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ANTIEPILEPTIC DRUGS – TREATING POPULATIONS

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Soong's enthusiasm encouraged me to persist with my work, and in times of need, our beautiful boys, Andrew and Jonathan, provided me with joyful diversion! Thanks also to my parents for their unfailing support.

DECLARATION

I am the sole author of this thesis and I have personally consulted all references listed. The work was undertaken by myself, and my colleagues, in the Epilepsy Unit, Division of Cardiovascular and Medical Sciences, Western Infirmary, Glasgow. My contributions included design of study protocols, ethics submissions, recruitment and interviewing of patients, venepuncture, and collection and analysis of data, consultation of references, and writing of articles. The studies in Papers 10 and 11 were collaborative works with colleagues Marek Dominiczak and David Shapiro of the Department of Clinical Biochemistry at Gartnavel General Hospital; Alistair McLellan and Joyce Harrison of the Division of Cardiovascular and Medical Sciences at the Western Infirmary also collaborated in Paper 10. This thesis, and the publications therein, have not been submitted previously for a higher degree.

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LIST OF ABBREVIATIONS

AED	Antiepileptic drug
MRI	Magnetic resonance imaging
CT	Computerised tomography
EEG	Electroencephalography
ILAE	International League Against Epilepsy
RCT	Randomised controlled trial
SUDEP	Sudden unexpected death in epilepsy
UK	United Kingdom
NICE	National Institute for Health and Clinical Excellence
SIGN	Scottish Intercollegiate Guidelines Network
JME	Juvenile myoclonic epilepsy
CNS	Central nervous system
COCP	Combined oral contraceptive pill
GABA	Gamma aminobutyric acid
PCOS	Polycystic ovarian syndrome

SUMMARY

Epilepsy affects 50 million people world-wide. Since 1982, the Western Infirmary Epilepsy Unit has provided a specialist service for over 6900 people with suspected and established seizure disorders. The twelve studies detailed in this thesis discuss the management of epilepsy in different patient populations, and explore beneficial and adverse effects of antiepileptic drugs (AEDs).

AED development has allowed advances in pharmacological treatment of localisation-related epilepsies. Thus, outcomes were investigated in 550 such patients followed-up at the epilepsy clinic over 13 years (Paper i). Of these, 312 (57%) became seizure-free on medication. Those with hippocampal sclerosis had the poorest outcome ($p < 0.01$), and a higher incidence of febrile convulsions ($p < 0.001$). Although many patients benefited from AED therapy, results may be biased, given this cross-sectional study analysed data from both newly diagnosed patients, and those with drug-resistant seizures.

Many people with epilepsy take more than one AED, although supportive evidence is sparse. Hence, polytherapy outcomes in 2881 patients registered with the Epilepsy Unit database were examined (Paper ii). Of these, 1617 (56%) were seizure-free, with 332 (21%) taking more than one AED (287 on two, 86%; 42 on three, 13%; 3 on four, 1%). There were 40 duotherapy and 28 triple therapy combinations resulting in seizure freedom. Therefore, combining two or three, but rarely four AEDs may be useful for patients not responding to monotherapy. Because this was a retrospective analysis of newly treated patients and those with refractory epilepsy, the analysis was subject to bias. Lack of a control group was also a weakness. Epilepsy Unit staff are

therefore now examining similar outcomes in a large population of newly treated patients only.

To establish the place of recently marketed AEDs in clinical practice, four studies examined prospectively the efficacy and tolerability of the novel agent, topiramate, in uncontrolled epilepsy. Adjunctive topiramate was administered in 170 patients with refractory seizures (Paper iii). Seizure frequency and adverse events were monitored. Patients were followed-up until seizure freedom for ≥ 6 months, $\geq 50\%$ or $<50\%$ seizure reduction, intolerable side-effects, or lack of efficacy occurred. Seizure freedom was achieved in 39 (23%) patients. A $\geq 50\%$ reduction in seizure frequency was reported in 80 (47%) others. Doses were often lower than those in regulatory studies. Efficacy as monotherapy was also demonstrated. Using the same end-points, topiramate was added to AED regimens of 64 patients with learning disabilities and epilepsy (Paper iv). Remission from seizures was established in 16 (25%).

In similar fashion, levetiracetam was started in 156 patients with uncontrolled epilepsy (Paper v). Of these, 40 (26%) became seizure-free, many on low doses. When the drug was added to AED regimens in 64 patients with learning disabilities, 24 (38%) became seizure-free for at least 6 months (Paper vi). Caregiver quality-of-life scores improved significantly with levetiracetam ($p < 0.001$). It is important to recognise that for all four audits results may be biased due to their observational nature, and the fact that they were undertaken at a single centre, with no control group. For patients with learning disabilities, small numbers, and retrospective baseline recordings for some could also have introduced bias.

In Papers vii, viii and ix, findings from longitudinal studies in teenagers, people with learning disabilities and epilepsy, and newly diagnosed elderly patients attending the Epilepsy Unit, are reported. At the Teenager Clinic, 301 adolescents were reviewed over four years (Paper vii). Epilepsy was excluded in 135 (45%), five taking AEDs. A single seizure occurred in 22 others. In the 144 with epilepsy, seizure freedom for \geq 12 months was attained in 76 (53%), but outcomes were poorer than expected. Neuroimaging was abnormal in 27 (43%). Newly diagnosed patients fared better than those taking treatment ($p < 0.05$). More teenagers with primary generalised seizures (60%) attained remission, compared to those with focal-onset seizures (46%) ($p < 0.02$). The retrospective nature of the analysis, and lack of control group may have biased results, thus making statistical conclusions inaccurate. Findings suggested the need for improved services.

Over four years, 214 patients with learning disabilities and refractory epilepsy were followed-up (Paper viii). Although it is generally thought these individuals' seizures are difficult to control, 59 (43%) became seizure-free for \geq 12 months with AEDs. There was no change in quality-of-life scoring during this time, and no relationship between extent of learning disability and seizure control. The observational nature of the audit, and lack of control group may have biased results.

Currently, there are few data on elderly people with epilepsy. Thus, outcomes over a 20-year period in 117 newly diagnosed senior citizens were examined (Paper ix). After starting AED treatment, 93 (79%) became seizure-free for \geq 12 months, 73 (62%) with their first drug. Prognosis was better than in younger patients, and for

those with fewer pre-treatment seizures ($p=0.0078$). Again bias may have been introduced because of the study's observational nature and lack of control group.

The final studies concentrate on AED-related adverse effects (Papers x, xi and xii). Bone changes have been reported with AED use. Hence, the relationship between bone mineral density, and long-term AED treatment in 78 older adults (47 post-menopausal women, 31 men), taking hepatic enzyme-inducing or non-inducing AEDs, was explored in a case-controlled study (Paper x). Men had significantly lower bone mineral density than controls at the lumbar spine ($p<0.01$), and neck of femur ($p<0.005$). Women had statistically reduced bone mineral density at the femoral neck ($p<0.05$). It was concluded that long-term AED treatment is an independent risk factor for reduced bone mineral density in people with epilepsy.

As sodium valproate may be associated with metabolic changes and polycystic ovarian syndrome, hormone profiles were compared in 76 young men and women taking sodium valproate or lamotrigine monotherapy, to assess whether a pharmacological effect of valproate was responsible (Paper xi). Results revealed only four obese females exhibiting biochemical characteristics of polycystic ovarian syndrome ($p=0.05$), with obese patients of both sexes ($p=0.01$), and valproate-treated men ($p=0.03$) having higher insulin concentrations. Results are not significant when corrected for multiple comparisons. It can therefore be concluded that no differences in metabolic indices between patients taking sodium valproate or lamotrigine existed.

To examine further effects on androgenic hormones, and the efficacy and tolerability of sodium valproate and lamotrigine monotherapy, a randomised, prospective study in

225 patients was performed (Paper xii). Patients were recruited if they presented with a minimum of two unprovoked seizures of any type, or a single seizure and underlying neuropathology. Of patients with partial-onset seizures, 81 received sodium valproate and 80 were randomised to receive lamotrigine. Of those with idiopathic generalised epilepsies, 30 received sodium valproate and 34 took lamotrigine. Seizure-free rates were identical in both arms at twelve months between the valproate and lamotrigine cohorts. There was a trend towards superiority for valproate (57% seizure-free) over lamotrigine (35% seizure-free) for patients with idiopathic generalised epilepsies ($p=0.09$), but a converse separation of outcomes for localisation-related epilepsies (43% seizure-free with valproate, 53% seizure-free with lamotrigine, $p=0.24$). More patients taking sodium valproate withdrew due to adverse events ($p=0.046$), eight because of weight gain. Neither drug altered testosterone, sex-hormone binding globulin, and androstenedione concentrations, or changed the free androgen index, at six and twelve months, but lack of further formal monitoring may have biased results.

These studies report results from different patient populations, including those with refractory epilepsy. Successful pharmacological outcomes were achieved in people with localisation-related epilepsies, and those taking polytherapy. Patients with learning disabilities and elderly individuals fared better than expected, although results were disappointing in adolescents. AEDs, can, however, be associated with adverse effects, and data show how certain patients may require screening for such changes, and/or avoidance of certain drugs. These findings have to be considered in the context that the design of several of the projects may have introduced inherent bias.

DISSERTATION

1. Introduction

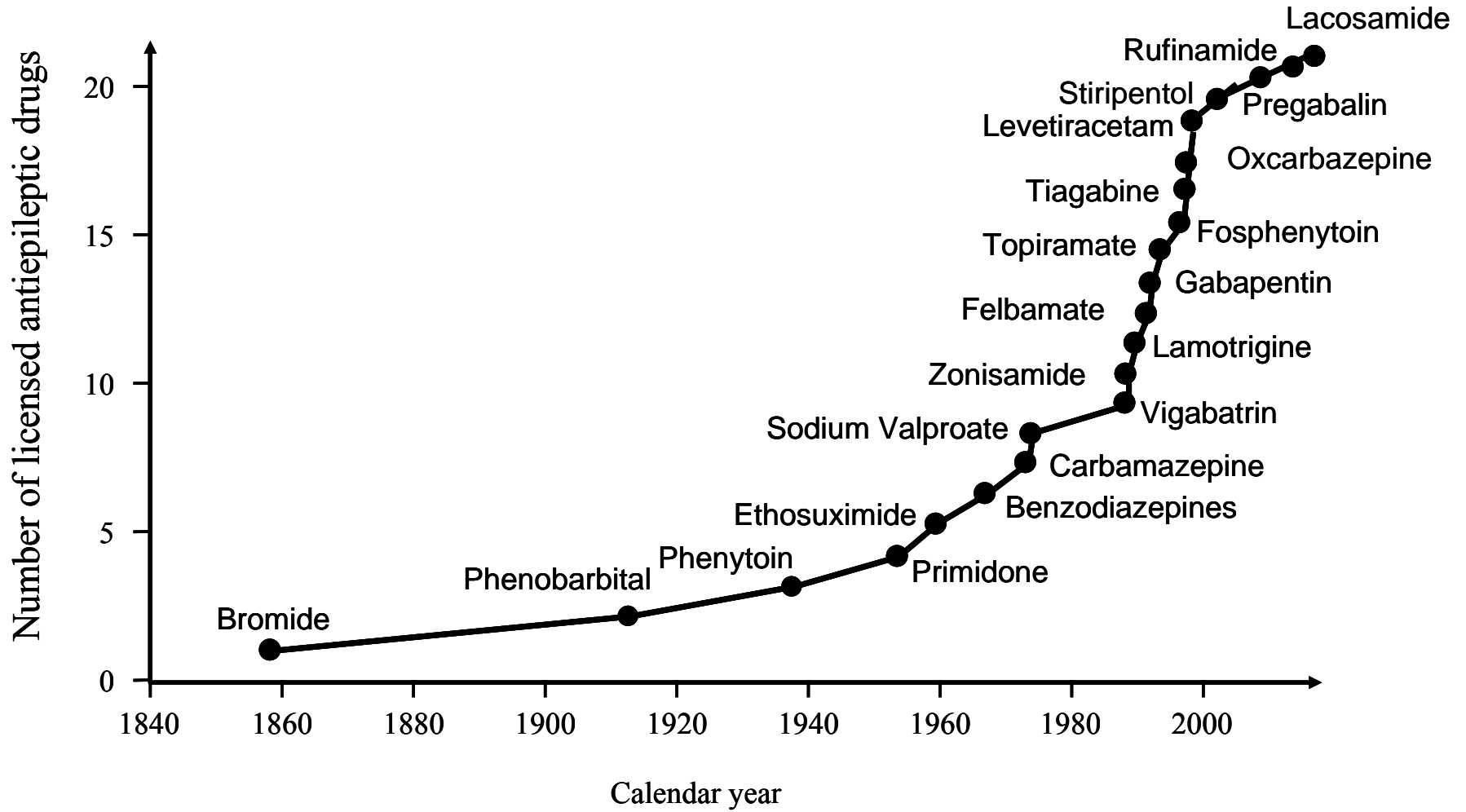
Antiepileptic drugs (AEDs) are the mainstay of treatment for people with epilepsy. In the last twenty years, there has been an explosion in novel agents, affording greater opportunities for therapeutic strategies, and the attainment of seizure freedom. At the Epilepsy Unit, in the Western Infirmary, Glasgow, a specialist clinical service for people with suspected and established seizure disorders has been running since 1982. There are now over 6900 patients registered with the service. This thesis centres on 12 publications, in which outcome data were derived from different patient populations studied by the author and associated Epilepsy Unit staff.

2. History of antiepileptic drug treatment

Epilepsy affects around 50 million people globally, with an annual incidence of 50-70 cases per 100,000 of the population (Hauser *et al*, 1996). Epilepsy is derived from ‘epilambanein’, the ancient Greek word which means ‘to seize’ or ‘to attack’. The history of the condition and its treatment can be traced back 4000 years (Gross, 1992). Details can be found in classical Chinese medical texts dating from 770 to 221 BC. Hippocrates called epilepsy the ‘Sacred Disease’ (Lebrun, 1992), and hypothesised that seizures were due to an overflow of phlegm from the brain. Early therapies were often derived from animals and plants. Such treatments included tortoise blood, genitals of seals or hare, hippopotamus, boar, ram and cock testicles. It was not until the mid 19th century, that Robert Bentley Todd and John Hughlings Jackson developed the first electrical theories of epilepsy (Reynolds, 2001). The anti-seizure properties of potassium bromide were beginning to be recognised around this time (Locock, 1857) and, although side-effects such as rash were common, its efficacy earned it a place in history as the first AED (Figure 1, page 21).

In 1911, the anticonvulsant properties of phenobarbital were discovered accidentally by Alfred Hauptmann (Hauptmann, 1912). Diphenylhydantoin was introduced by Merritt and Putman 27 years later (Merritt and Putnam, 1938). This was followed by primidone, ethosuximide, benzodiazepines, carbamazepine and, in 1973, valproic acid. After a 16-year gap, vigabatrin, the first of the newer AEDs, was licensed. This heralded the influx of thirteen more agents, with others to follow. Together with modern imaging techniques, these drugs have revolutionised the medical management of people with epilepsy.

Figure 1. Chronology of antiepileptic drug development in the United Kingdom



3. Managing patients with newly diagnosed epilepsy

3.1 Diagnosis and investigation

The onset of seizures can be terrifying, and has the potential to turn an individual's life upside-down. Optimal management is the key to obtaining the best outcome. An adult who is suspected to have had a first seizure should be referred to an epilepsy specialist for rapid assessment (SIGN, 2003). Diagnosis is based on the history, ideally from a witness. Partial (focal-onset) seizures can have many varied presentations from a brief sensory, autonomic or motor disturbance, to confusion and aggression lasting several minutes. Post-ictal symptoms and signs such as exhaustion, headache, muscle pain and Todd's paresis can provide useful clues if there is diagnostic difficulty. Tonic-clonic seizures usually have a more clear-cut presentation and may herald the onset of epilepsy. Given this scenario, it is worth asking about focal events, absence seizures and myoclonic jerks. These may have been occurring for many years, without a diagnosis having been made.

Magnetic resonance imaging (MRI) is the current standard of reference for people with seizure activity (NICE, 2004). Lesions detected have implications for prognosis and future management. Although computerised tomographic (CT) scanning can be useful in the urgent assessment of seizures, or where MRI is contraindicated, this tool is not sensitive enough to detect pathologies such as subtle cortical dysplasias and hippocampal sclerosis (Commission on Neuroimaging, ILAE, 1998).

Electroencephalography (EEG) is useful in supporting the classification of epileptic seizures and syndromes. The investigation can detect a photoparoxysmal response

which is present in around 5% of epilepsies, and generally has a favourable prognosis (Verrotti, 2004). A single routine EEG recording will show definite epileptiform abnormalities in 29-38% of adults who have epilepsy, rising to 69-77% with repeated recordings (SIGN, 2003). Sensitivity can also be increased with sleep deprivation (Leach *et al*, 2006). It is essential, also, to ensure that long QT syndrome, which can present with a seizure, is excluded by obtaining a routine electrocardiogram (Dunn *et al*, 2005). Together with a comprehensive history from a witness, information obtained from neuroimaging and EEG can help to classify the seizure type or syndrome.

3.2 Classification of seizure types and syndromes

Current classification of seizure type was defined by the International League Against Epilepsy (ILAE) in 1981 (Table 1, page 24), according to the clinical description of the event, as well as the EEG pattern (Commission on Classification and Terminology, ILAE, 1981). Partial seizures are those in which the first clinical and EEG signs indicate initial neuronal activation limited to part of one cerebral hemisphere. If consciousness is not impaired, the seizure is termed simple partial, whereas if consciousness is impaired, the event is classified as being a complex partial seizure. If the focal discharge propagates to both hemispheres, the seizure becomes secondary generalised. These may be tonic-clonic, or more rarely tonic, or clonic in type. Where a generalised seizure occurs without any clinical or electrophysiological evidence for a focal onset, the seizures, which involve both hemispheres simultaneously, may be convulsive or non-convulsive, and include absence, tonic-clonic, myoclonic, clonic, tonic, and atonic seizures.

