Epileptic Disord 2015; 17 (3): 243-53

The natural history and prognosis of epilepsy

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Received February 10, 2015; Accepted March 25, 2015

ABSTRACT – Epilepsy is a brain condition characterized by the recurrence of unprovoked seizures. Generally, prognosis refers to the probability of attaining seizure freedom on treatment and little is known about the natural history of the untreated condition. Here, we summarize aspects of the prognosis and prognostic predictors of treated and untreated epilepsy and of its different syndromes. Usually, epilepsy is a fairly benign condition. Most epilepsies have a good prognosis for full seizure control and eventual discontinuation of AEDs, but epilepsy syndromes have differing outcomes and responses to treatment. Prognostic factors include aetiology, EEG abnormalities, type of seizures and the number of seizures experienced before treatment onset, and poor early effects of drugs. Early response to treatment is an important positive predictor of long-term prognosis, while the history of a high number of seizures at the time of diagnosis, intellectual disability, and symptomatic aetiology are negative predictors. Different prognostic patterns can be identified, suggesting that the epileptogenic process is not static. Epilepsy carries a greater than expected risk of premature death. Aetiology is the single most important risk factor for premature death.

Key words: epilepsy, prognosis, epidemiology, prognostic predictor, mortality, treatment

Epilepsy is a chronic condition characterized by the recurrence of unprovoked seizures. The International League against Epilepsy (ILAE) recently defined epilepsy based on at least one of the following conditions: (1) at least two unprovoked (or reflex) seizures occurring more than 24 hours apart; (2) one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next ten years; (3) diagnosis of an epilepsy syndrome (Fisher *et al*., 2014).

As the majority of people diagnosed with epilepsy receive treatment, prognosis generally refers to the probability of attaining seizure freedom on treatment. Little is known about the natural history of the

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doi:10.1684/epd.2015.0751

untreated condition, which can usually only be investigated in people in resource-poor countries where the majority of those with epilepsy go untreated.
We review the prognosis of unprovoked seizures and epilepsy with reference to seizure recurrence and mortality. Psychosocial and other (non-seizure-related) complications are not addressed.

Methodological issues

As with most chronic conditions, the prognosis of epilepsy depends on the characteristics of the population at risk, the definition of seizures and epilepsy used, the duration of follow-up, and the presence of selected prognostic predictors, including treatment. Epilepsy must be differentiated from acute symptomatic seizures and single unprovoked seizures (Thurman *et al*., 2011). Acute symptomatic seizures are those occurring in close temporal relationship to an acute CNS insult, which may be metabolic, toxic, structural, infectious, or due to inflammation (Beghi *et al*., 2010).

Overall prognosis of epilepsy

The earlier studies on the prognosis of epilepsy showed seizure remission in a limited number of people (Rodin, 1968). Those included in these studies, however, were mostly seen in secondary and tertiary centres and, as such, they were at the most severe end of the spectrum. Population studies of people with newly diagnosed epilepsy followed for several decades revealed contrasting findings, showing that up to 80% enter prolonged periods of seizure remission and up to 50% continue to be seizure-free after treatment discontinuation (Annegers *et al*., 1979; Sillanpää and Schmidt, 2006). Other studies of people with newly diagnosed epilepsy have consistently shown that 55-68% achieve prolonged seizure remission (Jallon *et al*., 2003).
From a population perspective, the overall prognosis of epilepsy is favourable for the majority. Prevalence rates for active epilepsy mostly range between 4 and 10 per 1,000 population (Sander, 2008), while the median incidence rate is 50 per 100,000 per year (interquartile range: 34-76) (Ngugi *et al*., 2011). As the prevalence of a disease with a stable condition is the product of the incidence and the duration of the active condition, given a prevalence of 5 per 1,000 and incidence of 50 per 100,000 per year, the expected average duration of active epilepsy should be around ten years.

