The prognosis of newly diagnosed and treated epilepsies in adults

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I dedicate this thesis to the memory of my father Dr. KV Mohanrajan PhD

Declaration

All the data presented in this thesis represent original work carried out by me and has not been submitted for a higher degree previously. My projects were based on existing themes of research in the Epilepsy Unit and I received advice and assistance from several individuals with aspects of my work. The intellectual and technical input to each part of my thesis is as follows. For the clinical studies in section II, I designed the database, collected data by review of case notes and performed all analyses. For the pharmacogenomics studies in Section III, ethics approval had already been obtained by my supervisor Prof. Martin Brodie prior to my commencing studies. Blood samples were collected by nursing and medical staff at the Epilepsy Unit. Extraction, purification and quantification of DNA were performed by Elaine Butler, Senior Laboratory Technician. I identified the specific functional SNP (R19K) on the sodium channel gene SCN2A which could be assayed using the technology available. I performed the PCR and restriction enzyme digest analysis for the R19K polymorphism on 400 DNA samples under the guidance of Dr. Graeme Sills, Director of Research at the Epilepsy Unit. I also performed phenotyping of patients based on their response to treatment and the logistic regression and predictive value analyses. In section IV (studies of mortality), the process of collecting data on mortality from the General Registrar's office was already in place. I collated the data into separate databases for those with new onset and chronic epilepsy, reviewed classification of epilepsy and obtained causes of death from the Health authority records. For the analysis, I identified comparator populations from the General Registrar office website and decided the factors to be included in the Cox proportional hazards model. The analysis was performed by John Norrie, formerly of the Robertson Institute of Biostatisitics, University of Glasgow.

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Summary

The prognosis for seizure control is an important consideration for patients diagnosed with epilepsy. Reversing the social restrictions imposed by seizures and returning to a productive life requires complete and sustained seizure control. The epilepsies are a heterogeneous group of disorders and clinicians discussing the prognosis of epilepsy need to be aware of the natural history of each epilepsy syndrome. Longitudinal follow up studies in newly diagnosed patient populations are required to delineate the natural history of the various syndromes. Previous studies have suggested that the early course of epilepsy is predictive of its longer-term behaviour in the majority of cases. If response to individual antiepileptic drugs (AEDs) in specific epilepsy syndromes can be predicted, prognosis can be assessed more accurately. Genetic influences on response to treatment are probably important in this regard. The completion of the Human Genome Project has opened up the possibility of correlating variations in the human genome with the variability of response to drugs. The discipline of pharmacogenomics, which seeks to study the genetic influence on response to drugs, has the potential to allow drug therapy to be optimised for each patient, maximising the chances of success. Identification of single nucleotide polymorphisms (SNPs) in candidate genes correlating with response to AED treatment can help identify patients at risk of developing drug resistant epilepsy.

Epilepsy is associated with an increased mortality risk. The excess risk varies depending on the population studied, and is influenced by patients' clinical and demographic characteristics. Clinicians discussing mortality issues with patients need to be aware of the potential risk in each individual. This is best deduced from studies in representative patient groups. Risks need to be studied separately in patients with newly diagnosed and

chronic epilepsy, as the prognoses in these two groups are likely to be different, in terms of both seizure control and survival.

Treatment outcomes were analysed in patients newly diagnosed with epilepsy at the Epilepsy Unit, Western Infirmary, Glasgow over a 20-year period by retrospective review of research case notes. Response to treatment was defined as a 12-month seizure free period and those who remained seizure free till the end of follow up were considered to be in remission. A total of 890 patients had been diagnosed with epilepsy. Treatment outcomes were known for 780 who were included in the analysis of treatment outcomes. Four major categories of response to treatment were observed: those who responded rapidly and completely to treatment with the first AED (immediate responders), those who responded with further changes to therapy including combination treatment (delayed responders), those who had an initial period of good control before experiencing seizure recurrence and being subsequently uncontrolled (relapse), and those who never achieved 12 month seizure free period (uncontrolled). Over 90% of those responding to treatment achieved remission. Of those responding to treatment 83% had completed 12 seizure free months by 3 years from starting AEDs. Those failing the first AED had significantly lower likelihood of responding to further pharmacotherapy if the reason for failure was lack of efficacy rather than adverse effects. For patients failing 2 well tolerated antiepileptic drug regimes, the chances of seizure freedom with pharmacotherapy was less than 10% and for those failing 3 such regimes, this figure was only 3%. Alcohol abuse, history of head injury and febrile seizures, psychiatric co-morbidity and family history of epilepsy showed significant univariate association with uncontrolled epilepsy. Voltage gated sodium channels are important in the generation action potentials in the brain and also serve as molecular targets for a range of AEDs. SNPs resulting in altered

amino acid sequence in the sodium channel α subunit have the potential to influence the response to AED treatment. $Na_v1.2$, encoded on *SCN2A*, is the most widely expressed sodium channel α subunit in seizure-prone areas of the human brain. A case control association study was conducted to examine the prevalence of a specific SNP (*R19K*), in the *SCN2A* gene among responders and non-responders to AED treatment, identified from 400 epilepsy clinic attendees. The *R19K* polymorphism was significantly more prevalent in non-responders in this population (OR 2.07, 95% CI 1.08-3.97, p=0.024), but the predictive value of the polymorphism in identifying non-responders was low (test efficiency 48%).

Mortality was studied separately in the newly diagnosed patients (n=890) and in patients chronic epilepsy, referred after unsuccessful treatment elsewhere (n=2689). Comparison was made to an age and sex matched Scottish control cohort. Significantly more deaths were observed in both cohorts of patients than could be expected based on the mortality in the control population. Standardised mortality ratios (SMR) were 1.41 (95% CI 1.15 – 1.74) for the newly diagnosed patients and 2.04 (95% CI 1.82-2.27) for patients with chronic epilepsy. In the newly diagnosed patients, more deaths than expected were observed for patients with symptomatic and unclassified epilepsy, but not for those with idiopathic or cryptogenic epilepsy. In the chronic epilepsy cohort, excess mortality was seen for all types of epilepsy other than idiopathic generalised. Highest mortality was seen in younger patients, especially in those with symptomatic epilepsy. The incidence of Sudden Unexpected Death in Epilepsy (SUDEP) was 1.08 per 1000 patient years in newly diagnosed epilepsy, and 2.4 per 1000 patient years in chronic epilepsy in this analysis.

In conclusion, the prognosis of newly diagnosed epilepsy is obvious within the first 3 years of starting treatment. Patients who do not respond to the first 2 well tolerated AED regimes have les than 10% chance of achieving remission with further pharmacotherapy and should be evaluated in a specialist epilepsy centre. The approach of analysing single SNPs on candidate genes lacks the power to usefully predict response to AED treatment. Identifying a number of genetic markers that correlate with treatment and using more sophisticated analyses paradigms such as haplotype-based approaches can improve the predictive value. Mortality risks are higher in patients with chronic epilepsy compared to those with newly diagnosed epilepsy. This excess is most marked for younger patients, especially those with symptomatic epilepsy. SUDEP remains a rare event for patients with epilepsy, but is significantly more likely in patients with chronic epilepsy.

Part I

General Introduction

1. Determining pharmacological intractability in epilepsy

1.1. Introduction

1.1.1. Historical considerations

Mankind has known epilepsy since the earliest civilisations. There are descriptions of epileptic phenomena in the Babylonian tablets dating back to 2nd millennium BC (Arts and Vree, 2001). Descriptions that are suggestive of epilepsy can also be found in Persian Egyptian and Mesopotamian texts. The word epilepsy is derived from Greek *epilambanien*, which means to seize or attack. This terminology may have roots in the ancient belief that all diseases were caused by attacks of gods or demons. Ancient Greeks considered epilepsy the scared disease although Hippocrates ascribes its supposed divine origin to "men's inexperience and their wonder at its peculiar character" (Hippocrates, c.400 BC). The impressive nature of generalised seizures also probably led to the term 'the great disease' which finds its way into medieval French as *grand mal*, a term in use until recently. Robert Bentley Todd first proposed the electrical basis of nervous functioning. His successor John Huglings Jackson is generally credited with developing the electrical theory epilepsy, paving the way for modern epileptology (Reynolds, 2004).

1.1.2. Natural history of treated epilepsy

The term epilepsy covers a wide range of disorders with the common symptom of recurrent unprovoked seizures. The natural history and prognosis vary depending on the underlying aetiology and the specific epilepsy syndrome. Our understanding of the natural history of the different seizure disorders is imperfect. Some syndromes have a genetic aetiology, yet incomplete penetrance and phenotypic variability in most genetically mediated epilepsy syndromes suggest a strong environmental influence (Johnson and Sander, 2001). The majority of patients with acquired epilepsy are likely to

have an underlying genetic predisposition modified by environmental factors (Figure1). The dynamics of the causative and modifying factors determine the outcome of each epilepsy syndrome, including response to treatment.

Long-term prospective studies are required to accurately estimate the prognosis of each specific seizure disorder. It is important that studies of prognosis consider each epilepsy syndrome separately (Commission, 1993). If an approach of 'lumping' is followed in such studies, the observed outcome will be skewed towards that of the most frequent syndrome in the cohort. Certain benign epilepsy syndromes with onset in childhood have an excellent prognosis and enter remission regardless of drug treatment. Syndromes such as Juvenile Myoclonic Epilepsy (JME), on the other hand, respond relatively easily to treatment but have a high rate of recurrence if treatment is withdrawn. The long-term prognosis of adult onset epilepsy is less clear. Data from longitudinal studies suggest that patients diagnosed with epilepsy largely fall into two categories- those who enter remission early on and those who remain refractory from the outset (Goodridge and Shorvon, 1983; Kwan and Brodie, 2000). Patients who are difficult to control initially can still enter remission several years after starting AED treatment, albeit in small numbers. Similarly, those who enter remission early on can relapse and be subsequently difficult to control. A recent study in patients undergoing temporal lobectomy for refractory epilepsy found that 26% of patients had a history of one-year remission, and 8.5% had a history of 5-year remission, prior to developing refractory epilepsy (Berg et al, 2003). Thus, there appears to be a small group of patients in whom the seizure disorder displays a changing behaviour over time. Nonetheless, in the majority of patients, early course of epilepsy is a reliable indicator of the long-term treatment outcome (Hauser et al, 1996; Dlugos et al, 2001).

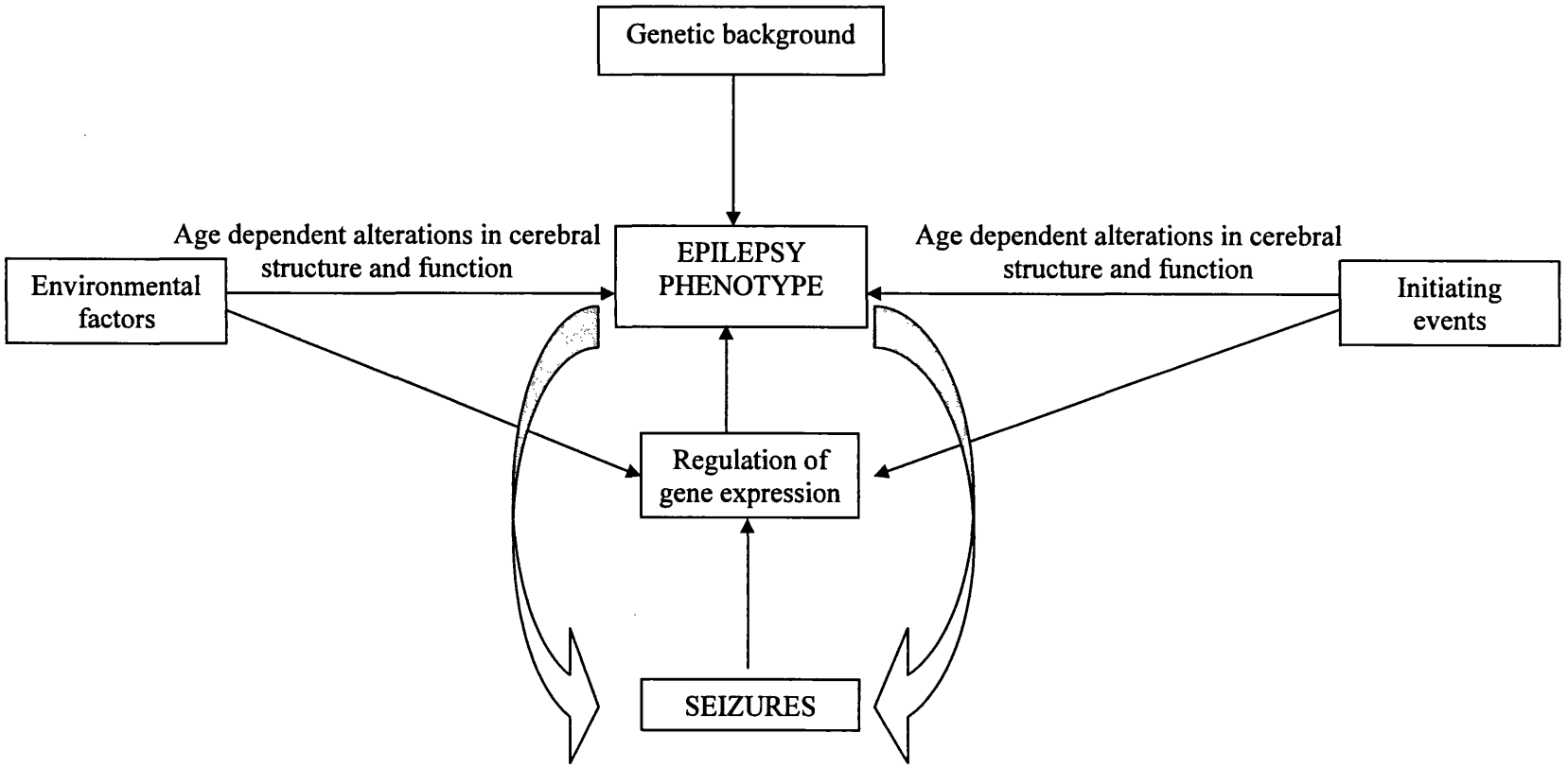


Figure 1. Paradigm for epileptogenesis in acquired epilepsies

1.1.3. Drug treatment of epilepsy

Effective treatment for epilepsy has been available since the latter half of the 19th century, since the discovery of anticonvulsant properties of bromides. The number of drugs available to treat epilepsy increased through the 20th century; thanks mainly to serendipitous discovery of antiepileptic drugs (AEDs). In the 1980s and 1990s, rational drug discovery programmes saw several new compounds with novel mechanisms of action added to the therapeutic armamentarium against epilepsy. This has resulted in an improved outlook for most patients with epilepsy, with a realistic prospect for a full productive life for most patients diagnosed with epilepsy. The ideal outcome in the treatment of epilepsy would be complete control of seizures with no adverse effects from medication enabling patients to return to full productive lifestyle consistent with his/her abilities (Engel, 2004). However, many patients in whom complete seizure control is not achieved are able to maintain a near normal lifestyle with only minimal restrictions. This concept of "acceptable control" aims at limiting the number and severity of seizures with tolerable drug burden and adverse effects. Acceptable seizure control in such situations varies depending on patients' expectations and social circumstances as well as the type of epilepsy.

In some severe epilepsy syndromes of infancy and childhood, usually associated with neurological morbidity and intellectual impairment, complete seizure control is often an unrealistic expectation (Shields, 2000). Reduction in seizure frequency and severity can improve the quality of life and prevent further intellectual impairment in such patients. Nonetheless, in the majority of patients with epilepsy, even relatively infrequent and mild seizures can have a significant impact on quality of life (Gilliam, 2002). Academic achievement and intellectual development of children with epilepsy is significantly

improved if seizures are well controlled (Austin et al, 1999; Zelnik et al, 2001). In adults, the diagnosis of epilepsy often results in loss of driving privileges and employment. Regaining these require demonstration of complete control of seizures over an extended period of time in most countries. Seizure freedom is thus the all-important treatment goal for the majority of patients with epilepsy.

1.1.4. Drug resistant epilepsy

There is now convincing epidemiological data to show that over 30 % of patients diagnosed with epilepsy will never achieve lasting control of seizures with currently available AEDs (Annegers et al, 1979; Cockrell et al, 1995; Mattson et al, 1996; Kwan and Brodie, 2000). There is, however, no consensus in the literature as to what constitutes drug resistant epilepsy. In epidemiological studies, the definition of drug resistant epilepsy varies, both in terms of the number of AEDs tried and time from diagnosis (Berg et al, 1996; Camfield and Camfield, 1996; Casetta et al, 1999; Lindsten et al, 2001). The terms refractory epilepsy, intractable epilepsy and drug resistant epilepsy are usually used interchangeably in this context. Whichever term is used, it encompasses a multidimensional disorder in which uncontrolled seizures cause deleterious neuronal plasticity with progressive cognitive decline, psychosocial dysfunction, reduced quality of life and increased mortality (Kwan and Brodie, 2002). Early identification and prediction of intractable epilepsy is of the greatest importance in deciding the timing of epilepsy surgery in patients with suitable seizure types. There is now robust clinical data to support the early use of surgical treatment in patients with refractory temporal lobe epilepsy (Weibe et al, 2001). In appropriately chosen patients surgery can result in seizure freedom, restoring quality of life and productivity. Yet, epilepsy surgery remains one of the most underutilised treatment modalities in the world (Engel, 2001). The

irreversible nature of surgery, along with fear of complications induces a degree of reluctance in patients and physicians to consider this treatment option until all pharmacological options have been exhausted. This approach to epilepsy surgery as a 'last resort' has resulted in patients suffering uncontrolled seizures for years before having curative surgery (Sperling et al, 1996). Defining a situation where additional medical treatment is unlikely to be successful can help optimise the timing of surgical referral as well as help in clinical decision-making.

1.2. 'Pseudo'-intractability

Patients fail pharmacotherapy for seizures for a variety of reasons. Non-compliance with treatment, diagnostic error, failure to attend follow up for adjustments in AED dosage and life-style factors can all cause AED therapy to be ineffective. While these patients could be considered treatment failures, they are not pharmacoresistant in the true sense of the word. Genuinely drug resistant patients form a hard core of all patients failing AED therapy. When non-pharmacological treatments are being considered, pharmacoresistance should be diagnosed only in patients who have a secure and accurate diagnosis of epilepsy, are on adequate doses of appropriate AEDs, are compliant with treatment with adequate serum, and therefore, presumably brain concentrations of AEDs.

1.2.1. Errors of diagnosis and classification

Diagnostic error is the most frequent cause of seizures failing to respond to treatment. Failure to respond to appropriate doses of standard AEDs should, in the first instance, prompt a review of the diagnosis. Common diagnostic pitfalls include wrong diagnosis of epilepsy (NEAD, syncope) and incorrect diagnosis of seizure types. Video-EEG monitoring is the only reliable method by which accurate diagnosis and classification of

seizures can be carried out, and should be available to all patients failing drug therapy, before non-pharmacological treatments are considered.

Non-epileptic attack disorders (NEAD) are common conditions (Benbadis and Hauser, 2000) and constitute a large proportion of cases referred for evaluation of possible seizure disorders (Francis and Baker, 1999). Diagnosis of NEAD can be challenging as they can co-exist with epilepsy, or may develop as substitute for seizures once epilepsy is controlled (Kuyk et al, 1997). Psychological factors such as anxiety or stress, depression, physical / sexual abuse and dysfunctional relationships are present in the majority of patients (Moore and Baker, 1997). Many patients have an underlying conversion or dissociation disorder or a borderline personality disorder. NEAD are classified into episodes of apparent loss of awareness with convulsive movements or with little or no obvious motor activity (swooning). These movements can involve uncoordinated thrashing, back arching and pelvic thrusting. Patients do not have conscious awareness of the attacks except in factitious disorder or malingering which are relatively rare (Betts and Boden, 1991).

Syncope resulting in prolonged reduction in blood flow to the brain can cause convulsions, which may be mistaken for seizures (Devinsky, 1994). History of attacks provoked by pain or anxiety or on assumption of upright posture and preceded by facial pallor and diaphoresis suggests a diagnosis of vasovagal syncope. The vast majority of these attacks are associated with some motor activity. myoclonic jerking is observed most commonly, but tonic and clonic movements or apparent automatisms may also be seen (Lempert et al 1994). Anoxic convulsions can occur if the patient remains upright during syncope or if cardiac out put remains low for a prolonged period of time, as may happen

with cardiogenic syncope. These may not have any or very short lived premonitory symptoms. ECG is mandatory in all patients presenting with episodes of collapse and 24-hour tape, implantable loop recorders and tilt table testing may be indicated if a cardiac cause or malignant vasovagal syncope is suspected.

Wrong classification of seizure types and syndromes can result in unsuccessful pharmacological treatment. Physicians are reliant on descriptions given by third parties to arrive at a diagnosis, but these are often highly unreliable. Diagnostic error arising from this (e.g.: - complex partial seizures misdiagnosed as absences) can lead to inappropriate drug selection. Wrong choice of antiepileptic drugs can potentially exacerbate epilepsy – carbamazepine and GABA-ergic drugs can exacerbate idiopathic generalised epilepsy especially myoclonic jerks and absences (See part II, section 3.4). EEG employing provocation (eg: sleep deprived EEG) or video-EEG monitoring should enable accurate classification of seizures and rationalisation of drug therapy.

1.2.2. Non-compliance and lifestyle issues

Non-adherence to prescription is a major factor in failure of drug treatment. Non-compliance is present in up to 50% of patients attending epilepsy clinics (Leppik, 1988). Compliance can be assessed by asking patients about medication taking habits, serial blood levels or by using automated monitoring devices. It has been suggested that once steady state concentration has been achieved, if the variability between three separate serum levels is less than 20-25%, compliance is likely (Leppik, 1988). Anti-epileptic drug treatment in most cases lasts years and many patients miss the occasional dose. Patients' motivation to continue regular treatment depends on the degree of control achieved (efficacy), adverse effects and possible consequences of loss of seizure control.

It is often impossible to separate these elements. Thus, the eventual effectiveness of any antiepileptic treatment is determined by both its efficacy and tolerability. As many patients diagnosed with epilepsy will have a mild disorder, drugs with fewer adverse effects are more likely to ensure better compliance than more potent but side-effect prone drugs, and therefore more likely to produce a favourable treatment outcome. Abuse of alcohol and drugs such as cocaine can cause seizures. Similarly, sleep deprivation and stress can also precipitate seizures in some epilepsy patients. A history of substance abuse is accompanied by non-adherence to prescription in large proportion of patients. Social and lifestyle factors should therefore be taken into account when evaluating the efficacy of drug treatment for epilepsy.

1.3. Refractory epilepsy – progressive or de novo?

Whether drug resistance occurs de novo in patients with epilepsy or arises as a result of repeated seizures is a subject of debate. The concept of "seizures beget seizures" was introduced by Gowers in the 19th century (Gowers 1881) and reinforced by the writings of Rodin in the 1960s. A long history of seizures and high numbers of pre-treatment seizures were thought to correlate with a poor outcome. This view was supported by Reynolds and colleagues in the early 1980s and early treatment of seizures was considered key to preventing the emergence of drug resistant epilepsy (Reynolds et al, 1983). Repeated seizures have been shown to cause neuronal loss and mossy fibre sprouting in the hippocampus, which in turn can cause seizures by forming excitatory recurrent circuits (Dalby and Mody, 2001, Holmes 2002). In humans, neuropsychological studies have shown cognitive decline in patients with refractory epilepsy; the severity of which is correlated with duration of epilepsy (Jokeit and Ebner, 2002). Cross-sectional MRI studies have demonstrated smaller hippocampal volumes ipsilateral to seizure focus

in patients with temporal lobe epilepsy and uncontrolled seizures (Theodore et al, 1999, Kalviainen and Salmenpera, 2002). The degree of hippocampal volume loss was related to the duration of epilepsy. Longitudinal studies employing repeat MRI scans have demonstrated progressive hippocampal and temporal neocortical volume loss and have suggested that neuronal loss is correlated to number of seizures (Briellmann et al, 2002, Fuerst et al, 2003). Thus in mesial temporal lobe epilepsy, hippocampal sclerosis does appear to be both the cause and consequence of seizures. Prevention of repeated seizures by effective drug treatment could theoretically prevent neuronal apoptosis and synaptic reorganisation, which cause further seizures.

On the other hand, studies in patients who have suffered seizures for several years, sustaining 100 or more generalised seizures before coming to medical attention have shown that a similar proportion go into remission as patients treated early after only a few seizures (Feksi et al, 1991). Moreover, treatment with AEDs after the first unprovoked seizure has been shown not to affect the long-term outcome, in spite of preventing seizures in the short term (Hauser et al, 1990; Musicco et al, 1997; Camfield et al, 2002). Several studies have shown a relationship of high initial seizure frequency with poor outcome (Juul Jensen, 1964; Rodin, 1968; Reynolds, 1987; Beghi and Tognoni, 1988; Sillanpaa, 1993). However, detailed analyses of data from observational studies have shown that this is true only for patients suffering complex partial seizures (Shinnar and Berg; 1996). It is likely that the epileptogenic process responsible for the high frequency of partial seizures is inherently pharmacoresistant. Seizure type would thus appear to be more important than seizure numbers in determining prognosis. This suggests that the prognosis of each seizure disorder is an inherent property of that syndrome.

1.4. Causes of true drug resistance

Despite advances in the field of cell biology, our understanding of the process of epileptogenesis at the molecular level remains incomplete. A few well-defined epilepsy syndromes of infancy and childhood have clear genetic basis, mainly mutations in ion channel genes. These results in altered ion channel structure and function and are often associated with catastrophic seizures (Berkovic and Scheffer, 2001). Disorders of neuronal migration are also associated with drug resistant epilepsy, as are cerebral tumours and trauma. Why such lesions result in hyperexcitability of neurons and hypersynchronised discharge of a large number of neurons, however, is not fully understood. The basic mechanisms that operate in rendering epilepsy pharmacoresistant, therefore, also remain largely unclear. Several hypotheses on the mechanisms involved in the evolution of drug resistant epilepsy have been proposed (Regesta and Tanganelli, 1999). These include ontogenic abnormalities in brain maturation, epilepsy induced alterations in network neuronal and glial properties in seizure prone areas such as the hippocampus, the phenomenon of kindling and reorganisation of cortical tissue in response to seizure induced disturbances in oxygen supply. These however have to be confirmed by studies in appropriate models of drug resistant epilepsy.

1.4.1. Neurobiology

Structural brain lesions have for long been known as a cause for epilepsy, these are summarised in Table 1 (Vinters et al, 1993). The nature of the underlying lesion has a strong influence on the prognosis of the seizure disorder (Semah et al, 1998; Stephen et al, 2001). Modern imaging techniques allow accurate characterisation of structural lesions, but histological diagnosis may be required to exclude malignancy in some cases

1.4.2. Malformative

Disorders if cortical development have been increasingly recogonised as the underlying cause for epilepsy since the advent of MRI. They include a spectrum of disorders of abnormal cortical development and/or architecture with varying severity of epilepsy summarised in Table 2. In recent years, there has been a greater understanding of their genetic bases, clinical presentations and the mechanisms involved in epileptogenesis (Guerrini and Carrozzo, 2002). Lissencephaly, the most severe abnormality of neuronal migration, is characterised by absent (agyria) or decreased (pachygyria) convolutions. Subcortical band heterotopia (SBH) is at the mild end of the agyria-pachygyria spectrum and shows simplified gyral pattern with increased cortical thickness. Bilateral periventricular nodular heterotopia (BPNH) consists of confluent and symmetrical subependymal nodules of grey matter located along the lateral ventricle, particularly along the ventricular body. Focal Taylor type cortical dysplasias have high intrinsic epileptogenicity (Palmini et al, 1995). The epileptogenic zone often extends beyond the visualised area and acute intraoperative electrocorticography is required to ensure adequate resection. Tuberous sclerosis (TS) is an autosomal dominant, multisystem disorder with a prevalence of 1:30000 to 50000. Most patients with TS have epilepsy; infantile spasms are often an early manifestation. In the brain, TS is characterised by cortical tubers, subependymal tubers and giant cell tumours (Guerrini and Carrozzo, 2002). Cortical tubers are directly related to epileptogenesis and show pathological features similar to focal cortical dysplasia. They are well visualised on MRI as abnormal gyri with atypical shape and abnormal signal intensity.

1.4.3. Neoplastic

Intracranial mass lesions can be identified in around 15% of patients with intractable epilepsy (Spencer et al, 1984). Low-grade gliomas and gangliogliomas constitute the majority of lesions. Dysembryoplastic neuro-epithelial tumour (DNET) is a benign tumour involving the cerebral cortex, which was first recogonised as a cause for epilepsy in 1988 (Daumas-Duport, 1988). They appear as hypodense intracortical lesions on CT scans and on MRI scans have a decreased T1 signal and high T2 signal. Lack of mass effect and lack of surrounding oedema are characteristic features (Stanescu Cosson et al, 2001).

Table 1. Structural brain lesions associated with epilepsy (adapted from Vinters et al, 1993)

Malformative
Cortical dysplasia
Microdysgenesis
Focal cortical dysplasia
Polymicorgyria
Lissencephaly / pachygyria Hemimegalencephaly
Vascular malformations
Arteriovenous malformation
Cavernous haemangioma
Familial and metabolic
With focal lesions, phacomatosis
Tuberous sclerosis
Neurofibromatosis
Encephalotrigeminal angiomatosis, Sturge-Weber disease
With diffuse lesions
Lysosomal enzyme deficiencies
Peroxisomal disorders
Mitochondrial enzyme disorders
Lipofuscinosis
Myelinopathies
Miscellaneous myoclonic epilepsies
Neoplastic
Gliomas Gangliogliomas
Metastatic tumours
Dysembryoplastic neuroepithelial tumour
Others
Cerebrovascular disease and trauma
Ischaemic
Haemorrhagic
Post-traumatic
Inflammatory / Infectious
Infective : Herpes encephalitis
Paraneoplastic: Limbic encephalitis
Autoimmune: Rasmussen's encephalitis
Multiple sclerosis
Cerebral vasculitis
Degenerative
Eg: Alzheimer's disease
Ammon's horn (hippocampal) sclerosis

Table 2. Disorders of cortical development (adapted from Palmini, 2000).

Mechanism	**Histopathologic fingerprints**	**Relevant disorders**
Abnormalities of neuronal and glial proliferation and differentiation	Abnormal cortical architecture Large aberrant dysplastic neurons	Taylor-type focal cortical dysplasia Hemimegalencephaly
Abnormalities of neuroblast migration	Immature neurons at heterotopic sites Neuronal disorientation No dysplastic neurons or balloon cells	Subcortical band heterotopia Lissencephalies Periventricular or nodular heterotopia
Abnormalities of cortical organisation	Abnormal cortical layering Gliosis and neuronal disorientation Microscopic heterotopia No dysplastic neurons or balloon cells	Polymicrogyria Schizencephaly Microdysgenesis

1.4.4. Hippocampal sclerosis

Hippocampal sclerosis (HS) is the most common pathological finding in temporal lobe epilepsy in surgical studies (See part II section 2.4). It is the most common underlying cause for medically refractory temporal lobe epilepsy (Semah et al, 1998; Bocti et al, 2003). HS is characterised by tissue shrinkage, cell loss and reactive gliosis in all hippocampal subfields as well as the entorhinal cortex. This process is triggered by an initial precipitating injury, which is likely to be seizures in infancy (Mathern et al, 2002). Occurrence of prolonged and / of complicated febrile seizures is associated with hippocampal injury and can lead to the development of mesial temporal sclerosis in later life (Lewis et al, 2002a). MRI scanning employing coronal slices perpendicular to the long axis of the hippocampal structures can identify HS. The characteristic features are atrophic hippocampus, increased signal on T2 weighted images and fluid attenuated inversion recovery (FLAIR) sequences and decreased signal on inversion recovery sequences (Kuzniecky et al, 1987; Cascino et al, 1991). HS coexists with a second pathology, most commonly cortical dysplasia, in a high proportion of cases. (Bocti et al, 2003; Mohamed et al, 2001)

1.4.5. Infectious/Inflammatory

Inflammatory disorders affecting the brain often cause epilepsy that is difficult to treat. Encephalitis usually causes neocortical epilepsy; however, both encephalitis and meningitis can result in mesial temporal sclerosis if they occur early in life. The risk of epilepsy is greater in patients with residual neurological deficits (Pomeroy et al, 1990). Infections and infestations are an important aetiological factor in epilepsy in the developing world. Neurocysticercosis is widely prevalent in several countries of Latin America, Asia and sub-Saharan Africa. It is thought to be the most common cause of

acquired epilepsy in many areas, although no studies have examined its relative contribution to all incident cases (Pal et al, 2000). Generally, prognosis for seizure control in neurocysticercosis is good and many patients are able to stop AEDs after successful anti-helminthic treatment (Carpio, 2002). Nevertheless, the preventable nature of cysticercosis offers the opportunity of reducing the disease burden of epilepsy in less developed countries.

1.4.6. Immunologic

Autoimmune mechanisms, both cellular and humoral, have been known to cause seizures. Rasmussen's encephalitis, a rare disorder mainly of childhood, is characterised by intractable partial seizures, unihemispheric inflammation with progressive neurological deficit (McLachlan et al, 1993). It is thought to have an immunological basis. Antibodies directed against the glutamate receptor GluR3 have been identified in some patients with Rasmussen's syndrome but this is not useful for diagnosis. It responds to treatment with intravenous immunoglobulins and other immunomodulants, but some patients require radical surgery for control of seizures. One study had reported increased prevalence of antibodies to GluR3 receptors in patients with partial epilepsy who do not have Rasmussen's encephalitis (Wiendl et al, 2001). Patients with other autoimmune conditions such as SLE are at increased risk of developing epilepsy (Palace and Lang, 2000, Table 3). Higher prevalence of glutamic acid decarboxylase, anticardiolipin and antinuclear antibodies has been reported in patients with epilepsy compared to controls (Eriksson et al, 2001; Verrotti et al, 2003). These have however not been convincingly associated with pharmacoresistance. Studies to date have not demonstrated a major role for immunologic mechanisms in the pathogenesis of pharmacoresistant epilepsy.

Table 3. Summary of the epilepsies with possible immune mediated mechanisms (adapted from Palace and Lang, 2000)

Syndrome	Putative antibody/target	Immunomodulatory treatment response	Epileptogenic effect of antibodies
Rasmussen's encephalitis	GluR3	Corticosteroids, IVIg, PP	+
Landau-Kleffner syndrome	Brain endothelial cells/neuronal nuclear proteins	IVIg	NR
West's syndrome and Lennox-Gastaut syndrome	?	IVIg	NR
Systemic lupus erythematosus	PL, CL, LAC,	Syndrome generally	NR
Stiff man syndrome	GAD	Syndrome generally	NR
Hashimoto's encephalopathy	?	Syndrome generally	NR
General epilepsies	CL, PL, ANA	Positive in one case report	NR
	GM1	IVIg, cytotoxic agents	+
	GluR1	NR	NR
	GAD	+	NR

NR=Not reported; PP=plasmapheresis; ANA=antinuclear antibody; LAC=lupus anticoagulant; CL=cardiolipin; PL=phospholipid.

1.4.7. Drug transporter proteins

Patients with pharmacoresistant epilepsy are by definition unresponsive to all AEDs. This raises the possibility of a common mechanism underlying pharmacoresistance. The removal of AEDs from their intended site of action by multidrug transporter proteins has received much attention in recent years. Multidrug transporters are ATP dependent efflux proteins, which include the P-glycoprotein (PGP) and multidrug resistance-associated protein (MRP) family. PGP is a transmembrane glycoprotein, which is naturally present in many organs (e.g.: - intestine, kidney) as well as the blood brain barrier and blood testis barrier. Its natural function is believed to be absorptive or excretory and/or protection from toxins and xenobiotics (Jette et al, 1995). Many traditional and new AEDs are believed to be substrates for PGP (Loscher and Potschka, 2002). Studies in mice have shown that deletion of the MDR1 gene, which codes for PGP, results in higher brain concentrations of several lipophillic drugs (Schinkel et al, 1996). The MRP family, which at present has seven members (MRP-1 - 7), act as organic anion transporters but can also transport neutral organic drugs. They have overlapping substrate specificity with PGP with several AEDs being substrates for both. Increased expression of MDR1 gene was first identified in surgically resected tissue from patients with refractory partial epilepsy in 1995 (Tishler et al, 1995). Since then, higher MRP1 and MRP2 levels have been demonstrated in brains of patients with refractory epilepsy (Loscher and Potschka, 2002). High levels of expression of PGP and MRP1 have been found in reactive astrocytes (Sisodiya et al, 2002) and neuronal elements (Aronica et al, 2003) of focal cortical dysplasia, DNET and HS compared to histologically normal adjacent tissue. These lesions are common causes for refractory epilepsy and PGP and MRP mediated efflux of AEDs from the site of origin of seizures resulting in inadequate

intraparenchymal concentrations could be one of the mechanisms underlying drug resistance.

1.4.8. Genetics

Several genetic factors modify the pharmacodynamics and pharmacokinetics of AEDs and can influence the response to treatment. Single nucleotide polymorphisms (SNP), which are stable heritable alterations of single nucleotides distributed through the genome, are the genetic markers of choice in pharmacogenomic studies (Part III, Section 1.2). They can occur in the coding regions of genes causing translational changes in the proteins they encode, or regulate gene expression if they occur in promoter regions. SNPs in genes coding for metabolising enzymes of the cytochrome P450 family can alter metabolic activity and affect serum levels and brain concentrations for the substrate AEDs (Ramachandran and Shorvon, 2003; Table 4). In spite of their influence on AED concentrations, SNPs in cytochrome P450 genes have not been shown to be associated with drug resistance in epilepsy. A SNP in the MDR1 gene resulting in increased expression levels of PGP has been reported to be associated with drug resistant epilepsy (Siddiqui et al, 2003). However, this observation has not been replicated (Sills et al, 2005). The contribution of any one gene in determining response to AEDs is likely to be small (see part III, section 1.2). In animal studies, attempts at breeding a population of phenytoin resistant amygdala kindled Wistar rats showed that phenytoin resistance could be inherited, but does not follow simple Mendelian patterns (Ebert and Loscher, 1999). It is likely that a large number of genes interact in complex ways to determine response to any given AED. As technology develops, high density SNP and haplotype maps, higher throughput genotyping technology and more powerful bioinformatics tools should enable greater predictability of response to individual drugs.

Table 4. AEDs and their metabolising enzymes of the cytochrome P450 family (adapted from Ramachandran and Shorvon, 2003).

Cytochrome P-450 subtype	AED substrate
CYP1A2	Carbamazepine Phenytoin
CYP2A6	Carbamazepine Losigamone Sodium Valproate
CYP2B6	Phenytoin Sodium Valproate Mephobarbital
CYP2C18	Phenytoin
CYP2C19	Phenobarbitone and other barbiturates Phenytoin Sodium Valproate Zonisamide
CYP2C8	Carbamazepine Phenytoin Trimethadione
CYP2C9	Phenobarbitone Phenytoin Trimethadione Sodium Valproate
CYP2D6	Carbamazepine Phenytoin
CYP2E1	Felbamate Phenobarbitone Phenytoin Trimethadione Sodium Valproate
CYP3A4	Carbamazepine Clonazepam Ethosuximide Ganaxolone Phenytoin Tiagabine Trimethadione Zonisamide
CYP3A5	Phenytoin Zonisamide
CYP3A7	Phenytoin

1.5. When is epilepsy intractable?

For physicians treating epilepsy, a number of questions need to be answered before a diagnosis of drug resistant epilepsy is made and non-pharmacological treatments considered. How long should one persevere with AED treatment before diagnosing pharmacoresistance? How many regimes should be tried before epilepsy is designated refractory? Should combination treatment be tried early on, and if so, which ones? Are some combinations better than others? This section will discuss some of the issues surrounding these questions.

1.5.1. Duration of treatment

Longitudinal studies of treated epilepsy in children and adults show that the natural history of the disorder can be recogonised early in the course of the disorder (Kwan and Brodie 2000; Arts et al, 1999; Hauser et al, 1996). Patients who are likely to enter remission tend to do so early, generally within the first year or two of starting AED treatment. Similar patterns have been observed in other studies (Hauser, 1992). Response to drug treatment, therefore, is usually obvious in the first two years of starting treatment. Patients who continue to have seizures after this period have a low chance of subsequent remission and should be evaluated in a comprehensive epilepsy programme.

1.5.2. Number of drugs

With the number of AEDs currently available, it is not possible to try all AED combinations before epilepsy is deemed intractable. The issue is the number of treatments the patient has to fail before the chance of success with further pharmacological treatment is sufficiently low to consider the seizure disorder pharmacoresistant. Historical and clinical trial data regarding the efficacy of individual

AEDs in various seizure types can only be a guide to therapeutic decision-making. No drug can be effective in all patients and patients who have not responded to one standard drug might well benefit from alternatives (Camfield et al, 1997; Kwan and Brodie 2001a).

1.5.3. Polytherapy

Since the early 1980s, monotherapy has been considered the gold standard for pharmacotherapy of epilepsy (Reynolds and Shorvon, 1981). Polytherapy was thought to produce higher incidence of toxicity, cognitive side effects and drug interactions without substantial improvement in outcome. This view has changed in recent years because of two factors. The emergence of several new compounds, all initially licensed as adjunctive treatment has moved combination therapy higher up the batting order. Moreover, certain combinations have been shown to be synergistic (Brodie and Yuen, 1997; Pisani et al, 1999) and could succeed where monotherapy with individual drugs have failed. Two randomised studies comparing alternative monotherapy to polytherapy found no differences between the two groups with regard to seizure control and neurotoxicity; however both involved small numbers of patients and were underpowered to detect small differences (Deckers et al, 2001; Beghi et al, 2003). Thus, patients who develop idiosyncratic reactions or have intolerable adverse effects on low doses their first AED should be treated with alternative monotherapy. If patients achieve only suboptimal seizure control at maximal tolerated dose of the first choice AED, a reasonable approach would be to reduce the dose of the first drug and add in a second AED. The first agent could then be withdrawn or the patient continued on combination treatment depending on clinical response and side effects.

Table 5. Proposed mechanisms of action of antiepileptic drugs (adapted from Kwan et al, 2001)

	↓Na^+ channels	↓Ca^{2+} channels	↑K^+ channels	↑Inhibitory transmission	↓Excitatory transmission
Established AEDs					
Phenytoin	+++				
Carbamazepine	+++				
Ethosuximide		+++			
Phenobarbital		+		+++	+
Benzodiazepines				++	+
Valproate	+	+		++	+
New AEDs					
Lamotrigine	+++	+			
Oxcarbazepine	+++	+	+		
Zonisamide	++	++			
Vigabatrin				+++	
Tiagabine				++	
Gabapentin	+	+		++	
Felbamate	++	++		++	++
Topiramate	++	++		++	++
Levetiracetam		+		+	+
Pregabalin		++		+	

+++ - Primary action ++ - Probable action + - Possible action

When combination therapy is used, the selection of individual components should take into consideration pharmacokinetic and pharmacodynamic interactions. Among the older AEDs, phenobarbitone, carbamazepine and phenytoin are powerful inducers of hepatic microsomal enzymes and can augment the elimination of other AEDs. When these drugs are co-administered with valproate, lamotrigine, topiramate, tiagabine or oxcarbazepine, the elimination half-life of the second drug is reduced (Patsalos et al, 2002). Conversely, when the enzyme inducing AED is withdrawn, the serum concentration of the concomitant AED increases. Combinations based on mechanism of action of individual AEDs have been proposed as a rational approach to combining AEDs. The predominant mechanisms of action are known for the older AEDs and mechanisms have been proposed for the newer ones. These are listed in Table 5. Pharmacodynamic interactions can improve the efficacy (e.g.: - valproate with lamotrigine) or cause adverse effects reducing tolerability (e.g.: - carbamazepine with lamotrigine). There is as yet no Class I evidence to prove the superiority of any one combination over others, but studies to date suggest that combinations of AEDs with different mechanisms of action are more likely to produce favourable outcomes (Deckkers et al, 2000). Thus, combining drugs with sodium channel blocking properties with GABA-ergic drugs may be better than the combination of two sodium channel blockers.

1.6. Predicting intractability

There is convincing evidence from epidemiological studies that the early course of epilepsy is predictive of its long-term outcome in the majority of patients. It should therefore be possible to predict the development of intractable epilepsy using information available early in the course of the disorder. Predicting the development of intractable epilepsy at the outset can help target early specialist intervention and optimise patient outcomes. Several studies have addressed this issue

over the years. There is considerable conflict among them in the factors found associated with refractory epilepsy. This is mainly due to the differences in study populations, inclusion and exclusion criteria, and definition of the individual factors. Ideally, studies of prognosis should be population based, prospective and should follow patients up form the same point in the course of their epilepsy (first seizure, start of treatment) to minimise bias (Shorvon 1984). However, such studies require immense resources and few have been carried out. Separate univariate analysis of prognostic factors is simplistic and can give distorted picture of the importance of each factor. Multivariate analysis techniques will allow the relative importance of each factor to be assessed.

1.6.1. Seizure type and epilepsy syndrome

As stated above, seizure types and the underlying epilepsy syndrome probably have the strongest influence on the prognosis of epilepsy. Several studies, especially in adults, have found that patients with localisation related epilepsy are more likely to be drug resistant than those with idiopathic generalised epilepsy (Annegers et al, 1979; Goodridge and Shorvon 1983; Elwes et al, 1984; Mattson et al, 1996; Cockrell et al, 1995; Aikia et al, 1999). Similarly, the presence of mixed seizure types has been found associated with a poor outcome in studies in both adults and children. (Goodridge and Shorvon, 1983; Brorson 1987; Beghi et al, 1988; Arts et al, 1999; Aikia et al, 1999).

1.6.2. Aetiology

Remote symptomatic seizures (those occurring more than a week after cerebral insult) have consistently been associated with a poor outcome in several studies. (Sillanpaa, 1993; Ko et al, 1999; Hauser et al, 1996; Casetta et al, 1999; Aikia et al, 1999; Berg et al, 2001). Perinatal hypoxia or intracranial injury, associated with neonatal seizures can cause epilepsy in later life in

approximately 30% of infants (Watanabe et al, 1980). The relevance of perinatal injury to the prognosis of adult onset epilepsy is doubtful. Moreover, obtaining accurate birth history from adult patients is difficult and is prone to inaccuracies. Studies in patients attending epilepsy centres have found wide variation in response rates amongst patients with symptomatic epilepsy due to various causes (Semah et al, 1998; Stephen et al, 2001). This suggests that the nature of the cerebral insult has a bearing on the prognosis of epilepsy.

1.6.3. Age at onset

Studies in children suggest that onset of epilepsy before the age of 12 months is a poor prognostic factor (Camfield et al, 1993; Ko et al, 1999; Casetta et al, 1999). Some studies in adults have found an association young age at onset with a poor prognosis (Aikia et al, 1999). It is likely that the difference in prognosis with age is a reflection of the epilepsy syndromes that are prevalent in the various age groups. Multivariate analyses of prognostic factors in both children (Berg et al, 2001) and in adults (Elwes et al, 1984, Lindsten et al, 2001) have found no independent correlation of age at onset with prognosis after other factors were accounted for.

1.6.4. Number of pre treatment seizures

Some authors have found high seizure numbers indicative of a poor prognosis in children (Beghi et al, 1988, Arts et al, 1999). Camfield and colleagues observed this effect only in patients suffering more than 20 seizures (Camfield et al, 1993). Studies in the developing world have suggested that good response to treatment could be obtained in patients who have suffered several generalised tonic clonic seizures prior to coming to medical attention (Feksi et al, 1991). Time from onset to starting treatment also has no significant impact on outcomes. However, some studies in adults and children have found a correlation of number of seizures over unit time

(seizure frequency) with prognosis (Elwes et al, 1984; Brorson et al 1987; Casetta et al, 1999; Berg et al, 2001).