Table 1. International classification of seizure types

(Commission on Classification and Terminology, ILAE, 1981)

Seizure Types	Features
Partial Seizures Simple Partial Seizures - With motor symptoms - Focal motor - Focal motor march (Jacksonian) - Versive - Postural - Phonatory - With somatosensory or special sensory symptoms - Somatosensory - Visual - Olfactory - Gustatory - Vertiginous With autonomic signs or symptoms With psychic symptoms Complex Partial Seizures Partial Seizures evolving to Secondary Generalised Seizures	EEG findings suggest focal onset Consciousness not impaired Vocalisation arrest of speech Simple hallucinations Epigastric sensations, pallor, sweating, flushing, piloerection, papillary dilation Disturbance of higher cortical function. Consciousness impaired EEG discharges rapidly generalise
Absence Seizures Typical absence Atypical absence	Regular and symmetrical 3-Hz spike-wave complex on EEG Irregular slow spike-wave complex on EEG
Myoclonic Seizures	Polyspike or slow spike-wave complex on EEG
Clonic Seizures	Fast activity or slow spike-wave complex on EEG
Tonic Seizures	Low-voltage fast EEG
Tonic-Clonic Seizures	Rhythm of less than 10Hz on EEG
Atonic Seizures	Polyspike-wave complex or low voltage fast wave on EEG
Unclassified Seizures	

EEG; Electroencephalogram

The ILAE Commission on Classification and Terminology has defined an epilepsy syndrome as ‘a complex of signs and symptoms that define a unique epilepsy condition.’ These include items such as seizure type, anatomy, precipitating factors, age of onset, severity, chronicity, diurnal and circadian rhythm, and sometimes prognosis (Table 2, page 27) (ILAE Commission on Classification and Terminology, 1989). Syndromes should be distinguished from epileptic diseases which are defined as ‘pathologic conditions with a single, specific, well-defined aetiology’.

Within the 1989 classification system, two key axes were defined, one for generalised versus localisation-related conditions and another for aetiology (symptomatic, idiopathic, and cryptogenic). Generalised seizures are defined traditionally as those which involve both cerebral hemispheres simultaneously and symmetrically during the actual seizure. Localisation-related (focal-onset) seizures arise from a discrete, lateralised region, usually in the cerebral cortex, regardless of later spread. There are, however, syndromes such as Landau-Kleffner and Dravet syndrome in which both focal and generalised features occur.

‘Symptomatic’ seizures can be thought of as those which have a preceding, non-acute insult or condition, such as stroke, head trauma and intracranial infection, the occurrence of which has been demonstrated to be associated with an increased risk of epilepsy (Hauser *et al*, 1993). Over 80 conditions are implicated (Engel, 2001).

‘Idiopathic’ was originally used to refer to seizures which were not symptomatic, but this definition now is used for well-characterised forms of epilepsy, mainly occurring in childhood and adolescence, and believed (though not always demonstrated) to have a genetic basis. The definition of ‘cryptogenic’ has changed throughout the years, but

now generally refers to epilepsies which do not fit the criteria for idiopathic conditions or have a remote symptomatic cause. Classification systems have been considered throughout the years (Engel, 2001; Engel, 2006), and revision is underway (ILAE Commission on Classification and Terminology, 2005-2009, in press).

Table 2. International classification of epilepsies and epileptic syndromes
(Commission on Classification and Terminology, ILAE, 1989)

<p>Localisation-related (focal, local, or partial)</p> <p>Idiopathic epilepsy with age-related onset</p> <ul style="list-style-type: none"> - benign childhood epilepsy with centrotemporal spikes (benign rolandic epilepsy) - childhood epilepsy with occipital paroxysms - primary reading epilepsy <p>Symptomatic epilepsy</p> <p>Cryptogenic epilepsy</p>
<p>Generalised</p> <p>Idiopathic epilepsy with age-related onset (listed in order of age at onset)</p> <ul style="list-style-type: none"> - benign neonatal familial convulsions - benign neonatal non-familial convulsions - benign myoclonic epilepsy in infancy - childhood absence epilepsy - juvenile absence epilepsy - juvenile myoclonic epilepsy - epilepsy with generalised tonic-clonic seizures on awakening - other idiopathic epilepsies <p>Cryptogenic or symptomatic epilepsy (listed in order of age at onset)</p> <ul style="list-style-type: none"> - West syndrome (infantile spasms) - Lennox Gastaut syndrome (childhood epileptic encephalopathy) - epilepsy with myoclonic-astatic seizures - epilepsy with myoclonic absence seizures <p>Symptomatic epilepsy</p> <ul style="list-style-type: none"> - Non-specific syndromes (early myoclonic encephalopathy, early infantile epileptic encephalopathy) - Specific syndromes (epileptic seizures as a complication of a disease, such as phenylketonuria, juvenile Gaucher's disease or Lundborg's progressive myoclonic epilepsy)
<p>Epilepsies undetermined whether focal or generalised</p> <p>With both generalised and focal features</p> <ul style="list-style-type: none"> - neonatal seizures - severe myoclonic epilepsy in infancy - epilepsy with continuous spike waves during slow-wave sleep - acquired epileptic aphasia (Landau-Kleffner syndrome) - without unequivocal generalised or focal features*
<p>Special syndromes</p> <p>Situation-related seizures</p> <ul style="list-style-type: none"> - febrile convulsions - seizures related to other identifiable situations, such as stress, hormonal changes, drugs, alcohol withdrawal or sleep deprivation <p>Isolated, apparently unprovoked epileptic events</p> <p>Epilepsies characterised by specific modes of seizure precipitation</p> <p>Chronic progressive epilepsia partialis continua of childhood</p>

* Includes cases in which the clinical and electroencephalographic findings do not permit classification of the epilepsy as clearly generalised or localisation-related, such as cases of tonic-clonic seizures during sleep.

Once classification has been decided upon (where possible), this leads to the question of how best to treat the particular seizure type(s) or syndrome. With the growing number of AEDS available, it is important to have a solid evidence base to guide clinicians in the most appropriate use of rational AED regimens. This evidence base takes the form of randomised, controlled trials (RCTs), systematic reviews and meta-analyses, and pragmatic studies.

4. Establishing the evidence base for the use of antiepileptic drugs

4.1 Randomised controlled trials

Regulatory authorities require proof of efficacy and safety before a licence for a new AED can be granted. When assessing the benefits and drawbacks of such health-related interventions, RCTs are considered the gold standard. Subsequent systematic reviews and meta-analyses may provide further information. As outlined in the CONSORT statement, a properly conducted RCT will minimise the risk of bias and will answer a specific question the study has been designed to examine (CONSORT Group, 2007). Adequate concealment methods of randomisation comprise central randomisation, numbered coded vehicles; and opaque, sealed, and sequentially numbered envelopes (Pildal *et al*, 2005). Blinding minimises bias further, with single blind studies in which patients are unaware of their treatment, double blind studies, where neither the patient, nor the clinician know the treatment, and triple blind studies, where neither patients, clinicians, nor those conducting the analysis are aware of treatment allocation. A rigorous RCT will include patients who are as similar as possible, and will exclude patients who receive additional treatments or who have co-morbid conditions, as these confounding factors may invalidate results. Bias is minimised where outcomes are fully, as opposed to selectively, reported.

When a pharmaceutical company initially plans to market an AED, it usually undertakes an RCT in the form of an add-on study, investigating a range of doses versus placebo in patients with refractory epilepsy. The aim is to show a clinically useful dose-response relationship, ideally including a non-effective dose, which will help identify the effective dosage range. The design of choice is that of a parallel-

group study, where patients are randomised to receive one of several doses of drug or matched placebo. Cross-over studies, where the patient receives the active drug and placebo in two separate phases, separated by a washout period, are considered less rigorous because there may be carry over effects during the washout period. There are also ethical and maintained consent issues, as any benefit obtained during the first period will be lost in the second. As monotherapy, the study drug can be compared to standard doses of an established AED in an active-control study. Patients participating in conversion to monotherapy studies receive active drug or control. The original AEDs are then tapered off and patients maintained, if possible, on the new monotherapy.

To minimise bias in RCTs, patients participating are usually highly selected, within a desired age range, and often with very refractory epilepsy. Those who are poorly adherent or who have comorbidities may be excluded. Compliance is strictly monitored, with close and frequent follow up, often different to that of the routine epilepsy clinic. There is generally a fixed number of patients recruited, and a fixed duration of treatment. Women of child-bearing age may be excluded if pregnancy is an issue, given that the human teratogenic potential of new AEDs is undetermined. The aim of these studies for European regulatory purposes, is to show equivalence of the new drug to the standard comparator; and for American regulatory purposes, to show superiority over the comparator.

4.2 Pragmatic studies of antiepileptic drugs

Taking the pros and cons of RCTs into account, how can other data regarding AED use be acquired? Although RCTs performed for regulatory purposes provide important data on specific issues, they are not a reflection of routine clinical practice. As such, RCTs do not provide the best evidence on flexible dosing schedules, chronic adverse effects, idiosyncratic reactions, or teratogenicity, and thus do not always provide information required for everyday decision making (Chadwick and Marson, 2007). Once an AED is licensed, it is important, therefore, to continue studying its effects through more pragmatic research in the clinical setting. There has been a call in recent months for improved observational studies. The CONSORT statement has recently been extended to guide clinicians on undertaking ‘pragmatic’ as opposed to ‘explanatory’ trials (Zwarenstein *et al*, 2008), where ‘pragmatic’ describes studies designed to help choose between options for healthcare, and ‘explanatory’ describes trials designed to test causal research hypotheses (Schwartz and Lellouch, 1967). This has been backed by the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement, a checklist of items which should be addressed in articles reporting cohort, case-control, and other observational studies (von Elm *et al*, 2007).

Cohort studies, which can be prospective or retrospective, are designed to answer questions of the type ‘What are the effects of this exposure?’. A group of people with a particular exposure are compared with another group who either have not had the exposure, or have had a different level of exposure. Case-control studies are designed to answer the question ‘What are the factors that caused this event?’. Individuals with an outcome are compared with other individuals from the same population who do not

have the outcome. Case-control design is generally used to assess the causes of a new problem, but may also be useful for the evaluation of population-based interventions such as screening. In the clinical setting, it can also be helpful to monitor the outcomes of an intervention, such as the addition of a new AED, in order to become familiar with its dosing and effects. The limitation of such observational research has to be recognised, however, as without randomisation, a control group, and exclusion of confounding factors, inherent bias occurs.

4.3 Research and audit – ethical issues

In an ideal world, ethical consideration should apply to all areas of medicine (Wade, 2005). Ethics committees are required to examine all research proposals, but most now exclude projects they consider to be audit. It is therefore important to differentiate between research and audit, although the distinction between the two is often not clear cut. Research has been defined as ‘a systematic investigation undertaken to discover facts or relationships and reach conclusions using scientifically sound methods’ (Hockey, 1996). Clinical audit is ‘a quality improvement process that seeks to improve patient care and outcomes through systematic review of care against explicit criteria and the implementation of change’ (NICE, 2007).

Research and audit are similar in many ways. Both start by posing a question, can be undertaken prospectively or retrospectively, involve careful sampling, questionnaire design and analysis of findings, and both activities should be professionally led. There are, however, a number of differences between research and audit (National Research Ethics Service, 2008), and these are summarised in Table 3 (page 34). Given this

information, it can be argued that some of the studies contained in this thesis can be classified as audit, whilst others fall into the category of research. The reasons for this are discussed in relation to each relevant publication in Chapters 6, 7, 8 and 9. For people with epilepsy, many of whom require to take long-term AED treatment, outcomes from research and audit projects provide crucial data informing on the diagnosis, investigation, treatment, and outcomes of the condition.

Table 3. Differences between audit and research – ethical considerations
(National Research Ethics Service, 2008)

Research	Clinical Audit
The attempt to derive generalisable new knowledge, including studies that aim to generate hypotheses, as well as studies that aim to test them.	Designed and conducted to produce information to inform delivery of best care.
Quantitative research – designed to test a hypothesis. Qualitative research – identifies/explores themes following established methodology.	Designed to answer the question: ‘Does this service reach a predetermined standard?’
Addresses clearly defined questions, aims and objectives.	Measures against a standard.
Quantitative research – may involve evaluating or comparing interventions, particularly new ones. Qualitative research – usually involves studying how interventions and relationships are experienced.	Involves an intervention in use ONLY (the choice of treatment is that of the clinician and patient, according to guidance, professional standards and/or patient preference).
Usually involves collecting data that are additional to those for routine care, but may include data collected routinely. May involve treatments, samples or investigations additional to routine care.	Usually involves analysis of existing data, but may include administration of simple interview or questionnaire.
Quantitative research – study design may involve allocating patients to intervention groups. Qualitative research uses a clearly defined sampling framework underpinned by conceptual theoretical justifications.	No allocation to intervention groups: the healthcare professional and patient have chosen the intervention before the clinical audit.
May involve randomisation.	No randomisation.

5. Rational antiepileptic drug monotherapy in adults

The decision to start AED treatment can be based on several criteria including the likelihood of seizure recurrence, the consequences of continuing seizures for the patient, and the beneficial and adverse effects of the pharmacological agent chosen (NICE, 2004). Risk of recurrence can vary depending on the seizure type or syndrome. Patients with epileptiform discharges on the EEG or congenital neurological defects are at high risk (up to 90%) of further seizures. Risk is also increased in people with symptomatic seizures, in those with cerebral lesions, and in patients with Todd's paralysis.

When considering whether or not to treat a first seizure, it is important to take into account the patient's views of the situation, as well as those of their family. To this end, it is vital that everyone concerned is provided with a clear explanation of events, and the likely consequences. For people who are anxious not to have another seizure, early introduction of treatment may be best. Further seizure activity may be unacceptable for those who need to drive, continue in employment, or are responsible for vulnerable family members. Those with a family history of epilepsy may be more inclined to accept long-term treatment. Occasionally, a person will have a relative who has succumbed to a seizure-related death and will, therefore, gain peace-of-mind by starting medication. At the opposite end of the spectrum, some patients will choose not to start treatment, even after a number of seizures, because they dislike taking medication. Others may have a problem with the stigma of the diagnosis of epilepsy, and all this entails. Treatment may be difficult in people who abuse drugs or alcohol, or who are unwilling or unlikely to take medication. These individuals should be counselled appropriately and be made aware of the implications of further seizure

activity, including the risk of sudden unexpected death in epilepsy (SUDEP) (Mohanraj *et al*, 2006).

When starting treatment, AED monotherapy is associated with better compliance and fewer side effects than combination regimens. As 60% of people will gain control of their epilepsy with the first or second AED, much attention should be given to the selection of initial drug, taking into account the efficacy of the AED for the seizure type or syndrome (Kwan and Brodie, 2000a).

5.1 Evidence-based guidelines

The number of available AEDs has increased rapidly in the last 20 years, giving more choice when initiating therapy. Major evidence-based guidelines have been developed during this time, assisting clinicians and patients in making appropriate treatment choices. These include the United Kingdom (UK) guidelines issued by the National Institute for Clinical Excellence (NICE) - 'The diagnosis and management of the epilepsies in adults and children in primary and secondary care' (NICE, 2004), the Scottish Intercollegiate Guidelines Network (SIGN) 'Diagnosis and management of epilepsy in adults' (SIGN, 2003), and 'Diagnosis and management of epilepsies in children and young people' (SIGN, 2005), the American Academy of Neurology / American Epilepsy Society Guidelines on treatment of new-onset epilepsy (American Academy of Neurology, 2004), and those compiled by the International League Against Epilepsy (Glaser *et al*, 2006). These guidelines are based on the 'best available evidence', but may not be a substitute for knowledge, skill, and experience in managing the individual patient.

5.2 Treatment goals

The goal of AED treatment should be complete seizure control without, or with minimal adverse effects. AED monotherapy is associated with better compliance, fewer adverse effects, fewer drug interactions, and less teratogenic potential, as well as being more cost-effective (Devinsky and Cramer, 2000). The drug of choice should have efficacy for the given seizure type or syndrome, with other important properties comprising safety, tolerability, pharmacokinetic properties, and formulation. Selecting the most suitable AED also requires detailed knowledge about the patient's medical and drug history, and their social circumstances.

5.3 Efficacy

The profile of activity against different seizure types and syndromes varies among AEDs (Table 4, page 38). Classification is therefore of paramount importance. Certain epilepsy syndromes have been found to be particularly responsive to specific agents. For example, juvenile myoclonic epilepsy (JME) responds well to sodium valproate (Sundqvist *et al*, 1998), and vigabatrin is regarded by many as the treatment of choice for infantile spasms secondary to tuberous sclerosis (Elterman *et al*, 2001). Conversely, narrow spectrum drugs such as carbamazepine (Liporace *et al*, 1994), phenytoin (Duarte *et al*, 1996), gabapentin (Ascapone, 2000) and oxcarbazepine (Gelisse *et al*, 2004) can worsen myoclonic jerks, and absence seizures. AED treatment of common epilepsy syndromes presenting in adulthood is discussed further in Chapter 6.

Table 4. Efficacy of antiepileptic drugs against common seizure types and syndromes

Antiepileptic Drug	Focal-onset seizures	Primary generalised seizures			Lennox Gastaut	Infantile Spasms
		Tonic clonic	Absence	Myoclonic		
Carbamazepine	+	+	↓	↓	0	0
Phenytoin	+	+	↓	↓	0	0
Phenobarbital	+	+	+	0	?	?
Primidone	+	+	0	?	?	?
Ethosuximide	0	0	+	0	0	0
Sodium valproate	+	+	+	+	+	+
Clobazam	+	+	?	+	+	?+
Clonazepam	+	+	?	+	?+	?+
Vigabatrin	+	?+	↓	↓	?	+
Lamotrigine	+	+	+	+*	+	?+
Gabapentin	+	?+	↓	↓	?	?
Topiramate	+	+	?	+	+	?
Tiagabine	+	?	↓	?	?	?+
Oxcarbazepine	+	+	↓	↓	0	0
Levetiracetam	+	+	?+	+	?	?
Pregabalin	+	?	?	?	?	?
Stiripentol	+	+	?+	+	?+	?+
Zonisamide	+	?+	?+	?+	?+	?+
Rufinamide	+	+	?+	?+	+	?
Lacosamide	+	?	?	?	?	?

