

EVIDENCE WORKSHEET

Guideline 9.2.4 First Aid Management of a Seizure

ARC Subcommittee: BLS

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Clinical (PICO) question:

P: in adults and children
I: who exhibit seizure activity
C: compared with victims who do not have a seizure
O: what proportion are related to cardiac arrest

P: in adults and children
I: who exhibit a seizure
C: compared with victims who do not have a seizure
O: what is the risk of cardiac arrest / sudden death

Search Strategies:

PubMed: (Search Completed: August 3, 2014): 445 results

Search: ((((((((*arrest[Title]) OR "cardiac arrest"[Title]) OR CPR[Title]) OR "sudden death"[Title]) OR "sudden cardiac death"[Title]) OR "unexpected death"[Title])) AND Humans[Mesh])) AND (((((((convulsion[MeSH Terms]) OR epileptic seizure[MeSH Terms]) OR epileptic seizures[MeSH Terms]) OR seizure*[Title]) OR fit*[Title]) OR epilep*[Title]) OR convulsion[Title]) AND (Humans[Mesh]))

Inclusion / exclusion criteria:

Inclusion criteria: Studies specifically looking at seizure activity as a precursor to cardiac arrest or sudden death in humans

Exclusion criteria: Animal studies, studies of medication management of seizure disorders, studies of seizures related to specific genetic or metabolic syndromes, studies of the effects of diet or seasonality on epileptic seizures, studies of seizure activity as part of post cardiac arrest syndrome, studies without detail about the seizure activity circumstances of death

Search results:

The combined searches outlined above yielded 445 studies:

- 24 were case reports of individual patient(s)
- 310 were deemed not relevant to the PICO question
- 82 were review papers and not scientific studies
- 13 were not published in English
- 2 were systematic reviews

Number of studies meeting inclusion / exclusion criteria for worksheet inclusion: 18

Six LOE III-3 studies and twelve LOE IV studies have provided evidence for this guideline

Methodological quality, levels of evidence & outcomes of studies examining pre-hospital oxygen use

Good The methodological quality of the study is high with the likelihood of any significant bias being minimal	Fair The methodological quality of the study is reasonable with the potential for significant bias being likely.	Poor The methodological quality of the study is weak possessing considerable and significant biases
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1. Studies *supportive* of seizure as a risk factor for cardiac arrest:

Good							
Fair					Bardai et al. 2012 (A) Hitiris et al. 2007 (E) Lamberts et al. 2012 (E) Stecker et al. 2013 (A)	Bennani et al. 1997 (B) Holst et al. 2013 (E) Kloster et al. 1999 (D) Lear-Kaul et al. 2005 (F)	
Poor						Leestma et al. 1989 (F) Nashef et al. 1996 (G)	
	I	II	III-1	III-2	III-3	IV	Extrapolated evidence
NH&MRC levels of evidence							

2. Studies *neutral* for seizure as a risk factor for cardiac arrest:

Good							
Fair					Walczak et al. (2001) (D)	Leestma et al. 1984 (H)	
Poor					Opeskin et al. 2003 (E)	Lip et al. 1992 (F) Nashef et al. 1995 (F) Opeskin et al 2000 (F) Pollanen et al. 2012 (F)	
	I	II	III-1	III-2	III-3	IV	Extrapolated evidence
NH&MRC levels of evidence							

3. Studies *opposing* seizure as a risk factor for cardiac arrest:

Good							
Fair						Dami et al. 2012 (C)	
Poor							
	I	II	III-1	III-2	III-3	IV	Extrapolated evidence
NH&MRC levels of evidence							

Endpoints:

- A = Sudden cardiac arrest: victims with and without epilepsy
- B = Sudden death in adult victims
- C = Cardiac or respiratory arrests in victims with seizure
- D = Sudden and non-sudden deaths in victims with epilepsy
- E = Sudden unexpected death: victims with and without epilepsy
- F = Sudden unexpected death: victims with epilepsy
- G = Apnoea & bradycardia during epileptic seizures
- H = Sudden unexpected death: victims with seizure disorders