1.6.5. Concomitant morbidity (Neurologic, Intellectual, Psychiatric)

Studies in children have found the presence of neurological deficit, especially associated with mental retardation indicative of a poor prognosis (Brorson et al, 1987; Hauser et al, 1996; Arts et al, 1999; Berg et al, 2001). The effect is less pronounced in adults although some studies have reported such an association (Elwes et al, 1984). Psychiatric problems are more frequent in patients with epilepsy, and association with refractory epilepsy has been reported before (Elwes et al, 1984). It is possible that the presence of a psychiatric co-morbidity early in the course of epilepsy points to a greater underlying cerebral dysfunction and is therefore predictive of a poor outcome.

Epilepsy is a multifaceted disorder. Seizures are just one manifestation of an underlying cerebral dysfunction. A high percentage of patients with epilepsy have other neuropsychiatric disorders, especially depression. There is emerging evidence to support a close relationship in the pathogenesis of epilepsy and depression (Kanner and Balabanov, 2002). It is likely that the same or related process is responsible for the coexistence of the two disorders. Similarly, many patients have impaired memory function. Impaired memory performance at the outset has been reported to be predictive of poor outcome (Aikia et al, 1999). There is no evidence to suggest that currently available AEDs modify the underlying processes. The therapeutic effect is merely suppression of the external manifestation, namely seizures and they are perhaps more accurately described as anti-seizure drugs. This being so, one could argue that all epilepsy is in essence refractory, as all that is achieved is control of symptoms (Hauser, 1992).

1.6.6. Febrile seizures

Febrile seizures have an almost uniformly benign prognosis. Epidemiological studies have found no causative association between febrile seizures and epilepsy. However, approximately 3% of patients develop epilepsy in later life (Knudsen, 2000). Complex febrile seizures (i.e. those that are prolonged, focal or recur within the same day), those occurring in children with pre-existing neurological deficit, and family history of epilepsy in a first degree relative all confer a higher risk of developing epilepsy. As discussed above, there is an association between febrile seizures in infancy and the development of HS in later life. However, the effects of seizures on the developing brain remain incompletely understood.

1.6.7. Family history of epilepsy

Studies in children (Berg et al, 2001) and adults (Elwes et al, 1984) have reported association of family history of epilepsy and a poor prognosis. In generalised epilepsy syndromes, this could be explained by genetically mediated mechanisms causing epilepsy, which might also be responsible for determining response to drugs. However, the occurrence of genetically mediated malformations of cortical could influence response to treatment in patients with focal epilepsies (Guerrini and Carrozzo, 2001). The relative contribution of these lesions to intractable epilepsy is unknown (see part II, section 2.4). Many patients, especially in the pre-MRI era, could have had undetected malformations of cortical development, causing intractable seizures.

1.6.8. EEG findings

Some studies, mainly in children, have found correlation of background slowing and focal spike and wave activity with a poor outcome (Ko et al, 1999; Aikia et al, 1999; Berg et al, 2001). EEG performed soon after seizures are more likely to detect such abnormalities, and are likely to have

greater prognostic value. Studies in adults have not found EEG to be independently predictive of outcome after adjusting for other factors (Elwes et al, 1984, Lindsten et al, 2001). Thus, in adults, the prognostic value of routine interictal EEG remains uncertain.

1.6.9. Response to first drug

Several studies have found the response to the first AED to be the strongest predictor of long-term outlook (Sillanpaa 1993; Camfield and Camfield 1996; Kwan and Brodie 2000; Dlugos et al, 2001). Patients whose seizures continue despite adequate doses of an appropriate AED have a significantly lower chance of subsequent seizure remission. Moreover, those who fail the first drug due to lack of efficacy seem to have a worse prognosis compared to those who do not tolerate the initial monotherapy agent (Kwan and Brodie, 2001).

1.7. Conclusions

Epilepsy is the most common serious neurological disorder affecting 0.5 to 1% of the population. Approximately one in three of patients diagnosed with epilepsy will never achieve lasting remission of seizures with currently available AEDs. These patients continue to suffer the physical, psychological and social consequences of intractable seizures and adverse effects from escalating drug burden. They also represent a massive burden on health care resources the world over. While there is a clear need for new AEDs with novel mechanisms of action, there is also a need to target available treatments, especially epilepsy surgery, more effectively. Early identification and prediction of patients likely to be unresponsive to drug therapy will allow earlier specialist intervention. Advances in cerebral imaging and molecular biological techniques have allowed a greater insight into the mechanisms underlying seizure generation and propagation. However, this knowledge is far from complete. The basic mechanisms of drug

resistance in epilepsy also remain largely unclear. Epidemiological data over the years have identified several factors that correlate with a poor prognosis in children and adults, although some of this data is conflicting. Similarly, pharmacogenomic studies employing more sophisticated genotyping and bioinformatics technologies promise greater predictability of response to individual AEDs. More long-term studies are required to assess the prognosis of each epilepsy syndrome.

Studies to date show that the early response to treatment is a powerful predictor of the long-term outlook of newly diagnosed epilepsy. Thus, a patient who does not achieve complete seizure control with the first two to three regimes (including combinations) of AEDs in the first one to two years after starting treatment, is unlikely to achieve complete control of seizures and could be considered to have drug resistant epilepsy. A uniform definition of intractable epilepsy that will fit all patients is, however, elusive. When drug therapy produces only less that complete control of seizures, the decision to pursue non-pharmacological treatments should be made on an individual case basis, taking into account the patients' expectations, social circumstances and likely prognosis of the specific seizure disorder.

2. Assessing the efficacy of antiepileptic drugs

2.1. Introduction

The epilepsies are a group of heterogeneous, multifaceted disorders that have physical, psychological and social implications (Engel, 2001a). Nine new chemical entities have been licensed world wide for the prevention of seizures since the late 1980s (Dichter and Brodie, 1996; Brodie and French, 2000). Nevertheless, only 60-65% of patients achieve remission with currently available antiepileptic drugs (AEDs, Annegers et al, 1979; Cockrell et al, 1995; Mattson et al, 1996; Kwan and Brodie, 2000). There is clearly a need for more new AEDs with novel mechanisms of action (Brodie, 2001). Trials conducted to assess AEDs vary in their design, methodology and end points depending on who wants the information from them. Regulatory authorities look for evidence of efficacy and safety, while patients and doctors seek data on longer-term clinical utility and tolerability. The pharmaceutical companies hope to meet the requirements of all parties. Most trials aimed at demonstrating efficacy to meet regulatory demands do not provide clinicians with the information necessary to make treatment decisions (Haynes et al, 2002).

The setting for regulatory clinical trials is necessarily artificial, the findings from which might not be reproducible in 'real life'. Nevertheless, stringent patient selection based on strict protocols and exclusion criteria are necessary to safeguard patients in these trials and to provide unequivocal evidence of efficacy for regulatory authorities (Moher et al 2001). Once efficacy in controlling seizures and reasonable safety have been demonstrated, a license is obtained, initially as adjunctive treatment and then as monotherapy, and clinicians can start to gain experience with the drug and decide its place in the therapeutic armamentarium. Indications, titration schedules and recommended doses can change and new adverse effects come to light in the post-marketing

period, which may have important implications for the drug's therapeutic usefulness. To adequately evaluate benefits and risks of treatment for chronic diseases, systematic reviews should consider data from observational studies in addition to randomised controlled trials (Elphick et al, 2002).

Observational studies can be useful adjuncts to randomised, controlled trials to see whether the demonstrated efficacy translates into effective treatment in routine clinical practice (Pocock and Elbourne, 2000). The following section will touch on some of pre- and post-licensing efficacy issues that need to be addressed before the value and usage of a drug can be determined with any degree of certainty.

2.2. Regulatory issues

While regulatory authorities require proof of efficacy and safety before a license can be granted, there are differences in what is acceptable in different parts of the world. The requirements for licensing an AED as add-on in patients with refractory epilepsy are largely non-controversial. Placebo-controlled, add-on studies usually include a range of randomised doses for the new AED. 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.

When a monotherapy claim for newly diagnosed epilepsy is requested, the Food and Drug Administration (FDA) in the United States usually insists on two randomised double blind trials showing evidence of superiority of test drug over control as proof of efficacy (Temple, 1982). As many patients with newly diagnosed epilepsy will have their seizures controlled with the first AED chosen (see part II, section 1.3) often at modest or moderate dosage (part II, section 4.3) a

dose response relationship can be difficult to identify in this population (Chadwick, 1998; Privitera et al, 2003).

The European Agency for Evaluation of Medicinal Products (EMEA) recommends trials using established AEDs as controls (active control). Demonstration of 'no difference' between the new drug and established treatment can be accepted as evidence of efficacy. Although no placebo-controlled trials have been carried out using the traditional AEDs, sufficient historical evidence exists to support their efficacy (Chadwick, 2001a). Active control trials can, therefore be considered valid if they reproduce the setting in which the comparator has been shown to be effective and for which it has been licensed by the regulatory authority. One advantage of active control studies is that they allow the new agent to be tested as monotherapy for the population of patients in whom it will later be licensed. The FDA takes the view that "equivalence" between the test drug and active control could be simply due to lack of efficacy of both or because the trial lacked sufficient sensitivity to differentiate between them (Leber, 1989). A number of strategies have been developed to overcome this dilemma, including high dose versus low dose or "pseudoplacebo" in withdrawal to monotherapy designs.

2.3. Adjunctive trials

All new AEDs are initially studied as adjunctive treatment in patients who continue to have seizures despite treatment with one or more AEDs. The use of placebo in this setting is not considered unethical as patients are already on treatment with conventional drugs and are protected from status epilepticus by their baseline medication. They are required to have a defined number of seizures per unit time (e.g. 4 per month) to be eligible for inclusion in a regulatory trial. In the pre-treatment phase, existing therapy remains stable and baseline seizure

frequency is recorded usually over 8 weeks. Modern studies tend to follow a parallel group design. Crossover studies have largely gone "out of fashion" because they are regarded as methodologically less sound. Patients with partial seizures with or without secondary generalisation are recruited initially, since there still is substantial need for effective treatment in this patient population (Semah et al, 1998; Stephen et al 2001). Similar studies in the generalised epilepsies are sometimes undertaken later although these are often slow to recruit (Biton et al, 1999). Efficacy against typical absences or myoclonic jerks can be difficult to demonstrate.

2.3.1. Crossover studies

This design involves patients receiving the drug and placebo randomly in two separate treatment phases separated by a washout period. Vigabatrin (Mumford and Dam, 1989) and lamotrigine (Stephen and Brodie, in press) underwent European regulatory programmes based on randomised, placebo-controlled, crossover studies. This design allows the effects of drug and placebo to be studied within subjects and can be particularly useful early in the development programme (Richens, 2001). There is a fundamental requirement for seizure numbers to remain stable and predictable. Only if seizure frequency returns to baseline when the first treatment is stopped can the second be evaluated under identical conditions. This can be a problem as many patients tend to be recruited during a period of exacerbation of their seizures which may remit over time irrespective of therapy. Furthermore, if there has been a clear beneficial effect during the first period of treatment, there are ethical concerns about switching patients and consent for the second period might not be forthcoming. Carry over effects can also influence results from the second period. In addition, if the response to or toxicity with the test drug is clearly different from that of placebo, blinding can be difficult to maintain. For these reasons, regulatory authorities are unlikely to accept crossover trials as primary proof of efficacy. However, useful

information on dose ranging, pharmacokinetic interactions and side-effect profiling can be obtained using this design (Leach et al, 1997).

2.3.2. Parallel group studies

This is regarded as the design of choice for the regulatory assessment of efficacy of new AEDs as adjunctive therapy in difficult-to-control epilepsy. Patients are randomised to receive one of several doses of drug or matched placebo. Groups are compared for measures of efficacy and tolerability. This design has the advantage that it is suitable for all stages of drug development and a range of dose levels can be included in the same study. The necessity for the seizure disorder to be stable is not vital in this design because the comparison is between rather than within subjects. Dose-response studies need to be carried out with compounds seeking approval as adjunctive therapy and demonstration of a clear-cut dose-response relationship reassures all concerned that efficacy has been demonstrated.

Results from these trials can be complicated by potential pharmacokinetic and pharmacodynamic drug interactions. Some limitations may be placed on the number and types of baseline AEDs to help minimise these problems, but they cannot be wholly eliminated. It can be argued, indeed, that such studies assess the efficacy and tolerability of AED combinations rather than the drug under study. Giving lamotrigine to patients already taking sodium valproate will produce a better response than those established on carbamazepine or phenytoin (Brodie et al, 1995). Indeed, synergism between sodium valproate and lamotrigine has been confirmed in an open, response-conditional, crossover design employing concentration measurement (Pisani et al, 1999). The combination of carbamazepine and lamotrigine, on the other hand, is more likely to produce neurotoxic side-effects due to an adverse pharmacodynamic interaction between the

drugs (Brodie et al, 1995; Pisani et al, 1999; Patsalos et al, 2002). Combination effects may also explain the substantial efficacy of the GABA-ergic AEDs, vigabatrin and tiagabine, as add-on therapy in refractory epilepsy; (Marson et al, 1997; Deckers, 2001) which was less impressive when the drugs were used as monotherapy in newly diagnosed localisation-related epilepsy (Brodie et al, 1997; Chadwick, 1999).

2.4. Monotherapy trials

Evidence of efficacy from add-on studies has to be available before such studies can be contemplated. Most patients with untreated epilepsy can expect to have their seizures controlled with one AED (Kwan and Brodie, 2000). The use of placebo control in patients with newly diagnosed epilepsy can be regarded, therefore, as ethically dubious (Chadwick and Privitera, 1999). For regulatory purposes, the FDA accepts only evidence of superiority over control as proof of efficacy. There are difficulties in designing clinically relevant monotherapy trials that meet their requirements. Randomising patients to placebo alone could be interpreted as being at odds with the Declaration of Helsinki which stated that, "In any medical study all patients - including those in the control group, if any - should be assured of the best proven diagnostic and therapeutic method". A revised version, issued in October 2000, included a new section (section 29) which stated "The benefits, risks, burdens and effectiveness of a new method should be tested against the best current prophylactic, diagnostic and therapeutic methods" (www.wma.net/e/policy/17-c_e.html). If interpreted literally, this would appear to rule out placebo-controlled trials, whenever licensed therapeutic options already exist.

However, judicious use of placebo is sometimes essential to establish the efficacy of new treatments (Lewis et al, 2002). A further "clarification" of this section issued in October 2001

stated that placebo controlled trials may be justifiable even when effective treatments are available if there are compelling and scientifically sound methodological reasons for their use with the caveat that patients subjected to placebo treatment are assured of no serious or long-lasting harm. In the context of epilepsy, this could be interpreted to mean that the use of placebo alone is justified only when genuine doubt exists as to the effectiveness of the treatment being evaluated (e. g. following first unprovoked seizure), or when the risks from further seizures are low (e.g. absence seizures).

In an attempt to avoid the ethical problems of using placebo controls, low doses of the study drug or suboptimal doses of a standard AED have been used as a "pseudoplacebo". The rationale for this has been that while a low dose will protect against catastrophic seizures, it will have little effect on the overall number of partial seizures (Schwabe, 2001). There is, however, no evidence to support this. In addition, it can be argued that the using a drug at a dose intended to be ineffective is equivalent to using a placebo. A number of innovative study designs have been used to satisfy regulatory requirements while maintaining patient safety. These "therapeutic failure" paradigms require the demonstration of worse seizure control in the low dose compared to the high dose group (Pledger, 2001). Even with tightly defined exit criteria, ethical concerns remain with such approaches (Perrucca and Tomson, 1999).

2.4.1. Pre-surgical withdrawal

These studies are carried out in patients who have had their AEDs discontinued as part of seizure localisation investigations prior to possible epilepsy surgery. Patients are randomised to the study drug or placebo control and are monitored until they meet pre-defined exit criteria. These can include a specified number of seizures, worsening of seizure severity, or completion of a period

on treatment. Primary efficacy variables are usually time to exit and the percentage of patients completing the study. This design can be used as "proof of concept" for AED efficacy.

Such protocols tend to last short periods (hours to days) and yield little clinically relevant information. Drugs that exhibit delay in onset of full clinical effect (e.g. sodium valproate) and those that show tolerance (e.g. benzodiazepines) may not be suitable for this design. Once the patient has had sufficient number of seizures for the purpose of localisation and video-monitoring has been discontinued, any further episodes will be for the benefit of the study alone. Modifications have been suggested to address such remaining ethical issues (Bien and Elger, 2001; Binnie, 2001a).

2.4.2. Conversion to monotherapy

Patients with difficult-to-control epilepsy taking AEDs are randomised to receive active drug or control. The original AEDs, usually one or two, are then tapered off in responders who are then maintained, if possible, on the new monotherapy. The use of placebo would be unacceptable in this population of patients and, therefore, suboptimal comparators (low dose of study drug or of another AED) are used instead as controls. The aim is to show that significantly more patients can be maintained on monotherapy with the study drug at high than on low dosage (Gilliam et al, 1998). Exit criteria are defined in terms of number and severity of seizures. This follows clinical practice to a limited extent inasmuch as it seeks to withdraw concomitant AEDs in patients whose seizures are controlled when a new drug is added (Kalviainen, 2001). However, target doses of the study drug are usually fixed and the substitution protocol is often rigid. Maintaining responders on monotherapy for an extended period can yield valuable safety information. These studies have a variable track record in demonstrating efficacy of new AEDs as monotherapy and

ethical concerns surrounding the use of pseudoplacebos remain. A recent proposal under discussion is to drop the low dose comparator and compare the withdrawal rate on high doses of new AEDs with "historical" controls from previous trials.

2.4.3. Active control

These trials are carried out in drug-naïve patients with newly diagnosed epilepsy. The study drug is compared to standard doses of an established AED using a randomised, double-blind design. This approach has the advantage of comparing the new drug head-to-head with standard treatment without the confounding effect of co-medication withdrawal. As the majority of newly diagnosed patients experience seizure remission with the first AED chosen, often at low or moderate dosage, demonstrating superior efficacy will require large numbers of patients followed-up over long periods of time using a flexible dosage design. Demonstrating 'equivalence' is usually accepted as evidence of efficacy by European regulators. These active-control studies aim to show that the study drug is not inferior to the standard AED which has historically been shown to be effective for the seizure type under study. Although the scientific validity of this design have been questioned (Beydoun and Milling, 2001), it would seem to be a logical method of assessing the effectiveness of AEDs drugs as potential first choice treatment in newly diagnosed epilepsy. Furthermore, there are fewer ethical implications in these types of studies, which are largely acceptable to patients and doctors (Karlawish and French, 2001).

Methodological integrity is important in equivalence studies. It is not acceptable to carry out the trial as a comparative study and interpret the lack of statistically significant difference as definite proof of equivalence (Jones et al, 1996). The null hypothesis is that there exists a difference between the treatments (delta – the confidence interval around equivalence). If this is rejected,

the alternative hypothesis, ie that the treatments are equivalent, is accepted. In demonstrating clinical equivalence, the limits of difference with respect to important outcomes such as seizure remission should be decided at the design stage. For AEDs, this is usually taken as 10%. If the study drug is shown to be no more than 10% different form the active comparator, it can be assumed that it is at worst 10% inferior to standard treatment (Chadwick, 2001). Sample sizes need to be large, although optimal numbers can be guaranteed by using a sequential design (Whitehead, 2001). Intention to treat analysis is no longer conservative and per protocol analysis should also be presented (Brodie et al, 2002). European regulators have ruled that delta should be set as far as possible from the placebo zone and that the natural history of the disorder should be taken into account when deciding it (Chadwick, 2001a).

Active control trials have been criticized in the past over choice of doses and titration schedules. If the established comparator is started at a low dose and titrated to moderate dosage in accordance with normal clinical practice, this may be interpreted as introducing bias in favour of the efficacy of the trial drug. If however more aggressive regimes are employed, the tolerability of the new AED can appear exaggerated.

2.5. Clinical end points

All new AEDs are initially evaluated as add-on treatment for patients with seizure disorders not controlled with one or more standard agents. Once adjunctive studies have proven the efficacy of the trial drug, a monotherapy programme can be initiated. Complete seizure control is not regarded as a realistic end point for the majority of patients with refractory epilepsy. Standard end points are manipulations in the number of seizures between the baseline and treatment periods. Seizures can be difficult to count especially if they occur in clusters (French, 2001). Distinguishing between the various types can also be problematic. The non-parametric nature of

the data can make analysis challenging. While seizure frequency can only be decreased by 100%, it can be increased infinitely. Several non-parametric paradigms have been devised to address this problem. The response ratio, for example, allows for normalization of the percent change in seizure frequency which always falls in the range of –100 to + 100 (UK Gabapentin study group, 1990; US Gabapentin study group, 1993).

2.5.1. Changes in seizure frequency

Seizures are counted over a defined period of time, e.g. 1 or 3 months, and the number occurring in patients receiving the test drug is compared with that in controls. When analysed as a continuous variable, seizure frequency is the most sensitive measure of efficacy and should be used whenever possible (Chadwick, 1998). However, skewed distribution can make data handling difficult using standard statistical methods without transformation. Percentage reduction in seizure frequency between baseline and treatment periods, although superficially an attractive alternative, is prone to be unduly influenced by outliers. Analysis using seizure frequencies during baseline and treatment periods (transformed if necessary) as covariates can be regarded as a better option.

2.5.2. Proportion of responders

When patients exhibit seizures within a wide range suggesting non-normal or multimodal distribution, frequency has to be assessed as a dichotomous (binary) variable. Percentage of subjects with 50% (or some other arbitrary figure) reduction in seizure frequency can be compared among groups. One advantage of such an analysis is that it has been used frequently and, therefore, allows comparisons with previous studies using different AEDs (Marson et al, 1996). A minimum of 50% reduction in seizure frequency is the dichotomous cut off point

usually quoted in clinical trials. This is arbitrary, however, and may miss important differences between treatments. Categorisation of seizure frequencies can be used instead of a single cut off point; e.g. 0-19%, 20-39%, 40-59%, >75% reductions etc (Chadwick, 1998). Seizure freedom is not generally quoted as a primary outcome measure, because of the refractoriness of epilepsy in this population and the use of predetermined titration schedules and fixed doses of AEDs. Nevertheless, this observation is probably underused.

2.5.3. Seizure free days

In studying the effect of levetiracetam in patients with refractory epilepsy, French and colleagues (French et al, 2000) reported an analysis of seizure-free days to determine efficacy. This was carried out by evaluation of seizure diaries. In contrast to standard analyses, where the total number of seizures in a set period of time are counted, this approach looks at each day individually to see whether or not a seizure has occurred. Such day by day evaluation can allow seizure patterns and response timings to be addressed. One aim of this approach is to obtain a flavour of the time-to-effect with the test drug compared to placebo control.

2.5.4. Time to n^{th} seizure

Time to first seizure is a commonly quoted end point for monotherapy trials especially in presurgical withdrawal studies. It has been shown that this type of analysis can be applied equally to adjunctive trials with fixed treatment periods (Pledger and Sahlroot 1993). This outcome measure has also been used in active control monotherapy comparisons (Chadwick et al, 1999; Brodie et al, 2002). One potential pitfall in newly diagnosed epilepsy is excluding the possibility that any difference between the new and established agent in time to first seizure was a consequence of differences in titration schedules or maintenance dosing. These values are

usually well known for the older agents, but not necessarily for the new AED at the time of the study. Time to second, third, fourth seizure etc can be more useful endpoints (Brodie et al, 2002).

2.5.5. Seizure severity

Even if a treatment does not abolish seizures completely, reduction in severity can be achieved. Examples are fewer secondary generalised seizures in relation to numbers of complex partial seizures or fewer complex partial compared to simple partial events with awareness retained. Shortening of the post-ictal recovery period could allow patients to return to normal activity sooner following a seizure. Three scales are available to measure the severity of seizures. These are the Veterans Administration Seizure Severity and Frequency Rating Scale (Cramer et al, 1983), the Liverpool Seizure Severity Scale (Baker et al, 1991) and the National Hospital Seizure Severity Scale (formerly known as the Chalfont Seizure Severity Scale; O'Donaghue et al, 1996). Each has its strengths and weaknesses (Cramer, 2001; Cramer and French, 2001). New instruments addressing their shortcomings are in development (Cramer et al, 2002). Seizure severity scales need to be reliable, valid and sensitive. Although the psychometric properties of these scales are well established, there is little evidence to support their clinical utility. Until more data become available, seizure severity scales cannot be recommended as standard outcome measures in evaluating the efficacy of AEDs (Baker et al, 1998).

2.5.6. Electroencephalography (EEG)

Once a drug has demonstrated anti-seizure activity in animal models, the decision whether to proceed with clinical development is a commercial one. Pivotal studies in man require prolonged administration over months in many patients with several types of seizures. This programme

takes years to complete and demands considerable resources. Preliminary evidence of efficacy is valuable to help with decision-making. Surrogate endpoints, such as electroencephalographic changes, can provide indications of potential efficacy. Generally, epileptiform discharges do not correlate with the severity of the seizure disorder (Binnie and Stefan, 1999). Nevertheless, under standard recording conditions meaningful effects of AEDs may be demonstrable in patients with suitably high and stable rates of epileptiform EEG discharges (Milligan et al, 1982). Acute experiments require a rapidly effective formulation of the drug (preferably intravenous) tested under rigorously standardised conditions. The drug is usually compared to both placebo and an active control (e.g. diazepam) employing a crossover design. The primary outcome measure is the spike count per minute or the percentage of the total recording occupied by discharges. Subacute experiments can be carried out over longer time periods (e.g. 24-48 hours) using telemetry or ambulatory EEG monitoring. These reduce problems with spontaneous variation in the rate of epileptiform discharges. This can also be achieved by measuring evoked responses such as the photoparoxysmal response in photosensitive subjects. Reduction in photosensitivity can be demonstrated after a single dose of various AEDs at clinically relevant plasma concentrations (Rowan et al, 1979). However, less than 1% of patients with epilepsy are suitable for such studies and the scarcity of subjects is a major limitation in recruitment (Binnie, 2001b).

Surrogate measures of efficacy using EEG techniques have not been widely used in the development of new AEDs, with the possible exception of lamotrigine, which underwent assessment for interictal spikes (Jawad et al, 1986) and photosensitivity (Binnie et al, 1986). While suppression of epileptiform discharges may encourage further development of the drug, lack of such efficacy should not be grounds for termination of development. The decisive test of efficacy for any AED is whether it prevents seizures and the earlier that this is demonstrated the

better. Attempts to use intensive EEG monitoring to support efficacy claims in absence epilepsy and severe epilepsy syndromes in infants have been tried with variable success (Frank et al, 1999; Sundqvist et al, 1999; Mattia et al, 2000; Stodieck et al, 2001; Gaily et al, 2001).

2.6. Effectiveness

2.6.1. Long term retention studies

The effectiveness of an AED is a function of its efficacy and tolerability. The single most relevant outcome measure that reflect both these factors is the life table that expresses the retention of patients on a particular treatment over a length of time (Mattson, 2001). Treatment with the investigational drug is withdrawn when a predetermined combination of insufficient seizure control and /or poor tolerability is reached. This approach conforms to everyday practice and can provide useful clinical information. Long-term retention on the investigational drug is useful for add on and monotherapy studies and in the post marketing phase. In monotherapy studies, lack of efficacy would result in inadequate seizure control and therefore lead to withdrawal, but in patients with poorly controlled epilepsy undergoing add on trials, a drug with only modest efficacy may be continued long term if adverse effects are mild. This needs to be taken into account while planning and interpreting these studies (Chadwick, 2001a).

Regulatory authorities seek, over and above everything else, evidence of efficacy. Long term retention time alone does not provide this and, hence, life table analysis alone is less suitable for regulatory trials. In addition, if patients are withdrawn from the trial for reasons other than those related to efficacy and tolerability (e.g. inappropriate titration schedule, poor compliance, lost to follow up etc) the results can be misleading. In such circumstances, the analysis can be done

excluding these data (evaluable population) in addition to including all randomized patients (intention to treat, Whitehead 2001).

2.6.2. Measures of efficacy

The main objective of treatment with antiepileptic medication is control of seizures with acceptable tolerability. Therefore, an essential outcome measure is the proportion of patients achieving a predefined period of seizure freedom (Mattson, 2001). Depending on the syndrome and the patient population under study, remission may or may not be a realistic goal. As the majority of newly diagnosed adult patients with epilepsy can expect to have their seizures completely controlled, seizure freedom from initiation of treatment or after titration is a sensitive end-point for this population. This would not be the case if the study population were, for instance, infants with Lennox-Gastaut syndrome.

The proportion of patients with complete control of seizures can be measured at one, two or three years from treatment initiation. This provides the most clinically meaningful data for predicting the long term efficacy of an AED (Chadwick, 1997). Time to achieving one year of seizure-freedom (or some similar end point) focuses directly on the main aim of treatment. It has the advantage that patients, who continue to have seizures for a period after starting on treatment, can also be included (Mattson, 2001). Both the above end points, while lending themselves to statistical and intuitive analyses, can be insensitive. They require complete control of seizures as evidence of efficacy, and discount patients who experience even a single seizure due, for instance, to a lapse in compliance or an intercurrent gastrointestinal infection. Detecting differences in efficacy among patients not fully controlled is possible using seizure rates i.e. number of seizures over a unit time. This can also be used to compare two treatments. If patients

are lost to follow up, this approach becomes less valuable. Although an "intention to treat" analysis addresses this issue, results can still be distorted.

2.6.3. Measures of adverse effects

While no important differences in efficacy have been shown among AEDs in regulatory trials, differences have been seen in tolerability (Mattson et al, 1985; Brodie et al, 1995), which is assessed by the incidence, prevalence, severity and the impact of side effects (Chadwick, 1998). Adverse events include issues relating to tolerability and safety. The most important outcome measure is withdrawal of a drug because of intolerable or life threatening side-effects. Surveillance for organ toxicity is maintained by history, physical examination and laboratory testing. Life threatening idiosyncratic reactions, with the exception of hypersensitivity rash, are extremely rare. Regulatory trials do not involve sufficient number patients to uncover these events. Post-marketing surveillance is more important in detecting these uncommon but potentially serious problems. Major safety concerns with felbamate and vigabatrin were identified in this phase.

Neurotoxic adverse effects such as sedation, dizziness and diplopia tend to resolve with a reduction in dose. This may not be allowable in a fixed dose study and so the patient may drop out and, therefore, not gain efficacy from the drug (Brodie et al, 1997). These and other systemic adverse effects, including gastrointestinal upsets, may also abate with time. The development of tolerance to initial neurotoxicity may allow higher doses to be used at a later date. An end point that records only the incidence of adverse effects will not make this distinction. Patient based scales have been developed to measure the neurotoxic effects of AEDs (Aldenkamp et al, 1995).

Historically, many clinical trials of AEDs have used incidence reporting of adverse events after passive inquiry. This is now recognised as inadequate (Chadwick, 1998). Studies have relied on spontaneous reporting of adverse effects by patients. While having the advantage of highlighting clinically relevant problems, this method is associated with substantial variability in sensitivity and detection. Spontaneous reporting tends to underestimate side-effects, as patients may not make the association between subtle problems and AED therapy. Patients might also not recall transient mild symptoms. Therefore, some form of standardisation in interview and examination has been recommended to supplement spontaneous reporting (Chadwick et al, 1998). Checklists should be used for recording adverse events during randomised trials.

Efficacy and tolerability of an AED cannot be sensibly separated in the setting of a clinical trial. They combine to form effectiveness. If a patient develops a rash or drops out of a study due to neurotoxicity, data from this individual will not contribute to the drug's efficacy. A major difference in tolerability can distort the clinical or scientific relevance of efficacy end-points. Thus, in a recent double-blind trial of carbamazepine versus lamotrigine in the elderly, no differences in efficacy could be demonstrated even though twice as many patients taking lamotrigine remained seizure-free due to its better tolerability and, therefore effectiveness (Brodie et al, 1999).

2.6.4. Dosage

Doses used in regulatory trials are frequently different from those subsequently found to be effective in routine clinical practice. Thus, gabapentin is now prescribed in higher amounts (up to 4800mg daily) than those doses originally studied (900-1800mg daily) and subsequently licensed (up to 2400mg daily) (Sivenius et al 1991; Anhut et al, 1994; Wilson et al, 1998;

McLean et al, 1998; Beran et al, 2001). On the other hand, the titration schedules (50mg weekly) and maintenance doses (200-800mg daily) for topiramate in regulatory studies were more robust than now recommended producing high responder rates but at the expense of numerous adverse events (Faught et al, 1996; Privitera et al, 1996; Sharief et al, 1996; Tassinari et al, 1996; Ben-Menachem et al, 1996; Rosenfeld et al, 1996). Prospective observational studies have shown that good outcomes can be obtained in many patients with substantially lower amounts of topiramate (50-200mg daily) than those used in regulatory trials (Stephen et al, 2000; Kelly et al, 2002). The recommended titration schedule now starts with 25mg topiramate daily with weekly or 2 weekly increments of 25-50mg daily. As the primary aim of a regulatory trial is to demonstrate efficacy, the tendency will be to err on the side of fast titration and higher dosing. Well-designed post-marketing studies can allow clinicians to gauge the optimal titration schedules and effective doses for less severely affected patients taking the drug in everyday clinical practice.

2.6.5. Concentration measurement

Serum levels of AEDs can be used to augment the daily dose in controlled clinical trials. Concentration-defined trials were used in the unsuccessful development of flunarizine (Pledger et al, 1994) and with lamotrigine (Binnie et al, 1989). The basis for this approach is the empirical observation that serum concentrations may correlate better with clinical response than does dose. This could reduce interpatient variability and make the trial statistically more efficient (Pledger, 2001). Drug levels are monitored and controlled in an effort to identify a concentration-effect relationship. Such data were helpful in supporting the license claim for zonisamide as add-on therapy in the US (Leppik et al, 1993). A concentration-response trial has also been carried out with sodium valproate as monotherapy in partial epilepsy (Beydoun et al, 1997). Many of the

newer AEDs, however, do not exhibit clinically relevant concentration-effect-toxicity relationships (Kilpatrick et al, 1996; Wilson et al, 1998; Stephen et al, 2000)

2.6.6. Quality of life

Health related quality of life (HRQOL) measurements have been an area of increasing interest in recent years (Jacoby, 1996). Several generic instruments measuring HRQOL can be used in patients with epilepsy (Baker et al, 1998). In addition, a number of scales specific to epilepsy have been devised. The latter include the Liverpool HRQOL battery (Baker et al, 1993), Epilepsy Surgery Inventory (Vickery et al, 1992) and QOL in Epilepsy (QOLIE) instruments (Devisky et al, 1995). These attempt to quantify emotional, functional and psychosocial wellbeing. They are heavily dependent on seizure freedom, however, and are unlikely to be independent outcome variables in clinical trials of AEDs (Birbeck et al, 2002).

2.7. Observational outcome studies

Epilepsy is a chronic condition. Most patients take AEDs for many years and many receive lifelong treatment. Studies that follow patients up over prolonged periods of years can provide an insight into the natural history of treated epilepsy. These data can help identify patients who are likely to enter remission and those who have a more progressive seizure disorder. These studies require substantial resources and do not usually attract the same level of commercial or grant funding as regulatory or comparative trials. However, they can help identify the best way of utilizing new treatments. The modern AEDs are, not surprisingly, more expensive than the older agents. A recent cost-benefit assessment of lamotrigine has, for instance, suggested that the costs associated with newer AEDs might be unjustifiably high (Messori et al, 1998). The assumptions in this study have been challenged (Bialer et al, 2002), but the fact remains that significant

proportion of health care budgets for epilepsy is taken up by the newer AEDs. There seems little doubt that they have helped patients whose seizures might otherwise have remained uncontrolled. In addition, the use of individual drugs can be of substantial value in specific epilepsy syndromes eg vigabatrin for infantile spasms (Appleton et al, 1999). It would, therefore, make economic sense to invest in studies of sufficient scope and magnitude that could help identify the optimal place and usage of AEDs in clinical practice.

2.7.1. Methodology

The basic requirement for any long-term outcome study is that it follows routine clinical practice as closely as possible. Exclusion criteria should be kept to a minimum. Patients with newly diagnosed epilepsy differ from those with difficult-to-control seizures in terms of expected outcomes, side effect profiles and quality of life issues. These groups should be studied separately. Patient care should not vary from normal except for closer follow up and more objective assessment of efficacy and tolerability. Rating systems should be used for documenting seizures and side-effects, taking into account their number and severity together with objective assessments of behavioural and cognitive status. Individual seizure types or epilepsy syndromes should be studied separately and rigorous standards applied to diagnosis and classification. Pre-defined protocols should be followed in investigating and monitoring patients. Sample sizes required to answer specific questions should be calculated prior to commencement, and anticipated losses due to non-drug related events should be taken into consideration. In newly diagnosed epilepsy, the incentive to continue treatment and attend follow up appointments may not be as persuasive as in patients with refractory seizures.

These studies can be observational where each patient's treatment is deliberately chosen or randomly assigned. Dosing schedules should be flexible tailoring therapy for the individual patient. This allows the therapeutic potential of each AED to be maximised. There is an unavoidable risk of selection bias and differences in outcomes might not always be due to differences in treatment. Adjustments for identifiable variation in patient characteristics at the analysis stage can mitigate this. However, unsophisticated post-marketing surveillance tends to cause more problems than it solves and these studies are best undertaken for safety than efficacy reasons (French, 2002).

2.7.2. End points

In monotherapy studies in newly diagnosed epilepsy, the majority of patients can be expected to enter remission with appropriate therapy. Time to first seizure can, therefore, be a relevant end point assuming appropriate AED titration and dosing. The number of patients who have not suffered a first seizure would represent the number who have remained fully controlled. In longer term studies of outcomes, the proportion of patients remaining free of seizures after one, two and three years of follow up will provide a useful indication of effectiveness. These measures, combined with quality of life issues such as employment, driving etc, reflect the real impact of AED treatment on the lives of people with epilepsy.

As discussed above, the incidence, prevalence and severity of adverse effects are important determinants of the success of AED treatment. Withdrawal of a drug because of adverse effects is a definitive end point in a clinical study. For patients with difficult-to-control epilepsy, drug burden can significantly impair quality of life. In the VA co-operative study a complex approach was used to quantify the efficacy and toxicity of phenytoin, carbamazepine, phenobarbital and

primidone (Mattson et al, 1985). Seizure frequency and severity, neurotoxicity, systemic and behavioural toxicity, and retention time on treatment were the primary variables. These were computed into a single composite score, which allowed relative effectiveness of each of the four drugs to be compared (Cramer et al, 1993).

2.8. Meta-analysis

In the absence of comparative studies, meta-analyses of individual clinical trials can give clinicians an impression of how new drugs might compare in terms of efficacy and side- effects. Meta-analyses of adjunctive clinical trials showed no significant differences in efficacy among the various new AEDs studied (Marson et al, 1996; Marson et al, 1997). These analyses were based on odds ratios, and it has been suggested that number-needed-to-treat might be better suited to demonstrate differences in efficacy (Elferink et al, 1997). This is the number of patients requiring treatment in order to achieve a single occurrence of a specified outcome. This measure has the advantage of being readily interpretable by clinicians, although it does have some undesirable statistical properties (Lesaffre et al, 2000).

In meta-analyses of AED trials, it is not possible to compare newer AEDs with traditional ones, as none of the older agents (with the exception of sodium valproate) has been evaluated as add-on treatment in a controlled clinical trial (Marson et al, 2002). Moreover, as most of these trials were restricted to adjunctive treatment for partial onset seizures, few conclusions can be drawn about the use of these drugs as monotherapy or in the treatment of other seizure types.

2.9. Conclusions

The epilepsies are a range of multifaceted disorders that can affect many aspects of a person's life. No single outcome measure can reflect their complex nature and impact in the individual patient. The aim of drug treatment is the prevention of seizures with no or tolerable side-effects. While this is possible for the majority of patients, there remains a significant proportion in whom ongoing seizures and increasing drug burden exact a heavy toll. Efficacy has to be the first consideration in the development of any new AED. However, trials aimed at demonstrating efficacy to meet regulatory requirements rarely produce data that are helpful to doctors who treat people with epilepsy. The outcome measures in these trials, while admirably suited to demonstrating statistical differences, are of dubious clinical relevance. The real test is how a new AED stands up to scrutiny in clinical practice. Well-designed observational studies can help doctors decide their value. The end points in these studies should include both global outcome measures, such as the life table of retention on treatment, as well as specific measures of efficacy and tolerability. Analyses should explore effects in different seizures types and epilepsy syndromes. Measures of subjective health status can be used as secondary endpoints. A combination of randomised and observational studies will help decide the eventual place of a new AED in the therapeutic armamentarium.

Part II

Clinical outcome studies in newly diagnosed epilepsy

1. Diagnosing refractory epilepsy

1.1. Introduction

Over 30% of people with epilepsy never achieve remission with antiepileptic drug (AED) therapy (Annegers et al, 1979; Cockrell et al, 1995; Mattson et al, 1996; Kwan and Brodie, 2000). These individuals suffer the physical, psychological, and societal consequences of intractable seizures with a heavy drug burden and an increased mortality (Kwan and Brodie, 2000). Refractory epilepsy, in addition, represents a significant drain on health care resources (Devinsky, 1999). Some of these patients could benefit from non-pharmacological treatment modalities, especially epilepsy surgery (Sisodiya, 2000; Engel et al, 2003; Murphy and Patil, 2003; Theodore and Fisher, 2004). Indeed, resective surgery in refractory temporal lobe epilepsy has been shown in a randomised trial to provide substantially better outcomes than continued manipulation of AED therapy (Wiebe et al, 2001). Many patients with remediable syndromes suffer seizures for more than 20 years before coming to surgery (Trevathan and Gilliam, 2003). Defining a situation where the epilepsy is likely to be pharmacoresistant will help identify early those patients who should be referred for further evaluation to an epilepsy service. We analysed outcomes in patients with newly diagnosed epilepsy followed up at a single centre over a 20-year period with the objective of correlating response to sequential drug schedules with prognosis.

1.2. Methods

1.2.1. Study design

We conducted a retrospective analysis of treatment outcomes in all patients diagnosed with epilepsy at the Epilepsy Unit, Western Infirmary in Glasgow over a 20-year period. Patients presenting with suspected seizure disorders were referred to the First Seizure Clinic by general practitioners, accident and emergency physicians and other clinicians. At the initial clinic visit,

detailed history and description of the episodes were obtained from patients and witnesses. A structured protocol was used to collect clinical information. Investigations including electroencephalography and brain imaging were carried out as clinically indicated (Brodie and French, 2000). When a diagnosis of epilepsy was made, patients were prescribed their first AED. Research notes were maintained for each patient in the Epilepsy Unit. Reviews were carried out at 4-6 weekly intervals. Serum anticonvulsant concentrations were measured routinely to guide dosage changes and monitor compliance. Adherence to treatment was assessed by direct questioning and serum concentration measurement.

1.2.2. Classification of seizures and epilepsy syndromes

Seizure types and epilepsy syndromes were classified according to criteria of the International League Against Epilepsy. Seizures were categorised as generalised, partial or unclassified based on history and semiology (Commission 1981, appendix 1). Epilepsy was broadly classified as idiopathic generalised and localisation-related (focal). Localisation-related epilepsies were further categorised into symptomatic and cryptogenic depending on the presence or absence of an underlying neurologic lesion (Commission 1989, appendix 2). Idiopathic epilepsies are presumed to have a genetic basis. Symptomatic partial epilepsies are considered to be the consequence of an identified structural abnormality. Cryptogenic epilepsy is presumed to have an underlying but unidentified focal onset on the basis of seizure semiology and results of investigations. Idiopathic and symptomatic epilepsies were further classed into specific syndromes taking into account clinical, EEG and cerebral imaging data (Engel 2001, appendix 3). Symptomatic and cryptogenic epilepsies were combined as localisation-related (focal) epilepsies for some analyses (Wolf, 1997).

1.2.3. Patients

A total of 890 patients were given a diagnosis of epilepsy and prescribed their first AED between July 1982 and May 2001. None had previously received an AED for any indication. One hundred and ten patients (12%) were excluded from analysis owing to lack of sufficient follow up information. Their demographic and clinical parameters did not differ significantly from those who continued in the study. Alcohol and/or drug abuse were present in 24% of those lost to follow up and in 18% of those continuing in the study ($\chi 2$ 2.13, p=0123). Outcomes were known for the remaining 780 (88%) patients. Of these 405 (52%) were male and 375 (48%) female. The median age at onset of epilepsy was 29 years (range 1 to 93 years) and at diagnosis was 31 years (range 9 to 93 years). Of these 709 (91%) had EEG, 649 (83%) had had brain imaging. CT scans were performed for 508 (65%) and MRI scans in 321 (41%); 180 had had both CT and MRI. Imaging studies were normal in 445 patients, based on radiology reports. Abnormalities were considered relevant if they were thought to be responsible for the patients seizure disorder. Abnormalities on cerebral imaging included gliosis (n=45), atrophy (n=43), tumour (n=25), infarction and ischaeima (n=42), hippocampal sclerosis (n=15), cortical dysplasia (n=15), vascular lesion (n=7), hydrocephalus (shunted) (n=3) porencepahlic cyst (n=2) calcification (n=2), arachnoid cyst(n=2), fat deposit (n=1), fracture (n=1), pineal Cyst(n=1), plagiocephaly (n=1). Cerebral atrophy was mentioned as a feature of patients with a history of cerebrovascular disease (without infarction), alcohol abuse, trauma and degenerative disease, who had partial onset seizures clinically and/or on EEG. EEG examinations were performed on the day of the first clinic visit or within a week, but were often several weeks after the clinical episode leading to the referral.

Overall, 244 patients had symptomatic epilepsy and 314 had cryptogenic epilepsy. Of the remaining 222 many had generalised tonic clonic seizures with no localising features, and only 104 had clinical or EEG evidence of idiopathic generalised epilepsy. However, all of these patients were classified as having idiopathic generalised epilepsy for purposes of deciding choice of treatment, including recruitment into randomised controlled trials and were included as such in this analysis. Patients had suffered a median of 4 seizures (range 1 to >100) before starting treatment. Median duration of follow up was 79 months (range 24 to 252 months). Patients were followed up until 1st May 2003, when all had received treatment for at least 2 years. A total of 93 patients died during the study period (Part IV, section 2).

