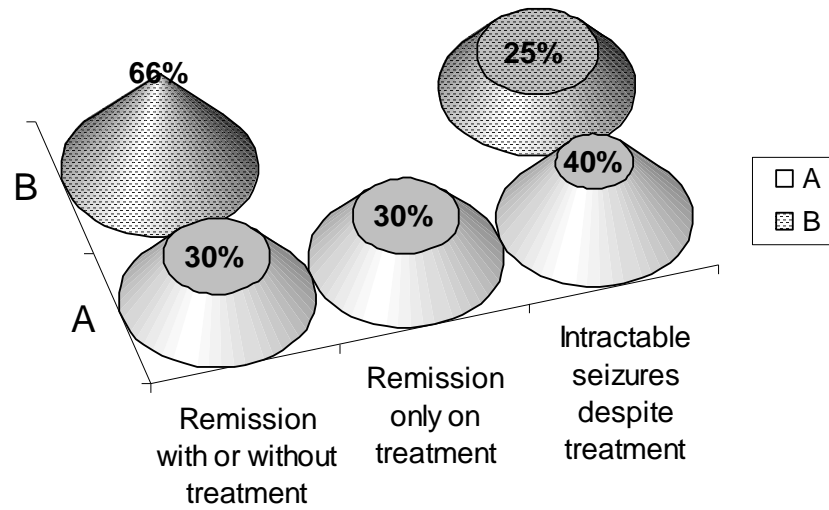
Figure 31. A comparison regarding the natural history of epilepsy between A: (Kwan and Sander, 2004) and B: this study.

Reanalysis of these three groups by splitting patients in the first category (patients with complete seizure control) into two groups based on the timing of starting seizure freedom in relation to the beginning of AEDs treatment resulted in four categories:

1. Patients with excellent prognosis who developed complete seizure control immediately after starting treatment with AEDs. 261 patients in this group constituted 24% of the total study population. It is assumed that this group of patients included those who would achieve remission even without AED treatment because spontaneous remission of the underlying epileptogenic process has taken

place (Sander, 1993). The issue of spontaneous remission has not attracted a lot of attention because of the ethical difficulty in conducting a study without supplying essential treatment to these patients (Kwan and Sander, 2004).

2. Patients with good prognosis of epilepsy who needed time to achieve seizure freedom using either single or multiple treatment regimens with AEDs. Some of these regimens may be in the form of monotherapy while others might be combined therapy. This group was represented by 467 patients (43%). Other studies have observed a remission range of 65-80% in this group of patients in whom it is believed the epileptogenic process does not remit and seizures will recur after AED withdrawal (Sander, 1995).

3. Patients with intractable seizures who did not have a period of at least 12 months seizure freedom during their follow up despite using multiple AED treatment regimens. They constituted 25% of the study population (n = 272). This confirms other hospital based (Sander and Sillanpaa, 1997;Sander, 1993) and community based studies (Annegers et al., 1979;Goodridge and Shorvon, 1983) which demonstrated that around 20-30% of newly diagnosed epilepsy patients do not enter remission (Kwan and Brodie, 2006). Some of these patients might have one of the epilepsy syndromes associated by low response rate to pharmacological intervention e.g. mesial temporal lobe epilepsy; these patients will need a surgical intervention that demonstrated a high remission rate in many cases (Engel and Shewmon, 1993;Hennessy et al., 2001;Holmes et al., 1997;Wieser et al., 1993). In patients with these syndromes, the intractable seizures will be of genetic origin. Genetic factors can also lead to refractory epilepsy as a result of recognised mechanisms i.e. multi-drug transporter hypothesis (Loscher and Potschka, 2002) and drug target hypothesis (Vreugdenhil and Wadman, 1999). Other explanations for these refractory seizures include epilepsy related factors such as early onset of seizures (Camfield et al., 1993;Casetta et al., 1999) or type of seizures (Aikia et al., 1999;Mattson et al., 1996) or family history of epilepsy (Berg et al., 2001;Elwes et al., 1984). Intractable seizures might also be due to reduced responsiveness to AEDs following prolonged exposure to these agents (Bogg et al., 2000;Frey et al., 1986).