Prognosis and prognostic predictors of a first seizure

The risk of relapse following a first seizure varies significantly according to whether the seizure is acute symptomatic or unprovoked. Acute symptomatic seizures have a fairly low recurrence rate (about 19% at ten years) compared to single unprovoked seizures (65%) (Hesdorffer *et al*., 2009).
The overall risk of relapse after a first unprovoked seizure has been reported to range from 23 to 71% (Beghi, 2003). The rates at two and five years are 21-69% and 34-71%, respectively. Differences are mostly explained by the population at risk, the duration of follow-up, and the methods used to assess the risk of seizure recurrence. Population studies (Annegers *et al*., 1986; Hart *et al*., 1990) provide more homogeneous relapse rates at one (36-37%) and two years (43-45%). In a systematic review of 16 reports (Berg and Shinnar, 1991), the average overall recurrence risk was 51% (95% CI: 49-53%). After a first unprovoked seizure, the probability of a relapse decreases with time; about 50% of recurrences occur within six months of the initial seizure and 76-96% within two years. After a second unprovoked seizure, the risk of a third seizure has been estimated at 73% and after a third seizure the risk of a fourth seizure has been estimated at 76% (Hauser *et al*., 1998).
The two most consistent predictors of recurrence are a documented aetiology and an abnormal (epileptiform and/or slow) EEG pattern. In a meta-analysis of 16 reports (Berg and Shinnar, 1991), the pooled recurrence risk in people with an idiopathic or cryptogenic first seizure was 32%, compared with 57% for a remote symptomatic seizure (*i.e*. a seizure with an underlying, non-acute, brain complication). The risk ranged from 27% with a normal EEG to 58% with an EEG showing epileptiform abnormalities. EEGs with epileptiform abnormalities tend to be associated with a higher risk of recurrence than those with non-epileptiform abnormalities. The two-year recurrence risk was 24% for an idiopathic or cryptogenic first seizure with a normal EEG, 48% for a remote symptomatic seizure *or* an abnormal EEG, and 65% with a remote symptomatic seizure *and* an abnormal EEG.
Other factors correlating with a higher risk of recurrent seizures include seizures occurring during sleep (Hopkins *et al*., 1988; Shinnar *et al*., 1996), focal seizures (even after controlling for aetiology and EEG abnormalities) (Camfield *et al*., 1985; Annegers *et al*., 1986), and a family history of seizures (idiopathic or cryptogenic first seizures in one study) (Hauser *et al*., 1990). A history of prior acute symptomatic seizures has been found to increase the risk of relapse, while evidence is inconclusive or lacking for gender, age, and presentation with status epilepticus (Berg and Shinnar, 1991).

There have been several randomized controlled studies assessing the effects of treatment of the first unprovoked seizure (Chadwick, 2008). Results of these consistently show that treatment of the first seizure seems to reduce the risk of short-term relapse, but is apparently ineffective regarding the chance of long-term seizure remission. These data are in keeping with several observational reports that the long-term prognosis of the first seizure is substantially unaffected by immediate treatment.

Prognosis of untreated epilepsy

With only a few exceptions (Zielinski, 1974; Keranen and Riekkinen, 1993; van Donselaar *et al*., 1997), the prognosis of untreated epilepsy has been assessed only in resource-poor countries (treatment gap ranging from 70 to 94%). In a population-based study in Ecuador (Placencia *et al*., 1992), the cumulative annual incidence was 190 per 100,000 and the prevalence of active epilepsy was 7 per 1,000, which implies a remission rate of at least 50%. Similar prevalence rates of active epilepsy were found in Nigeria (Osuntokun *et al*., 1987) and in Ethiopia (Tekle-Haimanot *et al*., 1990). In a study in Malawi (Watts, 1992), the duration of active epilepsy was similar to that of industrialized countries. All these findings lend support to the hypothesis that spontaneous remission of untreated epilepsy is common. In a study in Warsaw in the 1970s, almost one third of those who had never been treated, including some who had previously had frequent generalized seizures, were free of seizures for more than five years (Zielinski, 1974). A small retrospective Finnish study of people with untreated epilepsy revealed a 42% probability of remission at ten years after onset (Keranen and Riekkinen, 1993). In a study in the Netherlands, about 40% of children with untreated newly diagnosed tonic-clonic seizures had a decelerating seizure pattern during follow-up, with seizure freedom or increasing intervals between seizures (van Donselaar *et al*., 1997).