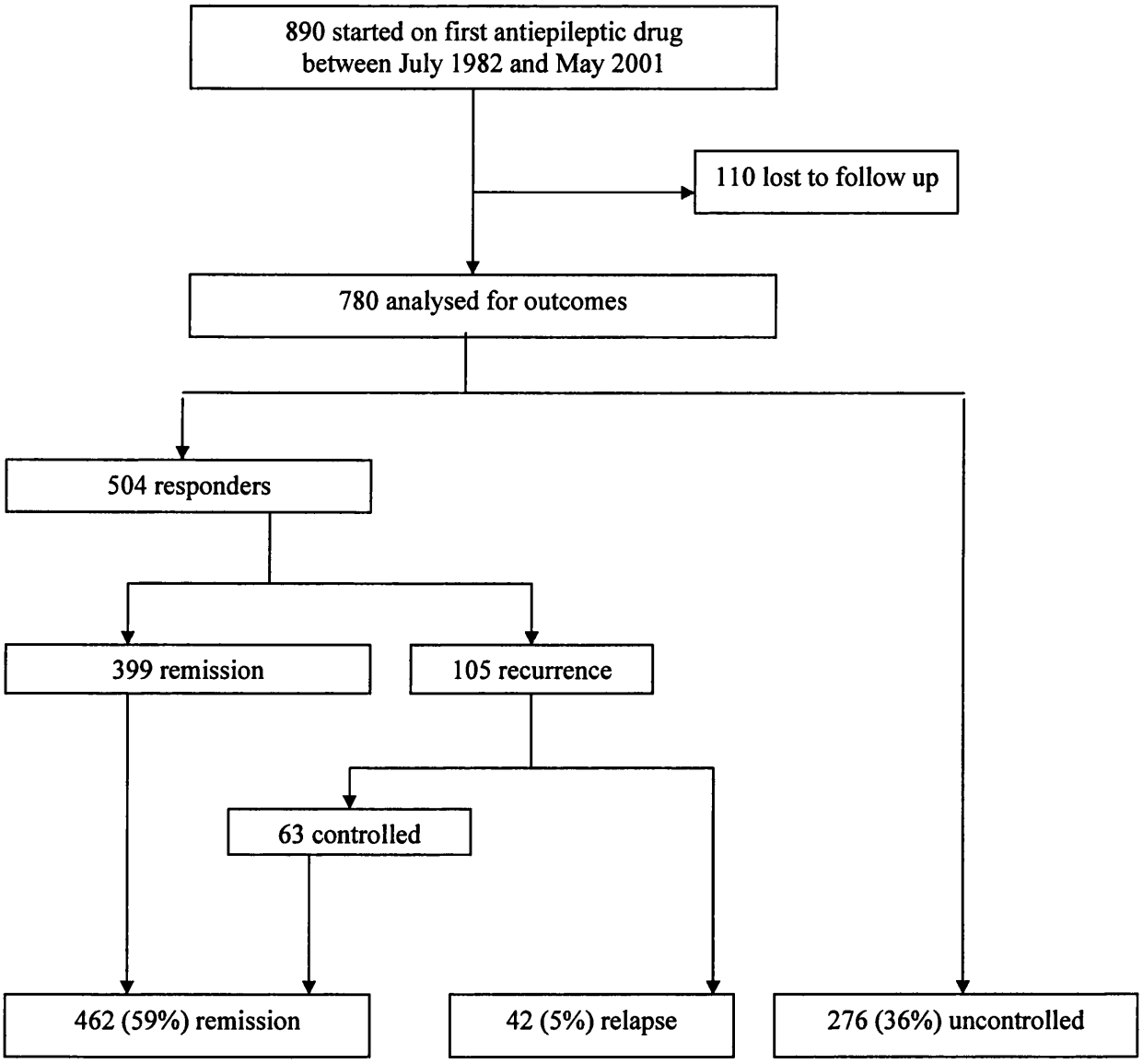
1.2.4. Treatment schedules

Monotherapy was employed initially in all patients. Treatment schedules were modified as necessary based on clinical response and drug tolerability. Patients were asked to maintain seizure diaries to facilitate objective assessment of response. Those developing idiosyncratic reactions, such as rash, or experiencing intolerable side effects, such as sedation, at low AED doses, were deemed to have failed treatment due to adverse effects. Adverse effects were considered significant only if they led to discontinuation of the AED. Patients who continued to experience seizures despite tolerating target doses of medication were designated as treatment failures due to lack of efficacy. Patients not tolerating their first AED were prescribed an alternative. Those failing treatment due to lack of efficacy either had the original drug substituted or were offered combination therapy. Not all patients failing to achieve seizure control for 12 months or more had their AED regime changed. This was because partial response was acceptable for patients if generalised seizures had been abolished and partial seizures were relatively infrequent, and many defaulted from follow up at this stage.

1.2.5. Data collection and analysis

End of follow up was May 2003, when the last patient in the study had been followed up for a period of 2 years. Data were collected by review of case notes and seizure diaries. Classification of epilepsy was reviewed at the time of data collection. The primary end point was the achievement of 12 months seizure freedom. This is the minimum period of seizure control required to regain driving privileges in the United Kingdom, and was, therefore, deemed a clinically relevant and easily measured outcome. Response to treatment was defined as achievement of 12 months' seizure freedom on an unchanged treatment schedule. Remission was defined as having no further seizures after responding to treatment till the end of follow up. Responders who suffered a recurrence of seizures and subsequently remained uncontrolled till the end of follow up were classed as relapse. Those who did not experience any 12-month seizure free periods were categorised as uncontrolled.

Data were collated on an electronic spreadsheet and analysed using Minitab for Windows statistical software (version 13.31). Categorical data were analysed using the χ^2 test and the Bonferroni method was used to correct for multiple comparisons. The Mann-Whitney test was used for analysis of non-parametric continuous data. Life table analysis using the actuarial method was employed to calculate time to achieving remission. The risk of relapse was quantified using Kaplan-Meier analysis. All statistical tests were two tailed.



Definitions:
Responder = seizure free for at least 12 months
Remission = control maintained until the end of follow up
Relapse = refractory epilepsy after initial response to treatment
Uncontrolled = never free of seizures for any 12 months

Figure 2. Outcomes in patients with newly diagnosed epilepsy over a 20-year period

1.3. Results

1.3.1. Response to treatment

Overall, 504 (64.6%) patients became seizure free for at least 12 months, 399 (79%) of whom remained in remission until the end of follow up (Figure 2). The remaining 105 (21%) responders reported further seizures after being free of attacks for 12 months or more. Seizure freedom was regained in 63, in whom the epilepsy remained controlled till the end of follow up. The other 42 initial responders (5.4% of the total population) developed refractory epilepsy and were classed as relapse. The remaining 276 patients (35.4%) never obtained adequate control of seizures for any 12-month period from the outset (uncontrolled). A total of 462 (59.2%) patients, therefore, achieved remission, 5% of whom subsequently had AED therapy withdrawn.

1.3.2. Time to achieving response

The majority of patients who responded to treatment did so early with 54% of responders achieving 12 months seizure freedom within the first 12 months of starting treatment. Overall, 93% of responders had done so within 3 years of initiation of therapy (Figure 3). Remission was achieved in 88% of cases who reported no seizures during the first 3 months of treatment (Table 6).

1.3.3. Immediate responders

Of those entering remission, 245 suffered no further seizures after starting on AED treatment. These immediate responders constituted 53% of all patients entering remission and 31% of the entire cohort. Immediate response is discussed in more detail in section 4.4.3.

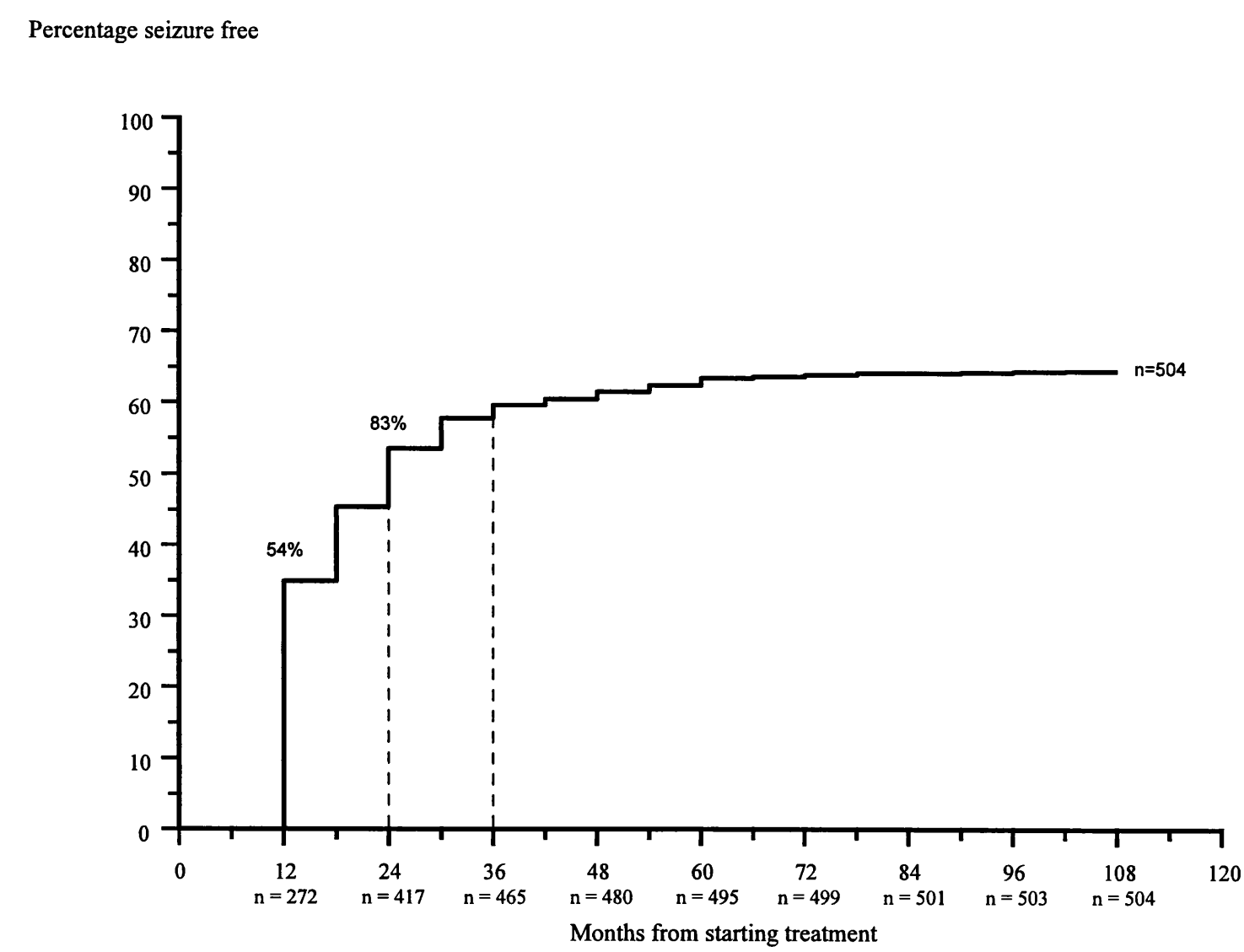


Figure 3. Time to achieving 12 months seizure freedom in 780 patients with newly diagnosed epilepsy

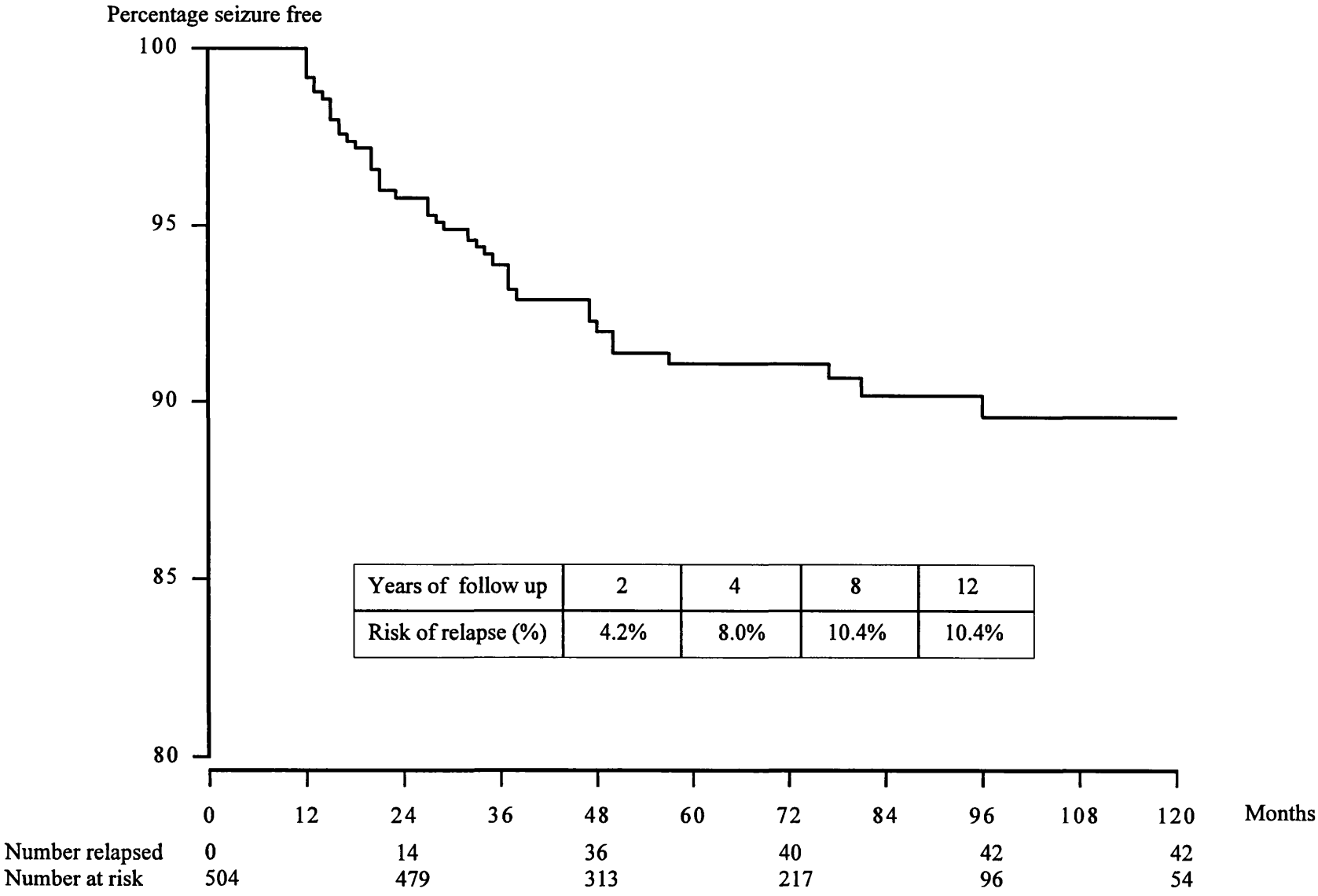


Figure 4. Time to relapse in 504 patients after initial response to AED treatment

1.3.4. Time to relapse

The median time to relapse was 25 months (range 12 to 97 months). Sixty nine percent of relapses occurred within 3 years of achieving initial response. Kaplan Meier plot of time to relapse showed a rate of 4.2% at 2 years rising to a maximum of 10.4% after 8 years of follow up (Figure 4). There were no further relapses after a further median observation period of 38 months (range 0-144).

1.3.5. Treatment leading to remission

Of the 504 patients responding to treatment, 462 (92%) did so on monotherapy usually with the first (n=393) or second (n=57) AED. Only 12 patients became seizure free with subsequent monotherapies. Forty patients responded to duotherapy. Combinations of 3 and 4 drugs produced seizure freedom in just one patient each. Thus, only 8% of responders (5.4 of total population) were controlled on more than one AED. Response rates with the first, second and third treatment regimens were 50%, 32% and 25% respectively. The chance of achieving seizure control was significantly better with the first regime compared to subsequent ones (Table 7).

1.3.6. Outcomes after failing the first AED

Of the 387 patients not responding to the first AED, 305 failed due to lack of efficacy and 82 because of adverse effects. Patients failing initial monotherapy were significantly less likely to enter remission with alternative monotherapy (n=179) or duotherapy (n=81) if the reason for failure was lack of efficacy rather than adverse effects (Table 8). The chance of success with a second monotherapy was lower if the reason for failure with the first was lack of efficacy rather than adverse effects (25% versus 41%, p=0.027). Similarly, patients who failed on the first AED due to lack of

efficacy rather than poor tolerability were more likely to fail a second monotherapy for the same reason (66% versus 48%, p=0.016). No patients failing 2 well-tolerated drugs became seizure free with further monotherapies, whereas 7% achieved control on AED combinations.

1.3.7. Outcomes after failing each AED regime

Remission rates were examined in patients failing sequential schedules to determine the number needed to be tried before pharmacoresistant epilepsy could be diagnosed. Only 8 (7%) of 117 patients failing 2 well-tolerated regimens achieved remission and for those failing 3 this figure fell to 3%. This pattern was observed when idiopathic and localisation-related (focal) epilepsy cohorts were analysed separately (Table 9). When considered as a proportion of the entire cohort, remission rates with the first, second and third regimen were 46%, 10.1% and 2.3% respectively with just 6 (0.8%) entering remission with further attempts at pharmacotherapy.

1.3.8. Factors affecting response to treatment

Patients with idiopathic epilepsies had higher remission rates (66%) than those with cryptogenic (57%, p=0.041) or symptomatic (56%, p=0.035) epilepsies (Figure 5). When analysed by age at starting treatment, a bimodal distribution was apparent (Figure 6), with the greatest likelihood of remission occurring in the youngest and oldest patients (Table 10). Increasing numbers of pre-treatment seizures was significantly associated with uncontrolled epilepsy (p=0.024, Figure 7). However, duration of epilepsy prior to starting treatment had not effect on outcomes (Figure 8). Influence of the various risk factors on the prognosis for achieving remission by logistic regression analysis is shown in Table 11. History of alcohol abuse, head

injury, febrile seizures, family history of epilepsy, presence of psychiatric co-morbidity and multiple seizure types were significantly associated with uncontrolled epilepsy in the univariate analysis. The presence of neurological deficits, learning disabilities, abnormalities on EEG and cerebral imaging had no adverse effect on prognosis in this analysis.

Table 6. Likelihood of remission in patients remaining seizure free for the first 3, 6, 12 and 24 months after starting treatment

	3 Months	6 Months	12 Months	24 Months
Remission	296 (88%)	276 (90%)	257 (92%)	246 (94%)
Uncontrolled	41 (12%)	31 (10%)	23 (8%)	17 (6%)
Total number	337	307	280	263

Table 7. Response to each of the first three regimes in newly diagnosed epilepsy

	First		Second		Third	
Responders	393*	50%	84*	32%	21*	25%
Failure due to adverse effects	82	11%	20	8%	13	15%
Failure due to lack of efficacy	305	39%	156	60%	51	60%
Total	780		260		85	

*Responder rate for first regime is higher than that for second ($p<0.001$, $\chi^2=25.66$) and third ($p<0.001$, $\chi^2=20.25$) regimes, but there is no significant difference between responder rates for second and third regimes

Table 8. Outcomes after failing the first AED, according to the reason for failure

Reason	**Remission**		**Uncontrolled**	
Lack of efficacy	64†	21%	241	79%
Adverse effects	39†	48%	43	52%
All patients	103	27%	284	73%

Prognosis for remission significantly better in patients failing due to adverse effects compared to those failing due to lack of efficacy (48% v/s 21% p <0.001)

Table 9. Likelihood of remission after sequential treatment failures due to lack of efficacy

Type of epilepsy	**n**	**First drug**	**Second regimen**	**Third regimen**
Idiopathic epilepsies	222	21%	4%	0%
Localisation-related epilepsies	558	21%	8%	4%
All epilepsies	780	21%	7%	3%

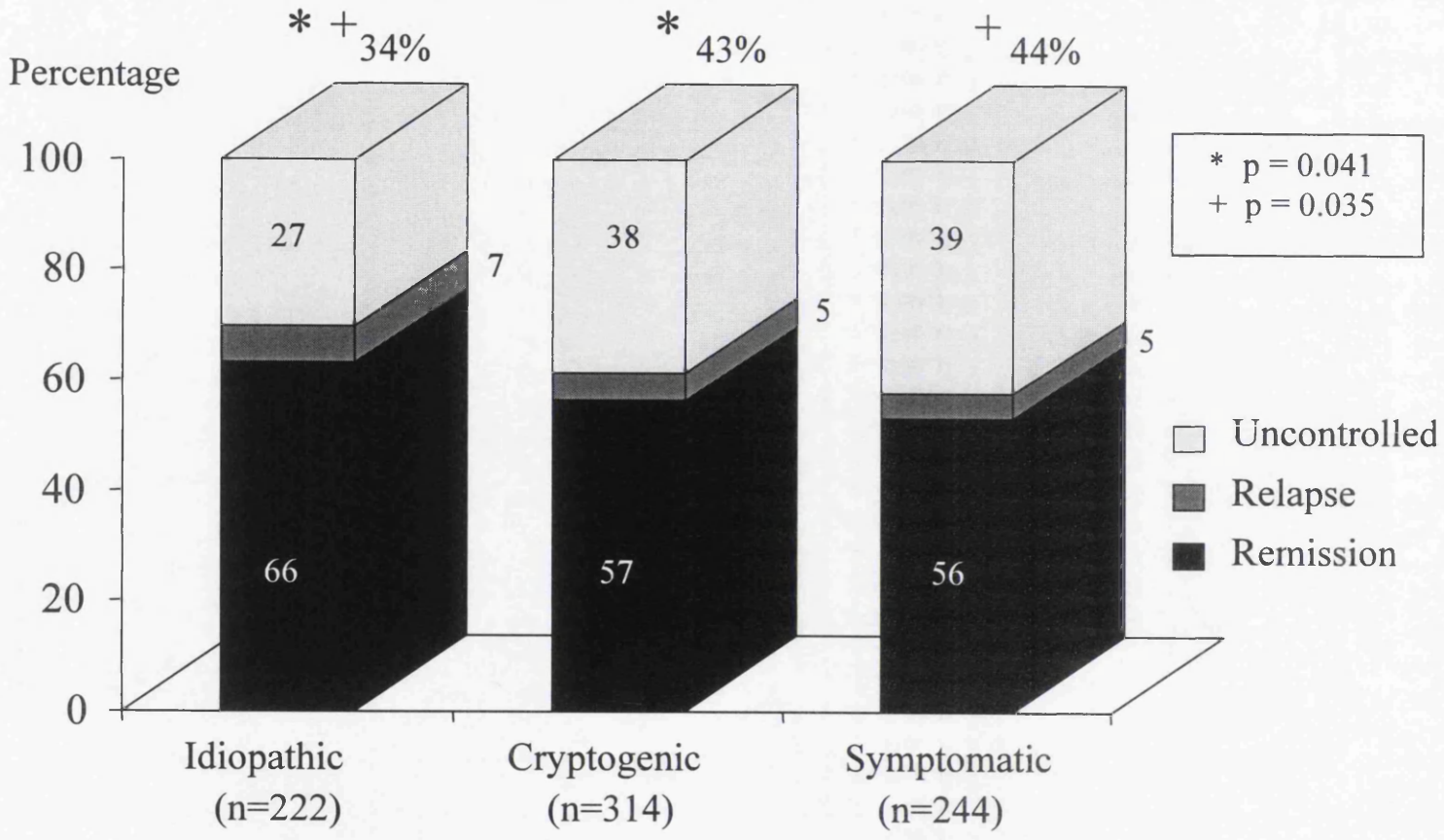


Figure 5. Treatment outcomes by type of epilepsy

Table 10. Treatment outcomes by age at starting treatment

Patient groups	n	Remission		Relapse		Refractory	
Adolescent (<20 years)	170	110	65%	21	12%	39	23%
Adult (20-64 years)	520	276	53%	20	4%	224	43%
Elderly (>64 years)	90	76	85%	1	1%	13	14%

* Adolescent have greater likelihood of entering remission compared to adults (p=0.008)

†Elderly patients more likely to enter remission compared to adolescent and adult (p<0.001)

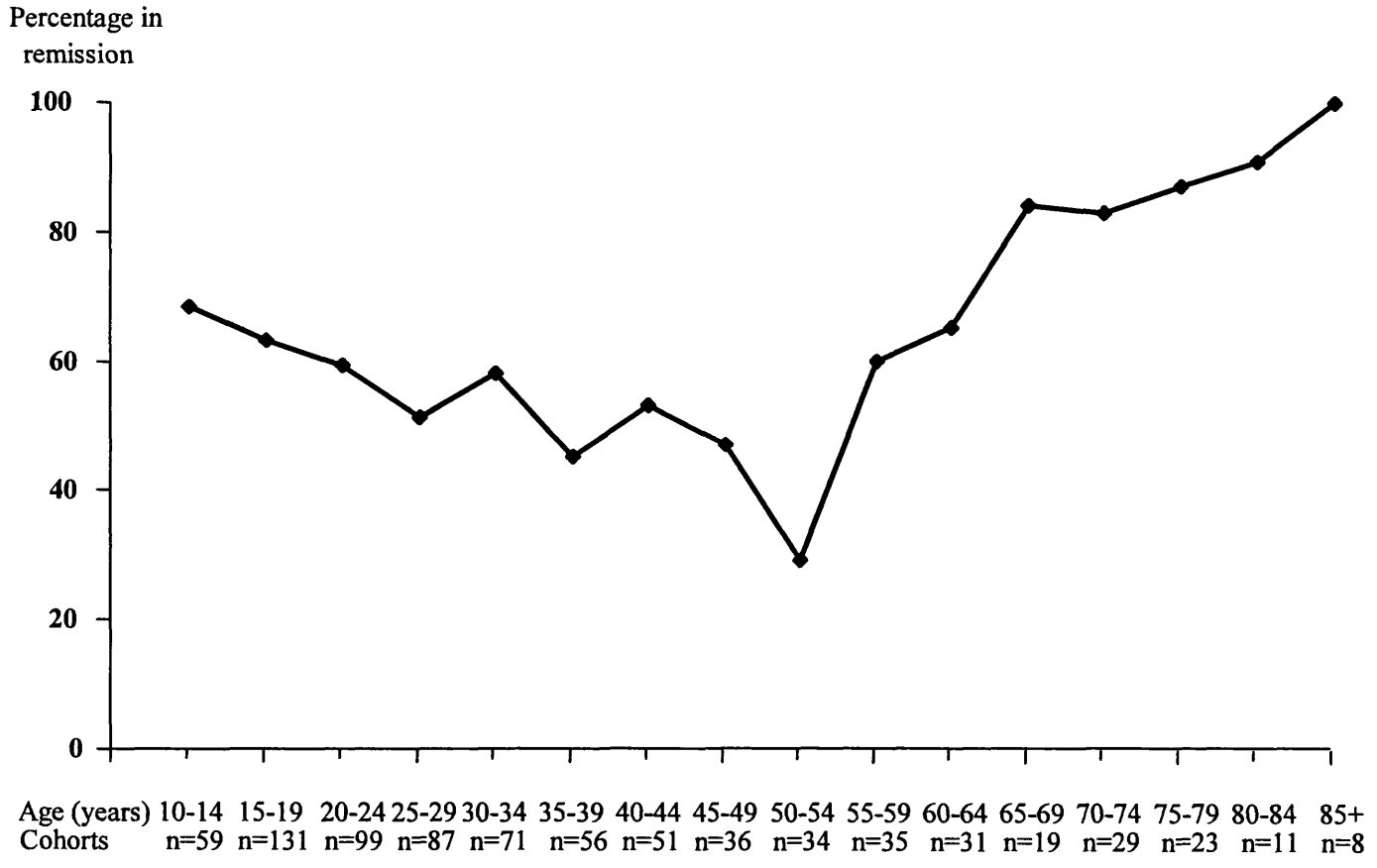


Figure 6. Percentage of patients entering remission in each age category

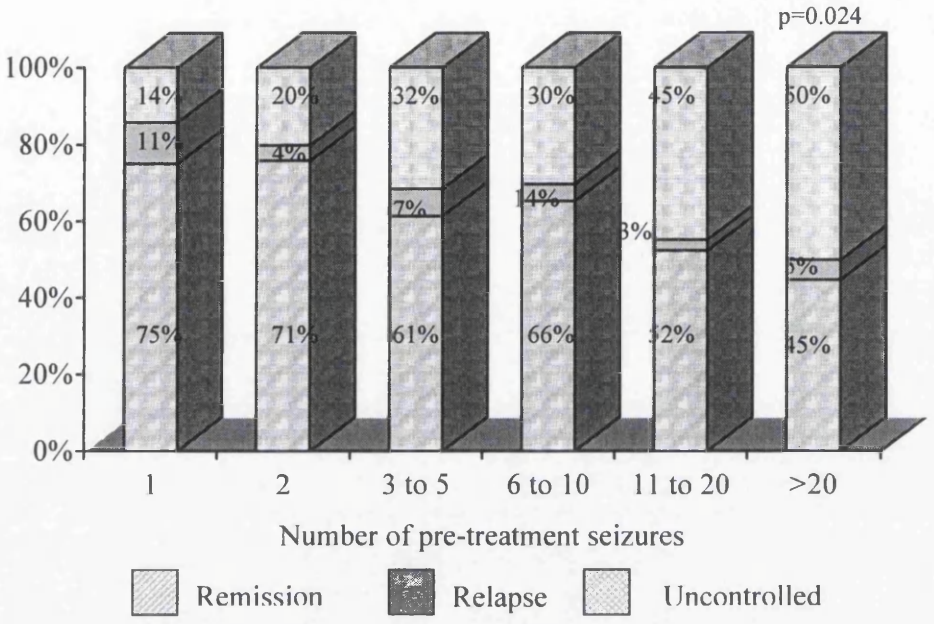


Figure 7. Outcomes in newly diagnosed epilepsy by number of seizures prior to starting treatment

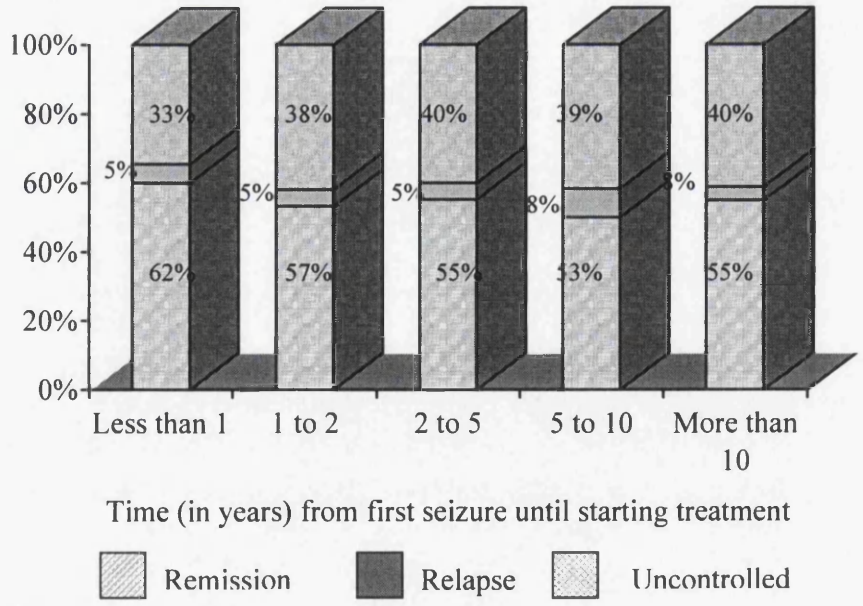


Figure 8. Outcomes in newly diagnosed epilepsy by duration of epilepsy prior to starting treatment

Table 11. Risk factors for uncontrolled epilepsy (univariate analysis).

Risk factor		Patients	Uncontrolled	%	OR (95% CI)	*p* value
Alcohol abuse	Yes	111	79	71%	4.44 (2.86-6.90)	<0.001
	No	669	239	36%		
h/o head injury	Yes	86	56	65%	3.08 (1.93-4.92)	<0.001
	No	680	255	38%		
Psychiatric co-morbidity	Yes	111	63	57%	2.13 (1.42-3.20)	<0.001
	No	669	255	38%		
h/o febrile seizures	Yes	35	23	66%	2.91 (1.42-5.95)	0.003
	No	652	259	40%		
Family h/o epilepsy	Yes	91	51	56%	2.02 (1.30-3.15)	0.002
	No	626	242	39%		
Multiple seizure types	Yes	295	135	46%	1.39 (1.04-1.87)	0.027
	No	485	183	38%		
Sex	Male	405	177	44%	1.29 (0.97-1.72)	0.083
	Female	375	141	38%		
Seizure clustering	Yes	21	759	57%	1.97 (0.82-4.74)	0.128
	No	12	306	40%		
h/o status epilepticus	Yes	27	13	48%	1.36 (0.63-2.94)	0.429
	No	753	305	41%		
Neurologic deficit	Yes	34	15	44%	1.15 (0.58-2.31)	0.685
	No	746	303	41%		
Other medical conditions	Yes	270	112	41%	1.05 (0.78-1.41)	0.768
	No	510	206	40%		
Learning disability	Yes	29	12	41%	1.03 (0.48-2.18)	0.946
	No	751	206	41%		
Imaging abnormality	Yes	203	81	40%	0.94 (0.67-1.31)	0.705
	No	446	185	41%		
Epileptiform EEG	Yes	262	97	37%	0.82 (0.60-1.13)	0.229
	No	447	186	42%		

1.4. Discussion

Most patients with newly diagnosed epilepsy responded rapidly and completely to AED treatment. Indeed, 31.4% of our population never had another seizure after taking the first dose of medication. Of the entire cohort, 56% of patients achieved remission with the first or second AED regimen while 35% of patients never achieved lasting control of seizures. Thus, more than 90% of this patient population either had a good response to their first or second treatment schedule or never achieved control. In the majority of cases, early response to treatment correlates with a good long-term prognosis. Patients who remained seizure free during the first 3 months of treatment achieved remission in 88% of cases, with the figure rising to just 94% after 2 years of seizure freedom. The minority of patients who relapsed following a period of good control largely did so in the first three years. These results suggest that the prognosis of epilepsy is evident within the first few years after starting treatment.

Only 42 patients (5.4%) developed refractory epilepsy after having been seizure free for 12 months or more. The relapse rate peaked at 10.4% after 8 years of follow up. This scenario has been recognised retrospectively in patients with refractory epilepsy undergoing work-up for epilepsy surgery (Berg et al, 2003), but has not previously been documented in newly diagnosed epilepsy. Interestingly, outcomes in the elderly were better than those in younger patients. This observation requires validation, but may be important since old age is now the commonest time in life to develop epilepsy (Stephen et al, 2000). Adolescents also appeared to have a better prognosis, although the relapse rate was highest in this population.

For patients failing initial monotherapy due to adverse effects, the subsequent chance of remission was similar to that in a drug naïve population. Prognosis was less good if treatment failed due to lack of efficacy. Thus, response to first AED is a powerful predictor of prognosis (Sillanpaa et al, 1993; Kwan and Brodie 2001; Dlugos et al 2001). Individuals not responding to 2 or 3 well-tolerated regimens had a greater than 90% or 95% chance respectively of remaining uncontrolled and could, therefore, be considered to have refractory epilepsy. These observations held good for both idiopathic and localisation-related (focal) epilepsies. Therefore, in patients intolerant to their first AED, alternative monotherapy should be tried. In those failing treatment due to lack of efficacy, outcomes with substitution and combination therapy were no different, either in terms of seizure freedom or tolerability. Thus, duotherapy with AEDs possessing different mechanisms of action (Deckers et al, 2000) may be as good a choice as alternative monotherapy in this situation (Kwan and Brodie, 2000; Deckers et al, 2001; Beghi et al, 2003). Indeed, no patient failing 2 well-tolerated AEDs became seizure free with further monotherapy, whereas 7% became seizure free on drug combinations.

A large number of seizures before starting treatment was a poor prognostic indicator, an observation that has been made previously (Collaborative group for the study of epilepsy 1992; Sillanpaa et al, 1993). However, duration of epilepsy was not a significant prognostic factor. In the univariate logistic regression analysis a history of alcohol abuse, head injury, febrile seizures, family history of epilepsy, presence of psychiatric co-morbidity and multiple seizure types were associated with a greater likelihood of uncontrolled epilepsy. The presence of abnormalities on EEG and cerebral imaging did not adversely affect prognosis in this analysis.

All patients diagnosed with epilepsy and started on AED therapy were included in this analysis, irrespective of underlying pathology, occasional lapses in adherence to treatment, and the presence of adverse lifestyle factors such as occasional recreational drug usage or high alcohol consumption. Error of diagnosis is an important reason for failure of AED treatment. No reliable figures were available for patients in whom the diagnosis of epilepsy later proved incorrect in this cohort.

These results, therefore, reflect "real life" outcomes. Clinic based studies are, however, liable to introduce a severity bias, as the patients who are lost to follow up tend to be those who achieve seizure control. In these patients, the incentive to return for clinic appointments is not as high as for those with ongoing seizures. It is possible therefore that the 110 patients lost to follow up had good seizure outcomes compared to the rest of the cohort. The true seizure free rates therefore are possibly higher than what we observed. Moreover, as these patients defaulted from follow up early on in the course of their disorder, remission is likely to have occurred immediately after starting treatment in this group. Thus, the true proportion of patients entering remission in the early years is also likely to be higher.

1.5. Conclusions

The prognosis for the majority of people with newly diagnosed epilepsy, whether good or bad, became apparent within a few years of starting treatment. Several factors such as age at diagnosis, type of epilepsy, seizure density immediately before starting treatment, presence of risk factors such as alcohol abuse, head injury, family history of epilepsy and psychiatric co morbidity showed an association with

uncontrolled epilepsy in this analysis. Their value in predicting the response to treatment in newly diagnosed patients needs to be confirmed in a prospective study. Early response to AED treatment is a powerful predictor of longer-term outcome. The elderly, and to a lesser extent teenagers, are more likely to respond to treatment than the remainder of the population. Approximately 5% of patients can be expected to relapse after initially responding to treatment and remain uncontrolled subsequently. Patients who do not attain seizure freedom with the first 2 or 3 well-tolerated schedules are unlikely ever to have a useful period of remission and could be diagnosed with refractory epilepsy. These patients should be referred to an epilepsy service for further evaluation including videotelemetry for diagnostic and classification purposes, optimisation of pharmacotherapy, and consideration of other therapeutic modalities, particularly epilepsy surgery.

2. Response to treatment in newly diagnosed localisation related epilepsies

2.1. Introduction

The temporal aspects of the natural history of seizure disorders should be taken into consideration in any study of outcome. The key to accurate assessment of prognosis is recruitment of patients at the same point in the course of the disorder (Shorvon, 1984). Specialist epilepsy clinics have a higher representation of patients with refractory epilepsy and cross sectional studies in such populations invariably report very low rates of seizure freedom. This factor accounts for the poor prognosis of epilepsy in much of the early literature (Gowers, 1881; Rodin, 1968). Longitudinal, population based studies in patients with new onset epilepsy provide a more reliable assessment of response to treatment (Cockerell et al, 1995; Sillanpaa et al, 1998; Kwan and Brodie, 2000; Berg et al, 2001).

With the widespread use of high resolution brain magnetic resonance imaging it has been possible to identify an underlying structural abnormality in many patients with localisation related epilepsy (Kuzneicky and Knowlton, 2002). Our understanding of the prognosis of these symptomatic epilepsies, nonetheless, is largely based on studies carried out in specialist centres. Thus, it is widely believed that certain types of symptomatic epilepsies, such as those associated with hippocampal atrophy and malformations of cortical development, frequently encountered in these clinic populations, respond poorly to pharmacological treatment (Semah et al, 1998; Kim et al 1999, Stephen et al, 2001). However, in most parts of the world epilepsy is treated at its onset by non-specialists. Patients who respond to antiepileptic drugs (AED) treatment may not undergo brain imaging. It is only when they prove refractory to pharmacotherapy that referral to a specialist centre is made and subtle underlying

structural abnormalities are identified. Populations of patients with newly diagnosed epilepsy are, therefore, required to assess accurately the response to antiepileptic drugs (AED) treatment in symptomatic epilepsy syndromes. We carried out an outcome study in patients with localization-related epilepsies diagnosed, treated and followed up at a single centre over a 20 year period.

2.2. Methods

Methods have been described in detail in Part II section 1.2. Data regarding treatment outcomes were collected from a series of 890 patients with newly diagnosed epilepsy by review of case notes. Classification of epilepsy was reviewed at the time of data collection based on all clinical, EEG and cerebral imaging investigations data available. Response to treatment was defined as complete seizure control for 12 months or more. Patients remaining seizure free till the end of follow up were considered to be in remission. Patients showing initial response to treatment before experiencing seizure recurrence and were subsequently uncontrolled were categorised as relapse. The χ^2 test was used to analyse categorical data and the Bonferroni method was used to correct for multiple comparisons. Logistic regression analysis was used to analyse the association of various risk factors with uncontrolled epilepsy. All statistical tests were 2 tailed. Analyses were carried out using Minitab for windows statistical software (version 13.21).

2.3. Results

2.3.1. Patient demographics

Of the total of 890 patients diagnosed with epilepsy and started on AED treatment, 625 (70%) patients were categorised as having localisation-related epilepsy.

Idiopathic generalised epilepsy could be diagnosed in 128 (15%) and in the remaining 137 (15%) patients epilepsy could not be classified. This group included patients who suffered GTCS with no localising features and had normal EEG and cerebral imaging investigations, who nevertheless responded rapidly to treatment and therefore were not investigated further. This group was included along with the idiopathic generalised epilepsies in the preceding analysis for reasons discussed in section 1.2.3., but were left out of analysis of outcomes in specific syndromes. In the cohort of patients with localisation related epilepsy, 67 (11%) were lost to follow up and treatment outcomes were known for 558 (89%) patients. This cohort comprised 296 (53%) males and 262 (47%) females. The median age at onset (first seizure) was 33 years (range 1 to 93 years) and that at diagnosis was 35 years (range 11 to 93 years). Patients reported a median of 5 (range 1 to >100) seizures before stating treatment. Of these 558 patients, 244 (44%) had a structural lesion identified on brain imaging and were classified as having symptomatic epilepsy. Post traumatic epilepsy was diagnosed in patients with localisation related epilepsy with onset after head trauma of at least moderate severity, with or without structural brain changes on imaging studies. The remaining 303 (54%) were designated as having cryptogenic epilepsy. Breakdown of the various underlying pathologies in patients with symptomatic epilepsy is shown in Figure 9. Of the remaining 11 (2%) with idiopathic localisation-related epilepsy, 6 patients had Benign Epilepsy with Centrotemporal Spikes, 4 had Benign Occipital Epilepsy, and 1 Benign Partial Epilepsy of Childhood.

2.3.2. Overall outcomes

Of the 558 patients started on AEDs, 343 (62%) responded to treatment by becoming seizure free for a period of 12 months or more (Table 12). Of the responders, 39

(11%) had a recurrence of seizures of which 27 never regained complete control. These patients constituted 5% of the entire cohort (8% of responders) and were categorised as relapse. Seizures remained well controlled until the end of follow up in a total of 316 (57%) patients who were classified as remission. The remaining 215 (38%) did not achieve seizure freedom for any 12-month period and were categorised as uncontrolled. No significant differences were observed in outcomes when cryptogenic and symptomatic epilepsies were analysed separately (Table 12).

2.3.3. Treatment leading to response

Monotherapy was successful in 315 (92%) of the 343 responders. Of these 264 (77%) were on their first ever AED. In patients failing the initial AED, a second regime was successful in 59 (17%) of patients, 42 of which were alternative monotherapy. Combination treatment with two AEDs was successful in 26 (8%) patients only. Carbamazepine (n=265), sodium valproate (n=200) and lamotrigine (n=175) were the most commonly used monotherapy agents. Successful monotherapy could be achieved with modest doses in most cases. The median daily doses in responders were: Carbamazepine 400mg/day (n=114), Lamotrigine 150 mg/day (n=93) and Valproate 1000mg/day (n=72).

2.3.4. Outcomes in individual syndromes

Outcomes in the various epilepsy syndromes are listed in Table 13. Patients with mesial temporal lobe epilepsy (MTLE) with hippocampal atrophy (HA) (50% remission) and those with malformations of cortical development (MCD) (60% remission) did not fare significantly worse than those with other types of symptomatic epilepsy. A number of patients responded immediately to treatment and suffered no

further seizures after starting on AED treatment. These immediate responders constituted between 20 and 40% of all patients with each specific epilepsy syndrome (Table 13). Interestingly, even patients with MTLE with HA and MCD responded mmediately to treatment in 21% and 33% of cases respectively. The clinical characteristics of patients with newly diagnosed epilepsy and underlying hippocampal sclerosis or cortical dysplasia are shown in Tables 15 and 16. The probability of achieving immediate response to treatment was highest for patients with epilepsy due to cerebrovascular disease (40%) or cerebral atrophy (40%). These patients also had the best prognosis for remission overall.

2.3.5. Risk of refractory epilepsy

Patients failing two appropriate well-tolerated AED regimes remained uncontrolled in over 90% of cases and these patients could be diagnosed with drug resistant epilepsy (Part II, section 1.2.7). We examined the risk of failing two AED regimes due to lack of efficacy in patients with various localisation related epilepsy syndromes in the present cohort of newly diagnosed patients. Patients with MTLE and HS, MCD, cerebral tumours and post traumatic epilepsy had the highest relative risk for failing two well tolerated regimes compared to other causes of LRE (Table 14). These differences, however, did not reach statistical significance.

