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THE COMORBIDITY OF EPILEPSIES AND THE IMPACT OF

MORTALITY IN PEOPLE WITH EPILEPSY

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Abstract

The thesis describes the epidemiology of selected somatic and psychiatric conditions in epilepsy and the health care demands of people with epilepsy, and presents broad estimates of life expectancy in people with epilepsy in the community in comparison to people without epilepsy.

A cross-sectional study was conducted extracting data from the General Practice Research Database for the period 1995-1998. Psychiatric disorders occurred twice as often and the risk of groups of most somatic disorders across categories was increased in people with epilepsy. The risk of neoplasia excluding intracranial tumours was not increased in epilepsy. The risk of brain tumours, meningiomas and neurodegenerative disorders was particularly increased. Other conditions occurring more frequently in epilepsy include upper gastrointestinal bleed, cardio- and cerebrovascular disorders, fractures, pneumonia and chronic lung diseases, and diabetes.

Analysis of data from the fourth national survey of morbidity in general practice (1991-92) revealed that patients with epilepsy used health services (consultations with a general practitioner, home visits, referrals to secondary care) more often than people without epilepsy, irrespective of age, sex and social class. A higher proportion of patients with epilepsy consulted for neoplasms, haematological and mental health disorders, dementia, stroke and gastrointestinal bleeding.

Previous studies have shown that epilepsy carries a risk of premature death. Life expectancy was estimated using data from a cohort of 564 patients with definite epilepsy followed for nearly 15 years (177 deaths) (registered through the National General Practice Study of Epilepsy) by employing a parametric survival model based on the Weibull distribution. Reduction in life expectancy can be up to 2 years for people with a diagnosis of idiopathic/cryptogenic epilepsy and the reduction can be up to 10 years in people with symptomatic epilepsy. Reductions in life expectancy are highest at the time of diagnosis but diminish with time.

People with epilepsy can be affected by a number of psychiatric and somatic conditions more frequently than people without the condition. They make a higher use of health services at all levels of care, which may be partly related to the presence of coexisting disorders. It appears that higher mortality rates in epilepsy translate into reductions in life expectancy.

Acknowledgements

Own contributions

Study design

The initial idea for the studies "Differences in the use of health services among people with and without epilepsy in the United Kingdom: socio-economic and disease-specific determinants" and "The epidemiology of the comorbidity of epilepsy in the general population" belongs to my supervisors Professor Josemir W Sander and Professor Azeem Majeed. The ideas for the papers were then refined into research questions in consultation with myself. I then took the lead role in the design of these studies, carried out the literature reviews, and wrote up the methodology with the help of Professor Azeem Majeed. The conception of the study "Life expectancy in people with newly diagnosed epilepsy" belongs to Professor Josemir W Sander and Professor Simon D Shorvon. Dr. Anthony L Johnson was responsible for the final design of this study and wrote up the methodology.

Background literature search

I conducted the entire literature search for each study, as well as for the reviews on the psychiatric comorbidity of epilepsy and mortality in epilepsy that are part of this thesis.

Data extraction and statistical analysis

Data for the studies "Differences in the use of health services among people with and without epilepsy in the United Kingdom: socio-economic and disease-specific determinants" and "The epidemiology of the comorbidity of epilepsy in the general population" was extracted by Dr.Kevin Carroll from the Fourth National Survey of Morbidity in General Practice (MSGP4) and the General Practice Research Database (GPRD) respectively. I contributed to the statistical analysis of data that was primarily performed by Dr. Kevin Carroll and Professor Azeem Majeed. My role in this was to specify the relevant analyses; to advise on the format and content of the tables; and to interpret the results and place them in their clinical, policy and public health settings. Data from the study "Life expectancy in people with newly diagnosed epilepsy" was extracted by Dr. Anthony L Johnson using the National General Practice Survey in Epilepsy (NGPSE) database, who also performed all statistical analyses for the study.

Data interpretation

I conducted the interpretation of data for the three studies and discussed the findings based on comparisons with other relevant studies in the literature. Contributions were made by Professor Josemir W Sander, Professor Azeem Majeed and Dr. Anthony L Johnson as appropriate. Professor David W Chadwick contributed to the discussion of the chapter on "Life expectancy in people with newly diagnosed epilepsy".

Published papers

I was the first author of the following publications that arose from the work described in this thesis. I took the lead role in specifying the format of the papers and in writing them. I dealt with the comments from the journal editors and referees, and revised the papers to make them suitable for publication.

A Gaitatzis, B Purcell, K Carroll, JW Sander, A Majeed. Differences in the use of health services among people with and without epilepsy in the United Kingdom: socio-economic and disease-specific determinants. Epilepsy Research 2002; 50(3): 233-241.

A Gaitatzis, K Carroll, JW Sander, A Majeed. The epidemiology of the comorbidity of epilepsy in the general population. Epilepsia 2004; 45(12): 1-10.

A Gaitatzis, MR Trimble, JW Sander. The psychiatric comorbidity of epilepsy. Acta Neurologica Scandinavia 2004;110(4):207-20.

A Gaitatzis, AL Johnson, DW Chadwick, JW Sander. Life expectancy in people with newly diagnosed epilepsy. Brain 2004 Nov;127(Pt 11):2427-32.

A Gaitatzis, JW Sander. The mortality of epilepsy revisited. Epileptic Disorders 2004; 6 (1): 3-13.

Contents

List of Boxes

Abbreviations

AD: Alzheimer's disease

AED: antiepileptic drug(s)

APD: antipsychotic drugs(s)

CAP: community acquired pneumonia

CHD: congenital heart disease

CNS: central nervous system

CPS: complex partial seizure(s)

CVA: cerebrovascular accident

CVD: cerebrovascular disease

DSM: diagnostic and statistical manual

DBS: deep brain stimulation

ECT: electroconvulsive treatment

EEG: electroencephalography

FLE: frontal lobe epilepsy

GABA: gamma aminobutyric acid

GCTS: generalised tonic clonic seizure(s)

GI: gastro-intestinal

GP: general practitioner

GPRD: general practice research database

ICD: international classification of diseases

IDD: interictal dysphoric disorder

IHD: ischaemic heart disease

ILAE: International League Against Epilepsy

MR: mental retardation

MRI: magnetic resonance imaging

MSGP4: 4th National Survey of Morbidity in General Practice

NEAD: non-epileptic attack disorder

NGPSE: National General Practice Study of Epilepsy

NICE: National Institute for Clinical Excellence

PD: Parkinson's disease

PMR: proportional mortality ratio

PR: prevalence ratio

RR: risk ratio or relative risk

SE: status epilepticus

SGTCS: secondarily generalised tonic clonic seizure(s)

SIR: standardised incidence ratio

SLPE: schizophrenia-like psychosis of epilepsy

SMR: standardised mortality ratio

SSRI: selective serotonin reuptake inhibitor(s)

TCA: tricyclic antidepressants

TIA: transient ischaemic attack

TLE: temporal lobe epilepsy

GENERAL INTRODUCTION

Epilepsy

Epilepsy is a multifactorial and multifaceted condition, with particular management considerations for different groups of patients, and has a significant impact on the lives of affected people and on society. *Epilepsy* is defined as the tendency in an individual to the occurrence of unprovoked seizures[1] and, in practice, is said to be present when two or more seizures have occurred.[2] It can occur as a consequence of a wide range of genetic disorders, structural and functional abnormalities, as well as metabolic and other insults; however, no clear cause is found in about 60% of cases.[3] The collective term *epilepsies* refers to those neurological conditions involving chronic recurrent epileptic seizures (Box 1).[4] According to the current aetiological classification of the International League Against Epilepsy (ILAE), epilepsies are divided into *idiopathic* (presumed to be genetic with no structural brain lesion and usually age-dependent), *symptomatic* (seizures are the consequence of a known CNS disorder), and *cryptogenic* (presumed to be symptomatic but with no identifiable aetiology).[5] Seizures are classified into *partial* or *focal* (where there is initial activation of only part of one cerebral hemisphere) and *generalised* (where there is initial activation of both cerebral hemispheres), according to their origin and manifestations as assessed clinically and by EEG.[6]

Epilepsy is one of the most common chronic neurological conditions, affecting an estimated 50 million people worldwide.[7] The incidence (40-70 cases per 100,000/year), point prevalence (6-10 cases per 1,000) and lifetime prevalence (2-5%) in industrialised countries[1] emphasise its numerical importance. Both the incidence and prevalence of epilepsy are dramatically higher among elderly people than among those who are younger.[1,8]

BOX 1.

Definitions according to the Glossary of Descriptive Terminology for Ictal Semiology, ILAE Commission Report[4]

EPILEPTIC SEIZURE

Manifestation(s) of epileptic (excessive and/or hypersynchronous), usually self-limited activity of neurons in the brain.

EPILEPSY

a) Epileptic Disorder: A chronic neurological condition characterised by recurrent epileptic seizures.

b) Epilepsies: Those conditions involving chronic recurrent epileptic seizures that can be considered epileptic disorders.

Epilepsy is associated with significant morbidity and mortality: Depending on its severity and response to treatment, epilepsy can have deleterious effects on a person's life, as it may affect cognitive, psychological and social development;[9,10] pose lifestyle restrictions;[11] be complicated by treatment side effects;[2] and be associated with increased mortality and risk of sudden death.[1,12] Although the prognosis is favourable for the majority of patients, 20-30% develop refractory epilepsy, meaning that they continue to experience seizures and/or unacceptable side effects, despite optimal antiepileptic drug (AED) treatment, that limit their ability to live life fully.[10,13] An important determinant of morbidity in epilepsy is comorbidity.

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The concept of comorbidity –the co-existence of two or more disorders in the same person- has not received adequate attention in epilepsy, although in clinical practice only a fraction of seizures occur in otherwise healthy individuals. Although the presentation, management and prognosis of numerous systemic disorders that cause seizures has been discussed,[14;15] information on the frequency of disorders co-existing with epilepsy in people with the condition is limited. This is particularly the case for somatic disorders. The great majority of studies on the frequency or risk of co-existing disorders in epilepsy has been conducted in small and/or special populations that do not provide estimates for these conditions in the general population. The medical care for the majority of people with epilepsy in UK is provided by general practitioners and neurologists in the community[16] and, therefore, it is important to know the risk of these disorders in an epilepsy population in this setting.

Mortality is known to be increased in epilepsy, especially in people with symptomatic epilepsy.[12] Standardised mortality ratios (SMRs) have been calculated for the major ILAE aetiological groups and for a number of specific conditions in epilepsy. However, the effect of the increased mortality rates on the life expectancy of people with epilepsy is not known.

This thesis addresses the issues of comorbidity and life expectancy in people with epilepsy. It attempts to estimate the prevalence ratio of a number of common disorders in people with epilepsy compared to people without epilepsy in the primary care setting, and to estimate the number of years of life lost in people with epilepsy compared to the general population using data from large health databases.

Part I

THE COMORBIDITY OF THE EPILEPSIES

Chapter 1

INTRODUCTION TO COMORBIDITY

People with epilepsy may develop any other condition during their lives that may precede, co-occur with, or follow the diagnosis of epilepsy. *Comorbidity* refers to the coexistence of more than one condition in the same person. The term was originally used by Feinstein with reference to coexistent conditions in clinical trials.[17] These conditions are then referred to as comorbid,[17] and the coexistence may also indicate an association between them that is more than coincidental.[17] This means that a statistically significant association may exist between two disorders. In a slightly different version, comorbidity has also been defined along the lines of concomitant but unrelated pathological or disease processes.[18]

As a general term, the comorbidity of epilepsy refers to the coexistence or co-occurrence of other conditions in a person with epilepsy. These conditions can be related or unrelated to the underlying cause of epilepsy. Lipton and Silberstein[19] have suggested a scheme of possible causal explanations for statistically significant comorbid conditions that may provide clues towards the pathogenesis of the studied condition.

First, the disorders may be unrelated and their apparent association may have arisen by coincidence or selection bias. For example, if patients with both epilepsy and depression are more difficult to treat and therefore more likely to be referred to an epilepsy specialist, then the association between the two disorders will be overestimated in studies conducted in epilepsy speciality clinics. This bias, also known as Berkson's bias, is a problem in clinic-based studies[20] and can be avoided by undertaking population-based studies.

A second explanation may be that one condition causes the other. An example is the relationship between epilepsy and migraine. Headaches have been associated with seizures as ictal or post-ictal phenomena, particularly in occipital lobe seizures, and migraine aura may trigger seizures.[21]

Third, the conditions may be related due to shared environmental or genetic risk factors. An example of a shared environmental factor is head injury, a risk factor for both epilepsy and migraine that may account for part of the relationship between the disorders. Shared genetic factors, such as mutations affecting genes encoding ion channels expressed in tissues outside the CNS as well, may account for associations between comorbid disorders.[22] For example, mutations in potassium channels may predispose to seizures, sensorineural hearing loss and long QT interval on ECG.[23]

A proposed fourth mechanism would involve independent genetic or environmental risk factors, producing a brain state that favours the association of two conditions. Migraine and epilepsy have been attributed to a condition of neuronal hyperexcitability that results from genetic as well as environmental risk factors such as head trauma.[24] In this context, a number of generalised epilepsies are associated with channelopathies that lead to neuronal hyperexcitability.[25] For example, abnormalities in calcium channels have been implicated in episodic ataxia, spinocerebellar ataxia, familial hemiplegic migraine and idiopathic generalised epilepsy.[26-29] The development of a particular brain state increases the probability of the two disorders developing in the same person.

The above scheme does not include conditions that can be the cause or the effect of the epilepsy. Duchowny and Bourgeois described the conditions that contribute to the development of epilepsy as "causal" comorbidity and the conditions presenting as

a consequence of repeated seizure activity or its treatment as "resultant" comorbidity.[30] People with epilepsy are at risk of dysfunction in a number of physiological systems. This can manifest clinically as disturbances in the sleep-wake cycles,[31] in autonomic nervous system[32;33] and endocrine function,[34;35] and in general medical and reproductive health.[36] Disorders in these physiological systems may be a consequence of the epileptic syndrome,[37;38] the interictal epileptiform activity,[39] the seizures,[40] or the antiepileptic drugs.[41-44] In addition, epilepsy and its treatment can have adverse cognitive and behavioural consequences.[45]

The study of the comorbidity of epilepsy is important for diagnosis and treatment, as well as for epidemiology and health services. For the clinician, a high degree of symptom overlap among co-occurring conditions may pose diagnostic difficulties. Both epilepsy and vertebrobasilar migraine can cause transient alterations of consciousness, as well as headache.[46] The challenge for the clinician is to recognise any other disease(s) that might be present in a patient with epilepsy. For the statistically significant comorbidity of epilepsy, the principle of diagnostic parsimony does not apply. In this case, the presence of epilepsy should increase, not reduce, the suspicion that other disorders might be present. For example, patients with epilepsy often have medically undiagnosed migraine or depression.[47;48]

It has been stated that "comorbidity refers to the effect of other diseases and conditions on the management of epilepsy and to the special problems posed by the underlying condition of epilepsy on the management of other diseases".[15] Coexisting disorders can provoke seizures in patients with epilepsy through lowering the seizure

threshold; systemic illness is known to cause severe psychological and physical stress.[49]

In the treatment of epilepsy, a comorbid disorder can provide therapeutic opportunities but also impose certain limitations. In some instances, a single drug may treat two conditions. For a patient with epilepsy and migraine or epilepsy and bipolar psychosis, sodium valproate may ameliorate the comorbid disorders. Tricyclic antidepressants and neuroleptics may lower the seizure threshold and exacerbate seizures in patients with epilepsy and depression or psychosis and therefore must be used cautiously. Patients with hepatic or renal insufficiency require careful adjustment of their antiepileptic medication. Interaction of AEDs with other medication needs to be taken into account when prescribing. Seizures can be a particular problem in patients with severe osteoporosis and high fracture risk, and in those with bleeding tendency. Long-term use of phenytoin has been associated with cerebellar atrophy and folate deficiency. The management of epileptic seizures in the presence of comorbidity in children and adults, as well as the medical causes of seizures have been extensively reviewed elsewhere.[14;15;49]

As a condition, epilepsy encompasses a plethora of types and syndromes that differ from each other in terms of aetiopathogenesis, localisation, age of onset, severity and prognosis. Its treatment, either medical or surgical, can have different (side-) effects on patients. The interaction of biological, clinical and therapeutic factors with the environment generates the phenocopy of epilepsy and possibly affects the presentation of (co)morbidity in each affected patient.

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DEFINITION For the purposes of this thesis *comorbidity* refers to the disorders that co-occur more frequently in people with a given condition than would be expected in the general population without the condition, irrespective of causal association. Comorbidity in epilepsy is divided in two major categories: the somatic, including all disorders arising from the body, and the psychiatric, including disorders arising from the mind.

In case-control studies, epilepsy has been associated with a number of somatic disorders, such as learning disability and cerebral palsy,[50;51] migraine[21] and cardiovascular conditions.[52] Information, however, on the risk of somatic comorbidity in epilepsy is limited.

Psychiatric disorders appear to occur more frequently in epilepsy, although most studies have been conducted in highly selected groups of patients, mainly with temporal lobe or refractory epilepsy. The psychiatric comorbidity in epilepsy has been studied much more rigorously than the somatic comorbidity, particularly the presentation of various psychiatric conditions in epilepsy, in association with specific types of seizures, antiepileptic drug treatment and surgical treatment. The subject of psychiatric comorbidity in epilepsy is extensively reviewed in the following chapter, in terms of epidemiology, clinical presentation, risk factors, aetiology, diagnosis and treatment.

Chapter 2

THE PSYCHIATRIC COMORBIDITY OF EPILEPSY

2.1 Introduction

Epilepsy can be accompanied by changes in cognition and behaviour and can also be associated with psychiatric illness.[45;53]

Psychiatric disorders accompanying epilepsy are comorbid with epilepsy and may precede, co-occur or follow a diagnosis of epilepsy. The increased risk for psychiatric disorders in epilepsy can be related to a number of clinical, psychosocial and biological factors (table 1).[53]

Psychiatric diagnoses in patients with epilepsy in published studies follow either the International Classification of Diseases (ICD) or the Diagnostic and Statistic Manual (DSM) classifications. The most commonly reported comorbid psychiatric conditions fall into the category of psychoses, neuroses and mood disorders (DSM-III-R axis I disorders), or of personality disorders (DSM-III-R axis II disorders) and behavioural problems. The psychiatric conditions can present either periictally (in prodromal, ictal or postictal periods), or interictally. Higher rates of psychopathology are observed in people with epilepsy compared with the general population, other neurological control groups, and people with chronic non-neurological disorders.[53]

A key question regarding psychiatric disorders occurring in patients with epilepsy is whether they are phenomenologically comparable to disorders in patients without epilepsy. Opposing views have been proposed, but the subject remains unclear.[54] The answer is important because the presence of recognisable psychiatric syndromes in patients with known brain pathology may lead to an understanding of the pathophysiology of these disorders in patients without epilepsy, and because specific

Clinical factors
Age at onset of epilepsy
Duration of disorder
Type and frequency of seizures
Hemisphere of cerebral dysfunction (if present)
Interictal and ictal EEG abnormalities
Family history of epilepsy or psychiatric disorder
Psychosocial factors
Chronic nature of disease
Low socio-economic status
Low educational level
Negative cultural approach to epilepsy
Difficulties in adjustment to the consequences of the illness
Fear of seizures
Social stigma
Overprotection by families
Legal limitations (i.e., driving regulations)
Low self-esteem
Biological factors
Neuropathologic damage to areas connected with psychic functioning (i.e., amygdala, limbic system , frontal cortex, basal ganglia)
Emotional and cognitive side effects of antiepileptic drugs
Forced normalisation

Table 1. Factors related to the risk for psychiatric disorders.

(Adapted from Torta & Keller, 1999[53])

psychiatric syndromes seen in patients with epilepsy may respond to specific psychiatric treatments.

The risk and characteristics of psychiatric disorders in patients with epilepsy have been assessed in a number of studies, which were conducted in different populations and employed different methodologies. The current epidemiology of psychiatric disorders in epilepsy is surveyed here taking into account these differences. A descriptive approach is adopted, where the risk of all psychiatric disorders, as well as individual disorders, in adults and children with epilepsy is described according to type of epilepsy and study population. The relationships between individual disorders and seizure occurrence are discussed, as well as the aetiology, recognition and treatment of these disorders in association with epilepsy.

2.2 Risk of any psychiatric disorder

2.2.i Studies of unselected populations

ADULTS

Few population-based studies have assessed the prevalence of psychiatric comorbidity in epilepsy. In a survey of 713 adults with active epilepsy in northern Sweden, 5.9% of patients were reported to have had psychoses, alcohol dependence syndrome, or other psychiatric disorders.[55] Lifetime mental abnormalities were reported in 6.7% of 225 patients with childhood-onset epilepsy.[56] In a population-based case controlled study with 35-year follow-up, concurrent illnesses were reported in 245 adults with childhood-onset epilepsy.[57] A 4-fold increased risk for psychiatric disorders was found, regardless of whether or not patients were still receiving AEDs. In a study of all individuals with epilepsy in Iceland (N=987), 52% had some non-psychotic mental abnormality, and 7% had psychosis at some time in

their life.[58] In a nation-wide survey in the UK, an annual rate of 0.1% was calculated for new cases of acute psychological disorders (N=64) among patients with active epilepsy attending neurology clinics (estimated N$\approx$60,000).[59]

Psychiatric disorders may pose a considerable burden in people with epilepsy. In a community-based survey in Rochester, Minnesota, 19% of an adult population with a recent history of active epilepsy (within five to six years) and without learning difficulties (N=125) were considered to have major psychosocial problems.[60] A community-based survey in North East England found that epilepsy patients with an associated neurological or psychiatric handicap had higher unemployment rates (79%) compared with all patients with epilepsy and with age/sex matched controls (59% and 16% respectively).[61]

CHILDREN

A population-based English study showed that the rate of psychiatric disorders was higher for children of school age with epilepsy (27%, N=63) than for children with other chronic physical conditions (12%, N=138) or children in the general population (7%, N=2,189).[62] In a population-based study in South India, 23% of 26 children with epilepsy aged 8-12 years were diagnosed with psychiatric disorders in comparison to 8.1% of controls from the general population (N=1166).[63] In another study, behaviour problems requiring mental health consultation affected 22% of patients of normal intelligence with childhood-onset epilepsy (N=337).[64]

2.2.ii Selected population studies

ADULTS

Case-controlled[65-67] and cross-sectional studies[68;69] have used a variety of methods to

detect psychiatric disorders in adult patients. Two studies found no significant difference in the prevalence of psychiatric disorders between people with epilepsy and a healthy control group.[67;69] In other studies, patients with epilepsy were at higher risk of developing psychopathological disorders than the general population,[65] but the risk was not greater than among patients with other chronic diseases[66] including neurological.[65] The percentage of patients identified with psychiatric disorders ranged between 19 and 48%[66;68;69] in a number of studies reflecting differences in methodology. The majority of patients with epilepsy included in these studies were adults of normal intelligence with no other neurological disorder. A review of the literature published in 1986 reported that patients with epilepsy demonstrated more emotional and psychiatric problems than healthy individuals and more difficulties than other patient groups with non-neurological disorders. They had about the same incidence of these problems as people with other neurological disorders.[70]

CHILDREN

A few studies have reported prevalence rates of behavioural problems in children with new-onset epilepsy. In one study, children with chronic and newly diagnosed epilepsy were significantly more disturbed (48% and 45% respectively) than those with newly diagnosed diabetes (17%) or children in the general population (10%).[71] In another study, the percentage of behavioural problems in children with previously unrecognised seizures was found to be 34%, compared with an expected 10% in the general population.[72] Presumed causes for the behavioural problems in childhood included the effects of seizures, effects of antiepileptic drugs (AEDs), poor child and

family adaptation to seizures, and neurological dysfunction that could be responsible for both seizures and behaviour problems.[71-73]

2.3 Risk of any psychiatric disorder in patients with temporal lobe or refractory epilepsy

<u>Selected population studies</u>

ADULTS

Acute psychological disorders appear to be more common in patients with complex partial seizures.[59] In 88 patients with epilepsy from a general practice cohort, the risk of developing psychiatric illness was higher among patients with temporal lobe epilepsy (TLE) (60%) and other focal epilepsy (54%) than among patients with primary generalised epilepsy (37%).[68] In one study, patients with TLE (N=20) had higher rates of psychiatric disorders (80%) than patients with juvenile myoclonic epilepsy (22%) and patients with diabetes (10%).[74] In a study of 21 patients from an epilepsy centre in the US who had auras –most of whom (72%) had complex partial seizures (CPS) - 71% met criteria for a psychiatric diagnosis.[75] In comparison, a retrospective study of patients with adult-onset idiopathic generalised epilepsy (N=42) reported that 33% were diagnosed and treated for mental disorders.[76]

Cross-sectional studies have assessed the prevalence of psychiatric disorders in cohorts of patients with refractory epilepsy, the great majority of whom had temporal lobe epilepsy. Lifetime prevalence ranged between 44 and 88% in candidates for epilepsy surgery or patients undergoing neurodiagnostic evaluation[54;77-80] and was 75% in a study of patients awaiting temporal lobectomy.[81] The lifetime prevalence for DSM axis I disorders ranged between 44 and 71% in several studies,[54;75;77-80] with

an estimated mean of 60%.[82] This compares to rates of 22% for patients followed for medical illnesses[83] and 26% for primary care patients.[84] Current prevalence in surgical candidates was reported at 36%,[79] and 35-87% in patients prior to surgery for epilepsy.[81;85-87] Patients with chronic, intractable, localisation-related epilepsies, who are on polytherapy and experience a range of psychosomatic symptoms appear to be particularly prone to developing psychiatric comorbidity.[59;69;78;81;88]

CHILDREN

A significantly greater number of children with temporal lobe epilepsy (N=62) experienced emotional disturbance (18% vs. 6%) and psychiatric abnormalities (79% vs. 47%) than children with generalised epilepsy (N=70).[89] Neuroses (37% vs. 16%), psychoses (19% vs. 10%), and personality disorders (23% vs. 21%) occurred more commonly in the TLE group (all statistically significant differences, p<0.001). In another study, 85% of children with TLE (N=100) followed into adult life suffered psychiatric problems.[90] However, the occurrence of overt psychiatric disorder in adult life was low: among people who were not gravely mentally retarded 70% were regarded as psychiatrically healthy.