Treatment recommendation: N/A

Class: N/A

Summary of science

There are no published high level studies that quantify the proportion of seizures that are the beginning stages of cardiac arrest or that quantify the risk of cardiac arrest in victims who exhibit seizure activity. There were five LOE III-3 studies located and all of these studies focused on epilepsy as the cause of seizure activity. Four studies compared cardiac arrest / sudden unexpected death in victims with and without epilepsy and concluded cardiac arrest / sudden unexpected death in victims is more common in victims who have epilepsy. None of these studies (Bardai et al. 2012; Hitiris et al. 2007; Lamberts et al. 2012; Stecker et al. 2013) could definitively quantify the proportion of seizures that were the beginning stages of cardiac arrest or whether seizure activity caused cardiac arrest / sudden death. The remaining study (Opeskin et al. 2003) used data collected from questionnaires were sent to treating doctors requesting information shortly after the death and found no significant difference between the number of witnessed deaths, and the number of seizures in witnessed deaths in the sudden and unexpected death from epilepsy group versus control group. It should be noted that there were only 50 patients in each group.

There were nine LOE IV studies identified. Of the studies with fair quality of evidence;

- one study (Bennani et al. 1997) examined all causes of sudden cardiac death in adults and found that 34% of sudden deaths in young adults were secondary to epilepsy.
- one study (Holst et al. 2013) found that sudden unexpected death were more frequent in patients with epilepsy when compared to those without epilepsy.
- two studies focused solely on patients with epilepsy and found the sudden unexpected deaths were more common than non-sudden deaths (Kloster et al. 1999) and that 58% of patients who suffered sudden unexpected deaths had evidence of recent seizure activity (Lear-Kaul et al. 2005).

Of the five studies with poor quality of evidence

- one study (Leestma et al. 1989) that 10 of 19 patients with plausible anatomical or toxicological cause of death had their death connected with seizure activity. Further 50% of victims in whom the cause of death was not directly related to seizure activity, had evidence of having a seizure close to time of death.
- one study (Nashef et al. 1996) showed that 58% of patients having a seizure had apnoea for >10 seconds

The remaining three studies focused on sudden and unexpected death in patients with epilepsy (Lip et al. 1992; Nashef et al. 1995; Opeskin et al 2000; Walczak et al. 2001; Pollanen et al. 2012) or known seizure disorders (Leestma et al. 1984) but these studies had no comparison groups of patients without epilepsy.

Reviewer's final comments:

There are no published high level studies that quantify the proportion of seizures that are the beginning stages of cardiac arrest or that quantify the risk of cardiac arrest in victims who exhibit seizure activity. Many of the studies are based on medical record audits or coronial data. It appears based on the evidence to date, victims who have epilepsy or exhibit seizure activity are

at higher risk of sudden cardiac arrest or sudden cardiac death than those without epilepsy or do not exhibit seizure activity. Victims in whom a generalised seizure has occurred should be assessed for cardiac arrest and the need for resuscitation when seizure activity stops. Victims of seizure should be reassessed for the need for resuscitation at regular intervals while they remain unresponsive.

Evidence gaps and research priorities:

The reliability of seizure activity as an indicator of cardiac arrest warrants further investigation.