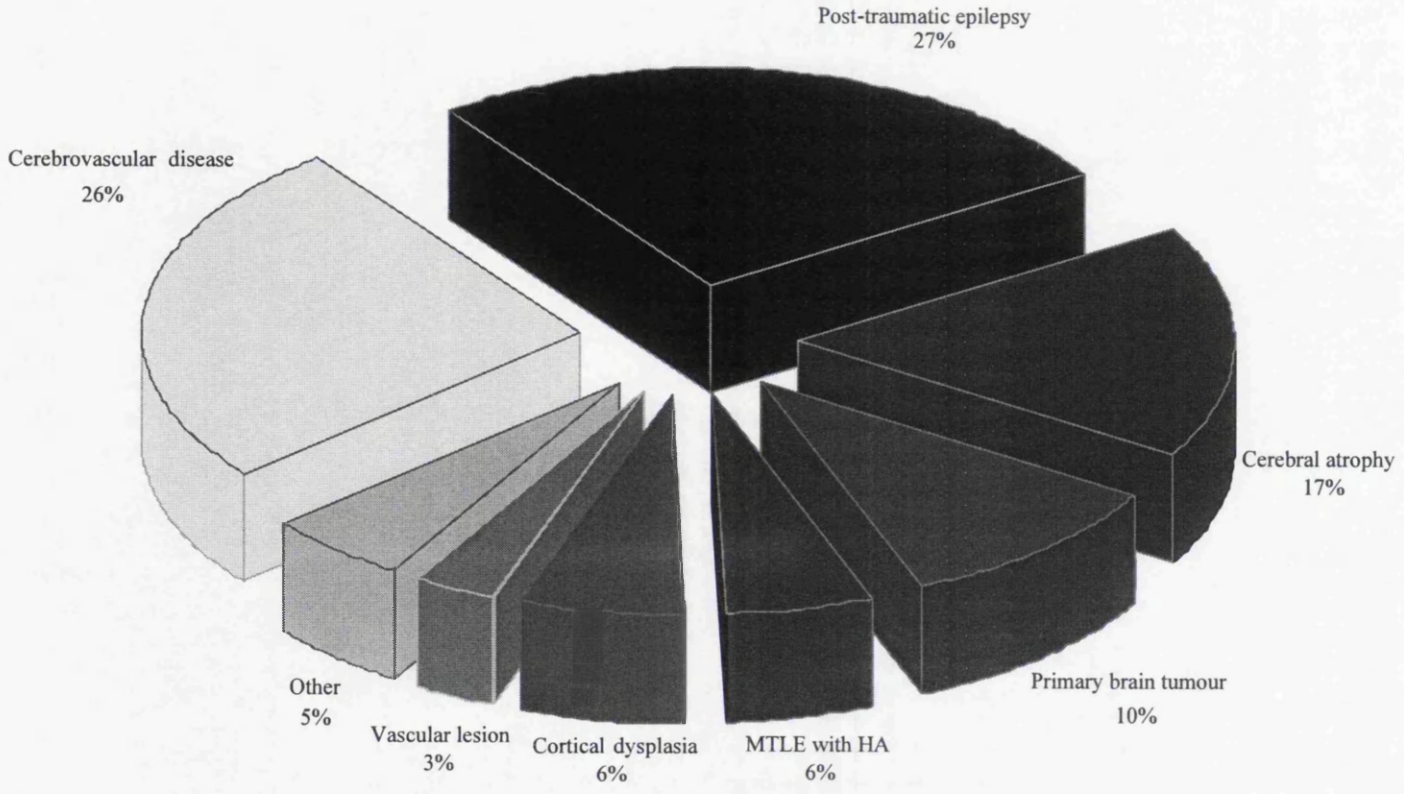


Figure 9. Underlying aetiology in 244 patients with symptomatic epilepsy

Table 12. Treatment outcomes in localisation related epilepsy syndromes

	All localisation related epilepsies		**Cryptogenic epilepsies ***		**Symptomatic epilepsies**	
Remission	316	57%	179	57%	137	56%
Relapse	27	5%	16	5%	11	5%
Uncontrolled	215	38%	119	38%	96	39%
Total	558	100%	314	100%	244	100%

* Idiopathic localisation-related epilepsies were included with cryptogenic group for analysis of outcomes

Table 13. Remission rates and immediate responders* in each epilepsy syndrome

	Total	Remission		Immediate responders*	
Idiopathic					
Benign epilepsy with centrotemporal spikes	6	5	(83%)	4	(67%)
Benign occipital epilepsy	4	3	(75%)	0	(0%)
Benign partial epilepsy of childhood	1	1	(100%)	0	(0%)
Symptomatic					
MTLE with HA	14	7	(50%)	3	(21%)
Cerebrovascular disease	63	44	(70%)	25	(40%)
Cerebral atrophy	42	30	(71%)	17	(40%)
Post-traumatic epilepsy	65	23	(35%)	13	(20%)
Primary brain tumours	25	13	(52%)	5	(20%)
Cortical malformations	15	9	(60%)	5	(33%)
Vascular lesion	7	4	(57%)	2	(29%)
Other lesions	13	7	(54%)	5	(38%)

* Immediate responders never had another seizure after starting on treatment

MTLE with HA = mesial temporal lobe epilepsy with hippocampal atrophy

Table 14. Risk of refractory epilepsy in patients with newly diagnosed localisation related epilepsy

Epilepsy syndrome	**Number failing two well tolerated AED regimes**	**Number in whole cohort**	**Relative risk (95% CI)**
Cryptogenic	46	303	1.01(0.72-1.43)
Post-traumatic	15	65	1.61(1.00-2.61)
Cerebrovascular disease	8	63	0.83 (0.42-1.63)
Tumour related	7	25	1.92 (1.00-3.68)
Cerebral atrophy	5	42	0.78 (0.33-1.81)
MTLE with hippocampal atrophy	4	14	1.93 (0.83-4.51)
Malformations of cortical development	4	15	1.8 (0.76-4.25)
Other lesional epilepsies	3	15	1.34 (0.48-3.74)

Table 15. Clinical characteristics of patients with newly diagnosed mesial temporal lobe epilepsy and hippocampal atrophy

	Sex	Age at first seizure (years)	Age at starting treatment (years)	Number of pretreatment seizures	Seizure types	Side	Treatment outcome	Successful therapy	Time to remission (months)	Duration of remission (months)
1	Male	59	59	15	GTCS	Right	Remission	Monotherapy	32	238
2	Female	6	50	12	GTCS	Left	Refractory			
3	Female	34	34	>100	SPS/GTCS	Right	Refractory			
4	Male	45	50	>100	GTCS	Right	Relapse	Monotherapy	12	137
5	Male	54	56	30	CPS	Right	Remission*	Monotherapy	6	52
6	Male	27	27	2	SPS/GTCS	Left	Refractory			
7	Female	30	30	3	CPS	Left	Remission*	Monotherapy	12	88
8	Male	37	38	35	CPS	Right	Refractory			
9	Male	29	30	2	GTCS	Left	Remission*	Monotherapy	9	78
10	Male	10	16	>100	CPS/GTCS	Left	Refractory			
11	Female	21	21	28	SPS/GTCS	Right	Remission	Monotherapy	27	32
12	Male	57	58	36	CPS/GTCS	Right	Remission	Monotherapy	17	36
13	Female	17	18	6	GTCS	Right	Remission	Duotherapy	27	25
14	Male	20	20	2	CPS/GTCS	Left	Refractory			

*Patients suffering no further seizures after starting treatment

SPS - Simple partial seizure CPS - Complex partial seizure GTCS – Generalised tonic clonic seizure

Table 16. Clinical characteristics of patients with newly diagnosed localisation related epilepsy and malformations of cortical development

	Sex	Age at first seizure (years)	Age at starting treatment (years)	No of pre-treatment seizures	Seizure types	Brain imaging	Treatment outcome	Successful therapy	Time to remission (months)	Duration of remission (months)
1	Male	14	15	8	GTCS	Left parieto-temporal heterotopia	Remission	Monotherapy	15	229
2	Female	27	28	28	SPS/GTCS	Multiple tubers	Refractory			
3	Female	51	51	1	SPS/GTCS	Left temporal hippocampal atrophy with cortical dysplasia	Remission*	Monotherapy	12	72
4	Male	19	20	12	GTCS	Left temporal cortical dysplasia	Remission	Monotherapy	16	68
5	Female	33	33	15	SPS/GTCS	Right temporal cortical dysplasia	Refractory			
6	Male	22	23	6	GTCS	Bilateral occipital band heterotopia	Remission*	Monotherapy	12	78
7	Male	21	22	2	SPS/GTCS	Left frontal cortical dysplasia	Refractory			
8	Male	15	15	3	GTCS	Right frontal cortical dysplasia	Remission*	Monotherapy	12	72
9	Male	17	17	4	SPS/GTCS	Right temporal cortical dysplasia	Refractory			
10	Female	14	17	3	CPS/GTCS	Left fronto-parietal cortical dysplasia	Remission*	Monotherapy	11	82
11	Male	16	16	7	GTCS	Right frontal cortical dysplasia	Relapse	Monotherapy	16	29
12	Male	14	14	5	SPS/GTCS	Lissencephaly, developmental 5^{th} and 6^{th} ventricle	Remission	Duotherapy	37	27
13	Male	15	16	4	GTCS	Left occipital heterotopia	Remission	Monotherapy	20	42
14	Male	36	36	2	GTCS	Left occipital heterotopia	Remission*	Monotherapy	12	37
15	Male	1	22	>100	CPS	Bilateral periventricular nodular heterotopia	Refractory			

* Patients suffering no further seizures after starting treatment

SPS - Simple partial seizure CPS - Complex partial seizure GTCS – Generalised tonic clonic seizure

2.4. Discussion

In our study population, 62% of patients started on AED responded to treatment by becoming seizure free for 12 months or more. This early response was maintained in 92% of responders who remained in remission till the end of follow up. 38% never achieved complete seizure control for any 12-month period. Response to treatment was achieved with standard AEDs used as monotherapy in the majority of cases. A number of patients with LRE showed immediate and complete response to AED therapy and suffered no further seizures since starting on treatment. The probability of immediate treatment response was highest for patients with cerebrovascular disease or cerebral atrophy, and lowest for patients with post-traumatic epilepsy. Patients with MTLE and HA, cerebral tumours, MCD and post traumatic epilepsy showed a higher tendency to develop refractory epilepsy, defined as failure of two well tolerated AED regimes. Thus, we observed two major categories of patients, those who responded to moderate doses of standard AED monotherapy (immediate responders) and those who did not achieve seizure control in spite of several alterations in therapy (refractory epilepsy). By contrast, patients who achieved seizure control with high dose monotherapy or combination of AEDs were relatively few. This suggests that the majority of patients diagnosed with epilepsy would be either easy to treat or unlikely ever to gain complete seizure control. Interestingly, both these groups were distributed across the various seizure syndromes although certain syndromes appeared to be more likely to be pharmacoresistant than others.

Temporal lobe epilepsy is the most common epilepsy syndrome (Engel et al, 1998) and hippocampal sclerosis occurs in 50-70% of patients with refractory temporal lobe epilepsy (Babb et al, 1987). The incidence of refractory epilepsy in all subjects with

HS, however, is unknown. Hospital based case series have reported remission rates ranging from 11% to 42% with AED treatment in patients with MTLE and HS (Semah et al, 1998; Kim et al, 1999; Kobayashi et al, 2001; Stephen et al, 2001; Kumlien et al, 2002). Recent studies employing hippocampal volumetry have identified HA in MTLE patients with good seizure control (Andrade Valenca et al, 2003; Kobayashi et al, 2003). MR evidence of HS has also been observed in patients without clinical or EEG evidence of MTLE (Kobayashi et al, 2002; Benbadis et al, 2002). Thus the relationship of HS with refractory epilepsy, and indeed seizures themselves, is far from clear. The majority of patients who undergo surgical treatment for MTLE with HS develop the seizure disorder in adolescence and typically have periods of remission before becoming refractory to treatment. In the present study, the age of onset of epilepsy is significantly higher and therefore these patients could not be said to be typical of those with MTLE and refractory epilepsy. However, our data suggests that the presence of HS does not necessarily predict poor outcomes in newly diagnosed epilepsy.

Similar to HS, MCD have been increasingly recognised as the underlying cause for localisation related seizures with the widespread use of high quality MR imaging in patients with epilepsy (Sisodiya 2004). In recent years, there has been a greater understanding of their genetic bases, clinical presentations and the mechanisms involved in epileptogenesis (Guerrini and Carrozzo, 2002). However the true prevalence of these abnormalities in the general population and in patients with epilepsy in not known. Subtle cerebral abnormalities have been demonstrated in asymptomatic relatives of patients with MCD and epilepsy (Merschhemke et al 2003). As with MTLE and HS, the relative contribution of MCD to refractory epilepsy remains unclear.

An important factor introducing bias into our analysis is the fact that MRI scanning was not available in the early years of the study period. Patients first seen during this period underwent MRI scanning only if they had poorly controlled epilepsy and continued to attend the epilepsy clinic for several years. This means that patients with underlying HS and MCD who responded to treatment in this period did not have the condition diagnosed. This biases the study towards detecting more MRI-diagnosed lesions in patients with uncontrolled seizures and inflates the relative risk of developing refractory epilepsy in patients with HS and MCD. Thus the true risk of pharmacoresistance in these conditions is likely to be lower than that found in our analysis.

The mechanism of action of the traditional AEDs and some of the newer ones are known (Kwan et al, 2001). However, the reason why they show varying efficacy in patients with the same underlying pathology is unclear. Several hypotheses on the mechanisms involved in the evolution of drug resistant epilepsy have been proposed (Regesta and Tanganelli, 1999). These include ontogenic abnormalities in brain maturation, epilepsy induced alterations in network, neuronal and glial properties in seizure prone areas such as the hippocampus, the phenomenon of kindling and reorganisation of cortical tissue in response to seizure induced disturbances in oxygen supply. These however remain largely speculative. Similar to the pathogenesis of the majority of epilepsy syndromes, it is likely that response to drug treatment is also governed by a number of genetic and environmental influences. Genetic polymorphisms cause variations in the levels and activity of drug metabolising enzymes and transporter molecules and affect the distribution and concentration of

AEDs (Sisodiya, 2003). Polymorphisms of drug targets may affect the affinity and activity of specific drugs (Hiratsuka and Mitzugaki, 2001). Similarly environmental factors including lifestyle issues such as abuse of proconvulsant recreational drugs can affect the efficacy of AEDs. In such a complex multifactorial outcome individual factors are likely to have only limited predictive value. The specific underlying epilepsy syndrome is only one such variable.

2.5. Conclusions

Prognosis for newly diagnosed patients with localisation related epilepsy might be better than what is assumed from studies in patients with refractory epilepsy. There were no significant differences in remission rates between patients with symptomatic and cryptogenic epilepsies and between the various types of symptomatic epilepsies. Patients with certain types of symptomatic epilepsies however did appear to be at a higher risk of developing refractory epilepsy.

3. Prognosis of newly diagnosed Idiopathic Generalised Epilepsies in the non-paediatric setting

3. 1.Introduction

3.1.1 Definition

Idiopathic generalised epilepsies (IGE) are clinically characterised by seizures in which the first clinical changes indicate the initial involvement of both hemispheres. The International League Against Epilepsy (ILAE) Commission on Classification And Terminology defines IGE as 'forms of generalised epilepsies in which all seizures are initially generalised (absences, myoclonic jerks and generalised tonic-clonic seizures; GTCS), with an electroencephalographic (EEG) expression that is a generalised bilateral, synchronous, symmetrical discharge' (Commission, 1989). The inter-ictal EEGs show normal background activity and generalised discharges, such as spikes, polyspike, spike-wave and 3 Hz polyspike-waves. Intellectual and neurologic deficits are absent and no structural brain abnormalities can be demonstrated by cerebral imaging. The aetiology is believed to be a genetic predisposition modified by environmental influences.

3.1.2 Pathophysiology of IGE

Jasper and Penfield first proposed the central role of interaction between cortical and subcortical structures in the generation of generalised seizures. The abrupt onset and cessation of the 3Hz generalised spike and wave discharges (GSWDs) out of a normal background led them to hypothesise the existence of a central pacemaker with diffuse cortical connections — the so called centrencephalic theory (Penfield and Jasper 1954). The evidence for this first came from animal studies in which stimulation of the

midline and intralaminar nuclei of the thalamus at 3Hz in the cat produced bilaterally synchronous GSWDs on the cortical EEG (Jasper and Drogleever-Fortuyn 1947). The demonstration of bilaterally synchronous 3Hz GSWDs originating from the thalamus of a child with absence epilepsy using depth electrodes provided support for subcortical involvement in human IGE (Williams, 1953). However other studies in animals point to a leading role for the cortex in generation of generalised seizures (cortical theory). It has been shown that application of proconvulsants to the surface of the frontal lobes can produce rhythmic GSWDs, which in unanesthetised monkeys produced absence like attacks (Marcus and Watson, 1968). Studies in the feline generalised penicillin epilepsy model have suggested that generation of GSWDs require the presence of a functional cortex as well as a thalamus (Gloor, 1968), leading to the hypothesis that discharges from certain deep structures escalate the epileptic state of the cortex and cause GSWDs (corticoreticular theory). Seminal work by Janz and colleagues found microdysgenesis of cortical neurons in the brains of patients with IGE (Meencke and Janz, D 1984). It has been suggested that the morphologic abnormalities that constitute microdysgenesis result in faulty development of synaptic connections in the cerebral cortex, which may result in a generalized state of hyperexcitability, leading to clinical seizures and generalized spike-wave discharges on the EEG (Blumenfeld, 2003). Thus, generalised seizures appear to result from bilaterally synchronous burst firing of a group of reciprocally connected neurons located in the thalamus and the cortex (Futasugi and Riviello, 1998).

3.1.3 Genetics of IGE

Genetic factors are believed to play a greater role in the causation of IGE than in localisation related epilepsy (Ottman et al, 1998). Since 1995, several susceptibility

genes have been identified in IGE syndromes by linkage analysis and association studies employing family, twin and candidate gene based approaches (Scheffer and Berkovic, 2003). The genetic bases of many IGE syndromes are mutations in voltage- and ligand-gated ion channel genes, which affect the structure and/or function of the channel encoded on the gene (Mulley et al, 2003). These 'channelopathies' result in altered ion channel kinetics and predispose to abnormal neuronal excitation. A list of identified mutations in IGE syndromes is shown in Table 17. The correlations of genotype to phenotype are however not simple. In the syndrome of GEFS+ for instance, mutations have been identified in SCN1A (Escayg et al, 2000), SCN2A (Sugawara et al, 2001), SCN1B (Wallace et al, 1998) and GABRG2 (Baulac et al, 2001, Wallace et al, 2001) genes. However, several familial cases with similar phenotypes lack any of the previously described mutations (Bonanni et al, 2004). Similarly, in families of patients with GEFS+, a spectrum of seizure disorders have been observed ranging from febrile seizures to syndromes such as Severe Myoclonic Epilepsy of Infancy (Singh et al, 2001; Marini et al, 2004). Thus considerable genetic heterogeneity and phenotype variability exists for this IGE syndrome. Resolving the complexities of genotype-phenotype correlations is likely to be the principal challenge in genetic studies of mono- and oligo-genic seizure disorders in the next few years. The vast majority of IGE syndromes are, however, polygenic or complex disorders. The epilepsy phenotype in individual patients is the result of interaction amongst several susceptibility genes as well as environmental factors. It is likely that a range of polymorphisms, rather than mutations, in candidate genes confer the genetic susceptibility to seizures (Scheffer and Berkovic, 2003). Search for these will need to employ higher throughput genotyping technology and more sophisticated bioinformatics paradigms.

Table 17. Epilepsy genes and their associated generalised epilepsy syndromes (adapted from Mulley et al, 2003).

Gene	Encoding	Syndrome
KCNQ2	Potassium channel KQT like	BFNS/myokymia
SCNQ3	Potassium channel KQT like	BFNS
SCN1B	Sodium channel β1 subunit	GEFS+
SCN1A	Sodium channel α1 subunit	GEFS+/SMEI
GABRG2	$GABA_A$ receptor γ2 subunit	CAE/FS/GEFS+
SCN2A	Sodium channel α2 subunit	GEFS+/(BFNIS)
GABRA1	$GABA_A$ receptor α1 subunit	ADJME

3.1.4 Prevalence and age distribution of IGE

IGE constitutes 20-40% of all new diagnoses of epilepsy (Gastaut et al, 1975, Joshi et al, 1977, Loiseau et al, 1990, Zarrelli et al, 1999). Although seizures generally begin in childhood and adolescence, onset of IGE after the second decade of life has previously been described (Gastaut, 1981). Panayiotopoulos and colleagues described a syndrome of adult onset IGE with phantom absences (3-4 second lapses in consciousness), infrequent generalised tonic clonic seizures (GTCS) and frequent absence status in 13 of a series of 86 patients with adult onset IGE (Panayiotopoulos et al, 1997). Gilliam and colleagues have described 11 patients with onset of myoclonic epilepsy at a mean age of 39 years, some of whom had absences (Gilliam et al, 2000). A recently published case series from a regional epilepsy clinic in the UK identified 8.5% patients with onset of IGE after the age of 20 years, based on clinical features and seizure types (Nicolson et al, 2004a). A similar series from New York based on retrospective review of clinical and EEG data identified 13.3% patients with adult onset of IGE (Cutting et al, 2001). A more rigorous approach to classification could identify many more such patients, as demonstrated by Marini and colleagues. They employed post ictal EEG within 24 hours of the initial seizure followed by sleep deprived EEG if necessary to classify epilepsy and identified adult onset of IGE in 28% of cases (Marini et al, 2003). There can be difficulties with identifying IGE based on EEG characteristics. Certain partial epilepsies, especially those caused by lesions in the mesial frontal lobe can cause generalised spike and wave abnormalities on surface EEG (Kubota et al, 1997; Tezer et al, 2004). True coexistence of IGE and partial epilepsy is rare. Nicolson and colleagues found that only less than 1% of 962 patients with IGE attending a specialist clinic had coexisting partial epilepsy (Nicolson et al, 2004c)

3.1.5 Prognosis of IGE

IGE is believed to have a better prognosis for remission than localisation related epilepsies. In a large clinic based series (n=2200) significantly more patients with IGE achieved seizure control for one year (82%) than those with cryptogenic (45%) or symptomatic (35%) partial epilepsy (Semah et al, 1998). There is no evidence to suggest that the adult onset IGE has a different underlying pathophysiology from childhood IGE, indeed, available data indicates that they share common biological determinants and are part of a life long spectrum of classic IGE (Yenjun et al, 2003; Marini et al, 2004). Studies of adult onset IGE have suggested that the prognosis remains good in older patients (Cutting et al, 2001). The prognosis for control does vary among the various seizure types. In a retrospective cohort study examining the response to treatment in patients with JME, Prasad and colleagues reported remission rate of 68-80% for GTCS and 58-59% for myoclonic seizures depending on the treatment used (Prasad et al, 2003). A recently reported study from a regional epilepsy clinic in the UK found 54% response rate (one year seizure freedom) overall for patients with IGE (Nicolson et al, 2004b). This, however, was a cross sectional study in a clinic population and would therefore be expected to have an overrepresentation of patients with drug-resistant epilepsy. Studies recruiting patients from the time of diagnosis and incorporating a diagnostic scheme designed to identify IGE are required to accurately assess the prognosis of various IGE syndromes. Moreover, in the non-paediatric setting different life style and environmental factors operate and treatment outcomes might not be translatable from studies in a younger population. We examined the response to treatment in an unselected series of adolescent and adult patients with newly diagnosed IGE at a single centre to assess the prognosis of IGE in a non-paediatric practice.

3.2. Methods

The protocol for evaluation of patients presenting with seizures has been described in Part II, section 1.2. A total of 890 patients were diagnosed with epilepsy after presenting to the first seizure clinic between August 1981 and May 2001 of whom sufficient follow up was available for 780 patients. Classification of seizure types and syndromes were reviewed at the time of data collection based on clinical and EEG data. Epilepsy was classified as IGE based on clinical and EEG criteria. Response to treatment was defined as complete seizure control for 12 months or more. Patients remaining seizure free till the end of follow up were considered to be in remission. Patients showing initial response to treatment before experiencing seizure recurrence and were subsequently uncontrolled were categorised as relapse. Logistic regression analysis was used to ascertain the influence of various risk factors on prognosis for remission. Categorical variables were compared using the χ^2 test on one degree of freedom. Analyses were carried out using Minitab for windows statistical software (version 13.21).

3.3. Results

3.3.1 Patient demographics

Of the entire cohort of 890 adult and adolescent patients, 128 (15%) fit the criteria for a diagnosis of IGE.. In the IGE cohort 15 were lost to follow up and the remaining 103 were analysed for treatment outcomes. This cohort consisted of 56 females and 47 males. The median age at onset was 17 years (range 5-51) and that at diagnosis was 18 years (range 9-71). The age distribution of the patients with various IGE syndromes is shown in Figure 10. Mild learning disability was present in 5 patients. Of these, 4 patients had Down's syndrome (trisomy 21), 3 of whom had a diagnosis of

late onset myoclonic epilepsy. JME was the most common IGE syndrome and was present in 55 (53%) of cases, followed by Epilepsy with GTCS Only in 28 (27%) patients. The other syndromes identified were Epilepsy with GTCS on awakening (n=7), Juvenile absence epilepsy (n=4), Epilepsy with GTCS during sleep (n=3), Late onset myoclonic epilepsy (n=3) Childhood absence epilepsy (n=2) and Epilepsy with myoclonic absences (n=1).

3.3.2 Response to treatment

Overall, 76 (74%) patients responded to treatment of whom 66 (64%) achieved remission and 10 (10%) relapsed. The remaining 27 (26%) patients did not achieve complete seizure control for any 12-month period. Treatment outcomes in the individual IGE syndromes are shown in Table 18. Treatment response was achieved with one AED (monotherapy) in 64 (84%) cases. Of these 53 (51%) responded to their first AED. When used as the first AED, VPA (66%) was more likely to produce treatment response than LTG (45%), however this difference did not reach statistical significance ($p=0.076$, $\chi^2=3.22$). When response to the first AED in individual syndromes was analysed, treatment with VPA was significantly more likely to be successful than that with LTG (75% v 39%, $p=0.014$, $\chi^2=5.99$) in patients with juvenile myoclonic epilepsy. Numbers of patients with other IGE syndromes were too small to make meaningful comparisons.

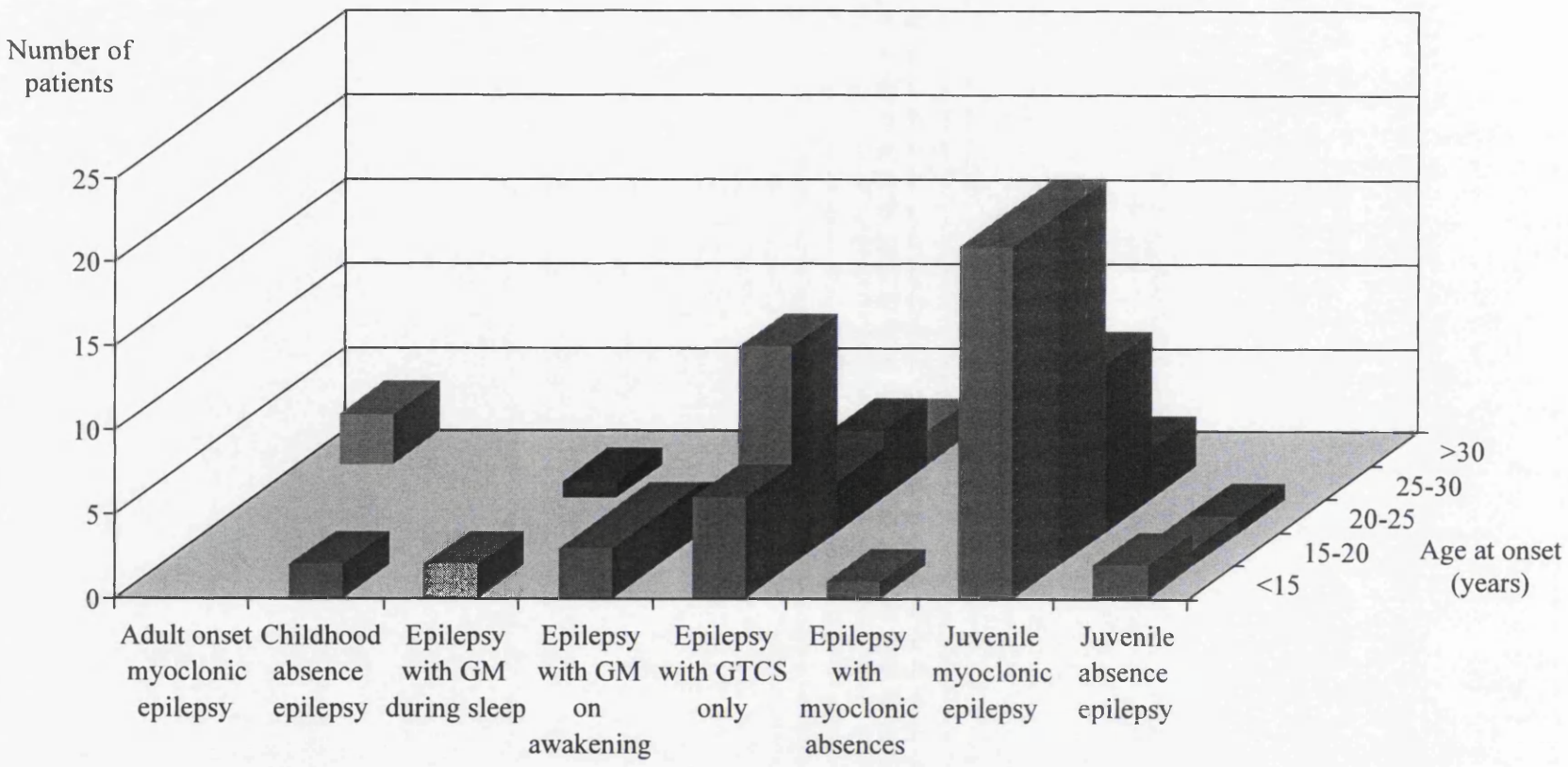


Figure 10. Age distribution of patients diagnosed with idiopathic generalised epilepsy syndromes

3.3.3. Remission of seizures

Patients with JME achieved remission in 40 (73%) cases. The remission rate for JME was significantly better compared to the rest of the cohort (p=0.05, χ^2= 3.83). The number of patients with other subtypes of IGE was insufficient to demonstrate significant differences in outcomes among the various syndromes (Table 18). Relapse occurred in 4 (7%) of patients with JME and 5 (18%) of patients with IGE with GTCS only, however the differences in relapse rate were not significant. Life style factors that could affect seizure control such as drug and alcohol abuse were present only in 5 patients in the cohort, all of whom remained uncontrolled. No patient with Down's syndrome and late onset myoclonic epilepsy achieved remission, although one patient responded to treatment for a 12-month period.

3.3.4. Treatment leading to remission

Patients who achieved remission were receiving monotherapy in 56 (85%) of cases. Valproate (=30) and lamotrigine (n=17) were the most common AED monotherapy resulting in remission, and were generally used in modest doses (Figure11). Of the patients achieving remission, 33 (50%) were immediate responders, suffering no further seizures after starting on AED treatment. The prognosis for immediate response was not influenced by the syndrome classification or the choice of the first AED. Patients failing monotherapy achieved remission with duotherapy in 10 (15%) patients.

3.3.5 Factors affecting prognosis

We analysed the influence of risk factors such as age at onset, sex, family history of epilepsy, history of febrile seizures, psychiatric co-morbidity, epileptiform

abnormalities on EEG and types of seizures on the prognosis for remission (Table 19). In the univariate analysis, a history of febrile seizures was the only factor associated with a significantly lower remission rate (OR 0.18, 95% CI 0.03-0.96, p=0.032).

Table 18. Treatment outcomes in individual IGE syndromes

Syndrome	Remission (%)	Relapse (%)	Uncontrolled (%)	Total
Juvenile Myoclonic Epilepsy	40 (73%)	4 (7%)	11 (20%)	55
Epilepsy with GTCS only	15 (54%)	5 (18%)	8 (29%)	28
Epilepsy with GTCS on awakening	5 (71%)		2 (29%)	7
Juvenile absence epilepsy	3 (75%)		1 (25%)	4
Late-onset myoclonic epilepsy		1 (33%)	2 (67%)	3
Epilepsy with GTCS during sleep	2 (67%)		1 (33%)	3
Childhood absence epilepsy	1 (50%)		1 (50%)	2
Epilepsy with myoclonic absences			1 (100%)	1
Grand Total	66 (64%)	10 (10%)	27 (26%)	103

Table 19. Factors affecting prognosis of IGE (univariate analysis)

Risk factor		Patients	Remission	%	Odds ratio	95% CI	*p*
Sex	Female	47	30	64%	0.98	0.44-2.20	0.962
	Male	56	36	64%			
Family history	Present	14	7	50%	0.46	0.15-1.43	0.183
	Absent	86	59	69%			
Febrile seizures	Present	7	2	29%	0.18	0.03-0.96*	0.032
	Absent	92	64	70%			
Psychiatric co-morbidity	Present	9	6	67%	1.13	0.27-4.82	0.865
	Absent	94	60	64%			
EEG	Epileptiform	87	55	63%	0.78	0.25-2.45	0.669
	Normal/non-specific	16	11	69%			
Seizure types	GTC only	37	20	54%	1.45	0.64-3.30	0.373
	MJs/absence w/w/o GTC	66	42	64%			
Age of onset	<15	37	25	68%	1.27	0.54-2.97	0.579
	15-20	38	23	61%	0.78	0.34-1.80	0.567
	20-25	15	12	80%	2.52	0.66-9.58	0.148
	25-30	8	4	50%	0.53	0.12-2.27	0.396
	>30	5	2	40%	0.35	0.06-2.22	0.262

*p=0.032

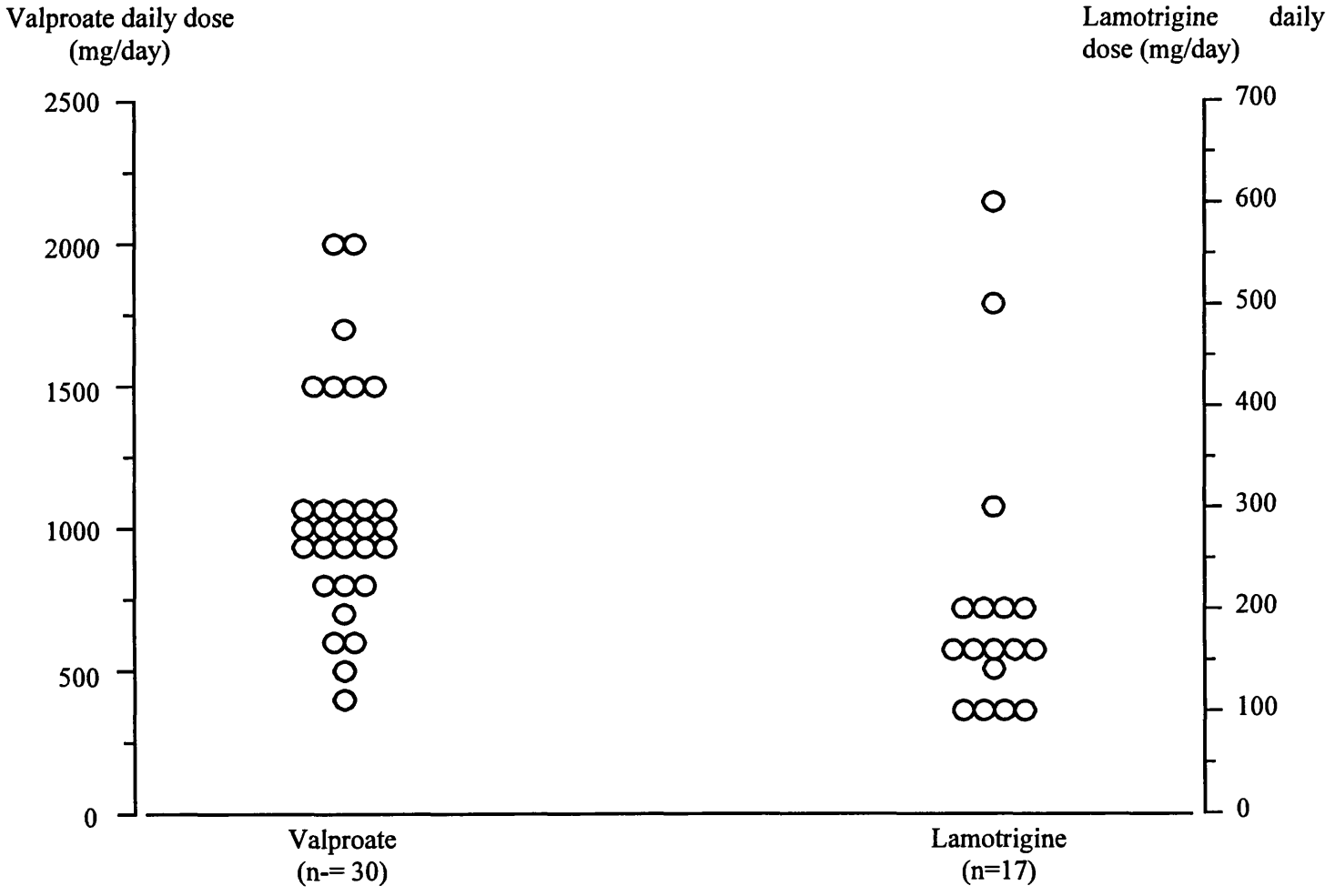


Figure 11. Daily dose of valproate and lamotrigine resulting in remission of seizures in patients with newly diagnosed IGE syndromes

3.4. Discussion

Recognition of IGE syndromes in the non-paediatric setting has important implications for management of patients. In this group of patients where onset of seizures raises concerns regarding potentially serious cerebral pathology, early accurate diagnosis can provide reassurance. If electrographic evidence of IGE is obtained, unnecessary imaging investigations can also be avoided. Identification of these patients is also important in clinical genetic studies and drug trials of AEDs. The greatest importance of accurate classification is in guiding choice of treatment. Certain AEDs such as phenytoin and carbamazepine have been shown to exacerbate seizures in patients with IGE (Berkovic, 1998, Genton, 2000). There have also been reports of exacerbation of myoclonic seizures by lamotrigine (Guerrini et al, 1999; Trinka et al, 2002). A recent study found that 48% of patients diagnosed with IGE in an epilepsy program had previously been started on AEDs known to worsen IGE (Benbadis et al, 2003). Valproate has traditionally been regarded as the drug of choice in the treatment of IGE syndromes. A recent meta-analysis found no evidence to support the use of VPA in the treatment of generalised epilepsies, however the studies analysed were possibly confounded by misclassification of epilepsy type (Marson et al, 2002). In our study, the highest response rates to initial monotherapy were observed with VPA. This was especially so in the case of JME where response to treatment with VPA was clearly superior to that with other drugs including LTG.

Patients with Downs' syndrome are known to have a bimodal pattern of onset of seizures with approximately 40% of epilepsy starting in the first year of life and another 40% in the 3rd decade (Pueschel et al, 1991). Late onset myoclonic epilepsy in Down's syndrome (LOMEDS) has been previously described (Li et al, 1995; Moller et al, 2001). This usually presents with rapidly progressive dementia in patients aged over 40 years (Genton and

Paglia, 1994). With increased survival of patients with Down's syndrome into middle age, this presentation is being increasingly recognised. In our series, 3 patients with Down's syndrome presented with myoclonic epilepsy at the ages of 42, 45 and 51 years. None of these patients achieved remission although one patient had 12 months of seizure freedom on treatment before relapsing.

Although IGE syndromes respond better to treatment than localisation related epilepsy, there remains a significant proportion of patients who do not achieve seizure remission with currently available treatment. Identifying these patients early could help optimise treatment strategy. Several studies have investigated the influence of risk factors in determining the prognosis of IGE syndromes. The findings from these studies are varied and reflect the methodological differences among studies in the definition of risk factors and classification of epilepsy. From their study of 962 paediatric and adult patients with IGE, Nicolson and colleagues found atypical presentation to be associated with a significantly worse response to treatment (Nicolson et al 2004b). This was defined as IGE with onset outside the expected age group of 3- 20 years or with atypical absence or myoclonic seizures. Prognosis for response to treatment also differs among the sub-syndromes of IGE. This study found that patients with GTCS only (64.5% remission) or GTCS on awakening (78% remission) had significantly better remission rates compared to prognosis for remission in the entire cohort. Fernando-Dongas and colleagues reported a higher prevalence of EEG asymmetry, atypical seizure characteristics and intellectual deficiency in patients with JME who failed to respond to valproate treatment (Fernando-Dongas et al 2000). Psychiatric problems have also been reported to be associated with drug resistant IGE (Gelisse et al, 2001; Cutting et al, 2001). In our cohort of patients, history of febrile seizures was the only factor associated with a failure to achieve remission. Febrile seizures are known to have a genetic component

and some of the genetic factors associated with IGE can give rise to febrile seizures (Baulac et al 2004). It is possible that the IGE syndromes associated with febrile seizures have a different pathophysiology and therefore require a different therapeutic approach to other forms of IGE.

3.5. Conclusions

The majority of patients with IGE have an excellent prognosis and can be expected to achieve lasting seizure remission. Prospective studies recruiting patients from the time of diagnosis and employing diagnostic schemes designed to identify IGE are required to elucidate the natural history of specific IGE disorders.

4. Pharmacological outcomes in newly diagnosed epilepsy over a 20-year period

4.1. Introduction

Several randomised studies have examined the efficacy and tolerability of standard antiepileptic drugs (AEDs) in the treatment of partial and generalised seizures in adults with epilepsy (Turnbull et al 1982, Mattson et al 1985, Callaghan et al 1985, Mattson et al 1992, Richens et al 1994, Heller et al 1995). However, there has been an explosion of newer AEDs licensed since these landmark studies reported (Dichter and Brodie, 1996). This has had a major impact on treatment choices the world over. Some traditional AEDs, such as phenobarbital, are no longer prescribed routinely in most developed countries and some newer AEDs, such as lamotrigine and oxcarbazepine, have acquired first line status. Currently there are few data available outside of regulatory clinical trials to guide treatment decisions in this changing milieu. The setting of such trials is artificial with strict exclusion and exit criteria, which are necessary to safeguard patients receiving investigational agents. These limitations prevent extrapolation of the results to the majority of patients with epilepsy who receive the drugs and these studies rarely help decision making in clinical practice (Mohanraj and Brodie 2003). Long-term prospective randomised studies comparing new and standard agents and newer agents with one another in patients with new onset epilepsy are needed, and, indeed, some are underway. Data from longitudinal observational studies can complement these projects. We conducted an observational study of treatment outcomes in newly diagnosed patients to assess the response to individual AEDs in various seizure types and epilepsy syndromes.

4.2. Methods

Methods of data collection and end points of efficacy and tolerability have been described in part I, section 1. 2. Tolerability and efficacy for each AED was analysed separately in patients with idiopathic generalised epilepsies and localisation related epilepsies. Results were compared using the χ^2 test with Bonferroni correction for multiple comparisons. Doses were compared using the Mann-Whitney test for non-parametric observations. The actuarial life table method was used to compare times to first seizure after starting on AED treatment.

4.3. Patients

A diagnosis of epilepsy was made in 890 patients, 110 (12%) of whom were lost to follow up. The remaining 780 were included in the analysis for efficacy and tolerability of individual AED regimes. This cohort comprised of 405 (52%) males and 375 (48%) females, who had a median age of 31 years (median 9-93 years) at initiation of treatment. Overall, 103 (13%) patients had idiopathic generalised epilepsy syndromes and 558 (72%) had localisation related epilepsies. The remaining 119 (15%) patients had generalised tonic clonic seizures with no localising features, and had been classed as having generalised epilepsy for purposes of deciding treatment. These patients were included with those with idiopathic generalised epilepsy in this analysis. Carbamazepine (CBZ, n=268), valproate (VPA, n=198) and lamotrigine (LTG, n=198) were the most commonly used first choice antiepileptic drugs in this population. The trends in the usage of the three main agents over the study period are shown in Figure 12. Other AEDs such as Felbamate (n=13), Gabapentin (n=30), Tiagabine (n=25), Oxcarbazepine (n=18) and Remacemide (n=16) were used as initial monotherapy as part of regulatory RCTs. Pheytoin was used in 11 patients and Topiramate in 3, outside of RCTs. Most patients diagnosed since 2000 have been entered into a randomised study comparing valproate and lamotrigine.

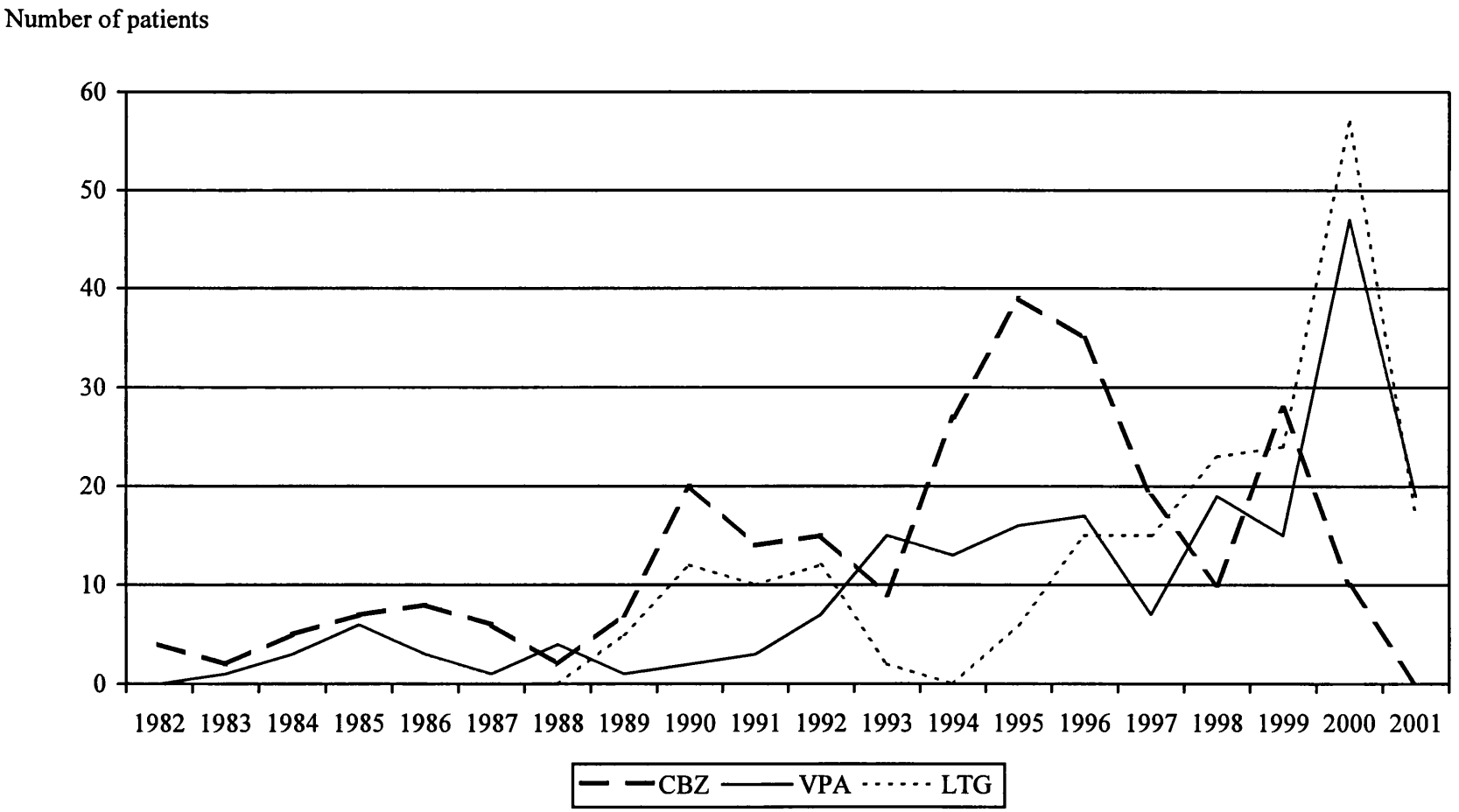


Figure 12. Trends in the use of carbamazepine, valproate and lamotrigine over the study period.

4.4. Results

4.4.1. Monotherapy

Overall, 504 (65%) of patients starting on AEDs responded to treatment. Of these, 462 (91.7%) were on treatment with one AED (monotherapy) and 40 (7.9%) were receiving two AEDs. Treatment with combinations of 3 and 4 AEDs produced seizure freedom in only one patient (0.2%) each. In total, 1020 attempts were made to treat patients with monotherapy. CBZ (n=312), VPA (n=315) and LTG (n=249) and others (n=144) were the drugs used. Of the 462 patients responding to monotherapy, 393 were on the first AED, 57 on the second, 8 on the third and 2 on the fourth. Only one patient each responded to 5^{th} and 6^{th} attempts at monotherapy. The response to each drug used as initial monotherapy in specific syndromes is shown in table 20.

4.4.2. The first AED

The rank order in which it is given is an important determinant of the effectiveness of any AED (Nicolson et al 2004). If the first appropriate AED does not succeed in controlling seizures, subsequent pharmacotherapy is less likely to be successful (Dlugos et al 2001, Kwan and Brodie 2000, Sillanpaa 1993). We analysed in detail the response to initial monotherapy in the various epilepsy syndromes. Of the 780 patients started on AED therapy, 392 (50%) responded to the first drug. Demonstrable differences in responder rate existed only between LTG (61% response) and CBZ (44% response, $p<0.001$, Figure 13). Adverse events leading to withdrawal of treatment was more frequent with CBZ (16%) compared to LTG (7%, $p=0.018$) and VPA (7%, $p=0.03$). Adverse events leading to failure of each AED used as first monotherapy is listed in Table 21. CBZ was more likely to cause rash than any other drug ($p<0.001$), but there were no significant differences in the occurrence of other adverse effects among the various drugs. No differences were observed in the incidence of

adverse effects between patients with idiopathic generalised and localisation related epilepsies.

4.4.3. Immediate response

A total of 245 (31%) patients suffered no further seizures after starting on AED treatment. These immediate responders constituted 49% of all responders and included 164 (29%) patients with localisation related epilepsies, 33 (32%) patients with idiopathic generalised epilepsies and 48 (40%) patients with unclassified seizures. There were no significant differences in the probability of achieving immediate response among patients with various types of epilepsy. The choice of AED did not significantly influence the probability of achieving immediate response.

4.4.4. Effectiveness in idiopathic generalised epilepsy

In patients with idiopathic generalised epilepsy, VPA produced the highest response rate (66%). LTG (45% response rate) and CBZ (31% response rate) were less efficacious but the numbers were insufficient to show statistically significant differences. Withdrawal due to adverse effects was more likely with CBZ (38%) than with VPA (5%, p=0.006) and LTG (6%, p=0.036) in this group of patients. When specific syndromes were analysed separately, significant differences were observed in responder rates for juvenile myoclonic epilepsy, with patients more likely to respond to VPA (75%) than LTG (39%, p = 0.014, Table 22).