+ proven efficacy; ?+ probable efficacy; 0 ineffective; ↓ worsens control; ? unknown

*Lamotrigine may worsen myoclonic seizures in some patients

AEDs currently licensed for use as monotherapy in the UK comprise carbamazepine, phenytoin, phenobarbital, primidone, ethosuximide, sodium valproate, clobazam, clonazepam, lamotrigine, gabapentin, topiramate, oxcarbazepine, and levetiracetam. With the emergence of many new agents in recent years, there is a growing evidence base of studies (Tables 5 and 6, pages 40-43), and systematic reviews (Table 7, page 44) comparing initial monotherapy treatments for different seizure types and syndromes. There is, however, currently no over-whelming efficacy evidence supporting use of a particular drug. This is due, principally to differences in study design, and the absence of thorough adverse effects data at equivalent dosage. There is a lack of properly conducted randomised, controlled trials, particularly for people with generalised tonic-clonic seizures. Recent data from the levetiracetam versus controlled-release carbamazepine trial suggested that most adults with newly diagnosed epilepsy will respond to a modest dose of any first line AED (Brodie *et al*, 2007). The more pragmatic SANAD trials favoured lamotrigine over carbamazepine, gabapentin, topiramate, and oxcarbazepine for partial epilepsy (Marson *et al*, 2007a), and sodium valproate over lamotrigine or topiramate for generalised and unclassifiable epilepsy (Marson *et al*, 2007b).

Table 5. Randomised controlled trials comparing antiepileptic drug (AED) monotherapies in patients with partial-onset seizures

Reference	AEDs compared	Study Population	Conclusions	Comments
Mikkelsen <i>et al</i> , 1981	Carbamazepine Clonazepam	36 adults with complex partial seizures	No significant difference was found between the 2 drugs during 6 months' treatment.	Small cohorts
Ramsay <i>et al</i> , 1983	Carbamazepine Phenytoin	87 adults with newly diagnosed partial-onset and primary GTCS	Efficacy and tolerability were the same for both drugs.	Double-blind study. Small patient numbers
Mattson <i>et al</i> , 1985	Carbamazepine Phenobarbital Phenytoin Primidone	622 adults with partial and secondary generalised seizures	Control of tonic-clonic seizures did not differ between the drugs. Carbamazepine more often controlled partial seizures compared to phenobarbitone or primidone. Primidone had efficacy similar to phenobarbital, but was tolerated less well.	Multicentre study
Dam <i>et al</i> , 1989	Carbamazepine Oxcarbazepine	235 adults with newly diagnosed partial-onset and primary GTCS	No significant differences in efficacy were found between the two drugs. There was a trend towards better tolerability with oxcarbazepine	Double-blind, multicentre study
Mattson <i>et al</i> , 1992	Carbamazepine Sodium valproate	480 adults with complex partial or secondary GTCS	Carbamazepine was superior to valproate in controlling complex partial seizures. Carbamazepine is as effective as sodium valproate in controlling secondary GTCS.	Double-blind, multicentre study
Richens <i>et al</i> , 1994	Carbamazepine Sodium valproate	300 adults with newly diagnosed partial-onset or primary GTCS	The drugs controlled seizures equally effectively. Significantly more patients continued on valproate than carbamazepine for at least 6 months.	Open label study
Brodie <i>et al</i> , 1995	Carbamazepine Lamotrigine	260 patients >13 years with untreated partial-onset or primary GTCS	Similar efficacy results were obtained for both drugs. Lamotrigine was significantly better tolerated	Double-blind, multicentre study
Christie <i>et al</i> , 1997	Oxcarbazepine Sodium valproate	249 adults with partial or GTCS	No significant differences in efficacy or tolerability found between the two drugs	Double-blind, multicentre study
Bill <i>et al</i> , 1997	Phenytoin Oxcarbazepine	287 adults with untreated partial-onset and primary GTCS	No significant differences in efficacy found between the two drugs. Oxcarbazepine was significantly better tolerated than phenytoin	Double-blind, multicentre study
Guerreiro <i>et al</i> , 1997	Phenytoin Oxcarbazepine	193 children and adolescents with epilepsy	No significant differences in efficacy found between the two drugs. Oxcarbazepine was tolerated and retained significantly better.	Double-blind, multicentre study
Chadwick <i>et al</i> , 1998	Gabapentin 300mg, 900mg and 1800mg Carbamazepine	292 patients aged 12-86 years with newly diagnosed partial-onset seizures	Gabapentin at 900mg or 1800mg/day is as effective and as safe as carbamazepine.	Open label study.
Steiner <i>et al</i> , 1999	Phenytoin Lamotrigine	181 newly diagnosed adults with partial-onset or primary GTCS	Efficacy results were similar for the two drugs. There was a trend towards better tolerability with lamotrigine.	Double-blind study. The high rash rate with lamotrigine was probably due to high starting doses

Table 5 (continued)

Reference	AEDs compared	Study Population	Conclusions	Comments
Brodie <i>et al</i> , 1999	Carbamazepine Lamotrigine	150 patients aged ≥ 65 years with newly diagnosed epilepsy	No difference was found between the 2 drugs in time to first seizure. More patients continued with lamotrigine than with carbamazepine.	Lamotrigine: carbamazepine treatment ratio was 2:1
Chadwick, 1999	Carbamazepine Vigabatrin	459 patients aged 12-65 years with partial-onset seizures	All efficacy outcomes favoured carbamazepine and failed to show equivalence between the two drugs. Time to first seizure was significantly greater with carbamazepine. Vigabatrin was associated with more psychiatric symptoms.	Double-blind, multicentre study.
Brodie <i>et al</i> , 2002	Lamotrigine Gabapentin	309 adults with partial-onset seizures or primary GTCS	The drugs were similar in efficacy and tolerability	Double blind, multicentre study
Privitera <i>et al</i> , 2003	Carbamazepine Sodium valproate Topiramate	621 children and adults with newly diagnosed partial-onset seizures or primary GTCS	No significant differences in efficacy were found between the three drugs	Double-blind, multicentre study
Gilliam <i>et al</i> , 2003	Topiramate 50mg/d, 200mg/d, or 500mg/d	Patients aged ≥ 3 years with partial-onset seizures	Seizure-free rates were significantly higher and time to first seizure was significantly longer with 200mg/d and 500mg/d	Double-blind, multicentre study
Arroyo <i>et al</i> , 2005	Topiramate 50mg/d, or 400mg/d	Patients ≥ 6 years old with untreated partial-onset or GTCS	The higher dose was significantly more likely to produce seizure freedom than the lower dose. More patients on the higher dose discontinued treatment.	Multicentre study
Rowan <i>et al</i> , 2005	Carbamazepine Lamotrigine Gabapentin	593 patients aged ≥ 65 years with newly diagnosed epilepsy	Seizure control outcomes were similar for the three drugs. Significantly more patients stopped carbamazepine due to adverse events compared to gabapentin and lamotrigine	Double-blind, multicentre study
Brodie <i>et al</i> , 2007	Controlled release carbamazepine Levetiracetam	579 patients ≥ 16 years with ≥ 2 partial-onset or GTCS in the past year	Seizure free rates were equivalent for both drugs	Double-blind, multicentre study
Marson <i>et al</i> , 2007a	Carbamazepine Gabapentin Lamotrigine Oxcarbazepine Topiramate	1721 adults with partial-onset seizures.	For time to treatment failure, lamotrigine was significantly better tolerated than carbamazepine, gabapentin or topiramate. For time to 12-month remission, carbamazepine was significantly better tolerated than gabapentin.	Multicentre study
Marson <i>et al</i> , 2007b	Sodium valproate Lamotrigine Topiramate	716 adults with newly diagnosed epilepsy	Valproate was significantly better than topiramate in time to treatment failure. For patients with idiopathic generalised epilepsies, valproate had significantly better efficacy than topiramate or lamotrigine. Valproate was significantly better tolerated than topiramate.	Multicentre study
Saetre <i>et al</i> , 2007	Controlled release carbamazepine Lamotrigine	186 patients aged ≥ 65 years with newly diagnosed epilepsy	Effectiveness was comparable for both drugs. There was a trend towards higher seizure free rates with carbamazepine and for better tolerability with lamotrigine.	Double-blind, multicentre study

GTCS; generalised tonic-clonic seizures

Table 6. Randomised controlled trials comparing antiepileptic drug (AED) monotherapies in patients with generalised tonic-clonic seizures (GTCS)

Reference	AEDs compared	Study Population	Conclusions	Comments
Shakir <i>et al</i> , 1981	Sodium valproate Phenytoin	33 adults with epilepsy	Sodium valproate was as effective as phenytoin	Small cohort
Turnbull <i>et al</i> , 1982	Phenytoin Sodium valproate	88 adults with untreated partial-onset or primary GTCS	No significant differences in efficacy between the drugs. Both were more effective for GTCS than partial seizures.	
Ramsay <i>et al</i> , 1983	Carbamazepine Phenytoin	87 adults with newly diagnosed partial-onset and primary GTCS	Efficacy and tolerability were the same for both drugs.	Small patient numbers
Turnbull <i>et al</i> , 1985	Phenytoin Sodium valproate	140 patients >16 years with partial or tonic-clonic seizures	No significant differences in efficacy between the two drugs	Single centre study
Callaghan <i>et al</i> , 1985	Carbamazepine Phenytoin Sodium valproate	181 adults with untreated epilepsy	All the drugs were highly effective in controlling generalised seizures, but less effective in controlling partial seizures.	Single centre study
Dam <i>et al</i> , 1989	Carbamazepine Oxcarbazepine	235 adults with newly diagnosed partial-onset and primary GTCS	No significant differences in efficacy were found between the two drugs. There was a trend towards better tolerability with oxcarbazepine	Double-blind, multicentre study
Aikia <i>et al</i> , 1992	Phenytoin Oxcarbazepine	37 adult patients with newly diagnosed epilepsy.	No significant differences in efficacy between the drugs.	Single centre, double-blind study. Small cohort
Placencia <i>et al</i> , 1993	Carbamazepine Phenobarbital	192 patients aged between 2 and 60 years with 2 or more untreated seizures	Both drugs had equal efficacy.	Community-based study
Richens <i>et al</i> , 1994	Carbamazepine Sodium valproate	300 adults with newly diagnosed partial-onset or primary GTCS	The drugs controlled seizures equally effectively. Significantly more patients continued on valproate than carbamazepine for at least 6 months.	Multicentre, open label study
Pullianen <i>et al</i> , 1995	Carbamazepine Phenytoin	43 adults with newly diagnosed partial-onset or primary GTCS	No significant differences in efficacy between the drugs.	Single centre, open label study
Heller <i>et al</i> , 1995	Phenobarbital Phenytoin Carbamazepine Sodium valproate	243 patients aged >16 years with untreated epilepsy	No significant differences in efficacy between the drugs. More patients stopped phenobarbital due to side effects	Two centre, randomised study

Table 6. (Continued)

Reference	AEDs compared	Study Population	Conclusions	Comments
Kalviainen <i>et al</i> , 1995	Carbamazepine Vigabatrin	100 patients aged 15 to 64 years with untreated epilepsy	Significantly more patients remained seizure-free with carbamazepine than with vigabatrin. The former was withdrawn more often due to adverse effects. The latter was statistically more often stopped due to lack of efficacy.	Single centre, open label study
Brodie <i>et al</i> , 1995	Carbamazepine Lamotrigine	260 patients >13 years with untreated partial-onset or primary GTCS	Similar efficacy results were obtained for both drugs. Lamotrigine was significantly better tolerated	Double-blind, multicentre study
Reunanen <i>et al</i> , 1996	Carbamazepine Lamotrigine	343 patients >12 years with untreated partial or GTCS	Carbamazepine and lamotrigine were equally efficacious, with a trend to better tolerability with lamotrigine.	Multicentre randomised study
Bill <i>et al</i> , 1997	Phenytoin Oxcarbazepine	287 adults with untreated partial-onset and primary GTCS	No significant differences in efficacy between the drugs. Oxcarbazepine was significantly better tolerated than phenytoin	Double-blind, multicentre study
Christie <i>et al</i> , 1997	Oxcarbazepine Sodium valproate	249 adults with partial or generalised seizures	No significant differences in efficacy or tolerability found between the two drugs	Double-blind, multicentre study
Steiner <i>et al</i> , 1999	Phenytoin Lamotrigine	181 untreated adults with partial-onset or primary GTCS	Efficacy results were similar for the two drugs. There was a trend towards better tolerability with lamotrigine.	The high rash rate with lamotrigine was probably due to high starting doses
Brodie <i>et al</i> , 2002	Lamotrigine Gabapentin	309 adults with partial-onset seizures or primary GTCS	The drugs were similar in efficacy and tolerability	Double blind, multicentre study
Privitera <i>et al</i> , 2003	Carbamazepine Sodium valproate Topiramate	621 children and adults with newly diagnosed partial-onset seizures or primary GTCS	No significant differences in efficacy were found between the three drugs	
Arroyo <i>et al</i> , 2005	Topiramate 50mg/d, or 400mg/d	487 patients \geq 6 years old with untreated partial-onset or GTCS	The higher dose was significantly more likely to produce seizure freedom than the lower dose. More patients on the higher dose discontinued treatment.	Double blind, multicentre study
Marson <i>et al</i> , 2007a	Sodium valproate Lamotrigine Topiramate	716 adults with newly diagnosed epilepsy	Valproate was significantly better than topiramate in time to treatment failure. For patients with IGEs, valproate had significantly better efficacy than topiramate or lamotrigine. Valproate was significantly better tolerated than topiramate.	Multicentre, randomised study

IGEs; Idiopathic generalised epilepsies

Table 7. Systematic reviews of antiepileptic drug monotherapy comparison studies

Reference	Antiepileptic drugs compared	Study Population	Conclusions	Comments
Marson <i>et al</i> , 2000	Carbamazepine Sodium valproate	Children and adults with partial-onset seizures, or generalised-onset tonic-clonic seizures	Some evidence supported use of carbamazepine for partial-onset seizures. No evidence to support use of valproate in generalised-onset seizures.	Misclassification of epilepsy may have confounded results.
Tudur Smith <i>et al</i> , 2001	Phenytoin Sodium valproate	Children and adults with partial-onset or primary generalised tonic-clonic seizures	No significant differences in efficacy outcomes between the two drugs.	
Tudur Smith <i>et al</i> , 2003	Carbamazepine Phenobarbital	Adults and children with partial-onset or primary generalised tonic-clonic seizures	Drugs were equally effective at controlling focal-onset and primary generalised tonic-clonic seizures.	
Taylor <i>et al</i> , 2003	Phenobarbital Phenytoin	Adults and children with partial-onset or primary generalised tonic-clonic seizures	Phenobarbital was significantly more likely to be discontinued than phenytoin. No difference in time to 12-month remission or first seizure.	Differences in study design made comparisons difficult.
Posner <i>et al</i> , 2005	Ethosuximide Sodium valproate Lamotrigine	Children and adolescents with absence seizures	Evidence was insufficient to make conclusions regarding efficacy	Trials included were of poor methodological quality with small patient numbers.
Muller <i>et al</i> , 2006	Phenytoin Oxcarbazepine	Children and adults with epilepsy	For patients with partial-onset seizures, oxcarbazepine is significantly less likely to be withdrawn. Data did not allow efficacy comparisons.	Misclassification of epilepsy types may have confounded results.
Gamble <i>et al</i> , 2006	Carbamazepine Lamotrigine	Children and adults with partial-onset seizures or generalised seizures with or without other seizure types	Carbamazepine may be superior to lamotrigine in terms of seizure control for time to first seizure.	Studies of a longer duration are required to assess long-term outcomes.

5.4 Safety

Establishing acceptable tolerability is a crucial function of regulatory studies performed by pharmaceutical companies for licensing purposes. On occasion, a safety issue will occur once a drug becomes available for general clinical use. This was the case with felbamate, which was found to cause hepatic failure and aplastic anaemia, severely limiting its use (Kaufman *et al*, 1997), and with vigabatrin, where peripheral visual field defects were first documented eight years after the drug was licensed (Krauss *et al*, 1998). Other AEDs, such as carbamazepine (Pellock, 1987), phenytoin (Haruda, 1979), lamotrigine (Brodie *et al*, 1995), oxcarbazepine (Bill *et al*, 1997), and zonisamide (Arif *et al*, 2007) have been associated with idiosyncratic hypersensitivity reactions. Recent data support a particular association between the HLA-B*1502 allele and AED-induced cutaneous reactions in Han Chinese (Man *et al*, 2007). Such idiosyncratic reactions are the result of an abnormal interaction between the drug and the patient, usually through cytotoxic or immunologic effects triggered by the drug or its metabolites (Ju and Uetrecht, 2002). These can be minimised by a low starting dose and slow titration schedule.

5.5 Teratogenicity

The incidence of minor and major foetal malformations increases in women with epilepsy, even if they are untreated (Holmes *et al*, 2001). Commonly quoted figures are 3 - 6% for women with epilepsy compared with 2 - 3% in the general population (Tomson *et al*, 2004). The risk increases disproportionately with the number of AEDs taken, being approximately 3% for one drug (similar to background risk), 5% for two, 10% for three and over 20% in women taking more than three AEDs. A syndrome

ascribed initially to hydantoins including phenytoin (foetal hydantoin syndrome), but now known to occur with other AEDs including carbamazepine and valproate, consists of facial dimorphism, cleft lip and palate, cardiac defects, digital hypoplasia and nail dysplasia (Tomson *et al*, 2004).

Current evidence suggests that the risk of major congenital malformations is 2-4 times higher with the use of valproic acid compared to other AEDs such as carbamazepine and lamotrigine, although this may be minimised by keeping the daily dose at or below 1000 mg (Harden *et al*, 2009). Absolute rates have ranged from 6 – 11%. Exposure to high dose valproic acid in utero may impair later cognitive function (Meador *et al*, 2009). The risk of major malformations with high dosage lamotrigine requires resolving (Morrow *et al*, 2006).

5.6 Tolerability

For an AED to be effective, it requires to be well-tolerated, as well as having efficacy. AEDs can produce unwanted dose-related side effects, with central nervous system (CNS) effects such as drowsiness, ataxia and dizziness being the most common. As with idiosyncratic reactions, these can be minimised by a low starting dose and slow titration schedule. Several of the newer agents have been shown to have superior tolerability (Dam *et al*, 1989; Brodie *et al*, 1995; Kalviainen *et al*, 1995; Reunanen *et al*, 1996; Bill *et al*, 1997), although seizure freedom may still be unattainable due to the development adverse effects in some patients. Specific adverse effects associated with AED treatment are discussed in detail in Chapter 9.