Citation List:

Bardai, A., Lamberts, R. J., Blom, M. T., Spanjaart, A. M., Berdowski, J., van der Staal, S. R., . . . Tan, H. L. (2012). Epilepsy is a risk factor for sudden cardiac arrest in the general population. *PLoS One*, 7(8), e42749. doi: 10.1371/journal.pone.0042749

BACKGROUND: People with epilepsy are at increased risk for sudden death. The most prevalent cause of sudden death in the general population is sudden cardiac arrest (SCA) due to ventricular fibrillation (VF). SCA may contribute to the increased incidence of sudden death in people with epilepsy. We assessed whether the risk for SCA is increased in epilepsy by determining the risk for SCA among people with active epilepsy in a community-based study. METHODS AND RESULTS: This investigation was part of the Amsterdam Resuscitation Studies (ARREST) in the Netherlands. It was designed to assess SCA risk in the general population. All SCA cases in the study area were identified and matched to controls (by age, sex, and SCA date). A diagnosis of active epilepsy was ascertained in all cases and controls. Relative risk for SCA was estimated by calculating the adjusted odds ratios using conditional logistic regression (adjustment was made for known risk factors for SCA). We identified 1019 cases of SCA with ECG-documented VF, and matched them to 2834 controls. There were 12 people with active epilepsy among cases and 12 among controls. Epilepsy was associated with a three-fold increased risk for SCA (adjusted OR 2.9 [95%CI 1.1-8.0], $p=0.034$). The risk for SCA in epilepsy was particularly increased in young and females. CONCLUSION: Epilepsy in the general population seems to be associated with an increased risk for SCA.

NHMRC:III-3. Case control study of 1019 cases of cardiac arrest and 2834 controls. Cases were patients with suspected out-of-hospital SCA. Controls were randomly drawn from the same source community as cases using GP database.

QUALITY: Fair

OUTCOME: Epilepsy was associated with three-fold increased risk of sudden cardiac arrest (adjusted OR 2.9 [95% CI 1.1–8.0], $p = 0.034$). The most common risk factors for SCA were heart failure (adjusted OR 9.9 [95% CI:5.8-17], $p<0.001$) and ischaemic cardiovascular disease (adjusted OR 6.7 [95% CI 5.0 – 8.8, $p<0.001$).

INTERVENTION: N/A

Bennani, F. K., & Connolly, C. E. (1997). Sudden unexpected death in young adults including four cases of SADS: a 10-year review from the west of Ireland (1985-1994). *Med Sci Law*, 37(3), 242-247.

Sudden unexpected death in young adults of 18-35 years account for an important subset of deaths in our autopsy population. The case notes and autopsy reports in 44 subjects were analysed during the period 1985-94 at the Department of Histopathology, University College Hospital, Galway to establish the underlying cause of death. Subjects who were involved in road traffic accidents, cases of drowning, and patients with known congenital heart disease, chronic renal failure and malignancy were excluded. We found that a large proportion of sudden deaths in young adults were secondary to epilepsy and chemical/drug poisoning, accounting for 34 per cent and 31.8 per cent respectively. Sudden adult death syndrome (SADS) accounted for 9 per cent of the study population. Detailed case history, meticulous post-mortem examination and complete toxicological screening are recommended to arrive at the underlying cause of death.

NHMRC: IV.

QUALITY: Fair

OUTCOME: Sudden adult death syndrome occurred in 9% of the study population: 34% of sudden deaths in young adults were secondary to epilepsy

INTERVENTION: N/A

Dami, F., Rossetti, A. O., Fuchs, V., Yersin, B., & Hugli, O. (2012). Proportion of out-of-hospital adult non-traumatic cardiac or respiratory arrest among calls for seizure. *Emerg Med J*, 29(9), 758-760. doi: 10.1136/emmermed-2011-200234