2.4 Risk and characteristics of individual psychiatric disorders

2.4.i Affective/Mood disorders

Risk & Predominant types

In a cohort of 100 patients with cryptogenic epilepsy and normal intelligence, 3% were diagnosed with dysthymia and 3% with depression.[69] In a UK nation-wide survey, 30% of patients with epilepsy presenting with acute psychological disorders suffered acute affective disorders (depressive, manic and dysthymic episodes).[59] The

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lifetime prevalence of mood disorders in patients with TLE or refractory epilepsy ranged between 24 and 72% in a number of studies,[54;75;79;81] while the respective current prevalence was between 24 and 30%.[79;81] Mania or bipolar psychosis are not considered more common in patients with epilepsy.[91] Rates of 5% have been reported in some studies of patients with partial and/or intractable epilepsy.[75;92]

Depression represents the most common interictal psychiatric condition in patients with epilepsy.[47;93] Depression appears to occur more frequently in patients with epilepsy than in patients with other neurological disorders,[94;95] chronic medical conditions, or normal controls.[74;96] Lifetime prevalence for major depression ranges between 8 and 48% in patients with TLE or refractory epilepsy,[54;75;77;79;80;86] with an estimated mean of ~30% across studies.[82] The corresponding rate in the general population has been reported as 6% and 17% in two major epidemiologic studies.[82] Reported rates for dysthymia in epilepsy range from 3-21% depending on the population studied.[54;68;69;75;79] Depression can develop de novo in 4-8% of patients following temporal lobectomy for refractory epilepsy[79;85;88] but rates as high as 38% have been reported.[86] Symptoms of depression appear to be also common in children with epilepsy.[97]

Clinical features of depression

PREICTAL

One third of patients with partial seizures report premonitory symptoms, usually before secondarily generalised tonic clonic seizures (SGTCS). Prodromal moods of depression or irritability may occur hours to days before a seizure and are often relieved by the convulsion. These prodromal symptoms may be related to subclinical

seizure activity, or to physiologic or biologic processes involved in the initiation of both the lowered mood and the seizure. In some patients, the presence of negative, depressed, or dysphoric mood in combination with negative life events may increase the likelihood of seizures.[98]

ICTAL

Depressed mood can occur as part of an aura in about 1% of patients and is more common in TLE. It is of sudden onset and occurs out of context (i.e., not related to environmental stimuli). Its severity ranges from mild feelings of sadness to profound hopelessness and despair.[98] In children, affective symptoms have been reported as part of benign partial epilepsy.[99]

POSTICTAL

Flattened or depressed affect has been observed, particularly in patients with TLE, lasting hours to days after seizures. It is postulated that this is a consequence of the inhibitory mechanisms involved in the termination of seizures.[98] Clinically, severity is variable and some people may even become suicidal.

INTERICTAL

Interictal depression is believed to affect up to two thirds of patients, especially those with severe and/or frequent seizures.[98] Diagnosis of major depression and dysthymia in epilepsy follows established criteria as in the rest of the population. Many patients with TLE, however, develop depressive symptoms characterised by a fluctuating course and a pleomorphic presentation.[78] Blumer coined the term "*interictal dysphoric disorder*" to describe a syndrome comprising eight symptoms, of which

patients must experience at least three: depressive moods, anergia, pain, irritability, insomnia, anxiety, fear, and euphoric mood.[78;88] In severe form, this disorder may become associated with sudden suicide attempts during episodes of intense depressive mood in some patients, and with psychotic features (hallucinations, paranoia, delusions or bizarre behaviour) in others. Affective and somatoform symptoms tend to be intermittent, lasting hours to a few days, while the interictal psychoses may last a few days to a few weeks. In one series of patients (N=75) with epilepsy undergoing neurodiagnostic monitoring, 44% were found to suffer from an interictal dysphoric disorder.[78] Similar symptomatology was also reported by others.[81]

Clinical / Risk factors

It appears that men with epilepsy are most at risk of developing depression, while the prevalence of depression in the general population is higher in women. Factors such as seizure type, laterality of epileptic focus, seizure frequency, and age of onset and duration of epilepsy have been implicated, but findings are inconsistent.[91;98]

Aetiology / Biological factors

Depression may be associated with a neurological condition that is also responsible for epilepsy (*e.g.* CVA, dementia, head injury) and may be commoner in patients with a structural lesion or patients with learning difficulties.[98] The development of depression may be a reaction to stresses in life (*reactive depression*), including the effect of any underlying conditions. Alternatively and more usually, depression may be related to biological factors, such as folate deficiency (due to AEDs),[47] frontal lobe dysfunction,[98] anterior temporal lobectomy,[88;98;100] and AEDs (particularly with

polytherapy, phenobarbital, vigabatrin, topiramate, and tiagabine)[98] (*endogenous*

depression). It has been suggested that a history of depressive episodes is a risk

factor for the occurrence of unprovoked seizures in adults and children.[93;101] In

addition, a family history of depression has been observed in over 50% of patients

with both epilepsy and depression suggesting a genetic predisposition.[93] These

findings, together with evidence of decreased serotonergic, noradrenergic,

dopaminergic and GABAergic activity in both disorders, suggest that epilepsy and

depression may share common pathogenic mechanisms.[93]

Recognition & Diagnosis of depression

In over 50% of paediatric and adult patients with epilepsy, depression may remain

undiagnosed. It is important to recognise depression in people with epilepsy, not only

to enable appropriate treatment but also to identify patients at risk for suicide.[82;93]

Additional burden imposed on patients with epilepsy

Major depression in epilepsy has been associated with significantly decreased self-

reported quality of life, increased disability and missed work, increased medical

utilisation and medical costs.[82;93] Mental illness, drug addiction, early onset of

epilepsy (particularly onset during adolescence), and personality disorder have been

associated with increased risk, with some evidence that risk of suicide may decline

with duration of epilepsy.[102;103] Anticonvulsants, particularly barbiturates, were used

in most cases of self-poisoning in the past.[104]

Suicide is an important and potentially avoidable cause of death in epilepsy, but the

extent of its risk varies considerably across studies. It has been reported that people

with epilepsy are at higher risk of committing suicide than the general population[103;105-111] but other investigators have been unable to demonstrate such an increase.[112-115] In these studies the proportion of deaths from suicide ranged between 0 and 20% and the SMRs between 1 and 5.8. Incidence cohorts[114;116] are known to have lower mortality rates than prevalence cohorts because the former include small numbers of cases with symptomatic or severe epilepsy, which are over-represented in prevalence cohorts and which are associated with higher mortality. In addition, people who attend hospitals have higher morbidity and mortality than community cohorts. In the large prevalence study of 9,061 adult patients who were once hospitalised for epilepsy in Sweden the SMR for suicide was 3.5 (95% CI 2.6-4.6).[108] A literature review based on studies published up to 1983 concluded that patients with severe epilepsy had a suicide rate 5 times higher, and patients with TLE 25 times higher, than the general population.[103] A later meta-analysis by the same group concluded that the overall SMR for death due to suicide in epilepsy was 5.1 (95% CI 3.9-6.6). This was based on studies mostly published in the 1970s and 1980s, and mainly including patients with TLE, institutionalised patients, patients from surgical series, and out-patients.[117] In this analysis, the highest suicide rates were observed in patients with surgically treated TLE whose risk was increased by a factor of 80 [SMR 87.5 (95% CI 35-180)].[117] However, this was estimated on the basis of earlier surgical series published in 1968[87] and 1969[118] that do not reflect current standards of treatment and/or patient selection criteria. Rates from these early studies may be higher than we would expect today with modern management and less use of barbiturates. The recently published follow-up results of the UK NGPSE study with a total of 11,400 patient-years did not show any excess of suicides.[116] Another recent study reported five suicides in a 12-year period in a total of 10,739 patients with

epilepsy seen at a single US centre from 1987 to 1999.[119] This number is comparable with the average number of suicides in the general US population of about one per 10,000 people per year. All suicide cases had a history of early onset (mean age 9.5 years), long-standing CPS (mean duration 29 years) and very high seizure frequency (often daily). Suicide occurred in all patients after a short interval (3 months to 3 years) of having obtained full seizure control for the first time after temporal lobectomy (3 patients), vagal nerve stimulation, or medication. These patients had been diagnosed with interictal dysphoric disorder (IDD), a syndrome described previously by the authors.[78] IDD comprises intermittent affective and somatoform symptoms, presenting with intense depressive moods with suicidal intensity in some, and with psychotic features and dysphoric symptoms (i.e., irritability, fear, anxiety) in others.[88] According to the authors, suicide in epilepsy results from specific neuropsychiatric disorders (including IDD and post-ictal depression) associated with epilepsy rather than as the result of unfortunate psychosocial difficulties imposed by the chronicity and severity of epilepsy.[119]

Treatments strategies for depression

Antidepressants remain the mainstay of pharmacological treatment for depressed patients, despite concerns about the potential lowering of seizure threshold by tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). Although pre-ictal and ictal depression does not usually require treatment, improvement in seizure frequency is expected to reduce its occurrence. Post-ictal depression may additionally require small doses of antidepressants.[98] Support groups and/or psychotherapy are sufficient to treat depressive reactions. SSRIs are considered first-line treatment of interictal depression. Non-fluoxetine SSRIs such as

sertraline, citalopram, and paroxetine are particularly recommended.[47] Nefazodone, moclobemide, and TCAs can be used as second-line drugs, but special caution is required for potential interactions with enzyme-inducing AEDs. In addition, TCAs have not been shown to ameliorate depressive symptoms in children.[47] Symptoms of interictal dysphoric disorder usually respond well to low doses of imipramine.[88] Electroconvulsive treatment (ECT) is not contraindicated in people with epilepsy and may be life-saving.[47] People with epilepsy and previous psychiatric history, including a history of suicide moods or attempts, should be referred to a neuropsychiatrist with experience in epilepsy.

2.4.ii Neuroses

Risk & Predominant types

Anxiety disorders appear to affect 10-25% of patients with epilepsy in the community[120] and in general practice populations.[68;121] Rates vary between 7 and 27% in hospital[89] and between 11 and 44% in patients with intractable epilepsy.[54;75;79;81;86;87;120;122] In one study, symptoms of anxiety were reported in 16% of an outpatient paediatric epilepsy population (N=44).[97] In the general population, one-year prevalence rates for generalised anxiety disorders range between 2.5 and 6%.[123] Phobia has been reported in up to 20% of patients with intractable epilepsy[54;79] but has been as low as 1% and 5% in less selected series.[69;75] Similarly, the rates for obsessive compulsive disorder ranged between 4 and 10% across studies.[75;79;87]

A probably small proportion of patients with epilepsy suffer from non-epileptic attack disorder (NEAD), a condition categorised with the dissociative disorders.[124] It

has to be noted that about 30% of people with NEAD do also have epilepsy.[125] Patients with NEAD are usually female and have high rates of psychopathology, especially dissociative disorders and post-traumatic stress disorder.[126]

Clinical features of anxiety

ICTAL

Nervousness, fear, anger, and irritability may occur as part of an aura. Fear is reported as an aura by 10-15% patients with partial seizures.[53] Ictal affective symptoms tend to be stereotyped, paroxysmal, of brief duration (30-120 min), unprovoked by environmental stimuli, and may be accompanied by autonomic signs. These symptoms can be mistaken for a panic disorder and not recognised as epileptic in nature.

POSTICTAL

Post-ictal anxiety, like post-ictal depression, is not uncommon. It may be a feature of temporal lobe epilepsy but most usually is associated with the stresses related to seizure occurrence.[127]

INTERICTAL

Symptoms of anxiety may develop as a result of stressful events. Some people with epilepsy develop anticipatory anxiety of the attacks in public and may become agoraphobic.[128] Many people find that periods of anxiety and stress increase the frequency of seizures.

Clinical / Risk factors

People with seizures originating in the left temporal lobe may be more prone to develop anxiety than people with seizures originating in the right. According to one study, patients with left-sided TLE systematically showed higher levels of anxiety and lower estimates of quality of life on self-assessment compared with patients with right-sided TLE.[129]

Aetiology / Biological factors

Anxiety symptoms can be attributed to the unpredictable nature of epilepsy, with lack of control, sudden onset of seizures, and the possibility of injury or embarrassment.[130] Such symptoms, however, may be biologically driven[127] and have been found to be more common in patients with TLE.[89]

Recognition & Diagnosis of anxiety

Anxiety symptoms (i.e., panic attacks) can be mistaken for epilepsy and vice versa, especially fear and anxiety as part of a simple partial seizure.[127;128] The diagnosis of these symptoms is more difficult in children who may present with disruptive behaviour and irritability and have their symptoms overlooked as a result.[97]

Additional burden imposed on patients with epilepsy

This is difficult to quantify. People with a history of suicide attempt had higher rates of anxiety than people without such history.[131] Older people with epilepsy diagnosed in later life were more anxious and depressed than those diagnosed earlier, and their overall perception of quality of life was more likely to be negative.[132]

Treatments strategies for anxiety disorders

Treatment options include counselling, cognitive behavioural therapy and anxiety-reducing measures. Benzodiazepines should not be used as anxiolytics in people with epilepsy[128] because of the danger of dependence and the potential for withdrawal seizures.

2.4.iii Personality disorders

Risk & Predominant types

Personality disorders in people with epilepsy have been diagnosed in between 0.7% and 2% of general practice populations,[55;68] and in 4% of people with cryptogenic epilepsy.[69] Rates of personality disorders range from 13% to 35% in patients with partial epilepsy (mainly TLE),[74;80;89;133] and from 18% to 42% in surgical candidates or patients who have undergone surgery.[54;79;81;85;122] In comparison, the prevalence of personality disorders in the general population ranges between 6 and 13%.[134-136] Reported types in epilepsy include antisocial,[79;89] avoidant,[54;133] obsessive-compulsive,[54;85] schizoid,[85] schizotypal,[54] dependent,[85;133] and dissociated personality.[85] In a recent study assessing these disorders in patients with intractable epilepsy (N=52), dependent and avoidant personality disorders were by far the most common diagnoses.[133] In a study assessing the long-term psychiatric outcome in children with TLE (N=100), 12% were diagnosed with antisocial personality during adulthood.[90] A diagnosis of organic personality disorder -signifying a profound and enduring change in personality attributed to an organic cause- has also been described.[74;81;85] An "epileptic" personality has been reported in 3-5 % of patients with TLE in some studies.[87;89]

Clinical features / Personality changes

It appears that some patients with epilepsy (particularly those with TLE) develop certain personality traits or an interictal behaviour syndrome. Estimated rates obtained from cluster analysis studies using the Minnesota Multiphasic Personality Inventory vary from 7% to 21%.[91] The most commonly described traits are a preoccupation with philosophical and religious concerns, anger, excessive emotionality, viscosity, circumstantiality, altered sexuality, and hypergraphia.[70;137;138] This profile has been suggested as more specific for patients with TLE and is sometimes referred to as the *Gastaut-Geschwind syndrome*. The same traits are also seen in patients with other chronic illnesses, either medical or psychiatric.[65;70;139]

Clinical / Risk factors

Factors such as type and frequency of seizure, age at onset and duration of epilepsy were found to be associated with personality disorders in some studies[65;140-142] but not in others.[133] The lateralisation of the epileptogenic region may contribute to certain personality traits in patients with TLE,[137;143] but this has not been consistent across studies.[133;144]

Aetiology / Biological factors

The presence of personality disorders in patients with epilepsy could be an adaptation or reaction to psychosocial factors (such as stigmatisation, low self-esteem, social isolation, etc.) and/or biological factors (such as long-term effects of seizures or interictal spike activity, head injury after recurrent seizures, brain lesions, and medication effects).[91]

Recognition & Diagnosis

There is considerable controversy about the existence of an "epileptic" personality as has been suggested in previous studies.[145-148]

Additional burden imposed on patients with epilepsy

Personality disorders may affect AED compliance in patients with epilepsy and can represent a problem of interpersonal behaviour, which in turn can affect management.[91]

Treatments strategies

There is some evidence that risperidone in low doses is useful for the treatment of severe personality disorders, such as the borderline personality disorder.[149]

2.4.iv Psychoses

Risk & Predominant types

The prevalence of psychoses in epilepsy in population-based studies varies from 2% to 7%.[55;58;150;151] In a study on the population with epilepsy in Iceland the prevalence of psychoses was 6% and 9% for males and females respectively.[58] In a general practice study in epilepsy the prevalence of psychoses was 4%,[68] while no such diagnosis was made in a population of people with cryptogenic epilepsy (N=100).[69]

A national Danish study reported rates, and estimated standardised incidence ratios (SIRs), of non-organic non-affective psychoses developing after a diagnosis of epilepsy in a cohort of all people admitted to a general hospital with a diagnosis of epilepsy within a 15-year period (N=67,116).[152] The prevalence of psychiatric disorder (ICD-8, 290-309) in the epilepsy cohort was 16.8% and the incidence 6.0%.

The SIR of non-organic non-affective psychoses (according to ICD-8) was 3.00 and remained significant even after patients with learning disabilities or substance misuse were excluded [SIR 2.30 (95% CI 2.02-2.59)]. The SIRs for non-affective psychosis and schizophrenia were 2.74 and 2.15 respectively. The risk of psychoses may be 6-12 times higher in patients with epilepsy than in the general population.[53] A study conducted at an epilepsy centre in Japan found an incidence rate of newly developed psychosis of 0.3%.[153]

The prevalence of psychoses in patients with TLE and/or refractory epilepsy varies from 10% to 19% in most studies[80;87;89;90;92;154] and was reported to be nearly double (19% vs. 10%) compared to respective rates in generalised epilepsy.[89] It has to be noted that patients with interictal psychoses were excluded in most recent epilepsy surgery series, as it was believed that these do not improve with surgery.[79;81;86] In older studies, the incidence of psychoses in patients with TLE was 11-12%[155;156] compared to 1% in patients with generalised epilepsy.[155] Frontal lobe epilepsy (FLE) can be also associated with inter- or post-ictal psychoses.[157] Patients undergoing epilepsy surgery (most commonly temporal lobectomy) are at risk of developing psychosis for the first time (de novo). Interictal psychoses (i.e., schizophrenia-like psychosis of epilepsy) can develop in 3-12% of patients many months after anterior temporal lobectomy[53;79;158] and seizure-related psychoses (usually post-ictal) can affect 1.3-13% of patients.[53;79;81;85;88;158-160]

Schizophrenia or schizophrenia-like psychoses appear to affect between 4.3 and 18% of patients with epilepsy,[80;87;89;122;161] the great majority of whom suffer from TLE. Patients with TLE appear to have higher prevalence of schizophrenia than patients

with generalised epilepsy (18% vs. 4% respectively).[89] Interictal schizophrenic disorders occurred in 9% of epilepsy outpatients (N=1,611) compared with only 1% of age-matched migraine outpatients (N=2,167) at the same centre over an 18 year period.[161] The prevalence of schizophrenia in the general population is ~1%.[162] A Danish national epidemiologic study compared the incidence of schizophrenia in patients who had been admitted to hospital for epilepsy with that of the general population.[151] A standardised incidence ratio of 1.48 for all epilepsy patients and 2.35 for patients with psychomotor epilepsy was reported, although the epilepsy sample defined by the need for inpatient care may be considered unrepresentative.

Clinical features

People with epilepsy seem particularly liable to develop psychoses. These may take the form of a chronic interictal psychosis that closely resembles schizophrenia (known as schizophrenia-like psychosis of epilepsy-SLPE) or of an episodic psychotic state that is usually related to seizure activity.[162] First presentation usually occurs 11 to 15 years after the onset of seizures.[91]

ICTAL PSYCHOSIS

Patients with absence status (generalised non-convulsive status) present with altered consciousness and some may experience delusions and hallucinations. Patients with complex partial (psychomotor, temporal lobe) status epilepticus may present with either a prolonged twilight or confusional state (continuous form), or a series of recurring seizures with partial responsiveness between seizures (cyclic form).[91] The duration of symptoms varies from hours to days and EEG shows status epilepticus. Treatment is with AEDs.

POSTICTAL PSYCHOSIS

This accounts for 25% of epileptic psychoses.[53] It often follows an increase in seizure frequency or presents after prolonged tonic-clonic seizures, usually after a lucid interval of 1-6 days.[53;91] In most patients, it presents as abnormal mood, with paranoid delusions and hallucinations. Consciousness may be normal or impaired and EEG sometimes shows increased epileptic and slow activity. Symptoms usually remit spontaneously within a few days, often without the need for neuroleptic treatment. In some cases, chronic psychosis may develop from recurrent or even a single episode of postictal psychosis.

PERIICTAL PSYCHOSIS

In periictal psychoses, psychotic symptoms develop gradually and in parallel to increases in seizure frequency.[91] Consciousness is usually impaired and duration of symptoms is from days to weeks. The EEG shows increased epileptic and slow activity and treatment requires improvement of seizure control.

INTERICTAL PSYCHOSIS

Interictal psychoses occur between seizures and are not directly related to the ictus. They are less frequent than periictal psychoses and account for 10-30% of diagnoses.[91] Despite similarities with schizophrenia, including the presence of first rank Schneiderian symptoms,[53] SLPE can be differentiated by the preponderance of purely delusional states (typically with paranoid, mystical, and religious themes), preservation of affect and personality, and predominance of visual rather than auditory hallucinations.[53;91] Psychoses in patients with generalised epilepsy may

differ from psychoses in temporal lobe epilepsy; they are short-lasting and relatively mild, they tend to present as confusional states and usually remit before delusions or hallucinations are seen.[91;122]

Clinical / Risk factors

Following the work by Slater and Beard,[163] who noted that 55 of their 69 patients with schizophrenia-like psychoses and epilepsy had a temporal lobe focus, several other studies demonstrated that psychoses in epilepsy were most often related to TLE,[53;152;154;156;164-170] whereas others failed to find such an association.[171] It appears that about 76% of epilepsy patients with psychosis suffer from TLE.[91] Other risk factors reported in the literature include: history of CPS (especially those involving mesial temporal or limbic structures); left temporal foci; severity of epilepsy (long duration, multiple seizure types, refractoriness, AED polytherapy); age of seizure onset before or around adolescence; forced normalisation (patients may become psychotic when their seizures come under control and the EEG becomes "normalised"); and temporal lobectomy.[53;91]

In some surgical series, a left temporal lobe focus was associated with preoperative SLPE in 85% of cases, while 85% of de novo psychoses followed right temporal lobectomy.[162]

Aetiology / Biological factors

Psychoses in epilepsy can be related to a number of factors: (1) neuropathologic changes (*e.g.* neuronal damage in hippocampal and other structures, hamartomatous lesions, gangliogliomas); (2) neurophysiologic modifications (*e.g.* seizure-suppressive inhibitory mechanisms that develop gradually in chronic epilepsy,[88]

altered dopaminergic activity); (3) biological factors (*e.g.* alcohol, menses, sleep deprivation), personality changes; psychosocial factors related to epilepsy (*e.g.* quarrels, agitation, fear of redundancy) and; (4) AEDs (*e.g.* due to forced normalisation, folate deficiency, drug toxicity or withdrawal, genetic predisposition).[53] AEDs particularly associated with development of psychoses include vigabatrin, topiramate, and ethosuximide.[53] Epilepsy and psychosis may arise out of cerebral dysfunction common to both, or psychosis may be a consequence of seizure activity (due to the effects of seizures on amygdala, hippocampal and septal areas).[53;162] A recent study found a significant (16-18%) bilateral enlargement of the amygdala in patients with SLPE (N=26) compared with patients with TLE without psychopathology (N=24) and healthy volunteers (N=20).[172] According to the authors, these findings support the notion that SLPE is a distinct nosologic entity differing from schizophrenia not only in clinical details but also in neurobiological aspects.

Recognition & Diagnosis

Diagnosis is based on the temporal relation of psychoses to the ictus, their duration and clinical characteristics, as well as on past psychiatric history and treatment in the case of interictal phenomena. Episodic psychoses (i.e., psychosis is related to increased seizure activity) tend to present as acute confusional states, while interictal psychoses can be more typical of schizophrenia.

Additional burden imposed on patients with epilepsy

Epilepsy patients suffering from episodic psychoses are often embarrassed and perplexed about what has happened to them while psychotic. They fear that further bouts will eventually lead to insanity. Patients with chronic psychoses, as well as

their families, may require the full resources of community care.[91] A study found that patients with refractory temporal lobe epilepsy and chronic psychosis who underwent temporal lobe resection (N=5) functioned better in activities of daily living, and that freedom from seizures improved their integration into psychiatric treatment facilities.[173] These results give a measure of the extra burden the condition of epilepsy poses on people with psychiatric comorbidity.

Treatments strategies

Treatment of psychoses in patients with epilepsy is similar to that of patients without epilepsy. There are special considerations, such as interactions with AEDs, the potential of all antipsychotic drugs (APDs) to lower seizure threshold and their side effect profile, and the polymorphism of the psychotic phenomena.[91;149] Neuroleptics with a low potential for seizure precipitation, such as haloperidol, pimozide and sulpiride, can be used in the setting of episodic psychoses or when there is no alteration of seizure frequency. Psychoses during withdrawal of AEDs may require a combination of haloperidol with chlorprothixene.[149] The first therapeutic step in alternative psychoses (i.e., the case of forced normalisation) is a moderate reduction of AEDs to release some excitation. If this is insufficient, risperidone or olanzapine can be useful. Interictal psychoses may require long-term treatment with APDs, such as risperidone or olanzapine. Blumer et al. viewed the interictal psychoses as interictal dysphoric disorders with psychotic features and recommended antidepressants (with the combination of a tricyclic antidepressant and a selective serotonin reuptake inhibitor), enhanced by a small amount of risperidone.[174] A combination of risperidone with an antidepressant can be used for the treatment of psychoses developing from postoperative mood disorders in postsurgical patients.[149]

The treatment of de novo postictal psychoses (arising with a relapse of seizures following epilepsy surgery) is similar to that of postictal psychoses. Clozapine may be used only in non-responders to all other APDs and needs to be introduced slowly, with EEG and haematological monitoring, as it increases seizure risk.[149] Co-administration of clozapine with carbamazepine is contraindicated because of risk of agranulocytosis, and valproate may be preferred on such occasions.