Patients with focal epilepsy are known to have a lower remission rate in comparison to those with idiopathic generalised epilepsy (Aikia et al., 1999;Kwan

and Brodie, 2000a;Mattson et al., 1996;Perucca, 2001b;Reutens and Berkovic, 1995). The underlying brain lesion may be one of the main responsible factors in this regard (Loiseau et al., 1990). In this current investigation, 82% (n = 222) of patients with refractory epilepsy had focal epilepsy with those with symptomatic epilepsy in which identified brain pathology was comprised 48% (n = 130).

4. 98 patients (9%) had fluctuation in response to AEDs between remission and relapse. Although some patients of this group developed remission of seizures as an ultimate outcome, they had some recurrences of seizures during their follow up course. Berg and colleagues reported up to five periods of remission interrupted by intervals of relapses with a greater risk of relapses after remissions in patients with idiopathic epilepsy (Berg et al., 2009). Patients with idiopathic generalised epilepsy comprised 26% of patients with a fluctuation in AED response in this study. Instead of being constant, Berg et al., also reported the fluctuation in AED responsiveness that might be due to shifts in the pathophysiological features on the underlying cerebral lesion (Berg et al., 2009).

Analysis of AED response among all patients on monotherapy on their last visit to the Epilepsy Unit demonstrated insignificant differences with regard to the ultimate outcome of epilepsy among the two generations of AEDs, and also among the two primary mechanisms of action (sodium channels blockage and potentiation of GABA inhibitory effect) whether analysed in terms of the ultimate outcome of epilepsy or rate of response of a particular regimen following failure of previous schedule acting by the same primary mechanism of action.

In conclusion, it seems that the first AED applied to newly diagnosed epilepsy patients is the major predictor of the ultimate outcome of epilepsy probably because it is the first exposure of the brain to AEDs leading to the highest observed response. In prolonged drug exposure, the brain might develop adaptation to these agents or pathophysiological changes of the underlying disorder might take place with subsequent variation in the drug response among the following treatment regimens. This could be the reason for the variation in the effectiveness of AEDs according to their order of prescription indicating that the effectiveness to these agents is a dynamic rather than a fixed process.

Complete seizure control was obtained in the majority of patients with most of the AEDs in this study using moderate doses of these agents. The same pattern was observed in case

of the tolerability. Therefore, it might be useful to restrict the use of these drugs to a slightly higher than moderate doses without reaching higher concentrations, while specifying a certain period of time for the trial of particular AEDs. The four patterns of response to AEDs observed in this study link some of the well known aspects of epilepsy together such as pathophysiology of seizures, biological basis of pharmacoresistance, prognosis, epileptogenesis process, genetics and epilepsy syndromes.

Insignificant differences were noticed among the two generations of AEDs and also among the two primary mechanisms of action of AEDs (sodium channels blockage and potentiation of GABA inhibitory effects) in terms of the ultimate outcome of epilepsy.

Conclusion

This is a large-scale retrospective study that followed up newly diagnosed epilepsy patients for almost 26 years. Patients were referred to the Epilepsy Unit of the Western Infirmary in Glasgow, Scotland between 1982 and 2005. Among around 1500 patients, 1098 met the inclusion criteria and were recruited. The ultimate outcome of epilepsy and effectiveness of AEDs applied were identified for the whole study population. Consequently, analysis was conducted in relation to a variety of demographic, clinical and pharmacological aspects.

A comparison has been made between the first and second generation AEDs in terms of efficacy and tolerability in special populations and regarding the ultimate outcome of epilepsy. Such a comparison has not been addressed previously in clinical trials as most of studies have concentrated on comparison between individual drugs rather than groups of drugs (generations). The efficacy of first generation AEDs were found to be significantly higher in elderly patients with epilepsy ($\geq$ 65 years old) than the second generation drugs. Other age groups (adolescents and adults) demonstrated insignificant difference between older and modern AEDs. Gender analysis showed a significantly higher efficacy and tolerability of both generations of AEDs in males than females. Insignificant difference was noticed between the older and newer AEDs in terms of idiopathic generalised and focal epilepsy. With regard to the ultimate outcome of epilepsy, there was insignificant difference between first and second generation AEDs.