Prognosis and prognostic predictors of treated epilepsy

In high-income countries, treatment of epilepsy is generally started at the time of diagnosis. About 60% of people with childhood-onset epilepsy will have a five-year remission period, followed by withdrawal of antiepileptic drug (AED) treatment (Sillanpää and Schmidt, 2015). Population-based studies on the long-term prognosis of treated epilepsy report a 58-65% cumulative five-year remission rate at ten years (Annegers *et al*., 1979; Cockerell *et al*., 1997). This number rises to about 70% by 20 years following seizure onset. The five-year remission rate at ten years is 61% in adults (Lindsten *et al*., 2001) and the three to five-year remission rate at 30 years in children is 74-76% (Sillanpää, 1993). In a Finnish cohort of people with childhood-onset epilepsy, after over 30 years of follow-up, 64% of cases were in five-year terminal remission, of whom 74% were off medications (Sillanpää *et al*., 1998).

The aetiology of epilepsy is the strongest prognostic predictor for seizure recurrence (*table 1*). Epilepsy due to (presumed) genetic causes has a better chance of remission than epilepsy due to structural/metabolic causes. In a population study from Rochester, Minnesota, people with symptomatic epilepsies had a significantly lower chance of five-year remission than those with idiopathic epilepsies (30 vs. 42% at 15 years, respectively) (Annegers *et al*., 1979). People with neurological dysfunction at birth had the lowest chance of remission (46%, with 30% off drugs at 20 years). Lower remission rates in those with symptomatic epilepsies, when compared to idiopathic/cryptogenic epilepsy, were also found in the UK, Sweden (adults) and Finland (children) (Jallon *et al*., 2003). Documented aetiology has also been found to be associated with seizure intractability in childhood-onset epilepsy (Sillanpää, 1993).

Other prognostic predictors have been also identified in population studies or in well-defined epilepsy cohorts. In the Connecticut study of childhood-onset epilepsy, early predictors of intractability included known aetiology, high initial seizure frequency, and focal EEG slowing (Berg *et al*., 2001). Other prognostic indicators of five-year remission in the Rochester, Minnesota population included absence of EEG epileptiform abnormalities and absence of generalized tonic-clonic seizures (GTC) (Shafer *et al*., 1988). In the UK National General Practice Study of Epilepsy (NGPSE), the only independent predictor of one-year and two-year remission was the number of seizures in the six months after the first seizure (Cockerell *et al*., 1997; MacDonald *et al*., 2000). When other prognostic predictors were taken into consideration, there was no evidence that age at onset of seizures affects seizure outcome. With the exception of epilepsies associated with rare inherited sex-linked disorders, gender has not been seen as a significant prognostic predictor.

In a 40-year median follow-up population-based study of 102 children in Turku (Finland), early seizure frequency was found to be associated with long-term seizure control during AED treatment but not mortality, while symptomatic aetiology was predictive for seizure outcome and mortality (Sillanpää and Schmidt, 2009a). The time to achieve an initial one-year period of remission was associated with long-term drug response in children; those who entered one-year remission within the first five years of treatment had

Table 1. Prognostic predictors.

Prognostic Predictor	Author, year
Symptomatic aetiology	Bonnett *et al.*, 2014; Wirrell *et al.*, 2012; Sillanpää *et al.*, 2012; Sillanpää and Schmidt, 2009a; Jallon *et al.*, 2003; Berg *et al.*, 2001; Ko and Holmes, 1999; Aikiä *et al.*, 1999; Sillanpää *et al.*, 1998; Annegers *et al.*, 1979
Abnormal intelligence	Sillanpää *et al.*, 2012; Wirrell *et al.*, 2012; Aikiä *et al.*, 1999; Sillanpää, 1993; Camfield *et al.*, 1993; Brorson and Wranne, 1987
Tonic or simple focal seizures	Bonnett *et al.*, 2014; Su *et al.*, 2013; Jonsson and Eeg-Olofsson, 2011; Del Felice *et al.*, 2010; Ko and Holmes, 1999; Shafer *et al.*, 1988
Complex focal or atonic seizures	Aikiä *et al.*, 1999; Sillanpää, 1993
Early childhood age at onset	Wirrell *et al.*, 2012; Sillanpää *et al.*, 2012; Ko and Holmes, 1999; Sillanpää, 1993; Camfield *et al.*, 1993
Prior neonatal seizures	Sillanpää, 1993; Camfield *et al.*, 1993
High seizure frequency prior to treatment	Su *et al.*, 2013; Berg *et al.*, 2001; Camfield *et al.*, 1993
High seizure frequency during early treatment	MacDonald *et al.*, 2000; Arts *et al.*, 1999; Cockerell *et al.*, 1997
Poor early effects of treatment	Bonnett *et al.*, 2014; Sillanpää *et al.*, 2012; Arts *et al.*, 1999; Sillanpää *et al.*, 1998; Annegers *et al.*, 1979
Neurological dysfunction	Annegers *et al.*, 1979
Abnormal interictal EEG	Berg *et al.*, 2014; Su *et al.*, 2013; Wirrell *et al.*, 2012; Berg *et al.*, 2001; Shafer *et al.*, 1988
Time to first remission	Sillanpää *et al.*, 2012; Sillanpää and Schmidt, 2009b