It is generally believed that psychoses do not improve with surgery and, therefore, patients with a history of florid psychosis are not considered candidates for surgery.[162;173] Chronic schizophrenia, however, need not be a contraindication to epilepsy surgery and carefully selected patients may benefit from surgery.[162;173] It has also been suggested that a history of postictal psychosis should be considered a positive indication for surgery.[162]

2.5 Conclusion

Several studies have assessed the type and prevalence of psychiatric comorbidity in people with epilepsy and compared them with healthy or other disease groups. Most are case-control or cross-sectional studies in highly selected subgroups of patients. They are characterised by considerable heterogeneity due to differences in methodology. These include the nosographic approach (method of disease classification), assessment method/case ascertainment, time frame of evaluation (duration of follow-up), study design, the size and characteristics of sample examined, selection of control groups, type of epilepsy, and the effect of treatment (Table 2). As a result, comparisons between them are difficult, as is the drawing of definite conclusions. Most of the available information shows that the prevalence of

psychiatric disorders is higher than expected in people with epilepsy and certain conclusions can be drawn based on the current evidence.

Psychiatric comorbidity is present in a significant proportion of people with epilepsy, at least for some time during their lives. Six percent of people with epilepsy in the general population appear to suffer from a psychiatric disorder, while this percentage rises to 20-50% in more selected populations (e.g. general practice and hospital populations). In patients with temporal lobe epilepsy and/or refractory epilepsy the prevalence of psychiatric disorders is between 60 and 80%, which appears to be higher than in patients with idiopathic generalised epilepsy (~ 20-30%) and those with chronic somatic disorders (10-20%). Mood disorders in general affect between 24 and 72% of people with epilepsy during a lifetime. Depression appears to be the most common psychiatric comorbidity in epilepsy affecting an average 30% (~10-50%) of patients with TLE during their lives. It occurs more commonly in patients with epilepsy than in patients with other neurological disorders,[94] chronic medical conditions, or normal controls.[96] Anxiety disorders in general appear to affect 10-25% of people with epilepsy in the community at one time.[68] Reported prevalence in hospital populations varies between 7 and 27% and between 11 and 44% in patients with intractable epilepsy.[69;121;175] Personality disorders were diagnosed in 1-2% in people with epilepsy in the community. Rates of personality disorders vary from 15-40% in patients with partial epilepsy and/or refractory epilepsy.[54;79;81;85] Psychoses appear to afflict 2-7% of people with epilepsy in the community. Rates in patients with TLE and/or refractory epilepsy are around 10-20%, twice as high as in patients with idiopathic generalised epilepsy. Schizophrenia-like psychosis in epilepsy (SLPE) is the most common psychotic disorder affecting 10-18% of patients, mostly

Nosographic approach DSM II[89] DSM-III[79] DSM-III-R[54;59;69;75;80;81;133;161] DSM IV[86] ICD (1949)[87] ICD-8[57;152] ICD-9[66;68] ICD-10[63;85]
Assessment method <u>Questionnaires</u> Epilepsy Questionnaire[78;88] Washington Psychosocial Seizure Inventory (WPSI)[60;75] Child Depression Inventory (CDI)[97] Revised Children's Manifest Anxiety Scale (RCMAS)[97] <u>Self report scales</u> Minnesota Multiple Personality Inventory (MMPI)[65;75] Beck depression inventory (BDI)[74;81] State trait anxiety inventory (STAI)[74;81] <u>Behaviour ratings</u>[71;88] Child Behaviour Checklist[72;73] <u>Structured / semistructured psychiatric interview</u>[86;88] Structured Clinical Interview for DSM-III-R (SCID)[81] SCID-P (Patient version)[54] SCID-II (Personality Disorders)[133] Schedule of Affective Disorders and Schizophrenia-Lifetime Version (SADS-L)[75] Schedule of Affective Disorders and Schizophrenia (SADS)[74] Clinical Interview Schedule[68;69] Mental Health Diagnostic Interview Schedule (DIS)[79;176;177] <u>Patient records</u> [66]
Time frame of evaluation Lifetime prevalence[54;56;77;79;177] Current prevalence[69;79;87;89;122;176]

Table 2. Methodological issues in studies of psychiatric comorbidity in epilepsy: differences in assessment methods used in studies.

those with TLE. It appears that the risk of schizophrenia in patients with all types of epilepsy and in those with TLE is 1.5 and 2.35 times respectively higher than in the general population.

The types of psychiatric disorders reported for children are often different from those reported for adults, and there is a relative paucity of data. However, the prevalence of psychiatric disorders appears to follow the same trends of the broad diagnostic categories as adults.

The psychiatric comorbidity among people with epilepsy appears to be related to the chronicity and severity of epilepsy and shows increasing prevalence when moving from community-based and primary care cohorts to cohorts of patients with refractory epilepsy or seen at tertiary care centres. It also appears to be related to endogenous (*e.g.* genetic factors, the effect of seizures themselves and of the underlying cause of epilepsy) and environmental (or exogenous) factors. The latter include iatrogenic causes (*e.g.* the effect of medication or surgery), psychosocial factors, and presence of somatic comorbidity, such as head injury. Certain clinical factors are important in the assessment of patients with co-existing psychiatric disorders. These include seizure localisation and laterality, type of neuropathology, refractoriness, and duration of epilepsy. The diagnosis of psychiatric conditions in people with epilepsy can be more straightforward for interictal conditions but may be more difficult when these are associated with the ictus. Their management needs to take into account the effect of drug treatment on seizures, the potential for drug interactions, and any particular considerations for specific types. An important issue is the underdiagnosis and undertreatment of these disorders, which may occur in over

50% of patients. Although it is very difficult to quantify the effect of comorbid conditions in epilepsy, it seems that they pose a significant burden on patients and their quality of life.

Chapter 3

DIFFERENCES IN THE USE OF HEALTH SERVICES AMONG PEOPLE WITH AND WITHOUT EPILEPSY IN THE UNITED KINGDOM: SOCIO-ECONOMIC AND DISEASE-SPECIFIC DETERMINANTS

3.1 Introduction

The impact of epilepsy on the individual can be affected by comorbidity[14] and adverse socioeconomic outcome.[9] People with epilepsy require medical care, which is organised across all levels and involves many different specialties.[178] In a population-based survey in Canada, people with epilepsy had the highest level of hospital, emergency, medical and psychosocial services than healthy individuals, the general population, and the chronically ill.[179] In an UK study, a relatively higher demand for inpatient services was found for patients with epilepsy among all hospitalised patients in a health district.[180] Among patients with epilepsy, newly or recently diagnosed cases, as well as patients with ongoing seizures, appear to make higher use of primary and secondary care services.[181;182]

The provision of health services for people with epilepsy in the UK has been assessed previously and recommendations made, in relation to the particular clinical needs and characteristics of patients, the standards of care and available resources.[16;183;184] Little, however, is known about the relative contribution of the comorbidity of epilepsy, and of socio-economic and demographic factors on the demand on health services in the UK by patients with epilepsy. Factors such as sex and socio-economic status appear to be related to the prevalence of epilepsy, with

higher prevalence found in males and in people in the lower socio-economic groups.[184-186] In addition, coexisting conditions, age and sex, and socioeconomic conditions are contributing factors to the cost of illness in epilepsy.[181;187] Understanding the pattern of health services utilisation by people with epilepsy is important for public health and planning of health services. The socio-economic, demographic and disease-specific determinants of the use of health services by patients with epilepsy of all age groups is examined compared to people without epilepsy using data from the fourth national survey of morbidity in general practice (MSGP4).

3.2 Methods

The fourth national morbidity survey was a one-year prospective cohort study of 502,482 patients registered with 60 general practices in England and Wales carried out between September 1991 and August 1992. The main objective of the survey was to examine the workload and pattern of disease in general practice in relation to the age, sex, and socio-economic status of patients. The study population comprised a 1% sample of the general population. The practices that took part in the survey were larger, more likely to be computerised and had a greater interest in the collection of morbidity data than the average general practice. Despite this, the sample of patients was representative of the population of England and Wales for characteristics such as age, sex, and social class.

Trained field workers collected socio-economic data on 83% of the patients in the survey. The remaining 17% of patients either refused to be interviewed or left the practice or died before they could be interviewed. The information collected included

details of employment status, occupation, housing tenure, household composition, ethnic group and marital status. For all patients in the survey, social class was derived from information on occupation and employment status (Box 2).

BOX 2

Definitions of social class groups

I – Professional & higher managerial

II – Managerial

IIIN – Skilled (non-manual)

IIIM – Skilled (manual)

IV - Partly Skilled

V –Unskilled

Where patients had retired from regular work, their main occupation before retirement was recorded and used to assign social class. For married or cohabiting women and for widows, social class was based on that of their partner or their former husband respectively. The Registrar-General's classification of social class is used, which is the standard social classification system used in the United Kingdom.

3.2.i Recording and validation of data

Before the survey started, doctors and staff from each practice attended three two-day training sessions on the recording of morbidity data. Practices then collected data for two to four weeks before the start of the survey. These data were analysed and any errors or inconsistencies reported to the practices. Once the morbidity survey started, general practitioners and nurses recorded information on all face-to-face

contacts with patients. Each reason for consulting and the place of contact was directly entered into patient records on the practice computer. Every consultation was assigned an ICD-9 (International Classification of Diseases Ninth Revision) code. When patients presented with more than one problem, doctors were asked to record a separate ICD-9 code for each problem. Hence, the number of diagnoses recorded was greater than the total number of contacts with general practitioners. However, the vast majority of contacts were for one problem only. Not all consultations resulted in a specific diagnosis. For example, some consultations may have been for preventive activities such as immunisation or for general advice. Where this occurred, relevant ICD-9 codes for preventive and health promotion activities were used. Data supplied by the practices were subject to regular checks to ensure validity.[188]

After the end of the survey, manual practice records were used to identify all patients seen either in the practice or elsewhere by the 60 practices on four separate days. Of the 28,000 patient contacts on these four days, 96% of contacts with doctors in the practice and 95% at home had been recorded in the data submitted by the practices. Finally, for a random sample of 999 patients, diagnostic data from paper records was compared with the electronic data submitted by the practices. This showed that 93% of diagnoses had been recorded correctly.

3.2.ii Health services workload and morbidity

General practitioners taking part in the survey were required to record confirmed diagnoses. For patients with epilepsy, this usually meant that a specialist had confirmed the diagnosis. Three measures of health services workload were calculated for patients with epilepsy (ICD-9 code 345) and for those without a diagnosis of

epilepsy. The measures were the number of general practice consultations, the number of home visits and the number of secondary care referrals per person. A consultation was defined as a face-to-face contact with a general practitioner (GP), either at the doctor's office, in the patient's home or elsewhere (for example, in a community hospital). A home visit was defined as a face-to-face contact with a general practitioner in the patient's home. A secondary care referral was defined as a decision to send a patient to see a hospital specialist, either in an outpatient clinic, as a hospital inpatient, or in an accident and emergency department.

3.2.iii Statistical methods

Risk ratios with 95% confidence intervals for the measures of health service workload were calculated using a generalised linear model with a Poisson error and a log link. The proportion of patients who consulted for disorders in each of the ICD-9 chapters and the proportion of patients who consulted for selected disorders that are important causes of ill health was also calculated. Risk ratios with 95% confidence intervals for each of these proportions were calculated using the epitab function in the Stata software package (Stata Corporation, Texas, USA).

3.3 Results

Patients with a general practitioner diagnosis of epilepsy accounted for 0.33% of all patients in the morbidity survey (1,662 / 502,482). People with epilepsy had significantly higher general practice consultation rates than people without epilepsy (Table 3). In both sexes, consultation rates were increased more than two-fold. These increases were not related to age group or social class. After stratification, people with epilepsy among all age groups and social classes had significantly higher

consultation rates than people without epilepsy. In both people with and without epilepsy, consultation rates were highest among older people and among people from social class V.

People with epilepsy also had significantly higher home-visiting rates than those without epilepsy (Table 4). Among males, home visiting rates were four-fold higher and among women, three-fold higher in people with epilepsy. Home-visiting rates increased with age in people with and without epilepsy. Among people without epilepsy, home-visiting rates also increased with decreasing social class. However, among people with epilepsy there was no consistent pattern between home-visiting rates and social class.

The mean annual number of referrals to secondary care was substantially higher among people with epilepsy than among those without (Table 5). In both males and females, there was a more than two-fold increase in referral rates to secondary care. After stratification for age, there was a much weaker association between age group and referral rates among people with epilepsy. This resulted in children with epilepsy having a more than five-fold relative increase in referrals to secondary care. After stratification for social class, there was still a more than two-fold increase in referral rates among all the social class groups in people with epilepsy than in those without epilepsy.

A significantly higher proportion of patients with epilepsy consulted for all the groups of diseases examined (Table 6), apart from infections. The greatest relative

	People with epilepsy		People without epilepsy		Rate ratio	95% CI
	Number of people	Consultations per person	Number of people	Consultations per person		
Sex						
Male	810	7.44	244790	2.93	2.54	2.48-2.61
Female	852	9.64	256030	4.46	2.16	2.12-2.21
Age group						
0-4	52	8.13	37852	4.72	1.72	1.57-1.89
5-15	157	5.83	68042	2.34	2.49	2.34-2.67
16-24	270	7.17	67439	3.01	2.38	2.28-2.49
25-44	531	8.67	153829	3.29	2.64	2.56-2.71
45-64	376	9.41	101950	4.14	2.27	2.20-2.35
65-74	155	9.86	39431	5.14	1.92	1.83-2.02
75-84	98	10.28	24695	5.83	1.76	1.66-1.87
85+	23	12.35	7582	5.55	2.23	1.99-2.50
Social class						
I	77	8.31	30347	3.37	2.47	2.28-2.67
II	242	8.57	96291	3.85	2.23	2.13-2.33
IIIN	186	8.45	54486	4.28	1.97	1.88-2.07
IIIM	386	9.03	118618	4.34	2.08	2.01-2.15
IV	286	8.82	61731	4.60	1.92	1.84-1.99
V	125	9.70	21387	4.89	1.98	1.87-2.10
Total	**1662**	**8.57**	**500820**	**3.71**	**2.31**	**2.27-2.35**

Table 3. Mean annual number of consultations per person

	People with epilepsy	People without epilepsy	Rate ratio	95% CI
Sex				
Male	0.84	0.21	4.09	3.79-4.41
Female	1.14	0.35	3.24	3.04-3.45
Age group				
0-4	1.10	0.41	2.70	2.08-3.50
5-15	0.78	0.12	6.51	5.45-7.77
16-24	0.41	0.09	4.50	3.73-5.43
25-44	0.51	0.10	4.84	4.28-5.45
45-64	0.78	0.16	4.81	4.28-5.40
65-74	1.83	0.54	3.36	2.99-3.78
75-84	3.64	1.47	2.47	2.23-2.75
85+	7.13	2.72	2.62	2.24-3.05
Social class				
I	0.71	0.16	4.46	3.42-5.81
II	0.90	0.22	4.14	3.62-4.73
IIIN	0.66	0.28	2.30	1.93-2.75
IIIM	0.99	0.29	3.44	3.11-3.81
IV	1.03	0.36	2.88	2.57-3.23
V	0.76	0.49	1.55	1.27-1.90
Total	**1.00**	**0.28**	**3.54**	**3.38-3.72**

Table 4. Mean annual number of home visits per person

	People with epilepsy	People without epilepsy	Rate ratio	95% CI
Sex				
Male	0.31	0.11	2.83	2.50-3.20
Female	0.39	0.14	2.70	2.43-3.01
Age group				
0-4	0.56	0.09	5.87	4.08-8.46
5-15	0.39	0.07	5.70	4.44-7.33
16-24	0.31	0.09	3.37	2.72-4.18
25-44	0.31	0.12	2.60	2.23-3.03
45-64	0.30	0.15	2.03	1.69-2.45
65-74	0.41	0.19	2.22	1.74-2.84
75-84	0.53	0.25	2.11	1.61-2.77
85+	0.48	0.25	1.88	1.04-3.09
Social class				
I	0.30	0.13	2.32	1.54-3.49
II	0.36	0.14	2.53	2.05-3.12
IIIN	0.33	0.15	2.26	1.76-2.91
IIIM	0.41	0.14	2.91	2.49-3.40
IV	0.39	0.15	2.64	2.19-3.19
V	0.35	0.15	2.32	1.72-3.13
Total	**0.35**	**0.13**	**2.76**	**2.54-2.97**

Table 5. Mean annual number of referrals to secondary care per person

	ICD-9 Chapter	People with epilepsy (%)	People without epilepsy (%)	Rate ratio	95% CI
I	Infections	15.0	14.0	1.07	0.95-1.20
II	Neoplasms	4.6	2.4	1.91	1.53-2.38
III	Endocrine	6.0	3.8	1.58	1.31-1.92
IV	Haematological	1.9	1.0	1.93	1.36-2.72
V	Mental health	17.7	7.3	2.43	2.19-2.70
VI	Neurological*	21.8	17.3	1.26	1.15-1.38
VII	Circulatory	14.2	9.3	1.53	1.36-1.72
VIII	Respiratory	36.0	30.7	1.17	1.10-1.25
IX	Digestive	13.7	8.7	1.57	1.39-1.77
X	Genitourinary	15.8	11.3	1.40	1.25-1.57
XIII	Musculoskeletal	19.0	15.2	1.25	1.13-1.38
XVII	Injuries & poisoning	23.8	13.9	1.71	1.57-1.86

*Excludes epilepsy (ICD-9 345).

Table 6. Percentage of patients consulting for each ICD—9 disease groups

increase (more than two-fold) in the proportion of patients consulting was for mental health disorders. Nearly two-fold increases were seen for neoplastic disorders and for haematological disorders. When specific disorders were examined (Table 7), a greater proportion of people with epilepsy consulted for each of the disorders examined, but because of the relatively small numbers in some groups, the increases were not always statistically significant. The largest relative increases in the proportion of patients consulting were seen for stroke and dementia. There was also a nearly five-fold increase in the proportion of patients who consulted for gastro-intestinal bleed.

3.4 Discussion

Patients with epilepsy as a whole made considerably greater use of health services than people without epilepsy, even after stratification for gender, age and social class. Moreover, a higher proportion of patients with epilepsy consulted for disorders in all disease groups examined, with the exception of infections. This was particularly the case for neoplasms, haematological disorders and mental health disorders. When some of the most common disorders seen in general practice were analysed separately, a higher proportion of patients with epilepsy consulted for dementia, stroke and gastrointestinal bleeding. A marginally higher proportion consulted for diabetes mellitus, ischaemic heart disease, heart failure, and arthritis. The association with gastrointestinal bleeding is particularly surprising, but should be interpreted with caution as it was based on a relatively small number of patients. Possible explanations could include a higher percentage of elderly people and a higher use of drugs with gastrointestinal toxicity by people in the epilepsy group.[189] Information on the factors influencing the use of health services by epilepsy patients in the UK is lacking and

Disorder	People with epilepsy (%)	People without epilepsy (%)	Rate ratio	95% CI
Diabetes mellitus	1.68	1.03	1.64	1.13-2.37
Ischaemic heart disease	2.23	1.59	1.40	1.02-1.93
Heart failure	1.62	0.83	1.97	1.35-2.86
Hypertension	4.27	3.90	1.09	0.87-1.37
Dementia	1.26	0.31	4.08	2.66-6.26
Stroke	2.83	0.36	7.77	5.84-10.34
Degenerative brain disorders	0.84	0.53	1.60	0.95-2.69
Peptic ulceration	0.66	0.47	1.40	0.78-2.53
GI bleeding	0.54	0.11	4.93	2.56-9.51
Arthritis	13.54	10.17	1.33	1.17-1.50

Table 7. Percentage of patients consulting for selected disorders

there is generally very little information from other countries. The presented data is based on an unselected sample of about 500,000 people registered in general practices, providing considerable power to detect differences among the subsets of patients examined (people with and without a diagnosis of epilepsy). In this study, only people with a diagnosis of epilepsy receiving treatment for epilepsy from their general practitioner were studied. Hence, people with epilepsy who did not consult their general practitioner for an epilepsy-related problem would not have been identified as having the condition. For this reason, the prevalence of epilepsy of 0.33% in this study was lower than the 0.5% found in some other studies.[184] Although a proportion of people with epilepsy may not be on treatment[190;191] or may not consult a doctor,[182] these patients are likely to be the ones with the least severe epilepsy.[182;183] This can introduce a bias, with more severe cases with greater morbidity being included, resulting in an increased use of health services. However, it is considered that patients being treated for epilepsy form the key group for the rational planning of services.

The generalisibility of these findings is potentially limited because the practices taking part in the survey had volunteered. This resulted in fewer practices from the inner city areas and hence lower rates of unemployment and ethnicity among the patients in the study. The study sample was, nevertheless, reasonably similar to the population of England and Wales for most socio-economic characteristics. The data was collected prospectively and the post survey validation study showed that the diagnostic data was recorded accurately.[188] The use of ICD-9 disease categories is helpful for the statistical analysis, but it cannot serve as an indicator of an association with other diseases. This problem was partly overcome by examining the proportion of patients who consulted for conditions encountered commonly in general practice, where more specific

associations can be made. No assumptions can be made in the study about the type of association or about any association with a particular type of epilepsy, as the information required doing this was not collected. Other limitations were that it was not feasible to stratify the health service utilisation tables by comorbidity and that the comorbidity rates in people with and without epilepsy were not age-standardised.

This is the first large-scale study of its kind and hence there is very little previous research against which it can be compared. A few studies have reported on the prevalence of associated conditions in cohorts of patients with epilepsy, without making any comparisons with the general population or assessing their effect on the utilisation of health services.[55;56] In case-control studies in particular, epilepsy has been associated with a number of other disorders, such as learning disability and cerebral palsy,[50;51] migraine,[21] psychiatric disorders (including depression, anxiety disorders, schizophrenia and behavioural disorders),[57;82;192] non-epileptic seizures[193] and cardiovascular conditions.[52] The sample size in the current study was not sufficiently large to allow for separate analysis of these disorders and it was not feasible to look at the temporal association between comorbid conditions and epilepsy. For example, where epilepsy is associated with stroke, it cannot be certain whether the stroke was the cause of the epilepsy or whether epilepsy was present before a first stroke took place.

The standards of the medical care received by, and the characteristics of, patients treated for epilepsy in the UK have been previously assessed.[16;183] No comparisons were made with the use of health services in the general population, although it was found that the majority of patients receiving treatment for epilepsy in the community

have long-standing epilepsy, often intractable to medical treatment, and associated with considerable social handicap. The higher use of health services by people with epilepsy across the different stratifications found in this study corroborates and extends findings from previous reports.[179;180] A rather surprising finding in this study is the relatively higher rate of GP consultations and home visits for people with epilepsy of higher socioeconomic classes. This suggests that the presence of epilepsy can lead to the loss of the "protective" effect of high social class on health status. An alternative explanation is that patients with epilepsy are receiving similar care irrespective of their social class, i.e., patients with epilepsy from lower social classes are not being discriminated against by the health service. This finding is in agreement with the results of another large UK study that found only a weak correlation between social deprivation and use of hospital in- and out-patient services by people with epilepsy.[185] Another morbidity survey was used to identify the socioeconomic determinants of consultation rates in the general population and found evidence supporting previous research linking individual "deprivation" characteristics and morbidity.[194] The authors, however, did not examine people with epilepsy separately. In a Finnish population study of the long-term prognosis of seizures with onset in childhood no differences were detected in socioeconomic status between patients and controls.[195] The association between the relatively greater demand of GP services and social classes I and II could be attributed to individual patient characteristics, since these are much more powerful predictors of consulting patterns than the characteristics of the areas in which patients live, and the effects of individual socioeconomic factors themselves vary in different geographical areas.[194] It might be that social class plays only a small role in the demand of health services among people with epilepsy. The differences in the use of health services in the various age groups cannot be compared

with any previous studies. However, they do not appear to follow the age-specific incidence and prevalence rate curves[196] and may be related to other factors.

3.5 Conclusions

Factors determining the demand on health services by people with epilepsy at all levels of care need to be studied and their effects taken into account in the design and organisation of health services. This study provides some insight into these factors and could serve as a guide for further and more detailed research.

Chapter 4

THE EPIDEMIOLOGY OF THE COMORBIDITY OF EPILEPSY IN THE GENERAL POPULATION

4.1 Introduction

The epidemiology of the comorbidity of epilepsies has not been well described. Data are limited on the cumulative incidence[21] and prevalence[55-58;120;150] of various comorbid conditions in adults with epilepsy in the community. One study compared rates of other conditions in controls and adults with childhood-onset epilepsy and reported increased psychiatric but not somatic comorbidity in the latter.[57] Community-based and unselected population case-control studies have reported a higher risk of various somatic disorders in epilepsy.[21;52;197-201] Psychiatric disorders also appear to occur more frequently in people with epilepsy, although most studies have been conducted in highly selected groups of patients, mainly with temporal lobe or refractory epilepsy.[53;82] Although case-control studies provide a measure of the association between epilepsy and other conditions, they do not provide the rates of these conditions in people with epilepsy and in the general population.

A cross-sectional population-based study was undertaken in order to describe the prevalence, and evaluate the prevalence ratios, of a number of somatic and psychiatric disorders in adults with epilepsy among a large cohort of people registered in general practices in the UK.