Analysis of the ultimate outcome of epilepsy by the end of study was calculated. Among the various age groups, elderly patients demonstrated a higher seizure freedom rate compared to adolescents and adults. In terms of gender, male patients with epilepsy had a remission rate higher than females. Regarding epilepsy classification, patients with idiopathic generalised epilepsy had a rate of complete seizure control higher than those with focal epilepsy.

The ultimate outcome of epilepsy of patients recruited to this study demonstrated a modest improvement over the last two decades; this may be assumed to be due to the longer duration of follow up of these patients accompanied by the application of wide range of available second generation AEDs and the various treatment regimens with different combination strategies. Therefore, it can be concluded that the newer AEDs have contributed to the modest improvement in the prognosis of epilepsy. The correlation

between the duration of follow up and the ultimate outcome of epilepsy was observed in elderly patients with focal epilepsy. These patients demonstrated an elevation in the total remission rate associated with an extension of their period of follow up following an initial analysis.

Observations from this study were consistent with findings from other studies regarding the number of AED treatment regimen failures needed before a patient can be considered as drug resistant. It was observed that failure of two appropriately selected and adequately tried AED treatment schedule was associated with a small opportunity to develop complete seizure control subsequently, keeping in mind that considering a patient as pharmacoresistant does not necessarily mean that seizure freedom state will never be achieved as AEDs can show fluctuation of response that is difficult to predict.

This study also provided an opportunity to analyse the response to AED therapy based on the mechanism of action, an issue that was addressed in a limited number of studies. Male patients with idiopathic generalised epilepsy showed a higher response rate to AEDs acting primarily by sodium channels blockage than females. For AEDs working mainly by potentiation of GABA inhibitory effect, males with IGE also had a significantly higher response rate than females. Among focal epilepsy patients, similar response rates were detected in males and females with regard to these two mechanisms of action. Patients with idiopathic generalised epilepsy generally had a higher remission rate on AEDs acting mainly by potentiation of GABA inhibitory effect than those acting by sodium channels blockage. In contrast, similar response rates were observed for these two mechanisms of action among all patients with focal epilepsy. Analysis of the ultimate outcome of epilepsy did not reveal any difference between these two mechanisms of action.

Response to the first ever AED therapy was found to be associated with the highest response rate with a gradual decline in the subsequent schedules. The variability in the response to AEDs might be explained by changes that take place in the brain. In association with genetic background and other factors such as seizures type and epilepsy syndrome, the variability of AED response has been found to follow multiple patterns of response. Minimizing the application of AEDs used as monotherapy to a moderate or slightly higher than moderate dose range has been shown to be sufficient to predict the response to these drugs eventually in terms of efficacy and tolerability.

Being a retrospective study, this has lowered the power of this investigation to detect a true difference between patient groups and to give a clear interpretation of results and recommendations because of the information bias associated with the lack of some required data. Therefore, the application of a prospective type of analysis would be a better alternative in this regard although this may require a long follow up of patients. Applying a retrospective study was the only way to follow up these recruited patients for such a long period of time (26 years approximately). Conducting an appropriately designed prospective study is therefore strongly recommended to obtain a good accuracy of data collection with accurate results consequently.

Appendices

AEDs combination	Regimens									Total	Efficacy
	1	2	3	4	5	6	7	8	9		
CBZ + FBM	-	0 (1)	-	-	-	-	-	-	-	0 (1)	0
CBZ + GBP	-	1 (7)	0 (5)	-	1 (1)	-	-	-	-	2 (13)	15 %
CBZ + LEV	-	1 (5)	0 (3)	1 (2)	0 (1)	-	-	-	-	2 (11)	18 %
CBZ + LTG	-	0 (8)	0 (1)	0 (3)	-	-	-	-	-	0 (12)	0
CBZ + PGB	-	2 (4)	0 (1)	-	-	-	-	-	-	2 (5)	40 %
CBZ + PHT	-	-	0 (1)	-	-	-	-	-	-	0 (1)	0
CBZ + TGB	-	0 (1)	1 (1)	-	-	-	-	0 (1)	-	1 (3)	33 %
CBZ + TPM	-	1 (3)	0 (3)	0 (1)	0 (2)	-	-	-	-	1 (9)	11 %
CBZ + VGB	-	1 (4)	0 (2)	-	-	-	-	-	-	1 (6)	17 %
CBZ + VPA	-	1 (5)	0 (2)	-	-	-	0 (1)	-	-	1 (8)	13 %
CBZ + ZNS	-	-	-	0 (1)	-	-	-	-	-	0 (1)	0
CBZ + AZM + TPM	-	-	-	-	-	-	-	0 (1)	-	0 (1)	0
CBZ + CLB + LEV	-	-	-	-	-	0 (1)	-	-	-	0 (1)	0
CBZ + CLB + VPA	-	-	-	-	-	-	0 (1)	-	-	0 (1)	0
CBZ + GBP + LEV	-	-	-	0 (1)	-	-	-	-	-	0 (1)	0
CBZ + GBP + LTG	-	-	-	0 (1)	-	-	-	-	-	0 (1)	0
CBZ + GBP +	-	-	1	0	0	-	-	-	-	1	20 %