5.7 Pharmacokinetic properties

Ideally, an AED should be absorbed fully, have low protein binding and undergo linear pharmacokinetics, with clearance unaffected by renal impairment (Perucca, 2005). It should neither induce nor inhibit hepatic mono-oxygenase or conjugating enzymes, interact with concomitant medication, nor produce neurotoxic or other adverse effects. A long elimination half-life is advantageous, allowing once or twice daily dosing. A well-established target dose should be achievable without titration. Many older AEDs, to some extent, undergo hepatic metabolism, with renal elimination of inactive metabolites (Table 8, page 49). Phenytoin pharmacokinetics are complex. With increasing doses, the eliminating enzyme system becomes progressively saturated. Thus, a small increase in dose can result in a large rise in plasma concentration and neurotoxicity (Valodia *et al*, 2000).

Phenobarbital, primidone, phenytoin, and carbamazepine induce the metabolism of lipid-soluble drugs such as the combined oral contraceptive pill (COCP) (Back *et al*, 1980), cytotoxic agents (Kivisto *et al*, 1995), antiretrovirals (Liedtke *et al*, 2004), statins (Ucar *et al*, 2004), and warfarin (Solomon *et al*, 1972). Newer AEDs are less likely to interfere with hepatic metabolism (Table 9, page 50), although oxcarbazepine (Klosterskov Jensen *et al*, 1992, Fattore *et al*, 1999), felbamate (Saano *et al*, 1995), and higher doses of topiramate (Rosenfeld *et al*, 1997a) can induce the oestrogenic component of the COCP (Patsalos *et al*, 2008). Lamotrigine reduces levonorgestrel concentrations, but has no effect on ethinyloestradiol concentrations (Sidhu *et al*, 2005). Conversely, lamotrigine clearance is increased two-fold by the co-administration of the COCP (Sabers *et al*, 2001; Sabers *et al*, 2003; Reimers *et al*, 2005; Christensen *et al*, 2007; Wegner *et al*, 2009), a likely consequence of the

induction of the uridine diphosphate glucuronosyltransferase system, via which lamotrigine is metabolised (Cohen *et al*, 1987).

Where there is a linear relationship between dose and plasma concentration, concentration monitoring can be helpful in assessing side effects, compliance, and in establishing the most effective concentration in a seizure-free patient (Patsalos *et al*, 2008). Routine measurement of plasma concentrations of newer AEDs is not recommended, as they do not correlate well on a population basis with efficacy or side effects. Therapeutic drug monitoring can play a useful role in individualising clinical management, provided that drug concentrations are measured at an appropriate time in an appropriate patient with a clear indication, and are interpreted correctly.

Table 8. Pharmacokinetic interactions of established antiepileptic drugs (AEDs)

References	AED	Undergoes hepatic metabolism	Affects hepatic cytochrome P450 enzymes	Affects metabolism of other AEDs	Metabolism affected by other AEDs
Hansen <i>et al</i> , 1971; Christiansen and Dam, 1973; Brodie <i>et al</i> , 1983; Kerr <i>et al</i> , 1994	Carbamazepine	Yes	Yes	Yes	Yes
Jawad <i>et al</i> , 1984; Sennoune <i>et al</i> , 1992	Clobazam	Yes	No	No	Yes
Lai <i>et al</i> , 1978; Khoo <i>et al</i> , 1980	Clonazepam	Yes	No	No	Yes
Warren <i>et al</i> , 1980; Giaccone <i>et al</i> , 1996	Ethosuximide	Yes	No	No	Yes
Christiansen and Dam, 1973; Callaghan <i>et al</i> , 1977; Eadie <i>et al</i> , 1977; Bruni <i>et al</i> , 1980	Phenobarbital	Yes	Yes	Yes	Yes
Christiansen and Dam, 1973; Khoo <i>et al</i> , 1980; Duncan <i>et al</i> , 1991; Bajpai <i>et al</i> , 1996	Phenytoin	Yes	Yes	Yes	Yes
Alvin <i>et al</i> , 1975; Porro <i>et al</i> , 1982; Brodie <i>et al</i> , 1983; Sato <i>et al</i> , 1992	Primidone	Yes	Yes	Yes	Yes
Bowdle <i>et al</i> , 1979; Bruni <i>et al</i> , 1980; Pisani <i>et al</i> , 1984; Sadeque <i>et al</i> , 1997	Valproate	Yes	Yes	Yes	Yes

Table 9. Pharmacokinetic interactions of modern antiepileptic drugs (AEDs)

References	AED	Undergoes hepatic metabolism	Affects hepatic cytochrome P450 enzymes	Affects metabolism of other AEDs	Metabolism affected by other AEDs
Fuerst <i>et al</i> , 1988; Graves <i>et al</i> , 1989; Wagner <i>et al</i> , 1994	Felbamate	Yes	Yes	Yes	Yes
Volmer <i>et al</i> , 1986 ; Hooper <i>et al</i> , 1991; Radulovic <i>et al</i> , 1994	Gabapentin	No	No	No	No
Ben-Menachem <i>et al</i> , 2007	Lacosamide	Yes	No	No	No
Cohen <i>et al</i> , 1987; Brodie <i>et al</i> , 1997; Besag <i>et al</i> , 1998	Lamotrigine	Yes	No	No	Yes
Nicolas <i>et al</i> , 1999; Gidal, <i>et al</i> , 2005	Levetiracetam	No	No	No	Yes*
Wagner and Schmidt, 1987; Larkin <i>et al</i> , 1991; McKee <i>et al</i> , 1994	Oxcarbazepine	Yes	Yes	Yes*	Yes
Brodie <i>et al</i> , 2005	Pregabalin	No	No	No	No
Lau <i>et al</i> , 1997; Gustavson <i>et al</i> , 1998a, Gustavson <i>et al</i> , 1998b	Tiagabine	Yes	No	No	Yes
Sachdeo <i>et al</i> , 1996 ; Rosenfeld <i>et al</i> , 1997b	Topiramate	Yes	Yes	Yes*	Yes
Haegle and Schechter, 1986; Rimmer and Richens, 1989	Vigabatrin	No	No	Yes*	No
Ojemann <i>et al</i> , 1986; Nakasa <i>et al</i> , 1993	Zonisamide	Yes	No	No	Yes

* effect modest

5.8 Formulation

Readily identifiable and palatable formulations can help to improve adherence, and thus seizure control. As well as being manufactured as tablets, several AEDs are available in alternative formulations such as syrup and sprinkles which can be useful in patients with swallowing difficulties, and for those with percutaneous endoscopic gastrostomy tubes. Parenteral formulations are invaluable in the rapid treatment of status epilepticus, and in other emergency circumstances where oral access is not available. The use of rectal diazepam to abolish prolonged seizure activity is now being superseded by the administration of buccal, or nasal midazolam (Scott *et al*, 1999; Wilson *et al*, 2004). Intravenous formulations are available for sodium valproate, levetiracetam, and lacosamide, in addition to phenytoin, fosphenytoin, phenobarbital, and the benzodiazepines, clonazepam, diazepam, lorazepam, and midazolam.

5.9 Cost

Despite the introduction of several novel agents, price remains an important factor in determining the global use of antiepileptic medication. With few differences in efficacy amongst AEDs, the low costs of older drugs such as phenobarbital and phenytoin make these agents an attractive option for third world countries. One thousand generic 100-mg phenobarbital tablets currently cost \$6.16 (International Drug Price Indicator Guide, 2009). This is considerably less than treatment with any of the new AEDs.

6. Antiepileptic drug treatment of common epilepsy syndromes

6.1 Idiopathic generalised epilepsy syndromes with onset in adulthood

As is discussed in Chapter 3, the term ‘idiopathic’ is now used for well-characterised forms of epilepsy, mainly occurring in childhood and adolescence, and believed (but not necessarily proven) to have a genetic basis. Inheritance is likely to be complex, and underlying genetic causes are slowly being unravelled. It has been shown recently that 1% of people with idiopathic generalised epilepsies have a recurrent microdeletion on chromosome 15q13.3, leading to the deletion of seven genes (Helbig *et al*, 2009). In young adults, there are three idiopathic generalised epilepsy syndromes which can present at this time of life – JME, juvenile absence epilepsy, and epilepsy with generalised tonic-clonic seizures on awakening.

6.1a Juvenile myoclonic epilepsy

JME, the commonest syndrome in this population, accounts for 3% to 12% of all epilepsies. Often life-long, the syndrome consists of tonic-clonic seizures, myoclonic, and absence seizures (Specchio and Beghi, 2004). Onset is generally in the second decade, but can be earlier, or later. Patients may initially present with tonic-clonic seizures, but on close questioning, it may transpire that myoclonic jerks occur with fatigue or sleep deprivation. A history of absence seizures can be elicited by direct inquiry about ‘blank spells’. These are often mild and simple, compared to those in absence epilepsies. Photosensitivity can occur in up to one third of patients with JME (Wolf and Goosses, 1986). During myoclonic jerks, the EEG may show spike-and-wave discharges which are often irregular, or polyspike-waves. These can occur between the jerks. Neuroimaging studies have shown abnormalities in mesial frontal structures in many, and more widespread cortical grey matter abnormalities in others

(Woermann *et al*, 1999). Like most idiopathic generalised epilepsies, it is likely that JME is often inherited as a multifactorial or complex trait, with the additive effects of several or many susceptibility genes, and interaction with environmental factors producing the final phenotype. Autosomal dominant inheritance was found in one family (Cossette *et al*, 2002). The GABRA1 gene, which encodes the $\alpha 1$ subunit of the GABA_A receptor, was postulated as a major effect gene. This was not the case in other series (Shaochun *et al*, 2006). Autosomal recessive inheritance has been suggested in some patients (Panayiotopoulos and Obeid, 1989). Susceptibility genes such as CLCN2 (Haug *et al*, 2003) and EFHC1 (Suzuki *et al*, 2004) have also been identified.

6.1b Juvenile absence epilepsy

Juvenile absence epilepsy usually manifests between the ages of 7 and 17, with a peak at 10 to 12 years (Janz, 1997). Absence seizures generally occur less often, and may be less severe than in childhood absence epilepsy. Automatisms are frequent. Random and infrequent myoclonic jerks, as well as infrequent generalised tonic-clonic seizures occur in most patients (Wolf and Inoue, 1984; Panayiotopolous *et al*, 1989). One fifth of patients also suffer attacks of absence status epilepticus (Agathonikou *et al*, 1998). As with childhood absence epilepsy, photosensitivity can be present, but in juvenile absence epilepsy this is significantly more likely to occur in female patients (Janz, 1997). Juvenile absence epilepsy is usually a life-long disorder, but absences tend to become less severe with age. A family history of epilepsy is common with 31% of relatives having childhood absence epilepsy and 2.5% having JME (Marini *et al*, 2004). The interictal and ictal EEG characteristically shows generalised symmetric

spike-and-wave discharges, generally faster than 3Hz (3.5 to 4Hz) with frontal accentuation (Panayiotopoulos *et al*, 1989). Functional MRI-EEG studies have shown activation predominating over deactivation in the thalamus, and the opposite in the cerebral cortex (Aghakhani *et al*, 2004).

6.1c Epilepsy with tonic-clonic seizures on awakening

Epilepsy with tonic-clonic seizures on awakening generally manifests during teenage years (ILAE Commission on Classification and Terminology, 1989). There is a male predominance. The vast majority of the tonic-clonic seizures occur shortly after awakening, regardless of time of day. There may be seizures in the evening during relaxation, or following sleep deprivation. Absence and myoclonic seizures can be associated with the condition, and there is a positive correlation with photosensitivity (Wolf and Goosses, 1986). The interictal EEG is abnormal in the majority, with spike-and-wave activity, slow waves, and disorganised background activity (Janz, 2000).

AEDs effective against idiopathic generalised epilepsies include valproic acid (Marson *et al*, 2007a), topiramate (Biton *et al*, 1999), levetiracetam (Abou-Khalil *et al*, 2003; Cohen, 2003; Kasteleijn-Nolst Trenité and Hirsch, 2003; Krauss *et al*, 2003; Lagae *et al*, 2003, Brodie *et al*, 2007), zonisamide (Yagi and Seino, 1992; Kyllerman and Ben-Menachem, 1998; Newmark and Dubinsky, 2004; Kothare *et al*, 2004; Wilfong and Schultz, 2005; Marinas *et al*, 2009), phenobarbital (Placencia *et al*, 1993), and clobazam (Keene *et al*, 1990) (Table 4, page 38). Lamotrigine also has efficacy, but may make myoclonic jerks worse (Guerrini *et al*, 1998; Guerrini *et al*, 1999; Carrazana *et al*, 2001). Ethosuximide (Posner *et al*, 2005) and lamotrigine (Holmes *et al*, 2008) are useful in controlling absence seizures.

6.2 Localisation-related epilepsies

People with localisation-related seizures have been reported to have a poorer outcome than those with idiopathic generalised epilepsies (Annegers *et al*, 1979; Devinsky, 1999; Kwan and Brodie, 2000a). The British National General Practice Study of Epilepsy reported 69% of people with idiopathic generalised epilepsies as having five years' seizure freedom at nine year follow-up, compared to 61% for those with remote symptomatic epilepsy (Cockerell *et al*, 1997). In recent years, the detection of subtle structural lesions in patients with localisation-related epilepsy has improved with the widespread use of high resolution MRI. Together with the influx of AEDs onto the marketplace, this has increased the scope for managing this patient population, with the possibility of improving prognosis.

Given these advances in management, it was decided, therefore, to investigate the response to AED treatment in an audit of 550 patients with localisation-related epilepsy, followed up at the Epilepsy Unit over 13 years (Stephen *et al*, 2001a - Paper i). Of these, 312 (57%) became seizure-free for a minimum of one year. Mesial temporal sclerosis was associated with the poorest outcome (n=73, 42% seizure-free, $p<0.01$), and a higher incidence of febrile convulsions ($p<0.001$) compared with arteriovenous malformation (n=14, 78% seizure-free), cerebral infarction (n=46, 67% seizure-free), primary tumour (n=35, 63% seizure-free), cortical gliosis (n=81, 57% seizure-free), cerebral atrophy (n=49, 55% seizure-free) and cortical dysplasia (n=63, 54% seizure-free). Patients with symptomatic, and with cryptogenic epilepsies had similar outcomes. A family history of epilepsy was more likely in people with mesial temporal sclerosis, cortical dysplasia, and cryptogenic epilepsy than other groups ($p=0.02$). It is acknowledged, however, that the cross-sectional nature of this study

and the fact that patients newly started on treatment, and those with refractory epilepsy were included, will have introduced bias, and thus any statistical conclusions drawn may not be robust.

6.2a Hereditary aspects of focal-onset seizures

One of the outcomes from the audit was that a family history of epilepsy was more likely with cortical dysplasia, cryptogenic epilepsy, and mesial temporal sclerosis than with other causes. There may be a number of reasons for this finding. In patients with abnormalities of cortical development genetic mutations are increasingly being identified. Underlying mechanisms include abnormal functioning proteins which can result in failure of initiation of neuronal migration, failure of ongoing migration, and failure in cortical lamination. These can lead to the spectrum of lissencephaly/pachygyria/subcortical band heterotopia, periventricular nodular heterotopia, and polymicrogyria.

Lissencephaly can be the result of failure of ongoing migration. In classical (type I) lissencephaly the brain surface is completely, or almost completely, devoid of gyri and sulci. The spectrum ranges from agyria and pachygyria to subcortical band heterotopia with a relatively normal gyral pattern (Palmini *et al*, 2004). Affected patients have been found to have defects in the LIS1 gene on chromosome 17p13.3 (Pilz *et al*, 1998). This is thought to lead to defects in cell migration, division, and morphogenesis, via disruption in the regulation of the microtubule motor protein cytoplasmic dynein, and problems with platelet-activating factor acetylhydrolase (Smith *et al*, 2000). LIS1 abnormalities are found in the Miller-Dieker syndrome and isolated lissencephaly sequence. Patients with Miller-Dieker syndrome have

lissencephaly at the severe end of the spectrum, distinct facial features, and other associated congenital abnormalities (Dobyns *et al*, 1991). Those with isolated lissencephaly sequence have small deletions or intragenic mutations of LIS1 (Pilz *et al*, 1998). X-linked lissencephaly can result from defects in the DCX (XLIS) gene. This affects doublecortin production, producing lissencephaly and subcortical band heterotopia (Haverfield *et al*, 2009). Abnormalities in the RELN gene can result in defects in reelin, an extracellular matrix-associated protein important in the regulation of neuronal migration during cerebral cortical development (Hong *et al*, 2000). This can produce lissencephaly and cerebellar hypoplasia (Kerner *et al*, 1999; Ross *et al*, 2001). Cobblestone (Type II) lissencephaly occurs in a group of disorders such as the Walker-Warburg syndrome, muscle-eye-brain disease and Fukuyama congenital muscular dystrophy. Inheritance is thought to be autosomal recessive in many of these conditions (Fukuyama *et al*, 1981; Dobyns *et al*, 1989; Santavuori *et al*, 1989).

Failure of neuronal migration to the cortical plate can result in periventricular nodular heterotopia (Fox *et al*, 1998). Based on imaging and clinical data, five classification groups have been proposed: bilateral and symmetrical, bilateral single-noduled, bilateral and asymmetrical, unilateral, and unilateral with extension to neocortex (Battaglia *et al*, 2006). Bilateral periventricular nodular heterotopia is the most common type and mutations in FLNA, encoding the protein filamin A, are responsible for the X linked dominant form (Sole *et al*, 2009). Linkage to the Xq28 chromosome, with defects in the FLN1 gene and filamin 1 abnormalities occur in many familial cases (Kamuro and Tenokuchi, 1993; Bielas *et al*, 2004). The condition can be associated with pregnancy loss and male lethality (Eksioglu *et al*, 1996).