4.2 Methods

4.2.i Data source

Data was extracted from the general practice research database (GPRD) for the period January 1, 1995 to December 31, 1998. The GPRD is a health database established in 1987, which contains prospectively collected data from participating general practices in England and Wales. It holds anonymous computerised patient records, including demographic information, information on significant consultations, details of all issued prescriptions, results of investigations, hospital referrals and admissions. Participating general practices submit anonymised records at regular intervals, following agreed guidelines for recording clinical and prescribing data. Coding of diseases is based on Read and OXMIS systems. The comprehensiveness and accuracy of the data has been previously documented.[202-204] The data for this study came from 211 general practices with a combined list size of 1.3 million, representing 2.6% of the population in England and Wales. The GPRD Scientific and Ethical Advisory Group approved the study.

4.2.ii Study population

Patients were included in the analysis if they were alive and permanently registered at the practice for the last six months of each analysis year from 1995 to 1998. This was to ensure better validity of data. Children under the age of 16 years were excluded from the study, as they tend to suffer from different diseases from adults, and chronic diseases are rare in children. All Read Code and OXMIS diagnosis codes were converted to ICD-9 codes using a table developed by the NHS Centre for Coding and Classification and the UK Office for National Statistics. Case ascertainment was based

on a clinical diagnosis of epilepsy recorded by the general practice, using codes for the various epileptic syndromes and seizure types (ICD-9, 345). All those who received a new diagnosis of epilepsy and/or consulted for epilepsy during the study period were identified from Read and OXMIS codes, and were used as the study group. The control group consisted of the remaining registered patients. The use of AEDs was not taken as a surrogate for the diagnosis of epilepsy, as not all people with epilepsy take AEDs, and AEDs can also be indicated for conditions other than epilepsy.

4.2.iii Measurement of study variables

A number of selected conditions were identified in both groups; these conditions may have preceded or followed the development of epilepsy. The selection of these conditions was based on their importance in adult clinical practice, either in terms of morbidity in the general population or in people with epilepsy (Boxes 3 & 4). This selection was also informed by the analysis of the MSGP4 (presented in Chapter 3). The diagnosis of epilepsy and all other conditions was based on entries by the general practitioner, informed - where available - by information from specialists, investigations and hospital admissions.

4.2.iv Outcome measures and statistical analysis

The period prevalence of epilepsy for 1995-1998 was calculated with a 95 percent confidence interval (estimated for a single proportion). Age- and sex-specific prevalence rates of the selected conditions, and of their diagnostic groups (ICD-9 chapters), were produced for both groups in two age groups (16-64 and 64+ years) in a cross-sectional design. Age-standardised prevalence ratios were calculated, to allow for differences in the age distribution between the groups. Prevalence ratios were

calculated per 10-year age band for the younger age group (16-24; 25-34; to 55-64)

and per 5-year age band for the older age group (65-69; 70-74; to 80-84; 85+).

BOX 3. Conditions selected for analysis, with ICD-9 codings	
MENTAL HEALTH	
Neuroses	300
-Obsessive-Compulsive disorder	300.3
-Anxiety	300.0
-Hysteria	300.1
Depression	311
Organic psychoses	291-294
Schizophrenia	295
Alcohol Dependence	303
Dementia	290
SOMATIC	
Fractures	800-829
Diabetes mellitus	250
Neoplasia	(140-208, excluding 191-192)
Brain neoplasms	191
Meningiomas (malignant & benign)	192.1 + 225.2
IHD	410-414
Heart Failure	428
Congenital heart disease	745-746
All CVAs	430-438
Haemorrhagic CVA	431
Ischaemic CVA	433-434
TIA	435
Migraine	346
Parkinson's disease	332
Pneumonias	480-486
Chronic bronchitis	491
Emphysema	492
Peptic ulcers	531-534
All GI bleed	578
Upper GI bleed	578.0
Lower GI bleed	578.1
Unspecified GI bleed	578.9
Eczema	691.8
Rheumatoid arthritis	714
Osteoarthritis	715
Cerebral degeneration	(290+331)-(331.3-.4)
Alzheimer's disease	331.0

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│ BOX 4. Coding for ICD-9 chapters                                          │
│ ICD-9 CHAPTERS                                          ICD-9 Coding      │
│ I. Infections and parasitic diseases                      001-139         │
│ II. Neoplasms                                             140-239         │
│ III. Endocrine, nutritional and metabolic diseases and immunity 240-279   │
│ disorders                                                                 │
│ IV. Diseases of blood and blood-forming organs            280-289         │
│ V. Mental disorders                                       290-319         │
│ VI. Disease of the nervous system and sense organs †      (320-389)-345   │
│ VII. Diseases of the circulatory system                   390-459         │
│ VIII. Diseases of the respiratory system                  460-519         │
│ IX. Diseases of the digestive system                      520-579         │
│ X. Diseases of the genitourinary system                   580-629         │
│ XI. Complications of pregnancy, childbirth and the puerperium  630-676    │
│ XII. Diseases of the skin and subcutaneous tissue         680-709         │
│ XIII. Diseases of the musculoskeletal system and connective tissue 710-739│
│ XIV. Congenital anomalies                                 740-759         │
│ XV. Certain conditions originating in the perinatal period  760-779       │
│ XVI. Symptoms, signs, and ill-defined conditions          780-799         │
│ XVII. Injury and poisoning                                800-999         │
│ † Excluding epilepsy (345)                                                │
│                                                                           │
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A pooled summary estimate for each age group was produced by the Mantel-Haenszel method.[205] Prevalence ratios were calculated for all subjects (males and females combined) for each age group, as well as for all individuals across all ages.

4.3 Results

1,041,643 people aged 16 years and over were identified in the study (48.9% males), of whom 5,834 had epilepsy. The distribution is shown in table 8. The overall prevalence of epilepsy in the study group was 5.6 per 1,000 (95% CI 5.5-5.7).

	16-64 years		64+ years	
	Epilepsy	Non-epilepsy	Epilepsy	Non-epilepsy
Male	2321	420312	533	86130
Female	2338	410851	642	118516

Table 8. Number of people identified in each subgroup.

<u>4.3.i Prevalence of selected individual conditions and of conditions per ICD-9 chapter</u>

<u>in epilepsy</u>

Individual conditions

The most common psychiatric conditions in epilepsy in adults were depression (18%), neuroses (15%) -especially anxiety (11%), and psychoses (9%). Neuroses were more pronounced in younger women (20%). Non-organic psychoses (Box 5) and dementia were particularly increased in the older age group (15% and 12% respectively). Schizophrenia affected less than 1% of patients. Overall, 41% of people with epilepsy received a diagnosis of a psychiatric disorder during the study period.

The most common somatic conditions in adults with epilepsy were fractures (10%), particularly in women over 64 years (17%), and asthma (9%), particularly in younger women (11%). Migraine was common in younger women (8%). In the older group the most common diagnoses in people with epilepsy were diabetes (9%), transient ischaemic attacks (18%), ischaemic heart disease (14%), heart failure (12%), neoplasia (7%), and osteoarthritis (12%). The most common neurological disorders in this age group were brain degenerative diseases (14%) and Parkinson's disease (4%).

BOX 5.

Organic Psychoses (291-294): Alcoholic psychoses, drug psychoses, transient organic psychotic conditions, chronic organic psychotic conditions

Other Psychoses (295-298): Schizophrenic psychoses, affective psychoses, paranoid states, other non-organic psychoses

Dementia (290): senile dementia, pre-senile dementia, arteriosclerotic dementia

Cerebral degeneration (290 + 331, excluding 331.3, 331.4):
Senile and presenile organic conditions (Senile dementia, simple type; Presenile dementia; Senile dementia, depressed or paranoid type; Senile dementia with acute confusional state; Arteriosclerotic dementia; Other; Unspecified)

Other cerebral degenerations (Alzheimer's disease, Pick's disease, Senile degeneration of brain, Creutzfeldt-Jakob disease, Progressive multifocal encephalopathy, Cerebral degeneration in other diseases classified elsewhere, Other cerebral degeneration, Unspecified)

Excludes communicating hydrocephalus and obstructive hydrocephalus

Conditions grouped by ICD-9 chapter

Disorders of the respiratory system (61%) and skin (46%), injury & poisoning (45%), infections (41%), and psychiatric disorders (40%) appear more often in all adults with epilepsy. Diseases of the respiratory (61%), circulatory (59%), nervous (59%), and musculoskeletal (59%) systems are diagnosed more frequently in those over 64 years.

4.3.ii Prevalence ratios of selected conditions and conditions per ICD-9 chapter

Individual conditions

Among psychiatric conditions in epilepsy, organic psychoses, alcohol dependence, schizophrenia, and non-organic psychoses have a 4-6 times higher prevalence in people with epilepsy than the general population without epilepsy (tables 9, 10 & 11). Hysteria is diagnosed four times more often in the younger age epilepsy group than in

the non-epilepsy group, with men having a higher prevalence ratio than women, although the prevalence of hysteria is higher in women. Interestingly, with the exception of obsessive-convulsive disorder and hysteria in the older group (which have small numbers), all individual psychiatric disorders studied have significantly higher prevalence ratios in epilepsy in both age groups (tables 9, 10 & 11).

Brain tumours and meningiomas are diagnosed 55 and 31 times respectively more often in people with epilepsy. The prevalence ratio of brain tumours is more pronounced in the younger adult age epilepsy group than in the older group. The inverse picture is observed with meningiomas, where the risk is higher in the older epilepsy group (tables 9 & 10). The prevalence ratio of Alzheimer's disease or stroke is higher in people with epilepsy, considerably so in the younger adult group (tables 9 & 10). With the exception of osteoarthritis, rheumatoid arthritis, eczema and emphysema, all other studied conditions occur more frequently in adults with epilepsy. The prevalence of migraine is 60% higher in adults with epilepsy but only 40% higher in younger women with epilepsy, where prevalence of the condition is high (tables 9 & 10). Prevalence ratios of individual comorbid disorders in all individuals, irrespective of age or gender are presented in table 11.

Conditions grouped by ICD-9 chapter

In the younger adult group, congenital anomalies are encountered nearly 3 times more frequently in epilepsy, especially in men (table 12). Mental health (chapter V) and blood disorders (chapter IV) occur twice as often in people with epilepsy and, again, the risk is higher in males. Males with epilepsy have a 50% increased prevalence ratio for neoplasia, but females do not. With the exception of conditions arising in the

16-64 YEARS

	MEN			WOMEN			OVERALL
	Epilepsy (N=2321)	Non-Epilepsy (N=420312)	Rate Ratio (95% C.I.)	Epilepsy N=2338	Non-Epilepsy N=410851	Rate Ratio (95% C.I.)	Rate ratio (95% C.I.)
	N (%)	N (%)		N (%)	N (%)		
MENTAL HEALTH DISORDERS							
Neuroses	281 (12.1%)	22020 (5.2%)	2.36 (2.11-2.63)	471 (20.1%)	45355 (11%)	1.87 (1.72-2.02)	**2.03 (1.90-2.17)**
Obsessive-Compulsive disorder	5 (0.2%)	427 (0.1%)	2.08 (0.86-5.02)	12 (0.5%)	675 (0.2%)	3.10 (1.76-5.49)	**2.71 (1.68-4.37)**
Anxiety	219 (9.4%)	15829 (3.8%)	2.56 (2.25-2.90)	333 (14.2%)	30902 (7.5%)	1.95 (1.77-2.16)	**2.16 (2.0-2.34)**
Hysteria	6 (0.3%)	207 (0.05%)	5.36 (2.38-12.06)	13 (0.6%)	639 (0.2%)	3.72 (2.15-6.43)	**4.13 (2.62-6.50)**
Depression	332 (14.3%)	23661 (5.6%)	2.59 (2.35-2.86)	550 (23.5%)	54850 (13.3%)	1.79 (1.67-1.93)	**2.04 (1.92-2.16)**
Schizophrenia	19 (0.8%)	1004 (0.2%)	3.45 (2.19-5.42)	14 (0.6%)	562 (0.1%)	4.59 (2.70-7.78)	**3.83 (2.72-5.40)**
Organic psychoses	79 (3.4%)	2120 (0.5%)	6.67 (5.35-8.31)	43 (1.8%)	1233 (0.3%)	6.26 (4.63-8.46)	**6.48 (5.42-7.74)**
Other psychoses	107 (4.6%)	4008 (1.0%)	4.89 (4.05-5.89)	116 (5.0%)	6375 (1.6%)	3.26 (2.73-3.90)	**3.89 (3.42-4.43)**
Alcohol Dependence	94 (4.0%)	2960 (0.7%)	5.94 (4.86-7.25)	32 (1.4%)	1173 (0.3%)	5.01 (3.53-7.1)	**5.64 (4.74-6.72)**
Dementia	7 (0.3%)	57 (0.01)	24.30 (11.13-53.08)	9 (0.4%)	72 (0.02%)	26.40 (13.19-52.84)	**25.22 (15.02-42.33)**
SOMATIC DISORDERS							
Fractures	235 (10.1%)	20317 (4.8%)	2.01 (1.78-2.23)	166 (7.1%)	11434 (2.8%)	2.61 (2.25-3.02)	**2.20 (2.00-2.42)**
Diabetes mellitus	65 (2.8%)	7654 (1.8%)	1.66 (1.31-2.10)	58 (2.5%)	5601 (1.4%)	2.00 (1.55-2.58)	**1.80 (1.52-2.15)**
Neoplasia	27 (1.2%)	3152 (0.7%)	1.68 (1.16-2.44)	22 (0.9%)	4788 (1.2%)	0.90 (0.60-1.38)	**1.22 (0.92-1.61)**
Brain neoplasms	15 (0.6%)	52 (0.01%)	54.69 (30.84-96.98)	19 (0.8%)	38 (0.01%)	90.36 (52.19-156.46)	**70.70 (47.70-104.80)**
Meningiomas	0	0	0	1 (0.04%)	8 (0%)	23.62 (2.84-196.24)	**13.57 (1.75-105.20)**
IHD	63 (2.7%)	8085 (1.9%)	1.56 (1.23-1.98)	33 (1.4%)	3853 (0.9%)	1.76 (1.26-2.46	**1.63 (1.34-1.98)**
Heart Failure	14 (0.6%)	1122 (0.3%)	2.49 (1.48-4.20)	7 (0.3%	628 (0.2%)	2.31 (1.01-4.85)	**2.44 (1.59-3.73)**
Congenital heart disease	10 (0.4%)	155 (0.04%)	11.63 (6.14-22.02)	7 (0.3%)	183 (0.04%)	6.62 (3.11-14.07)	**8.89 (5.47-14.46)**
CVA	70 (3.0%)	1187 (0.3%)	11.65 (9.24-14.69)	72 (3.1%)	807 (0.2%)	17.75 (14.04-22.43)	**14.19 (12.04-16.73)**
Haemorrhagic CVA	9 (0.4%)	69 (0.02%)	24.63 (12.31-49.26)	5 (0.2%)	40 (0.01%)	24.28 (9.50-62.04)	**24.43 (13.99-42.66)**
Ischaemic CVA	8 (0.3%)	210 (0.05%)	7.54 (3.73-15.22)	12 (0.5%)	127 (0.03%)	18.74 (10.37-33.88)	**11.87 (7.57-18.61)**
TIA	35 (1.5%)	986 (0.2%)	7.09 (5.11-9.84)	38 (1.6%)	867 (0.2%)	8.89 (6.47-12.22)	**7.95 (6.33-9.98)**
Migraine	84 (3.6%)	6745 (1.6%)	2.22 (1.80-2.74)	182 (7.8%)	22116 (5.4%)	1.44 (1.25-1.65)	**1.63 (1.45-1.83)**
Parkinson's disease	2 (0.1%)	230 (0.05)	1.71 (0.43-6.88)	3 (0.1%)	167 (0.04%)	3.63 (1.16-11.35)	**2.51 (1.041-6.06)**
Pneumonias	27 (1.2%)	1555 (0.4%)	3.25 (2.22-4.74)	36 (1.5%)	1417 (0.3%)	4.71 (3.40-6.55)	**3.94 (3.08-5.05)**
Asthma	173 (7.5%)	24129 (5.7%)	1.26 (1.10-1.46)	265 (11.3%)	31481 (7.7%)	1.45 (1.29-1.62)	**1.37 (1.25-1.50)**
Chronic bronchitis	5 (0.2%)	768 (0.2%)	1.29 (0.54-3.10)	14 (0.6%)	884 (0.2%)	3.18 (1.88-5.37)	**2.30 (1.46-3.60)**
Emphysema	4 (0.2%)	283 (0.1%)	2.82 (1.05-7.55)	3 (0.1%)	203 (0.05%)	3.00 (0.96-9.39)	**2.92 (1.38-6.14)**
Peptic ulcers	31 (1.3%)	3157 (0.8%)	1.88 (1.32-2.67)	25 (1%)	1759 (0.4%)	2.73 (1.84-4.03)	**2.17 (1.67-2.81)**
GI bleed	35 (1.5%)	1697 (0.4%)	3.80 (2.73-5.30)	27 (1.2%)	1085 (0.3%)	4.56 (3.12-6.66)	**4.09 (3.19-5.25)**
Upper GI bleed	24 (1.0%)	1001 (0.2%)	4.34 (2.90-6.49)	22 (0.9%)	628 (0.2%)	6.25 (4.10-9.54)	**5.06 (3.78-6.77)**
Lower GI bleed	7 (0.3%)	544 (0.1%)	2.45 (1.16-5.15)	5 (0.2%)	368 (0.1%)	2.57 (1.07-6.21)	**2.50 (1.41-4.41)**

64+ YEARS

	MEN			WOMEN			OVERALL
	Epilepsy N=533	**Non-Epilepsy** N=86130	**Rate Ratio** (95% C.I.)	**Epilepsy** N=642	**Non-Epilepsy** N=118516	**Rate Ratio** (95% C.I.)	**Rate ratio** (95% C.I.)
	N (%)	N (%)		N (%)	N (%)		
MENTAL HEALTH DISORDERS							
Neuroses	51 (9.6%)	4104 (4.8%)	2.00 (1.54-2.60)	70 (10.9%)	11473 (9.7%)	1.14 (0.92-1.43)	**1.36 (1.15-1.61)**
Obsessive-Compulsive disorder	1 (0.2%)	38 (0.04%)	4.24 (0.58-30.79)	0	91 (0.1%)	0	**1.36 (0.19-9.70)**
Anxiety	40 (7.5%)	3237 (3.8%)	1.99 (1.47-2.69)	58 (9.0%)	9291 (7.8%)	1.17 (0.91-1.49)	**1.37 (1.13-1.65)**
Hysteria	1 (0.2%)	29 (0.03%)	5.54 (0.76-40.49)	1 (0.2%)	102 (0.1%)	1.83 (0.26-13.12)	**2.67 (0.66-10.77)**
Depression	73 (13.7%)	4867 (5.7%)	2.39 (1.93-2.96)	108 (16.8%)	13277 (11.2%)	1.5 (1.26-1.78)	**1.72 (1.50-1.97)**
Schizophrenia	8 (1.5%)	85 (0.1%)	15.39 (7.50-31.56)	1 (0.2%)	187 (0.2%)	1.00 (0.14-7.21)	**5.85 (3.02-11.32)**
Organic psychoses	9 (1.7%)	242 (0.3%)	5.95 (3.07-11.50)	10 (1.6%)	503 (0.4%)	3.46 (1.86-6.43)	**4.23 (2.72-6.70)**
Other psychoses	66 (12.4%)	2062 (2.4%)	4.94 (3.94-6.21)	105 (16.4%)	4704 (4.0%)	3.75 (3.15-4.46)	**4.10 (3.57-4.70)**
Alcohol Dependence	9 (1.7%)	333 (0.4%)	4.47 (2.32-8.60)	8 (1.2%)	166 (0.1%)	9.22 (4.56-18.64)	**6.13 (3.80-9.90)**
Dementia	52 (9.8%)	1135 (1.3%)	6.92 (5.32-9.00)	87 (13.6%)	2626 (2.2%)	5.38 (4.43-6.52)	**5.83 (4.99- 6.81)**
SOMATIC DISORDERS							
Fractures	54 (10.1%)	2761 (3.2%)	3.10 (2.40-4.01)	111 (17.3%)	10398 (8.8%)	1.89 (1.59-2.24)	**2.10 (1.82-2.43)**
Diabetes mellitus	46 (8.6%)	6893 (8.0%)	1.08 (0.82-1.42)	64 (10.0%)	7179 (6.1%)	1.66 (1.31-2.10)	**1.37 (1.15-1.64)**
Neoplasia	40 (7.5%)	7078 (8.2%)	0.89 (0.66-1.20)	39 (6.1%)	6839 (5.8%)	1.03 (0.76-1.40)	**0.97 (0.78-1.20)**
Brain neoplasms	2 (0.4%)	16 (0.02%)	20.87 (4.83-90.12)	0	0	0	**11.55 (2.78-48.08)**
Meningiomas	1 (0.2%)	3 (0.00)	57.88 (5.73-584.21)	1 (0.2%)	1 (0.00)	184.67 (12.44-2740.43)	**91.88 (16.70-505.47)**
IHD	87 (16.3%)	12005 (13.9%)	1.16 (0.96-1.41)	78 (12.1%)	11551 (9.7%)	1.23 (0.99-1.51)	**1.21 (1.05-1.40)**
Heart Failure	55 (10.3%)	6015 (7.0%)	1.41 (1.10-1.81)	81 (12.6%)	7885 (6.7%)	1.74 (1.42-2.13)	**1.60 (1.37-1.88)**
CVA	129 (24.2%)	3547 (4.1%)	5.69 (4.89-6.62)	134 (20.9%)	4441 (3.7%)	5.15 (4.43-5.97)	**5.46 (4.91-6.07)**
Haemorrhagic CVA	0	80 (0.1%)	0	3 (0.5%)	94 (0.1%)	5.72 (1.82-17.98)	**2.92 (0.93-9.13)**
Ischaemic CVA	20 (3.8%)	484 (0.6%)	6.62 (4.27-10.27)	12 (1.9%)	424 (0.4%)	5.14 (2.91-9.08)	**6.09 (4.30-8.62)**
TIA	89 (16.7%)	3361 (3.9%)	4.15 (3.42-5.02)	125 (19.5%)	4752 (4.0%)	4.52 (3.86-5.29)	**4.38 (3.88-4.94)**
Migraine	7 (1.3%)	551 (0.6%)	2.10 (1.00-4.42)	9 (1.4%)	1784 (1.5%)	0.98 (0.51-1.88)	**1.23 (0.76-2.00)**
Parkinson's disease	25 (4.7%)	1184 (1.4%)	3.28 (2.23-4.82)	22 (3.4%)	1215 (1.0%)	3.2 (2.12-4.84)	**3.29 (2.48-4.36)**
Pneumonias	31 (5.8%)	2139 (2.5%)	2.25 (1.59-3.17)	50 (7.8%)	2596 (2.2%)	3.19 (2.46-4.15)	**2.78 (2.25-3.426)**
Asthma	36 (6.8%)	5557 (6.5%)	1.05 (0.76-1.44)	39 (6.1%)	7882 (6.7%)	0.94 (0.69-1.28)	**0.99 (0.79-1.23)**
Chronic bronchitis	16 (3.0%)	1872 (2.2%)	1.36 (0.84-2.20)	13 (2.0%)	1707 (1.4%)	1.43 (0.83-2.45)	**1.41 (0.98-2.03)**
Emphysema	2 (0.4%)	651 (0.8%)	0.49 (0.12-1.96)	1 (0.2%)	332 (0.3%)	0.58 (0.08-4.12)	**0.54 (0.17-1.67)**
Peptic ulcers	20 (3.8%)	1700 (2.0%)	1.89 (1.23-2.92)	8 (1.2%)	1417 (1.2%)	1.04 (0.52-2.08)	**1.55 (1.08-2.25)**
GI bleed	18 (3.4%)	1228 (1.4%)	2.30 (1.46-3.64)	24 (3.7%)	1402 (1.2%)	2.96 (2.0-4.39)	**2.67 (1.98-3.60)**
Upper GI bleed	12 (2.3%)	529 (0.6%)	3.53 (2.00-6.22)	12 (1.9%)	654 (0.6%)	3.16 (1.80-5.55)	**3.36 (2.25-5.01)**

ALL INDIVIDUALS	
	Prevalence ratio
	(95% C.I.)
MENTAL HEALTH DISORDERS	
Neuroses	1.90 (1.79-2.02)
Obsessive-Compulsive disorder	2.57 (1.61-4.10)
Anxiety	1.99 (1.85-2.14)
Hysteria	3.92 (2.55-6.04)
Depression	1.98 (1.87-2.09)
Schizophrenia	4.13 (3.05-5.61)
Organic psychoses	6.05 (5.13-7.14)
Other psychoses	3.98 (3.62-4.38)
Alcohol Dependence	5.70 (4.84-6.71)
Dementia	6.34 (5.47-7.35)
SOMATIC DISORDERS	
Fractures	2.17 (2.00-2.35)
Diabetes mellitus	1.57 (1.39-1.78)
Neoplasia	1.05 (0.89-1.25)
Brain neoplasms	55.05 (38.00-79.75)
Meningiomas	31.44 (9.16-107.91)
IHD	1.34 (1.19-1.50)
Heart Failure	1.68 (1.45-1.95)
Congenital cardiac abnormalities	7.34 (4.58-11.75)
CVA	6.96 (6.38-7.60)
Haemorrhagic CVA	10.62 (6.52-17.32)
Ischaemic CVA	7.49 (5.69-9.86)
TIA	4.94 (4.44-5.50)
Migraine	1.60 (1.43-1.80)
Parkinson's disease	3.19 (2.44-4.18)
Pneumonias	3.19 (2.72-3.74)
Asthma	1.30 (1.19-1.41)
Chronic bronchitis	1.67 (1.26-2.21)
Emphysema	1.25 (0.67-2.34)
Peptic ulcers	1.92 (1.55-2.37)
GI bleed	3.37 (2.78-4.08)
Upper GI bleed	4.31 (3.41-5.46)
Lower GI bleed	2.16 (1.43-3.25)
Unspecified GI bleed	2.85 (1.77-4.59)
Eczema	0.90 (0.47-1.74)
Rheumatoid arthritis	0.99 (0.67-1.47)
Osteoarthritis	1.02 (0.91-1.15)
Cerebral degeneration	6.80 (5.96-7.76)
Alzheimer's	8.05 (5.89-11.00)

Table 11. Prevalence ratios of comorbid disorders in all individuals, irrespective of age or gender

perinatal period (chapter XV), diseases in all other chapters occur slightly more often in people with epilepsy.

