



What We Do — and Don't — Know About Sudden Unexplained Death in Epilepsy

Although the causes of SUDEP are uncertain, there are a number of effective ways to lower a patient's risk of this tragic outcome.

Sudden unexplained or unexpected death in epilepsy (SUDEP) is a somewhat uncommon but very serious cause of mortality in persons with seizures that are not completely controlled. Other causes of mortality in people with epilepsy include seizure-related death (due to an accident or drowning during the seizure), status epilepticus, suicide and deaths due to the treatment of epilepsy. The higher standard mortality ratios (SMRs) occur in persons with refractory epilepsy. So what exactly is SUDEP? It is sudden, unexpected, witnessed or unwitnessed, non-drowning or atraumatic death in someone with epilepsy in whom the autopsy does not reveal a specific cause.¹

Mortality rates are higher among people with seizures than those without epilepsy. One way to quantify this is by looking at the SMR, a measure that compares the rate of death to age-matched, sex-matched healthy individuals. An SMR of 1.0 signifies no difference from the reference population. In persons with epilepsy, the SMR ranges from 1.3 to 9.3.² Of course, the higher SMR could reflect any cause of death. SUDEP accounts for a smaller percentage of these deaths, causing 2-18 percent of the deaths in people with epilepsy.³ The most often quoted number is that SUDEP affects 1:1000 individuals. However, the risk may be much higher, perhaps as high as 1:100.⁴ In this study, the higher rate of SUDEP was reported in people who had been referred for epilepsy surgery (*i.e.*, their seizures were refractory to medical management).

What Causes SUDEP?

By definition, the exact cause is unknown. However, several theories have been proposed. Of these, the leading possibility is that the cause of death is due to a cardiac arrhythmia, probably induced by a seizure.⁵ Evidence in support of this hypothesis is the observation during video-EEG monitoring that seizures can cause an increase in heart rate, tachycardia, or the opposite, bradycardia. Of the two types of arrhythmia, tachycardia is the more common, occurring in up to 99 percent of temporal lobe seizures.^{6,7}

Rarely, seizures have been described as causing asystole.⁸ In one study, 20 people with epilepsy were implanted with a subcutaneous device that records cardiac rhythms. One in five (21 percent) were found to have periods of bradycardia or asystole. Three of the four patients experienced the change on cardiac rhythm around the time of a seizure.⁹

If the arrhythmia is not directly attributable to seizures, it has been proposed that the abnormal cardiac rhythm could be due to the treatment of seizures. Case reports have linked both phenytoin and carbamazepine to changes in cardiac rhythms. In addition, abrupt withdrawal of either of these medications has been shown to increase the frequency of premature ventricular beats.¹⁰ There is little

if any information regarding the newer antiseizure medications and changes in cardiac rhythm.¹¹ The vagus nerve stimulator has been shown to cause asystole during the lead test,¹² and can cause beat-to-beat heart rate variability.¹³ The clinical significance of the changes in cardiac rhythms remains unclear. Although some have proposed that this is the link between seizure therapies and sudden unexplained death, no specific drug or therapy has been shown to be associated with SUDEP.¹¹

The leading theory about SUDEP's etiology is that the cause of death is due to a cardiac arrhythmia, probably induced by a seizure, as evidenced by the observation during video-EEG monitoring that seizures can cause an increase in heart rate, tachycardia, or the opposite, bradycardia.

The second possible cause of SUDEP is pulmonary: some have proposed that seizure-induced apnea may cause unexpected death. For instance, seizures have been associated with both obstructive and central sleep apnea.^{14,15} Perhaps the seizure causes a prolonged apnea, which then leads to death. Another possibility is that the apnea induces an irregular cardiac rhythm. Finally, the chain of events may be that apnea, if prolonged, causes cardiac ischemia and then a cardiac arrhythmia. Further research is needed to more carefully understand the link between seizures, therapy for seizures, and SUDEP. If the exact link can be understood, measures could be instituted to prevent the mortality associated with seizures.

Table 1. Risk Factor for SUDEP

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| • Age 20-40 |
| • Early age of onset of seizures |
| • A history of developmental delay |
| • Poor compliance with therapy |
| • Polytherapy |
| • Continued generalized tonic-clonic seizures |
| • Refractory seizures (continue despite treatment) |

Risk Factors for SUDEP

Many risk factors for SUDEP have been identified (see Table 1). The patient's history may reveal several of these: an age between 20-40, a history of generalized tonic-clonic seizures, frequent seizures, a history of developmental delay, and an early age of onset of seizures. In people whose seizures which respond poorly to medication, are on many medications (polytherapy), are poorly compliant with their therapy, or those which persist after epilepsy surgery are also at risk for SUDEP.^{16,1}

In one study, persons with epilepsy who were successfully treated with epilepsy surgery did not experience SUDEP, while those who did not respond to surgical treatment continued to be at risk for this.¹⁷ In other words, those who continue to have seizures (whether due to non-compliance or the refractory nature of their seizure) will continue to be at risk for SUDEP. By stopping the seizures, as the Sperling study suggests, one can eliminate the mortality due to SUDEP in this group of people.

What Can Be Done to Prevent SUDEP?

When one looks at the list of risk factors for SUDEP, several stand out: continued generalized tonic-clonic seizures, polytherapy, poor compliance and resistance to medications or surgery. In other words, ongoing seizure activity increases the chance of sudden death. One of the risks, non-compliance, is the easiest (in theory)

to correct and should be discussed at each office visit. If non-compliance is due to side effects of the current therapy, consider alternative treatment. In addition, many physicians advocate the education of persons with epilepsy about this risk: by stressing the importance of good seizure control (compliance), the risk of SUDEP may be reduced.

If seizures do not respond well to medication, consider more aggressive interventions. Two non-pharmacologic treatments have been studied. The first is epilepsy surgery. The findings of Dr. Sperling have already been reviewed, illustrating the reduction of SUDEP in patient who were successfully treated with resective epilepsy surgery.¹⁷

In addition, Annegers studied the effect of the vagus nerve stimulator on SUDEP. Following a cohort of 1,819 patients, he found that the SMR was reduced with duration of treatment. In addition, the rate of SUDEP was reduced from 5.5:1000 to 1.7:100 after two years of therapy.¹⁸ Although interpretation of these results is difficult, one possible explanation is that the people who continued with VNS therapy beyond two years had experienced a reduction of seizures. In other words, those who had improved seizure control experienced a lower rate of SUDEP.

Conclusions

The cause of SUDEP remains unknown. However, there are several leading hypotheses, including seizure-induced arrhythmia, apnea or cardiac ischemia. Persons who are most at risk for SUDEP are those who continue to experience seizures, especially generalized tonic-clonic seizures. Appropriate treatment for seizures, which means complete seizure control, appears to reduce (or possibly eliminate) the risk of SUDEP in this group. In other words, physicians must institute aggressive therapy, and educate

patients about the need for good compliance in order to reduce this cause of mortality. Future research, aimed at treating the cardiac and pulmonary causes of SUDEP is needed. **PN**

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Steven Karceski, MD is Assistant Clinical Professor of Neurology at the College of Physicians & Surgeons of Columbia University and Director of the Columbia Epilepsy Center at the Atlantic Neuroscience Institute.