TPM			(2)	(2)	(1)					(5)	
CBZ + LEV + TPM	-	-	0 (1)	0 (1)	0 (1)	0 (1)	-	-	-	0 (4)	0
CBZ + LTG + LEV	-	-	0 (1)	-	-	-	-	-	-	0 (1)	0
CBZ + LTG + PHT	-	-	-	0 (1)	-	-	-	-	-	0 (1)	0
CBZ + LTG + TPM	-	-	0 (1)	-	-	-	-	-	-	0 (1)	0
CBZ + LTG + VGB	-	-	0 (1)	-	-	-	-	-	-	0 (1)	0
CBZ + PGB + TPM	-	-	-	-	-	0 (1)	-	-	-	0 (1)	0
CBZ + TPM + PGB	-	-	0 (1)	-	-	-	-	-	-	0 (1)	0
CBZ + AZM + TPM + ZNS	-	-	-	-	-	-	-	-	0 (1)	0 (1)	0
CBZ + LEV + TPM + PGB	-	-	-	0 (1)	-	-	-	-	-	0 (1)	0
VPA + CLB	-	-	-	-	0 (1)	-	-	-	-	0 (1)	0
VPA + FBM	-	-	0 (1)	-	-	-	-	-	-	0 (1)	0
VPA + GBP	-	-	1 (3)	-	0 (2)	-	-	-	-	1 (5)	20 %
VPA + LEV	-	2 (5)	1 (6)	1 (2)	-	-	-	-	-	4 (13)	31 %
VPA + LTG	-	27 (58)	5 (18)	0 (2)	0 (3)	-	-	-	-	32 (81)	40 %
VPA + OXC	-	-	0 (1)	-	-	-	-	-	-	0 (1)	0
VPA + PGB	-	-	0 (1)	0 (1)	-	0 (1)	-	-	-	0 (3)	0
VPA + TPM	-	0 (1)	1 (5)	2 (4)	0 (1)	0 (1)	-	-	-	3 (12)	25 %
VPA + VGB	-	-	0 (1)	-	-	-	-	-	-	0 (1)	0
VPA + ZNS	-	-	1	-	-	-	-	-	-	1	100 %

			(1)							(1)	
VPA + CLB + LEV	-	-	-	-	-	0 (1)	-	-	-	0 (1)	0
VPA + CLB + LTG	-	-	-	0 (1)	-	0 (1)	-	-	-	0 (2)	0
VPA + GBP + TPM	-	-	-	-	-	0 (1)	-	-	-	0 (1)	0
VPA + LEV + TPM	-	-	-	-	1 (1)	-	-	-	-	1 (1)	100 %
VPA + LTG + ZNS	-	-	0 (1)	-	-	0 (1)	-	-	-	0 (2)	0
VPA + LTG + GBP	-	-	0 (1)	-	0 (1)	-	-	-	-	0 (2)	0
VPA + LTG + LEV	-	-	0 (4)	0 (2)	0 (1)	-	-	-	-	0 (7)	0
VPA + LTG + PHT	-	-	-	0 (1)	-	-	-	-	-	0 (1)	0
VPA + LTG + TPM	-	-	0 (4)	0 (1)	0 (1)	-	-	-	-	0 (6)	0
VPA + PGB + ZNS	-	-	-	-	-	-	0 (1)	-	-	0 (1)	0
VPA + GBP + LEV + LTG	-	-	-	0 (1)	-	-	-	-	-	0 (1)	0
VPA + LEV + LTG + PGB	-	-	-	-	0 (1)	-	-	-	-	0 (1)	0
VPA + LEV + LTG + TPM	-	-	-	1 (2)	-	-	-	-	-	1 (2)	50 %
VPA + LTG + PGB + TPM	-	-	-	-	0 (1)	-	-	-	-	0 (1)	0
LTG + AZM	-	-	-	-	-	-	-	0 (1)	-	0 (1)	0
LTG + GBP	-	0 (2)	0 (1)	0 (2)	-	-	-	-	-	0 (5)	0
LTG + LEV	-	2 (18)	1 (8)	-	0 (1)	-	-	-	-	3 (27)	11 %
LTG + OXC	-	0 (1)	-	-	-	-	-	-	-	0 (1)	0
LTG + PGB	-	-	-	0	1	-	0	-	-	1	33 %