In the older group, the prevalence ratio of mental disorders in people with epilepsy is twice that of the background non-epilepsy population (table 13). Similarly, the prevalence ratios of infections, blood and genitourinary disorders, injuries & poisoning are about 50% higher. The prevalence ratio of cardiovascular, nervous and digestive disorders, although common in older adults with epilepsy, is only 20-40% higher. Musculoskeletal conditions do not occur more often in people with epilepsy in this age group (table 13).

4.4 Discussion

4.4.i Principal findings

In this large population-based study, the frequency of selected conditions, as well as groups of conditions, is described in a primary care cohort of adults with and without epilepsy, stratified by age and sex. As expected, conditions common in the general population were also common in adults with epilepsy. However, the prevalence ratio of all specific disorders under study was increased in adults with epilepsy with the exception of eczema, rheumatoid arthritis and osteoarthritis. Psychiatric disorders occurred twice as often. The prevalence ratio of somatic disorders across categories was increased in people with epilepsy with the exception of musculoskeletal and connective tissue disorders in older adults. Congenital anomalies were increased in younger adults with epilepsy, but perinatally acquired conditions were not (probably related to poor survival in this group).

16-64 YEARS							
	MEN			**WOMEN**			**OVERALL**
	Epilepsy	Non-Epilepsy	Rate Ratio	Epilepsy	Non-Epilepsy	Rate Ratio	Rate ratio
	N=2321	N=420312	(95% C.I.)	N=2338	N=410851	(95% C.I.)	(95% C.I.)
	N (%)	N (%)		N (%)	N (%)		
ICD-9 CHAPTERS							
I. Infections and parasitic diseases	783 (33.7%)	96840 (23.0%)	1.45 (1.37-1.53)	1157 (49.5%)	148663 (36.2%)	1.34 (1.29-1.40)	**1.39 (1.34-1.44)**
II. Neoplasms	128 (5.5%)	15541 (3.7%)	1.52 (1.29-1.80)	173 (7.4%)	29477 (7.2%)	1.06 (0.91-1.22)	**1.22 (1.09-1.36)**
III. Endocrine, nutritional and metabolic diseases and immunity disorders	197 (8.5%)	26493 (6.3%)	1.45 (1.27-1.65)	341 (14.6%)	32283 (7.9%)	1.98 (1.80-2.18)	**1.75 (1.62-1.89)**
IV. Diseases of blood and blood-forming organs	75 (3.2%)	4993 (1.2%)	2.75 (2.19-3.44)	250 (10.7%)	27283 (6.6%)	1.58 (1.41-1.78)	**1.78 (1.60-1.97)**
V. Mental disorders	840 (36.2%)	57612 (13.7%)	2.68 (2.54-2.83)	1009 (43.2%)	97878 (23.8%)	1.84 (1.76-1.93)	**2.15 (2.08-2.23)**
VI. Disease of the nervous system and sense organs	905 (39.0%)	110608 (26.3%)	1.50 (1.43-1.58)	1125 (48.1%)	146322 (35.6%)	1.37 (1.31-1.43)	**1.43 (1.38-1.47)**
VII. Diseases of the circulatory system	416 (17.9%)	48281 (11.5%)	1.67 (1.54-1.81)	437 (18.7%)	56934 (13.9%)	1.45 (1.34-1.57)	**1.55 (1.47-1.65)**
VIII. Diseases of the respiratory system	1255 (54.1%)	186419 (44.4%)	1.21 (1.16-1.25)	1584 (67.8%)	242827 (59.1%)	1.14 (1.11-1.17)	**1.17 (1.14-1.20)**
IX. Diseases of the digestive system	748 (32.2%)	79881 (19.0%)	1.73 (1.63-1.84)	926 (39.6%)	104843 (25.5%)	1.58 (1.50-1.66)	**1.65(1.58-1.71)**
X. Diseases of the genitourinary system	306 (13.2%)	40594 (9.7%)	1.39 (1.25-1.54)	1286 (55.0%)	189918 (46.2%)	1.19 (1.15-1.24)	**1.24 (1.19-1.29)**
XI. Complications of pregnancy, childbirth and the puerperium				661 (28.3%)	94718 (23.1%)	1.19 (1.11-1.27)	
XII. Diseases of the skin and subcutaneous tissue	961 (41.4%)	120743 (28.7%)	1.43 (1.36-1.50)	1134 (48.5%)	156394 (38.1%)	1.26 (1.12-1.32)	**1.34 (1.30-1.38)**
XIII. Diseases of the musculoskeletal system and connective tissue	985 (42.4%)	157827 (37.5%)	1.16 (1.10-1.21)	1203 (51.5%)	182490 (44.4%)	1.20 (1.15-1.24)	**1.18 (1.15-1.22)**
XIV. Congenital anomalies	35 (1.5%)	1782 (0.4%)	3.48 (2.50-4.85)	34 (1.5%)	2432 (0.6%)	2.37 (1.70-3.32)	**2.84 (2.24-3.60)**
XV. Certain conditions originating in the perinatal period	1 (0.04%)	146 (0.03%)	1.22 (0.17-8.72)	10 (0.4%)	1831 (0.4%)	0.89 (0.48-1.66)	**0.93 (0.51-1.68)**
XVI. Symptoms, signs, and ill-defined conditions	1744 (75.1%)	181805 (43.3%)	1.75 (1.71-1.79)	1961 (83.9%)	247043 (60.1%)	1.40 (1.38-1.43)	**1.55 (1.53-1.58)**
XVII. Injury and poisoning	1095 (47.2%)	132692 (31.6%)	1.47 (1.41-1.53)	1022 (43.7%)	110863 (27.0%)	1.62 (1.54-1.69)	**1.53 (1.48-1.58)**

Table 12. Rates of disease groups per gender and epilepsy status in people aged 16-64 years.

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64+ YEARS							
	MEN			**WOMEN**			**OVERALL**
	Epilepsy	Non-Epilepsy	Rate Ratio	Epilepsy	Non-Epilepsy	Rate Ratio	Rate ratio
	N=533	N=86130	(95% C.I.)	N=642	N=118516	(95% C.I.)	(95% C.I.)
	N (%)	N (%)		N (%)	N (%)		
ICD-9 CHAPTERS							
I. Infections and parasitic diseases	192 (36.0%)	20940 (24.3%)	1.47 (1.31-1.65)	279 (43.5%)	34049 (28.7%)	1.50 (1.38-1.64)	**1.48 (1.38-1.59)**
II. Neoplasms	65 (12.2%)	9595 (11.1%)	1.08 (0.86-1.35)	78 (12.1%)	10772 (9.1%)	1.33 (1.08-1.64)	**1.21 (1.04-1.41)**
III. Endocrine, nutritional and metabolic diseases							
and immunity disorders	113 (21.2%)	16513 (19.2%)	1.11 (0.94-1.31)	193 (30.1)	21579 (18.2%)	1.67 (1.48-1.88)	**1.41 (1.28-1.552)**
IV. Diseases of blood and blood-forming organs	54 (10.1%)	4935 (5.7%)	1.71 (1.33-2.21)	82 (12.8%)	9623 (8.1%)	1.51 (1.23-1.84)	**1.57 (1.34-1.84)**
V. Mental disorders	218 (40.9%)	12974 (15.1%)	2.69 (2.42-2.98)	297 (46.3%)	27338 (23.1%)	1.96 (1.81-2.14)	**2.19 (2.05-2.33)**
VI. Disease of the nervous system							
and sense organs	324 (60.8%)	40164 (46.6%)	1.29 (1.21-1.38)	373 (58.1%)	58219 (49.1%)	1.17 (1.10-1.25)	**1.22 (1.17-1.28)**
VII. Diseases of the circulatory system	335 (62.9%)	39743 (46.1%)	1.35 (1.26-1.44)	393 (61.2%)	54863 (46.3%)	1.31 (1.23-1.39)	**1.33 (1.27-1.39)**
VIII. Diseases of the respiratory system	335 (62.9%)	44285 (51.4%)	1.22 (1.14-1.30)	391 (60.9%)	63663 (53.7%)	1.13 (1.07-1.21)	**1.17 (1.12-1.22)**
IX. Diseases of the digestive system	285 (53.5%)	33204 (38.6%)	1.37 (1.27-1.49)	346 (53.9%)	46993 (39.7%)	1.34 (1.25-1.44)	**1.36 (1.29-1.43)**
X. Diseases of the genitourinary system	203 (38.1)	21275 (24.7%)	1.52 (1.37-1.70)	305 (47.5%)	36745 (31.0%)	1.52 (1.40-1.65)	**1.51 (1.42-1.62)**
XI. Complications of pregnancy, childbirth							
and the puerperium				138 (21.5%)	19382 (16.4%)	1.33 (1.15-1.55)	
XII. Diseases of the skin and subcutaneous tissue	264 (49.5%)	33249 (38.6%)	1.28 (1.17-1.39)	341 (53.1%)	50071 (42.2%)	1.25 (1.16-1.34)	**1.26 (1.19-1.33)**
XIII. Diseases of the musculoskeletal system							
and connective tissue	302 (56.7%)	45985 (53.4%)	1.06 (0.98-1.14)	390 (60.7%)	73074 (61.7%)	0.99 (0.93-1.05)	**1.01 (0.96-1.06)**
XIV. Congenital anomalies	2 (0.4%)	378 (0.4%)	0.85 (0.21-3.41)	8 (1.2%)	564 (0.5%)	2.64 (1.32-5.28)	**1.85 (0.99-3.44)**
XV. Certain conditions originating							
in the perinatal period	0	0	0	1 (0.2%)	80 (0.1%)	2.27 (0.32-16.22)	**1.51 (0.21-10.82)**
XVI. Symptoms, signs, and ill-defined conditions	481 (90.2%)	58142 (67.5%)	1.33 (1.29-1.37)	580 (90.3%)	86137 (72.7%)	1.24 (1.20-1.27)	**1.27 (1.25-1.30)**
XVII. Injury and poisoning	216 (40.5%)	21105 (24.5%)	1.64 (1.48-1.82)	319 (49.7%)	38921 (32.8%)	1.49 (1.37-1.61)	**1.53 (1.44-1.63)**

Table 13. Rates of disease groups per gender and epilepsy status in people aged 64 years and older.

4.4.ii Strengths and weaknesses of the study

This study uses information from the GPRD, a large and well-validated general practice derived database that has been used for epidemiological research for over 10 years.[206] The population of participating practices was large: 1.3 million in 1998 (over one million adults), and the age/sex distribution of this population was broadly similar to that of England & Wales in the same year. All practices passed quality tests on the data they supplied to the database. Selection criteria for the study population resulted in under-representation of more mobile – and possibly healthier - population groups and exclusion of people who died. Because prevalence is the result of both the condition's incidence and its mortality rate, factors influencing survival may lead to spurious associations between disorders. However, it is considered unlikely that the studied conditions affected survival differently in adults with and without epilepsy. An under-representation of healthy individuals in the study cohort may also result from young people without illness who are not registered with a GP. This would lead to overestimation of disease rates compared to the total population and, subsequently, to underestimation of PRs in epilepsy. Ninety eight percent of the UK population, however, is registered with a GP[207] and the degree of any such underestimation of ratios would be small.

The calculated prevalence ratios are weighted averages of the age band-specific PR estimates. The stratum-specific PRs appear to be consistent across the 10-year age bands (although not always statistically significant due to smaller numbers). The consistency of estimated ratios across different practices could not be assessed (so as to check for any regional or urban-rural variations), as the information on practice

characteristics is not released for confidentiality purposes. However, the population is representative of the population of England and Wales.

The main limitation of this study is that the diagnosis was not validated, for example, by examining whether patients had their diagnosis confirmed by a specialist, because of resource constraints. Misdiagnosis is an important problem in the management of epilepsy, with as many as 20% of cases inaccurately diagnosed.[3;208] Another limitation is that the study only includes people coming into contact with the health service and would not include cases that had not come to a GP's or specialist's attention. A proportion of people with epilepsy may not consult a doctor, especially prevalent cases of epilepsy, the elderly, and people whose seizures are well controlled.[182] This can introduce an admission-rate bias, with more severe cases with greater morbidity being included in the study. People with epilepsy are known to make higher use of health services than people without epilepsy (refer to Chapter 3) however, it is not known what proportion of the health services requirement is due to the severity of epilepsy, its treatment, aetiology or other factors. It was not feasible to look at the temporal association between epilepsy and comorbid disorders. For example, where epilepsy is associated with a brain tumour, it cannot be established whether the brain tumour was the cause of epilepsy or whether epilepsy was present before the development of the tumour.

4.4.iii Comparison with other studies

The period prevalence of epilepsy between 1995-1998 in the study was 5.6 per 1,000 (95% CI 5.5-5.7/1,000). This is lower than the 1998 age-standardised prevalence reported previously by the researcher's group (7.4/1,000) using the same GPRD

practices.[209] This discrepancy arose because of differences in case selection. In the previous study the prevalence figure included people who had a diagnosis of epilepsy recorded several years prior to the study period.[209] In the current analysis no prior information was available. Hence, only diagnoses recorded during the study period would have been included and the method used resulted in a lower prevalence of epilepsy.

This is the first large-scale study of the comorbidity of epilepsy in an unselected population. Its findings are consistent with those of previous community-based and unselected population case-control studies that suggest a higher risk of vascular disorders (strokes, myocardial infarction, peripheral vascular disease, hypercholesterolaemia, left ventricular hypertrophy),[52] migraine,[21] hypertension,[199;201] dementia,[200] brain tumours,[210] fractures,[197] and depression[210] in epilepsy. The size of the risk (here expressed as a prevalence ratio) cannot be compared, however, as some of these studies were conducted in incident cases of epilepsy[199-201;210] and studied the prevalence of conditions before the development of epilepsy,[199;200;210] or assessed the incidence of co-occurring conditions.[21;197]

The higher prevalence ratio of somatic disorders in this study contrasts with the results from a population-based cohort study in Finland, which reported increased psychiatric but not somatic comorbidity in comparison to controls.[57] That study, however, was conducted in adults with childhood-onset epilepsy and a mean age of 35.6 years at the end of follow-up, who have different baseline characteristics from the younger adult epilepsy group in this study. In addition, the sample size of only 220 people with epilepsy may not have been large enough to detect any real differences. A population-

based prevalence study in 713 adults with epilepsy in Sweden reported a 5.9% prevalence of psychiatric disorders and a 50% prevalence of somatic disorders and disabilities.[55] This compares with a 40% period prevalence of psychiatric disorders in this study and a much higher prevalence of somatic disorders.

The MSGP4 showed that higher proportion of people with epilepsy consulted for neoplasms, haematological and mental health disorders, diabetes, ischaemic heart disease, heart failure, dementia, stroke and gastrointestinal bleeding than people without epilepsy in the community (refer to Chapter 3). Although these estimates were not age-standardised, and rate ratios compared proportions rather than prevalence rates, results were very similar to this study, adding further support to the GPRD findings. It is noteworthy that in both studies the risk of gastrointestinal bleeding was significantly raised (Risk Ratio [RR] 4.93 in the MSGP4 study and PR 3.37 in this study) (further discussion below under PEPTIC ULCERS AND GASTROINTESTINAL BLEED).

4.4.iv Association of individual disorders with epilepsy

The conditions that appear to occur more frequently in people with epilepsy in this study and their possible association with epilepsy, according to the scheme proposed by Lipton and Silberstein[19] and discussed earlier (Chapter 1), are discussed here in more detail. Eczema, rheumatoid arthritis and osteoarthritis are not discussed, as they do not occur more frequently in epilepsy. The psychiatric conditions (with the exception of alcohol dependence) are also omitted from further discussion, since they have been reviewed previously in the thesis (Chapter 2).

FRACTURES

Two reasons may underlie the association of fractures and epilepsy: fractures may occur as a result of injury in people with epilepsy, or post-traumatic epilepsy may develop as a result of accidents causing head trauma.[211] Injuries are common in epilepsy, with up to 30% of people with the condition reporting injuries.[212] The incidence of extremity fractures in a group of adult patients with epilepsy attending an outpatient clinic in Sweden (expressed as the Standardised Morbidity Ratio) was 2.4 times higher (95% CI 1.5-3.6) in comparison to the general population.[213] Nearly half of the fractures in the study were definitely or possibly seizure related.[213] Seizures associated with falls (atonic and tonic-clonic seizures, in particular) increase the risk of injury, but any seizure that is associated with alteration of consciousness may result to injury. Epilepsy and its treatment, including the newer drugs, are risk factors for low bone density[214] and may, therefore, predispose further to osteoporotic fractures. The elderly may be particularly at risk, as epilepsy was shown to be an independent risk factor for osteoporotic hip fractures in women aged 70 years and over[215] and women 65 years and older on AEDs have a two- to three-fold risk of fractures compared to women of similar age without epilepsy.[216;217] Another study also showed that men 45 years or older were at higher risk of fractures.[213] In the currrent study, however, the PR of fractures was no different between the age groups [PR 2.20 (95% CI 2.00-2.42) for the 16-64 years vs. PR 2.10 (95% CI 1.82-2.43) for the 64+ years group] (tables 9 & 10). A large population-based study by Annegers et al.[197] found no definite evidence to support the contention that the incidence of fractures is greatly increased by long-term AED use, as it would be expected in the case of AED-induced osteoporosis. Taken together, these data suggest that the role of AED-induced

osteoporosis in the incidence of fractures in people with epilepsy in the community may be limited.

DIABETES

Diabetes does not appear to be directly associated with epilepsy and, so far, long-term use of AEDs is not known to predispose to the development of diabetes. Diabetes is a major risk factor for cerebro- and cardiovascular disorders, that are known risk factors for epilepsy,[52] and thus indirectly predisposes to epilepsy.

ISCHAEMIC HEART DISEASE (IHD) & HEART FAILURE

These conditions reflect systemic vascular disease (including cerebrovascular) and share risk factors for epilepsy, such as hypertension, left ventricular hypertrophy, myocardial infarction, and peripheral arterial disease.[52;199;201] Cerebral arteriosclerosis without a history of stroke is associated with higher incidence of late onset epilepsy and is often the only finding on imaging in elderly patients with new-onset seizures.[218] Compared with subjects free of these conditions in the population, IHD increases the risk of stroke by 2 and heart failure by 4.[219] IHD and heart failure are also associated with atrial fibrillation that further increases the risk of stroke in their presence by a factor of 2-3, especially in the elderly.[219;220] In the Rochester study, the incidence of IHD in people with epilepsy (expressed as a Standardised Morbidity Ratio) was 1.63 (95% CI, 1.20-2.15) times higher compared to people in the community.[221] The risk was 50% higher in people with idiopathic epilepsy and nearly 100% higher for those with remote symptomatic epilepsy.[221] In the current study the prevalence of these conditions is higher in the younger adult age group (PR 1.63 vs. 1.21 in the 64+ group) (tables 9 & 10), most probably because of their lower prevalence in the general

population of the same age group, and because it appears that the attributable risk of stroke for these conditions decreases with age.[219]

STROKES/CEREBROVASCULAR DISEASE

Cerebrovascular disease is the most commonly identified antecedent of epilepsy, accounting for 11% of cases, particularly in the elderly.[222] The incidence of epilepsy as a late sequel of stroke has been estimated at 2.5% and 3.3% in two large population-based studies with adequate follow-up.[223;224] Seizures occur more commonly with haemorrhagic stroke than with ischaemic stroke,[224] with the prevalence of epilepsy in patients with primary intracerebral haemorrhage reported to be 6.5% in 2- to 5-year survivors.[225] The risk of haemorrhagic stroke in patients with epilepsy in current study was much higher than the risk for ischaemic stroke, particularly in the younger age group (tables 9 & 10). The small numbers of patients with haemorrhagic stroke in the older age groups may be related to misclassification or reflect the poor survival of these patients in the study. Risk factors for the development of epilepsy following ischaemic stroke are early seizure occurrence (within 2 weeks of stroke), stroke recurrence and increased disability.[223;224] In this study, the risk of ischaemic stroke was higher among women in the younger age group (18.74% vs. 7.54% in men), because of the significantly lower number of strokes in the non-epilepsy population in this group (127 women vs. 210 men). Strokes are the most common cause of seizures in the elderly accounting for up to 37% of new cases.[226;227]

CONGENITAL HEART DISEASE (CHD)

CHD occurs in at least 10 per 10,000 live born children.[228] Over the past 20 to 30 years, major advances have been made in the diagnosis and treatment of CHD in

children. As a result many children with such disorders survive to adulthood. The CNS is one of the most common sites of complications associated with CHD and, in addition, cardiac abnormalities can be associated with congenital cerebral dysgenesis.[228;229] Any kind of acquired CNS injury (such as hypoxic-ischaemic encephalopathy, vascular events and brain abscesses) or developmental anomaly can result to seizures. Cerebrovascular and/or hypoxic events can be the result of cyanotic conditions with right-to-left shunt (transposition of the great arteries and tetralogy of Fallot's account for 90% of such complications), acyanotic conditions with right-to-left shunt (i.e., patent foramen ovale) and paradoxical embolisation, and hypothermic cardiopulmonary by-pass operations in young infants.[228] CHD also occurs in syndromes with multiple congenital abnormalities, further predisposing them to seizures, such as Down's syndrome,[230] Kallmann's syndrome[231] and tuberous sclerosis.[232] Coarctation of the aorta may be associated with intracranial aneurysms, which increase the risk for stroke if not repaired early.[233] In this study, no patients with CHD were detected in the 64+ age group, most probably due to premature death.

INTRACRANIAL NEOPLASMS

Intracranial tumours are a common cause of epilepsy in adults. Seizures occur at presentation in 15-95% of patients with intracranial tumours, depending on the type of tumour, with low-grade gliomas and meningiomas presenting more commonly with seizures (65-95% and 40% respectively).[234] The most frequent primary brain tumours in adults are gliomas and primary CNS lymphomas.[235] Incidence of gliomas is around 5-10 per 100,000 of the general population.[235] Low-grade gliomas affect mainly young adults (mean age, 35 years in astrocytomas and 45 years in oligodendrogliomas).[235] Primary glioblastomas tend to occur in older patients (mean age, 55 years), whereas

secondary glioblastomas tend to occur in younger adults (45 years of age or less).[234] In this study, the highest PR of primary brain neoplasms is seen in the younger age group (PR 70.70 vs. 11.55 in the older age group, (tables 9 & 10), particularly in women (PR 90.36 vs. 54.69 in men (table 9). In contrast, no brain neoplasms were detected in women of the older age group (table 10).

Meningiomas have a total annual incidence of around 8 per 100,000,[234] with a peak incidence around 45 years of age and female preponderance.[234;236] The majority are asymptomatic discovered incidentally at autopsy; their incidence in symptomatic patients is about 2 per 100,000.[234] The higher PR of meningiomas is seen in the older age group in this study (PR 91.88 vs. 13.57 in the younger group, tables 9 & 10). This may be explained by the fact that their incidence appears to increase with age,[236] that they are associated with a high post-operative seizure occurrence (even in patient with no pre-operative seizure disorder),[237;238] and that they have a high rate of recurrence after resection.[234] In addition, the majority of meningiomas are slow growing, benign tumours associated with favourable outcome and, therefore, survival to an older age.[234]

NEOPLASIA (excluding brain tumours)

Metastatic disease to the brain occurs in 15-28% of all cancer patients[239;240] and epilepsy can be the presenting symptom in these patients, observed in 15-25% of cases.[236] However, people with epilepsy in this study do not appear to have higher rates of neoplasia other than brain tumours (tables 9 & 10). This is because cancer cases with secondary brain metastases that could give rise to seizures have been excluded. This finding may mean that tumours that do not metastasise to the brain do not increase the risk of seizures.

MIGRAINE

Data from the Epilepsy Family Study of Columbia University showed that the incidence of migraine in people with epilepsy is 2.4 times higher (95% CI, 2.0-2.9) than in people without epilepsy.[241] This study used information from structured telephone interviews and its results indicated that migraine and epilepsy were strongly correlated, irrespective of seizure type, age of onset, aetiology, or family history of epilepsy. It is possible that the comorbidity of migraine and epilepsy is based on an underlying state of neuronal hyperexcitability that increases the risk of both disorders[242] but does not appear to be due to a shared genetic susceptibility.[24] In this study, men with epilepsy were diagnosed twice as often with migraine compared to the non-epilepsy population in both age groups, but in women the prevalence was increased only in the younger age group (PR 1.44 vs. 0.98 in the older group) (tables 9 & 10). The discrepancy in the risk of migraine between the genders is difficult to explain. In the Epilepsy Family Study, the risk of migraine among people with epilepsy was 1.4 times higher in women compared to men.[243] It may be that migraine is underdiagnosed in men without epilepsy or in women with epilepsy by general practitioners in UK. The prevalence of migraine in adults with epilepsy in the above study was 24%, a much higher percentage than the 4.8% prevalence in this study. As noted by Andermann and Andermann [244], findings in this area are difficult to interpret because of variations in definitions of migraine and epilepsy, method of patient identification, and sample size. One important aspect is that migraine is commonly underdiagnosed in people with and without epilepsy: According to a US study,[48] 29% of men and 40% of women with migraine in the general population reported a medical diagnosis, and in the Epilepsy Family Study only 44% of people with epilepsy reported physician-diagnosed migraine.[245] Why is the comorbidity of migraine and

epilepsy not adequately recognised? Epilepsy may be considered as a more serious disorder than migraine. As a result, the migrainous symptoms of patients with epilepsy may be overlooked or attributed to the seizures. In addition, the diagnosis of atypical migraine symptoms can be difficult in the presence of epilepsy,[244;246] and some patients with both conditions may not report their headaches because these are effectively treated with an AED (e.g., sodium valproate).[247]

ASTHMA, CHRONIC BRONCHITIS, EMPHYSEMA

These conditions appear to occur more frequently in people with epilepsy between 16-64 years compared to those without epilepsy, but not in people with epilepsy over 64 years (tables 9 & 10). For asthma the excess prevalence is rather small (37% higher or PR 1.37), however the PR for chronic bronchitis and emphysema in people with epilepsy is 2.3 and 2.92 times higher, respectively.