The polymicrogyria spectrum can vary in severity from unilateral focal disease to bilateral generalised disease. Neurological problems tend to be associated with the more severe forms. Polymicrogyria most often occurs as an isolated feature, although it can occur with other brain abnormalities. It is a feature of several genetic syndromes characterized by intellectual disability and multiple birth defects. These include 22q11 deletion syndrome (Bassett *et al*, 2005), Adams-Oliver syndrome (Temtam *et al*, 2007), Aicardi syndrome (Saito *et al*, 2009), Galloway-Mowat syndrome (Kucharczuk *et al*, 2000), Joubert syndrome (Parisi, 2009), and Zellweger syndrome (Krause *et al*, 2009). Some families with a history of polymicrogyria have PAX6 gene mutations; others with bilateral frontal polymicrogyria and bilateral generalised polymicrogyria have autosomal recessive disorders (Chang *et al*, 2004). Patients with autosomal recessive bilateral generalised polymicrogyria have symmetrical polymicrogyria most prominent in the fronto-parietal cortex, leading to seizures, cognitive and motor delay. Sporadic cases of bilateral frontal polymicrogyria are also recognised, where the polymicrogyria is found from the frontal poles to the pre-central gyrus, resulting in cognitive and motor delay, seizures, and spastic quadriparesis (Guerrini *et al*, 2000). Bilateral parasagittal parieto-occipital polymicrogyria occurs in sporadic fashion (Guerrini *et al*, 1997). These patients have bilateral polymicrogyria in the parasagittal areas and in the medial aspects of the occipital cortex, resulting in partial seizures and mental impairment.

Failure in cortical lamination is generally sporadic, resulting in focal cortical dysplasias and microdysgenesis. These are discussed in detail later in this chapter. EMX2 gene defects have been linked to a few familial cases of schizencephaly (Tietjen *et al*, 2007).

With an increasing number of genetic defects being found in patients with these cerebral anomalies, some patients with cortical dysplasias in the audit may have had such diagnoses, thus explaining the high likelihood of a positive family history for epilepsy or seizures. Unfortunately, the original dataset no longer exists to examine this hypothesis.

It is perhaps conceivable, that although 63 patients were classified as having focal cortical dysplasias, tuberous sclerosis could have been the underlying pathology in a small number. This again could account for a positive family history in some patients. Tuberous sclerosis, an autosomal dominant disorder, results from mutations in one of two non-homologous protein encoding genes, TSC1 and TSC2 (Niida *et al*, 1999). The TSC1 gene encodes hamartin, which may contribute to cell adhesion and migration. The TSC2 gene encodes tuberin, involved in regulation of DNA synthesis and the cell cycle. This results in the development of multiple hamartomas involving many organs. The major features of CNS tuberous sclerosis are giant cell astrocytomas, subependymal nodules, and cortical tubers, all of which can result in seizures. Cortical tubers are histologically characterised by the presence of dysplastic neurones and abnormal balloon cell glia, and have histological similarities to focal dysplasia lesions. It has been suggested that focal cortical dysplasias may represent a ‘forme fruste’ of tuberous sclerosis (Taylor *et al*, 1971). Usually the distinction between the two can be made, taking into account clinical, radiological and genetic information. Recent genetic and pathological research suggests that the two are of independent aetiology (Baybis *et al*, 2004; Chandra *et al*, 2007).

It may be that some of the patients classified as having cryptogenic epilepsy and having normal brain MRIs, had cortical malformations which were not detected with this investigation. Such lesions include focal cortical dysplasias Type I and II as defined by Palmini and colleagues (Palmini *et al*, 2004), and mild malformations of cortical development generally referred to as microdysgenesis. Such lesions are too subtle to be detected with MRI, with diagnosis requiring histological confirmation. These dysplasias are presumed developmental abnormalities of the cortical plate cytoarchitecture, usually with preservation of the gyral pattern. They can be graded histologically into type I (no dysmorphic neurons or balloon cells) and type II (dysmorphic neurons with or without balloon cells), with further subgrading according to the presence or not of architectural abnormalities.

The term microdysgenesis, covers a wide spectrum of microscopic tissue findings, probably the result of cortical maldevelopment. The name itself, together with diagnostic criteria and diverse terminology, are the subject of much debate. These lesions have also been found in patients who do not have epilepsy (Kaufman *et al*, 1989; Humphreys *et al*, 1990). As well as being the primary underlying cause of seizure activity, microdysgenesis may be a ‘dysplastic susceptibility factor’ contributing to the pathogenesis of hippocampal sclerosis (Blumke *et al*, 2002; Kasper *et al*, 2003). It may therefore be a predisposing factor to the development of hippocampal sclerosis after an insult such as a febrile convulsion. Evidence to suggest that some microdysgenesis lesions have a genetic component include the fact that when relatives of affected patients underwent quantitative MRI, a greater number of structural abnormalities were revealed than would be expected (Merschhemke *et al*, 2003). Original reports of microdysgenesis were derived from patients with primary

generalised epilepsy (Meencke and Janz, 1984; Meencke and Janz, 1985), which may have a genetic basis in some (Panayiotopoulos and Obeid, 1989; Cossette *et al*, 2002; Haug *et al*, 2003; Suzuki *et al*, 2004; Shaochun *et al*, 2006).

It was found in the audit that patients with mesial temporal sclerosis were more likely to have a family history of epilepsy or seizures. Familial temporal lobe epilepsy is a recognised clinical syndrome (Berkovic *et al*, 1996). In one subgroup, patients generally had a good prognosis, with frequent simple partial seizures, but infrequent complex partial seizures and rare secondary generalisation (Berkovic *et al*, 1996). Of 22 affected families fulfilling the diagnostic criteria for familial temporal lobe epilepsy, MRI findings were variable, with 57% of 68 patients having hippocampal atrophy (Kobayashi *et al*, 2001). Seizure control also varied widely, but tended to be poorer in those with more severe hippocampal atrophy (Kobayashi *et al*, 2003). A genetic locus for this group has been identified on chromosome 4q (Hedera *et al*, 2007). Another series of affected relatives in whom clinical presentation was more heterogeneous, and outcome not so positive, was studied (Cendes *et al*, 1998). Pedigree analysis suggested autosomal dominant inheritance with incomplete penetrance. Genetic loci for temporal lobe epilepsy preceded by febrile seizures have been identified on chromosome 12q22-q23, and a bilineal inheritance on 18q and 1q25-q31 (Baulac *et al*, 2001; Claes *et al*, 2004). Mutations of the leucine-rich, glioma-inactivated 1 (LGI1) gene have been identified as a cause of a lateral temporal lobe epilepsy with frequent auditory auras (Kalachikov *et al*, 2002; Morante-Redolat *et al*, 2002; Ottman *et al*, 2004; Hedera *et al*, 2004).

6.2b Repeat analysis in a cohort of newly diagnosed patients

Because of the nature of the audit, these measures were repeated, therefore, in a cross-sectional study 558 subjects with newly diagnosed localisation-related epilepsy, followed up over a period of 20 years (Mohanraj and Brodie, 2005a). Although this audit was again limited by its observational nature, compared with the previous project (Stephen *et al*, 2001a - Paper i), a higher percentage of patients with hippocampal atrophy (50% versus 42%) and cortical dysplasia (60% versus 54%) became seizure-free. Overall, 343 (62%) subjects became controlled on AED treatment. These results show that localisation-related epilepsies are not necessarily associated with poor outcomes. Others have corroborated this finding ((Andrade-Valenca *et al*, 2003). Improved seizure freedom rates in this second analysis may reflect the fact that this cohort contained newly diagnosed patients only, around 60% of whom will control on their first or second monotherapy (Kwan and Brodie, 2000a).

7. Antiepileptic drug treatment of refractory epilepsy

7.1 Defining ‘refractory epilepsy’

Although many new AEDs have been introduced in recent years, around one third or people with epilepsy will never achieve remission (Annegers *et al*, 1979; Cockerell *et al*, 1995; Mattson *et al*, 1996; Kwan and Brodie, 2000a; Mohanraj and Brodie, 2005b). Medically refractory epilepsy is increasingly accepted as a distinct multi-faceted entity. The definition of the condition and the understanding of underlying mechanisms is the cause of much debate. This is reflected in the fact that two different definitions of refractory epilepsy were employed in the studies of adjunctive topiramate (Paper iii) and levetiracetam (Paper v) contained in this thesis.

The subject of drug resistant epilepsy is being examined currently by a Task Force of the ILAE Commission on Therapeutic Strategies (Commission on Therapeutic Strategies Task Force, ILAE, *in press*). The Task Force has developed a core definition which states that ‘drug refractory epilepsy may be defined as failure of adequate and appropriate trials of two well tolerated and appropriately chosen and used antiepileptic drugs (whether as monotherapies or in combination) to achieve seizure freedom for either one year or three times the pre-intervention inter-seizure interval, whichever is the longer.’ Refractory epilepsy is multi-dimensional, with failure to respond to AED treatment being associated with neurobiochemical plastic changes, cognitive decline, and psychosocial dysfunction (Kwan and Brodie, 2002). These, in turn, can lead to dependent behaviour and a restricted lifestyle.

7.2 Mechanisms of resistance

Studies suggest there are at least four categories of AED resistance – some patients have refractory seizures *de novo*, whereby remission is never achieved from the onset of epilepsy (Camfield *et al*, 1997; Kwan and Brodie, 2000b). Others have developed progressive refractoriness, where there is initial seizure freedom, but seizures then recur and become uncontrollable (Camfield *et al*, 1997; Berg *et al*, 2003; Mohanraj and Brodie, 2006). There may also be a wax-and-wane pattern where the epilepsy alternates between being controlled and uncontrolled (Mohanraj and Brodie, 2006). In around 12% of patients the epilepsy is drug-resistant initially, but with time and AED manipulation, becomes drug responsive (Kwan and Brodie, 2000a; Kwan and Brodie, 2000b; Mohanraj and Brodie, 2006). Several hypotheses have been used to explain medically refractory epilepsy, including the target hypothesis and the multidrug-transporter hypothesis.

7.2a Target hypothesis

The target hypothesis postulates that an alteration in the cellular targets of AEDs leads to a reduction in their sensitivity to treatment (Remy *et al*, 2003). Evidence for this theory includes the loss of voltage-dependent sodium channels of dentate granule cells by carbamazepine in hippocampi resected from patients with carbamazepine-resistant temporal lobe epilepsy (Remy *et al*, 2003). Alterations in GABA_A receptor subtype expression were found in a group of patients with drug-resistant temporal lobe epilepsy (Loup *et al*, 2000). However, the mechanism of action of many AEDs is not fully understood, and this theory does not explain why some patients have epilepsy resistant to AEDs with multiple mechanisms of action, or to different AEDs with different mechanisms of action.

7.2b Transporter hypothesis

The transporter hypothesis suggests there is over-expression of efflux drug transporters at the cerebral capillary endothelium which constitute the blood-brain barrier. Efflux transporters, which include P-glycoprotein and multidrug-resistance-associated proteins, are transmembrane molecules situated in the apical membrane of capillary endothelial cells which form the blood brain barrier. These actively pump their substrates against the concentration gradient, thus reducing intracellular accumulation. Overexpression would therefore decrease the accumulation of substrate AEDs at the site of action, making their action ineffective. The actions of P-glycoprotein have been studied widely (Tischler *et al*, 1995; Sisodiya *et al*, 2002). Pathologically elevated expression of P-glycoprotein has been found in the region of experimentally induced seizure foci, and in association with a number of clinical neuropathologies associated with uncontrolled seizures (Sisodiya *et al*, 2002).

A number of AEDs have been mooted as substrates for P-glycoprotein, and/or multidrug-resistance-associated proteins, although there are few data to support this hypothesis. It is unclear, however, as to whether over-expression of drug transporter proteins is intrinsic or a consequence of uncontrolled seizures, AED treatment, or both. Initial evidence suggested that the 3435>T polymorphism of the ABCB1 (also called MDR1) gene which encodes P-glycoprotein may be associated with a poorer response to AED treatment in Caucasians (Siddiqui *et al*, 2003). Others think this may be an epiphenomenon (Tan *et al*, 2004; Sills *et al*, 2005). Problems arise as the majority of research has been performed in patients with pharmaco-resistant epilepsy, the definition of which has varied in different studies. Specimens have been obtained from patients who have undergone epilepsy surgery, and there is a lack of suitable

controls. Experimental models have provided little evidence to back the human data, and are complicated by probable species differences in the P-glycoprotein transport of AEDs (Crowe and Teoh, 2006; Baltes *et al*, 2007a, Baltes *et al*, 2007b).

7.2c Other factors

There may be other factors contributing towards the development of refractoriness. These include disease-related causes such as neuropathology, disease progression, structural brain changes, hypexcitable and disinhibited neuronal network reorganisation (for example - mossy fibre sprouting) (Tauck and Nadler, 1985; Okazaki *et al*, 1995). Other mechanisms include alterations in neuroreceptors (for example - composition/functioning of GABA/glutamate receptors) (Kapur and Macdonald, 1997; Macdonald and Kapur, 1999; Jones *et al*, 2002), ion channelopathies (Singh *et al*, 1998; de Fusco *et al*, 2000; Wallace *et al*, 2001; Claes *et al*, 2003), reactive autoantibodies (McKnight *et al*, 2005), and impaired drug penetration (Potschka *et al*, 2002). Drug-related mechanisms include loss of efficacy (tolerance) and ineffective mechanism of action.

7.3 Managing patients with refractory epilepsy

Medically refractory epilepsy can pose a significant clinical challenge. Where seizures prove hard to control, it is worthwhile re-examining the diagnosis, as up to 30% of people with ongoing seizures have been found to have non-epileptic attacks (Smith *et al*, 1999). It is also important to ensure the patient is adherent with their medication. As discussed in Chapter 5, measurement of circulating AED concentrations can be

useful to this end. In those for whom the diagnosis of epilepsy is secure, ensuring optimisation of AED therapy appropriate for the seizure type or syndrome may improve seizure control.

7.4 Pharmacological treatment

Polytherapy has remained widely used in the treatment of epilepsy, although there is a lack of a robust evidence base and continued controversy over when and how it should be employed. Before the advent of the newer AEDs, it was commonplace to initiate treatment with polytherapy. This strategy changed following the observation that patients treated with two or more drugs had fewer side effects and improved seizure control when they were changed to monotherapy (Shorvon and Reynolds, 1979; Schmidt, 1983). Conversion from polytherapy to monotherapy led to more adverse effects with only a modest increase in seizure frequency (Schmidt, 1982). However, these studies were performed in the days when AEDs consisted mainly of sodium channel blocking agents, the combining of which not infrequently leads to pharmacokinetic and pharmacodynamic interactions (Table 8, page 49; Table 9, page 50). The licensing of newer AEDs, many of which have novel mechanisms of action, introduced the potential for combining drugs.

The goal of combination treatment is to improve or completely control seizures with no or the fewest side effects and the least impact on quality-of-life. In general terms, several outcomes are possible – the combination may be of no benefit, or the drugs may work against each other; there can be equal benefit and/or side effects that are

less than or equal to the effect of each drug when given alone (additive); or there can be benefit and/or side effects that are greater than the effect of each drug when given alone (supra-additive).

7.5 Drug Load

It has been argued that the efficacy and toxicity of AED polytherapy is more related to total drug load than to number of drugs (Lammers *et al*, 1995; Deckers *et al*, 1997a).

Drug load can be measured by the prescribed daily dose/defined daily dose ratio (Deckers *et al*, 1997b). The WHO defined daily dose indicates the assumed average maintenance dose per day used for its main indication in adults (WHO, 2009).

Although this is a useful concept, it is currently difficult to apply in everyday clinical practice.

7.6 Drug interactions

When combining AEDs, it is important to take drug interactions into account.

Pharmacokinetic interactions are the effects of drugs upon the disposition of one another, including changes in absorption, metabolism, protein binding, and excretion.

These interactions may increase the risk of side effects and may impact on efficacy.

The AEDs with the greatest potential for interaction are metabolised by the hepatic cytochrome P450 superfamily, and include phenobarbital, phenytoin, carbamazepine, primidone, and to some extent, topiramate and oxcarbazepine (Table 8, page 49).

Valproic acid is a weak inhibitor of mono-oxygenase and conjugating enzymes, which can slow the clearance of other AEDs such as phenytoin and lamotrigine. In

comparison, fewer of the new AEDs interfere with the cytochrome enzyme system and are generally less likely to affect the metabolism of other AEDs to a clinically significant extent (Table 9, page 50).

7.7 Mechanism of action

With information increasingly becoming available on mechanism of action, it would seem sensible to combine drugs with different mechanisms, although it is becoming apparent that several AEDs act in multiple ways which are not yet understood fully. Three broad mechanisms of AED action are recognised: (i) modulation of voltage-dependent ion channels, (ii) enhancement of inhibitory neurotransmission, and (iii) attenuation of excitatory neurotransmission (Table 10, page 70). It is now recognised, however, that all AEDs, with one or two exceptions, have multiple cellular effects. While it is convenient to categorise the mechanisms of actions of AEDs in this way, it is important to remember that understanding of the pathogenesis of seizure generation and propagation, and that of how drugs modulate these processes, remains rudimentary. The discovery that astrocytes may play a key role in seizure activity, and that in part, several AEDs may act to suppress astrocytic intracellular calcium ion signalling, challenges the traditional view (Tian *et al*, 2005).

Table 10. Perceived mechanisms of action of antiepileptic drugs

(Adapted from Kwan and Brodie, 2007)

Antiepileptic Drug	↓Na ⁺ channels	↓Ca ²⁺ channels ^{**}	↑GABA transmission	↓ Glutamate transmission
<i>Established</i>				
Benzodiazepines			++	
Carbamazepine	++			
Ethosuximide		++ (T-type)		
Phenobarbital		?	++	?
Phenytoin	++			
Valproate	?	? (T-type)	+	?
<i>Modern</i>				
Felbamate	+	?	+	+
Gabapentin	?	++ (α2δ)	+	
Lacosamide	+ ^a			
Lamotrigine	++	?		
Levetiracetam*		?	?	?
Oxcarbazepine	++			
Pregabalin		++ (α2δ)		
Rufinamide	++			
Stiripentol			?+	
Tiagabine			++	
Topiramate	+	+	+	+
Vigabatrin			++	
Zonisamide	+	+ (T-type)		

GABA; Gamma aminobutyric acid

*Levetiracetam acts by binding to synaptic vesicle protein 2A

^aLacosamide also binds to collapsin-response mediator protein 2

**Unless otherwise stated, action on high voltage activated calcium channels

++ Primary action; + Probable action; ? Possible action

7.8 When should combination therapy be used?

7.8a Initiation of treatment

In the last 30 years, monotherapy has been generally recommended for patients starting treatment for newly diagnosed epilepsy. This is because evidence suggested combinations of older AEDs led to more side effects, with no improvement in efficacy (Shorvon and Reynolds, 1979; Schmidt, 1982; Schmidt, 1983). Using treatment calculated by drug load, this theory was challenged by a multicentre randomised double-blind study which found no difference in seizure frequency, neuro- or systemic toxicity between cohorts taking monotherapy or polytherapy (Deckers *et al*, 2001). A prospective observational project came to similar conclusions (Kwan and Brodie, 2000b). Never-the-less, with 60% of patients becoming seizure-free with a modest dose of monotherapy (Kwan and Brodie, 2000a), and taking into account the enhanced teratogenic potential of polytherapy regimens (Harden *et al*, 2009), it would seem appropriate to start with a single drug before opting for combination regimens.