OBJECTIVES: To measure the proportion of adult non-traumatic cardiac or respiratory arrest among calls for seizure to an emergency medical dispatch centre and to record whether known epileptic patients present cardiac or respiratory arrest together with seizure. METHODS: This 2-year prospective observational investigation involved the collection of tape recordings of all incoming calls to the emergency medical dispatch centre, in which an out-of-hospital non-traumatic seizure was the chief complaint in patients >18 years, in addition to the paramedics' records of all patients who presented with respiratory or cardiac arrest. The authors also recorded whether the bystander spontaneously mentioned to the dispatcher that the victim was known to have epilepsy. RESULTS: During the 24-month period, the call centre received 561 incoming calls for an out-of-hospital non-traumatic seizure in an adult. Twelve cases were classified as cardiac or respiratory arrest by paramedics. In one case, the caller spontaneously mentioned that the victim had a history of epilepsy. The proportion of cardiac or respiratory arrest among calls for seizure was 2.1%. CONCLUSION: Although these cases are rare, dispatchers should closely monitor seizure patients with the help of bystanders to exclude an out-of-hospital cardiac or respiratory arrest, in which case the dispatcher can offer telephone cardiopulmonary resuscitation advice until the paramedics arrive. Whenever the activity of the centre allows it and no new incoming call is on hold, this can be achieved by staying on the line with the caller or by calling back. A history of epilepsy should not modify the type of monitoring performed by the dispatcher as those patients may also have an arrest together with seizure.

NHMRC: IV

QUALITY: Fair

OUTCOME: The proportion of cardiac or respiratory arrest among calls for seizure was 2.1%.

INTERVENTION: N/A

Hitiris, N., Suratman, S., Kelly, K., Stephen, L. J., Sills, G. J., & Brodie, M. J. (2007). Sudden unexpected death in epilepsy: a search for risk factors. *Epilepsy Behav*, 10(1), 138-141. doi: 10.1016/j.yebeh.2006.11.010

Sudden unexpected death in epilepsy (SUDEP) is the commonest cause of seizure-related mortality in people with refractory epilepsy. Of the 6140 patients registered with the Epilepsy Unit at the Western Infirmary in Glasgow between 1982 and 2005, 529 had died, 62 (11.7%) of whom succumbed to SUDEP. All but 2 deaths occurred at home; 3 were witnessed. Two living controls were matched with each SUDEP case for year of birth, gender, and syndromic classification. Mean duration of epilepsy was significantly longer in cases compared with controls ($P=0.001$). More people succumbing to SUDEP had had a seizure within the previous year ($P=0.007$). There were no significant associations between SUDEP and a history of generalized tonic-clonic seizures, drug polytherapy, and current use of carbamazepine. There is an urgent need for a large-scale, prospective, international, community-based study of SUDEP to explore more closely the risk factors to plan preventive strategies.

NHMRC: III-3 Cases = patients who had a sudden unexpected death in epilepsy. Controls = living controls for each case were matched for year of birth (± 3 years), gender, and syndromic classification (idiopathic, cryptogenic, or symptomatic). For each case, two controls were randomly chosen from this eligible

population by computed number generation.

QUALITY: Fair

OUTCOME: Sudden unexpected death in epilepsy accounted for 11.7% of all deaths in this cohort over the period. Six deaths fitted the criteria for definite SUDEP, and 56 deaths were classified as probable SUDEP. Three witnessed deaths: the victims had had a convulsive episode prior to death in all three cases. Mean duration of epilepsy was significantly longer in cases compared with controls ($P = 0.001$). More people succumbing to SUDEP had had a seizure within the previous year ($P = 0.007$).

INTERVENTION: N/A

Holst, A. G., Winkel, B. G., Risgaard, B., Nielsen, J. B., Rasmussen, P. V., Haunso, S., . . . Tfelt-Hansen, J. (2013). Epilepsy and risk of death and sudden unexpected death in the young: a nationwide study. *Epilepsia*, 54(9), 1613-1620. doi: 10.1111/epi.12328