Asthma is a complex syndrome with many clinical phenotypes in both adults and children. For many patients, the disease has its roots in infancy, and both genetic factors (atopy) and environmental factors (viruses, allergens, and occupational exposures) contribute to its inception and evolution.[248] A case-control study suggested a higher incidence of allergy (including asthma) in children with epilepsy than in controls.[249] Respiratory syncytial virus (RSV) -an extremely common cause of childhood respiratory infections- has been implicated with the development of asthma in children.[250] It has also been associated with the development of encephalopathy presenting with seizures in a minority (1.8%) of children with bronchiolitis.[251] The relevance of these findings in an adult population is, however, unknown. A number of studies have suggested that epilepsy and asthma may be related conditions. There has,

however, been little epidemiologic data published to support this association. A recent retrospective study found no association between idiopathic epilepsy and asthma.[252] The association between the two conditions may be indirect through shared risk factors: smoking is a risk factor for persistence of asthma into adulthood,[253] as well as for vascular disease and cancer.[254] The latter two conditions can cause epilepsy through strokes and metastases.

An association between pseudoseizures and asthma has been reported recently.[255] According to the authors, both asthma and anxiety hyperventilation may be important risk factors for the development of pseudoseizures, and somatisation, anxiety hyperventilation and dissociative elaboration may have accounted for the observed association. If people with epilepsy (with or without pseudoseizures) suffer a higher incidence of "psychogenic" asthma is not currently known.

The association of chronic bronchitis and emphysema with epilepsy can perhaps be explained through smoking. The commonest cause for these conditions is cigarette smoking,[256] which is also a known risk factor for cerebrovascular disease and cancer[254] that can cause epilepsy.

PNEUMONIAS

Pneumonia can occur nearly 3-4 times more often in people with epilepsy in this study (tables 9 & 10). Does this reflect -at least in part- the higher prevalence of chronic bronchitis and emphysema in people with epilepsy in this cohort? These conditions, along with diabetes, renal failure, heart failure, alcoholism and neoplastic disease (among others) that occurred more frequently in people with epilepsy in this cohort

(tables 9 & 10), are associated with the severity of CAP and are risk factors for mortality.[257] It is not known, however, if these conditions are risk factors for CAP in adults.[258]

Community acquired pneumonia (CAP) is usually due to *Streptococcus pneumoniae* and *Haemophilus influenzae*, with less common causes including atypical pathogens (*Mycoplasma pneumoniae*, Legionella and *Chlamydia pneumoniae)*, viruses and aspiration.[259] Mycoplasma infection is associated with the development of meningoencephalitis that can be complicated with seizures,[260] however this is observed more commonly in children.[261] Aspiration pneumonia may complicate seizures (particularly GTCS), although this does not appear to be a common occurrence.[262]

Pneumonia is a common terminal event in people with epilepsy,[263] especially those with severe epilepsy, such as institutionalised patients[264] and patients with mental retardation.[265] In the NGPSE the total number of deaths from pneumonia in the cohort of people with definite and probable epilepsy (N=792) was 39 among 199 deaths over a period of 11-14 years.[266] The majority of these deaths occurred in people over 50 years and in the first 7 years of follow up. This may be due to the high incidence of strokes in this age group that can be complicated by aspiration. Aspiration pneumonia is the commonest cause of death in patients with dysphagia due to neurologic disorders.[267] Among patients with stroke, pneumonia is seven times as likely to develop in those in whom aspiration can be confirmed than in those who do not aspirate.[268] This association may partly explain the higher risk of pneumonia in people with epilepsy.

DEMENTIAS

A considerably higher prevalence ratio for Alzheimer's disease (AD) appears to exist in the younger adult epilepsy group than the older group (PR 40 vs. 7 respectively) (tables 9 & 10). Findings were similar for all dementias (PR ~25 vs. ~6) and cerebral degeneration (PR 27 vs. 6) (tables 9 & 10). Both a diagnosis of AD and a diagnosis of other dementias have been associated with at least a six-fold increased risk of unprovoked seizures, after controlling for age and sex, and in the absence of other prior neurologic insult.[269] The discrepancy between the age groups in this study may be related to the severity of the underlying condition associated with epilepsy and, therefore, reflect more aggressive early-onset disease. One study in patients with uncomplicated, definite AD on autopsy found that patients with new-onset, unprovoked seizures had a younger age of dementia onset than did the AD patients without seizures and that, at seizure onset, they had advanced dementia, averaging 6.8 years into their AD.[270] The development of new-onset seizures in advanced AD was also described in another study[271] and appears to accelerate the progression of dementia.[272] Although the latter finding was described in institutionalised patients with a clinical diagnosis of probable AD, it raises the question that seizures "facilitate" the diagnosis of dementia in some patients, possibly because it forces them to require medical attention and because the manifestations of dementia become more prominent and easy to diagnose.

Epilepsy itself may be a risk factor for the development of AD. In a re-analysis of eight case-control studies on AD, more cases than controls reported epilepsy before the onset of AD (PR 1.6, 95% CI 0.7-3.5), especially for epilepsy with an onset within 10 years of onset of dementia.[273] This may be due to shared risk factors such as

cerebrovascular disease. Indeed, permanent cognitive impairment resulting from cerebrovascular disease is the second most common form of dementia in most parts of the world[274] and cerebrovascular disease is also the most commonly identified antecedent of epilepsy accounting for 11% of cases,[222] as described above. In addition, epilepsy (particularly TLE) has been associated with focal or generalised cerebral and cerebellar volume loss.[275-283] It has been proposed that this damage is primarily the result of a prior neurological insult and not of epilepsy.[278] The increased risk of cerebral atrophy in epilepsy does not appear to be related to seizure recurrence and is associated with age and multiple AED exposure.[278;284]

PARKINSON'S DISEASE

Parkinson's disease (PD) occurs about 3 times more commonly in people with epilepsy (tables 9,10 &11). The association between the two disorders is intriguing because they involve different parts of the CNS.

Pathologically, PD is characterised by progressive cell loss in the substantia nigra and other subcortical nuclei in association with the presence of Lewy bodies and Lewy neurites.[285] The cerebral cortex (particularly the cingulate gyrus and entorhinal cortex) and the hippocampus can be also affected in PD, although this appears to contribute to the cognitive dysfunction in this group of patients[286] and it is not known if it increases the risk of seizures. A large study of patients with parkinsonism (N=368) found that epilepsy was significantly less frequent in this group, especially in Parkinson's disease.[287]

Seizures and AED treatment do not appear to be risk factors for the development of

PD.[286] Wennberg et al. analysed intracranial potentials recorded from DBS electrodes

in association with scalp EEG spikes and sleep discharges in six patients with

intractable epilepsy treated with thalamic deep brain stimulation (DBS) and one

patient with PD treated with DBS of the subthalamic nucleus.[288] They showed that the

intracranial waveforms represented volume conduction from discharges generated in

the neocortex and not locally generated activity from cortical-subcortical neural

propagation.

The diagnosis of PD is made clinically, however other disorders with prominent

symptoms and signs of parkinsonism, such as drug-induced and arteriosclerotic

parkinsonism, may be confused with Parkinson's disease until the diagnosis is

confirmed at autopsy.[285] This may particularly be the case in a primary care setting,

such as the one used for this study. If parkinsonism is substituted for PD,

cerebrovascular disease and dementia arise as shared risk factors that may explain the

association between epilepsy and PD.

Parkinsonian symptoms such as rigidity and postural instability develop in roughly

30% of patients with AD. A similar percentage of patients with PD eventually have

dementia due to AD or other causes.[289] The risk of AD in the current study is

considerably high in both age groups and particularly the younger group (PR 40 vs. 7)

(tables 9, 10 & 11 and comments on dementia above).

Dementia with parkinsonism as an early feature frequently progresses more rapidly

than uncomplicated AD.[274] In many cases of dementia with parkinsonism, Lewy

bodies can be found in areas of the brain where they do not typically occur in idiopathic PD, such as the cerebral cortex. These bodies can occur either without the prominent changes typical of AD (diffuse Lewy-body disease) or with them (the Lewy-body variant of AD).[274] These pathological findings suggest more extensive neurodegeneration (particularly in the cortex) than either condition alone that may increase the risk of seizures in these patients.

Parkinsonian features are also common in vascular dementia, the second most common cause of dementia in most parts of the world.[274] Vascular parkinsonism accounts for around 12% of all cases,[290] and although it is probably a distinct clinical entity to PD[291] it is not always easy to differentiate from PD. Patients with parkinsonism associated with vascular disease have a history of stroke and risk factors for stroke.[292]

In conclusion, cerebrovascular disease is a common cause both of epilepsy (see comments above) and parkinsonism, and its presence would predispose patients to both disorders. Similarly, AD and dementia appear to be shared risk factors both for epilepsy and parkinsonism.

PEPTIC ULCERS AND GASTROINTESTINAL BLEED

The PR of gastrointestinal (GI) bleeding is significantly raised in this study (PR 3.37), as well as the risk of peptic ulcers (RR 1.92). The PR of bleeding is higher in the younger adult group (PR 4.09 vs. 2.67 in the older group) and is mainly attributed to upper GI bleeding (PR 4.31 vs. 2.16 for lower GI bleeding). A possible explanation is higher use of aspirin, non-steroidal anti-inflammatory drugs, or excess alcohol

consumption by people with epilepsy, factors that contribute significantly to upper GI bleed.[293] Aspirin is an important part of treatment in conditions such as IHD, occlusive CVA, and TIA, which occurred more frequently in people with epilepsy in this study (tables 9,10,11). Alcohol dependence is also more common in this group (tables 9,10,11). AEDs are not known to increase the risk of GI bleeding, as it is for example the case with selective serotonin uptake inhibitors (SSRIs).[294]

ALCOHOL DEPENDENCE

The relationship between alcohol and seizures is complex and multifaceted. Excessive alcohol use (exceeding 51 grams of ethanol per day) was shown to be an independent, dose related risk factor for unprovoked seizures.[295] Alcohol itself may induce seizures[296] or exacerbate pre-existing epilepsy.[297] In addition, people who chronically abuse alcohol have an increased frequency of structural abnormalities in the brain that may contribute to seizures, including cerebral vascular lesions and lesions due to head injury.[298-300] Alcohol use may result in low AED levels in patients with epilepsy and lead to seizure exacerbation, due to poor compliance, reduced absorption, and hepatic enzyme induction.[301]

Patients are described as alcohol dependent when they meet the criteria for substance dependence.[302] Epidemiological data suggest the prevalence of epilepsy in alcohol-dependent patients of western industrialised countries may be at least triple that in the general population, whereas the prevalence of alcoholism is only slightly higher in patients with epilepsy than in the general population.[303] In this study, however, the prevalence of alcohol dependence was nearly 6 times higher in the epilepsy than in the non-epilepsy group (tables 9,10,11). The much higher risk may be due to different

rates of case identification in people with and without epilepsy. According to a hospital-based study, fewer than half of patients that screened positive for alcohol dependence and abuse were identified by their physicians and detection rates differed according to speciality.[304] In addition, patients with alcohol problems are more likely to be identified by their physicians if they have medical complications[304] and women are less likely to be identified than men.[305] Therefore, an admission-rate bias may have accounted –at least in part- for the results in this study.

The highest prevalence of alcohol dependence was observed in younger males (16-64 years) with epilepsy in comparison to the other age and sex groups (4% vs. 1.4% of younger females vs. 1.7% of older males and 1.2% of older females) (tables 9,10,11). These findings are in accord with epidemiological studies which found that the prevalence of alcohol abuse and dependence is higher in males than females[306;307] and that heavy drinking is inversely associated with age.[308]

4.4.v Implications for practice

These results demonstrate higher comorbidity in adults with epilepsy than in those without. Their generalisibility is potentially limited because of the case selection that possibly favoured more severe cases and cases of symptomatic epilepsy being included in the cohort; people with epilepsy in remission and no comorbidity may not consult a doctor.[182;183;190] The results are, however, valid for adults with epilepsy who come to medical attention. In this setting, increased awareness is needed for the diagnosis and treatment of diseases co-occurring with epilepsy, as this may have profound consequences for the quality of life and mortality of patients, as well as for the burden on health services. Co-occurrence of conditions in a person can complicate

diagnosis or have adverse prognostic implications. For example, patients with epilepsy often have medically undiagnosed –and untreated- migraine,[309] depression,[82] or anxiety.[53] -The presence of epilepsy in people with AD may reflect more aggressive early-onset disease,[310] and this may be the case for other neurodegenerative disorders (comments in the preceding discussion under DEMENTIA).

Conditions such as neoplasms -in particular brain tumours-, cerebrovascular and ischaemic heart disease, and pneumonias are associated with increased mortality in people with epilepsy.[12] The risk of these conditions was found to be higher in the epilepsy cohort in this study, which might explain the high mortality associated with remote symptomatic epilepsy.[12] It is not known what proportion of the health services requirements is due to the comorbidity of epilepsy, its treatment, or other factors. The MSGP4 study has shown that people with epilepsy make higher use of health services and consult more frequently for a number of disorders than people without epilepsy (Chapter 3), suggesting that comorbidity contributes significantly to the burden on health services for people with epilepsy. Epilepsy is known to be more common in people from lower socio-economic groups[311] and this may also contribute to the higher prevalence of comorbidity in people with epilepsy.

4.5 Conclusions

The findings suggest that the risk of many common psychiatric and somatic disorders is increased in adults with epilepsy who consult a primary care physician. This means that the presence of epilepsy should increase, not reduce, the suspicion that other disorders may be present. Conditions commonly seen in primary care are also common in people with epilepsy; however, doctors should also have a high degree of

suspicion for other disorders. The findings also emphasise the importance of taking a holistic view of the health of people with epilepsy when they consult doctors. This requires treating the epilepsy itself but also any other present conditions, as well as ensuring that patients are given adequate advice on the general aspects of their health.

Part II

MORTALITY IN EPILEPSY

Chapter 5

REVIEW OF MORTALITY IN EPILEPSY

5.1 Introduction

Despite an overall good prognosis for seizure control[312;313] epilepsy is a potentially life-threatening condition and carries an excess mortality. This is consistently shown, both in population-based studies and in studies of more selected populations, such as institutionalised patients and clinic attendees.[12;314] People with epilepsy have a *mortality rate* (the number of deaths that occur in a defined population divided by the person-years at risk in that population) 2-3 times higher than that of the general population.[12] This is better expressed as the *Standardised Mortality Ratio* (SMR), which is the ratio of the observed number of deaths in an epilepsy population to that expected based on the age- and sex-specific mortality rates in a reference population in a given time.[315] The causes of death in people with epilepsy can be classified into 3 groups: deaths that are unrelated to epilepsy; those that occur as a result of the cause of epilepsy; and those in which the epilepsy itself is the cause of death (Box 6).[314]

The proportion of deaths due to a particular cause in a cohort of patients in a given period can be described by the *Proportional Mortality Rate* (PMR), which compares the relative contribution of various causes to the overall mortality in this population.[12;316] PMR is not a direct measure of the ratio of rates of death between populations and does not express the risk of members of a population contracting or dying from a disease. Comparisons of PMR between groups or populations can be meaningful only if the cause-specific mortality rates are known so that differences

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BOX 6. Causes of death in epilepsy

Unrelated deaths

Neoplasms outside the central nervous system

Ischaemic heart disease

Pneumonia

Others

Related to underlying disease

Brain tumours

Cerebrovascular disease

Cerebral infection-abscesses and encephalitis

Inherited disorders, e.g. Batten's disease

Epilepsy related deaths

Suicides

Treatment related deaths

  Idiosyncratic drug reactions

  Medication adverse effects

Seizure related deaths

  Status epilepticus

  Trauma, burns, drowning

  Asphyxiation, aspiration

Aspiration pneumonia after a seizure

Sudden unexpected death in epilepsy

Adapted from Nashef et al. 1995[317]

between populations relate to variations either in the number of deaths of interest (numerators) or the total number of deaths (denominators).[12] For example, an observed excess of a particular cause of death in an epilepsy group may represent a true increased risk, but may also merely represent a deficit of deaths due to other causes.

The underlying disease, of which epilepsy is a symptom, is the main cause of death in newly diagnosed cases, and is associated with increased mortality whether epilepsy is present or not.[318] Epilepsy itself, and probably to a very much lesser extent its treatment, is a major cause of death in chronic epilepsy.[319] It has been suggested that the long term use of antiepileptic drugs (AEDs) increases the incidence of malignant neoplasia and osteoporosis, thereby potentially affecting long term mortality rates in people with epilepsy.[318]

5.2 Measures and Methods

Methodological difficulties permeate studies of the mortality of epilepsy. Definitions of epilepsy and classification of seizures may differ between studies, as well as the accuracy of epilepsy diagnoses and the classification of causes of death. The International League Against Epilepsy (ILAE) has published guidelines for epidemiological research,[315] which deal with the issue of definition and classification, and are based on the ILAE classification of epileptic seizures and syndromes.[5;6] For example, until recently, the term cryptogenic was interchangeable with idiopathic. In the new classification the term "idiopathic" is reserved for seizures occurring in epilepsy with a presumed genetic origin, and "cryptogenic" characterises seizures occurring in otherwise normal people with no clear cause. Other problems included the exact definitions of sudden unexpected death in epilepsy (SUDEP) and other seizure-related deaths,[320] as well as the inclusion in the epilepsy group of patients with acute symptomatic seizures, a category known to be associated with increased mortality.[319]

The accuracy of information on the cause of death depends on the methods employed. Death certificates can be an unreliable source[114;321;322] and, although autopsy and supplementary clinical data improve accuracy, they are subject to bias and error.[319] In the ongoing UK National General Practice Study of Epilepsy,[323] epilepsy was mentioned in 10 of 181 patients with definite epilepsy (own data). Furthermore, SMR cannot be calculated in studies utilising registers of death certificates because the number of person-years at risk in the study population is usually not known. Diagnostic inaccuracy in life may be as high as 15-20%, owing to confusion with syncope and psychogenic attacks or as a result of overinterpretation of EEGs.[108;324] Case ascertainment is subject to bias: retrospective studies based on hospital records may significantly underestimate the number of cases in the community,[324] especially the elderly, the very young and individuals whose seizures were not witnessed;[113] and population-based studies may include people without epilepsy.[325]

Despite the small number of mortality studies in epilepsy, different study types and reference populations have been used, rendering comparison between studies and application to the general population problematic.[326] Studies from selected populations, such as hospital-based case series[105;108;327-329] epilepsy residential centre[106;111;115] and epilepsy centre case series[110] offer the advantage of more reliable diagnoses and accurate classification of cause of death. Their disadvantages are that most include small numbers of patients and, most importantly, suffer from selection bias, as they tend to represent more severe and chronic cases. This is likely to exaggerate mortality and epilepsy related deaths, and results cannot be applied to the general epilepsy population. Cross sectional and prevalent population studies fail to ascertain new cases of epilepsy and therefore miss the high initial mortality of

epilepsy, and can misrepresent particular causes of death such as brain tumours.[113]

Insurance cohorts[330;331] represent highly selected prevalent cases and utilise the lower

mortality rates of non-rated policy holders as the standard.[318] The heterogeneity

between studies was evident in a recent attempt at a meta-analysis of comparative

studies investigating mortality in epilepsy patients.[326] The authors performed a

detailed quantitative review of relevant follow-up studies conducted in the last 100

years, in order to investigate the extent and causes of the differences found in studies

of mortality in epilepsy. Nineteen studies matched their criteria, assessing community,

general medical and institutional populations. A summary estimate, however, could

not be calculated because of considerable variation in mortality risk ratios of the

studies. This variation was explained mainly by differences in the "source population"

(which characterises the setting from which patients were recruited) and secondarily

by case selection.

The ideal approach is of large scale, general population based prospective incidence

studies with comprehensive case ascertainment, accurate diagnosis, sound aetiological

assignment, long follow-up and efficient tracing of patients.[324] The National General

Practice Study of Epilepsy (NGPSE) studies in the UK,[113;116] the study conducted in

Rochester, Minnesota[114] and the study in Västerbotten County in Northern Sweden[332]

appear to fulfil these criteria to a great extent.

5.3 Overall Mortality

Premature mortality in patients with epilepsy is reported to be significantly higher than

in the general population.[326] SMRs for community-based studies range between 1.3

and 3.1 (1.6 and 2.6 for studies using incident cases) (Box 7).

A community-based study of mortality in children aged 1-14 years using a state-wide paediatric mortality surveillance system in Victoria, Australia found an all-cause SMR of 13.2 (95% CI: 8.5-20.7).[333] A long term study in which a cohort of 245 Finnish children with epilepsy were followed up for more than 30 years reported an increased risk of death and decreased probability of survival in those who had not entered remission.[195] A community-based cohort study in Nova Scotia, Canada which followed 692 children who developed epilepsy between 1977 and 1985 reported SMRs >5 in the first 15-20 years after diagnosis.[334] The majority of deaths in people whose seizures start in childhood occur in adulthood.[335;336]

Studies of selected populations tend to have higher SMRs. In a large cohort study of all patients over 15 years old in whom a diagnosis of epilepsy was recorded at discharge from any hospital in Stockholm during 1980-1989, an SMR of 3.6 (95% CI 3.5-3.7) was estimated.[108] This cohort comprised a total of 53,520 person-years and 4,001 deaths. In a retrospective study of the survival status of out-patients seen in a Dutch epilepsy centre over a 40 year period (38,665 person-years, 404 deaths), the SMR was 3.2 (95% CI 2.9-3.5).[110] In a cohort of adult outpatients with epilepsy at a tertiary referral centre in the UK (1849 patient-years) the SMR was 5.1 (95% CI 3.3-7.6).[337] SMRs for institutionalised populations (i.e., patients living in epilepsy residential centres) range between 1.9 and 3.0.[111;115;326]

5.3.i Risk factors/Determinants of mortality

The higher risk of premature death does not apply equally to all people with epilepsy and serves only as a summary measure, masking important differences in mortality among the population with epilepsy. Studies of mortality in epilepsy calculate

mortality rates according to aetiology, duration and type of epilepsy, age, and sex. In its published guidelines for epidemiological studies the ILAE proposed that the epilepsies and epileptic seizures be categorised into aetiological groups: idiopathic, cryptogenic, acute symptomatic, remote symptomatic, and progressive symptomatic.[315] No studies to date have strictly adhered to the new classification scheme. Prior to this new scheme, the three major aetiological groupings usually included the idiopathic (or cryptogenic, or primary), remote symptomatic (or postnatally acquired secondary epilepsy), and (congenital) neuro-deficit group.

Idiopathic (and/or cryptogenic) epilepsy has the lowest long-term mortality with SMRs ranging from 1.5 to 1.8 in population studies[109;114;327] suggesting that mortality rates in this group are above those of the general population by only 50-80%. Other studies, however, failed to show a significant increase in mortality in this group.[116;332;339] Studies in children follow the same population trends in mortality in idiopathic and cryptogenic cases[329;333] as well as in cases without severe neurological deficit.[334]

Although the overall chances of achieving remission are similar in patients with remote symptomatic epilepsy and idiopathic epilepsy, the same is not true of their relative risk of premature death.[313] Long-term mortality is greatly increased in remote symptomatic epilepsy with reported SMRs of 2.2 (95% CI 1.8-2.7) in the Rochester study,[114] 2.3 (95% CI 1.4-3.5) in an Icelandic study,[339] 3.7 (95% CI 2.9-4.6) in the NGPSE,[116] and 3.3 (95% CI 2.4-4.5) in the Västerbotten County study.[332] Considering people with symptomatic epilepsy, the risk of death appears to be over ten times

BOX 7. Community-based studies of overall mortality of epilepsy

Study	Setting	Method	Age at entry	Person-years	SMR (95% CI)*
Alström 1950 [327]	Sweden	clinical series	23yrs	N/A	2.4 (2.0-2.8)
Voute 1967 [338]	Europe	insurance policy holders	Adults	N/A	3.1
Zielinski 1974 [321]	Warsaw	3-yr prevalence cohort	All	~20,000	1.8
Hauser et al. 1980 [114]	Rochester, MN, USA	29-yr retrospective incidence cohort	All	8,233	2.3 (1.9-2.6)
Olafsson et al. 1998 [339]	Iceland	30-yr retrospective incidence cohort	N/A	6,308	1.6 (1.2-2.2)
Loiseau et al. 1999 [340]	Gironde, France	1-yr prospective incidence cohort †	All	804	9.3 (7.9-10.9)
Lindsten et al. 2000 [332]	Sweden	11-yr prospective incidence cohort	>17yrs	850	2.5 (1.2-3.2)
Lhatoo et al. 2001 [116]	United Kingdom	14-yr prospective incidence cohort	All	11,400	2.1 (1.8-2.4) ‡
Camfield et al. 2002 [334]	Nova Scotia, Canada	>15-yr retrospective incidence cohort	28d-16yrs	N/A	8.8 (4.1-13.4)

* CI denotes confidence interval.

† Early mortality was assessed.

‡ The NGPSE study[113;116] included patients with symptomatic and unprovoked seizures.