4.4.5. Effectiveness in localisation related epilepsy

In patients with localisation related epilepsy, LTG (63% response rate) was more likely to achieve seizure control than VPA (42% response rate, p=0.006), CBZ (45%, p=0.006) and other drugs (p=0.001). There were no significance differences in tolerability among the

various drugs in these patients. Among the various localisation related epilepsies, cryptogenic seizures showed better response to treatment with LTG (67%) compared to CBZ (47%, p=0.036) and VPA (40%, p=0.012). No significant differences in response rates could be demonstrated in other types of localisation related epilepsies, however the number of patients in each subgroup was small (Table 23).

4.4.6. Dosing

Successful monotherapy could be achieved in most cases with modest doses of all AEDs. The median daily doses resulting in remission were CBZ 400 mg/day, VPA 1000 mg /day and LTG 150 mg /day (Figure 14). There were no significant differences in successful monotherapy dosing between patients with idiopathic generalised and localisation related epilepsies. We examined the time to first seizure after starting on AED treatment in 551 patients in whom this data was available from seizure diaries (Figure 15). No significant differences could be demonstrated among the 3 first line agents in this analysis.

4.4.7. Substitution versus combination of AEDs

In patients failing initial monotherapy, alternative monotherapy was attempted in 179 patients and combination therapy with two AEDs in 81 (Table 22). The remission rates and withdrawal due to adverse effects were not significantly different between the two treatment strategies. Over the study period, 139 attempts were made to use combination of two drugs. The response rates with each regime are shown in (Table 23). The most commonly employed combination based on mechanism of action was of a sodium channel blocking AED and one with multiple mechanisms of action. Numbers of patients treated with other types of combinations were insufficient for comparison of efficacy based on mechanisms of action.

Table 20. Response to initial monotherapy in specific epilepsy syndromes

	Carbamazepine			Valproate			Lamotrigine			Other			
Epilepsy syndrome	Total	Responders	Percent	Total	Responders	Percent	Total	Responders	Percent	Total	Responders	Percent	Total
IDIOPATHIC GENERALISED	**39**	**14**	**36%**	**90**	**61**	**68%***	**63**	**36**	**57%**	**30**	**18**	**60%**	**222**
Juvenile myoclonic epilepsy	3	0		28	21	75%	18	7	39%	6	4	67%	55
Other generalised epilepsies	18	5	28%	26	12	46%	18	8	44%	10	4	40%	72
GTCS with no localising features	18	9	50%	36	28	78%	27	21	78%	14	10	71%	95
LOCALISATION RELATED	**229**	**103**	**45%**	**108**	**45**	**42%**	**135**	**85**	**63%**	**86**	**30**	**35%**	**558**
Idiopathic localisation related	6	4	67%	4	4	100%	0	0		1	0	0%	11
Cryptogenic	111	52	47%	62	25	40%	76	51	67%	54	15	28%	303
Post-traumatic	29	10	34%	14	2	14%	11	5	45%	11	4	36%	65
Cerebrovascular disease	25	17	68%	11	3	27%	19	10	53%	8	4	50%	63
Cerebral atrophy	19	7	37%	9	7	78%	9	7	78%	5	3	60%	42
Tumour-related	14	5	36%	4	2	50%	5	3	60%	2	1	50%	25
Cortical malformations	7	2	29%	2	1	50%	3	2	67%	3	3	100%	15
MTLE with HS	9	3	33%	1	0	0%	3	1	33%	1	0	0%	14
Other lesional epilepsies	9	3	33%	1	1	100%	9	6	67%	1	0	0%	20
Total	**268**	**117**	**44%**	**198**	**106**	**54%**	**198**	**121**	**61%**	**116**	**48**	**41%**	**780**

Table 21. Adverse effects leading to withdrawal of each drug used as first monotherapy

	Carbamazepine (n = 268)	**Valproate (n = 198)**	**Lamotrigine (n= 198)**	**Others (n=116)**
Rash	22	1	5	2
Sedation	7	0	0	2
Tiredness	3	1	2	1
Ataxia	0	2	0	4
Headache	3	1	0	0
Nausea/vomiting	5	5	3	1
Mood changes	2	0	1	1
Tremor	0	3	1	0
Weight gain	0	2	0	0
Others	3	2	3	2
Total	45	17	15	13

Table 22. Response to substitution and combination in patients failing initial monotherapy

	Idiopathic generalised				**Localisation related**			
Response	Substitution		Combination		Substitution		Combination	
Remission	16	42%	10	48%	43	31%	19	32%
Not tolerated	2	5%	0	0%	17	12%	2	3%
No efficacy	20	53%	11	52%	81	57%	39	65%
Grand total	38		21		141		60	

Table 23. Response to individual two-drug combinations

Combination	Number	Responders	Response rate
Valproate + Lamotrigine	61	25	41%
Carbamazepine + Gabapentin	11	2	18%
Carbamazepine + Lamotrigine	10	1	10%
Carbamazepine + Topiramate	9	3	33%
Carbamazepine + Vigabatrin	7	1	14%
Carbamazepine + Valproate	7	2	29%
Valproate + Topiramate	5	1	20%
Carbamazepine + Levetiracetam	3	1	33%
Carbamazepine + Phenytoin	3	0	0%
Lamotrigine + Topiramate	3	1	33%
Lamotrigine + Vigabatrin	3	0	0%
Valproate + Gabapentin	3	1	33%
Lamotrigine + Levetiracetam	2	0	0%
Valproate + Vigabatrin	2	0	0%
Others	10	2	20%
Grand Total	139	40	29%

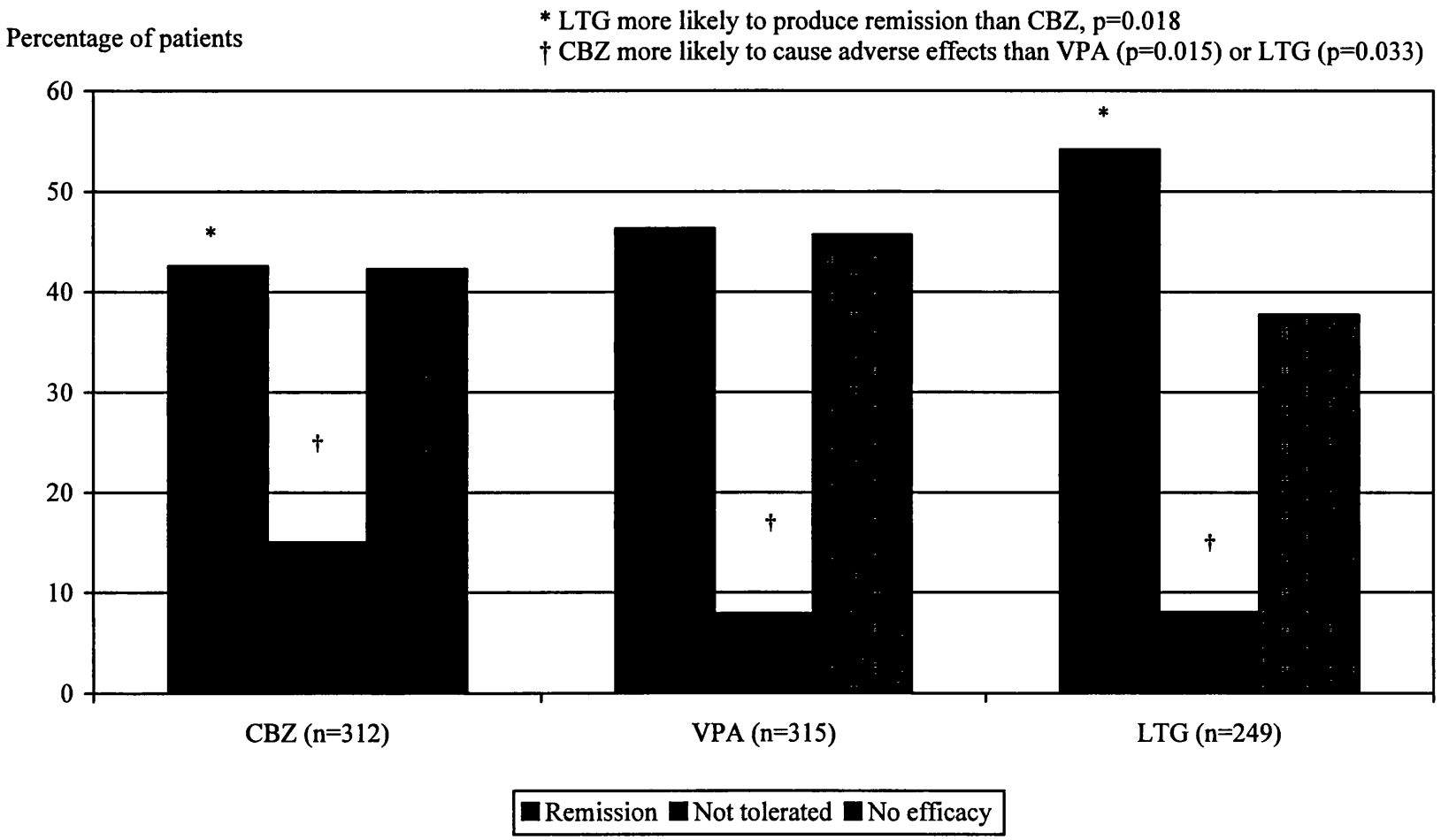


Figure 13. Response to carbamazepine, valproate and lamotrigine used as monotherapy

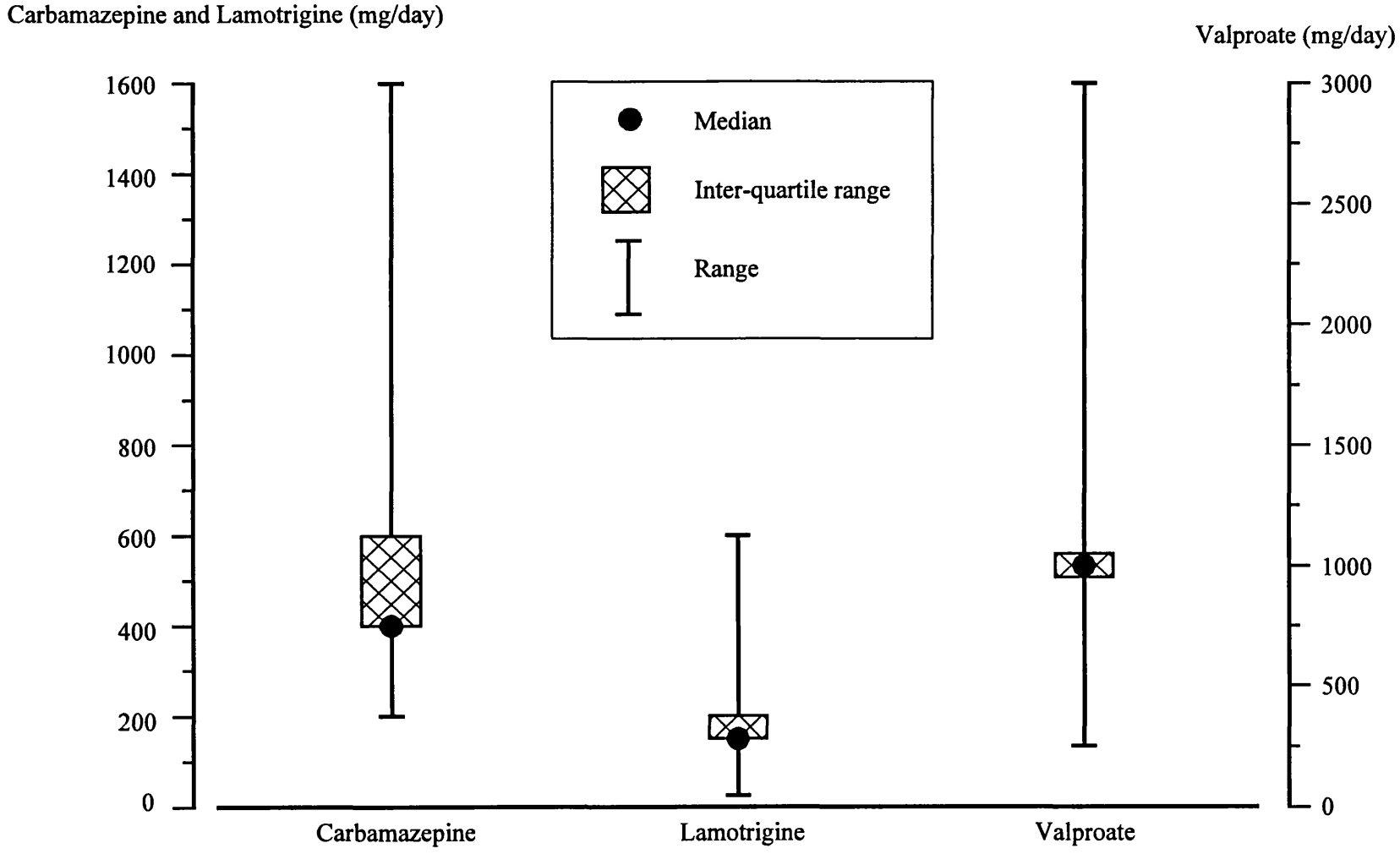


Figure 14. Dose of carbamazepine, valproate and lamotrigine in patients in remission

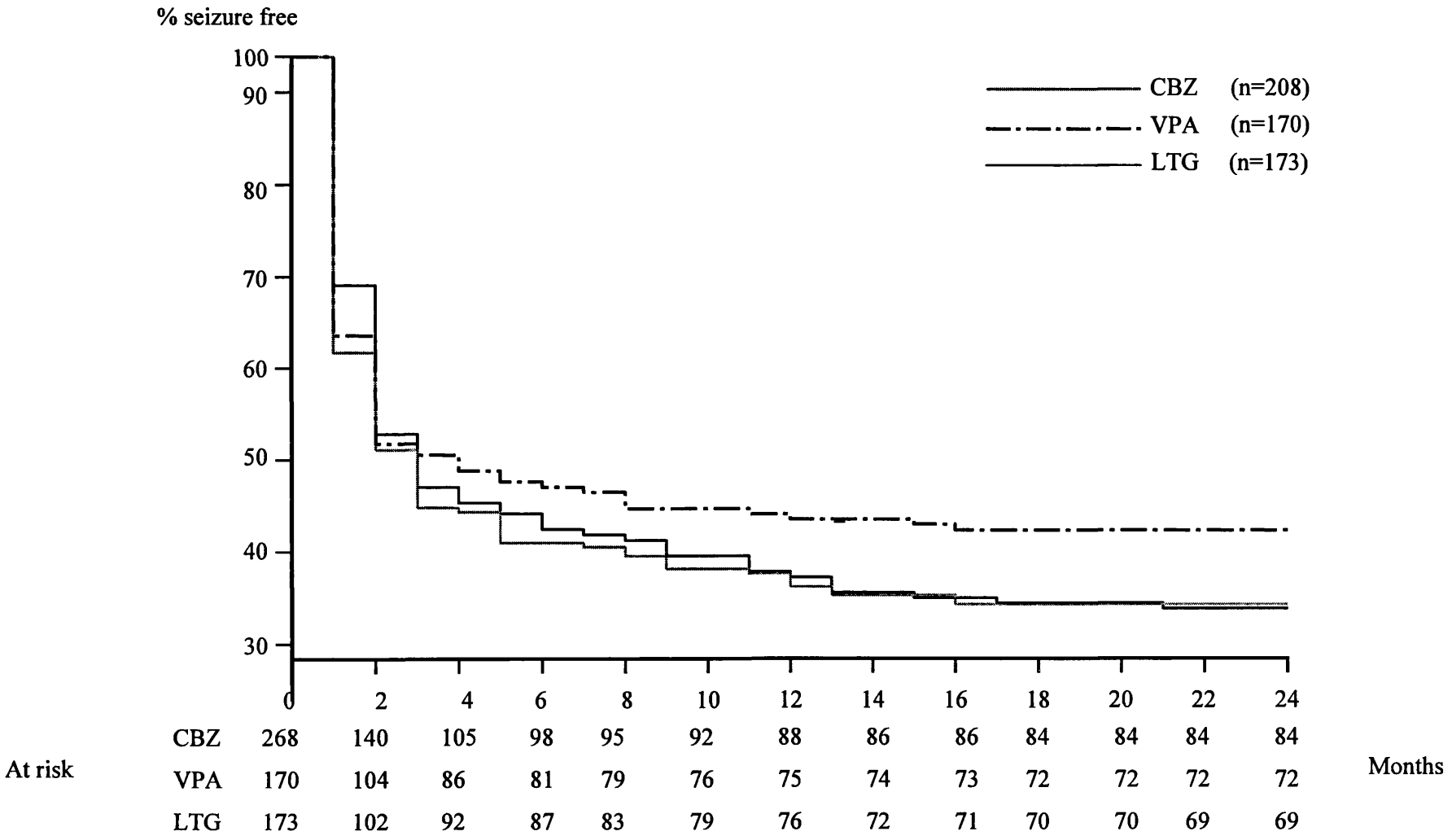


Figure 15. Time to first seizure after starting treatment with carbamazepine, valproate and lamotrigine

4.5. Discussion

Our understanding of the underlying epileptogenic process in the majority of the patients with epilepsy is rudimentary (Regesta and Taganelli, 1999). Similarly, the mechanisms of action of AEDs, especially newer ones, are not completely known (Kwan et al, 2001). Therefore, in contrast to many areas of therapeutics, pharmacological treatment of epilepsy is not a process of correcting a specific functional or biochemical deficit (Perucca, 2003). Rather, drug selection in epilepsy is an empirical process based on previous clinical observations in representative patient groups. As new treatments emerge, ongoing observational and randomised studies will be required to guide drug selection in patients with new onset epilepsy.

In this cohort of 780 patients with newly diagnosed epilepsy, we compared responder rates defined as complete seizure control for a year or more with various AED regimes and treatment schedules. Patients with idiopathic generalised epilepsy were significantly more likely to achieve response to treatment than those with localisation related epilepsy. Most patients who achieved remission were on treatment with one AED (monotherapy) generally at moderate doses. In patients failing initial monotherapy response to a combination of two AEDs was not significantly different from that to alternative monotherapy.

An interesting observation was of immediate response to treatment wherein patients suffered no further seizures after starting on AED treatment. Overall, 31% of patients starting on treatment were in this category. The probability of immediate response tended to be higher in patients with idiopathic generalised epilepsy. The choice of AED did not influence the probability of immediate response. Similarly, no significant differences

were observed among patients started on CBZ, VPA and LTG when time to first seizure was compared. This, along with the fact that response could be obtained with moderate doses of AEDs in most cases, suggests that prognosis for response to treatment is an inherent property of the specific epilepsy syndrome.

In all patients we started on antiepileptic medication, the overall response rates were significantly different only between LTG and CBZ. CBZ was also more likely to cause intolerable adverse effects compared to LTG and VPA. This has previously been observed in 2 randomised controlled trials comparing LTG and CBZ monotherapy in newly diagnosed patients (Brodie et al 1995; Brodie et al, 1999). The differences in effectiveness were ascribed to difference in tolerability as patients on CBZ had a higher incidence of intolerable adverse effects. Gillham and colleagues studied 260 patients with newly diagnosed epilepsy who were randomised to treatment with carbamazepine and lamotrigine using health related quality of life as the main outcome measure and found that lamotrigine was associated with better tolerability and quality of life (Gillham et al, 2000). In the present analysis, we found significant differences in tolerability in patients with idiopathic generalised epilepsy, in whom CBZ was more likely to cause adverse effects than any other drug. CBZ is known to worsen certain types of idiopathic generalised epilepsy syndromes and cause seizure exacerbation (Perucca et al, 1998). It is thus inappropriate choice as a first line monotherapy agent for patients with idiopathic generalised epilepsy (Benbadis et al, 2003). It is possible that the lack of efficacy or even exacerbation of seizures caused by such inappropriate treatment reduces the subjective tolerability to otherwise trivial adverse effects. Thus, even when an AED has been withdrawn ostensibly due to adverse effects, efficacy reasons often have had a role to play.

In idiopathic generalised epilepsies, treatment with VPA produced the highest responder rates although the differences in responder rate with LTG and CBZ did not reach statistical significance. However, when specific syndromes were analysed responder rates in Juvenile Myoclonic Epilepsy was significantly higher with VPA than with LTG. There is relatively little controlled trial data on the comparative efficacy of VPA and LTG in idiopathic generalised epilepsy. One randomised open label study of patients with typical absences reported a greater proportion entering remission on treatment with VPA (63%) compared to those treated with LTG (37%, Coppola et al, 2004). The difference was not statistically significant mainly owing to the small size of the study (n=38). The results of the ongoing SANAD study, comparing new and standard AEDs in newly diagnosed epilepsy in a prospective randomised design should clarify the issue further.

For localisation related epilepsy syndromes overall, LTG produced significantly better responder rates than any other AED. When subtypes were analysed, this observation held true for cryptogenic seizures. For other types of localisation related epilepsy syndromes including those resulting from cerebral trauma, cerebrovascular disease, cerebral atrophy, neuronal migration disorders and mesial temporal sclerosis, numbers were insufficient to show significant differences amongst the various drugs. Superior outcomes have been reported previously in patients with partial epilepsy treated with lamotrigine compared to those treated with carbamazepine. Nieto-Barrera and colleagues studied 618 patients randomised to CBZ and LTG and found comparable rates of seizure control (75% and 65% respectively), but significantly more patients withdrawn due to adverse effects in the CBZ treated group (8% versus 13%; Nieto-Barrera et al, 2001).

Ours is an unrandomised retrospective observational study and is prone to bias from varying treatment policies over the study period of 20 years. The data presented cannot, therefore, be considered reliable evidence of superiority of any particular AED over others, but do compliment observations made in randomised control trials discussed above. Our findings suggest that LTG is likely to produce better response rates in localisation related epilepsies, especially cryptogenic seizures than CBZ or VPA. In idiopathic generalised epilepsies, treatment with VPA produced the best response rates, although statistical superiority in response rate could be demonstrated only in patients with juvenile myoclonic epilepsy. These findings, appropriately validated, could help guide treatment decisions in patients with new onset epilepsy.

4.6. Conclusions

Patients with localisation related epilepsies, especially cryptogenic seizures responded better to LTG than CBZ or VPA. For idiopathic generalised epilepsies, especially juvenile myoclonic epilepsy, highest response rates were seen with VPA. The majority of patients who responded to treatment did so rapidly and completely with modest doses of AEDs.

Part III

Genetic influences on response to treatment in epilepsy

1. Pharmacogenomic studies in epilepsy

1.1 Introduction

Pharmacogenomics (or pharmacogenetics) is the study of genetic variations affecting response to drugs (Roses, 2001). Pharmacogenomics specifically refers to the study of all of the many different genes that determine drug behaviour, where as pharmacogenetics refers to the study of inherited genetic variation in drug metabolism and response. The distinction between the two terms is considered arbitrary, however, and the two terms are used interchangeably. It has been known for several decades that genetic differences are responsible for inherited variability in response to drugs (Weinshilboum, 2003). The identification of drug metabolising enzymes and drug target molecules, the genes that encode them, and sequence variants that correlate with drug response, have made it possible to elucidate the genetic basis for a variety of drug effects, such as idiosyncratic adverse reactions (Patsalos, 2000; Pirmohamed and Park, 2001). This has opened up the possibility of individualising drug therapy.

1.1.1. Clinical relevance of predicting drug response in epilepsy

Epilepsy is the most common serious neurological disorder with an annual worldwide incidence of 40-70 per 100,000 population (Sander, 2003). Long-term epidemiological studies have shown that approximately one in three patients with newly diagnosed epilepsy do not achieve useful control of seizures with currently available antiepileptic drugs (AEDs; Annegers et al, 1979; Cockrell et al, 1995; Mattson et al, 1996; Kwan and Brodie, 2000). In most patients, the diagnosis of epilepsy has social and economic as well as health implications. In children, uncontrolled epilepsy results in impaired intellectual development and reduced academic achievement. In adults, a diagnosis of epilepsy can result in the loss of driving privileges and employment. Regaining these requires

demonstration of complete control of seizures for an extended period of time. Thus, from the patients' perspective, prognosis for control of seizures is especially important in returning to a full functioning life. Studies have shown that the most powerful predictor of long-term treatment outcome in epilepsy is the response to the first AED (Sillanpaa, 1993; Camfield and Camfield, 1996; Dlugos et al, 2001; Kwan and Brodie, 2001). If response to AED treatment can be predicted, choice of drug therapy and long term prognostication can be improved. Identifying genetic markers correlating with specific drug effects could help predict effectiveness of individual AEDs.

1.1.2. Types of genetic variation

The completion of the Human Genome Project and data from the ongoing HapMap project has resulted in the cataloguing and annotation of a large number of variants of the human genome (Cravchik et al, 2001). The DNA sequence in all humans is 99.9% identical. Variations occur as a result of single nucleotide polymorphisms (SNPs), insertions, deletions, substitutions and simple tandem repeats (STRs). Any variation of the human genetic sequence from normal is considered a mutation; this however assumes a normal variant that is prevalent in the majority of the population. A polymorphism, on the other hand, is relatively common in the population. No single allele is considered normal, but there are 2 or more equally acceptable variants. The arbitrary cut off in prevalence between a mutation and polymorphism is 1% (Clancy and Kass, 2003).

1.1.3. Single nucleotide polymorphisms

SNPs are the simplest form of genetic polymorphism and are estimated to occur every 100 to 300 base pairs in the human genome (Chakravarty, 1999). They constitute 90% of the variability in the human genome and are the genetic markers of choice in

pharmacogenetic studies (Gray et al, 2000). They can occur in the non-coding regions of the genome (promoter regions, introns, 3' and 5' untranslated regions (UTR) and intergenic regions) or in the coding regions. Coding SNPs (cSNPs) could potentially affect the structure of the protein encoded on the gene. The degenerate nature of the genetic code (64 possible triplet sequences encoding 20 amino acids) means that the same amino acid can be specified by more than one triplet code. Thus, some cSNPs do not alter the amino acid sequence of the encoded protein (synonymous SNPs). Those cSNPs that alter the triplet code to specify a different amino acid are referred to as non-synonymous SNPs. Non-synonymous SNPs can have significant biological effects. It alters the primary structure of the protein, by changing the amino acid sequence. This can result in diminished activity or diminished quantity of the protein encoded (Weinshilboum and Wang, 2004). This could in turn affect the pharmacokinetics and pharmacodynamics of drugs that are metabolised or transported or those that bind to these proteins. Non-coding SNPs can also have biological consequences (e.g.: - influence gene expression if they occur in the promoter regions) or may simply serve as markers in linkage disequilibrium (LD, see section 1.2.1 below) with an unidentified susceptibility allele in association studies (Roden, 2001).

1.2. Methodological considerations

1.2.1. Study design

Genetic influence on drug responsiveness is complex and multifactorial. Studies in animals have suggested that pharmacoresistance to AEDs is genetically determined, but does not follow simple inheritance patterns. There is likely to be considerable environmental modification of genetic factors in determining response to drugs (Ebert and Löscher, 1999). Pharmacogenomic studies are therefore similar to genetic studies of

polygenic diseases inasmuch as there is no simple correlation between genotype and phenotype. The favoured design in genetic studies of complex diseases is family based association study (Romero et al, 2002). Polymorphisms co-segregating with the disease phenotype are considered to be in linkage disequilibrium (LD) with the susceptibility gene. This approach uses polymorphisms as genetic markers rather than ascribing a causative role and has the advantage of not making assumptions about the genes involved. However, in pharmacogenomic studies, the possibility of recruiting sufficient numbers of related individuals receiving treatment with the same drug is remote. In studies of polygenic diseases, familial inheritance, homogenous populations and relatively straightforward ascertainment of affected individuals allow for LD mapping. When unrelated individuals are being studied, the extent of LD can be affected by several factors including population admixture, genetic drift, mutation and natural selection. LD mapping methods in pharmacogenomic studies therefore have given rise to concerns regarding sample sizes, extent of LD, number of SNPs needed in a map and interpretation of results. Evidence to date suggests that this is likely to be an unreliable paradigm (McCarthy and Hilfiker, 2000).

Pharmacogenomics generally employs association studies based on a candidate gene approach (Ring and Kroetz, 2002). This utilises *a priori* knowledge of the biological basis of disease pathogenesis and mechanism of action of drugs to identify genes relevant to drug responsiveness. Polymorphisms identified in these genes are then tested for statistical association with the outcome of interest (responsiveness, adverse effects) in patients enrolled in case-control or cohort studies. Cohort studies are less prone to ascertainment bias but require a longer study period and more resources. Case-control

studies are easier to perform, but the definition of cases and controls has to be standardised as rigorously as possible to ensure that the populations are comparable.

1.2.2. Sample size and power in candidate gene studies

The number of patients required to find statistically significant association between the presence of a SNP and drug response depends on a number of factors including the frequency of drug response, proportion of patients possessing the SNP allele, a minimum detectable effect, the level of statistical significance (p value) and the power (ability to detect a true association; McCarthy and Hilfiker, 2000). Therefore, the selection of candidate SNPs will have to take into account not only the presumed biological relevance, but also the expected prevalence of the minor alleles and heterozygosity to ensure adequate power of the study without having to recruit impracticably large numbers of patients. On average cSNPs have a minor allele frequency of only about 7% (Halushka et al, 1999); and possibly even lower for those cSNPs of biological relevance (Cargill et al, 1999). This factor limits the predictive value of any single cSNP.

1.2.3. Hardy-Weinberg equilibrium

The Hardy-Weinberg model describes and predicts genotype and allele frequencies in a non-evolving population. The model has five basic assumptions: 1) the population is large; 2) there is no gene flow between populations, (e.g.-from migration); 3) mutations are negligible; 4) individuals mate randomly; and 5) natural selection is not operating on the population. Given these assumptions, a population's genotype and allele frequencies will remain unchanged over successive generations, and the population is said to be in Hardy-Weinberg equilibrium. The Hardy-Weinberg equation states that for a single gene

trait with two alleles, A and a, with allele frequencies of p (A) and q (a) where $p + q = 1$, the frequencies of the three possible genotypes are given by

$$p^2 (AA) + 2pq (Aa) + q^2 (aa) = 1$$

In pharmacogenomic studies, the genotype frequencies of the population studied should be within Hardy-Weinberg expectations for the results to be interpretable. Deviations from Hardy-Weinberg equilibrium can inflate the chance of a false-positive association (Schaid and Jacobsen, 1999).

1.2.4. Haplotypes

Haplotype is a way of denoting the collective genotype of a number of closely linked loci on a chromosome (www.ornl.gov/TechResources/Human_Genome/glossary). Several SNPs may be inherited together as a haplotype so that identifying the state of one would allow prediction of the state of others. Analysis based on haplotypes of a gene can have advantages over analysis based on individual SNPs (Judson et al, 2000), especially if multiple susceptibility alleles are being studied (Morris and Kaplan, 2002). Haplotype based analysis has been shown to reduce variations in the strength of genotype-phenotype association in candidate gene studies (Saunders et al, 2001). However, if the number of SNPs being studied is less than the number of haplotypes, analysis based on haplotypes may not be advantageous (Bader, 2001).

1.2.5. Definition of the phenotype

The definition of drug response in pharmacogenomic studies has to be precise and accurate for the results to be valid. This is often not straightforward. Imperfect adherence

to prescribed treatment, partial response, pharmacokinetic and pharmacodynamic interactions with other prescription and non-prescription drugs, diet and lifestyle factors can all cloud the issue (Clancy and Kass, 2003). It is necessary therefore that standardised definitions for categorising response be set before the study is undertaken and that these are applied uniformly in the population under study. Study personnel involved with categorising treatment response should be blinded to the outcome of genotyping studies.

1.2.6. Analysis

In case control studies the magnitude of the effect of the SNP on drug response is commonly estimated and expressed as an Odds Ratio. Owing to the multifactorial nature of drug response, the magnitude of the effect conferred by a single SNP is likely to be low, in the range of 1.5 to 3.0 (McCarthy and Hilfiker, 2000). Studies testing for multiple SNPs will need to employ higher significance levels depending on the number of hypotheses being tested. However, the usual methods of correcting for multiple testing (e.g.: - Bonferroni correction) will be too conservative as they assume independence between the factors. The effects of multiple SNPs may not be independent and the risk of a Type II error (of not finding an association where one exists) is high. Special statistical techniques need to be used to address this (Romero et al, 2002).

1.2.7. Selection of candidate genes

Several genes influence the pharmacokinetics and pharmacodynamics of AEDs. Genes involved in pharmacokinetics encode drug metabolising enzymes and transport proteins. Polymorphisms in these genes can alter the expression and function of these proteins (Hiratsuka and Mizugaki, 2001; Ramachandran and Shorvon, 2003). Altered metabolism affects serum and therefore brain concentrations of AEDs. Similarly, polymorphisms

resulting in increased expression levels and activity of drug transporter proteins can result in lower intraparenchymal concentrations of AEDs and can contribute to the failure of drug therapy (Siddiqui et al, 2003). For commonly used AEDs, blockade of voltage dependent sodium channels and potentiation of γ-aminobutyric acid (GABA) mediated inhibitory transmission are the two principal mechanisms of action (Kwan et al, 2001; Rogawski and Löscher 2004). Genes encoding the subunits of voltage gated sodium channels and GABA receptors therefore influence the pharmacodynamics of AEDs. Polymorphisms in these genes, affecting the structure and/or function of the subunits they encode, could potentially render specific mechanisms inoperative and cause failure of AED treatment.

1.3. The voltage gated sodium channel

1.3.1. Molecular biology of the voltage gated sodium channel

Voltage-gated sodium channels are mainly responsible for the generation and propagation of action potentials in the nervous system. Mammalian sodium channels are heterotrimers, with a central 260 kDa α subunit, linked non covalently to a 36 kDa β1 subunit and through a disulphide bridge to a 33kDa β2 subunit (Whittaker et al, 2000). The α subunit is necessary and sufficient to confer the principal properties of the voltage gated sodium channel: voltage-dependent activation, rapid inactivation and selective ion conductance (Yu and Caterall, 2003). The β subunit modulates channel expression and function (Patton et al, 1994; Ragsdale and Avoli, 1998). Co-expression of β1 subunits with the α subunit in the developing brain has been associated with an increased appearance of voltage gated sodium channels on the cell surface (Isom et al, 1992). Coexpression of both β1 and β2 subunits with the α subunit serves to increase the functional expression of ionic currents, by influencing the gating kinetics of the channel

(Isom et al, 1995; Hanlon and Wallace, 2002). The β2 subunit, which is exclusively expressed in neurons, also has structural homology to cell adhesion molecule contactin/F3 (Joho et al, 1990; Isom, 2000). This suggests a potential role for the β2 subunit in the localisation and stabilisation of the sodium channel on the cell membrane.

Nine α subunits have been functionally characterised and denoted $Na_v1.1$ – $Na_v1.9$, and a tenth related isoform, NaV_x may also function as a sodium channel (Yu and Catterall, 2003, Table 24). Three different β subunits have also been identified — β1- β3. The various isoforms of the α subunit exhibit a high degree of sequence homology and likely share a similar tertiary structure (Ragsdale and Avoli, 1998). Sequence analysis suggests four repeats of a structural motif each consisting of six putative α helical transmembrane segments. The four channel domains are believed to form a square array with the ion-conducting pore located in the centre. The S4 segments in each domain function as the voltage sensors for voltage-dependent activation of the channel. The S5 and S6 segments in each domain and the short SS1/SS2 segments between them form the pore of the channel. The intracellular loop between domains III and IV forms the inactivation gate, which folds into the pore and occludes it within 1 ms of channel opening (Catterall, 1999).

1.3.2. Voltage gated sodium channels as AED targets

The neuronal voltage-gated sodium channel is arguably the most important molecular target of currently available AEDs. It represents the principal site of action of phenytoin (PHT), carbamazepine (CBZ), lamotrigine (LTG) and oxcarbazepine and a potentially important contributor to the pharmacology of sodium valproate, felbamate, gabapentin, topiramate and zonisamide. It also serves as a drug target for Class I antiarrhythmic drugs

and local anaesthetics. The activity of such diverse classes of drugs on the voltage gated sodium channel is brought about by preferential binding of these agents to the various subtypes in the open and inactivated channel states. CBZ, the archetypal sodium channel blocking AED, has been shown to exert both a voltage- and use- dependent block of sodium channels (Ragsdale et al, 1991). It exerts a modest block of sodium channels in their resting state at hyperpolarised membrane potentials. This effect is enhanced when the membrane is depolarised. The blocking properties of CBZ are most pronounced when the membrane is repeatedly and rapidly depolarised. It stabilises the inactivated state of the channel and by slowing recovery from the inactivated state, reduces the ability of the channel to maintain high frequency action potential firing during sustained membrane depolarisation. As use-dependent block causes a preferential reduction in the availability of sodium channels during high but not low frequency firing, this mechanism is thought to be key to the antiepileptic properties of CBZ. Use- and voltage- dependent block is brought about by binding to specific sites on the inactivated sodium channel. There is experimental evidence to suggest that this site is probably on the α subunit at the transmembrane segment S6 in domain IV (Catterall, 1999). Studies also suggest that this site is common to LTG, PHT and CBZ (Kuo, 1998). Alteration to the amino acid sequence at this site by experimental mutagenesis has been shown to dramatically alter the affinity of drugs that act by binding to voltage dependent sodium channels (Ragsdale et al, 1996).

Table 24. Voltage gated sodium channel α subunits (adapted from Wood and Baker, 2001)

Channel	Previous name	Gene symbol	Chromosome (human)	Pharmacology
$Na_v1.1$	Type I	SCN1A	2q24	TTX-s
$Na_v1.2$	Type II	SCN2A	2q23-24	TTX-s
$Na_v1.3$	Type III	SCN3A	2q24	TTX-s
$Na_v1.4$	SkM	SCN4A	17q23-25	TTX-s
$Na_v1.5$	Cardiac	SCN5A	3p21	TTX-r
$Na_v1.6$	NaCh6	SCN8A	12q13	TTX-s
$Na_v1.7$	PN1	SCN9A	2q24	TTX-s
$Na_v1.8$	SNS/PN3	SCN10A	3p21-24	TTX-r
$Na_v1.9$	NaN	SCN11A	3p21-24	TTX-r
Na_x	NaG	SCN6A/SCN7A	2p21-23	?

TTX-s Tetrodotoxin sensitive

TTX-r Tetrodotoxin resistant

1.3.3. Genes encoding sodium channel subunits

Genes encoding sodium channel α subunits $Na_v1.1$, $Na_v1.2$, Nav1.3 and $Na_v1.7$ are located on chromosome 2 (Yu and Caterall, 2003). These isoforms share sequence homology and biophysical characteristics, are blocked by nanomolar concentrations of tetrodotoxin and are widely distributed in the nervous system. A second cluster of genes on chromosome 3p21-24 encode sodium channels Na_v 1.5, Na_v 1.8 and Na_v 1.9 which are characterised by varying degrees of tetrodotoxin resistance, although they have approximately 75% sequence homology with the channels encoded on chromosome 2. Na_v 1.5 is the principle cardiac isoform and mutation in this gene has been implicated in Brugada syndrome, an autosomal dominant disorder of potentially fatal cardiac dysrhythmia. $Na_v1.8$ and $Na_v1.9$ are preferentially expressed in peripheral sensory neurons. Of the remaining isoforms, $Na_v1.4$ is mainly expressed in muscle cells and Nav1.6 is abundant in glial cells in the CNS. Phylogenetic analysis suggests a distant evolutionary relationship as these isoforms are encoded on human chromosome 11 and 15 respectively. However, both have a high degree of sequence homology and share the biophysical properties and tetrodotoxin sensitivity with the chromosome 2 encoded isoforms.

1.3.4. Expression patterns of α and β subunit isoforms

There is considerable variation in the spatial and temporal patterns of expression of voltage gated sodium channel subtypes in human brain (Wood and Baker, 2001; Kohling, 2002). At least 20 exons code for the nine α subunit isoforms and several splice variants are also expressed (Yu and Caterall, 2003). The differential distribution of sodium channel subtypes suggests that they have distinct roles that are likely to be important in maintaining the functional heterogeneity of central nervous system neurons. Several

studies have examined the distribution of the various subtypes in rat brain using immunoprecipitation, Northern blot, RT-PCR, and immunohistochemistry. Studies using human brain tissue from epilepsy surgical specimens and normal post-mortem samples have been performed using the ligase detection method (Lombardo et al, 1996) and in situ hybridisation (Whittaker et al, 2000). The distribution of the various subtypes in rat and human brain is broadly similar, the major exception being $Na_v1.3$. This isoform is embryonic and is present only in negligible amounts in adult rats but it is widely distributed in the human adult brain (Chen et al, 2000; Whitaker et al, 2001a). The distribution of various isoforms of α and β subunits estimated by assay of mRNA levels is shown in Table 25.

Several conditions including epilepsy cause changes in the expression patterns of sodium channels. The ratio of $Na_v1.1$ to $Na_v1.2$ was found to be higher in surgical specimens from patients with refractory temporal lobe epilepsy (Lombardo et al, 1996). Further studies have suggested that this could be due to a down regulation of the $Na_v1.2$ subtype rather than up regulation of the $Na_v1.1$ subtype (Whitaker et al, 2001b). This study also found a significantly increased expression of $Na_v1.3$ subtype in the human epileptic hippocampus compared to normal controls. Sodium channels isolated from surgically excised brain tissue of patients with refractory epilepsy have been shown to be insensitive to the blocking effects of CBZ (Remy et al, 2003). This suggests that sodium channel functionality may be an important factor in pharmacoresistant epilepsy.

Table 25. Expression comparisons between sodium channel and subunits in human parahippocampal gyrus, cortex, and cerebellum (adapted from Whitaker et al, 2000)

	Subtype				
Brain Region	$Na_V1.1$	$Na_V1.2$	$Na_V1.3$	β1	β2
Parahippocampal gyrus					
CA4	+	++	±	++	++
CA3	+	+++	+	+++	++
CA2	+	+++	±	++	++
CA1	+	++	±	++	++
Dentate gyrus	++	+++	++	+++	+++
Subiculum	+	+++	+	+++	++
Cortex					
Layers II/III	+	+++	+	++	++
Layers V/VI	++	+++	+	+++	++
Cerebellum					
Granular layer	++	++++	++	++++	+++
Purkinje cells	++	-	-	+++	++
Deep cerebellar nuclei	++	-	-	+++	-
Molecular layer	+	+	-	++	+

++++ Very strong expression
+++ Strong expression
++ Moderate expression
+ Weak expression
± Very weak/scattered expression
- No expression.

1.4. Summary

Non-synonymous SNPs in the genes encoding drug targets could influence response to antiepileptic drug treatment. Given the central role of the voltage gated sodium channel in neuronal excitation and its function as the principal target for several AEDs, genetic variations affecting the structure and function of these proteins could play a role in resistance to AEDs. Evidence to date suggests that $Na_v1.1$, $Na_v1.2$, $Na_v1.3$ and $Na_v1.6$ are the most widely distributed voltage-dependent sodium channel α subunit isoforms in the human brain. Genes encoding these isoforms, *SCN1A, SCN2A, SCN3A* and *SCN8A* are therefore candidate genes in pharmacogenomic studies of AEDs.

2. Association between a polymorphic variant of SCN2A and response to antiepileptic drug treatment

2.1. Introduction

In the normal human brain, Nav1.2, encoded on *SCN2A* is the most widely expressed voltage gated sodium channel α subunit in the seizure prone areas such as the hippocampus and the cerebral cortex. (See Part II, section 1.3.4.). A specific non-synonymous SNP on this gene (*R19K*) has previously been reported to be associated with Generalised Epilepsy with Febrile Seizures Plus (GEFS+) in Japanese patients (Sugawara et al, 2001). The polymorphism is defined by a G-to-A transition at nucleotide position 56 (relative to the ATG start codon), resulting in the substitution of an arginine (R) residue with lysine (K) in the encoded protein. We have investigated the prevalence of this polymorphism in responders and non-responders to AED treatment, to determine whether *SCN2A* genotyping might help in predicting response to drug treatment in patients with epilepsy.

2.2. Methods

2.2.1. Patients

This study was approved by the West Research Ethics Committee, North Glasgow University Hospitals NHS Trust and all participants provided informed consent. All patients attending the Epilepsy Unit at the Western Infirmary, Glasgow, Scotland were requested to participate in the study. Patients who had stopped attending the clinic as they had achieved remission of seizures were contacted by letter and invited to participate in the study. A total of 400 adult and adolescent patients (200 male; median age 40 years, range 14 to 84 years) were recruited. Specific exclusions were significant learning

disability, a history of alcohol-related seizures, infrequent seizures (less than 4 seizures in a year) and evidence of non-compliance with medication. The epilepsy was classified as localisation-related in 270 (67.5%) patients, idiopathic generalised in 118 (29.5%) and was unclassified in the remaining 12 (3%) individuals. An underlying structural lesion was identified in 122 patients with localisation related epilepsy. Patients had received treatment with a median of 2 AEDs (range 2-12).

2.2.2. Isolation of genomic DNA

Genomic DNA was isolated from 20ml of venous blood using a 4-step process (Wizard DNA Purification kit, Promega, Southampton, UK). Blood samples were obtained in EDTA tubes and added to 30 ml of cell lysis solution in a 50 ml centrifuge tube. This was incubated for 10 minutes at room temperature mixing once to lyse the red blood cells. The solution was then centrifuged at 2000 x *g* 10 minutes and the supernatant removed. This step was repeated until the residual pellet was white. The tube was then agitated to resuspend the cells and 10 ml of the Nuclei Lysis Solution added to lyse leucocytes. The mixture was incubated at room temperature for 2 hours. After incubation, 3.3 ml of protein precipitation solution was added to the nuclear lysate, mixed thoroughly and centrifuged at 2000 x *g* for 10 minutes. The supernatant containing genomic DNA was removed into 10 ml of isopropranolol using a pasteur pipette, taking care not to contaminate the DNA with the precipitated protein. This precipitated genomic DNA, which was centrifuged, air dried for 2 hours and rehydrated overnight using 200 µl of sterile H_2O. The DNA was then quantified by spectrophotometry based on optical density at 260nm and reconstituted in sterile H_2O to a concentration of 100ng/µl.

2.2.3. Polymerase Chain Reaction

Genotyping of the *R19K* SNP was performed by Polymerase Chain Reaction (PCR), followed by restriction enzyme digest and detection of restriction fragment length polymorphism on gel electrophoresis (Nakayama et al, 2002). A 400 base-pair strand of genomic DNA containing the site of the *R19K* SNP was amplified using the following oligonucleotides; sense 5'-AAT CAC CTT TTA TTC TAA TGG TC-3', antisense 5'-CAG TGA AGG CAA CTT GAC TAA GA-3' (MWG-Biotech, Milton Keynes, UK). The PCR reaction was performed in a final volume of 20µl with 100ng genomic DNA, 10mM tris-HCl (pH 8.3), 50mM KCl, 2mM $MgCl_2$, 250µM each dNTPs, 20pmols each primer and 1U *Taq* DNA polymerase (all Invitrogen, Paisley, UK). The PCR conditions were as follows: a denaturing step at 95°C for 10 minutes, followed by 36 cycles at 94°C for 30 s, 60°C for 30 s, 72°C for 30 s, and a final incubation at 72°C for 3 minutes. PCR products were electrophoresed on a 3% agarose gel to confirm amplification of the appropriate fragment of DNA before restriction digest

2.2.4. Restriction digest and identification of R19K genotype

A 10µl aliquot of the PCR product was digested with 5U of *ScrF1* endonuclease (New England BioLabs, Hitchin, UK) at 37°C for 4 hours. A 5µl aliquot of digest product was mixed with 5µl loading dye (bromophenol blue / xylene cyanole in 50% glycerol; all Sigma, Poole, UK), electrophoresed on a 2.5% agarose gel, and visualized by ethidium bromide staining and ultraviolet transillumination. The *R19K* SNP was identified by loss of the ScrF1 restriction site; the *R*-encoding allele yielding 178, 130, 64 and 28 bp fragments and the *K*-encoding allele yielding 206, 130 and 64 bp fragments (Figure 16, 17).

