

Death in epilepsy: is it preventable?

John W. Dunne

Department of Neurology, Royal Perth Hospital, Perth, Western Australia

Abstract

The risk of premature death is higher in people with epilepsy, but many other factors have a potentially bigger role than epilepsy and its treatment. Most people with epilepsy will not die as a direct result of their epilepsy, but as a result of the underlying disorder causing epilepsy and of comorbidity, both somatic and psychiatric. Death in epilepsy is preventable. All patients require accurate diagnosis and optimal seizure control, treatment of the underlying cause when possible, minimising treatment side effects and maximising compliance. Comorbidities need to be recognised and treated. For optimal outcomes, we need to listen to our patients, and to all people we care for.

INTRODUCTION

The risk of premature death is higher in people with epilepsy. The standardised mortality ratio (SMR), the ratio of observed number of deaths in a condition and the expected number of deaths in the general population, is 2-3 for epilepsy.¹⁻³ Many other medical conditions have similar increases in SMR, for example asthma and ischaemic heart disease.

Morbidity and mortality in epilepsy may be due to the underlying cause/process, epileptic seizures themselves, comorbidities and external influences, including treatment. Most people with epilepsy *will not* die as a direct result of their epilepsy, but as a result of the underlying disorder causing epilepsy and of comorbidity, both somatic and psychiatric.¹⁻³ Somatic comorbidities include pneumonia, cerebrovascular disease, malignancy and heart disease.

DIRECT EPILEPSY-RELATED DEATHS

Direct epilepsy-related deaths are infrequent, and are more likely with remote symptomatic epilepsy, increasing frequency and severity of seizures, and with poor antiepileptic drug (AED) compliance.¹⁻⁴ Status epilepticus occurs in 5% of adults and more children with epilepsy, and has a 5-20% mortality, mainly determined by the underlying cause and age. Fatal accidents and drowning may be caused by seizures, with 6% of deaths in epilepsy due to accidents.¹ Seizures may also cause fatal aspiration pneumonia (SMR 6.6).

SUDDEN UNEXPECTED DEATH IN EPILEPSY (SUDEP)

SUDEP has received increasing attention in recent years. SUDEP may be defined as sudden, unexpected death in a person with epilepsy that is not due to any known causes, but for which there is often evidence of an associated seizure. Rather than a cause of death, SUDEP is a description of a clinical scenario with several possible mechanisms, including seizure-related fatal cardiac or respiratory dysfunction.⁵ SUDEP accounts for about 4% deaths in patients with epilepsy, higher in refractory epilepsy. Whilst is the most important direct epilepsy-related cause of death in middle age, it remains very uncommon, with a mean annual incidence of 3-4/1000 patients/year. The possibility of SUDEP does not alter the goals of epilepsy management: to optimise seizure control and maximise AED tolerability and compliance. No data indicate that any other clinical strategy will prevent SUDEP.^{5,6} A single case-control study from UK suggested that ongoing nightly supervision might be protective for people with severe epilepsy living in the residential care facilities.⁷ This suggestion, if verified, is not relevant or possible for most people with epilepsy, given the importance of independent living and the penalties of intrusive monitoring and living in fear.

TREATMENT RELATED

Fatal drug toxicity and idiosyncratic AED reactions are rare. FDA reports estimate the incidence of 1 reaction per 5,000 to 10,000 exposures, fatal

in about 1 per 50,000 exposures, higher in some groups (Han Chinese with HLA-B*1502). Patients need to be aware of these rare allergic reactions, and instructed to immediately stop an AED if a rash emerges, and report for assessment.

PSYCHIATRIC COMORBIDITY

Psychiatric comorbidity is common.⁸ Depression is present in up to 20 to 55% of tertiary care patients with more severe epilepsy, but 3 to 9% in patients with well-controlled epilepsy. However, many other risk factors other than epilepsy and its treatment have a potentially bigger role in depression including environmental, social (poverty, unemployment, personal debt, family discord) and other biological factors. Parents of people with epilepsy and patients with other medical conditions have similar increases in depression.

