

What is epilepsy?

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Introduction

- Epilepsy is a tendency to suffer recurrent epileptic seizures (📖 see Chapter 3a, pp.61–73 for detailed descriptions of epileptic seizures).
- Pragmatically, epilepsy can be defined as having two or more unprovoked epileptic seizures occurring within a time frame of 2 years. The term '**unprovoked**' refers to the absence of acute conditions that can produce seizures in patients who do not normally have seizures (conditions such as hypoglycemia, alcohol withdrawal, hypercalcemia, encephalitis, electroconvulsive therapy, etc.; 📖 see epileptic seizures without epilepsy, pp.156–157).
- In a small proportion of patients with epilepsy, seizures can be triggered by specific stimuli that do not trigger seizures in the general population (e.g. flashing lights, visual patterns, reading). This is called reflex epilepsy.
- Epilepsy is one of the most common serious neurological conditions.
- Epilepsy can affect any age group from any socio-economic background.

The epilepsies

- The term 'epilepsy' includes many different disorders. Hence, there is currently a trend towards using the term 'the epilepsies'.
- The epilepsies identify patients who experience recurrent unprovoked seizures with a vast range of underlying aetiologies.
- The epilepsies can be subdivided into 'syndromes'. An epilepsy syndrome is a cluster of signs and symptoms that occur together with a frequency higher than chance due to a common cause. They define a unique epilepsy condition associated with specific clinical history, seizure types, EEG findings, and prognosis.
- There are approximately 30 different syndromes and around 40 different seizure types.¹

Incidence

- The incidence is the number of newly diagnosed cases of a condition within a period of time (usually 1 year).
- In the UK, the annual incidence is approximately 46 per 100,000 or 0.46 cases per 1000 population.
- Approximately 27,400 new cases are diagnosed per year or 75 new cases each day in the UK.
- It is estimated that the incidence of epilepsy in developing countries is approximately 100 per 100,000 people per year (estimates vary from 49.3–190).

Prevalence

- The prevalence of a disorder is the proportion of a population with the disorder at a given time.
- The overall prevalence of epilepsy is around 1 in 131 people (approximately one tenth of the prevalence of diabetes)
- Approximately 300,000 people in the UK have epilepsy.¹
- It is estimated that the total number of people under the age of 18 years with a diagnosis of epilepsy is approximately 42,000 or 1 in 242.
- The highest prevalence is among those above the age of 65 years. The total is approximately 105,000 or 1 in 91.¹
- Epilepsy prevalence is 25% higher in the most socially deprived areas compared to the least socially deprived.³
- The World Health Organization (WHO) has estimated that around 50 million people in the world have epilepsy at any one time and the life time prevalence is approximately 100 million people.⁴

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3. Purcell B, Gaitatzis A, Sander JW, et al. (2002). Epilepsy prevalence and prescribing patterns in England and Wales. *Health Statistics Quarterly*, **15**, 23–30.
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Useful contact

- www.ilae-epilepsy.org—website of The International League Against Epilepsy (ILAE).

Prognosis

Remission

The prognosis of epilepsy has traditionally been considered poor. However, between 70–80% of patients become seizure free with medical treatment. The prognosis largely depends on the specific epilepsy syndrome and its aetiology. A question often asked in clinical practice and in the literature is if the prognosis of epilepsy is the same regardless of whether it is treated or untreated with drugs. In other words, whether medical treatment alters the natural evolution of epilepsy.

Definitions

- **Terminal remission:** a seizure free period of 5 years or more lasting to the time of the most recent follow up.
- **Chronic epilepsy:** epilepsy still active 5 years after onset.
- **Prognosis:** the probability of entering terminal remission once a pattern of recurrent epileptic seizures has been established.

Prognosis after a single seizure

The risk of suffering recurrent seizures after having a single seizure is unclear. Estimates vary between 27–81%. Hospital-based studies show lower values than community-based or studies that include patients after 24 hours of the first seizure. This may be due to the fact that the risk of having a second seizure after a first seizure decreases with time.

Risk factors for recurrence after a first seizure

Family history: debatable, perhaps for idiopathic epilepsies.

Etiology: recurrence 12 months after a first seizure was 100% if congenital neurological deficits were present, 75% after acquired central nervous system (CNS) lesions and 40% if associated with an acute precipitant.¹

Neurological abnormalities: increased risk if neurological examination is abnormal, but only in symptomatic epilepsies.

EEG abnormalities: increased risk, particularly for idiopathic epilepsies.