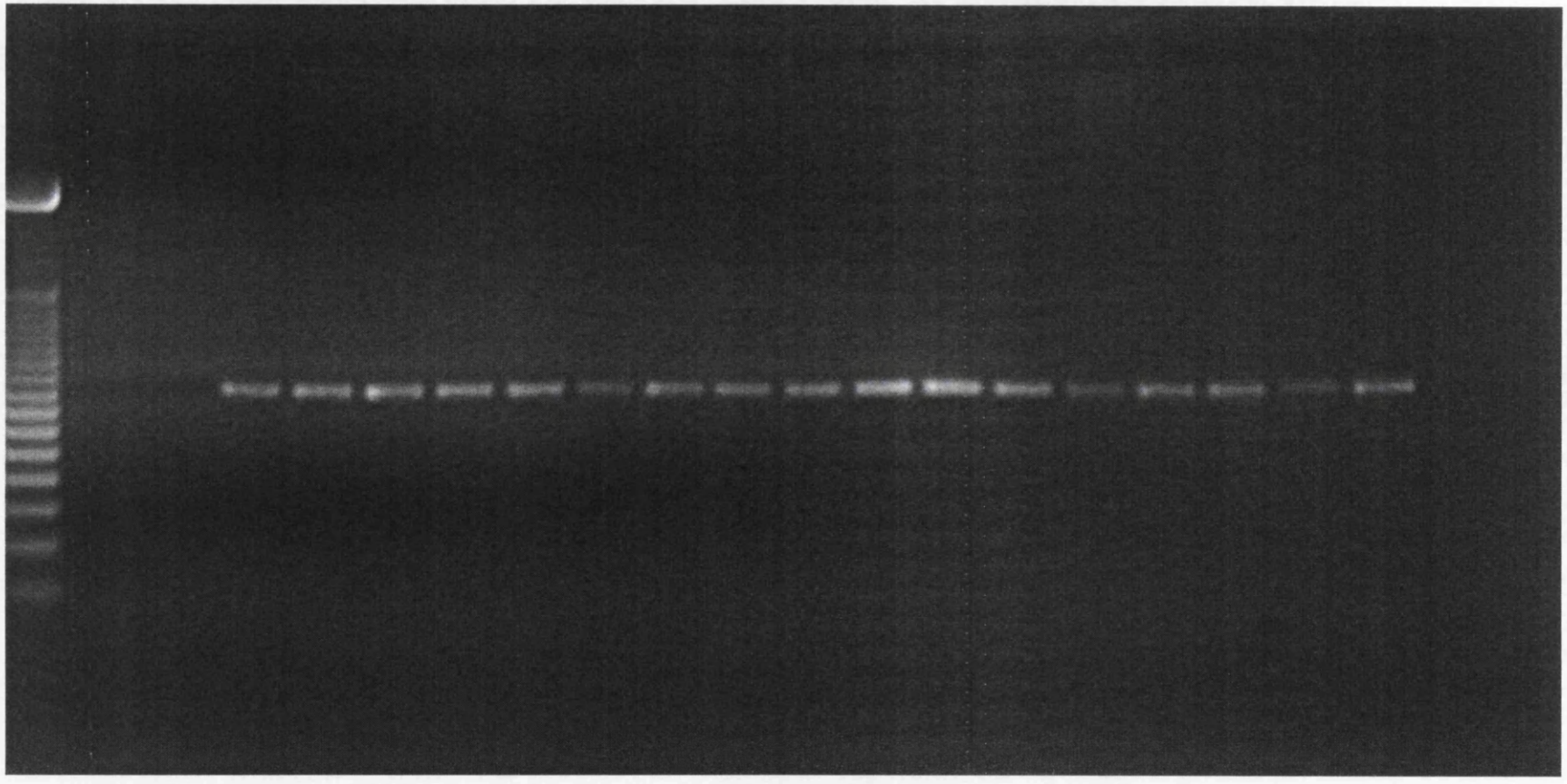


Figure 16. Amplification of a 400 bp fragment of SCN2A bearing the site of the *R19K* SNP by Polymerase Chain Reaction visualised on agarose gel by ethidium bromide staining and ultraviolet transillumination.

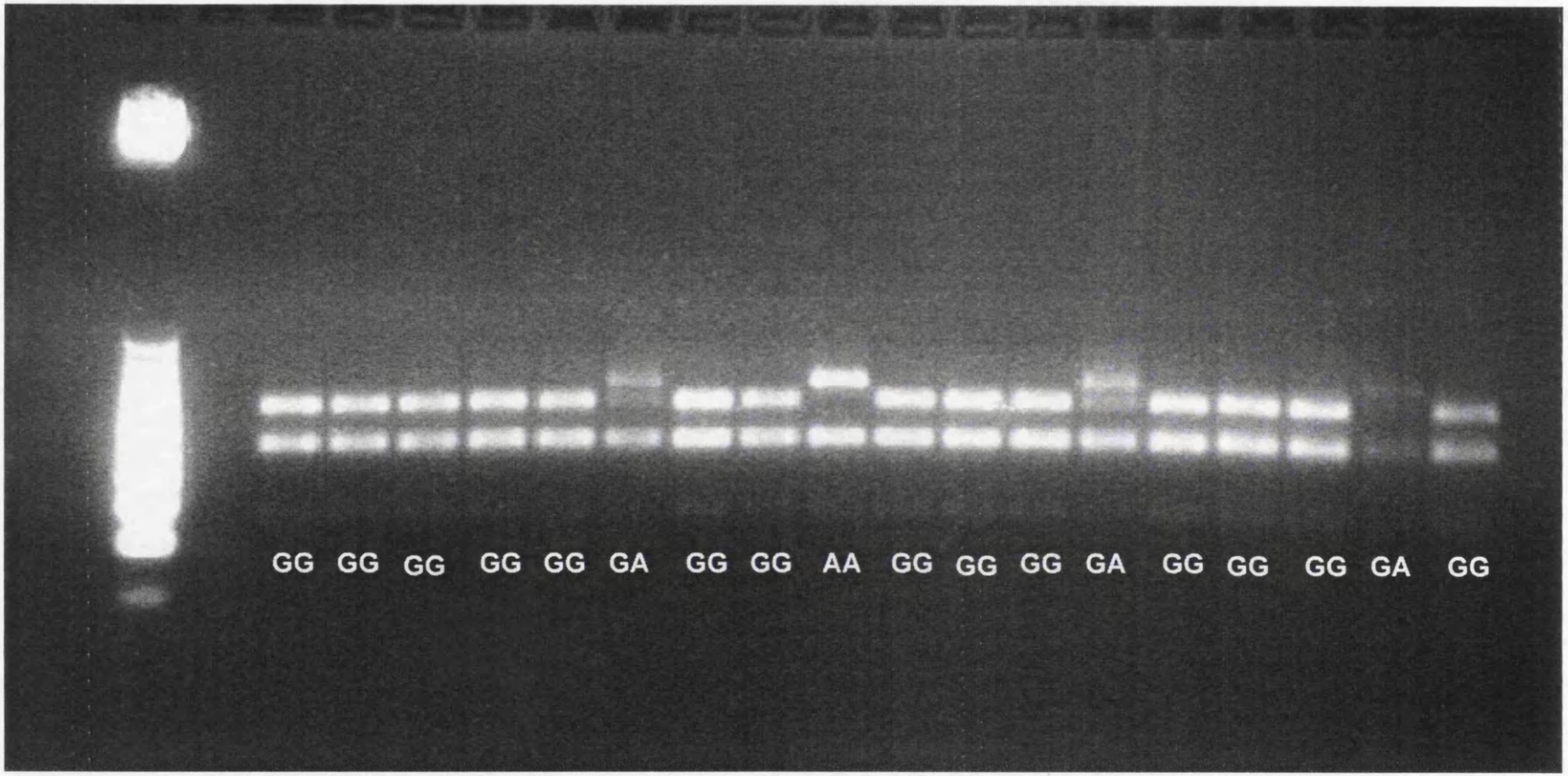


Figure 17. Determination of *R19K* genotype of *SNC2A* by ethidium bromide-stained gel electrophoresis following Polymerase Chain Reaction and endonuclease digestion with *Scr*F1. The *R*-encoding allele (G residue) is identified by 178, 130, 64 and 28 bp fragments and the *K*-encoding allele (A residue) by 206, 130 and 64 bp fragments. The 28 bp fragment was not visible in this case.

2.3. Analysis

Response to treatment was assessed by this researcher in a blinded fashion by review of clinical case notes and seizure diaries. Studies of clinical outcomes in newly diagnosed epilepsy had shown that responders enter remission by 6 months after starting treatment in 90% of cases (see Table 6). Therefore, patients were considered responders if they remained seizure free for a minimum period of six months on an unchanged AED regime (dosage adjustments to alleviate side-effects permitted). Similarly, patients failing to achieve seizure control with two well-tolerated and appropriate AED remain uncontrolled in over 90% of cases (see table 8). Thus, patients who had continued to experience seizures after treatment with two appropriate AED in adequate doses and had been compliant with treatment were classed as non responders. Genotype and allele frequencies among responders and non-responders were compared by binary logistic regression analysis using Minitab for Windows statistical software (version 13.32). Significance level was set at 0.05. The strength of association was expressed as Odds Ratios (OR) with 95% confidence intervals.

2.4. Results

2.4.1. Association of R19K SNP with response to treatment

A total of 170 (42.5%) patients were classified as responders and 230 (57.5%) as non-responders. The *K*-encoding allele of the *R19K* polymorphism was present in 50 patients, of whom 45 were heterozygous (GA genotype) and 5 homozygous (AA genotype. Genotype frequencies in the cohort were 88% GG, 11% GA and 1% AA, which were consistent with Hardy-Weinberg expectations. The *K*- encoding allele (genotype GA or AA) was present in 14 (8%) responders and 36 (16%) non-responders (OR=2.07, 95% CI

1.08-3.97, p=0.024; Figure 18). Of the 5 patients who were homozygous for the *R19K* polymorphism (AA genotype), 3 were responders.

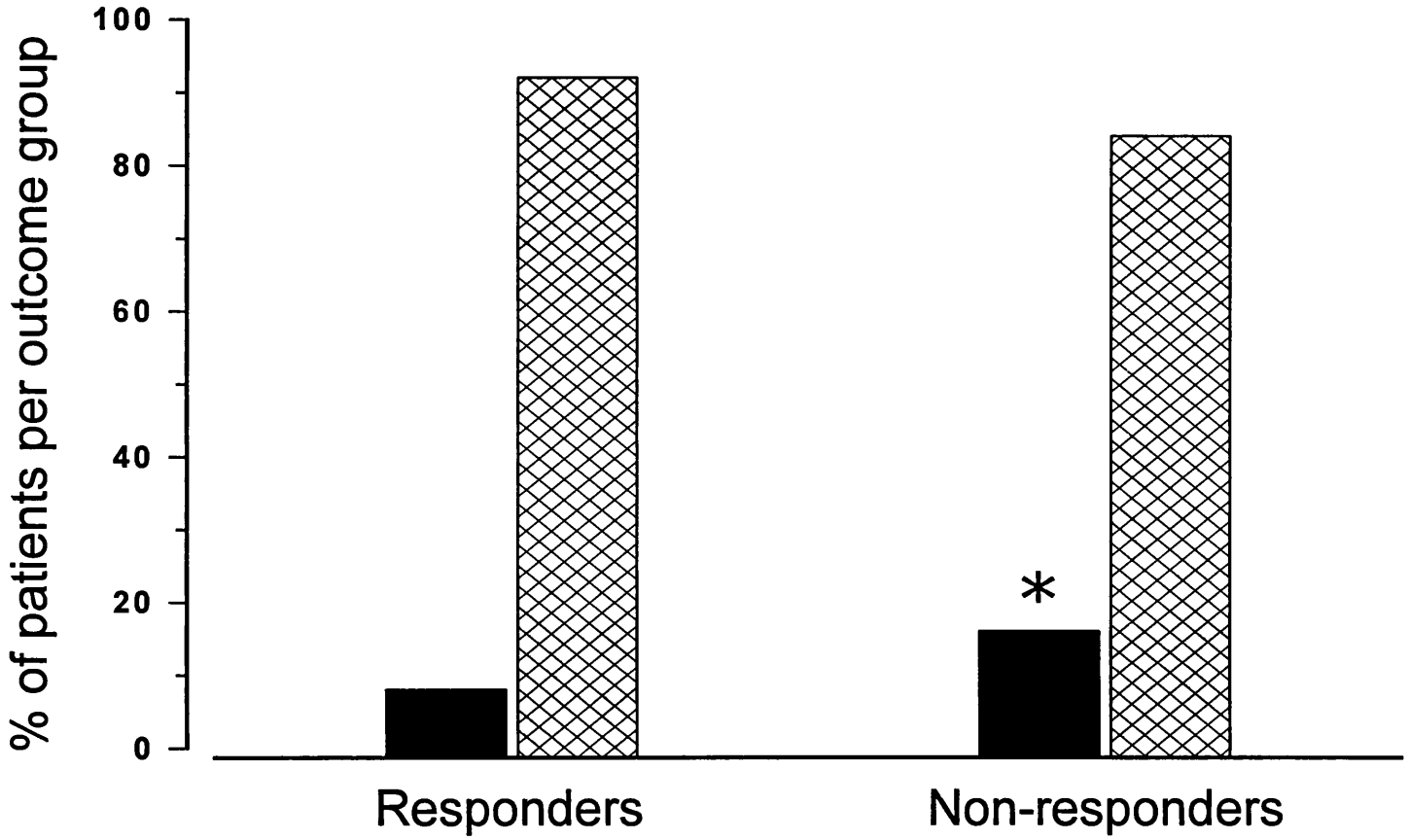


Figure 18. Distribution of *K*- encoding alleles in responders and non-responders to antiepileptic drug treatment. Results are expressed as the percentage of patients in each outcome group possessing at least one *K*-encoding allele (solid bars) vs no *K*-encoding alleles (hatched bars). Statistical significance was determined by binary logistic regression analysis (odds ratio=2.07, 95% CI 1.08-3.97, p=0.024)

2.4.2. Subgroup analysis – type of epilepsy

Among the 270 patients with localisation related epilepsy, the K-encoding allele of the R19K polymorphism was present in 25 (16%) of 159 non-responders and 8 (7%) of 111 responders (OR =2.40, 95% CI 1.04-5.54, p=0.031). Among those with idiopathic generalised epilepsy, the *K*-encoding allele was present in 11 (17%) of 64 non-responders and 5 (9%) of 54 responders (OR =2.03, 95% CI 0.66-6.27, p=0.204).

2.4.3. Subgroup analysis – type of AED

Subgroup analysis was performed for patients currently or previously treated with PHT, CBZ, LTG or OXC, as these drugs exert their principal effects on the voltage-gated sodium channel. A total of 332 patients had received treatment with one or more of these AEDs. In this subgroup, the *K*-encoding allele was present in 31 (14%) of 208 non-responders and 11 (9%) of 124 responders (OR =1.80, 95% CI 0.87-3.72, p=0.102). Most of the remaining patients had received treatment with sodium valproate, which has also been reported to possess sodium channel blocking properties. When these patients were also included (n=62), statistical significance was restored. (OR=2.04, 95% CI 1.06-3.91, p=0.027).

2.4.4. Predictive value of R19K SNP

We assessed he sensitivity, specificity and efficiency of the *R19K* SNP as a test for non-response to AED treatment. Non-responders with at least one *K*-encoding allele (GA or AA genotype) were considered true positives and responders with no *K*-encoding allele (GG genotype) were considered true negatives (Table 26). As a predictor of lack of response to AED treatment, the presence of at least one *K*-encoding allele had a sensitivity of 16% and a specificity of 92%. The positive predictive value of the SNP in identifying non-responders was 72% and the negative predictive value in excluding non-responders was 45%, resulting in a test efficiency of 48%.

Table 26. Efficiency of *K*-encoding allele in predicting non-response to antiepileptic drug treatment (TP = true positive, FP = false positive, TN = true negative, FN = false negative).

	At least one *K*-encoding allele	No *K*-encoding alleles
Non-responders	36 (TP)	194 (FN)
Responders	14 (FP)	156 (TN)

Sensitivity $\frac{TP}{TP+FN} = \frac{36}{36+194} = 16\%$

Specificity $\frac{TN}{FP+TN} = \frac{156}{14+156} = 92\%$

Predictive value (positive test) $\frac{TP}{TP+FP} = \frac{36}{36+14} = 72\%$

Predictive value (negative test) $\frac{TN}{TN+FN} = \frac{156}{156+194} = 45\%$

Test efficiency $\frac{TP+TN}{TP+FP+TN+FN} = \frac{36+156}{36+14+156+194} = 48\%$

2.5. Discussion

We investigated the prevalence of a known SNP in the *SCN2A* gene, which encodes the α-subunit of the $Na_v1.2$ sodium channel, in a series of patients attending a specialist epilepsy clinic. There was a significant association between genotype of the *R19K* polymorphism in *SCN2A* and response to AED treatment, with non-responders twice as likely to have at least one copy of the K-encoding allele. This association was maintained in patients with localisation-related epilepsies, but was not significant for those with idiopathic generalised epilepsies. However, the cohort of patients with IGE in this study was relatively small (n= 118). Interestingly, there was no significant association between genotype and response to treatment in the 332 patients with current or prior exposure to recognised sodium channel blockers (PHT, CBZ, LTG, OXC). However, the majority of other patients had received treatment with sodium valproate, which also has been reported to posses sodium channel blocking properties (Löscher, 1999). Inclusion of these patients in the analysis restored statistical significance.

These data suggest that the *K*-encoding allele of the *R19K* polymorphism in *SCN2A* is associated with non-response to AED treatment and points to a possible link for this SNP to the molecular basis of drug resistant epilepsy, at least in some patients. However, analysis of predictive value shows only 48% test efficiency (accurate prediction of treatment response by genotype) for the presence of the *K*-encoding allele in predicting non-response to AED treatment. Thus, the use of R19K genotype alone was of limited use in predicting treatment outcomes in this cohort of patients. In our population, the minor allele had a prevalence of 7%, which is consistent with previous reports (Haug et al, 2001; Sugawara et al, 2001; Nakayama et al, 2002; Weiss et al, 2003). The genotype was not significantly more predictive of response in patients exposed to sodium channel blocking drugs than in the study population as a whole. It is likely, however, that the influence of the polymorphism on drug

response is not directly related to pharmacological mechanisms, but arises as a result of subtle alterations in neuronal functioning and network properties.

In this regard, the functional significance of the *R19K* polymorphism remains to be clarified. In terms of genetic sequence, it is somewhat removed from the region corresponding to the AED binding site on the α-subunit which might explain the lack of a direct association with response to sodium channel blocking drugs. The arginine to lysine substitution at this site does not appear to influence the electrophysiological properties of the channel when expressed in human embryonic kidney cells (Sugawara et al, 2001). Arginine is a relatively conserved residue amongst the major CNS sodium channel α-subunit genes *SCN1A*, *SCN2A* and *SCN3A* and also in the *SCN4A* and *SCN5A* genes expressed by skeletal and cardiac muscle, respectively (Haug et al, 2001). Lysine is, however, present in the corresponding position in *SCN6A* and *SCN9A*, suggesting that significant functional relevance of this sequence variant is unlikely. In clinical studies examining the pathogenesis of seizure disorders, the *K*-encoding allele appears to be a relatively benign variant (Haug et al, 2001; Nakayama et al, 2002; Weiss et al, 2003) although it has been suggested to aggravate the disease phenotype in patients with generalised febrile and afebrile seizures (Sugawara et al, 2001).

Pharmacogenetic studies are analogous to genetic association studies of complex diseases inasmuch as there is often no simple correlation between genotype and phenotype (Ring and Kroetz, 2002). Expression patterns of several genes, gene-gene and gene-environment interactions as well as several non-genetic factors such as drug dosing, diet and other aspects of lifestyle undoubtedly influence the response to drug treatment. Expression patterns of the various sodium channel subtypes are also subject to spatial and temporal variations in

response to a variety of stimuli (Bartolomei et al, 1997, Whittaker et al, 2001) and significant differences are reported in the relative expression of $Na_v1.1$ and $Na_v1.2$ in the various brain regions of patients with epilepsy, when compared to normal brains (Lombardo et al 1996). The predictive value of any single genetic polymorphism in determining treatment response is therefore likely to be modest and the low test efficiency in spite of a statistically significant association in our study is not surprising (McCarthy and Hilfiker, 2000). Given the number of factors that could potentially influence response to AED treatment, the possibility of an association arising by chance is also exists. These results will therefore need to be replicated in other patient populations.

2.6. Conclusions

There are no reported studies of a significant association between a known genetic variation in a common AED target and the response to treatment in an unselected epilepsy population. If these results are replicated in other patient groups with epilepsy, genotyping of the *R19K* polymorphism in *SCN2A*, along with identification of other genetic variants that correlate with treatment response, could help identify patients at risk of developing refractory epilepsy.

Part IV

Mortality of epilepsy

1. Studies of mortality in epilepsy

1.1. Introduction

Epilepsy is an illness of various shapes and horrible; in the paroxysms, brutish, very acute and deadly; for, at times, one paroxysm has proved fatal *Aretaeus*

The fact that epilepsy could endanger the life of sufferers has been known since ancient times (Aretaeus c.100). The traditionally held view of the medical community, however, had been that for the majority of patients, epilepsy was a benign disorder with no important effect on life expectancy. Gowers observed that 'the danger to life of patients with epilepsy is not great' (Gowers, 1885). This view changed in the latter half of the 20th century with several epidemiological studies reporting consistently increased mortality rates in patients with epilepsy. Rodin in his treatise on epilepsy stated "it is quite obvious that the life expectancy of the epileptic individual does not reach that of the average person" (Rodin, 1968). Over the last 30 years, a number of studies, both community and institution based, have shed light on mortality risks in various subgroups of patients with epilepsy (Sander and Bell, 2004).

1.2. Study methodology and interpretation of results

Results from studies of prognosis and mortality in epilepsy differ substantially according to the methods used. The major methodological variations are with selection of the patient population for the study, case ascertainment, classification of epilepsy and cause of death. These differences complicate interpretation and comparison of results from various studies of mortality. A recent systematic review of mortality studies in epilepsy in the last 100 years found such wide variation in mortality rates that a summary risk could not be calculated (Shackleton et al, 2002). Most of this variation could be explained by differences in the source population and case selection.

1.2.1. Source population

Community based studies provide the most accurate estimate of risks for the population of patients with epilepsy as a whole. Longitudinal studies are necessary to achieve this as cross-sectional community surveys can miss new onset cases and fail to account for the high initial mortality of epilepsy. This can lead to the mortality risk being underestimated. The ideal study of prognosis should be large scale, population based, with comprehensive case ascertainment, accurate diagnosis, sound aetiological assignment, long follow up and efficient tracing of patients (Gaitatzis and Sander, 2004). No study in the current literature meets all of these standards but some, notably the Rochester study (Hauser et al, 1980) the National General Practice Survey of Epilepsy (NGPSE, Cockrell et al, 1994), the Vaserbotten county study in Sweden (Lindsten et al 2000) and the Iceland study (Rafnsson et al, 2001) meet many of these criteria. Results from these population-based studies best reflect mortality risks for patients with epilepsy in the general population. The excess mortality observed in these studies ranges from 40% to 110%.

Cohort studies that follow up patients attending specialist clinics or in resident care can provide detailed information about the group under study, but the results may not be relevant to other populations of patients with epilepsy. Generally, higher mortality rates have been reported from institutions and specialist centre based studies. Institution- and clinic-based studies have the advantage of more accurate diagnosis and classification of epilepsy. They are, however, liable to selection bias, as they tend to have an overrepresentation of more severe cases of epilepsy.

1.2.2. Case ascertainment

Community based studies present several difficulties in case ascertainment. Many studies rely on patients' primary care health records for recruiting cases of epilepsy. This is prone to error as the diagnosis of epilepsy can be wrong in a high proportion of patients in the non-specialist setting (Smith et al, 1999). Studies utilising primary care health records thus run the risk of including patients who do not have epilepsy. In addition, clinical coding often does not make the distinction between provoked seizures and true epilepsy in this setting. Death certification is notoriously prone to underreporting epilepsy as a causative or contributory factor to death (Hauser et al, 1980; Sander and Shorvon, 1987). Studies relying on death certificates to identify deaths in patients with epilepsy could therefore miss a significant proportion of cases. Moreover, excess risk cannot be accurately quantified as these studies employ the presumed prevalence of epilepsy in the community to estimate the population at risk. Some population-based studies use long-term AED prescriptions as a surrogate marker for the prevalence of epilepsy (Jick et al, 1992; Derby et al, 1996). This method has the advantage of not including patients with provoked seizures, but would also recruit patients taking long-term AEDs for other indications, and the issue of diagnostic inaccuracies remain unresolved.

1.2.3. Recruitment of patients

As with studies of treatment outcomes, the temporal aspects of seizure disorders also have important effects on the mortality statistics. When patients presenting with their first ever seizure are included the mortality risks are dramatically higher (Loiseau et al, 1999). In the NGPSE, the mortality rates in patients seen after their first ever seizure (where the index event was also the first event) was higher than for those patients seen after more than 2 seizures (Lhatoo et al, 2001). A proportion of first ever seizures would be acute symptomatic seizures resulting from an neurological insult, a condition known to be associated with high

mortality in the short and long term (Logroscino et al, 1997; Logroscino et al, 2002). Although many of these patients can develop epilepsy, their natural course tends to be different from patients presenting with recurrent unprovoked seizures. Thus, including these patients would suggest a higher mortality risk in studies of prognosis of epilepsy.

1.2.4. Identifying cause of death

Ascertaining cause of death in epidemiological studies of epilepsy is often not straightforward, owing to inconsistencies and inaccuracies in death certification (National sentinel audit of death in epilepsy, 2002; Bell et al, 2004). In many cases, cause of death is cited without firm pathological evidence, and in other cases all medical conditions the patient suffered are listed even when they had not contributed to death. Sudden Unexpected Death in Epilepsy (SUDEP) is now recognised as the most common epilepsy-related cause of death (Lhatoo and Sander, 2002). This is typically unwitnessed and tends to be underreported on death certification. A firm diagnosis of SUDEP requires post mortem and toxicological data, which are not often available to epidemiological investigators. If SUDEP is thought likely from clinical information, in the absence of comprehensive post mortem data, deaths are considered possible or probable SUDEP as proposed by Leetsma and colleagues (Leetsma et al, 1997). Respiratory infections, especially aspiration pneumonia, frequently cause death in institutionalised patients with epilepsy, who have coexisting neurological deficits (De Toledo et al, 2004). Whether seizures contribute to death from respiratory problems can be difficult to ascertain in retrospective death certificate based studies.

1.2.5. Measurement of mortality

Survival of patients is usually measured using the Kaplan Meier or life table method. Standardised Mortality Ratio (SMR) is the most commonly used expression of mortality risks in epidemiological studies of epilepsy. This is calculated as the ratio between the number of deaths observed in the population under study and the number of deaths expected based on the age and sex specific mortality rates for the general population. Contribution of each cause of death to the mortality of epilepsy is quantified as the Proportional Mortality Rate (PMR). In addition, the ratio of observed and expected deaths from each cause can be calculated and expressed as the cause-specific SMR.

1.3. Causes of death in epilepsy

Bacon classified the causes of death in epilepsy (excluding secondary causes) as those arising from the long continued effects of the disease on the body, deaths after a rapid succession of fits, sudden deaths in a fit, accidents due to fits (Bacon, 1868). Currently deaths due to status epilepticus (SE), SUDEP, accidents, treatment related deaths and suicide are considered epilepsy related deaths (Langan, 2000). Wannamaker reviewed the literature from 1910 to 1974 and concluded that on average, 47.2% of deaths in patients with epilepsy could be attributed to epilepsy (Wannamaker, 1990). These studies were largely institution-based and other studies in similar settings have reported epilepsy as the main cause of death in 19-31% of cases (White et al, 1972; Iivaninen and Lehtinen, 1979; Klenerman et al, 1993). Population based studies such as the Rochester study (3% epilepsy related deaths) and NGPSE (4% epilepsy related deaths) have found considerably fewer cases where epilepsy was the main contributor to death.

1.3.1. Epilepsy related deaths

SUDEP is the commonest seizure related cause of death in patients with epilepsy with a PMR of 1-13 % in community studies and 18-41% in special populations (see part IV, section 1.5). SE has an annual incidence of 18-41 per 100,000 in the general population (DeLorenzo et al, 1996; Hesdorffer et al, 1998). It can be the first presentation of epilepsy in 30% cases (Hesdorffer et al, 1998). Approximately one third of cases are acute symptomatic and the remaining occur in patients with established epilepsy. The case fatality rate of SE can be up to 20% (Logroscino et al, 2002). SE is thought to account for 12.5% of all deaths in epilepsy with SMRs ranging from 2.8 to 3.8 depending on the underlying cause (Gaitatzis and Sander, 2004). As with other epilepsy related causes of death, this tends to be lower in patients in the community compared to institutionalised patients. Accidents account for 1.2 to 6.5% of deaths among patients with epilepsy in the community. Epilepsy patients are at significantly increased risk of having fatal accidents compared to the general population, as evidenced by the cause-specific SMR of 2.4 to 5.6 (Nilsson et al, 1997; Shackleton et al, 2002). Suicide has also been reported to be more common in certain groups of patients with epilepsy (Nilsson et al, 1997; Shackleton et al, 1999), although community based studies have not demonstrated a significantly elevated risk (Hauser et al, 1980; Cockerell et al, 1994). This is however an important and preventable cause of death in patients with uncontrolled epilepsy in whom co-existing depression is common (Nilsson et al, 1997). Pneumonia is a frequent cause of death in patients with epilepsy and could be caused by aspiration during a seizure. The PMR of respiratory infections is in the region of 25% in institutionalised patients (White et al, 1972; Zielinski et al, 1974; Iivaninen and Lehtinen, 1979; Klenerman et al, 1993) and approximately 5% in community based studies (Hauser et al, 1980). Deaths from respiratory infections are more common in elderly patients and in infants and children with severe epilepsy and psychomotor retardation (Klenerman et al, 1993; Harvey et al, 1993; Nilsson et al, 1997).

1.3.2. Deaths form other causes

Deaths that are unrelated to seizures themselves are predominantly caused by underlying conditions causing epilepsy. Malignant neoplasia account for 16 to 29 % of deaths in community and hospital based case series, 1/4 to 1/3 of which are brain tumours (Hauser et al, 1980; Nilsson et al, 1997; Lhatoo et al, 2001). Cerebrovascular disease has a PMR of 14-16% in community studies and 5-6% in hospital studies (Hauser et al, 1980; Shackleton et al, 2002). It is thus responsible for proportionately more deaths in epilepsy patients in the community than among those attending epilepsy clinics. This in part owing to the fact that patients with epilepsy due to cerebrovascular disease generally respond well to treatment, and the majority can be successfully managed in the community (Stephen and Brodie, 2000). PMR for ischaemic heart disease follows similar trends to that for cerebrovascular disease. The majority of deaths from IHD occur in older patients although the Rochester study did find increased heart disease mortality in patients under the age of 65 (Annegers et al, 1984). Cause specific SMR for IHD range from 1.1 to 1.6 in community based studies (Hauser et al, 1980; Shackleton et al, 1999; Rafnsson et al, 2001).

1.4. Risk factors for premature death in epilepsy

1.4.1. Age and sex

The risk or premature death in epilepsy varies depending on factors such as age, sex, type of epilepsy, coexisting conditions and response to treatment. Previous studies have shown an increased SMR in younger patients, with little excess mortality in patients aged over 50 years (Hauser et al, 1980; Nilsson et al, 1997; Shackleton et al, 1999). This is owing to a combination of the high mortality observed in children with epilepsy and psychomotor retardation and the low number of expected deaths in this age group. One population based incidence cohort study found excess mortality risk only in males, and not in females

(Rafnsson et al, 2001). Some other authors have reported excess mortality in males compared to females (Hauser et al, 1980; Shackleton et al, 1999); however other studies have not found a significant sex difference for mortality risks (Sperling et al, 1999; Lindsten et al, 2000; Lhatoo et al, 2001).

1.4.2. Seizure type and epilepsy syndrome

A major difficulty in interpreting differences in mortality among patients with various epilepsy types of is the inconsistency of classification of epilepsy in the various studies. The currently used clinical classification of epilepsy (Commission, 1989) has not been followed in many studies of mortality. Several older studies employ the terms idiopathic and cryptogenic interchangeably. Idiopathic epilepsies have been found to have an increased risk of mortality in the Rochester study (SMR 1.8; Hauser et al, 1980) as well as the earlier reports from the NGPSE (Cockerell et al, 1997). In the most recent report from the NGPSE, though, the SMR for IGE was not significantly elevated (1.3; 95% CI, 0.9-1.9). However, most studies have found a consistently elevated mortality risk in patients with symptomatic epilepsy (older studies employ the term remote symptomatic epilepsy). SMR in this group of patients in population based studies were 2.2 in the Rochester study, 3.3 in the NGPSE and 3.7 in the Vaserbotten county study in Sweden (Hauser et al 1980; Lhatoo et al 2001; Lindsten et al, 2001).

Seizure type is also important in determining the risk of premature death. Patients with absence seizures have no excess mortality risks and those with generalised tonic clonic seizures appear to have the highest excess risks (Hauser et al, 1980; Lindsten et al, 2001). In the Rochester study SMR for myoclonic epilepsy was found to be significantly elevated (4.1) but there was no excess mortality in patients with complex partial seizures. The Vaserbotten

county study however did find higher mortality rates in patients with complex partial seizures (SMR 2.1, 95% CI 1.2-3.6).

1.4.3. Coexisting intellectual / neurologic handicap

The highest SMRs are seen for patients with remote symptomatic epilepsy associated with neurological or intellectual deficit. One study reported an SMR of 22 in children with neurological deficit compared to those without (Harvey et al, 1993). In the Rochester study those with congenital or perinatally acquired neurological or intellectual impairment had the highest long-term mortality, resulting in an SMR of 11. As discussed above, this is due to a combination of high fatality and the low expected mortality in this age group

1.4.4. Duration of increased risk

The highest excess mortality is seen in the early years after the onset of seizures (Cockrell et al, 1994; Olaffson et al, 1998; Lindsten et al, 2000). In the Rochester study, patients who responded to treatment, had an SMR of 2 in the first 5 years, but thereafter there was no excess risk of mortality (Hauser et al, 1980). In the NGPSE, mortality rates were seen to fall to same level as the general population after 4 to 9 years of follow up (Lhatoo et al, 2001). Most of the early excess mortality is ascribable to underlying organic brain lesion (Loiseau et al, 1999). However, patients who do not achieve seizure control with AED treatment appear to remain at high risk of premature death (Gaitatzis and Sander; 2003)

1.4.5. Severity of epilepsy

Control of seizures has been shown to affect mortality in several studies. In a study in learning-disabled patients, Strauss and colleagues found the highest mortality risk of in patients with a recent history of status epilepticus followed by those who continued to suffer generalised seizures and then by those who continued to experience partial seizures. Patients

who had not suffered recent seizures did not have excess mortality rate compared to control subjects without epilepsy (Strauss et al, 2003). Similarly, no increased mortality risk has been observed in post surgical patients who become seizure free while those continuing to suffer seizures were at high risk of premature death (Sperling et al, 1999).

1.5. SUDEP

1.5.1. Definition

SUDEP is the most common epilepsy-related cause of death in patients with epilepsy. The widely accepted definition of SUDEP is '*sudden unexpected witnessed or unwitnessed, non traumatic and non drowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which post mortem examination does not reveal a toxicologic or anatomical cause for death'* (Nashef, 1997). Post mortem examination and toxicological data are often not available to epidemiological investigators. In these circumstances if SUDEP is suspected on clinical grounds, deaths are categorised as probable or possible SUDEP (Nashef, 1997; Leetsma et al, 1997).

1.5.2. Incidence of SUDEP

Several studies have attempted to quantify the incidence of SUDEP in patients with epilepsy. Some community-based studies use coroners' records to identify cases of SUDEP and use the presumed prevalence of epilepsy in the community as the denominator. The incidence of SUDEP in these studies range from 1in 525 to 1 in 2100 patient years (Terrence et al, 1975; Leestma, 1984; Langan, 1998). The UK National Clinical Sentinel Audit of Epilepsy Related Deaths audited 595 deaths in which epilepsy was mentioned on the death certificate and found that 60% all epilepsy related deaths were attributable to SUDEP and a further 7% were due to possible SUDEP (National sentinel audit on epilepsy death, Report 2002). However, the sensitivity of this method in identifying cases of SUDEP is low. A recent study found that

epilepsy is mentioned in only 25% of death certificates of patients with epilepsy (Bell et al, 2004). Moreover, as the prevalence of epilepsy in the community is not accurately estimated in these studies, they are prone to erroneous quantification of risk. Studies using AED prescriptions to estimate the prevalence of epilepsy in the community report incidence of SUDEP ranging from 1in 452 to 1 in 1850 depending on definition of cases (Jick et al, 1992; Derby et al, 1996). Ficker and colleagues evaluated mortality in all patients diagnosed with epilepsy in Rochester, Minnesota between 1935 and 1994 and found a SUDEP incidence of 0.35 per 1000 patient years (Ficker et al, 1998) while a prospective cohort study of newly diagnosed epilepsy patients have found incidence of SUDEP to be 1.2 per 1000 patient years (Walczak et al, 2001). The NGPSE in the UK has reported the first case of SUDEP after 8000 patient years of follow up, suggesting that SUDEP is a rare event in newly diagnosed epilepsy populations (Lhatoo et al, 1999).

Incidence of SUDEP is higher in patients with more severe epilepsy. Patients with chronic epilepsy attending a tertiary referral centre had incidence of 1/200 patient years (Nashef et al, 1995). Studies in institutionalised patients with epilepsy have shown a SUDEP rate of 1/260 to 1/290 person years (Klenerman et al, 1993; Nashef et al, 1995). Follow up studies of patients in epilepsy surgery programmes have shown SUDEP rates between 1/100 and 1/455 person years (Dasheiff, 1991; Sperling et al, 1999; Hennessey et al, 2001; Nilsson et al, 2003). Most deaths occur in patients whose seizures are inadequately controlled after surgery. SUDEP rates are even higher in patients who are evaluated in a surgical programme but do not under go operation (Vickery, 1997; Nilsson et al, 2003).

1.5.3. Risk factors for SUDEP

Most witnessed cases of SUDEP occur shortly following a seizure, which is typically generalised in nature (Langan et al, 2000). The majority of SUDEP deaths however are

unwitnessed (Nashef, 1998). Most patients are found in their beds having died in their sleep, but many have features suggestive of the occurrence of a seizure (Langan, 1998). Thus, available evidence suggests that SUDEP is a seizure related event. Higher sudden death rates have been observed in patients with intractable epilepsy (Langan, 2000 b). Patients are generally young with the mean age at death between 20 and 40 in most series (Leestma et al, 1989; Timmings et al, 1993; Nashef et al, 1995). Most studies have found a higher risk in males (Leestma et al, 1989; Lip and Brodie 1992; Timmings et al, 1993) although other authors have not found a significant difference in risk between the sexes (Nashef et al, 1995; Ficker et al, 1998). SUDEP occurred more commonly among patients with localisation related epilepsy than among those with idiopathic generalised epilepsy in most series (Annegers et al, 1984; Nashef et al, 1998). One study found the highest incidence of SUDEP in males with idiopathic generalised epilepsy (Nilsson et al, 1999). This study also identified polytherapy and frequent dosage changes as risk factors for sudden death.

1.5.4. Mechanisms underlying SUDEP

The mechanisms underlying SUDEP have not been fully elucidated. Pulmonary oedema, congestion of liver and cardiac enlargement have consistently been observed at post mortem examination in cases of SUDEP (Earnest et al, 1992; Stollberger and Finsterer, 2004). The degree of pulmonary oedema is however not sufficient to cause death on its own. Suggested mechanisms of SUDEP include cardiac arrhythmia due to myocardial damage, autonomic imbalance, hypoxia, arrhythmogenic effect of AEDs and central or obstructive apnoea (Nashef et al, 1996; Natelson et al, 1998; Hilz et al, 2002; Lathers and Schraeder, 2002). Disturbance of cardiac rhythm has been extensively investigated as a possible mechanism involved SUDEP (Tavernor et al, 1996; Nei et al, 2004). Interstitial myocardial fibrosis, focal leucocytic infiltration and abnormalities of the cardiac conducting system have been found in SUDEP victims at autopsy (Stollberger and Finsterer 2004). Localisation related

(especially temporal lobe) seizures are commonly associated with tachycardia and tachyarrhythmias (Blumhardt et al, 1986; Di Gennaro et al, 2004). Ictal bradycardia has been reported by several authors, occurring either as a primary event (Rocamora et al, 2003; Devinsky et al, 1997) or in relation to ictal apnoea (Nashef et al, 1996; So et al, 2000). There is evidence for deranged regulation of cardiovascular reflexes in patients with temporal lobe epilepsy with or without hippocampal sclerosis (Ansakorpi et al, 2004; Mayer et al, 2004). Reduced heart rate variability has been reported in patients with temporal lobe epilepsy and could be a marker of disturbed autonomic control (Tomson et al, 1998; Ansakorpi et al, 2002; Ferri et al, 2002). Seizure associated apnoea is another important potential mechanism of SUDEP. Cases of SUDEP occurring in patients undergoing video EEG monitoring suggest that respiratory compromise rather than cardiac causes maybe the mechanism underlying SUDEP (Bird et al, 1996; So et al, 2000). Central respiratory depression owing to ictal activity, post ictal hypotonia of the muscles of respiration and reduction in tidal volume in the prone position can all cause respiratory compromise.

1.5.5. Antiepileptic drugs and risk of SUDEP

Some reports suggest an increased risk of SUDEP in patients taking carbamazepine (Timmings et al, 1993), but other investigators have not found such an association (Leestma et al, 1997; Nilsson et al, 1999). The possible effect of AEDs such as phenytoin and carbamazepine on cardiac conduction is also important in this regard (Walczak, 2003). There is conflicting data regarding AED serum levels and SUDEP risk. Some studies have found low serum and hair levels in SUDEP cases (Terrence et al, 1975; Leestma et al, 1989; George and Davies 1998), and poor adherence to prescription is considered a risk factor for SUDEP. It has been suggested that abrupt withdrawal of AEDs can increase the autonomic dysfunction causing cardiac arrhythmias (Kenneback et al, 1997, Hennessey et al, 2001). Other studies, however, have failed to find an association between lower serum levels and

SUDEP (Opeskin et al, 1999; Walczak et al, 2001). Nilsson and colleagues reported polytherapy, frequent dose changes and high carbamazepine concentrations to be more common in patients dying of SUDEP than controls (Nilsson et al, 2001). This could however merely be indicative of the severity of the epilepsy than a causative role for AEDs in SUDEP. To date there is no clear evidence to implicate any specific AED in SUDEP.

1.6. Summary

While patients diagnosed with epilepsy clearly have a higher mortality risk compared to the general population, this is not uniform in all patients. Several demographic factors as well as the type, underlying aetiology and severity of epilepsy all affect the prognosis for life. SUDEP is the most frequent epilepsy related cause of death. Individuals with uncontrolled epilepsy are at highest risk of SUDEP, especially those with co existing intellectual deficits and those who have failed evaluation for epilepsy surgery. Population based longitudinal studies can provide the most realistic picture of risks in the epilepsy patients living in the community. Such data are important from the public health perspective and can inform health service planning. Cohort studies in representative patient group will provide the most accurate assessment of risks to help counsel patients with epilepsy.

2. Comparison of mortality in adults with newly diagnosed and chronic epilepsy

2.1. Prognosis for life

It is generally accepted that patients with epilepsy are at higher risk of premature death compared to the general population. Whether mortality risks should be discussed with patients routinely, however, is a matter of debate (Beran et al, 2004). Physicians have a responsibility to discuss fully and frankly the material risks associated with any medical condition and /or treatment. Material risk in this context is considered one that the doctor knows, or should know, that the individual patient will rate as significant (Beran et al, 2004). While it is clear that the risk of premature death, especially SUDEP, is increased manifold in certain subgroups of patients with epilepsy, the overall risk for patients with epilepsy in the community probably remains small (Part IV, section 1.5.4). Routinely discussing mortality issues with patients at the time of the first specialist consultation could cause undue alarm and impede the return to independent and productive life, which is the goal of treatment for most patients with epilepsy. Clinicians have to balance this consideration against the need for patients and their relatives to be provided information on risks. Studies that help to quantify risks in specific groups of patients and identify clinical and demographic characteristics of those at particularly high risk of premature death could help in this process.

Data from community-based studies is of limited use to clinicians in counselling patients in specific settings. Cohort studies in representative patient groups provide more relevant data to help assess risks in individual patients. High death rates are seen in the early years after diagnosis of epilepsy, most of which is attributable to the underlying condition causing epilepsy. Much of the late mortality in epilepsy is seen in patients who do not achieve seizure control with AED treatment (Part IV section 1.4.5). Thus, different factors operate in determining the prognosis for life in patients with newly diagnosed and chronic epilepsy.

Several studies have shown that the prognosis for seizure control is considerably worse in patients failing their first AED compared to treatment naïve patients (Part II, section 1.4). Therefore, any discussion of mortality risks with patients should take the prognosis for seizure control into consideration. For this reason, patients with newly diagnosed and chronic epilepsy need to be treated separately in studies of mortality. We analysed mortality data in cohorts of patients with newly diagnosed and chronic epilepsy attending the Epilepsy Unit, Western Infirmary, Glasgow, Scotland to quantify the risk of premature death in the two patient groups.

2.2. Methods

2.2.1. Newly diagnosed cohort

This group consisted of 890 patients diagnosed with epilepsy after presenting with seizures between August 1981 and May 2001 (Part II, Section 1.2.3). There were 465 (52%) males and 425 females (Table 27). The median age at onset of seizures was 29 (range 1 to 93) years and at diagnosis of epilepsy was 31 years (range 9 to 93). Epilepsy was classified as localisation related in 625 (70%) patients of which 268 (30%) had identifiable cerebral lesions on imaging investigations and were categorised as symptomatic epilepsy. Of the remaining patients 117 (13%) had idiopathic generalised epilepsy and in 148 (17%), epilepsy could not be classified. Learning disabilities were present in 30 patients, 25 of whom was classified as mild. The mean follow up period of survivors was 92 months and the total follow up for the cohort was 6480 person years.