The risk of suicide in epilepsy is increased in some studies but not in others. A recent large, population-based control study from Canada found people with epilepsy were not more likely to attempt suicide, once important medical and psychiatric comorbidities were adjusted for.⁹ Like depression, many factors beyond epilepsy and its treatment influence an individual's risk of suicide. Suicide accounts for approximately 2000 Australians/year (10/100,000/year), 1-2% of all deaths.¹⁰ Amongst young men, suicide is responsible for nearly 20% of all deaths, second only to motor vehicle accidents. Risk factors in Australia include the male sex, people in rural or remote communities, and alcohol dependence.^{10,11} AEDs themselves were the subject of a FDA alert in 2008, raising concern of an increase in suicidality with add-on AEDs compared to add-on placebo. The overall difference was very small and the methodology of data analysis controversial.¹² These findings were not seen for all drugs (carbamazepine and valproate were protective), were wildly inconsistent across studies, and data from many studies without spontaneous reports of suicidality were excluded from the analysis. In contrast to this controversial analysis, non-adherence to antiepileptic medications clearly increases mortality, with over three times the risk of death and an 86% increased of hospital admissions.^{3,4}

In summary, depression and suicidality are very common in the community. All people who we care for require monitoring for mood and behavioural problems, whether they have epilepsy or not, or are prescribed AEDs or not.

PATIENT INFORMATION: EDUCATE PATIENTS AND FAMILIES

We should provide adequate information to patients and their families in an understandable way and as part of education about epilepsy. This information should not be alarming or frightening, because it is not. In contrast, living in fear is harmful. Information should be put in perspective. Most people with epilepsy will not die as a direct result of their epilepsy or its treatment. SUDEP occurs in a minority of people with epilepsy, with a risk comparable to accidental death in a traffic accident. Most patients/carers should have information about SUDEP, especially those with severe epilepsy. There is controversy about whether all patients (including those at low risk) should be warned, and at what stage. Severe AED reactions are rare, of similar to or less likely than food allergies to shellfish and peanuts. The suicide risk in people taking AEDs is low. The most important safety advice to give to patients taking AEDs is to take them regularly.

CONCLUSION

Death in epilepsy is preventable. All patients require accurate diagnosis and optimal seizure control, treatment of the underlying cause when possible, minimising AED side effects and maximising compliance. Comorbidities, somatic and psychiatric, need to be recognised and treated. For optimal outcomes, we need to listen to our patients and to all people we care for.

REFERENCES

1. Hauser WA, Annegers JF, Elveback LR. Mortality in patients with epilepsy. *Epilepsia* 1980; 21:399-412.
2. Neligan A, Bell GS, Johnson AL, Goodridge DM, Shorvon SD, Sander JW. The long-term risk of premature mortality in people with epilepsy. *Brain* 2011; 134:388-95.
3. Neligan A, Bell GS. The mortality of epilepsy. Chapter 37 in *Epilepsy 2011: From Science to society*. <http://www.epilepsysociety.org.uk/Forprofessionals/Articles>
4. Faught E, Duh MS, Weiner JR, Guerin A, Cunnington MC. Nonadherence to antiepileptic drugs and increased mortality: findings from the RANSOM Study. *Neurology* 2008; 71:1572-8.
5. Shorvon S, Tomson T. Sudden unexpected death in epilepsy. *Lancet* 2011; 378:2028-38.
6. Leone MA, Vallalta R, Solari A, Beghi E, FIRST Group. Treatment of first tonic-clonic seizure does not affect mortality: long-term follow-up of a randomised clinical trial. *J Neurol Neurosurg Psychiatry* 2011; 82:924-7.

7. Langan Y, Nashef L, Sander JW. Case-control study of SUDEP. *Neurology* 2005; 64:1131-3.
8. Kerr MP, Mensah S, Besag F, *et al.* International consensus clinical practice statements for the treatment of neuropsychiatric conditions associated with epilepsy. *Epilepsia* 2011; 52:2133-8.
9. Kwon C, Liu M, Quan H, *et al.* Motor vehicle accidents, suicides, and assaults in epilepsy: a population-based study. *Neurology* 2011; 76:801-6.
10. Living Is For Everyone (LIFE) – Statistics on Suicide in Australia (2007). Commonwealth Department of Health and Ageing: Canberra.
11. Sher L. Alcohol consumption and suicide. *Q J Med* 2006; 99:57-61.
12. Hesdorffer DC, Kanner AM. The FDA alert on suicidality and antiepileptic drugs: Fire or false alarm? *Epilepsia* 2009; 50:978-86.