an 11-fold better chance of entering five-year terminal remission and a nine-fold better chance of entering five-year terminal remission without medication (Sillanpää and Schmidt, 2009b). In the same study, 82% of people with epilepsy entered a first period of remission of at least five years; 60% had no relapse and 40% had a seizure relapse. Of those who had a relapse, 12% never re-entered a five-year period of remission (Sillanpää *et al.*, 2012). The predictor of seizure relapse for those who entered a five-year or longer period of remission was cognitive impairment, and significant predictors of premature retirement were relapse, symptomatic aetiology, and early onset of epilepsy (Sillanpää *et al.*, 2012). In another small population-based study in Sweden in children and adolescents, after a ten-year period, 34 of 45 individuals were in remission; 24 of them had focal seizures and 15 rolandic seizures (Jonsson and Eeg-Olofsson, 2011). In a population-based study, a third of children presenting with epilepsy before 36 months had medically intractable seizures with higher mortality and poorer intellectual outcome (Wirrell *et al.*, 2012). In this study, negative prognostic indicators included age ≤12 months at diagnosis, developmental delay at initial diagnosis, abnormalities on neuroimaging, and focal slowing on initial EEG.

Longitudinal cohort studies, in particular the National General Practice Study of Epilepsy, showed that 65-85% of cases entered long-term remission, and that by definition, remission is more likely in people with newly diagnosed epilepsy than in those with chronic epilepsy (Shorvon and Goodridge, 2013).

In a prospective community-based cohort of children with non-syndromic epilepsy, 58% achieved complete remission (both drug-free and seizure free for ≥5 years) (Berg *et al.*, 2011). An older age at seizure onset was associated with a lower chance of remission. In another recent study (Su *et al.*, 2013), people with newly diagnosed epilepsy who had not received AED treatment previously were followed for at least two years. Predictors of recurrence were multiple seizure types, epileptiform EEG abnormalities, and more than one seizure monthly before treatment. The strongest negative predictors of seizure recurrence were found to be previous relapses and persistence of epileptiform EEG abnormalities within one year.

In an Italian cohort of adults with epilepsy, the cumulative time-dependent probability of two-year remission

Table 2. Long-term prognosis of epilepsy syndromes.

Syndrome	Study design	Cases	Follow-up (years)	Sz-free %	Author, year
BECTS	Retrospective cohort	29	12-17	**89**	Callenbach *et al*., 2010
Panayiotopoulos	Retrospective cohort	93	1-14	**41**	Specchio *et al*., 2010
CAE	Retrospective cohort	47	12-17	**93**	Callenbach *et al*., 2009
CAE/JAE	Retrospective cohort	163	3-69	**56 (CAE)** **62 (JAE)**	Trinka *et al*., 2004
JME	Retrospective cohort	186	1-41	**58**	Martínez et al., 2006
West	Retrospective cohort	214	20-35	**33**	Riikonen, 2001
LGS	Retrospective cohort	107	>3 in 74	**3**	Goldsmith *et al*., 2000
Dravet	Retrospective cohort & review	24	Up to age 50	**8**	Genton *et al*., 2011
Landau-Kleffner	Retrospective cohort	9	6-25	**0**	Cockerell *et al*., 2011
ESES	Prospective cohort	32	>3	**43 (>90% reduction)**	Liukkonen *et al*., 2010
EGMA	Retrospective cohort	42	40	**62**	Holtkamp et al., 2014

BECTS: benign childhood epilepsy with centrotemporal spikes; CAE: childhood absence epilepsy; JAE: juvenile absence epilepsy; JME: juvenile myoclonic epilepsy; LGS: Lennox-Gastaut syndrome; ESES: encephalopathy with status epilepticus during sleep; EGMA: epilepsy with grand mal on awakening.

was 56% at two years, 63% at three years, 69% at five years, and 79% at 10 years, and partial seizures and the number of seizures prior to treatment were predictors of late remission (Del Felice *et al*., 2010).