PURPOSE: Patients with epilepsy are at increased risk of premature death from all causes and likely also from sudden unexplained death (SUD). Many patients with epilepsy have significant comorbidity, and it is unclear how much of the increased risk can be explained by epilepsy itself. We aimed to chart the incidence of sudden unexpected death in epilepsy (SUDEP) and estimate the risk of death from all causes and SUD conferred by epilepsy independently. METHODS: We conducted a historical cohort study using data from Danish registries and a complete manual review of all death certificates. The population studied consisted of all Danish residents in the age group 1-35 years, in the period 2000-2006 (inclusive), and the main outcome measures were risk of death and SUD. KEY FINDINGS: We identified 33,022 subjects with epilepsy (median follow-up 3.7 years) and 3,001,952 subjects without (median follow-up 7.0 years). Among 685 deaths in the population with epilepsy, we identified 50 cases of definite and probable SUDEP corresponding to an incidence rate of 41.1 (95% confidence interval [CI] 31.6-54.9) per 100,000 person-years. Incidence rates increased with age from 17.6 (95% CI 9.5-32.8) in the age group 1-18 years to 73.8 (95% CI 52.5-103.8) for the age group 24-35 years. Having epilepsy increased the crude risk of death with a hazard ratio (HR) of 11.9 (95% CI 11.0-12.9). When adjusting for sex and comorbidities often encountered in patients with epilepsy (neurologic disease including cerebral palsy, psychiatric disease including mental retardation, and congenital disorders), as well as the Charlson comorbidity score, the HR fell to 5.4 (95% CI 4.9-6.0). The crude HR for SUD was 27.5 (95% CI 18.1-41.8) and fell to 16.3 (95% CI 9.8-26.9) when adjusted for the same covariates as above. SIGNIFICANCE: Epilepsy in and of itself carries a significant risk of premature death and SUD. These findings highlight the potential gains of risk factor modification for the prevention of premature death and SUDEP in patients with epilepsy.

NHMRC: IV

QUALITY: Fair

OUTCOME: 33,022 subjects with epilepsy and 3,001,952 subjects without: 685 deaths in epilepsy patients aged 1-35 years. There were 50 cases of sudden unexpected death in epilepsy (26 definite / 24 probable) = 6 were witnessed. Sudden unexpected death rate in the non-epilepsy population = 0.80 (95% CI 0.68-0.95). The incidence rate for definite and probable sudden unexpected death in the epilepsy population was 41.1 (95% CI 31.6-54.9) per 100,000 person-years.

INTERVENTION: N/A

Kloster, R., & Engelskjøn, T. (1999). Sudden unexpected death in epilepsy (SUDEP): a clinical perspective and a search for risk factors. *J Neurol Neurosurg Psychiatry*, 67(4), 439-444.

OBJECTIVES: To examine the risk factors and their relative importance and possible role in sudden unexpected death in epilepsy (SUDEP). METHODS: The study was conducted as a retrospective analysis of deaths in an outpatient population of a tertiary referral centre, based on clinical and pathological data.

RESULTS: Of a total of 140 deaths, 61 (44%) had not been to postmortem and were excluded, 37 (26%) had a verified cause of death and formed the non-SUDEP group, and 42 (30%) were classified as SUDEP. In

the SUDEP group there was pulmonary oedema in 62%, signs of preceding seizures in 67%, no visible seizures in three of six observed deaths. A high seizure frequency prevailed in SUDEP as well as non-SUDEP. Sixty per cent of deaths were sleep related. Various other circumstances were temporally associated with death. The prone position at death was seen in 71% of the SUDEP patients; possible interpretations are discussed. Supposedly subtherapeutic serum concentrations of one or more antiepileptic drugs were found in 57% of those with reported serum concentrations. Alcohol was not a factor in the material, whereas hyponatraemia was seen in two cases. CONCLUSIONS: Most cases of SUDEP are preceded by seizures; their presence, frequency, type, aetiology, tractability, and the use of antiepileptic drugs are factors in the demise. No common risk factor, present in all cases of SUDEP, could be found, suggesting the probability of multiple mechanisms behind SUDEP.

NHMRC: IV

QUALITY: Fair

OUTCOME: 140 patients with epilepsy who died between 1965 and 1996: 42 patients with sudden unexpected death in epilepsy and 37 non-sudden unexpected death in epilepsy. Patients with sudden unexpected death in epilepsy. In the SUDEP group, 67% had signs of seizures immediately before death (observed seizures, fresh bites, blood on the pillow, and cyanosis, reported sounds of ongoing seizures) compared with 35% of the non-SUDEP group ($p=0.002$).