7.8b After failure of one monotherapy regimen

The management of the 30-40% of patients who do not become seizure-free on their first drug is widely debated. If the drug has to be discontinued because of side effects, the change to another drug is unavoidable. If however, persistence of seizures is the problem, clinical practice varies widely in whether to switch to another AED, or add a second drug (Baldy-Moulinier *et al*, 1998; Karceski *et al*, 2005). Switching resulted in seizure freedom in 13% of 470 newly diagnosed adults with a variety of seizure types in one prospective study (Kwan and Brodie, 2000a). Similar seizure-freedom and side

effect rates were found in patients who received substituted monotherapy (Kwan and Brodie, 2000b). A pragmatic randomised open-label multicentre study addressed this question in 157 patients with partial-onset seizures (Beghi *et al*, 2003). There was no significant difference in AED retention rate or probability of seizure freedom at 12 months. There was a non-significant trend towards a lower percentage of patients experiencing or withdrawing as a result of adverse effects in the add-on group compared with the substitution group, but the study was under-powered.

7.8c After failure of more than one monotherapy regimen

There have been no controlled studies looking at the number of single AED regimens that should be trialled and failed before commencing combination therapy. In one prospective project of 470 adult patients newly diagnosed with epilepsy, 47% became seizure-free with their first drug, 13% with their second AED, but only 1% with their third drug (Kwan and Brodie, 2000a). Similar results were obtained from an updated analysis five years later (Mohanraj and Brodie, 2006). These results suggest that if treatment with two appropriately chosen monotherapy regimens fails, the chances of complete seizure control with a third agent are slim.

7.9 Studies of antiepileptic drug combination therapy

Although many people with uncontrolled epilepsy take two or more AEDs, polytherapy regimens are rarely scrutinised in the clinical setting. Experimental models have suggested synergism when combinations of valproate with phenytoin (Chez *et al*, 1994) or ethosuximide (Bourgeois, 1988), topiramate with carbamazepine or phenobarbital (Shank *et al*, 1994), topiramate with lamotrigine or levetiracetam (Sills *et al*, 2004), or felbamate with carbamazepine, phenytoin, phenobarbital or

valproate are employed (Gordon *et al*, 1993). These have proved difficult to replicate in large scale clinical studies, and systematic reviews of phase III add-on trials have generally failed to identify major differences in efficacy or tolerability in the newer AEDs for the treatment of refractory localisation-related epilepsies (Marson *et al*, 1997; Cramer *et al*, 1999; Marson *et al*, 2001).

One randomised double-blind trial compared gabapentin with vigabatrin as first-add-on drug for partial seizures which were not controlled with initial monotherapy (Lindberger *et al*, 2000). This study had to be terminated at 8 weeks, however, because of emerging concerns about vigabatrin-related visual field defects. There was no significant difference in the improvement rate, proportion of seizure-free patients, or quality-of-life scores.

During a trial in 347 patients designed to assess the efficacy of lamotrigine, patients were administered lamotrigine with sodium valproate, carbamazepine, or phenytoin (Brodie *et al*, 1997). Superior efficacy was shown for the valproate/lamotrigine combination with 83% becoming seizure-free, compared to 43% taking carbamazepine/lamotrigine and 34% taking phenytoin/lamotrigine. Given the magnitude of the valproate/lamotrigine response, it was thought to be the result of a pharmacodynamic as well as a pharmacokinetic interaction between the two drugs (Pisani *et al*, 1999). Five patients with absence seizures refractory to either sodium valproate or ethosuximide became seizure-free with a combination of the two drugs (Rowan *et al*, 1983). High dose lamotrigine and topiramate led to complete seizure control in two patients previously refractory to either monotherapy (Stephen *et al*, 1998).

7.10 Practical considerations

When choosing an AED for a combination regimen, it is important to add in an agent appropriate for the seizure type or syndrome. The adverse event and interaction profile should have the potential to produce seizure freedom without intolerable adverse effects. Other factors such as age, sex, weight, psychiatric history, co-medication and co-morbidity can all have a bearing on the selection process (Stefan *et al*, 2006). If the patient becomes seizure-free, or develops side effects, the dose of the initial monotherapy can be reduced, or the drug withdrawn in some instances. Many controlled patients, however, prefer to remain on polytherapy if they have struggled to gain seizure freedom with a single agent. Around 1% who fail to control on two drugs may become seizure-free with triple therapy, but control is unlikely to be achieved with four or more AEDs, and the risk of adverse effects increases with the heavier drug burden (Kwan and Brodie, 2000a). For patients deemed to have epilepsy refractory to AED treatment, those with surgically remediable causes may be suitable for epilepsy surgery (Wiebe *et al*, 2001), or other non-pharmacological options.

7.11 Non-pharmacological options

7.11a Epilepsy surgery

Some patients with medically resistant epilepsy, in particular those with discrete resectable lesions, can benefit from epilepsy surgery. In a randomised controlled trial, 58% of patients with medically intractable temporal lobe epilepsy became seizure-free one year after anterior temporal lobectomy together with removal of hippocampus and amygdala, compared with only 8% for those who continued to have medical treatment alone (Wiebe *et al*, 2001). Although the procedure has low mortality and morbidity, it

is invasive with possible negative sequelae on memory function (Martin *et al*, 2002). When it is not possible to remove the presumed epileptogenic focus or foci, palliative procedures such as hemispherectomy, corpus callosotomy, or multiple subpial transaction, may be performed to disrupt the pathways important for the spread of epileptiform discharges in order to reduce the frequency and severity of the seizures.

7.11b Vagal nerve stimulation

An alternative to epilepsy surgery is the implantation of a vagal nerve stimulator. This is a multiprogrammable pulse generator which delivers intermittent signals of electrical current to the vagus nerve (Schachter, 2002). It is thought that with the nerve's extensive projection to the various neuronal network systems, including the reticular-activating system, and the diffuse noradrenergic projection system (Henry, 2002), its stimulation leads to a reduction in seizure frequency and intensity, with a few patients becoming seizure-free (Kuba *et al*, 2009).

7.11c Ketogenic diet

The ketogenic diet is a restrictive high-fat, low protein and very low-carbohydrate diet mostly given to children (aged 5-10 years) with a variety of medically intractable seizure types (Levy and Cooper, 2003). There is much less experience to guide its use in younger children, adolescents, or adults. How it acts to suppress seizures is unclear, but the diet mimics the biochemical changes associated with starvation, thus creating ketosis (Hartman *et al*, 2007). The ketogenic diet is also effective in patients with deficiency of the glucose transporter, GLUT1. It has recently been found that 12% of children with early-onset absence epilepsy have GLUT1 mutations, and this may be a

mechanism by which the diet has efficacy in these patients (Suls *et al*, 2009).

Adherence may be difficult, but in a recent randomised, controlled trial of 147 children with refractory epilepsy, the mean percentage of baseline seizures was significantly lower in the diet group than in controls (Neal *et al*, 2008).

7.11d Strategies in development

A number of innovative techniques are currently being developed to overcome treatment resistance in patients with refractory seizures. These include the discovery of novel drug targets, new drug delivery systems (Stein *et al*, 2000), electrical brain stimulation (Boon *et al*, 2007), automated seizure detection and predication (Fountas *et al*, 2005), cell transplantation (Chu *et al*, 2004), and gene therapy (Raol *et al*, 2006).

7.12 Antiepileptic drug polytherapy audit

To gain more information on combination regimens in patients registered with the Epilepsy Unit, an audit was performed to explore polytherapy outcomes in 2881 patients taking more than one AED (Stephen and Brodie, 2002 - Paper ii). Of these, 1617 (56%) were seizure-free for over one year, with 332 (21%) taking more than one AED. Effective combinations comprised 40 different duotherapies, 28 triple therapies, but only three patients took four AEDs. It was concluded that treatment with two or three, but not four AEDs, may be a useful therapeutic option for patients not responding to monotherapy. Because this was a retrospective analysis of newly treated patients and those with refractory epilepsy, the analysis was subject to bias. Lack of a control group was also a weakness. Epilepsy Unit staff are therefore now examining similar outcomes in a large population of newly treated patients only.

7.13 Outcomes with adjunctive topiramate in refractory epilepsy

Topiramate can be prescribed as add-on and monotherapy in adults and children with partial-onset, myoclonic and generalised tonic-clonic seizures, and as adjunctive treatment of seizures associated with Lennox Gastaut syndrome. Shortly after the drug gained a UK licence, colleagues at the Western Infirmary Epilepsy Unit undertook a prospective study, to gain information on its efficacy and tolerability in a patient population with refractory localisation-related and idiopathic generalised epilepsies, in the everyday clinical setting (Stephen *et al*, 2000 - Paper iii).

Topiramate is a sulphamate-substituted monosaccharide which exhibits its pharmacological properties via blockade of sodium channels, attenuation of kainate-induced responses, and enhancement of gamma aminobutyric acid (GABA)-mediated inhibition (Petroff *et al*, 1999). There is also inhibition of carbonic anhydrase activity (Shank *et al*, 1994). In regulatory studies, effectiveness was demonstrated as add-on (Ben-Menachem *et al*, 1996) and as monotherapy (Sharief *et al*, 1996; Faught *et al*, 1996; Privitera *et al*, 1996), in adults with focal-onset seizures. Topiramate was more effective than placebo in patients with idiopathic generalised epilepsies (Biton *et al*, 1999), and as add-on treatment for children with focal-onset seizures (Elterman *et al*, 1999). It is also effective as adjunctive therapy for seizures associated with Lennox-Gastaut syndrome (Sachdeo *et al*, 1999), and may be useful for infantile spasms (Glauser *et al*, 1998). When compared with carbamazepine or valproate monotherapy in newly diagnosed epilepsy, a daily dose of 100mg or more was as effective (Privitera *et al*, 2003).

Topiramate administration has no clinically relevant effect on other AED concentrations, but the drug may reduce phenytoin clearance by selective inhibition of isoform 2C19 of the cytochrome P450 super family (Sachdeo *et al*, 2002). Higher doses of the drug can reduce the effectiveness of the COCP (Rosenfeld *et al*, 1997a). Enzyme-inducing AEDs, such as phenytoin and carbamazepine, accelerate topiramate metabolism, lowering concentrations by around 40%.

For the purposes of this project, patients were categorised as having refractory epilepsy if they had been having monthly seizures for more than five years despite treatment with at least four AED monotherapy or combination regimens. Following a three month baseline, topiramate was added to current AED therapy in 170 patients, using a standard titration schedule. Doses were titrated until one of four end-points was reached: seizure freedom for six months or more, $\geq 50\%$ or $< 50\%$ reduction in seizure frequency for at least six months compared with baseline, or topiramate withdrawal because of lack of efficacy, side-effects, or both. Seizure freedom for six months or more was achieved in 39 (23%) patients, eight on monotherapy. A $\geq 50\%$ reduction in seizure frequency over a six month period compared with baseline, was reported in 80 (47%) others. The drug was discontinued in 51 (30%) patients, mainly due to fatigue, weight loss and irritability, paraesthesiae, depression and headache, all recognised side-effects. Many patients obtained a good response with doses lower than those employed in regulatory studies, a not uncommon phenomenon. There was a wide variation in dose-response and dose-toxicity relationships, making the use of plasma concentration monitoring unnecessary.

It is important to recognise that because this observational study was undertaken in the routine clinical setting at a single centre, with no control group, this may have biased results. As discussed in Chapter 4, however, naturalistic trials are valuable in informing practical decision making, once the efficacy and safety of an AED has been established in rigorous regulatory randomised controlled studies. Because the study involved venesection of patients which would not normally be undertaken as clinical practice, the project was defined as research, and thus was submitted for (and subsequently granted) local ethical approval. A six month time period on a stable topiramate dose was selected, as this is employed in many regulatory studies, and was considered to be a reasonable time frame within which to assess drug outcomes. This study enabled staff to use topiramate confidently, with the knowledge that therapeutic drug monitoring is generally unhelpful. Doses employed were often smaller than those in regulatory trials.

7.14 Topiramate in patients with learning disabilities and refractory epilepsy

Given that there are few data on AED treatment in patients with learning disabilities, it was decided to assess the impact of topiramate in this population attending the Epilepsy Unit (Kelly *et al*, 2002 - Paper iv). In a pragmatic fashion, adjunctive topiramate was started in 64 patients with learning disabilities and refractory epilepsy. As patients were already attending the epilepsy service, carers had kept a record of seizure frequency over at least the three months prior to the addition of topiramate. None of the patients were included in the previous study. End-points were the same as those described in Paper iii. Carers were asked to monitor appetite, sleep, alertness and behaviour, both before, and after the addition of the drug. Of the patients who

participated, 16 (25%) became seizure-free, and 29 (45%) had a $\geq 50\%$ reduction in seizure frequency. A further 10 (16%), who obtained some improvement with topiramate, continued treatment. The drug was discontinued in nine (14%) patients. Mean carer scores did not worsen with topiramate. This investigation showed topiramate to be effective as add-on therapy in patients with learning disabilities, with seizure freedom being a realistic goal.

Patients attending the Epilepsy Clinic have a blood sample taken for plasma concentration monitoring of valproate, phenobarbital, carbamazepine and phenytoin at first visit, when dosing is changed, or if drug adherence is an issue. When the use of topiramate was monitored in patients with learning disabilities, only those who were venesected for routine monitoring of AED concentrations for these reasons also underwent topiramate concentration monitoring. As this involved no extra procedures, the project was deemed to be clinical audit rather than research, and thus did not require ethical approval. A six month time period on a stable topiramate dose was again considered to be a reasonable time frame within which to assess drug outcomes. As with the previous study, results may be biased because of the observational nature of the project and the fact that there was no control group. Some of the baseline seizure recordings were retrospective, as it was not considered practical for certain patients with learning disabilities to have unchanged medication for a three month baseline period. This will also have introduced bias. Although no significant statistical conclusions were drawn from the project, the validity of these would be questionable, given its design.

7.15 Outcomes with adjunctive levetiracetam in refractory epilepsy

Levetiracetam can be prescribed as monotherapy and adjunctive treatment for partial seizures, with or without secondary generalisation, and for adjunctive treatment of myoclonic seizures and primary generalised tonic-clonic seizures. Following its licensing, a prospective audit was designed by Epilepsy Unit staff to assess the clinical value of the drug (Mohanraj *et al*, 2005 - Paper v).

Levetiracetam binds to synaptic vesicle protein 2A (Lynch *et al*, 2004), and its mechanisms of action appear different from other AEDs (Klitgaard and Pitkanen, 2003). Placebo-controlled trials using the drug demonstrated reduction in seizure numbers and improved quality-of-life in patients with partial seizures, with or without secondary generalisation (Cereghino *et al*, 2000; Cramer *et al*, 2000; Shorvon *et al*, 2000). As add-on therapy, levetiracetam was efficacious against partial-onset and secondary generalised seizures in double-blind, placebo-controlled, add-on trials at doses of 1000mg-3000mg daily (Betts *et al*, 2000; Grant and Shorvon, 2000; Chaisewikul *et al*, 2001; Boon *et al*, 2002). Levetiracetam monotherapy is more efficacious than placebo against refractory partial-onset seizures (Ben-Menachem and Falter, 2000), and as effective as sustained-release carbamazepine against partial or generalised tonic-clonic seizures in a multicentre, double-blind trial (Brodie *et al*, 2007). In a systematic review, the drug had a more favourable 'responder-withdrawal ratio' than zonisamide or oxcarbazepine for drug-resistant localisation-related epilepsies (Marson *et al*, 2001). Studies have suggested efficacy for absence, myoclonic and generalised tonic-clonic seizures (Abou-Khalil *et al*, 2003; Cohen, 2003; Kasteleijn-Nolst Trenite and Hirsch, 2003; Krauss *et al*, 2003; Lagae *et al*, 2003). In a prospective multicentre open-label study in 42 patients with epilepsy and

learning disabilities, adjunctive levetiracetam reduced median seizure frequency from baseline levels of 4.3 per week to 2.2 per week for those followed up for 6 months. (Beavis *et al*, 2009).

Levetiracetam is not prone to pharmacokinetic drug interactions. Common adverse effects include somnolence, asthenia, dizziness, vertigo and headache. Behavioural problems such as anxiety, depression and psychoses have been reported in 7% of patients. There are no pharmacokinetic interactions with the drug. Lower doses may be needed in patients with moderate to severe renal impairment.

At the Epilepsy Unit, adjunctive levetiracetam was started in 156 patients with refractory localisation-related or idiopathic generalised epilepsies following a three month baseline, and doses titrated according to clinical need. End-points were seizure freedom for at least six months, $\geq 50\%$ reduction or $< 50\%$ reduction in seizures for a six month period compared with baseline, or levetiracetam withdrawal due to side-effects, lack of efficacy, or both. An end-point was reached by all 156 patients, 40 (26%) of whom became seizure-free for at least 6 months, with 33 (21%) having a $\geq 50\%$ reduction in seizure frequency for 6 months, compared with baseline. Of the seizure-free patients, 25 (63%) took 1000mg or less of the drug. Patients with idiopathic generalised epilepsies fared particularly well, with 8 (40%) becoming seizure-free. Levetiracetam was withdrawn in 46 (29%) patients due to adverse effects (n=27), lack of efficacy (n=8) or both (n=11). It was concluded that the drug is effective against a variety of seizure types, often at low doses.