Head injury: The risk of epilepsy is about 2% if associated with mild trauma (amnesia or loss of consciousness (LOC) <30 min and no cranial fracture); 2–5% if moderate trauma (non-depressed skull fracture, 30 min <amnesia or LOC <24 hours); 12–15% after severe head injury (intracranial bleeding, brain contusions, dural tear, amnesia or LOC > 24 hours); 50% after missile or penetrating injury. Early seizures (within a week of injury) are not epilepsy but increase the likelihood of having epilepsy later.

Intracranial infection: any intracranial infection increases the risk of epilepsy. Postnatal meningitis, brain abscess, and encephalitis increase the risk 3-fold.

Seizure type: partial (focal) non-convulsive seizures are more likely to recur than convulsive seizures. Nocturnal seizures are also likely to recur.

Early medical treatment: appears to reduce the risk of recurrent seizures:²

- After 24 months: 26% risk if treated versus 51% if untreated.
- After 12 months: 50% risk if treated versus 67% if untreated.
- After 36 months: 57% risk if treated versus 78% if untreated.

Natural history of treated epilepsy

Newly diagnosed epilepsy can be defined as having two or more unprovoked seizures. It is unclear whether medication should be started after a single unprovoked seizure. After a second unprovoked seizure medication should be started. Under these circumstances:

- The probability of remission within the first year is 65–80%.
- The likelihood of remission is lower for complex partial than for secondarily generalized seizures (remission rates 16–43% versus 48–53%).
- The likelihood of remission is lower in the presence of multiple seizure types, neurological deficits, behavioural, or psychiatric disturbances.
- No particular antiepileptic drug appears to be better in population studies, but individual patients and syndromes may respond better to some antiepileptic drugs.
- Remission rates increase with time: 42% after 1 year; 65% after 10 years, 76% after 15 years.³

Once epilepsy becomes chronic, 20–30% of patients do not enter remission (confirmed by hospital based and community studies); only 20% of patients have seizure free periods; and only a few eventually become seizure free on antiepileptic drugs (AEDs).

The majority of patients on AED treatment eventually become seizure free and drug withdrawal is contemplated. The overall risk of seizure relapse after drug withdrawal is 11–41%. The risk of recurrence with withdrawal is lower in children than in adults. The risk of relapse after AED withdrawal is higher in the presence of long history of seizures, more than one seizure type, structural brain lesions, neurological signs, learning difficulties, history of remissions and relapses, juvenile myoclonic epilepsy, acute symptomatic seizures, and EEG abnormalities.

Natural history of untreated epilepsy

Most of what we know about the natural history of epilepsy is from treated patients. This raises two questions that have not been satisfactorily addressed in the literature:

- Is there remission without treatment?
- What is the effect of early treatment on prognosis?

Spontaneous remission without treatment

The prevalence of epilepsy in developed and developing countries seems to be similar, suggesting that remission rates are similar. Measured remission rates in developed and developing world are also similar (40–50%). Since epilepsy in the developed world is usually treated and in the developing world is largely untreated, these findings raise the question of whether medical treatment affects prognosis.

Effects of early treatment on prognosis

Around 50% of treated patients remit in the second 6 months after a previous untreated 6 month period in Kenya, Ecuador, and Malawi. This is similar to that reported with treated epilepsy, suggesting that early treatment may not improve remission rates. However, this does not exclude an effect on prognosis (see Risk factors for recurrence after a first seizure).

Prognosis of specific syndromes

The prognosis in epilepsy largely depends on the underlying syndrome (see Chapter 3b, pp.75–130). The prognoses of a few syndromes are summarized here as examples:

- **Benign familial (idiopathic) neonatal convulsions** ('5th day fits'): only 10% have epilepsy later in life.
- **Neonatal convulsions** (occurring within the first 4 weeks of life): these affect 0.5% of infants. 30% die within the year; 25% suffer seizures into adulthood or have learning difficulties or spasticity; only 40% fully recover. Poor prognostic factors are prematurity, early onset seizures (first 2 days), focal brain lesion or malformation, intracranial bleeding, inborn errors of metabolism, abnormal EEG. The prognosis is better if no aetiology is found.
- **Idiopathic generalized epilepsies**: these make up one third of all epilepsies under 20 and generally have good a prognosis:
 - *Childhood absence epilepsy*: 80% become seizure free. Poorer prognosis if tonic–clonic convulsions or other seizure types occur.
 - *Juvenile absence epilepsy*: slightly worse outcome than in childhood absence epilepsy.
 - *Juvenile myoclonic epilepsy*: good response to treatment, but seizures recur if treatment stops; often requires lifetime treatment.
 - *Epilepsy with generalized tonic–clonic seizures on awakening*: seizures remit in most; no mental deterioration.
- **Idiopathic focal epilepsies**: generally good prognosis with complete seizure remission. In focal epilepsy with centrotemporal spikes (Rolandic epilepsy), only 2% have lifelong seizures; in other idiopathic focal epilepsies, up to 10% have lifelong seizures.
- **Symptomatic/cryptogenic generalized epilepsies**: neurological and/or cognitive impairment is present in 90% of patients. Prognosis depends on the underlying syndrome but is generally poor:
 - *Infantile spasms* (West syndrome): one in five die and 90% of survivors suffer learning difficulties and chronic epilepsy.
 - *Lennox-Gastaut syndrome*: 60% of patients suffer status epilepticus (convulsive or non-convulsive). Seizure remission occurs in 10%.
 - *Severe myoclonic epilepsy in infancy*: onset in first year of life, generalized tonic–clonic and myoclonic seizures. 16% of patients die within 10 years of onset, all survivors have uncontrolled seizures, and 90% severe learning difficulties.
- **Symptomatic/cryptogenic focal (partial) epilepsies**: prognosis depends on the underlying lesion. Poorer seizure prognosis in congenital lesions (malformations, tuberous sclerosis, Sturge–Weber syndrome). Surgery can be a treatment option. Excellent response to surgery in mesial temporal sclerosis.
- **Epilepsia partialis continua (Kojewnikow's syndrome)**:
 - *Rasmussen's encephalitis*: progressive, neurological deficits and mental impairment, antiepileptic drugs are generally not effective, surgical treatment should be considered.
 - *Dysplastic lesions, tumours, vascular malformations*: outcome depending on cause.

- **Epilepsy with continuous spike-and-wave during slow wave sleep:** usually this is a type of symptomatic generalized epilepsy. There is an identifiable cause in 20-30% (meningitis, birth injury, cytomegalovirus infection). It is associated with developmental arrest and behavioural difficulties. The EEG abnormality is age dependent, and seizures remit in many patients but learning and behaviour difficulties tend to persist.
- **Landau-Kleffner syndrome** (acquired epileptic aphasia): 80% of patients enjoy seizure remission, and 60% have persistent learning (particularly language) difficulties.

References

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Mortality

Introduction

- There are methodological problems in the study of mortality in epilepsy. These relate to differences in definitions, selection bias in cohorts under study, incomplete data particularly in population-based studies, and inconsistent death certification.
- The prevalence of epilepsy depends on incidence, remission, and mortality. An excess mortality is observed in cohorts of patients with epilepsy. Most of the mortality in the first years after diagnosis is related to underlying disease causing the epilepsy. Throughout, there is also a small excess mortality related to the epilepsy itself. This excess is in part preventable. It includes deaths due to accidents, drowning, status epilepticus and sudden death in epilepsy (SUDEP). Deaths related to complications of the treatment of epilepsy can also occur but are very rare. Finally, suicides due to associated psychiatric morbidity are increased in a subgroup of people with epilepsy.

📖 See Box 1.1.

Standardized mortality ratio (SMR)

Mortality rates are measured using the SMR. The rate observed in a given cohort is compared to that expected, based on known death rates in the general population standardized for age and sex. SMR in epilepsy is 2–3 compared to the general population, but is much higher in selected cohorts; particularly those with intractable epilepsy, or epilepsy associated with other handicap or disease.

Proportionate mortality

This term refers to the proportion of deaths within a given cohort due to a particular cause. Proportions differ depending on the cohort under study. Causes of death usually include cerebrovascular and cardiac disease, neoplasms including brain tumours, pneumonia, suicide, accidents, SUDEP, and other seizure-related deaths.


Box 1.1 Causes of death in epilepsy (these categories may overlap):

- Unrelated to epilepsy
- Death from underlying/associated disease.
- Epilepsy-related:
 - Seizure-related
 - Status epilepticus.
 - Trauma, burns, or drowning consequent to a seizure.
 - Majority of sudden unexpected deaths in epilepsy.
 - Deaths in a seizure with secondary cause identified e.g. clear severe aspiration or airway obstruction by food.
 - Deaths provoked by habitual seizures due to co-existing cardio-respiratory disease.
 - Deaths as a consequence of medical or surgical treatment of epilepsy.
 - Suicides.

Status epilepticus

Mortality associated with status epilepticus is of the order of 20%. Although status epilepticus is more common in children, the mortality rate is higher in adults. In tertiary centres, death is reported largely due to the underlying condition rather than the status per se. Nevertheless, status epilepticus from any cause, particularly if convulsive, should be considered a life-threatening medical emergency requiring prompt treatment.

Accidental deaths—drowning, trauma, and burns

The risk of injury relates to seizure frequency as well as seizure type (seizures associated with falls, carry the highest risk). Epileptic seizures are also a cause of vehicle driver collapse. Drowning is exposure dependent.  See Box 1.2.