INTERVENTION: N/A

Lamberts, R. J., Thijs, R. D., Laffan, A., Langan, Y., & Sander, J. W. (2012). Sudden unexpected death in epilepsy: people with nocturnal seizures may be at highest risk. *Epilepsia*, 53(2), 253-257. doi: 10.1111/j.1528-1167.2011.03360.x

PURPOSE: Most people with epilepsy who die suddenly and whose death is attributed to sudden unexpected death in epilepsy (SUDEP) are found in or by the bed for unknown reasons. We assessed whether those with sleep-related SUDEP were more likely to have nocturnal seizures, and whether seizure patterns (diurnal vs. nocturnal) differed from people dying suddenly and living controls with epilepsy. METHODS: Seizure patterns in a cohort of 154 people with epilepsy who died suddenly and after autopsy conformed to the definition of SUDEP and 616 controls living with epilepsy were classified as having "exclusively diurnal" or "nocturnal seizures." Comparisons were made between the groups. SUDEP was classified as sleep-related or non-sleep-related based on eyewitness accounts and the circumstances surrounding death. KEY FINDINGS: SUDEP was primarily a sleep-related (58%) and unwitnessed (86%) event. If sleep-related, SUDEP was more likely to be unwitnessed [odds ratio (OR) 4.4, 95% confidence interval (CI) 1.6-12]. Those with sleep-related SUDEP were more likely to have a history of nocturnal seizures than those who had non-sleep-related SUDEP (OR 3.6, 95% CI 1.4-9.4). Those who died were more likely to have a history of nocturnal seizures than living controls (OR 3.9, 95% CI 2.5-6.0). After correction for previously established SUDEP risk factors (Langan et al., 2005), the presence of nocturnal seizures remained significant (OR 2.6, 95% CI 1.3-5.0). SIGNIFICANCE: Nocturnal seizures seem to be an independent risk factor for SUDEP. These findings underscore the importance of preventive measures, which may include night supervision.

NHMRC: III-3 Case-control study. 154 autopsy confirmed SUDEP cases identified by coroners, neurologists, and self-referred family members. Each case had four controls matched for age (≤ 5 years) and geographic location

QUALITY: Fair

OUTCOME: After correction for previously established SUDEP risk factors the presence of nocturnal seizures remained significant in SUDEP group (OR 2.6, 95% CI 1.3-5.0)

INTERVENTION: N/A

Lear-Kaul, K. C., Coughlin, L., & Dobersen, M. J. (2005). Sudden unexpected death in epilepsy: a retrospective study. *Am J Forensic Med Pathol*, 26(1), 11-17.

Patients with epilepsy have a mortality rate higher than that of the general population; sudden unexpected death represents a significant category of mortality in these patients. The precise frequency of occurrence of sudden unexpected death in epilepsy (SUDEP) is not well defined, with a range of 1 in 370 to 1100 in the general epileptic population. A major difficulty with incidence studies is the continued reluctance in using the term SUDEP as a cause of death, making reliance solely on death certificates inconsistent and incomplete. Knowledge about SUDEP remains limited, as no single common risk factor has yet been identified, although predisposing conditions have been suggested. The purpose of this study is to review the association between several clinical variables and SUDEP to elucidate risk factors. The characteristics of the 67 cases in this series correlate with published findings in previous studies. Attributes that may be used to define an at-risk group of epileptics include age less than 40 years, male gender, long history of seizure disorder, undermedication or poorly controlled seizure activity, and mental or physical stress. Education of physicians as to the existence of SUDEP and risk factors is imperative in improving patient education and reduction in mortality.