As patients were treated no differently to others attending the clinic, with no allocation to intervention groups, the project was categorised as audit, and as such, did not require ethical approval. Because this observational study followed up patients recruited at a single centre epilepsy clinic in a pragmatic fashion, and there was no control group, results are therefore subject to bias. Although no significant statistical conclusions were drawn from the project, because of its biased design, these may have been difficult to interpret. Patients were followed up for six months on a stable dose of levetiracetam. This is a reasonable time period over which to assess the impact of the drug, being similar to that used in many regulatory studies. Although response may have changed with continued follow-up, it was felt that this would not be practical in our patient cohort.

7.16 Levetiracetam for people with learning disabilities and refractory epilepsy

To gain experience with adjunctive levetiracetam in patients with learning disabilities and refractory epilepsy in the everyday clinical setting, the drug was assessed in an audit undertaken at the Epilepsy Unit (Kelly *et al*, 2004a - Paper vi). Levetiracetam was added to AED regimens of 64 patients after a three month baseline, during which carers kept a record of seizure frequency. Doses were then adjusted in response to seizure frequency and tolerability. Patients were different to those included in the previous study with levetiracetam. End-points were seizure freedom for six months or more, $\geq 50\%$ or $< 50\%$ reduction in seizure frequency for at least six months compared with baseline, or discontinuation of levetiracetam due to adverse effects, lack of efficacy, or both. Caregivers were asked to assess the person's sleep, appetite, alertness and behaviour whilst taking the drug.

Of the cohort, 24 (38%) became seizure-free, and 18 (28%) had an improvement in seizure frequency. A marginal benefit was obtained in 8 (12%) patients.

Levetiracetam was discontinued in 14 (22%) patients because of worsening seizures (n=6), lack of efficacy (n=1), or adverse effects (n=7). Caregiver scores were 'improved' at the end of follow up ($p < 0.001$). These outcomes have given Epilepsy Unit colleagues valuable experience in using levetiracetam in people whose seizures are often perceived to be refractory. Many patients' seizures became controlled, with the majority benefiting from the addition of the drug. As an additional benefit, levetiracetam may have improved quality-of-life.

As with the preceding studies, findings from this project would have been enhanced if there had been comparison with a control group, although it was felt that use of a control group may have led to difficulties if relatives and carers perceived a lack of intervention. The small number of patients and the fact that outcomes were derived from a single centre may also have biased results. On occasion, some of the baseline seizure recordings were retrospective, given the difficulties in obtaining such recordings in this patient group. This may also have introduced bias, and made any statistical results difficult to validate. More detailed quality-of-life measures may have given greater insight into any effects derived from levetiracetam. It was decided to opt for a simple likert scale, as this was thought to be easier to use in the routine clinical setting. Because patients were managed in the same way as those routinely attending the epilepsy clinic, apart from the administration of a simple questionnaire, this study was categorised an audit, and thus did not require ethical approval.

8. Outcomes in different patient sub-groups with epilepsy

The management of people with seizure disorders can be complicated. As well as taking into account the varying properties of available AEDs, the circumstances of the patient are of paramount importance. Age, gender, seizure type or syndrome, lifestyle factors, fertility, comorbidity, and comedication all play a crucial role. For these reasons, it was decided to investigate outcomes in teenagers (Stephen *et al*, 2003 - Paper vii), people with learning disabilities (Kelly *et al*, 2004b - Paper viii), and elderly patients (Stephen *et al*, 2006 - Paper ix) referred to the Epilepsy Unit.

8.1 Teenagers

Epilepsy is the commonest neurological condition to affect adolescents (Wheless and Kim, 2002), occurring in more than 60 in 100,000 young people (Hauser, 1992). The teenage years can be a difficult time to be given the diagnosis of epilepsy. The emotional upheaval of adolescence with its attendant pressures may lead to difficulties in accepting the diagnosis and adherence with medication. Assessment of seizure activity can be complicated by experimentation with alcohol, and drugs, and sleep deprivation. Epilepsy is associated with school absenteeism, and impacts on travel opportunities and future employment (Baker *et al*, 2008). Adolescents can present with poorly controlled primary generalised, or partial-onset seizures, which arose in childhood. Teenage years are a time when idiopathic generalised epilepsies are likely to manifest (Brodie and French, 2000). Photosensitive seizures are also commoner at this time of life. There have been recent advances in the understanding of genetic abnormalities, leading to some juvenile epilepsy syndromes.

History taking can be challenging in adolescents, and is improved by establishing a rapport and winning the patient's trust. Help can be gained from a witness, who may provide objective evidence of seizure activity. As with adults, EEG can aid classification of seizure type or syndrome, and MRI is the imaging procedure of choice (King *et al*, 1998). A wide range of pharmacological options is now available for treatment of epilepsy in this population. Epilepsy surgery can produce excellent results in selected young people with drug-resistant epilepsies (Cossu *et al*, 2008).

In 1996, a nurse-led clinic for adolescents was established at the Epilepsy Unit. As there are few published reports on outcomes in this population, a retrospective audit of all patients referred over the first four years was performed (Stephen *et al*, 2003 - Paper vii). A total of 301 adolescents were seen, 135 (45%) of whom did not have epilepsy, including five taking AEDs. A single seizure occurred in another 22 (7%). Of the 144 patients with epilepsy, 76 (53%) were taking AED treatment and 68 (47%) were newly diagnosed. Neuroimaging was abnormal in 27 (43%). Following pharmacological intervention, ≥ 1 year's seizure freedom was achieved by 76 (53%) patients. Of these, four (5%) remained seizure-free off medication. Seizures continued in 52 (36%) patients. Another 16 (11%) were lost to follow-up. Prognosis was better for newly diagnosed, than for treated epilepsy (59% versus 47% seizure-free; $p < 0.05$), and for primary generalised, than focal-onset seizures (60% versus 46% seizure-free; $p < 0.02$). It is recognised, however, that this was a retrospective analysis with no control group, and thus the biased results may invalidate some of the statistical conclusions reached.

These poor outcomes prompted a service review, and a new clinic for teenagers attending the Epilepsy Unit is currently being instituted. This will include a liaison programme with the local children's hospital, with on-site medical, nursing and psychologist staff. One of the aims of the new programme is to randomise patients to standard care, or to be managed by the new clinical team.

8.2 People with learning disabilities

Epilepsy is common in people with learning disabilities. Seizures have been reported in 25-40% (Sunder, 1997; McDermott *et al*, 2005), with the prevalence rising to 50% for institutionalised patients (Coulter, 1993). The more profound the disability, the more likely the person is to have epilepsy (Gillberg and Soderstrom, 2003). Obtaining an accurate history can be problematic, as difficulties with communication are common, and these individuals often present with multiple seizure types (Hannah and Brodie, 1998a). Intolerance of investigations, comorbidities, behavioural factors, psychiatric disorders, concomitant medication, and difficulties with AED adherence and formulations can complicate diagnosis and management (Hannah and Brodie, 1998b).

Uncontrolled seizures and resultant injuries can impair quality-of-life with carers (Espie *et al*, 1998) and patients having concerns about the sequelae of seizures, the consequences of taking AEDs, and social attitudes (Watkins *et al*, 2006). Outcomes are commonly perceived to be poor (Kerr and Espie, 1997), and those affected are more likely to suffer ill health (Morgan *et al*, 2003). There is a lower likelihood of seizure remission than in the general population with epilepsy (Sillanpää *et al*, 1998). In a study in 40 general practices, of 318 adults with learning disabilities 58 (18%)

had epilepsy. Of these 26% were seizure-free, but 34% had extremely poor seizure control (Matthews *et al*, 2008).

Mortality rates are higher in people with learning disabilities and epilepsy than in the general population (Klenerman *et al*, 1993). There is a higher incidence of seizure-related death, in particular, SUDEP, than in those without learning disabilities (Walczak *et al*, 2001; Tellez-Zenteno *et al*, 2005; Hughes, 2009). Of 310 pupils with severe epilepsy and learning difficulties attending a residential school, 14 of 28 deaths over a 23 year period were attributed to SUDEP, the incidence being 1:295/year, compared to a population-based incidence of 1:1000/year (Nashef *et al*, 1995). In a long-term residential care setting, SUDEP was the cause of death in 6% of 113 deaths during an 11 year period (Klenerman *et al*, 1993). When incidence of sudden death was examined in patients with learning disabilities with (n=180) and without epilepsy (n=125) at a residential facility, the rate was significantly higher at 3.6 per 1000 patient years in the epilepsy group, compared with 1.3 per 1000 patient years in the non-epilepsy group (McKee and Bodfish, 2000). Of the 55 deaths in the epilepsy group, 11 (20%) were attributed to SUDEP. Poorly controlled seizures are thought to be a risk factor (Hitiris *et al*, 2007), as well as non-ambulatory status, although the latter may be an indirect cause, being a marker of increased susceptibility to morbidity (McKee and Bodfish, 2000). Patients with learning disabilities are also at increased risk of cardiovascular and pulmonary disease (Patja *et al*, 2001), and evidence suggests that some cases of SUDEP may have an underlying cardiac (Dasheiff and Dickinson, 1986; Howell and Blumhardt, 1989; Tavernor *et al*, 1996; Opherk *et al*, 2002; Rugg-Gunn *et al*, 2004) or respiratory cause (Terrence *et al*, 1981; Morentin and Alcaraz, 2002).

There are few randomised double-blind, placebo-controlled AED studies in people with learning disabilities and epilepsy. There are three notable exceptions. Motte and colleagues (Motte *et al*, 1997) studied, in double-blind fashion, the effects of adjunctive lamotrigine in 169 children and adults with Lennox Gastaut syndrome. The median reduction in seizure count from baseline for those taking lamotrigine (32%) was significantly greater than for placebo (9%). Statistically more lamotrigine-treated patients had a reduction of at least 50% in the frequency of all major seizure types. Sachdeo and co-workers entered patients with learning disabilities into a multicentre double-blind placebo-controlled trial of topiramate (Sachdeo *et al*, 1999). Of the 98 children and adults who participated, there was a significant reduction in drop attacks and tonic-clonic seizures with topiramate, compared to placebo. Kerr and co-workers also compared topiramate with placebo in this population (Kerr *et al*, 2005). Topiramate reduced seizure frequency by 30% compared to a 1% improvement with placebo, but because of low recruitment, analyses were underpowered.

In a randomised multicentre open-label study, Crawford and colleagues compared gabapentin with lamotrigine in 109 patients with learning disabilities (Crawford *et al*, 2001). No statistical differences in seizure frequency were found, although when carer-rated visual analogue scales were analysed for seizure severity, attention, general health and sleeping pattern, patients taking gabapentin had significantly improved in all, whereas those taking lamotrigine had improved seizure severity only.

As discussed in Chapter 7, Beavis and colleagues explored the response to adjunctive levetiracetam in 42 patients with epilepsy and learning disabilities in a prospective multicentre open-label study (Beavis *et al*, 2009). Recruitment and retention were

low. Median seizure frequency reduced from baseline levels of 4.3 per week to 2.2 per week for those followed up for 6 months.

It has been shown that a systematic approach to epilepsy management in people with learning disabilities can yield benefits (Whitten and Griffiths, 2007). Although modern treatment strategies strive for monotherapy, at least 40% of learning disabled patients with epilepsy take more than one AED (Hogg, 1992; Singh and Towle, 1993). Using AED treatment, improvement in seizure control can be seen in people with all degrees of learning disability (Huber *et al*, 2007; Beavis *et al*, 2007).

However, patients with milder intellectual problems tend to have better outcomes than those with more profound disability (Huber *et al*, 2005).

Because of the unique issues involved in the management of this patient group, an audit of prospective outcomes in 214 people with learning disabilities and epilepsy, newly referred to the Western Infirmary Epilepsy Unit over a four year period, was performed (Kelly *et al*, 2004b - Paper viii). Median duration of follow-up was 18 months (range 13-36 months). It was found that 17 (8%) patients had non-epileptic attacks only, 10 of whom were being treated with AEDs. The remaining 197 (92%) had epilepsy, the majority (n=151, 77%) presenting with focal seizures. A total of 22 patients were started on AED treatment, with seizure freedom for at least one year being achieved in 10 (45%). AED manipulation was undertaken in a further 136 patients, resulting in 59 (43%) becoming seizure-free. No relationship was found between extent of learning disability and seizure control. There was no deterioration in mean caregiver scores rating sleep, appetite, alertness and behaviour. This is perhaps surprising, given that patients were started on an additional 54 AEDs during

the course of follow-up, and that AED burden has been associated with deterioration in quality-of-life in these patients (Pellock, 2002). Results are, perhaps, a reflection of the impact of improved seizure control on both patients and carers. It may also be that use of novel AEDs, some of which have a lesser propensity for drug interactions than more traditional agents, together with the judicious use of AED doses and combinations, reduced the likelihood of unwanted effects. Because patients were managed routinely, and the only intervention was a simple questionnaire, the project was categorised as an audit and did not require ethical approval.

Although study findings would have been strengthened by the use of a control group, given the complex issues surrounding the management of epilepsy, and assessment of outcomes in this population, it can be particularly difficult to assign patients to different interventions. It was decided, therefore, not to proceed with this strategy. The study design may have biased results, and although no statistically significant conclusions were reached, analyses would have been difficult to interpret accurately. Results from this audit suggest AED therapy can result in seizure freedom in more than 40% of learning disabled people with epilepsy, without producing unacceptable toxicity.

8.3 Elderly People

Old age is the commonest time to develop seizures (Hauser, 1992). As the global elderly population grows year by year, so does the number of senior citizens with epilepsy. It has been estimated that at this time of life, the annual prevalence of the condition is 1%, with an incidence of 134 per 100,000 (Sander *et al*, 1990). About 10-30% of these patients will present with tonic-clonic status epilepticus (DeLorenzo *et al*, 1996). Older people who present with a single seizure are also more likely than younger adults to re-seizure (Hopkins *et al*, 1988). Despite these statistics, access to epilepsy services is adversely associated with increasing age (Stolarek *et al*, 1995), and under- and mis-diagnosis of the condition is common. The situation is compounded further by a paucity of good clinical studies in elderly people. Care of these patients will place a growing burden on healthcare services.

Epilepsy can have a profound physical and psychological impact in old age (Baker *et al*, 2001). The stigma of the diagnosis can be hard to deal with at this time of life. The unpredictable nature of seizures may lead to social withdrawal. Loss of confidence and reduced independence can result in premature admission to care homes. Elderly people can be particularly vulnerable to physical injury sustained through seizures. Quality-of-life may also be affected adversely by the loss of a driving licence which may never be recovered. The situation can be complicated by a range of neurodegenerative, cerebrovascular and neoplastic comorbidities, and problems with concomitant medication are common (Bergey, 2004). Mortality in elderly people with epilepsy is high (Luhdorf *et al*, 1987), as are rates of SUDEP (Jallon *et al*, 1999).

Because of a relative paucity of randomised double-blind controlled trials of AEDs in elderly patients, choice of AED for older people is often based on evidence derived from studies in younger adults (Stephen and Brodie, 2000). There are three exceptions. Brodie and colleagues randomised newly diagnosed older patients to receive lamotrigine to carbamazepine in a 2:1 ratio over at least 24 weeks (Brodie *et al*, 1999). A significantly smaller percentage of patients discontinued treatment with lamotrigine (18%) than carbamazepine (42%), due to side-effects. Over 40 weeks, Saetre and co-workers randomised newly diagnosed elderly people to receive lamotrigine or carbamazepine (Saetre *et al*, 2007). There was no significant difference in seizure-free rates or tolerability between the two drugs. The US Veterans Administration Study was an 18 centre, randomised, double-blind double-dummy, parallel investigation of 593 senior subjects with newly diagnosed seizures (Rowan *et al*, 2005). The primary outcome measure was 12-month retention in the trial. Early termination, mainly due to adverse events, was reported for 44% of lamotrigine-treated patients, 51% of patients taking gabapentin and 64% of those prescribed carbamazepine ($p=0.0002$). There was no significant difference in seizure control between treatment groups. From these three studies, it appears that the major difference between newer and established AEDs in elderly people may be tolerability, assuming equivalence in dosing.

Given the relatively few publications which concentrate on epilepsy in elderly people, outcomes were explored in an retrospective audit of 117 older patients (67 men, 50 women; aged 65-92 years) in whom partial seizures were diagnosed, and treatment begun at the Western Infirmary Epilepsy Unit over a twenty year period (Stephen *et al*, 2006 - Paper ix). Of these, 73 (62%) became seizure-free for at least 12 months on

their first AED, with 30 (26%) failing to respond, and 14 (12%) not tolerating initial treatment. Following pharmacological manipulation, 93 (79%) patients attained remission, 87 (93%) on monotherapy and 6 (7%) on duotherapy. Seizure freedom was achieved with the initial AED in 73 (62%) individuals. No individual AED was more likely to confer seizure freedom than any other. Patients attaining remission were more likely to have had fewer pre-treatment seizures ($p=0.0078$) than those who did not obtain full seizure control. It was concluded that the prognosis for epilepsy in later life may be better than in younger people, perhaps reflecting lower lesional epileptogenicity and genetic predisposition. Given the retrospective nature of this analysis, and the lack of a control group, the results are, however, subject to bias. This may throw into question any statistical outcomes.

9. Antiepileptic drugs and adverse effects

Problems with AED tolerability limit the potential for optimal seizure control in certain patients. This is despite similarity in efficacy for major seizure types (SIGN, 2003). Adverse effects are common and are more likely to be associated with AED polytherapy (Moran *et al*, 2004). Of 509 Italian patients, 157 (79% taking polytherapy) reported 232 adverse events (Collaborative Group, 1986). When questioned at an epilepsy clinic, 134 of 767 adults and children had 155 adverse effects (Buchanan, 1992). The AEDs implicated in order of frequency were phenytoin, sodium valproate, carbamazepine, clonazepam, barbiturates, vigabatrin, and clobazam.

Adverse drug reactions can generally be thought of as pharmacology-related or idiosyncratic (Zaccara *et al*, 2007). Idiosyncratic reactions have been discussed previously in Section 5.4. Pharmacology-related effects are a consequence of the known pharmacological actions of a drug, and are usually predictable and relatively common. They are more usual at the start of treatment or dose increase, and can mainly be reversed by dose reduction or drug withdrawal. When starting AED treatment, a patient should be informed of associated risks. Many adverse effects become apparent within days or weeks, and may be minimised by starting with a low dose, and a slow titration schedule. Plasma concentration monitoring can be useful to this end.