The prognosis of epilepsy cannot be predicted by response to the first drug. Seventy-five percent of individuals enrolled in the SANAD (Standard and New Antiepileptic Drug) trials achieved 12-month remission by six years of follow-up after a first treatment failure (Bonnett *et al*., 2014). These individuals were mostly young, without tonic-clonic seizures, with normal brain imaging (CT or MRI), and had treatment failure due to adverse events. The initial drug (carbamazepine, gabapentin, lamotrigine, oxcarbazepine, topiramate or valproate) was not predictive for remission. Tonic-clonic seizures and inadequate seizure control with the first drug were predictors of second treatment failure.

Prognosis of epilepsy syndromes

An epileptic syndrome is a symptom complex, characterized by a fairly uniform clinical and electrographic picture. The features defining an epileptic syndrome include family history, age at onset, putative aetiology, EEG, and neuroimaging findings (Commission on Classification and Terminology of the International League Against Epilepsy, 1989). To some extent, particularly in children, epileptic syndromes have differing outcomes and responses to treatment. For epidemiological purposes (Sander, 1993), epilepsy syndromes can be classified into four different prognostic groups:

- (1) *Excellent prognosis* (about 20-30% of the total) with high probability of spontaneous remission; these include neonatal seizures, benign partial epilepsies, benign myoclonic epilepsy in infancy, and epilepsies provoked by specific modes of activation.
- (2) *Good prognosis* (about 30-40%) with easy pharmacological control and possibility of spontaneous remission; these include infantile absence epilepsy, epilepsies with GTC seizures secondary to specific conditions, and some focal epilepsies.
- (3) *Drug-dependent prognosis* (about 10-20%), in which seizures may respond to drugs, but tend to relapse after treatment withdrawal; these include juvenile myoclonic epilepsy and most focal epilepsies (symptomatic or cryptogenic). This could, however, also be a subgroup of those with a poor prognosis (Kwan and Sander, 2004).
- (4) *Poor prognosis* (about 20%) in which seizures tend to recur despite intensive treatment; these include epilepsies associated with congenital neurological

defects, progressive neurological disorders, and some symptomatic or cryptogenic focal epilepsies.

A number of reports on the long-term prognosis of epilepsy syndromes have been published. The results of these studies are illustrated in *table 2*.

The long-term outcome of epilepsy varies significantly according to the epilepsy syndrome, however, the large majority of the studies have been performed in cohorts of people enrolled in secondary and tertiary centres and, as such, they do not reflect the entire spectrum of the epilepsies in well-defined populations.

Prognosis of epilepsy after treatment withdrawal

As the long-term prognosis of treated epilepsy is favourable in the majority and seizure remission can be achieved even in those untreated, discontinuation of treatment is an option for people who are seizure-free for two years or longer. In a critical appraisal of 28 studies of people, most of whom had at least two years of seizure remission, the proportion with relapses during or after treatment withdrawal ranged from 12 to 66% (Specchio and Beghi, 2004). The differences can be explained by study population, length of the seizure-free period during treatment, duration of follow-up, and the methods used to assess the relapse risk. The cumulative time-dependent probability of remaining seizure-free in children was 66-96% at one year and 61-91% at two years. The corresponding values in adults were 39-74% and 35-57%. The relapse rate was highest in the first 12 months (especially in the first six months) and tended to decrease thereafter. In a meta-analysis of 25 studies, the pooled relapse risk was 25% at one year and 29% at two years (Berg and Shinnar, 1994).

A number of factors have been associated with seizure outcome after treatment discontinuation. Factors consistently suggesting a higher-than-average risk of seizure relapse include adolescent-onset epilepsy, focal seizures, presence of an underlying neurological condition, and abnormal EEG findings (in children). Factors associated with a lower-than-average risk of relapse were childhood-onset epilepsy, idiopathic generalized epilepsy, and (in children) normal EEG. Selected epilepsy syndromes (*e.g.* benign epilepsy with centro-temporal spikes and juvenile myoclonic epilepsy) may be associated with significantly different outcomes after treatment withdrawal (Specchio and Beghi, 2004). In a meta-analysis of 25 studies, those with onset of seizures in adolescence had a 30% higher risk of relapse than those with adult age at onset (Berg and Shinnar, 1994). People with remote symptomatic seizures or with an abnormal EEG prior to drug discontinuation had a 50% higher risk of relapse. In the same review, prognosis following drug withdrawal was similar whether a two-year or a four-year seizure-free interval was considered.