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higher for those with congenital neurological deficit or CNS tumours, and 2-3 times higher in patients with cerebrovascular disease or alcohol abuse.[116] The reported SMR in a prevalent paediatric population with epilepsy in Australia was 49.7 (95% CI 31.7-77.9) for remote symptomatic epilepsy.[333] In a population-based study, children with disorders sufficient to cause functional neurological deficit were 22 times more likely to die prematurely than those without.[334] The authors concluded that children with remote symptomatic epilepsy and no neurological deficit are unlikely to die as a result of seizures.[334]

The neuro-deficit group, consisting of patients with gross neurological deficit and/or learning difficulties presumed to have been present or acquired at birth, has the highest long-term mortality with reported SMRs in the range of 11.0 (95% CI 6.9-16.4)[114] and 25 (95% CI 5.1-73.1).[116] The excess mortality is attributed to the small number of deaths expected in the young age group and the high death rate among children with neurological deficit, irrespective of the presence of epilepsy.[318]

Seizure type also plays a role: Patients with *absence seizures* do not appear to be at higher risk of death [114], while those with *generalised tonic-clonic seizures* carry SMRs of 3.5-3.9 for the first 5-10 years from diagnosis[114;332] and those with *myoclonic seizures* of 4.1.[114] The SMR for *complex partial seizures* was not significantly increased in the Rochester study[114] but was reported as 2.1 (95% CI 1.2-3.6) in the Västerbotten County study.[332]

Mortality risk increases with severity of epilepsy, usually assessed by seizure frequency. In one study, patients with "severe" epilepsy or frequent seizures had significantly

higher SMRs compared with patients with "slight" epilepsy or free from seizures.[328]

Patients whose seizures responded to AED treatment exhibited lower mortality than people with poorly controlled seizures (SMR 2.13 vs. 3.77 respectively).[328] In the Rochester study[114] patients entering remission had a SMR of 2 for the first five years of seizure freedom but the SMR was not significantly elevated thereafter. These results were corroborated in two recent studies assessing long-term mortality in cohorts of patients who underwent epilepsy surgery.[325;341] SMRs in patients with persistent seizures were 4.69 (95% CI 2.33-7.75)[325] and 7.4,[341] with a reported rate of death of 1.37 per 100 person-years.[325] In contrast, mortality in patients who became seizure-free post-operatively did not differ from that of the general population.[325;341].

Age-specific SMRs show increased death rates at all ages among people with epilepsy, although this increase is more pronounced in people under 50 years of age and declines sharply after age 60.[108;110;114;116;321;328;339]. SMRs have been reported for age groups up to 50 years of between 6 to 8, in comparison to SMRs of <2 for patients older than 70 years.[114;314;328] This may be explained by the high mortality in patients with neurological deficit at birth and in young patients with remote symptomatic epilepsy due to head trauma and brain tumours, as well as the highly increased risk for sudden death in younger adults with epilepsy[114;318] An important factor contributing to the high SMRs in the young is also the very low mortality observed in children and the younger age groups in the general population.

Mortality rates in epilepsy vary over *time*, being higher in the first years after diagnosis. SMRs reported for all cases for the first year were 3.8 in the Rochester study,[114] 6.6 in the NGPSE study,[116] and 7.3 in the Västerbotten County study.[332] SMRs for the first

four years ranged between 2.0 and 3.1.[114;314;339] Mortality rates declined to near normal

in years 4-9 in the NGPSE study,[116] in years 2-9 in the Västerbotten County study,[332]

and after the first ten years in the Icelandic[339] and Rochester studies.[114] Rates increased

again in years 25-29 of follow-up in the Rochester study,[114] in years 9-14 in the NGPSE

(but not in the idiopathic epilepsy group)[116] and in years 9-11 in the Västerbotten

County study.[332] Trends in the Rochester study[114] persisted for the three aetiological

groups (idiopathic, remote symptomatic, neurodeficit group) when analysed separately,

with much higher initial SMRs for the neurodeficit group. Results similar to this last

group were reported by a study of mortality in attendees of a Dutch epilepsy centre

cohort.[110]

Higher SMRs have been reported in males than females in some studies[109;110;114;191;328]

but not in others.[111;116;325;332;337]

5.4 Cause-specific mortality

Cause-specific mortality refers to deaths occurring in the population or a cohort due to a

particular cause.

5.4.i Epilepsy related deaths

Deaths attributed to epilepsy itself include suicide, treatment related deaths, SUDEP,

and seizure related deaths, such as deaths occurring in status epilepticus and accidents

caused by seizures such as drowning and burns (table 14). The proportion of deaths due

to epilepsy is described by PMR which tends to be higher in selected population studies,

ranging between 18 and 41%[105-107;110;111;115;328] than in community studies where it is

between 1 and 13%.[114;116;321;333] However, two community studies of children in

Finland[195] and Victoria, Australia[333] found the epilepsy PMR to be 45% and 22% respectively. A review of the literature from 1910 to 1974, which consisted mainly of studies in institutionalised patients, reported an average epilepsy PMR of 42.7%.[342] The wide range of the epilepsy PMR may be explained by differences in patient characteristics and population selection, diagnostic criteria, duration of follow-up, and classification of causes of death.

Deaths in **status epilepticus** (SE) follow the population trends of epilepsy related deaths and comprise up to12.5% of all deaths. Status appears to be an important cause of death, especially for patients in epilepsy hospitals and centres.[106;107;111] The *case-fatality rate* in SE may be as high as 20%, but can be much higher in patients with acute symptomatic seizures, myoclonic seizures, and elderly patients (especially those >65 years).[343;344] In a study of incident cases of generalised convulsive status epilepticus, the case fatality rate was highest in patients with a diagnosis of anoxia, CNS infection, or stroke.[344] The long-term mortality of SE was assessed in patients who survived at least 30 days after a first episode of SE in Rochester, Minnesota.[343] The overall SMR was 2.8 (95% CI 2.1-3.5), but the SMR was significantly elevated in all subgroups with symptomatic SE: acute [3.8 (95% CI 2.5-5.4)], remote [3.0 (95% CI 1.8-5.0)], and progressive [3.1 (95% CI 1.6-5.0)]. SE was considered progressive symptomatic in the presence of non-static central nervous system (CNS) conditions, such as CNS tumours and degenerative neurologic disorders.[343] There was no increase in mortality in patients without an underlying cause of SE (i.e., idiopathic/cryptogenic), suggesting -according to the authors- that SE by itself does not alter long-term mortality.[343] This finding is further supported by other studies, which report that patients who develop status

following discontinuation of AEDs or as part of unprovoked epilepsy, and children with epilepsy have low mortality rates.[345-348]

Accident related deaths comprise between 1.2 and 6.5% of all deaths in community-based stuides[114;116;321] and between 7.3 and 42% in selected population studies, with SMRs ranging from 2.4 -5.6.[105-109;111;115;326;328] People with epilepsy may sustain a fatal accident either during a seizure or as a consequence of a seizure. These could be due to traffic, burns, trauma, aspiration or drowning. The uniformly elevated SMRs and PMR suggest that all people with epilepsy are at higher risk of dying due to accidents than the general population. People with symptomatic epilepsy may be particularly at risk as is suggested in a population-based incidence cohort study in Iceland. The authors reported that the SMR for deaths due to accidents, poisonings and violence was 7.27 (95% CI 1.96-18.62) for male patients with remote symptomatic epilepsy and 1.76 (95% CI 0.47-4.51) for those with idiopathic/cryptogenic seizures.[109] In countries where bathing is favoured over showering, a higher rate of death from drowning might be expected although this has never been properly investigated.

SUDEP is defined as a 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 anatomic cause for death.[349] Specific criteria may be applied to classify SUDEP into *definite, probable* and *possible*. Patients who do not meet these criteria can be classified as *non-SUDEP deaths*, and there is also a category of *insufficient data*.[350] In the UK it is estimated that 500 deaths per annum are SUDEP.[351] Reported risk factors for SUDEP include frequent generalised tonic-clonic seizures; age 20-40 years; acquired epilepsy (primarily from traumatic brain injury or

encephalitis/meningitis); intractable epilepsy; frequent changes of AEDs; and early-onset epilepsy, with seizure severity being the strongest factor.[212;352-356] AED polytherapy may be an additional independent factor in adults[354] but not in children.[357] Most sudden epilepsy deaths are unwitnessed and occur during sleep.[358] When witnessed, most deaths occur in association with a seizure and respiratory compromise is a prominent feature.[353] In some cases, the patient begins recovering from the seizure but then has a secondary cardiac arrest, possibly related to hypoventilation.[359] Proposed mechanisms for SUDEP include central and obstructive apnoea and cardiac arrhythmia, although the exact mechanism remains unknown. SUDEP has been reported to be responsible for 2-18% of all deaths in epilepsy.[212;342;360] Interestingly, SUDEP accounted for 6 of 11 deaths in a selective group of patients with recurrent seizures following epilepsy surgery.[325] Its incidence rates range from 0.35-1.2 per 1,000 person-years in population-based studies[317;353;356;360-364] to 5 per 1,000 in referral populations[115;337;352;354;365-367] and to 1 per 100 in surgical series.[325;368] In a well-designed study, the SMR for SUDEP was 23.7 (95% CI 7.7-55.0) compared with sudden death in the general population.[356] The risk in children remains uncertain, although a rate of 1:1,500 has been estimated.[320] Children of school age with severe epilepsy and learning difficulties appear to be at high risk of SUDEP, with an incidence of sudden death 1:295 cases per year.[317] The overall age and sex standardised mortality ratio in this young cohort was 15.9 (95% CI 10.6-23).

It has been reported that people with epilepsy are at higher risk of committing **suicide** than the general population[103;105-111] but other investigators have been unable to demonstrate such an increase.[112-115] In these studies the suicide PMR range between 0 and 20% and the SMRs between 1 and 5.8. Incidence cohorts[114;116] are known to have

lower mortality rates than prevalence cohorts because they include small numbers of cases with symptomatic or severe epilepsy, which are over-represented in prevalence cohorts and which are associated with higher mortality. In addition, people who attend hospitals have higher morbidity and mortality than community cohorts. In the large prevalence study of 9,061 adult patients who were once hospitalised for epilepsy in Sweden the SMR for suicide was 3.5 (95% CI 2.6-4.6).[108] The rate of suicide may be extremely high among depressed patients with epilepsy. Major depression in epilepsy has been associated with significantly decreased self-reported quality of life, increased disability and missed work, increased medical utilisation and medical costs.[82;93] Mental illness, drug addiction, early onset of epilepsy (particularly onset during adolescence), and personality disorder have been associated with increased risk, with some evidence that risk of suicide may decline with duration of epilepsy.[102;103] People with epilepsy were reported to have a fivefold-increased risk of suicide attempts compared with the general population. Anticonvulsants, particularly barbiturates, were used in most cases of self-poisoning.[104] A literature review based on studies published up to 1983 concluded that patients with severe epilepsy had a suicide rate 5 times higher, and patients with TLE 25 times higher, than the general population.[103] A later meta-analysis by the same group concluded that the overall SMR for death due to suicide in epilepsy was 5.1 (95% CI 3.9-6.6). This was based on studies mostly published in the 1970s and 1980s, and mainly including patients with TLE, institutionalised patients, patients from surgical series, and out-patients.[117] In this analysis, the highest suicide rates were observed in patients with surgically treated TLE whose risk was increased by a factor of 80 [SMR 87.5 (95% CI 35-180)].[117] This was, however, estimated on the basis of earlier surgical series published in 1968[87] and 1969[118] that do not reflect current standards of treatment and/or patient selection criteria. Rates from these early studies may be higher

than we would expect today with modern management and less use of barbiturates. The recently published follow-up results of the UK NGPSE study with a total of 11,400 patient-years did not show any excess of suicides.[116] Another recent study reported five suicides in a 12-year period in a total of 10,739 patients with epilepsy seen at a single US centre from 1987 to 1999.[119] This number is comparable with the average number of suicides in the general US population of about one per 10,000 people per year. All suicide cases had a history of early onset (mean age 9.5 years), long-standing CPS (mean duration 29 years) and very high seizure frequency (often daily). Suicide occurred in all patients after a short interval (3 months to 3 years) of having obtained full seizure control for the first time after temporal lobectomy (3 patients), vagal nerve stimulation, or medication. These patients had been diagnosed with interictal dysphoric disorder (IDD), a syndrome described previously by the authors.[78] IDD comprises intermittent affective and somatoform symptoms, presenting with intense depressive moods with suicidal intensity in some, and with psychotic features and dysphoric symptoms (i.e., irritability, fear, anxiety) in others.[88] According to the authors, suicide in epilepsy results from specific neuropsychiatric disorders (including IDD and post-ictal depression) associated with epilepsy rather than as the result of unfortunate psychosocial difficulties imposed by the chronicity and severity of epilepsy.[78;119] Management of specific psychiatric disorders and, hence, prevention of suicide in epilepsy can be attained by appropriate use of antidepressant (tricyclic antidepressants and selective serotonin receptor inhibitors) and psychotropic medication.[119] People with epilepsy and previous psychiatric history, including a history of suicide moods or attempts, should be referred to a neuropsychiatrist with experience in epilepsy.

5.4.ii Deaths unrelated to epilepsy

Most deaths are not attributed to epilepsy and can be related or unrelated to the underlying cause of epilepsy (Table14). Deaths in the remote symptomatic group most commonly occur as a result of the underlying cause of epilepsy or from a complication of it.[114;116;195;329;333;334] Causes include neoplasia, cerebrovascular disease (CVD), ischaemic heart disease (IHD), and pneumonia. The first three causes do not contribute to mortality in children populations.[329;333]

Malignant neoplasia accounts for 16-29% of deaths in community and hospital-based studies and carries increased mortality with SMRs ranging from 1.7-4.8.[108;109;114;116;321;326;340] SMRs are significantly higher in patients with remote symptomatic seizures than in patients with seizures of unknown origin.[109] Epilepsy centre studies probably underrepresent neoplasia, as these patients tend to be admitted to other facilities.[115]

Brain tumours are an important cause of epilepsy as well as cause of death, and may contribute from ¼ to 1/3 of all deaths due to neoplasia in epilepsy.[108;114;116] It is estimated that the incidence of primary brain tumours among patients with epilepsy is 22 times higher than in the general population.[369] Reported SMRs range from 3.4-5.4[111;326;332] although in one study hospitalised patients with epilepsy appeared to be at much higher risk with a reported SMR of 29.9.[108] The question of brain tumour association with anticonvulsant exposure and/or duration of seizures was raised in a number of reports.[370-377] It appears that the excess numbers of brain tumours occurred within 5-10 years of the seizure disorder diagnosis and decreased significantly over time, which suggests that the brain tumours account for the seizures and are not due to

AED exposure.[111;369;378;379] The SMR for neoplasia remains 1.4-2.5 even when CNS tumours are excluded.[108;110;111;114;116] No specific tumour type or site showed significant excess of deaths in large studies[108;111;114] with the exception of studies showing excess deaths due to lung,[110;116] pancreatic and hepatobiliary cancer (although the latter could be artefact due to small numbers).[115] There may be a small risk of developing cancer following exposure to AEDs and a relationship between lung cancer and barbiturates and between non-Hodgkin's lymphoma and phenytoin has been shown in two large studies.[379;380] The incidence of non-CNS cancers in a population-based cohort of patients diagnosed with seizure disorder in Rochester, Minnesota was not found to be elevated in comparison to the general population.[369] In the same study, there was no association between cancer incidence and duration of seizures or use of AEDs.

People with **learning difficulties** and epilepsy are subject to mortality rates that are 5-16 times higher than in the general population.[337;381] The risk of death appears to be highest in those with generalised seizures (SMR 8.1, 95% CI 5.7-11.5), lowest in people with partial seizures without secondary generalisation (SMR 3.7, 95% CI 1.0-13.6), and intermediate in people with secondarily generalised seizures.[381] In comparison, people with learning difficulties and no epilepsy have an SMR of 1.6 (95% CI 1.3-2.0).[381] These results indicate that, in this group of patients, mortality is either increased as a result of the seizures or reflects the severity of the underlying condition. The risk of death among children with epilepsy and learning difficulties or cerebral palsy was reported as 1 per 100 person-years in one study.[109]

Cerebrovascular disease (CVD) PMR is 14-16% in population-based series[109;114;116;321] and in a large hospital-based series,[108] and 5-6% in referral populations.[106;111;115;326;328]

SMRs range between 1.8 and 5.3 reflecting a mortality spectrum from epilepsy centre cohorts to general population cohorts, with hospital cohorts in the middle.[108;111;114;116;326;332] CVD is the major cause of epilepsy among the elderly[382] and in a large Swedish hospital-based study it accounted for 44% of deaths in people with epilepsy over 75 years in whom the SMR was almost 4.[108] Patients with remote symptomatic epilepsy are at particular risk[114;116] suggesting that the underlying pathology is responsible for deaths in this group. This is supported by the finding that people with idiopathic epilepsy in the Rochester Study had a SMR for CVD of 1.4 (95% CI 0.6-2.6).[114]

PMR for **ischaemic heart disease** (IHD) are similar to those for CVD.[106;107;110;111;114;116;321;328] IHD events include angina pectoris, myocardial infarction and sudden cardiac death. The latter is defined as death in individuals who had no previous clinical diagnosis of IHD and who died within 24 hours of onset of symptoms suggestive of acute coronary insufficiency.[383] The vast majority of IHD deaths in epilepsy occur in patients over 45 years.[108] Mortality rates for IHD are not significantly increased overall for people with epilepsy, with SMRs reported in most studies between 1.1 and 1.6.[109-111;114;116;221] In contrast, an SMR for heart disease of 2.5 (95% CI 2.3-2.7) was reported in a cohort of hospitalised persons over 15 years old diagnosed with epilepsy.[108] Raised SMRs for heart disease in epilepsy have also been reported for patients under 65 years old,[221] for patients with remote symptomatic epilepsy[116;221] and patients with neurodeficit.[114;221] In the Rochester study[221] there was an increase in the incidence of myocardial infarction both in patients with idiopathic and remote symptomatic epilepsy, as well as of sudden cardiac death in patients with remote symptomatic epilepsy. There was no relationship between the use of AEDs and

incidence rates for IHD or sudden cardiac death.[221] In the Västerbotten County study of a cohort with newly diagnosed unprovoked seizures, myocardial infarction was not associated with a significantly increased SMR in epilepsy [1.5 (95% CI 0.73-3.2)].[332]

Pneumonia is a common cause of death in epilepsy especially in institutionalised patients, and often reflects a terminal event in patients with poorly controlled seizures, poor general condition and debilitation.[106;108;111;115;116;321] PMR for pneumonia range from 25% in studies of inpatients in epilepsy institutions and hospitals[106;111;115;116;321] to 5% in studies of patients in the community,[112;114;321] as well as in series based on hospital admissions and epilepsy centre attendance.[108;110] SMRs range between 3.5 and 10.3.[108;110;111;114;116] The majority of deaths due to pneumonia occur in elderly patients[108;115;116;321] which may denote increased susceptibility to pneumonia in this epilepsy population.[108;113] Pneumonia, however, is an important cause of death in children with epilepsy, especially those with remote symptomatic seizures,[333] infantile spasms and severe psychomotor retardation.[329] Pneumonia accounted for 30% of deaths in a study of children with epilepsy in the community,[333] as well as in another study of a population with onset of seizures in childhood.[195] SMR due to pneumonia in young age groups appears to be higher than in the elderly[108;110] reflecting the low incidence of this cause of death in the corresponding age group in the general non-epilepsy population and the severity of the underlying condition or its complications in children and young adults with epilepsy. In a large hospital-based study, the overall SMR for pneumonia was 4.2 (95% CI 3.6-4.8) with 40% of deaths due to pneumonia occurring in patients >75 years, in whom the SMR was 2.4 (95% CI 1.9-2.9). Although the relevant SMR was not reported, it appears that the high SMR for pneumonia was due to fewer cases but higher SMR for pneumonia in the younger age groups.

5.5 The size of the problem

In the UK, at any one time, there are at least 300,000 people treated for epilepsy.[351] The recently published National Sentinel clinical audit of deaths in people with

epilepsy in the UK commissioned by the National Institute for Clinical Excellence (NICE) looked at the post-mortem investigations and medical care received by patients who died and had epilepsy mentioned in the death certificate.[351] The audit found 2,412 deaths with epilepsy on the death certificate among all individuals who died in the UK between September 1999 and August 2000, although it could not establish the true number of deaths in people with epilepsy from national data. Epilepsy was considered to be the probable cause in 812 of these deaths (~34%) from examination of the death certificate and clinical notes from primary and secondary care as well as post-mortem findings. The audit identified a series of shortcomings in the patients' care that "may have contributed to a substantial number of potentially avoidable deaths". Findings included poor record keeping throughout primary and secondary care, deficient management (such as inadequate access to specialist care, inadequate drug management in 20% of adults and 45% of children, lack of appropriate investigations, and inconsistent follow-up), poor information to patients and their families, and inadequacies in the investigations of deaths. There were particular problems in the management of epilepsy in patients with associated problems such as learning difficulties. It is notable that only 3% of the patients who died (none of them children) were known to be seizure-free at the time of their last visit to a physician, but 7% of patients were not on antiepileptic treatment at the time of death. The audit estimated that deaths in 39% of adults and in 59% of children were "potentially or probably avoidable".

Specific measures for the prevention of SUDEP have been proposed elsewhere based on the findings of this audit.[384] Patients at risk should be identified, and they and their families educated about this possibility. Early and aggressive treatment should be directed to patients with continuing seizures (especially generalised convulsions) and should include measures to promote compliance and identification of seizure precipitants. Patients with seizures not responding promptly to treatment should be referred early to a neurologist for the classification of seizure type and epilepsy syndrome, appropriate diagnostic work-up, and development of a patient-specific treatment plan. Patients whose seizures are refractory to treatment for more than 2 years despite best efforts should be referred to a comprehensive epilepsy centre for re-evaluation and consideration of surgery, or other treatments such as vagal nerve stimulation and clinical trials of AEDs under development. Finally, pathologists should be educated and alert about SUDEP, and they need to look for evidence for or against such a diagnosis.

5.6 Conclusion

Patients with epilepsy are subject to higher standardised mortality rates than people in the general population, with overall SMRs between 2 and 3. Although numbers may vary due to differences in methodology and the population studied, findings have been fairly consistent across studies. Mortality is significantly higher in people with symptomatic epilepsy, especially those with an accompanying neurological deficit, in which case it tends to follow the mortality of the underlying cause of epilepsy. SMRs are higher in the first 5-10 years after diagnosis of epilepsy and in younger people due to the low expected mortality in this age group. People with idiopathic epilepsy and people who enter long-term remission seem also to be affected, but to a much lesser

extent. Major contributors to death in patients with epilepsy are brain tumours, cerebrovascular disorders, and pneumonia in elderly or institutionalised patients. SUDEP is the most important cause of epilepsy-related deaths, particularly in the young, and in people with frequent seizures and/or suboptimal AED treatment. Despite the adverse prognosis for particular groups of patients, it is important to realise that a proportion of seizure-related deaths, as well as SUDEP, can be prevented by optimising treatment and care for these patients. In addition, patients and their families need to be aware of the risk of death associated with epilepsy. In the event of death, appropriate post-mortem investigations should be carried out in order to classify the cause of death. The circumstances of death and the received medical care should be looked at to identify any management inadequacies.

Chapter 6

LIFE EXPECTANCY IN PEOPLE WITH NEWLY DIAGNOSED EPILEPSY

6.1 Introduction

Epilepsy is a potentially life-threatening condition and carries a risk of premature mortality. This has been consistently shown both in population-based studies and in studies of more selected populations, such as institutionalised or hospitalised patients.[12;314] Standardised mortality ratios (SMR) for epilepsy range between 2 and 3 in community studies.[12]

The higher SMRs in people with epilepsy might suggest a diminished life expectancy in this group. The mean life span of a subgroup of patients in a Polish study was 12.5 years after the onset of seizures, an average 20 years shorter than that of the general population.[321] This subgroup excluded patients whose epilepsy was due to brain tumours or cerebrovascular diseases. In a study of Finnish children with epilepsy 94% were alive 10 years after the onset of seizures, 88% 20 years after onset, and 75% 40 years after onset.[195] Ninety six percent of these children reached the age of 10 years, 89% the age of 20 years, and 80% the age of 40 years. In the same study, 87% of children with idiopathic seizures reached 40 years of age, compared with 93% of those with cryptogenic seizures, and 73% of those with remote symptomatic seizures. These studies suggest a shortening of life expectancy in people with epilepsy, the extent of which is not precisely known. Carrol and Barnes[385] suggest this shortening to be in the order of one to two years if the epilepsy is well controlled and up to five years for very severe refractory epilepsy. However, these figures are not based on precise data and reflect the authors' practice.[385]

An estimation of life expectancy in a cohort of people with epilepsy and a comparison to that of the general population is attempted here. Data from the UK National General Practice Study of Epilepsy (NGPSE), a prospective, population-based study of epilepsy were used.[323] Two previous studies using data from the NGPSE reported increased SMRs for all-cause mortality following a diagnosis of epilepsy up to a maximum of 14 years of follow-up.[113;116] In these analyses, SMRs were highest during the first years after diagnosis and declined with time.[116] The absolute reduction in life expectancy in this cohort is reported here, which was estimated using a parametric survival model based on the Weibull distribution.

6.2 Patients and Methods

6.2.i Life-Expectancy in the general population

Life expectancy at a given age in a specific population is derived from a life table for that population and is defined as the average number of years a person of that age will live when subject to the mortality rates contained in the life table.[386] It is determined by the mortality rates at each age within the specified population over the entire age range of the life table. The most recent life table (English Life Tables No. 15) was used, based on mortality in England and Wales centred on the census year 1991.[387] Separate life tables are published for men and women, and for each year from birth, and provide information on:

- the number of survivors (l_x) to age x of 100,000 live births (of the same sex who subsequently experience mortality similar to that of the population of that sex in England and Wales during 1990-1992),

- the mortality rate (q_x) between age x and ($x+1$), (defined as the number dying between age x and ($x+1$) in the same population, divided by l_x), and

- the average expectation of life (e_x) (the average number of years that those aged x will live thereafter)[387]

The *mortality rates* at each age in these Life Tables are modified as described below to estimate life expectancies for people with epilepsy.