Table 27. Demographic characteristics of patients with newly diagnosed and chronic epilepsy

		Newly diagnosed epilepsy (n=890)		Chronic epilepsy (n=2689)	
Age at first visit	Range (Median)	9-93 (31)		11-90 (33)	
Sex	Male	465	52%	1276	47%
	Female	425	48%	1413	53%
Type of epilepsy	Idiopathic	117	13%	218	8%
	Symptomatic	268	30%	723	27%
	Cryptogenic	357	40%	963	36%
	Unclassified	148	17%	785	29%

2.2.2. Chronic epilepsy cohort

This cohort consisted of patients previously diagnosed with epilepsy and treated with AEDs who were referred to the Epilepsy Clinic because of inadequate control of seizures. A total of 2689 patients who had been treated unsuccessfully with between one and nine AEDs were seen over the study period. This included 1276 (47%) males and 1413 females with a median age of 33 years (range 11 to 90) at the first clinic visit (Table 27). The median age at onset of epilepsy was 17 years (range 0 to 87 years). Epilepsy was classified as localisation related in 1683 (63%) and idiopathic generalised in 218 (8%) patients. In 785 (29%) patients epilepsy was unclassified. Underlying structural abnormalities could be identified in 723 (27%) patients with localisation related epilepsy who were designated as symptomatic epilepsy. Survivors in this cohort had a mean follow up of 108 months, with a total follow up of 22931 person years for the whole cohort.

2.2.3. Data collection

The study was granted approval by the West Ethics Committee of the Greater Glasgow Health Board. Clinical details and demographic information of all patients attending the Epilepsy Unit are maintained on an electronic database. The patient list was matched against the death database at the General Register Office for Scotland, Edinburgh. Death certificate copies were obtained for patients whose demographic information matched. Deaths were also reported by patients' General Practitioners (GP) and carers. In these cases, cause of death was ascertained from the GP or the health authority (Greater Glasgow Health Board) records. Both cohorts were followed up until death or censored on 1st of October 2003.

2.3. Analysis

2.3.1. Survival

Comparison was made with an age and sex matched cohort constructed from the UK Government Actuary Departments' Interim Life Tables (http://www.gad.gov.uk/Life_Tables/Historical_Interim_life_tables.htm) to reflect the expected mortality in the Scottish population over the study period. Kaplan-Meier survival curves were plotted separately for each of the epilepsy cohorts and controls. Patients were categorised into 10 year age bands from 20 and under to 70 and over. The number of expected deaths was calculated by summing individual expected mortality over study period. Observed and expected deaths were compared using a χ^2 statistic on 1 degree of freedom. Standardised Mortality Ratios (SMRs) were calculated as the ratio of observed to expected deaths, for all patients and separately for each age category and epilepsy type. Confidence intervals (95% CI) for SMR were derived from the confidence interval for the binomial proportion of observed deaths, regarding the expected deaths as a known constant.

2.3.2. Cause of death

Causes of death were categorised as malignant neoplasia, ischaemic heart disease, cerebrovascular disease, respiratory diseases, accidents, intentional self-harm and 'other causes', to calculate proportional mortality rates. Expected proportion of deaths from each cause was calculated for males and females separately in each age band based on the General Registrar Office for Scotland mortality statistics (GROS Vital Events Reference Tables, Table 6.2. Death rates by sex, age and cause, 2001). Observed and expected deaths were compared using a χ^2 statistic on 1 degree of freedom. Cause-specific SMRs and 95% CI s were calculated as described in section 2.3.1.

2.3.3. Cox proportional hazards model

Cox proportional hazards models of time to death were constructed to analyse the effect of age, sex and type of epilepsy on survival in both the newly diagnosed and chronic epilepsy cohorts. Age was used as a categorical variable in 5-year bands. Univariate and multivariate models were analysed.

2.4. Results

2.4.1. Survival of patients

There were 93 deaths (56 male, 37 female) in the cohort of 890 patients with newly diagnosed epilepsy (crude death rate 10.4%). This was significantly higher than the 66 deaths expected based on the mortality data for age and sex matched Scottish population (χ^2=10.5; p=0.0007). The overall ratio of observed to expected number of deaths was 1.41 (95% CI 1.15 – 1.74). The Kaplan Meier survival curves for patients and age and sex matched controls (Figure 19) shows that the excess mortality is largely in the early years after diagnosis of epilepsy.

In the cohort of patients with chronic epilepsy (n= 2689) there were 316 deaths (193 male, 123 female) during the study period resulting in a crude death rate of 11.8%. The expected number of deaths based on the age and sex matched controls cohort was 155, which was significantly lower than the observed number of deaths (χ^2=167; p<0.0001). The overall ratio of observed to expected number of deaths for this cohort was 2.04 (95% CI 1.82-2.27). Kaplan-Meier survival curve for patients with chronic epilepsy and age and sex matched controls are shown in Figure 20.

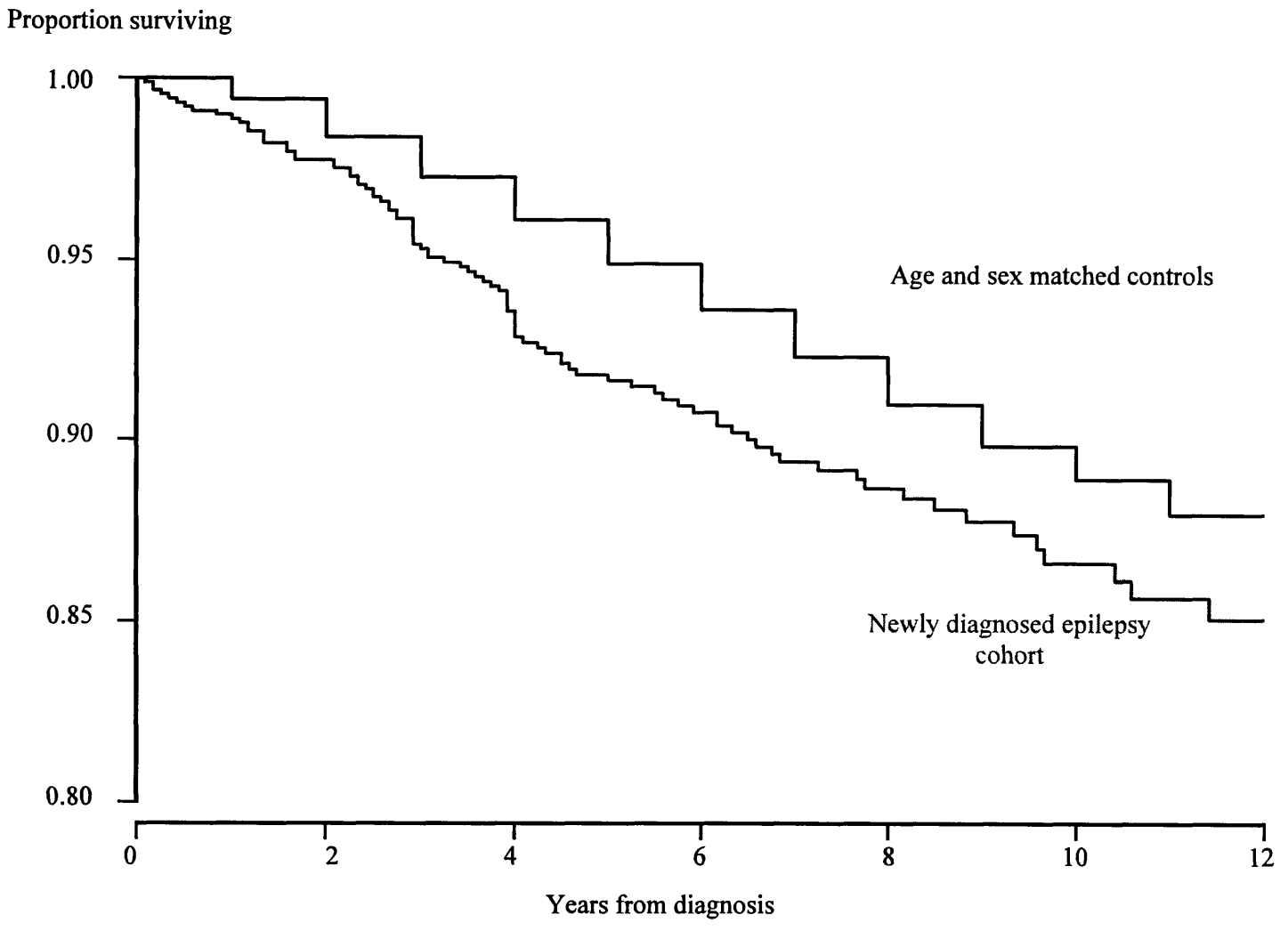


Figure 19. Kaplan Meier plot of survival in patients with newly diagnosed epilepsy.

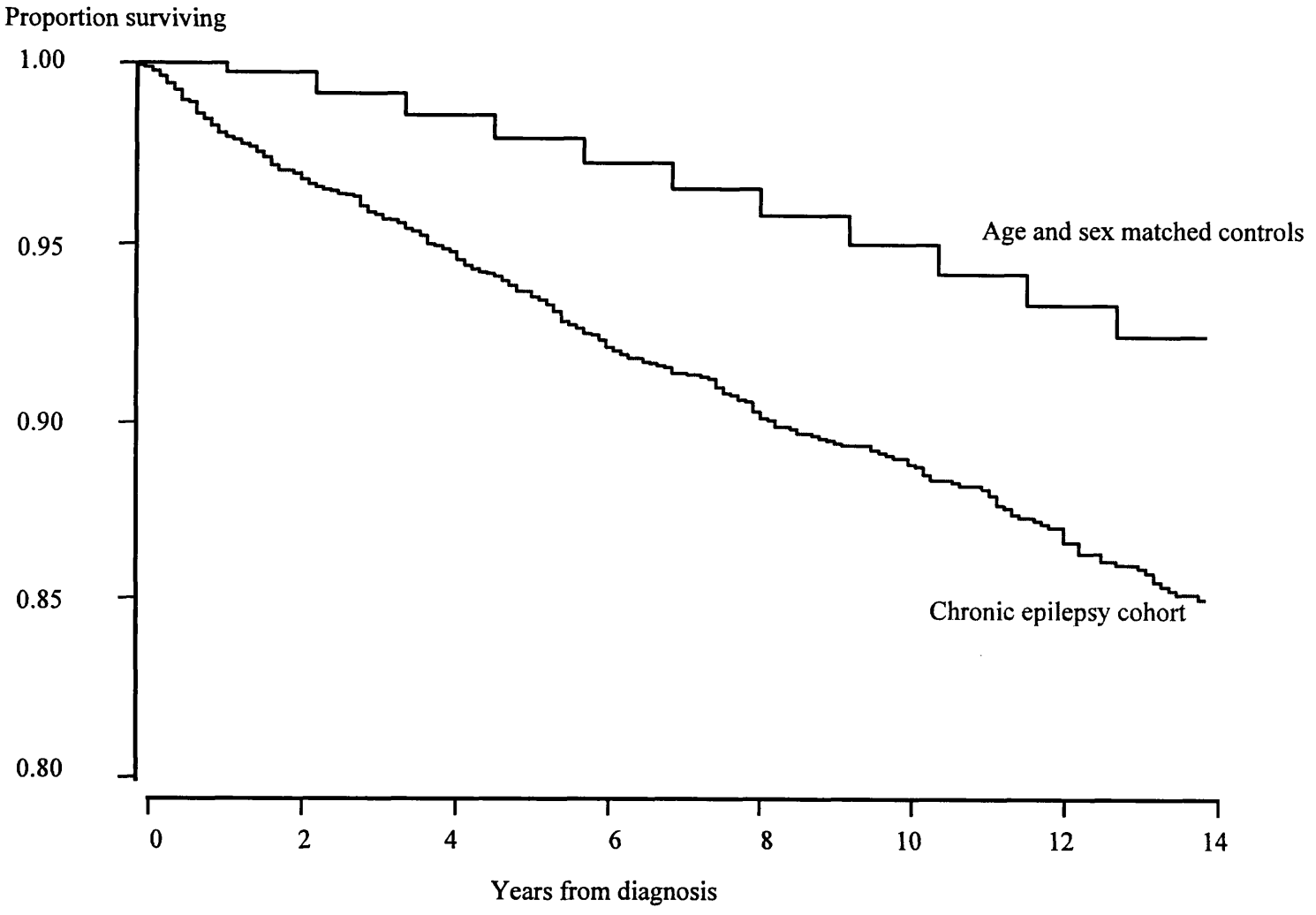


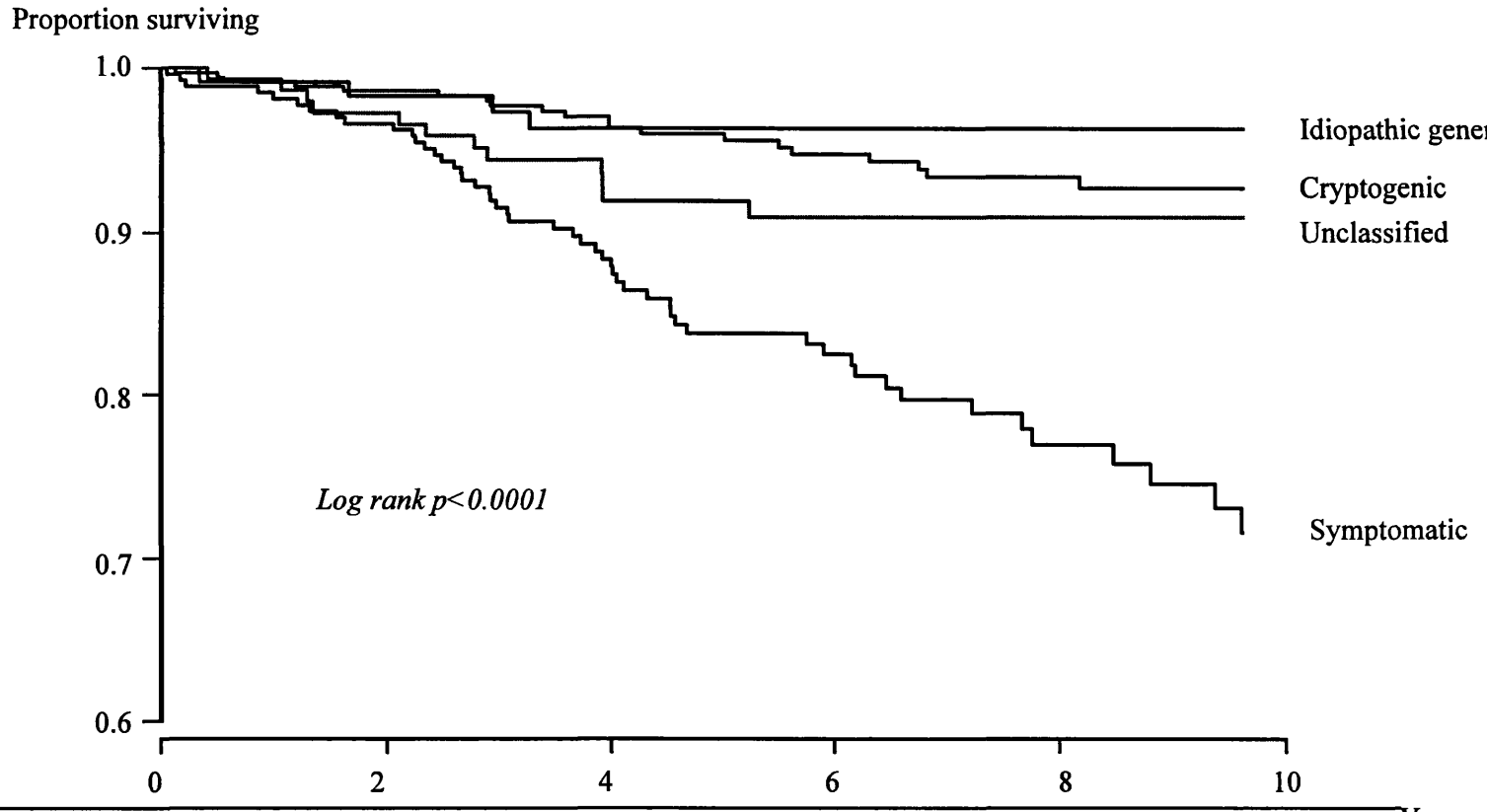
Figure 20. Kaplan Meier plot of survival in patients with chronic epilepsy.

2.4.2. Mortality by type of epilepsy

In the newly diagnosed cohort, Kaplan Meier analysis by type of epilepsy shows significantly reduced survival for patients with symptomatic epilepsy compared to those with other types of epilepsy ($p<0.001$; Figure 21). Comparison with expected number of deaths revealed SMR of 3.14 (95% CI 0.86-7.81; $p=0.016$) for idiopathic generalised epilepsy, 1.12 (95% CI 0.68-1.56; $p=0.60$) for cryptogenic epilepsy, 1.96 (95% CI 1.15-3.32; $p=0.018$) for unclassified epilepsy and 1.44 (95% CI 1.10-1.78; $p=0.007$) for symptomatic epilepsy (Figure 22).

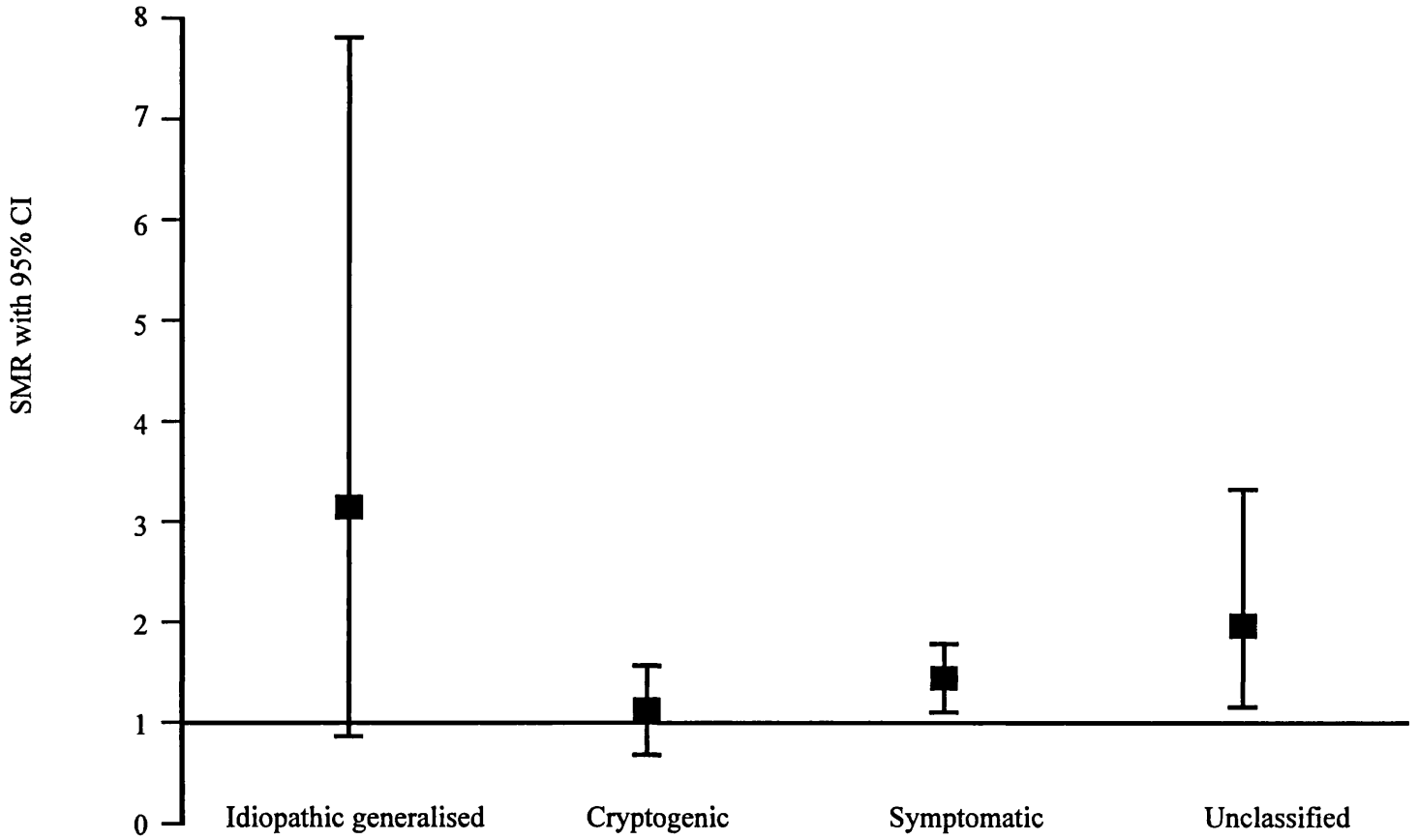
In the chronic epilepsy cohort, Kaplan Meier analysis showed a significantly decreased survival for patients with cryptogenic, symptomatic and unclassified epilepsy, but not for those with idiopathic generalised epilepsy ($p<0.001$; Figure 23). SMR for idiopathic generalised epilepsy was 1.21 (95% CI 0.25-3.48; $p=0.74$), for cryptogenic epilepsy was 2.25 (95% CI 1.85-2.66; $p<0.0001$), for unclassified epilepsy was 2.23 (95% CI 1.87-2.58, $p<0.0001$) and for symptomatic epilepsy was 1.67 (95% CI 1.32-2.21 $p<0.0001$; Figure 24).

There were important differences in the age of onset of the different types of epilepsy which would contribute to differences in survival. In both cohorts, patients with symptomatic epilepsy were older at diagnosis that those with cryptogenic or unclassified epilepsy who in turn were older than those with idiopathic generalised epilepsy (Table 28 and 29). Thus patients with symptomatic epilepsy could be expected to have reduced survival on account of being older. In the chronic epilepsy cohort, however, there was a significant difference in mortality only for idiopathic generalised epilepsy, with all other types showing higher mortality rates.



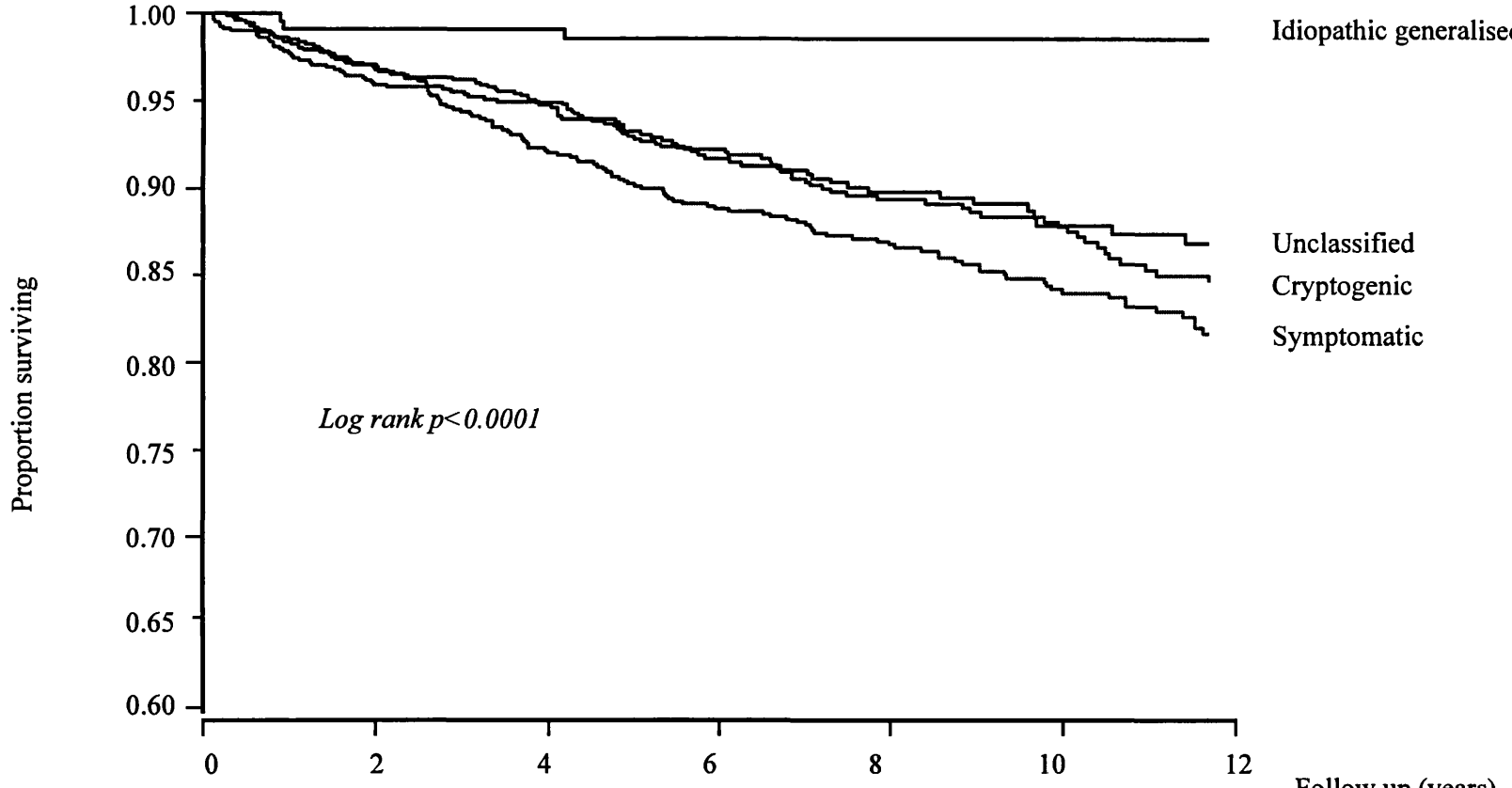
Number at risk (Number of deaths)						
Idiopathic gen	117(0)	112(2)	89(4)	66(4)	42(4)	28(4)
Cryptogenic	357(0)	351(5)	279(12)	216(16)	154(19)	91(20)
Symptomatic	268(0)	256(9)	182(30)	126(40)	71(47)	52(42)
Unclassified	148(0)	141(4)	108(11)	82(12)	59(12)	43(12)

Figure 21. Survival of 890 patients with newly diagnosed epilepsy according to type of epilepsy.



	Idiopathic generalised	Cryptogenic	Symptomatic	Unclassified
n	117	357	268	148
Expected Deaths	1.3	20.6	37.5	6.1
Observed Deaths	4	23	54	12

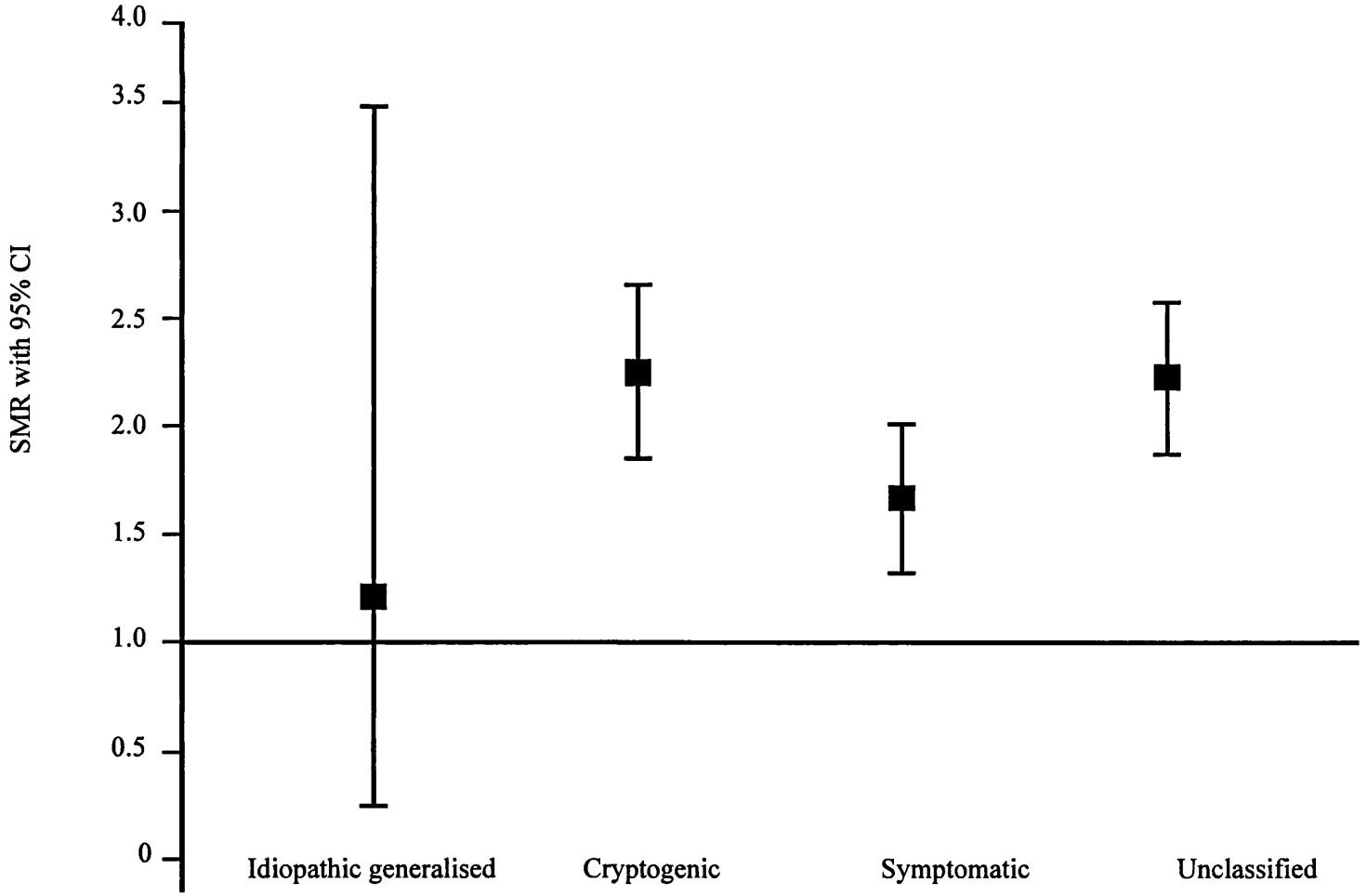
Figure 22. Standardised mortality ratios by type of epilepsy in 890 patients with newly diagnosed epilepsy



No. at risk (No. of deaths)

Idiopathic	218(0)	216(2)	184(2)	149(3)	110(3)	75(3)	58(3)
Cryptogenic	963(0)	932(31)	748(47)	554(66)	421(81)	300(87)	230(98)
Symptomatic	723(0)	702(21)	590(37)	442(54)	329(62)	209(67)	159(69)
Unclassified	785(0)	753(32)	699(62)	621(85)	503(98)	391(112)	254(120)

Figure 23. Survival of 2869 patients with chronic epilepsy according to type of epilepsy



	Idiopathic generalised	Cryptogenic	Symptomatic	Unclassified
n	218	963	723	785
Expected Deaths	2.47	47.07	47.94	57.02
Observed Deaths	3	106	80	127

Figure 24. Standardised mortality ratios by type of epilepsy in 2689 patients with chronic epilepsy.

Table 28. Age at diagnosis by type of epilepsy in patients with newly diagnosed epilepsy

	n (%)	Male (%)	Mean age (SD)	Range
Idiopathic Generalised	117 (13%)	55 (47%)	21 (9.2)	9.2 to 71.2
Cryptogenic	357 (40%)	156 (44%)	35 (17.2)	11.2 to 82.8
Symptomatic	268 (30%)	169 (63%)	48 (21.1)	13.2 to 93.0
Unclassified	148 (17%)	85 (57%)	32 (15.5)	12.3 to 80.0
Total	890	465 (52%)	36 (19.4)	9.2 to 93.0

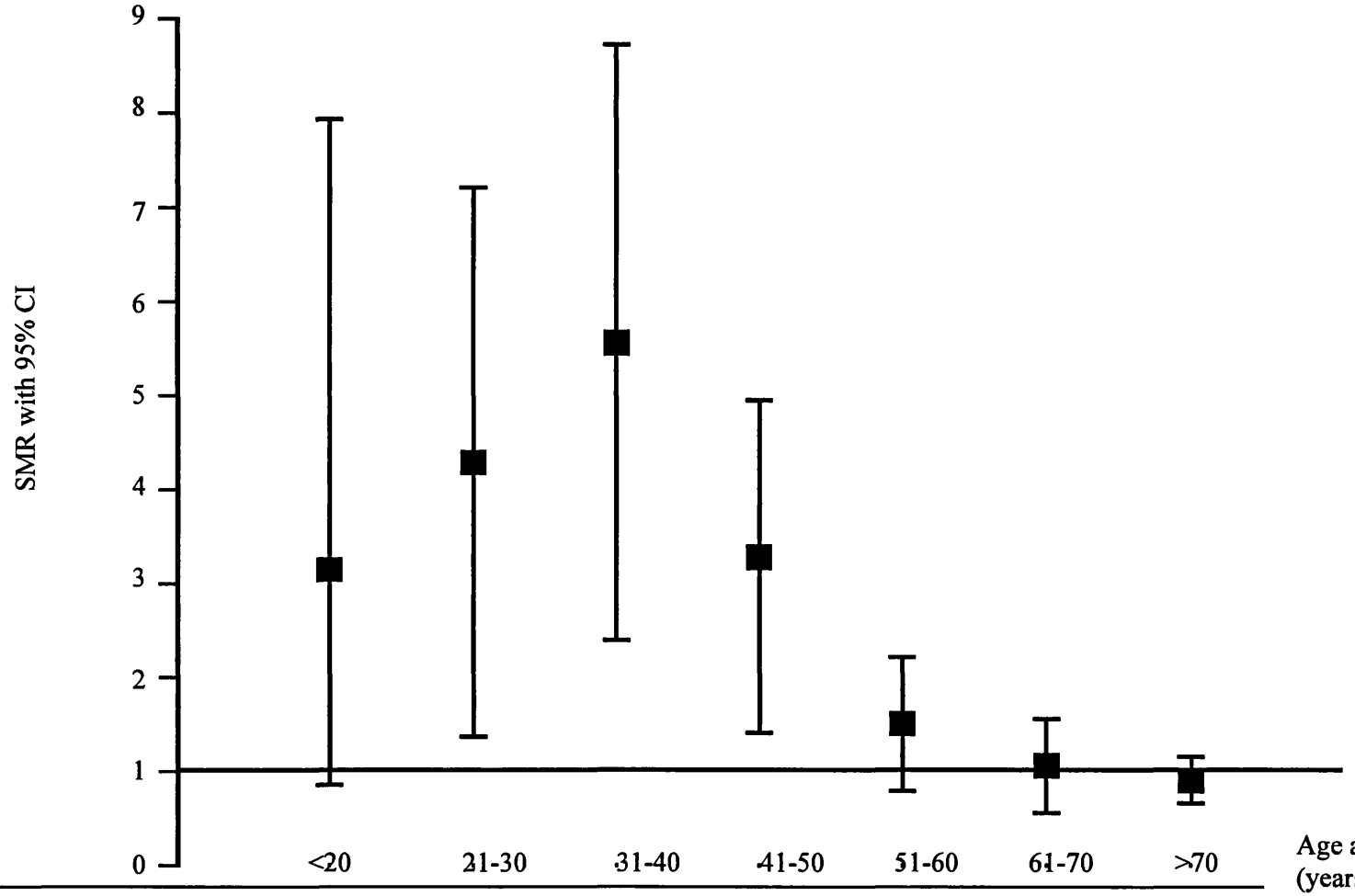
Table 29. Age at diagnosis by type of epilepsy in patients with chronic epilepsy

	n (%)	Male (%)	Mean age (SD)	Range
Idiopathic Generalised	218 (8%)	85 (39%)	24 (9.9)	12 to 73
Cryptogenic	963 (36%)	408 (42%)	35 (14.7)	11 to 85
Symptomatic	723 (27%)	382 (53%)	41 (16.5)	11 to 90
Unclassified	785(29%)	401 (29%)	36 (14.7)	12 to 88
Total	2689	1276 (47%)	36 (15.5)	11 to 90

2.4.3. Mortality by sex and age at diagnosis

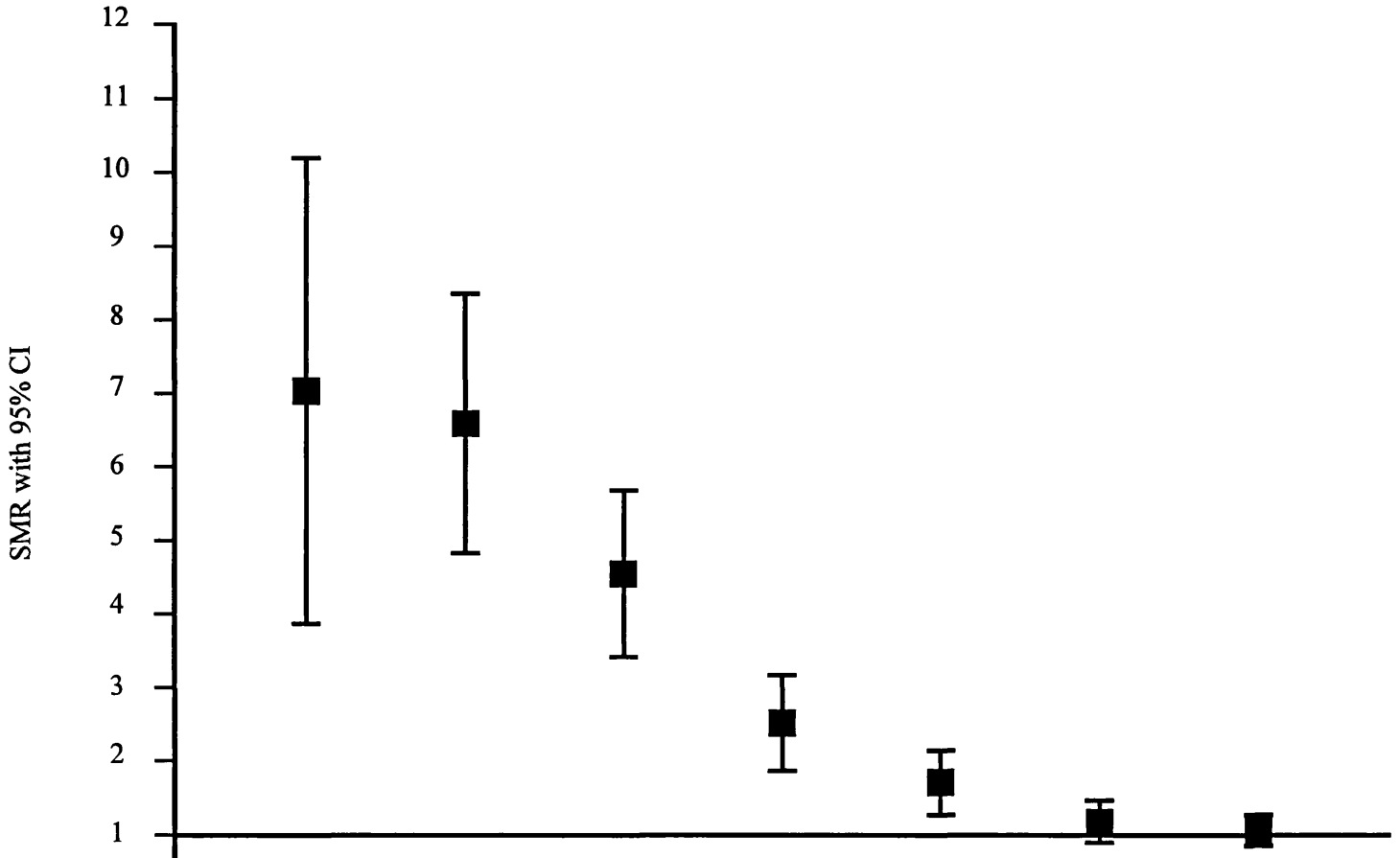
There were 56 deaths among the 465 males with newly diagnosed epilepsy (expected 42.2, SMR 1.33; 95% CI 1.00-1.65). The female cohort (n=425) had 37 deaths (expected 23.3; SMR 1.59; 95% CI 1.10— 2.07). Thus, there was no significant difference in mortality between the sexes ($\chi 2$ 2.64, p=0.104) and gender did not appear to have a significant influence on survival in this cohort of patients (see Cox model, Part 4, section 2.4.7). In the newly diagnosed cohort, the highest excess mortality was seen in patients in the 31 to 40 year age group (Figure 25). Mortality risks in younger patients were generally higher in comparison to the control population, whereas patients aged over 60 years at diagnosis did not appear to have a significant excess mortality risk.

In the chronic epilepsy cohort, there were 193 deaths among the 1276 males (expected 91, SMR 2.11, 95% CI 2.11-2.39, p<0.0001). Among the 1413 female patients in this cohort, there were 123 deaths (expected 63, SMR 1.95, 95% CI 1.62-2.28, p<0.0001). Thus, there was a significant excess mortality in both sexes, but this was more pronounced in males (χ^2=26.6, p<0.0001) and gender had a significant effect on survival in patients with chronic epilepsy (See Part IV, section 2.4.7). The highest excess mortality risk was seen for youngest patients (Figure 26). SMR fell with rising age and those over the age of 60 had no elevated mortality risk compared to age and sex matched controls.



n	203	227	150	100	77	53	80
Expected deaths	1.3	1.9	2	3.5	9.3	12.3	35.4
Observed deaths	4	8	11	11	14	13	32

Figure 25. Standardised mortality rates by age in 890 patients with newly diagnosed epilepsy



	≤20	21-30	31-40	41-50	51-60	61-70	>70
n	363	747	626	444	264	154	91
Expected deaths	2.56	7.59	12.33	20.29	28.13	39.25	44.35
Observed deaths	18	50	56	51	48	46	47

Figure 26. Standardised mortality ratios by age in 2689 patients with chronic epilepsy

2.4.4. Mortality by age and type of epilepsy

SMRs were calculated for cryptogenic, unclassified and symptomatic epilepsies based on age at diagnosis. Idiopathic epilepsy was not subject to this analysis as very few patients in either cohort were diagnosed after the 3rd decade of life. The highest excess mortality was seen for patients diagnosed with symptomatic epilepsy below the age of 40 years, and those with unclassified epilepsy diagnosed under the age of 50 (Table 30). In the chronic epilepsy cohort the youngest age categories had the highest SMRs across all epilepsy types (Table 31).

2.4.5. Mortality risks and response to treatment

Patients with newly diagnosed epilepsy were evaluated for mortality risks based on response to treatment. Of the 890 patients in this group 462 achieved seizure freedom and 318 failed to do so. Response to treatment was not known for the remaining 110. Amongst those who failed to respond to treatment (n=318), there were 42 deaths while only 16.5 deaths could be expected based on population statistics (SMR 2.54, 95% CI 1.84 -3.44). Among patients entering remission with AED treatment (n=462), there were 41 deaths with 43.1 expected (SMR 0.95, 95% CI 0.68 - 1.29). Among patients whose response to treatment was not known (n=110) there were 5.9 deaths expected and 10 observed (SMR 1.69, 95% CI 0.81 - 3.12). Thus, almost all of the excess mortality was observed in patients who did not achieve seizure freedom on treatment. Furthermore, the excess mortality in this group of patients was similar to that seen in the chronic epilepsy cohort, suggesting that only patients who fail to respond to treatment are subject to higher risks.

Table 30. SMR by age and epilepsy type in newly diagnosed epilepsy

Type	Age (years)	n	Deaths		SMR (95% CI)	χ^2 p-value
			Observed	Expected		
Idiopathic generalised.	All	117	4	1.3	3.14 (0.86 – 7.81)	0.016
Cryptogenic	<40	244	4	2.1	1.90 (0.52 - 479)	0.19
	>40-60	73	8	4.0	1.99 (0.88 – 3.72)	0.047
	>60	40	11	14.5	0.76 (0.38 – 1.14)	0.36
Symptomatic	<40	116	11	1.3	8.64 (3.78 – 13.50)	<0.0001
	>40-60	69	10	7.1	1.42 (0.61 – 2.23)	0.27
	>60	83	33	29.2	1.13 (0.83 – 1.43)	0.48
Unclassified	<50	129	7	1.6	4.53 (184 – 9.05)	<0.0001
	>=50	19	5	4.6	1.09 (0.38 – 2.13)	0.84

Table 31. SMR by age and epilepsy type in chronic epilepsy

Type	Age (years)	n	Death		SMR (95% CI)	$\chi 2$ p-value
			Observed	Expected		
Idiopathic generalised	All	218	3	2.478	1.21 (0.25 – 348)	0.74
Cryptogenic	<40	648	46	7.499	6.13 (4.43 – 7.84)	<0.0001
	>40	315	60	39.573	1.52 (1.17 – 1.86)	0.0012
Symptomatic	<40	365	26	5.057	5.14 (3.24 – 7.05)	<0.0001
	>40	358	54	42.881	1.26 (0.95 – 1.57)	0.090
Unclassified	<40	522	50	8.281	6.04 (4.45 – 7.63)	<0.0001
	>40	263	77	48.737	1.58 (1.28 – 1.88)	0.0001

2.4.6. Cause of death

The proportion of deaths from each cause in the newly diagnosed population is shown in Figure 27. Cause specific SMR was particularly high for respiratory disorders, with 18 deaths occurring where only 7 could be expected based on population mortality statistics (Figure 28). Of these, 14 patients died of pneumonia. There were no extra deaths from cardiovascular and cerebrovascular disorders when the two groups were analysed separately, but when combined as deaths from vascular disease, there were significantly more deaths than expected. The proportion of deaths from malignancies were lower than expected, but not significantly so (13 deaths observed, 17.3 expected, p=0.24). Deaths from accidents and intentional self-harm were also higher than expected, but as the expected numbers of deaths were less than 5 in each case, the two categories were combined for χ^2 analysis. Statistical significance was maintained in the combined analysis. There were 7 cases of probable SUDEP in this cohort, resulting in an incidence of 1.08 per 1000 patient years (1 per 926 patient years). The median age of patients dying of SUDEP was 28 (range 18-31) years. SUDEP occurred after a median of 73 months (range 10 to 146) after diagnosis of epilepsy. There were 2 males and 5 females in this group, one had idiopathic generalised epilepsy, and 2 patients each had post traumatic, cryptogenic and unclassified epilepsy.

Proportion of deaths from each cause in the chronic epilepsy cohort is shown in Figure 29 SMRs were elevated for all causes of death although this did not reach statistical significance for deaths from cancer and ischaemic heart disease (Figure 30). The greatest excess mortality was from respiratory disorders, cerebrovascular disease and accidents and deaths from other causes. There were 55 cases of probable SUDEP and a further 18 cases of deaths from status epilepticus in this cohort. The incidence of SUDEP was significantly higher among patients with chronic epilepsy than those with newly diagnosed epilepsy (χ^2 13.02,

$p<0.0001$). In this cohort of patients the incidence was 2.4 per 1000 patient years (1 per 417 patient years). The median age at SUDEP was 35 years (range 17-81). SUDEP occurred after a median of 255 months (range 5 to 738) after diagnosis of epilepsy. Of the patients dying of SUDEP, 33 (60%) were male. Only 1 patient had idiopathic generalised epilepsy; 8 had symptomatic, 18 cryptogenic and 28 unclassified epilepsy.

Respiratory disorders are not generally classed among seizure related causes of death. However, aspiration pneumonia is a frequent cause of death in institutionalised patients, especially those with co existing intellectual impairment (White et al, 1972; Zielinski et al, 1974; Iivaninen and Lehtinen, 1979; Klenerman et al, 1993). The high PMR for deaths from respiratory disorders seen in both newly diagnosed and chronic epilepsy cohort would suggest that this is an important cause of death in patients in the community as well. Deaths from SUDEP, SE, accidents, suicide and treatment related deaths are conventionally classed as epilepsy related in epidemiological studies. Treatment related deaths in this regard includes deaths directly attributable to adverse effects of AEDs (eg: Steven Johnsons syndrome), those caused by deleterious drug interactions (eg: Carbamazepine and Warfarin) and those occurring as a direct consequence of surgical treatments for epilepsy (temporal lobectomy, implantation of VNS). Epilepsy related causes of deaths were significantly more common in patients with chronic epilepsy than in those with newly diagnosed epilepsy ($\chi 2 = 11.7$; $p=0.0001$). Similarly deaths due to SUDEP were also more common in the chronic epilepsy cohort ($\chi 2=7.2$; $p=0.006$).