Continued treatment of epilepsy affects the long-term outcome of the disease, at least in some individuals. In one randomized controlled trial on the effects of AED withdrawal on seizure relapse, 22% of people randomized to continue treatment had relapsed by two years, while 41% of those randomized to slow drug withdrawal had relapsed (Medical Research Council Antiepileptic Drug Withdrawal Study Group, 1991). This differential risk of relapse was maximal between one and two years, and declined thereafter. After two years, the risk of subsequent relapse was the same for both treatment groups. The risk of further recurrence was also similar in people who relapsed after withdrawal of AEDs and in those who relapsed while remaining on treatment (Chadwick *et al.*, 1996). In this study, independent predictors of relapse included a history of focal seizures, primary or secondary GTC seizures or myoclonic seizures, use of more than one AED, seizures after initiation of treatment, and a shorter seizure-free period at randomization. In a second more recent trial (Lossius *et al.*, 2008), only 15% of people randomized to treatment withdrawal and 7% of those randomized to remain on treatment had a relapse at 12 months; a non-significant difference.

Prognostic patterns

In the last few years, a number of studies have addressed the outcome of epilepsy focusing on the chance and timing of seizure remission. The results of these studies modified to some extent the belief that long-term prognosis of epilepsy is related to the early response to AEDs. In a population-based study from Finland, a prolonged observation of the outcome of epilepsy with onset in childhood revealed different prognostic patterns (Sillanpää and Schmidt, 2006). These included early seizure remission followed by terminal remission, early seizure remission followed by seizure relapse and by a new period of remission (relapsing-remitting pattern), early seizure remission followed by seizure relapse with no further periods of remission, and early seizure recurrence followed by pharmacological and eventually terminal remission (delayed remission). These patterns have been partly confirmed by others (Shorvon and Goodridge, 2013). In 613 children with newly diagnosed epilepsy, followed prospectively for 10 or more years, early sustained remission was recorded in a third, late sustained remission in 12%, and remission-relapse episodes in 35% (Berg and Rychlik, 2015). It was concluded that seizure prognosis was highly variable and not always predicted by early remission status, and

a 20-year follow-up period may be insufficient to fully capture lifetime seizure outcomes. All this suggests that the epileptogenic process is not static and several factors may be implicated in the long-term outcome of epilepsy. Among these is drug treatment, as shown by the long-term chance of remission documented in people deemed "drug-resistant" (Callaghan *et al*., 2007; Luciano and Shorvon, 2007; Neligan *et al*., 2011). There is no evidence that AEDs "cure" epilepsy (Temkin *et al*., 2001; Pitkänen and Lukasiuk, 2011), but one cannot exclude some influence of drug treatment in epilepsies with early or delayed seizure remission, followed by terminal remission.

Mortality

Despite the overall good seizure prognosis, epilepsy carries a greater risk of premature death relative to the general population. As epilepsy may be the symptom of several clinical conditions, some of which are associated with a high risk of premature death, mortality is frequently attributed to the underlying epileptogenic condition. The mortality rate of people with epilepsy ranges from 1 to 8 per 100,000 population per year, but international vital statistics suggest an annual mortality rate of 1-2 per 100,000 (Gaitatzis and Sander, 2004).