6.2.ii NGPSE and mortality

In the NGPSE cohort[116;323] patients between 1 and 90 years old with newly diagnosed epilepsy were recruited from 275 general practices. Seven hundred and ninety two patients were followed from index seizure either to death or to the end of the follow-up period. The index seizure was the seizure leading to diagnosis of epilepsy. Five hundred sixty four patients were diagnosed with definite epilepsy -defined as the occurrence of one or more afebrile seizures- and 228 with possible epilepsy. In the first analysis, considering patients with definite epilepsy,[113] the SMR was highest during the first year after diagnosis [SMR 6.6 (95% CI 4.8 to 8.7)], approximately halved during the subsequent 3 years [SMR 3.1 (95 % CI 1.8 to 5.1)], and then halved again between 4 and 6 years [(SMR 1.6 (95% CI 0.6 to 3.5)]. The SMR declined to 1.3 (95% CI 0.5 to 2.9) 6 to 8 years after diagnosis, which, though suggesting higher mortality than the general population, is not statistically significant. The second analysis[116] with follow-up extended to 14 years, produced a similar pattern, with a significantly increased SMR of 1.8 (95% CI 1.1 to 2.7) even 9 to14 years after diagnosis. SMRs differed according to the aetiological grouping of epilepsy (Box 8): 1.3 (95% CI 0.9 to 1.9) for the idiopathic/cryptogenic group (N=346), 3.7 (95% CI 2.9 to 4.6) for the remote symptomatic (N=119), 3.0 (95%CI 2.0 to 4.3) for the acute symptomatic (N=83), and 25 (95%CI 5.1 to 73.1) for the congenital deficit group (N=16).[116] The highest SMRs were observed in the 0-49 and 50-59 years group with definite epilepsy [5.4 (95%CI 3.2

to 8.4) and 8.4 (95%CI 5.3 to 12.7) respectively]. It is expected that the increased SMRs

will produce a reduction in life expectancy compared with the general population.

BOX 8.

Definitions of aetiological epilepsy groups in the NGPSE,[323]and number of people and number deaths per group in the current study.

Idiopathic/Cryptogenic: patients with idiopathic seizures or seizures of no known predisposing cause [344 people; 45 deaths]

Acute symptomatic: patients with seizures starting within 3 months of an acute insult (eg, alcohol-related seizures and metabolic disorders) [83 people; 37 deaths]

Remote symptomatic: patients with seizures associated with central nervous system lesions acquired postnatally (eg, previous brain trauma and cerebrovascular accident) [83 people; 57 deaths]

Congenital deficit: patients with seizures associated with congenital or perinatally acquired neurological abnormality (eg, cerebral palsy and neurological deficits present at birth) [16 people; 3 deaths]

For the purpose of this analysis, subjects were divided into 2 groups, idiopathic/cryptogenic and symptomatic. The latter group comprised patients previously in the acute symptomatic, remote symptomatic and congenital deficit groups with the exceptions of patients with epilepsy due to brain tumours who were excluded from the analysis.

6.2.iii NGPSE and life expectancy

Complete information on survival status in the NGPSE is available up to 31 December

2001, which extends observations reported previously by four years[116] and updates

previous analyses both for numbers of deaths, and for interval of follow-up from index

seizure. For those with definite epilepsy there have been 177 deaths (31%), with median (quartiles) follow-up of 15.4 (10.9, 16.4) years, and a total of 7,147 person years. The present analysis excluded 38 patients (35 deaths) for whom the likely aetiology at diagnosis of epilepsy was a brain tumour (Box 8). For each patient, the interval from date of index seizure to death or 31 December 2001, whichever is earlier, was calculated in weeks. These data together with various covariates were fitted to the Weibull survival model, using the program BMDP 2L (see Box 9). Covariates used were gender, age at diagnosis (and its square), and idiopathic/cryptogenic onset (yes/no), together with the product of the last factor and age at diagnosis (that is, the interaction between them). As expected, the value of the shape parameter (Box 9), was less than one, indicating decline in risk of premature death with interval from diagnosis.

Annual mortality rates were predicted for each year following diagnosis of epilepsy for different combinations of the covariates gender, age at diagnosis, and idiopathic/cryptogenic onset. Diagnosis was assumed to occur six months after a birthday, and the death rate at that age was estimated by averaging the corresponding rate from the English Life Tables and that predicted by the Weibull model at a quarter year after diagnosis. Subsequently, the predicted death rates from the Weibull model (at mid-year points) replaced those in the English Life Tables, for as long as they exceeded them; estimates of life expectancy from the time of diagnosis, and subsequent years thereafter, were then calculated from the revised life table. Life expectancy calculations were performed using a Microsoft Excel database.

BOX 9

Weibull hazard function

This is one of several flexible functions that are used to model survival data; it has two parameters, λ and γ, and the hazard function (risk of death), h(t), is defined by:

$$h(t) = \lambda.\gamma.t^{\gamma-1}, \tag{1}$$

where t is the interval from start of follow-up. The two parameters determine the shape (γ) and scale (λ) of the hazard function, which increases when $\gamma>1$, and decreases when $\gamma<1$. When γ is equal to one h(t) is equal to the constant, λ, so the risk of death does not change with the interval from start of follow-up, and the survival curve is exponential.[388] The two parameters, γ and λ, are determined by fitting the Weibull model to survival data using statistical software such as the program BMDP 2L.[389] With the NGPSE data, the risk of death decreases with time from diagnosis, so we expect γ to be less than one.

Although the risk of dying depends upon the interval from diagnosis, it also varies with other factors (covariates) such as age and gender, and these must be taken into account when fitting the Weibull model. This is achieved by using a more general form of the model represented in equation (1), specifically:

$$h(t) = \exp(B_1.x_1 + B_2.x_2).\lambda.\gamma.t^{\gamma-1}, \tag{2}$$

where "exp" denotes the exponential function, B_1 and B_2 are regression coefficients estimated when fitting equation (2) to data, and x_1 and x_2 denote the corresponding covariates (for example, age and gender). Equation (2) is similar in form to the Cox proportional hazards regression model, the only difference being that the underlying hazard function is estimated parametrically by the Weibull model, whereas in the Cox model it is estimated directly (that is, without a functional form, or *semi-parametrically*) from the data. Once the parameters, γ and λ, B_1 and B_2, have been determined by fitting equation (2) to data, the risk of death at time, t, after diagnosis, can be determined and plotted for any appropriate values of the covariates.

The output from program BMDP 2L does not tabulate directly the values of the parameters in model (2) above, instead it uses a different parametrization of the Weibull model.[388] Specifically, the program lists values of a constant (μ), a scale parameter (σ), and regression coefficients (α_i), where λ is equal to $exp(-\mu/\sigma)$, γ equals $1/\sigma$, and B_i is equal to $-\alpha_i/\sigma$. Further, since the follow-up intervals are recorded in weeks in the NGPSE, and mortality rates per year are required, the time-scale in equation (2) has to be re-scaled; this is achieved by multiplying λ (the scale parameter) by 52.18^{γ} (average number of weeks per year raised to the power, γ).

Using the Weibull survival model as described above life expectancy was estimated for men and women. Life expectancy was then compared to that in people of the same age and sex in the general population according to the English Life Tables. The estimated reduction in life expectancy is expressed as years of life lost.

6.3 Results

In this analysis of 526 patients, age at diagnosis ranged from less than one to over ninety years, with deciles at 6, 11, 16, 20, 27, 38, 50, 63, and 73 years. Age at death (142 patients) ranged from 3 to 97 years, with 20 (14%) under 50 years, 31 (22%) between 50 and 69 years, and 91 (64%) aged over 69 years; 54 (38%) were eighty years and over. The number of deaths in each aetiological group is given in Box 6. Estimated years of life lost and percentage of normal life expectancy lost by age at diagnosis, and years after diagnosis are shown in Tables 14 and 15 for men and women.

The reduction in life expectancy is minimal for people with idiopathic/cryptogenic epilepsy, who have about the same life expectancy as the general population. In this group, the reduction of life expectancy tends to be less than 2 years at age 50 or over and is less than one year before age 30. Women with symptomatic epilepsy lose 11 years of life and men 12 years. The negative impact on life expectancy in people with symptomatic epilepsy is greater in the young and declines progressively with advancing age at diagnosis (Tables 14 & 15). People with symptomatic epilepsy continue to experience a decreased life expectancy even after 20 years from diagnosis (3 years lost in men and women diagnosed at age 20) (Table 15).

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Men with symptomatic epilepsy appear to suffer a slightly greater reduction in life expectancy than women when the diagnosis of epilepsy is made in the first 10 years of life and in the first 5 years from diagnosis. When, however, the number of years lost is expressed as a percentage of the life expectancy then the differences become less obvious (Table 15). There is a trend towards diminishing number of years of life lost the longer someone survives and towards a progressively increased percentage of normal life expectancy lost with advancing age at diagnosis.

6.4 Discussion

People with newly diagnosed epilepsy appear to have a reduced life expectancy compared with the general population. The number of years of life lost is considerably higher for people with symptomatic epilepsy than for those with idiopathic or cryptogenic epilepsy at any age and, with longer survival, approaches zero.

To the best of my knowledge, there is no other publication reporting life expectancy estimates in people diagnosed with epilepsy so these results cannot be directly compared with other work. Some comparison, however, can be made with a retrospective study[321] of 218 people with prevalent epilepsy who died between 1967 and 1969 in Warsaw, the only study where information on life expectancy was reported. In this cohort, the observed average survival was 38 years shorter than expected in people with onset of epilepsy in the first decade of life and this loss diminished progressively to 15.5 years with onset of epilepsy after the age of 40. The average shortening of survival was 25 years when the cause of epilepsy was unknown. Although not directly comparable, the reported shortenings of survival appear to be far in excess of the estimates from our study. This may be explained by the Polish study being a prevalent

cohort with 55% of patients having secondary epilepsy and 58% having permanent neurological deficit.[321]

Men with symptomatic epilepsy appear to suffer a slightly greater life expectancy loss, possibly due to higher mortality associated with head injuries. When the number of years of life lost is expressed as a percentage of life expectancy in the general population the differences between the sexes tend to disappear.

The gradual reduction of years of life lost over time from diagnosis as estimated in this study is consequent upon the statistical model used and is based on the declining risk of death over time from diagnosis in the NGPSE. This, however, may not be entirely the case in other populations for the whole length of follow-up[114;332] even in the NGPSE during the last five years of follow-up (years 4-9: SMR 1.5; years 9-14: SMR 1.8).[116]

The Weibull model confers both advantages and disadvantages. It is easy to fit to survival data using standard statistical software, and the incorporation of important covariates, such as age, is also simple. The Weibull model, though, imposes either a decreasing, constant, or increasing risk of death (according to whether the shape parameter is less than, equal to, or greater than one) over the entire follow-up period from diagnosis. It has already been demonstrated that within the NGPSE cohort the risk of death declines with interval from diagnosis. This assumption, however, can only be valid for comparatively short periods since annual mortality rates increase with age.[387] A more realistic survival model that allows a bathtub (or U-shaped) hazard requires a more complicated hazard function and a period of follow-up that is longer than that

available for the NGPSE. Choice of covariates and the way in which they influence overall mortality rates is partly limited by the amount of data available; just 142 deaths are considered, a number that is small, and can provide only limited guidance about influential factors and their form; age and gender were included, since they are known to affect annual mortality rates, as well as idiopathic or cryptogenic onset since these may well influence the mortality rates. An interaction between age at diagnosis and idiopathic or cryptogenic onset is also included since this was of statistical importance. The use of a Weibull model does not allow for the incorporation of a time-dependent covariate, such as seizure recurrence. Therefore, it was not feasible to determine the extent to which seizures contribute to shortening of life expectancy. In the previous analysis of the NGPSE cohort[116] it was found that seizure recurrence and antiepileptic drug treatment did not influence mortality rate.

The exclusion of patients with brain tumours aims to provide a better estimate of life expectancy in cases of acquired epilepsy. This is based on the premise that the tumour and not the occurrence of seizures determines mortality in people with epilepsy with an underlying brain tumour. Information on survival following diagnosis of a brain tumour is available elsewhere.[390] The majority of deaths in the NGPSE were due to neoplasia, ischaemic heart disease, cerebrovascular disease and pneumonias.[116] These conditions are associated with increased mortality irrespective of the development of epilepsy or not.[381;390-392]

In modelling the effect of epilepsy on mortality rates certain crucial assumptions were made. First it is assumed that the mortality rate increases suddenly at the age of diagnosis and not before. This assumption may not be valid,

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Men									
Age at diagnosis (years)	Years after diagnosis								
	0	1	2	3	4	5	10	15	20
1	0.6	0.6	0.5	0.5	0.4	0.4	0.2	0.0	0.0
5	0.6	0.6	0.5	0.4	0.4	0.3	0.1	0.0	0.0
10	0.6	0.6	0.5	0.4	0.4	0.3	0.2	0.1	0.0
20	0.8	0.8	0.7	0.7	0.6	0.5	0.3	0.1	0.0
30	1.2	1.1	1.0	0.8	0.7	0.6	0.2	0.0	0.0
40	1.3	1.2	1.0	0.8	0.7	0.5	0.1	0.0	0.0
50	1.4	1.2	0.9	0.7	0.5	0.4	0.0	0.0	0.0
60	1.3	1.1	0.8	0.5	0.3	0.2	0.0	0.0	0.0
70	1.6	1.4	1.0	0.6	0.4	0.2	0.0	0.0	0.0

Women									
Age at diagnosis (years)	Years after diagnosis								
	0	1	2	3	4	5	10	15	20
1	0.6	0.6	0.6	0.6	0.5	0.5	0.3	0.2	0.1
5	0.7	0.7	0.6	0.6	0.6	0.5	0.3	0.2	0.1
10	0.8	0.7	0.7	0.6	0.6	0.5	0.3	0.2	0.1
20	0.9	0.9	0.8	0.7	0.7	0.6	0.3	0.1	0.0
30	1.1	1.0	0.9	0.8	0.7	0.6	0.2	0.0	0.0
40	1.3	1.2	1.0	0.8	0.7	0.6	0.1	0.0	0.0
50	1.5	1.3	1.1	0.9	0.7	0.5	0.0	0.0	0.0
60	1.7	1.5	1.2	0.9	0.7	0.5	0.0	0.0	0.0
70	2.3	2.0	1.5	1.1	0.8	0.5	0.0	0.0	0.0

Years of life lost

(Based on gender and age specific annual mortality rates from English Life Tables No 15, and from a Weibull survival model from age of diagnosis of epilepsy with gender, age at diagnosis and its square, idiopathic / cryptogenic onset, and its interaction with age at diagnosis, as covariates)

Table 14: Estimated years of lost life expectancy following diagnosis of idiopathic/ cryptogenic epilepsy

Men									
Age at diagnosis (years)	Years after diagnosis								
	0	1	2	3	4	5	10	15	20
1	13 (*18*)	13 (*18*)	12 (*18*)	12 (*17*)	12 (*17*)	11 (*16*)	9 (*14*)	7 (*12*)	6 (*10*)
5	13 (*18*)	12 (*18*)	12 (*18*)	11 (*17*)	11 (*17*)	10 (*16*)	8 (*14*)	7 (*12*)	5 (*10*)
10	12 (*18*)	12 (*18*)	11 (*18*)	10 (*17*)	10 (*17*)	10 (*16*)	8 (*14*)	6 (*12*)	4 (*9*)
20	11 (*20*)	10 (*20*)	10 (*19*)	9 (*18*)	9 (*18*)	8 (*17*)	6 (*14*)	4 (*11*)	3 (*8*)
30	10 (*22*)	10 (*22*)	9 (*21*)	8 (*20*)	8 (*19*)	7 (*18*)	5 (*14*)	3 (*10*)	1 (*6*)
40	9 (*26*)	9 (*25*)	8 (*24*)	7 (*23*)	7 (*21*)	6 (*20*)	4 (*14*)	2 (*8*)	0 (*2*)
50	8 (*30*)	8 (*30*)	7 (*28*)	6 (*25*)	5 (*24*)	5 (*22*)	2 (*12*)	1 (*4*)	0 (*0*)
60	7 (*37*)	6 (*36*)	5 (*33*)	5 (*30*)	4 (*27*)	3 (*24*)	1 (*11*)	0 (*1*)	0 (*0*)
70	5 (*47*)	5 (*46*)	4 (*42*)	4 (*38*)	3 (*34*)	3 (*30*)	1 (*11*)	0 (*0*)	0 (*0*)
Women									
Age at diagnosis (years)	Years after diagnosis								
	0	1	2	3	4	5	10	15	20
1	11 (*14*)	11 (*14*)	11 (*14*)	10 (*14*)	10 (*13*)	10 (*13*)	8 (*12*)	6 (*10*)	5 (*9*)
5	11 (*15*)	11 (*14*)	10 (*14*)	10 (*14*)	9 (*13*)	9 (*13*)	7 (*11*)	6 (*10*)	4 (*8*)
10	10 (*15*)	10 (*15*)	10 (*14*)	9 (*14*)	9 (*13*)	8 (*13*)	7 (*11*)	5 (*10*)	4 (*8*)
20	10 (*16*)	9 (*16*)	9 (*15*)	8 (*15*)	8 (*14*)	8 (*14*)	6 (*11*)	4 (*9*)	3 (*7*)
30	9 (*18*)	9 (*18*)	8 (*17*)	8 (*16*)	7 (*16*)	7 (*15*)	5 (*12*)	3 (*8*)	2 (*5*)
40	9 (*22*)	8 (*21*)	8 (*20*)	7 (*19*)	7 (*18*)	6 (*17*)	4 (*12*)	2 (*7*)	1 (*3*)
50	8 (*27*)	8 (*26*)	7 (*24*)	6 (*23*)	6 (*21*)	5 (*20*)	3 (*12*)	1 (*6*)	0 (*1*)
60	7 (*34*)	7 (*33*)	6 (*30*)	6 (*28*)	5 (*26*)	4 (*24*)	2 (*13*)	0 (*3*)	0 (*0*)
70	6 (*44*)	6 (*43*)	5 (*39*)	4 (*36*)	4 (*33*)	3 (*29*)	1 (*12*)	0 (*0*)	0 (*0*)

Years of life lost (*percentage of normal life expectancy lost*)

(Based on gender and age specific annual mortality rates from English Life Tables No 15, and from a Weibull survival model from age of diagnosis of epilepsy with gender, age at diagnosis and its square, idiopathic / cryptogenic onset, and its interaction with age at diagnosis, as covariates)

Table 15: Estimated years of lost life expectancy following diagnosis of symptomatic epilepsy

particularly in individuals with stroke, cerebral palsy or mental retardation (MR), although the occurrence of epilepsy in people in the latter two conditions increases mortality further (SMR for MR only 1.6 vs. 5.0 for MR and epilepsy vs. 5.8 for MR and epilepsy and cerebral palsy).[381] It is likely that any pathological or physiological process that ultimately manifests as seizures starts before the diagnosis of epilepsy is established, however there is no means of determining exactly when this happens. In addition it is assumed that the death rate at age of diagnosis is an average of that from the English Life Tables (first six months), and that predicted by the Weibull model at 3 months from diagnosis (second six months). Thereafter, it is assumed that mortality rates will follow those from the Weibull model until they are exceeded by the annual rates in the standard population. Theoretically the "Weibull rates" themselves should perhaps increase as they converge to meet the standard population rates. Finally, in fitting a single model for mortality across the entire age range, we require broad age distributions for both age at diagnosis, and age at death. In this analysis of 526 patients, age at diagnosis ranged from less than one to over ninety years and age at death ranged from 3 to 97 years. While the idiopathic/cryptogenic group can be considered relatively homogeneous in terms of mortality, the symptomatic group is heterogeneous and includes people who may differ appreciably in terms of the aetiology and mortality of epilepsy.

The tables give predictions of years of life lost according to broad aetiologic groups of epilepsy, as well as age at, and interval from, diagnosis. They aim to provide a rough estimate of the average decrease in life expectancy in people with epilepsy (in UK). Their predictive value for an individual patient who falls in one of the two aetiologic groups cannot be established yet, particularly in the case of the symptomatic epilepsy

group, given its heterogeneity. In addition, these predictions refer to a population with newly-diagnosed epilepsy and may overestimate survival in the case of a prevalent cohort or of specific subgroups of patients, such as those with refractory epilepsy, and those referred for epilepsy surgery.[325] Nevertheless, these estimates may prove useful in clinical practice and the counselling of patients and their relatives, given the paucity of information in this area. These data may be useful in the medico-legal arena, where life expectancy is crucial in the calculation of damages resulting from acquired brain insults that may be complicated by epilepsy.

SMRs are increased in all types of epilepsy (with the possible exception of typical absence seizures).[114] This model shows that in people with newly diagnosed epilepsy higher SMRs translate into a decrease in life expectancy, which is more pronounced in those with symptomatic epilepsy. Clearly, more work is needed in this area to produce more accurate estimates of life expectancy for the particular epilepsy types or syndromes, aetiology, presence of comorbid conditions, and refractoriness to treatment.

GENERAL CONCLUSION

GENERAL CONCLUSION

Epilepsy is a multifaceted and multifactorial condition with particular management considerations for different groups of patients and a significant impact on the lives of affected people and the society. Apart from the effect of seizures and their treatment on the individual, the impact of epilepsy on the individual can be further burdened by coexisting disorders and an increased risk of death.

A number of different definitions exist for "comorbidity" but for the purposes of this thesis the term refers to the disorders that co-occur more frequently in people with a given condition than would be expected in the general population without the condition, irrespective of causal association. I have studied the comorbidity of epilepsy at a general practice level in the UK using data from the GPRD, reviewed the relevant literature on psychiatric comorbidity, and discussed the association of epilepsy with a number of somatic disorders that occur more frequently in epilepsy. The psychiatric comorbidity includes organic and non-organic psychoses (including schizophrenia), alcohol dependence, neuroses and depression. Some interictal psychiatric disorders, such as schizophrenia-like psychosis of epilepsy and interictal dysphoric disorder appear to occur exclusively in epilepsy. These, together with the periictal psychiatric manifestations, such as forms of anxiety, depression and psychosis, appear phenomenologically different from those in people without epilepsy, although this is not yet recognised in the current disease classification systems. The somatic comorbidity commonly includes brain tumours and meningiomas, neurodegenerative disorders (including Parkinson's disease, Alzheimer's disease and other dementias), cerebrovascular accidents (including TIAs), congenital heart disease,

gastrointestinal bleeding (especially from the upper GI tract), and pneumonias. Other disorders less strongly associated with epilepsy include neoplasias (only in men), peptic ulcers, diabetes mellitus, asthma, chronic bronchitis, emphysema (in younger adults), migraine, heart failure, and ischaemic heart disease. This list is not exclusive and other disorders (not studied here) may also occur more frequently in epilepsy. Eczema, rheumatoid arthritis, and osteoarthritis do not appear to be more frequent in epilepsy. The risk of somatic disorders across the diagnostic groups (ICD-9 categories) was increased in people with epilepsy with the exception of musculoskeletal and connective tissue disorders in older adults. Congenital anomalies were increased in younger adults with epilepsy, but perinatally acquired conditions were not (probably related to poor survival in this group).

The specific conditions studied here could cause epilepsy directly (*eg* stroke or tumour) or indirectly (*eg* congenital heart disease –via hypoxia/ischaemia or stroke), result from epilepsy (*eg* fracture following a seizure, depression or anxiety) or be associated with epilepsy via shared genetic (*eg* depression or migraine) or environmental factors (*eg* migraine, via head injury, gastrointestinal bleeding, via use of aspirin). In some cases epilepsy may indicate the severity of the underlying condition (*eg* degenerative conditions such as Alzheimer's disease). In general terms, comorbidity could be characterised as causal or resultant, depending on its cause and effect relationship with epilepsy.

Analysis of data from the MSGB4 showed that people with epilepsy make a higher utilisation of health services compared with people without the condition in the community. They require more visits to the general practitioner, more home visits by

the general practitioner, and more referrals to secondary care. I have shown that these people visit their GP more often for a number of comorbid disorders. It is, therefore, possible that the presence of comorbidity increases health care needs in this population, although this could not be shown directly by the data. The study of comorbidity can provide information for public health and the planning of health services. In the UK, services for epilepsy in both primary and secondary care are often fragmented and do not adequately meet the needs of people with epilepsy. This has been recognised and there is now greater awareness of the need to improve health services for this group.[393]

Mortality in epilepsy can reflect the mortality of the underlying conditions causing epilepsy or be associated with the effect of seizures. A review of the literature presented here showed that epilepsy carries an excess mortality, which is 2 to 3 times higher than in the general population and is expressed as the SMR. This mortality does not affect all patients equally, but is more pronounced in people with symptomatic epilepsy or epilepsy due to neurological deficit at birth than in people with idiopathic or cryptogenic epilepsy. Cause-specific SMRs in epilepsy show increased mortality from neoplasia (including brain tumours), cerebrovascular and ischaemic heart disease, pneumonias, and learning difficulties, which are comorbid in epilepsy. Therefore, it is safe to conclude that the presence of comorbidity increases mortality in epilepsy. Emphasis should be given to preventable causes of death in epilepsy, such as SUDEP, drowning and suicide.

Data on mortality from the NGPSE cohort was used to estimate life expectancy in people with newly diagnosed epilepsy by employing a survival model. I have found

that the increased mortality risk translates into reduced life expectancy in people with epilepsy. This is only minimal in people with idiopathic/cryptogenic epilepsy and considerable in people with symptomatic epilepsy, suggesting again the adverse role of comorbidity in the risk of death.

People with epilepsy in the community who visit their GP suffer more frequently from a number of psychiatric and somatic disorders, which can be associated with increased mortality and, subsequently, reduced life expectancy. These people also have increased health care needs, which may –to an extent- be due to presence of disorders comorbid with epilepsy.

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