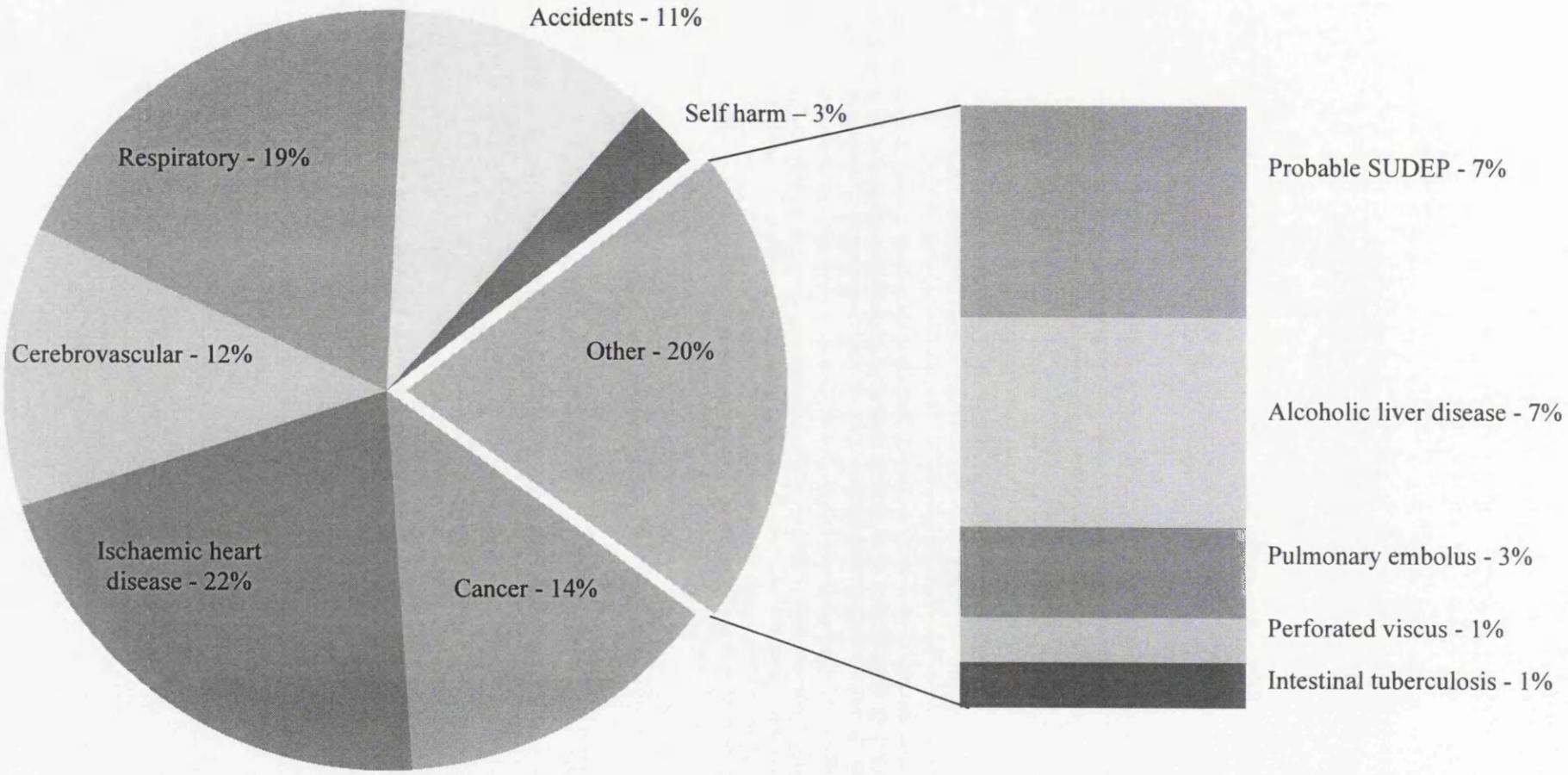
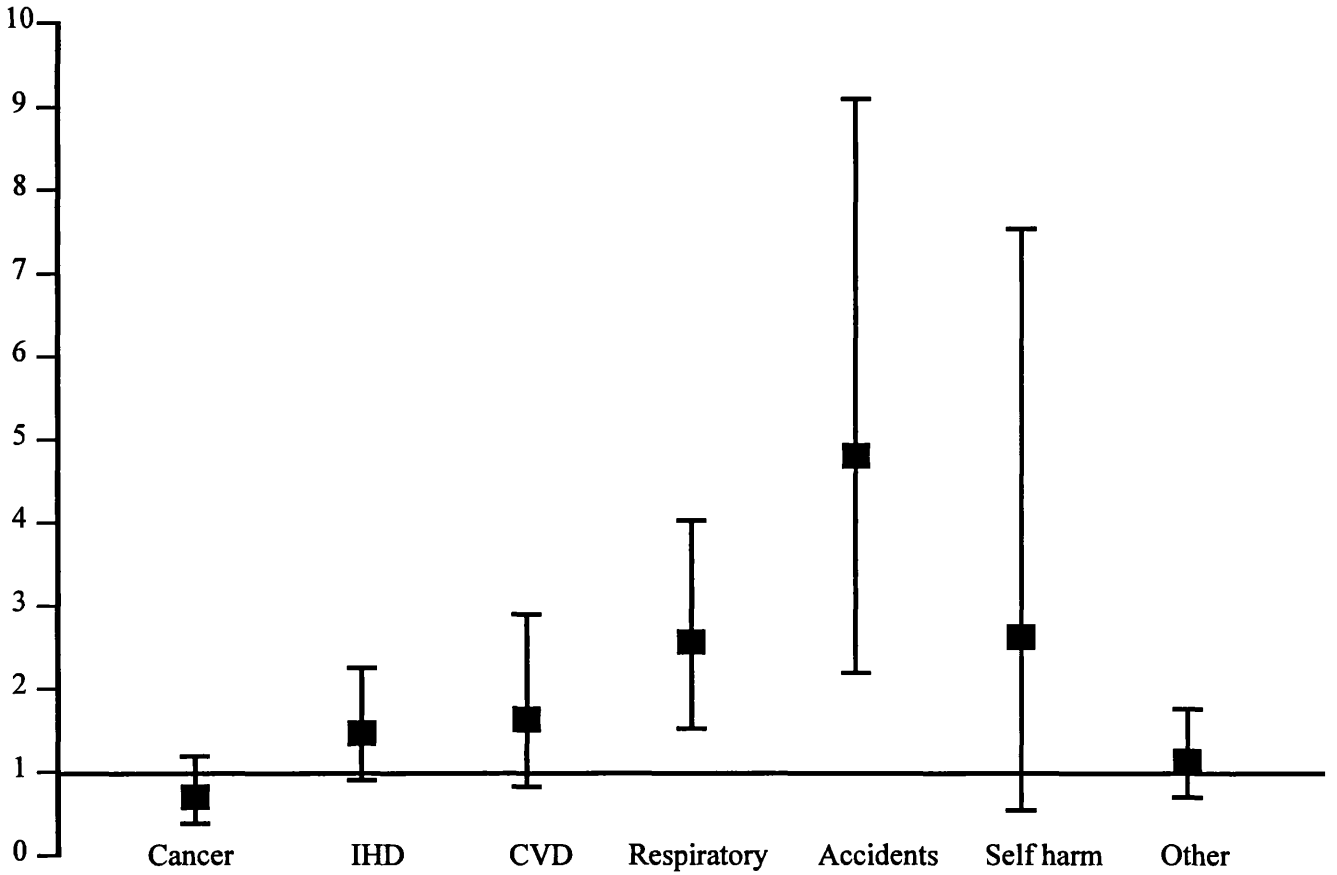


Figure 27. Proportion of deaths from each cause in 93 patients with newly diagnosed epilepsy.



	Cancer	IHD	CVD	Respiratory	Accidents	Self harm	Other
Observed	13	20	11	18	9	3	19
Expected	18.48	13.60	6.74	7.06	1.83	1.13	16.70
p-value	0.20	0.083	0.10	<0.0001	<0.0001		0.57

Figure 28. Cause specific SMR in patients with newly diagnosed epilepsy

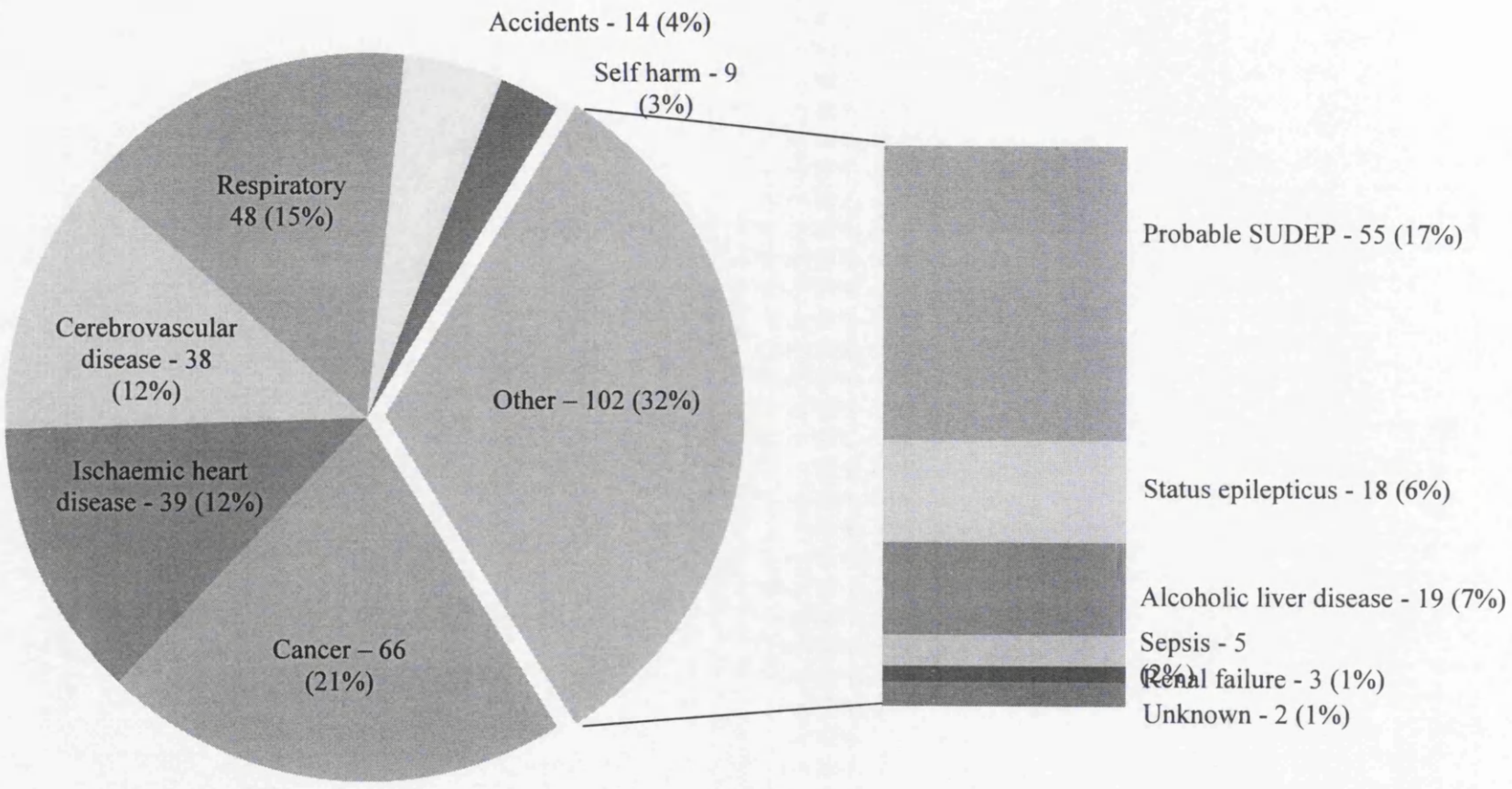
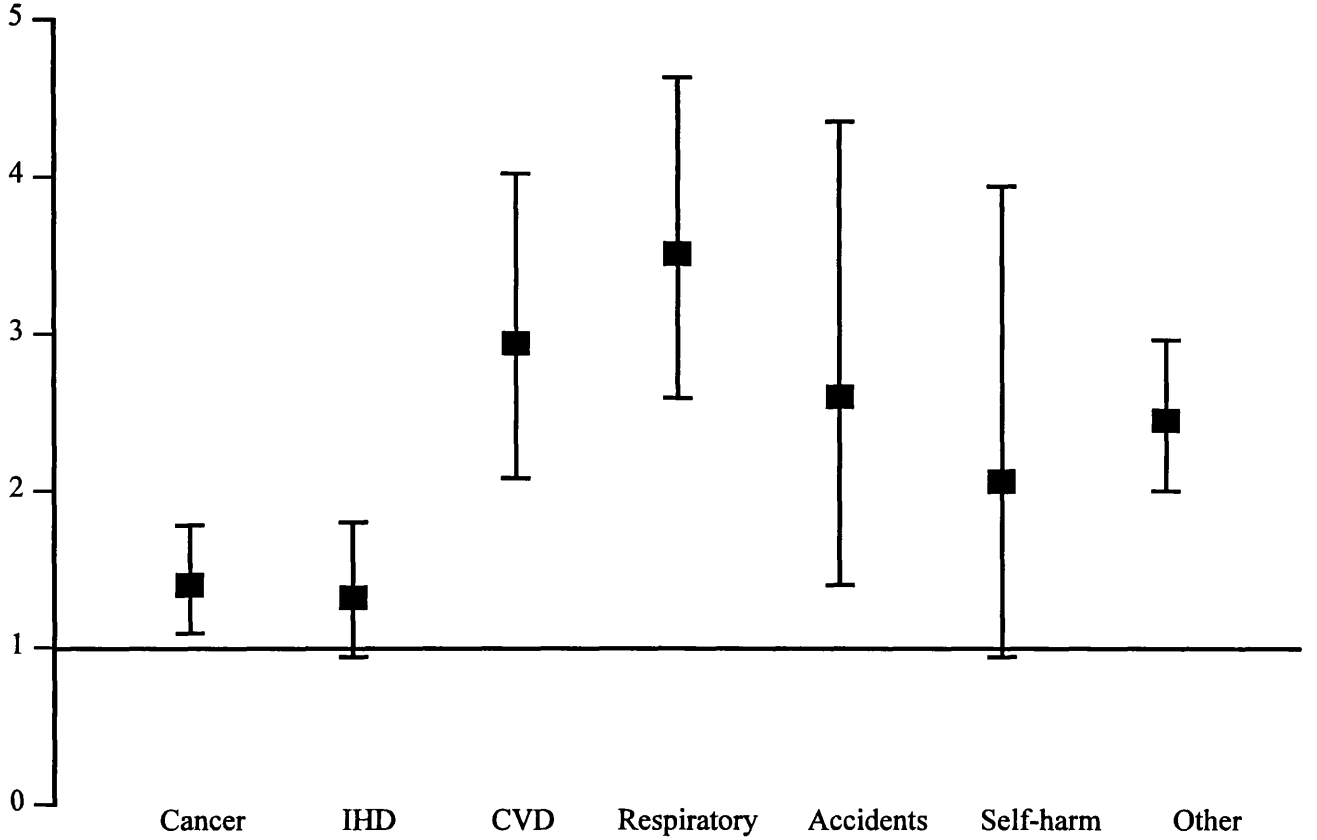


Figure 29. Proportion of deaths from each cause in 316 patients with chronic epilepsy.



	Cancer	IHD	CVD	Respiratory	Accidents	Self-harm	Other
Observed	66	39	38	48	14	9	102
Expected	47.07	29.54	12.92	13.65	5.31	4.34	41.68
p-value	0.0058	0.082	<0.0001	<0.0001	<0.0002	0.025	<0.0001

Figure 30. Cause specific SMR in patients with chronic epilepsy

2.4.7. Cause of death by age

Expected and observed numbers of deaths from each cause was analysed separately for patients aged less than and over the age of 60, using the $\chi 2$ test. In the newly diagnosed cohort overall numbers of deaths were significantly higher than expected in patients aged less than 60 years at diagnosis but not in older patients (Table 32). Important differences were observed in the incidence of cancer related deaths with significant excess mortality in patients over the age of 60, but not in younger patients. Deaths from intentional self-harm and accidents were higher in the younger age group but not in patients over the age of 60, although this result should be interpreted with caution as the numbers were small. Similarly, deaths from cerebrovascular disease and ischaemic heart disease showed significant excess in the younger age group when analysed as a combined group of deaths from vascular disease.

In the chronic epilepsy cohort, as in the newly diagnosed cohort, overall numbers of deaths were significantly more than expected only in the younger age group, not in those aged over 60 years at diagnosis. Patients aged less than 60 years had excess mortality in all categories, but in older patients only deaths from respiratory disorders and cerebrovascular disease were in excess of the expected number of deaths. Deaths from 'other' causes was higher in the older age group, most of which were from cancer (n=31) respiratory infections (n=24) ischaemic heart disease (n=19) and cerebrovascular disease (n=18).

Table 32. Cause of death by age in newly diagnosed epilepsy

	< 60 years old			> 60 years old		
	Obs	Exp	χ^2 p-value	Obs	Exp	χ^2 p-value
Cancer	8	5.48	0.28	5	13.02	0.026
IHD	8	2.79		12	10.82	0.72
CVD	1	0.90	0.0058	10	5.84	0.086
Respiratory	4	1.03	0.0035	14	6.03	0.0012
Accidents	8	1.11		1	0.71	
ISH	3	1.04	<0.0001	0	0.09	0.82
Other	16	5.49	<0.0001	3	11.16	0.015
Total	48	17.85	<0.0001	45	47.69	0.70

Table 33. Cause of death by age in chronic epilepsy

	< 60 years old			> 60 years old		
	Obs	Exp	χ^2 p-value	Obs	Exp	χ^2 p-value
Cancer	42	22.14	<0.0001	24	24.92	0.85
IHD	25	10.80	<0.0001	14	18.74	0.27
CVD	20	3.52	<0.0001	18	9.41	0.0051
Respiratory	24	3.85	<0.0001	24	9.80	<0.0001
Accidents	13	4.08	<0.0001	1	1.23	0.71
ISH	9	4.11	0.016	0	0.23	
Other	94	22.40	<0.0001	8	19.28	0.010
Total	227	70.90	<0.0001	89	83.6	0.55

Obs – Observed Exp - Expected

2.4.8. Factors affecting survival after diagnosis of epilepsy

Cox proportional hazards models of time to death were constructed to analyse the effect of age at diagnosis, sex and type of epilepsy on survival. Increasing age at diagnosis and symptomatic epilepsy was associated with reduced survival in the univariate analysis, while patients' gender showed no effect on survival. However, in the multivariate model, only increasing age at diagnosis remained independently predictive of reduced survival (Table 34).

In patients with chronic epilepsy cohort, increasing age was significantly showed significant univariate association with reduced survival, while female sex and idiopathic generalised were associated with improved survival. These factors remained independently predictive in the multivariate model (Table 35). Unlike with the newly diagnosed cohort, symptomatic epilepsy was not associated with reduced survival in this cohort. This probably indicates the differences in the underlying aetiology in patients with symptomatic epilepsy among patients with newly diagnosed and chronic epilepsy.

Table 34. Cox proportional hazards model of time to death in patients with newly diagnosed epilepsy

		Univariate analysis			Multivariate analysis		
Factor	**Level**	**Hazard Ratio**	**95% CI**	**p-value**	**Hazard Ratio**	**95% CI**	**p-value**
Age	5 years	1.29	1.23 - 1.36	<0.0001	1.27	1.20 - 1.34	<0.0001
Gender	Female	0.7	0.46 - 1.06	0.089	0.8	0.52 - 1.21	0.28
Type	Cryptogenic	Reference			Reference		
Overall:	Symptomatic	3.65	2.24 - 5.94	<0.0001	1.88	1.13 - 3.13	0.016
p<0.0001 (Univariate)	Idiopathic	0.56	0.19 - 1.60	0.28	1.27	0.43 - 3.79	0.67
p=0.12 (Multivariate)	Unclassified	1.3	0.65 - 2.62	0.46	1.5	0.74 - 3.04	0.26

Table 35. Cox proportional hazards model of time to death in patients with chronic epilepsy

		Univariate analysis			Multivariate analysis		
Factor	**Level**	**Hazard Ratio**	**95% CI**	**p-value**	**Hazard Ratio**	**95% CI**	**p-value**
Age	5 years	1.29	1.25 - 1.33	<0.0001	1.28	1.24 - 1.33	<0.0001
Gender	Female	0.55	0.44 - 0.68	<0.0001	0.57	0.45 - 0.71	<0.0001
Type	Cryptogenic	Reference			Reference		
Overall:	Symptomatic	1.00	0.75 - 1.34	0.99	0.75	0.56 - 1.01	0.056
p=0.0004 (Univariate)	Idiopathic	0.12	0.04 - 0.36	0.002	0.23	0.07 - 0.74	0.013
p=0.0037 (Multivariate)	Unclassified	1.22	0.95 - 1.58	0.13	1.11	0.85 - 1.44	0.44

2.5. Discussion

Examining mortality of epilepsy separately in patients with newly diagnosed and chronic epilepsy provides instructive insights into the risks in these two disparate groups of patients with very different outlooks in terms of seizure control and prognosis. Such data enable risks in individual patients to be placed in perspective and aid counselling during specialist consultation. This study analysed mortality risks in patients with newly diagnosed epilepsy and those referred following unsuccessful trial of at least one antiepileptic drug at a single centre.

Overall mortality shows an increase of approximately 40% in the newly diagnosed epilepsy patients compared to an age and sex matched Scottish cohort. When 10-year age bands were examined separately, the highest mortality was seen for younger patients, rising to a peak SMR of 8.0 in the 31-40 year age group. Analysis based on type of epilepsy showed significantly higher number of deaths than expected among patients with symptomatic and unclassified epilepsy, but not among those with idiopathic or cryptogenic epilepsy. The most marked excess mortality was seen for patients diagnosed with symptomatic epilepsy under the age of 40 (SMR 8.64). Overall, there were 54 deaths among patients with newly diagnosed symptomatic epilepsy, where only 38 were expected. The leading causes of death in this group of patients were malignancy including brain tumours (n=9), cerebrovascular disease (n=8) and ischaemic heart disease (n=7). In this cohort, 73 patients had epilepsy due to cerebrovascular disease, and it is therefore not surprising from vascular disorders such as strokes and myocardial infarctions were a leading cause of death in this group. This death rate was significantly higher than expected only in younger patients, who would generally not be expected to develop vascular disease. There was no excess mortality from this cause in

patients aged over 60 at diagnosis. Thus the mortality of newly diagnosed epilepsy largely reflects the natural history of the underlying condition causing seizures.

Survival was worse in the chronic epilepsy cohort with over double the expected number of deaths occurring as could be expected. The highest SMR were seen for the youngest patients with no excess mortality in those aged over 60. Significantly reduced survival was seen for symptomatic, cryptogenic and unclassified epilepsy but not for those with idiopathic generalised epilepsy. This is possibly due to the better prognosis for seizure control in this type of epilepsy with appropriate AED treatment. Many patients with idiopathic generalised epilepsy remain uncontrolled because of treatment with inappropriate antiepileptic drugs (Benbadis et al, 2003). Once they come to specialist attention and drug therapy is rationalised, seizure control can be achieved relatively easily.

When cause of death was analysed for newly diagnosed patients, greatest number of excess deaths were seen for respiratory disorders (including inhalation pneumonia), accidents, intentional self-harm and deaths from vascular disease (cerebrovascular and ischaemic heart disease). These effects were seen equally for males and females. The majority of excess mortality was seen in patients aged less than 60 years at diagnosis. There was no significant increase in mortality risk for older patients. In patients with chronic epilepsy, the cause specific SMRs were elevated for all causes of death, chiefly in patients age less than 60 years at diagnosis.

Of the 316 deaths in this cohort, 55 were considered to be due to SUDEP, and a further 17 occurred in relation to status epilepticus. The incidence of SUDEP was significantly more likely in patients with chronic epilepsy compared to those with newly diagnosed epilepsy.

The overall incidence of SUDEP in this analysis was 1.08 per 1000 patient years in the newly diagnosed patients. As discussed in part IV, section 1.5.2. the incidence of SUDEP in the Rochester study was 0.35 per 1000 patient years, while a prospective study in newly diagnosed patients reported SUDEP incidence of 1.2 per 1000 patient years (Ficker et al, 1998; Walczak et al, 2001). The NGPSE reported its first case of SUDEP after 8000 patient years of follow up, suggesting that SUDEP was a rare event in newly diagnosed patients (Lhatoo et al, 1999). In patients with chronic epilepsy, however, SUDEP rate was 2.4 per 1000 patient years. SUDEP rates ranging from 3 to 10 per 1000 patient years have been reported in institutionalised patients, those attending specialist clinics with uncontrolled epilepsy, and those in surgical programmes (See part IV, section 1.5.2.) The population with chronic epilepsy in this study had a mixture of varying severity of epilepsy, intellectual impairment and other risk factors. The rate of SUDEP is significantly higher in this population than in the newly diagnosed cohort.

Cox model analysis showed patients with symptomatic epilepsy and those with increasing age at diagnosis had significantly shortened survival compared to those with other types of epilepsy. In patients with chronic epilepsy, increasing age at diagnosis was associated with shortened survival, while female sex and idiopathic generalised epilepsy were associated with improved survival. Increased mortality in males with epilepsy has been reported by other authors (Rafnsson et al, 2001). A clear explanation for this observation is not forthcoming, but is possibly related more to lifestyle factors than biological ones. Most of the deaths in newly diagnosed epilepsy occurs in the early years after diagnosis and reflects the natural course of the underlying cerebral pathology. The association of symptomatic epilepsy with reduced survival observed in newly diagnosed patients but not in those with chronic

epilepsy probably reflects the variations in underlying aetiology of epilepsy in the two groups, and the differences in their natural course and outlook.

2.6. Conclusions

There is an approximately 40% increase of mortality in patients with newly diagnosed epilepsy, most of which is seen in younger patients with symptomatic epilepsy. No significant excess mortality was seen in patients with other types of epilepsy or those aged over 60 years at diagnosis. However, in those who fail treatment with at least one AED, mortality risks are significantly higher. This is most marked in younger patients and for all epilepsy types except idiopathic generalised epilepsy. The data confirms that SUDEP is a rare event in patients with newly diagnosed epilepsy. However, in patients who fail to achieve seizure control, this is significantly more likely. These factors should be taken into consideration while counselling patients with epilepsy.

General discussion

Being diagnosed with epilepsy can be a devastating event for patients. It not only has significant health consequences, but social and economic implications too. For the majority of adults, the onset of epilepsy leads to several lifestyle restrictions (Gilliam et al, 1997). The unpredictable and uncontrollable nature of epileptic seizures engenders a sense of loss of control in the sufferer. Certain elements of seizures such as incontinence can also be a source of embarrassment, which often leads to restricted social activity and isolation. Loss of driving privileges is probably the most frequent cause for concern for adult patients and can have a significant impact of quality of life for patients in the developed world. Furthermore, for those employed in potentially hazardous occupations, such as operating machinery or working at heights, being diagnosed with epilepsy results in loss of employment and livelihood. Regaining these requires the complete and sustained control of seizures. Hence, for a patient diagnosed with epilepsy, the most important question is "how likely are the seizures to stop?" Knowing the likely outcome of treatment also helps patients cope with the emotional strain of being diagnosed with a chronic disorder. It could be said that as far as the patient is concerned, the prognosis is probably more important than the diagnosis in this situation. Prognosis for seizure control should therefore be an integral part of the discussion between clinician and patient at the time of making the diagnosis of epilepsy.

Epilepsies are a heterogeneous group of disorders with varying underlying pathology, much of which is not clearly understood (Part I, section 1). An ever-increasing number of epilepsy syndromes are being recognised, thanks to progress in molecular biology and cerebral imaging technology. Our understanding of the natural history of these syndromes however has lagged behind the insights gained into their underlying pathophysiology. A discussion of the prognosis of epilepsy syndromes requires knowledge of the natural history of the condition. Epidemiological studies examining the course of the disorder over an extended

period of time are required to fully appreciate the long-term behaviour of any chronic condition. In addition to demographic and clinical factors, genetic variations among individuals could also play an important part in determining outcome of antiepileptic drug (AED) treatment, and should also be taken into consideration in any study of prognosis. The overall objective of this thesis was to utilise an existing database of epilepsy patients to study the natural history of treated epilepsy in adult and adolescent patients, both in terms of seizure control and of survival. It is hoped that the observations from these studies will inform and guide clinicians in discussing the prognosis of epilepsy with patients.

Patterns of response to treatment

The clinical studies in newly diagnosed epilepsies reveal some interesting aspects of the course of treated epilepsy. Response to treatment was usually obvious in the first few years after starting treatment. The majority of patients responding to treatment did so immediately, with 50% of all patients entering remission doing so by the end of the first year on treatment. These immediate responders constituted one third of all patients. Those who failed to enter remission within 3 years of starting treatment had very little chance of achieving remission. Over 90% of responders were taking their first or second AED regime. Of those failing two well-tolerated regimes, less than 10% achieved seizure freedom with further pharmacotherapy. The dose of AEDs resulting in treatment response was modest in most cases. Combination treatment with two or more AEDs resulted in seizure freedom only in a small number of patients. The majority of patients responding to treatment remained seizure free till the end of follow up and were considered to be in remission, while approximately 10% relapsed and developed uncontrolled epilepsy.

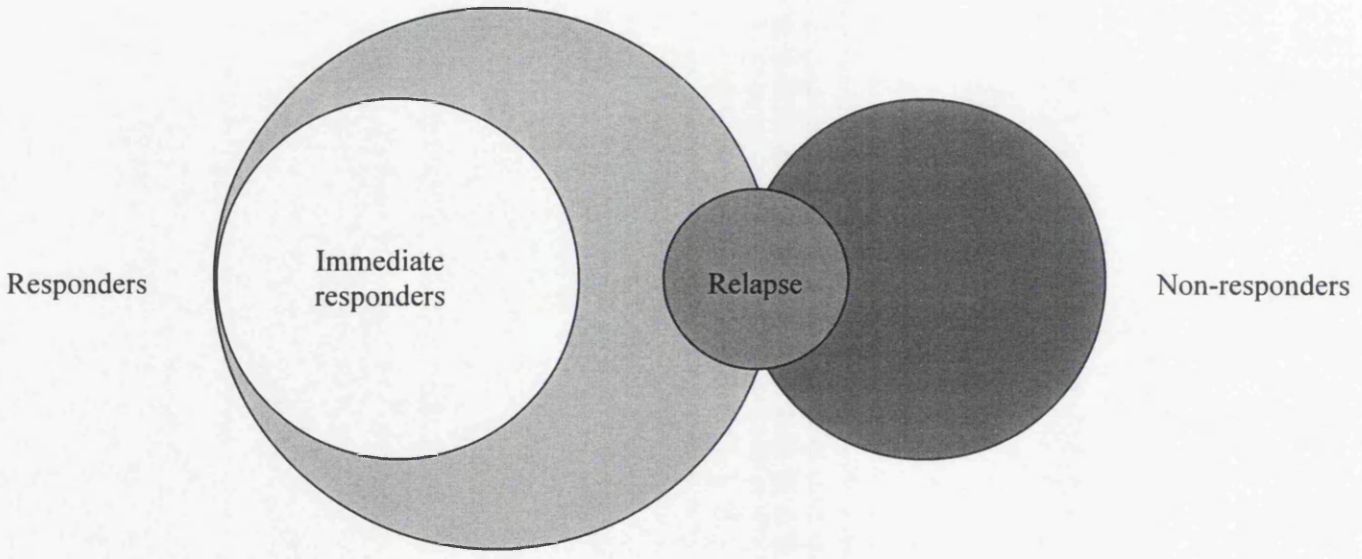


Figure 31. Categories of response to treatment in newly diagnosed epilepsy

Thus, we observed four major categories of response to AED treatment (Figure 31). The first category, constituting approximately one third of patients, responded rapidly and completely to treatment with the first AED. A smaller proportion entered remission with the subsequent treatment attempts, including combination treatment. Approximately 10% of responders later developed uncontrolled epilepsy and were classified as relapse. The remaining one third of patients never gained complete control of seizures is spite of several changes to AED regime. In the majority of cases, these groups can be reliably identified in the first few years of treatment of epilepsy. This allows management strategies to be formulated appropriately and also enables specialist services to be better targeted.

Identifying drug resistant epilepsy

In patients failing the first AED, prognosis for subsequent control varied with the reason for failure of initial treatment. Those failing because of adverse effects had a remission rate similar to treatment naïve patients, while those who received the initial AED at target doses and failed to achieve seizure control had significantly lower chances of entering remission with further pharmacotherapy. However, the overall responder rates with subsequent treatments were significantly lower than that with the first drug. The prognosis for seizure control therefore declined with each failed AED regime, with only 8% of those failing 2 well tolerated AED regimes achieving seizure control and with further pharmacotherapy; this figure falling to 3% after failure of 3 such regimes. This pattern was observed for both idiopathic generalised and localisation related epilepsy. Thus, patients failing 2 well-tolerated AED regimes remain uncontrolled in over 90% of cases and are likely to have drug resistant epilepsy. These patients should ideally be referred to a regional epilepsy programme, as they require confirmation of the diagnosis

and classification of epilepsy, rationalisation of pharmacotherapy and evaluation for possible epilepsy surgery.

Is epilepsy a progressive condition?

The phenomenon of relapse that we observed in approximately 10% of responders does suggest that in some cases, seizure disorders do progress. This has been documented in patients undergoing epilepsy surgery evaluation, a substantial proportion had had periods of perfect seizure control, but has hitherto not been quantified in newly diagnosed epilepsy (Berg et al, 2003). This is because many epidemiological studies adopt a simplistic approach to evaluating outcomes, whereby patients are considered in remission or not. The real life outcomes in patients are more complex and many patients can have periods of remission followed by relapse. There is some evidence from animal studies as well as serial imaging studies in human epilepsy that some seizure disorder may be associated with progressive structural changes in the brain (Briellmann et al, 2002; Liu et al, 2002; Fuerst et al, 2003). The proposed underlying mechanisms for worsening of seizure disorders over time include a progressive primary aetiology, an initial precipitating injury followed by a slowly evolving cellular events, development of pharmacological tolerance, seizure induced plasticity and kindling with the progressive structural and functional alterations induced thereby and genetic factors (Sutula, 2004). Identification of patients who exhibits a progressive deterioration of seizure control could help test these hypotheses in the clinical setting.

Outcomes in symptomatic epilepsy syndromes

No significant differences in outcomes were observed among patients with various localisation-related epilepsy syndromes. Even patients with Mesial Temporal Lobe

Epilepsy with Hippocampal Sclerosis and Cortical Dysplasia, syndromes commonly believed to respond poorly to AED treatment, showed immediate response to treatment in a sizeable proportion of cases (Part II, section 2.4). Thus the response to treatment in these syndromes is better than that reported from previous studies carried out in selected populations (Semah et al, 1998, Stephen et al, 2001). This also implies that clinical outcomes cannot be reliably predicted from the clinical characteristics of the epilepsy alone. The data suggest the existence of unidentified factors that determine response to treatment, which could include genetic and environmental background and also gene–gene and gene–environment interactions.

Role of pharmacogenomics in predicting treatment outcomes

Clinical characteristics of seizure disorder alone are therefore insufficient to predict the likelihood of response to treatment. Genetic influences that determine response to treatment are important in this regard. Single nucleotide polymorphisms (SNPs) in genes that encode proteins involved in the pharmacokinetic and pharmacodynamics of AEDs could play a role in determining response to drug treatment in epilepsy, especially if they alter the amino acid sequence of the protein (Part III, section 1.3.). Voltage gated sodium channels, which are primarily responsible for the generation of action potential in nervous tissue, are also the chief molecular target for a number of commonly used antiepileptic drugs. The α subunit confers the essential properties of the voltage-gated sodium channel and bears the binding site for the antiepileptic drugs that act thereon (Ragsdale et al, 1996). Studies of expression patterns of the sodium channel α subunit subtypes have shown that $Na_v1.2$, encoded on *SCN2A* is the most widely expressed isoform in the seizure prone areas of the human brain (Whittaker et al, 2000). We conducted a case control association study to examine the prevalence of a specific coding

SNP (*R19K*) on the *SCN2A* gene in responders and non-responders AED treatment. The prevalence of the *K*-variant allele was significantly higher in non-responders compared to responders, defined as those remaining seizure free for at least 6 months after starting on treatment. This result, if replicated, would indicate that the polymorphic variant of *SCN2A* is linked to the molecular basis of drug resistant epilepsy, at least in some patients. The predictive value of the polymorphism in identifying non-responders however was limited, with a test efficiency of only 48%. Response to drug treatment is governed by a multitude of genetic and environmental factors, and the low predictive value of one SNP in such a multifactorial outcome is not surprising. The discipline of pharmacogenomics is at present in its infancy. Screening for a large number of SNPs in several candidate genes using high throughput genotyping techniques and the use of more sophisticated bioinformatics paradigms for analysing the relationship with response to treatment promise to allow better predictability of response to AED treatment.

Outcomes in elderly patients

In this analysis, the best outcomes with treatment were seen in the elderly population with 85% achieving remission with AED treatment. Good prognosis for epilepsy with onset after the age of 60 has also been reported by other authors (Ramsay et al, 2004). Thus, old age is the commonest time to develop epilepsy as well as the age group with the best response to AED treatment. One possible explanation that links these two phenomena is that relatively trivial processes, which would normally not cause seizures in younger subjects, bring about recurrent seizures in older patients. These would be controlled relatively easily by AEDs. Another possibility is that the aging brain is incapable of undergoing the structural changes required to develop pharmacoresistant epilepsy owing to reduced neuronal plasticity. These hypotheses, however, are

speculative and would be difficult to test. Even if proven correct, these would not impact on the current approach to management of seizures in the elderly. An alternative explanation is that many of the seizures observed in this age group are acute symptomatic events resulting strokes that do not cause clinically obvious neurological deficits. Roberts and colleagues studied 132 patients with late onset epilepsy using CT scanning and found that 21% of patients aged over 60 had clinically silent cerebral infarction (Roberts et al, 1988). Early seizures occur in up to 33% patients with ischaemic strokes, but only 2-4% of patients develop post-stroke epilepsy (Camilo and Goldstein, 2004). Thus acute symptomatic seizures accompanying strokes would have low risk of recurrence and would not normally require treatment with AEDs. If shown to be correct, this would mean that many older patients presenting with seizures might not be at as high a risk of recurrence as commonly believed, and a more conservative approach may be safely adopted in deciding the need for AED treatment. This is especially important as AEDs often cause cognitive adverse effects and problems with drug interactions in this group of patients. Moreover, persons aged over 65 years constitute the fastest growing segment of the population of most developed countries and seizures in the elderly is likely to assume greater public health importance. This hypothesis however needs to be tested prospectively using specialised cerebral imaging techniques designed to identify acute infarcts in non-eloquent cortex in older patients presenting with seizures.

The mortality of epilepsy- what to tell the patient?

It is now widely accepted that epilepsy is associated with an increased mortality. However, clinicians remain uncertain as to whether mortality risks should be discussed routinely with patients. There is a potential for causing harm by imparting information that the patient does not actively seek as it can produce undue alarm and impede the

return to a productive life. As patients are relatives have a 'right to know' about the risks associated with their condition, it can also be argued that they have a 'right not to know', especially if the knowledge would not alter the management of the condition (Beran et al, 2004). However, material risks (those that the patient is likely to consider significant) need to be discussed. Cohort studies in representative patient groups provide the most useful data to help assess risks in individual patients.

We found a 40% increased mortality in patients with newly diagnosed epilepsy compared to age and sex matched controls whereas the chronic epilepsy cohort had a 110% increase in mortality risk. In newly diagnosed patients, highest excess mortality was seen for younger patients especially those with symptomatic epilepsy. Mortality risk was highest in the 30-40 year age group. When types of epilepsy were analysed separately, patients with symptomatic and unclassified epilepsy had higher SMR with no significant excess death rates seen for patients with cryptogenic and idiopathic epilepsy. Analysis of SMR based on age and type of epilepsy showed SMR of 8.64 for patients diagnosed with symptomatic epilepsy below the age of 40. These results suggest that the excess mortality of newly diagnosed epilepsy is largely seen in younger patients with symptomatic epilepsy, and most likely represents the natural history of the underlying condition causing seizures in these patients.

For patients failing to achieve seizures control with their first AED, the chances of seizure control with further pharmacotherapy is significantly lower than for treatment-naïve patients (Part II, section 1.5). These patients are at high risk of developing pharmacoresistant epilepsy. Studies to date suggest that mortality risks in patients with drug resistant epilepsy are likely to be higher than those in patients with well-controlled

epilepsy (Part IV, section 1.4.5). In the present analysis, patients with chronic epilepsy, defined as those failing treatment with at least one AED, were over twice as likely to die as their age and sex matched controls. The excess risk was observed for all epilepsy types except idiopathic generalised epilepsy. Youngest age groups had the highest excess mortality, which was equally high for patients with symptomatic, cryptogenic and unclassified epilepsy. Analysis of cause of death showed significantly more deaths than expected from all causes, but this excess was restricted to patients aged less than 60 years. Thus, as with newly diagnosed epilepsy, younger patients with chronic epilepsy are at higher risk of premature death.

High profile cases of SUDEP in otherwise healthy young people have been reported in the lay press and the efforts of patient organisations and charities have raised the profile of epilepsy as a potentially life threatening condition in the public consciousness (National sentinel audit on epilepsy death, Report 2002). In the present analysis, the incidence of SUDEP in newly diagnosed patients was approximately 1 per 1000 patient years, and in the chronic epilepsy this was 2.4 per 1000 patient years. Thus, SUDEP is a rare event, but significantly more likely in those with uncontrolled epilepsy than in those with new onset epilepsy. These facts need to be borne in mind while counselling patients regarding risks associated with epilepsy.

Future studies - Predicting outcomes in individual patients

Clinical prediction models are intended to reduce the uncertainty in clinical practice and to guide decision-making. The methodological standards in developing prediction models have been well established (Wasson et al, 1985; Braitman and Davidoff, 1996; Laupacis et al, 1997). The data collected will be analysed further with a view to constructing a

prediction model to identify patients likely to develop drug resistant epilepsy early. Factors influencing the likelihood of response to each AED regime will be assessed in a multivariate model. Time to event analysis using the Kaplan Meier method is envisaged, with Cox proportional hazards method to study the effect of risk factors on prognosis for achieving remission. The findings from this analysis would then be tested prospectively in other populations of adult and adolescent patients with new onset epilepsy. This could enable stratification of the risk of drug resistant epilepsy at the time of diagnosis and can help target specialist services. More detailed descriptive studies of various subgroups of patients with specific epilepsy syndromes will also be undertaken. Immediate responders to treatment and those remaining uncontrolled probably represent the two ends of the spectrum of response to treatment. A comparative analysis of the two subgroups of patients will also be performed.

Conclusion

The clinical studies presented have identified the common patterns of response to treatment in newly diagnosed epilepsy and shed light on the long-term behaviour of several well-defined epilepsy syndromes. Pharmacogenomic data in conjunction with the clinical characteristics of patients has the potential to help predict the response to treatment. The risk of premature death is not uniform in patients with epilepsy, but varies depending on the type and severity of the epilepsy and the underlying condition. These data will help clinicians to discuss prognosis with patients at the time of making the diagnosis of epilepsy.

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Appendices

Appendix 1. International classification of epileptic seizures

I. Partial (focal) seizures (seizures beginning locally)
    A. Simple (consciousness not impaired)
        1. With motor symptoms
        2. With somatosensory or special sensory symptoms
        3. With autonomic symptoms
        4. With psychic symptoms
    B. Complex (with impairment of consciousness)
        1. Beginning as simple partial seizure (progressing to complex seizure)
        2. Impairment of consciousness at onset
            a. Impairment of consciousness only
            b. With automatisms
    C. Partial seizures becoming secondarily generalised
II. Generalised seizures
    A. Absence seizures
        1. Typical
        2. Atypical
    B. Myoclonic seizures
    C. Clonic seizures
    D. Tonic seizures
    E. Tonic-clonic seizures
    F. Atonic seizures
III. Unclassified seizures

Adapted from Commission 1981

Appendix 2. International classification of epilepsies and epileptic syndromes

1. Localisation related (Partial, Focal)
    1.1. Idiopathic (age related onset)
        - Benign epilepsy with centrotemporal spikes
        - Benign epilepsy with occipital paroxysms
        - Primary reading epilepsy
    1.2. Symptomatic (defined by location and aetiology)
        - Chronic epilepsia partialis continua of childhood
        - Seizures with specific modes or precipitation
        - Temporal lobe epilepsies
        - Frontal lobe epilepsies
        - Parietal lobe epilepsies
        - Occipital lobe epilepsies
    1.3. Cryptogenic

2. Generalised
    2.1. Idiopathic (with age related onset)
        - Benign neonatal familial convulsions
        - Benign neonatal convulsions
        - Benign myoclonic epilepsy in infancy
        - Childhood absence epilepsy
        - Juvenile absence epilepsy
        - Juvenile myoclonic epilepsy
        - Epilepsy with GTCS on awakening
        - Others
    2.2. Cryptogenic
        - West syndrome
        - Lennox-Gastaut syndrome
        - Epilepsy with myoclonic-astatic seizures
        - Epilepsy with myoclonic absences
    2.3. Symptomatic
        - Non specific
            - Early myoclonic encephalopathy
            - Early infantile epileptic encephalopathy with burst suppression
            - Others
        - Specific syndromes
            - Epilepsies in other disease states

3. Undetermined whether focal or generalised
    - Neonatal seizures
    - Severe myoclonic epilepsy of infancy
    - Epilepsy with continuous spike-and-waves during slow-wave sleep
    - Acquired epileptic aphasia (Landau-Kleffner syndrome)
    - Other
4. Special syndromes
    - Situation related seizures

Adapted from Commission 1989

Appendix 3. Epilepsy syndromes and related conditions

Benign familial neonatal seizures
Early myoclonic encephalopathy
Ohtahara syndrome
†Migrating partial seizures of infancy
West syndrome
Benign myoclonic epilepsy in infancy
Benign familial infantile seizures
Dravet's syndrome
†Myoclonic status in nonprogressive encephalopathies
BECTS
Early-onset benign childhood occipital epilepsy (Panayiotopoulos type)
Late-onset childhood occipital epilepsy (Gastaut type)
Epilepsy with myoclonic absences
Epilepsy with myoclonic–astatic seizures
Lennox–Gastaut syndrome
Landau–Kleffner syndrome (LKS)
Epilepsy with continuous spike-and-waves during slow-wave sleep
Childhood absence epilepsy
Progressive myoclonus epilepsies
Idiopathic generalized epilepsies with variable phenotypes
- Juvenile absence epilepsy
- Juvenile myoclonic epilepsy
- Epilepsy with generalized tonic–clonic seizures only

Reflex epilepsies
- Idiopathic photosensitive occipital lobe epilepsy
- Other visual sensitive epilepsies
- Primary reading epilepsy
- Startle epilepsy

ADNFLE
Familial temporal lobe epilepsies
†Generalized epilepsies with febrile seizures plus
†Familial focal epilepsy with variable foci

Symptomatic (or probably symptomatic) focal epilepsies
Limbic epilepsies
- Mesial temporal lobe epilepsy with hippocampal sclerosis
- Mesial temporal lobe epilepsy defined by specific aetiologies

Other types defined by location and etiology
Neocortical epilepsies
- Rasmussen syndrome
- Other types defined by location and etiology

Adapted from Commission, 2001