Box 1.2 Some measures to prevent accidental injury and death in epilepsy

- Avoid potentially dangerous situations in the event of a seizure, including:
 - Unprotected heights.
 - Unprotected waterfronts.
 - Proximity to fires/heat.
 - Proximity to dangerous machinery.
 - Driving.
- Use sit-down showers with thermostat-controlled water-temperature rather than baths.
- Follow driving regulations.
- Take care as a pedestrian and cyclist avoiding traffic.
- Take care with cooking, hot water, and with home appliances.
- In severe epilepsy with frequent drop attacks, consider helmet or wheelchair use.

Sudden unexpected ('unexplained') death in epilepsy (SUDEP)

Otherwise well patients with epilepsy sometimes die unexpectedly without a cause for death found at post-mortem examination, although pulmonary congestion is frequently noted, and sometimes congestion in other organs. The majority of deaths are unwitnessed; most often the person is found dead in bed. Often there is evidence suggestive of an epileptic seizure. There is some dispute over definitions with a few investigators excluding death in a documented seizure. A pragmatic workable definition for SUDEP is: sudden, unexpected, witnessed or unwitnessed, non-traumatic, and non-drowning death in epilepsy, with or without evidence of a seizure and excluding documented status epilepticus, where post-mortem examination does not reveal a structural or toxicological cause for death. This definition does not address sudden death in epilepsy with concomitant disease, a category which also needs study.

Where information is incomplete or autopsy is not available the level of uncertainty may be indicated as follows: definite SUDEP (sudden death in benign circumstances with no other known cause and autopsy performed), probable (as before but without autopsy), possible, and not SUDEP.

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Incidence rates in different cohorts are listed in Box 1.3. The most likely cause is cardio-respiratory compromise during or shortly after an epileptic seizure. Some risk factors identified in case control studies are listed in Box 1.4. The most important is a history of generalized tonic-clonic seizures and uncontrolled epilepsy. Individual susceptibility is not fully explained and risk prediction is difficult.

Box 1.3 SUDEP incidence

- New onset epilepsy: < 1:5000 person years.
 - Controlled epilepsy MRC AED withdrawal study 2:5000 person years.¹
 - Population based studies minimum 0.35/1000 person years.
 - UK death certificates for those aged 15–60 = 350–400 individuals in 1997.
 - Multicentre hospital series: large unselected 1.21/1000 person years.
 - Cohorts with epilepsy and other disability 1:300 person years.
 - Hospital series/Intractable cohorts 1:250 person years (higher in pre-surgical cohorts and those with failed epilepsy surgery).
- For a recent review see⁽²⁾.

Suicides

An excess in suicides is mostly reported in selected cohorts, less in population based surveys, for example, in intractable cohorts with temporal lobe epilepsy, suggesting that the pathophysiology of the underlying conditions plays a role. The excess observed is not simply due to the burden of chronic disease. Patients who undergo temporal lobectomy for the treatment of their epilepsy are also at potential risk. There has also been recent concern about the possible modifying effects on risk of AEDs.

Practical implications

The excess mortality associated with epilepsy has practical implications to management both in relation to information provision, treatment decisions, as well as service provision. It also has medico-legal implications. Guidelines generally advocate more information provision to patients regarding risks associated with epilepsy—including SUDEP—than is reportedly commonly practised. While this may be subject to debate, and particularly where the individual is faced with treatment or social choices, an awareness of the risks associated with epilepsy is a prerequisite to informed choice (Box 1.5).

Box 1.4 Some risk factors for SUDEP shown in different case control studies⁽²⁾

Seizures⁽²⁾

- History of generalized tonic clonic seizures.
- Tonic clonic seizure in past 3 months.
- Tonic clonic seizure in past year.
- More frequent seizures.

Circumstances

- Prone body position at death.
- Bedroom shared by supervising individual (protective).
- Listening devices (protective).

Treatment

- Never treated.
- On two AEDs compared to none or one.
- History of treatment with >4 AEDs ever compared to 1 to 2.
- Polytherapy.
- Frequent medication changes.
- Carbamazepine level greater than usual quoted range; on carbamazepine.
- Increased variation in AED levels in sequential hair samples.

Other

- Full scale IQ <70 compared to >79.
- Younger age of onset of epilepsy.

Box 1.5 Prevention of epilepsy-related deaths

- Prevention of injury and drowning.
- Prevention of seizures.
- Reduction in seizure severity.
- Detection and treatment of psychiatric co-morbidity.
- Choice of treatment appropriate for severity of epilepsy.
- Adequate response to convulsive seizures to minimize cardio-respiratory compromise and risk of injury.

References

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