				(1)	(1)		(1)			(3)	
LTG + PHT	-	-	-	0 (1)	-	-	-	-	-	0 (1)	0
LTG + TGB	-	-	-	-	-	0 (1)	0 (1)	-	-	0 (2)	0
LTG + TPM	-	5 (11)	0 (7)	0 (3)	0 (1)	1 (1)	-	-	-	6 (23)	26 %
LTG + VGB	-	0 (2)	-	-	0 (1)	-	-	-	-	0 (3)	0
LTG + ZNS	-	-	1 (2)	-	-	0 (1)	-	-	-	1 (3)	33 %
LTG + GBP + LEV	-	-	-	-	0 (1)	-	-	-	-	0 (1)	0
LTG + LEV + PGB	-	-	-	0 (1)	-	-	-	-	-	0 (1)	0
LTG + LEV + TPM	-	-	0 (3)	0 (2)	-	-	-	-	-	0 (5)	0
LTG + LEV + ZNS	-	-	-	0 (1)	-	-	-	-	-	0 (1)	0
LTG + TGB + VGB	-	-	0 (3)	-	-	-	-	-	-	0 (3)	0
LTG + TPM + ZNS	-	-	-	-	0 (1)	-	-	-	-	0 (1)	0
LTG + VGB + CLB	-	-	-	-	0 (1)	-	-	-	-	0 (1)	0
LTG + VGB + TPM	-	-	-	0 (1)	-	-	-	-	-	0 (1)	0
LTG + VGB + ZNS	-	-	-	-	-	0 (1)	-	-	-	0 (1)	0
FBM + PHT	-	-	-	0 (1)	-	-	-	-	-	0 (1)	0
GBP + LEV	-	-	1 (1)	0 (1)	-	-	-	-	-	1 (2)	50 %
GBP + OXC	-	-	-	0 (1)	-	-	-	-	-	0 (1)	0
GBP + PHT	-	-	0 (1)	-	-	-	-	-	-	0 (1)	0
GBP + TPM	-	-	-	-	-	-	1	-	-	1	100 %

							(1)			(1)	
LEV + OXC	-	1 (3)	1 (2)	-	0 (1)	-	-	-	-	2 (6)	33 %
LEV + PGB	-	-	0 (1)	-	-	-	-	-	-	0 (1)	0
LEV + TPM	-	1 (2)	-	0 (1)	-	-	-	-	-	1 (3)	33 %
LEV + ZNS	-	0 (1)	-	-	-	-	-	-	-	0 (1)	0
LEV + PGB + ZNS	-	-	-	0 (1)	-	-	-	-	-	0 (1)	0
LEV + PGB + TPM + ZNS	-	-	-	-	0 (1)	-	-	-	-	0 (1)	0
OXC + PGB	-	0 (2)	0 (1)	-	0 (1)	-	-	-	-	0 (4)	0
OXC + TPM	-	-	0 (1)	-	-	-	-	-	-	0 (1)	0
OXC + ZNS	-	-	-	0 (2)	-	-	-	-	-	0 (2)	0
Total of responders on polypharmacy	-	45	15	5	3	1	1	0	0	70	-
Total of Non-responders on polypharmacy	-	99	89	46	26	12	6	3	1	286	-
Total	**-**	**144**	**104**	**51**	**29**	**13**	**7**	**3**	**1**	**356**	**-**

Appendix 1. Efficacy of AEDs combinations in patients on polypharmacy.

List of References

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