9.1 Central nervous system effects

AEDs are commonly associated with CNS effects. Cognitive impairment is not infrequent in patients with epilepsy, particularly in those with focal epilepsies (Dodrill, 1992). Of the established AEDs, phenobarbital perhaps has the greatest potential for cognitive and behavioural toxicity. Dose-related impairment occurs in attention and vigilance, reaction time, short-term memory, and performance IQ (Camfield *et al*, 1979; Sulzbacher *et al*, 1999). Phenobarbital may also produce hyperactivity, and aggravation of behavioural disorders. Phenytoin can cause a decline in concentration, memory, mental speed, visuomotor functions, and intelligence (Gillham *et al*, 1988). The adverse cognitive and psychomotor effects found with carbamazepine are likely to be caused partly by the active metabolite carbamazepine-epoxide (Gillham *et al*, 1988; Gillham *et al*, 1990).

When studied in older patients, valproic acid generally had minimal cognitive impact (Craig and Tallis, 1994; Prevey *et al*, 1996; Read *et al*, 1998), although the drug occasionally can impair attention, visuomotor function, complex decision making, and psychomotor speed. Some patients develop a dose-related fine hand tremor (Hyman *et al*, 1979), or reversible parkinsonism (Armon *et al*, 1996) with valproic acid.

Comparing the cognitive effects of carbamazepine, phenobarbital, phenytoin, and primidone, the Veterans Administration Cooperative study found few pre- to post-AED treatment neuropsychological changes in patients with new-onset epilepsy (Mattson *et al*, 1985). A second Veterans Administration study found mild cognitive changes using carbamazepine and valproic acid monotherapy in the initial treatment of partial-onset seizures, although there were no significant differences between the two drugs (Prevey *et al*, 1996).

Some of the newer AEDs with multiple mechanisms of action have a poorer neuropsychiatric profile than drugs which block voltage-dependent sodium channels such as phenytoin, carbamazepine, oxcarbazepine, and lamotrigine. Vigabatrin has been associated with agitation, ill-temper, disturbed behaviour and depression (Levinson and Devinsky, 1999). Levetiracetam can increase irritability in some patients (Mula *et al*, 2003), although others may experience positive behavioural effects (Bootsma *et al*, 2008). Depression may be more common with this AED (Brodie *et al*, 2007). Topiramate produced somnolence, slowing, memory problems, and language difficulties in clinical trials (Ben-Menachem *et al*, 1996). When the cognitive effects of levetiracetam and topiramate were compared in patients with refractory epilepsy, no significant differences were found between the two drugs (Huang *et al*, 2008). Lamotrigine has mood stabilising properties as adjunctive and monotherapy in patients with bipolar depressive disorder (van der Loos *et al*, 2009; Geddes *et al*, 2009). Compared to levetiracetam, lamotrigine significantly improved anger-hostility subscale scores as add-on therapy in patients with partial seizures (Labiner *et al*, 2009). Zonisamide may impair learning (Berent *et al*, 1987) and has been associated with depression or psychosis in some patients (Miyamoto *et al*, 2000). A few patients taking each of these drugs have developed paranoid and psychiatric symptoms, although this seems most likely to occur in patients treated with topiramate (Fritz *et al*, 2005; Meador *et al*, 2005).

9.2 Bone abnormalities

Bone disease is common in people with epilepsy, and a reduction in bone mineral density occurs more frequently in people taking long-term AEDs for epilepsy than in the normal population (Souverein *et al*, 2006). Osteoporosis affects up to 40% of women and 12% of men in the Western world (Kanis *et al*, 1997). The resultant morbidity and mortality are associated with major public health and economic implications (Walker-Bone *et al*, 1998). The situation is not straightforward, however, as evidence supporting the deleterious effects of AEDs on bone mineral density is sparse and conflicting (Boglium *et al*, 1986; Timperlake *et al*, 1988; Bauer *et al*, 1993; Valimaki *et al*, 1994; Chung and Ahn, 1994; Sheth *et al*, 1995). Poor bone mineralisation can occur when physical activity is limited by focal neurological deficits or cerebral palsy. Institutionalised patients are at an increased risk (Swanton *et al*, 2007). Fear of precipitating seizure activity can lead to restriction of physical exercise, and a more sedentary existence (van Linschoten *et al*, 1990; Gates and Spiegel, 1993; Wong and Wirrell, 2006). Lifestyle factors such as smoking, chronic disease, concomitant medication, and a family history of osteoporosis, all make the condition more likely.

Phenobarbital, primidone, phenytoin and carbamazepine increase the breakdown of vitamin D, leading to secondary hyperparathyroidism, osteomalacia and increased bone turnover, although not all studies back such a hypothesis (Farhat *et al*, 2002). Other mechanisms include a direct effect of AEDs on osteoblasts, osteocytes and osteoclasts, resistance to parathyroid hormone, inhibition of calcitonin secretion, and impaired calcium absorption (Fitzpatrick, 2004). Phenytoin may inhibit vitamin K metabolism, leading to bone turnover problems (Scott *et al*, 1987; Vernillo *et al*,

1990). Research has shown an association between elevated homocysteine, reduction in bone mineral density, and increased fracture incidence (Elliot *et al*, 2007). In all, six AEDs (phenytoin, carbamazepine, phenobarbital, primidone, oxcarbazepine, lamotrigine) have known anti-folate properties, and thus the potential to increase homocysteine concentrations.

In view of this information, a case-controlled study was conducted to explore the relationship between bone mineral density and long-term AED treatment in 78 older adults (47 women; 31 men, aged 47 to 76 years) treated with hepatic enzyme inducing or non-inducing AEDs (Stephen *et al*, 1999 - Paper x). Each was matched with a non-epileptic control for age, sex, height and weight. Controls were derived from a database of values from normal volunteers recruited following an advert. They had no known health problems and were not taking any AEDs, or drugs known to predispose to osteoporosis. Patients and controls underwent bone densitometry at the lumbar spine and femoral neck, and had blood sampling and urine collected for a range of bone markers.

The results showed men had significantly lower bone mineral density compared to controls at the lumbar spine ($p < 0.01$), and neck of femur ($p < 0.005$). Women had statistically reduced bone mineral density at the femoral neck ($p < 0.05$) only. The influence of enzyme inducing versus non-enzyme inducing AEDs was assessed by multiple regression analysis. No significant influence on femoral bone mineral density was seen with either subtype. Similar results have since been reported by other researchers (El-Hajj Fuleihan *et al*, 2008, Ensrud *et al*, 2008). This suggests that although hepatic enzyme induction is associated with increased breakdown of vitamin

D (in this study, mean serum vitamin D concentrations were significantly lower in patients taking enzyme inducing AEDs compared to those on non-enzyme inducing agents), and increased bone turnover, this mechanism alone is not responsible for the reduction in bone mineral density associated with AED treatment.

It was concluded, therefore, that long-term AED treatment is an independent risk factor for reduced bone mineral density in people with epilepsy. All patients with bone pathology were prescribed appropriate treatment in the form of vitamin D, biphosphonates and calcium. Epilepsy Unit staff now give dietary and lifestyle advice routinely, and offer bone densitometry to patients at risk of developing osteoporosis.

9.3 Soft tissue and muscle changes

Chronic dosing with phenytoin can produce gum hypertrophy (Angelopoulos and Goaz, 1972), which is minimised with continuing attention to dental hygiene. Long-term treatment with phenobarbital may be associated with a range of fibrosing disorders such as reflex sympathetic dystrophy, shoulder-hand syndrome, frozen shoulder and Dupuytren's contracture (Falasca *et al*, 1994).

9.4 Metabolic effects

Over the past twenty years, it has come to light that some people with epilepsy may have hormonal and metabolic abnormalities (Rasgon, 2004). The effects of seizures and AEDs on metabolism are complicated, and have been difficult to assess in a variety of studies due to differences in sample sizes, and variability in methodology

(Meo and Bilo, 2003). Weight gain has been associated with sodium valproate (Dinesen *et al*, 1984), vigabatrin (Chadwick, 1999), gabapentin (De Toledo *et al*, 1997), and pregabalin (Brodie *et al*, 2005). Conversely, treatment with topiramate (Ben-Menachem *et al*, 1996) and zonisamide (Schmidt *et al*, 1993) may result in weight loss in some patients.

There has been a particular interest in the relationship between polycystic ovarian syndrome (PCOS) and epilepsy. PCOS has been defined as the presence of ovulatory dysfunction (*i.e.* menstrual irregularity), hyperandrogenism, or clinical evidence of hyperandrogenism and the exclusion of other endocrine diagnoses (Zawadski and Dunaif, 1992). Changes associated with PCOS occurred in up to 64% of Finnish women taking valproic acid (Isojärvi *et al*, 1993; Isojärvi *et al*, 1996). Indian researchers reported weight gain (40%), hirsutism (20%) and PCOS (20%) in 25 women taking valproic acid for one year (Prabhakar *et al*, 2007). Similar results were reported in a Korean study, affecting 42% of women (Kim and Lee, 2007). In other studies, PCOS has been found in 7.7% (Luef *et al*, 2002a), 9.1% (Luef *et al*, 2002b), 11.1% (Bauer *et al*, 2000), 28% (Betts *et al*, 2001), and 48.6% (Isojärvi *et al*, 2001) of women with epilepsy. Some researchers report PCOS changes in 5.7% to 16.7% of patients with carbamazepine monotherapy (Bauer *et al*, 2000; Isojärvi *et al*, 2001; Luef *et al*, 2002b), but not all (Betts *et al*, 2001). A recent Finnish analysis found sodium valproate to be a predictor for development of PCOS and polycystic ovaries, as well as hyperandrogenism (Löfgren *et al*, 2007).

The situation surrounding metabolic influences of AEDs is complex, and not yet understood fully. Because research tends to be conducted in small cohorts, with

designs which may bias outcomes, results need to be interpreted with caution. Epilepsy, itself, may be responsible for endocrine abnormalities (Herzog *et al*, 1986). It has been suggested that hepatic enzyme inducing AEDs accelerate hepatic biotransformation, increasing testosterone binding and metabolism, thus reducing testosterone concentrations. In men, this mechanism may lead to sexual dysfunction (Patsalos *et al*, 1990). In women, this may account for the discrepancy between valproic acid and enzyme inducing AEDs being associated with differing prevalences of PCOS (Cramer *et al*, 2007). Others suggest the weight gain associated with valproic acid may be responsible for insulin resistance and resultant endocrine changes (Isojärvi *et al*, 1996).

In an attempt to shed further light on this interesting area, two projects examining the effects of sodium valproate or lamotrigine in patients with epilepsy were performed at the Epilepsy Unit. The first was a cross-sectional study in 40 men and 36 premenopausal women taking either drug as monotherapy (Stephen *et al*, 2001b - Paper xi). Each had blood sampled for fasting insulin, glucose, cholesterol, triglycerides, high and low density lipoproteins, testosterone, dihydroepiandrosterone, androstenedione, sex hormone binding globulin, luteinising hormone, follicle stimulating hormone, and AED concentrations. Free androgen index and body mass index were calculated. Of the cohort, only four obese valproate-treated women were hyperinsulinaemic ($p=0.05$); three with abnormal menstrual cycles, and one with raised testosterone. Testosterone ($p=0.02$) and triglyceride ($p=0.02$) concentrations, and the free androgen index ($p=0.03$), were higher in valproate-treated women, compared to those taking lamotrigine. Obese patients of both sexes ($p=0.01$) and valproate-treated men ($p=0.03$) had higher insulin concentrations. It is conceivable,

however, that the positive statistical tests were found as a result of chance, as the likelihood of false positive results being found increases with the number of comparisons made. If the Bonferroni correction is applied, with 0.05 as the critical significance level, and taking into account the 13 different comparisons made, the actual critical significance level in this study is 0.0038 (*ie* 0.05/13). Thus none of the results are statistically significant. It can therefore be concluded that there were no differences in metabolic indices between patients taking sodium valproate or lamotrigine. The study would have been strengthened further by comparison of treatment groups with a matched cohort not taking AED therapy.

These findings were corroborated by a randomised, prospective study undertaken in 225 patients with newly diagnosed epilepsy (Stephen *et al*, 2007 - Paper xii). The aim was to compare the efficacy and tolerability of sodium valproate (n=111) and lamotrigine (n=114) monotherapy, and effects of these drugs, on circulating androgenic hormones. AED-naïve patients were randomised to receive sodium valproate or lamotrigine, with doses titrated according to clinical need. Of patients with partial-onset seizures, 81 received sodium valproate and 80 were randomised to receive lamotrigine. Of those with idiopathic generalised epilepsies, 30 received sodium valproate and 34 received lamotrigine, with numbers of patients with different syndromes being too small to warrant analysis of these subgroups. Seizure-free rates in both treatment arms were identical at 12 months (47%). There was a trend towards superiority for valproate (57% seizure-free) over lamotrigine (35% seizure-free) for patients with idiopathic generalised epilepsies ($p=0.09$), but a converse separation of outcomes for localisation-related epilepsies (43% seizure-free with valproate, 53% seizure-free with lamotrigine, $p=0.24$). More patients taking sodium valproate

withdrew from the study due to adverse effects ($p=0.046$), eight on account of weight gain. Although some of these patients continued to attend the epilepsy clinic, further formal monitoring and data collection were not undertaken after stopping sodium valproate. Thus, no conclusions could be drawn as to long-term outcomes in these individuals. Neither sodium valproate, nor lamotrigine altered circulating testosterone, sex-hormone binding globulin, androstenedione concentrations, nor changed the free androgen index at six and 12 months. These results have to be considered together with the fact that eight patients withdrew from the valproate arm of the study because of weight gain. As the long-term consequences of continued sodium valproate could not be monitored in these individuals, hormonal findings may be spurious. It was concluded that there is little difference between these agents in terms of efficacy when used as initial monotherapy in people with newly diagnosed epilepsy. Lamotrigine appeared to be tolerated better.

10. Conclusions

The series of studies presented in this thesis demonstrate how AEDs can be used in different populations, taking into consideration beneficial and adverse effects.

Localisation-related epilepsies are often considered less easy-to-control than idiopathic generalised epilepsies. The audit in this volume showed the majority of patients with focal-onset seizures became seizure-free for over one year with AED treatment. Mesial temporal sclerosis was associated with the poorest outcomes, but patients with this diagnosis were controlled with drug treatment. Bias may have been introduced, however, given the cross-sectional nature of the audit and the fact that outcomes from patients with newly diagnosed and refractory epilepsy were analysed.

Data demonstrate also, that people taking AED polytherapy can gain full control of their seizures. Treatment with two or three drugs, but rarely four, was successful, although retrospective analysis, lack of control group, and inclusion of patients with newly diagnosed and drug-resistant epilepsy may have biased results. Epilepsy staff are therefore now examining similar outcomes in a large patient population of newly treated patients only.

Given the recent influx of new AEDs, it is important for clinicians to gain experience in using these drugs, both singly, and in combination. The publications detailing the addition of topiramate and levetiracetam to AED regimens in patients with refractory epilepsy, showed these drugs to be effective in everyday clinical practice, often in doses lower than those recommended by the manufacturers. Efficacy as monotherapy was also achieved. Topiramate plasma concentrations varied widely with different doses. Concentration measurement is, therefore, largely unhelpful when using this

drug. The observational nature of these single centre audits, and lack of control groups may have biased results.

Many patients with learning disabilities have seizures which appear refractory to AED treatment. Data presented demonstrate this is not necessarily the case. Careful and considered follow-up make seizure freedom a realistic goal, without producing unacceptable side-effects. Use of topiramate, or levetiracetam in this population, can result in good outcomes. Care-giver scoring suggested quality-of-life may improve in the majority of patients started on levetiracetam. Again, bias may have been introduced by the observational nature of these single centre audits, and lack of control groups. Small patient numbers and retrospective baseline seizure recordings in some may also have influenced results.

Epilepsy can strike at any time of life, but the condition may have different influences on an individual, depending on when it occurs. Despite this, there are few studies examining outcomes in different age groups. Results from the nurse-led teenager clinic at the Epilepsy Unit were surprisingly poor, with seizure freedom being achieved in just over half of patients started on AED therapy. This has been the incentive for the institution of a new service for adolescents, linked with the local children's hospital, and providing medical, nursing and psychological support. Pharmacological outcomes in older people with epilepsy were better, given that 79% of patients became controlled with drug treatment, the majority on monotherapy. Conclusions have to be considered in light of the fact that neither observational audit employed a control group and analyses were retrospective.

Adverse effects of AEDs are a common clinical problem. The case-controlled study presented explored the relationship between long-term AED use and bone mineral density, in older adults with epilepsy. AED treatment was found to be an independent risk factor for reduced bone mineral density. With the high morbidity and mortality associated with osteoporosis, this result has prompted Epilepsy Unit staff to identify at-risk patients, and offer appropriate screening and intervention.

The final papers, comparing hormonal outcomes in patients taking sodium valproate, or lamotrigine monotherapy, concluded that if any metabolic changes are associated with valproic acid, these only affect a minority of people. The case-controlled study found significantly higher insulin concentrations in obese people taking sodium valproate, but only four obese women had hormonal abnormalities. When results were corrected for multiple comparisons, however, no differences in parameters were found between sodium valproate and lamotrigine. The randomised, controlled study confirmed this, with no significant hormonal differences, or significant differences in efficacy, between the two arms. Continued monitoring may have provided further valuable information and reduced bias. These results have helped colleagues to counsel patients appropriately, when starting these medications.

In recent times, the emergence of new AEDs, and modern investigative techniques have revolutionised the management of seizure disorders. This body of work has added to current knowledge on outcomes in localisation-related epilepsies, results with different polytherapy regimens, the pragmatic utilisation of novel drugs, prognosis in different age groups, and adverse effects associated with AEDs. Findings

should be considered in the context that the design of several of the projects may have introduced inherent bias.

With accurate classification of seizure type or syndrome and timely management, the outlook for individuals with epilepsy has never been more positive. In coming years, genomic research may shed further light on seizure pathophysiology and the reasons underlying refractoriness and adverse drug effects. As such, it is hoped this may allow a more precise selection of AED treatment, and greater potential for seizure freedom.

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