Seizure aetiology is the single most important risk factor for the increased risk of premature mortality in people with a first epileptic seizure. In the Gironde region in France, the overall standardized mortality ratio (SMR) was 9.3 (Loiseau *et al*., 1999). The SMR was 4.1 for unprovoked seizures, 6.5 for remote symptomatic seizures, 10.1 for acute symptomatic seizures, and 19.8 for seizures secondary to progressive neurological conditions. There were no deaths in people with idiopathic seizures and mortality was not increased in those with cryptogenic seizures. Based on a meta-analysis of mortality studies of the previous 100 years (Shackleton *et al*., 2002), the SMR for epilepsy (intended here as repeated unprovoked seizures) was found to range from 1.3 to 9.3 (0.3-3.1 in community-based studies and 1.9-5.1 in institutionalized populations). People with a CNS lesion presumed to be present at birth experience the highest mortality rate, with an SMR between 11 and 25 (Gaitatzis and Sander, 2004). The mortality rate is greater in men than in women, as shown in the majority of population-based studies (Forsgren *et al*., 2005). There is an inverse correlation between SMR and age. The highest mortality rate, found in children, may be explained by the rate expected in the general population, which is lowest in children, and by the higher proportion of neurodeficits in this age group. There is also an inverse correlation between SMR and duration of epilepsy during the first 10 to 14 years of disease (Shackleton *et al*., 2002). GTC and myoclonic seizures, but not absence seizures, have been associated with increased mortality (Forsgren *et al*., 2005). In contrast, data regarding mortality in people with focal seizures are inconsistent. Status epilepticus is associated with significant mortality.

Accident-related deaths are common in people with epilepsy and are responsible for up to 6% of all deaths (Tomson *et al*., 2004), with SMRs ranging between 2.4 and 5.6. People with epilepsy are at higher risk of suicide than the general population (Bell and Sander, 2009). The proportionate mortality rate for suicide ranges from 0 to 20% and SMRs from 1 and 5.8 (Gaitatzis and Sander, 2004). People with severe epilepsy have a fivefold increased risk and those with temporal lobe epilepsy, a 25-fold increased risk of suicide. Suicide rates may be even higher (SMR: 87.5; 95% CI: 35-180) in people with temporal lobe epilepsy undergoing surgical treatment. Antipsychotic drug intake was associated with a four-fold increase in the risk of suicide in a Swedish case-control study, after adjusting for psychiatric illness and alcohol abuse (Nilsson *et al*., 2002). The highest overall mortality rate is reported in the early years after diagnosis but higher than expected mortality rates are also observed through the course of epilepsy (Shorvon and Goodridge, 2013).

Conclusion

In the past, based on studies from tertiary referral centres, epilepsy was regarded as a chronic, progressive, unremitting disease (Rodin, 1968). Epidemiological evidence suggests that the poor prognosis observed in earlier studies was largely the result of selection bias. More recently, the results of epidemiological studies and randomized clinical trials have greatly changed our understanding of the nature and natural history of seizures and epilepsy. Epilepsy can thus be considered a fairly benign condition in the majority of cases, with a good prognosis for seizure control and, ultimately, discontinuation of AEDs. Many different epilepsy syndromes have, however, been recognized with differing outcomes and responses to treatment. Prognostic factors include aetiology, EEG abnormalities, generalized tonic-clonic seizures, and the number of seizures experienced before and after the onset of treatment. Early response to treatment is an important predictor of the long-term prognosis of newly diagnosed epilepsy because individuals who do not achieve remission with the first two appropriate AEDs in the first two years of treatment have a poorer chance of becoming seizure-free and a higher chance of becoming drug-resistant (Mohanraj and Brodie, 2013). Different prognostic patterns can be identified when newly diagnosed people from well-defined

populations are followed for several decades (Sillanpää and Schmidt, 2006; Shorvon and Goodridge, 2013). This suggests that active epilepsy is a dynamic process and that response to treatment can be expected even in individuals with persisting seizures after several medication attempts.

Epilepsy carries an increased risk of premature mortality. The majority of epilepsy-related deaths are attributed to seizure aetiology. □

Supplementary data.

Summary didactic slides are available on the www.epilepticdisorders.com website.

Acknowledgements and disclosures.

EB received honoraria for board membership by VIROPHARMA and EISAI, travel funding and speaker honoraria from UCB-Pharma, and GSK, and grants for research activities from the Italian Drug Agency, Italian Ministry of Health, Sanofi-Aventis, and the American ALS Association. GG has no conflicts of interest to disclose. JWS received research support from the Dr. Marvin Weil Epilepsy Research Fund, Eisai, GSK, EU FP7, WHO, and EU FP7, and has been consulted by and received fees for lectures from GSK, Eisai, Lundbeck, Teva, and UCB.

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For further reading

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TEST YOURSELF

(1) What is the overall relapse rate of a first unprovoked seizure? Also comment on observed differences between different studies.

(2) Can we identify different prognostic patterns in people with epilepsy?

(3) Does epilepsy carry a higher risk of premature death?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".