NHMRC: IV

QUALITY: Fair

OUTCOME: 16 of the 67 deaths were witnessed, with reports of seizure activity in 12 deaths. 14 patients received treatment in the ED or by paramedics or other medical personnel) but were not able to be resuscitated. At autopsy, evidence suggesting recent seizure activity (tongue lacerations and contusions and/or superficial cutaneous abrasions and contusions) was detected in 39 cases (58%). The cause of death listed on the death certificate was termed SUDEP in 8 cases (12%); the majority of cases were signed out as seizure disorder or complications thereof (38 cases, 57%) or probable seizure (18 cases, 28%). Three cases listed other causes on the death certificate, including positional asphyxia and complications of blunt impact trauma to the head

INTERVENTION: N/A

Leestma, J. E., Kalelkar, M. B., Teas, S. S., Jay, G. W., & Hughes, J. R. (1984). Sudden unexpected death associated with seizures: analysis of 66 cases. *Epilepsia*, 25(1), 84-88.

We have analyzed 66 cases of sudden unexpected death (SUD) in persons with seizure disorders, which were examined by the Office of the Medical Examiner, Cook County (Chicago), Illinois. The individuals ranged in age from 10 months to 60 years (mean age, 28 years). Autopsy findings were insufficient to explain death, and there was no evidence of major systemic pathology. Approximately 40% of victims were found dead in bed, and the remainder in some other room at home, apparently having been engaged in normal activity. Several died in an emergency room following a seizure at home.

Cardiopulmonary resuscitation was attempted but was ineffective. Neuropathological examination revealed brain lesions, which probably caused the seizures, in 60% of the cases. In 68% the anticonvulsant blood level was subtherapeutic or below detectable levels. The prevalence of seizure-associated SUD may be between 1:525 and 1:2,100 among epileptics. The mechanism of death in these cases probably involves cardiac arrhythmias mediated by sympathetic autonomic events occurring during the seizure.

NHMRC: IV

QUALITY: Fair

OUTCOME: 66 cases of sudden unexpected death in persons with seizure disorders: 17% died in the ED or ICU having been brought to hospital with a seizure. The number of other victims in whom seizure activity was witnessed or likely immediately prior to death is not reported.

INTERVENTION: N/A

Leestma, J. E., Walczak, T., Hughes, J. R., Kalelkar, M. B., & Teas, S. S. (1989). A prospective study on sudden unexpected death in epilepsy. *Ann Neurol*, 26(2), 195-203. doi: 10.1002/ana.410260203

Sudden unexpected death accounts for a substantial portion of deaths among epileptics. The incidence of

this phenomenon is probably 1 in 370 to 1 in 1,110 in the general epileptic population but may be even higher in the 20- to 40-year age group, and still higher if epileptics with symptomatic epilepsy are selected. Sudden unexpected death in epileptics has been observed at least once weekly by the Office of the Medical Examiner of Cook County (Chicago), Illinois, for many years. A year-long prospective study revealed that victims of this complication of epilepsy are most commonly black males averaging 35 years of age who have infrequent generalized seizures and usually have some structural lesion in the brain responsible for their seizures. They tend to abuse alcohol and have poor compliance with anticonvulsant medication. The electroencephalograms display considerable variability from record to record. At autopsy the heart, lung, and liver weights were heavier and the brain weights were lighter than expected. The mechanisms involved in sudden unexpected death in epileptics may include autonomically mediated cardiac arrhythmia alone or in combination with sudden "neurogenic" pulmonary edema and "backward" cardiac failure.

NHMRC: IV

QUALITY: Poor

OUTCOME: 79 cases in which death appeared to be sudden or unexpected or both in an individual known to suffer or suspected of suffering from a seizure disorder (epilepsy). A plausible anatomical or toxicological cause of death was found in 19 of these cases: 5 apparently suffered serious head injury in connection with their seizures; 3 died of drug overdoses, 3 died of coronary occlusions, 3 drowned in the bath (probably with a seizure), and 2 died following aspiration while in a seizure state. Ten victims sustained a witnessed seizure while at home and engaged in normal activity: in most [does not say how many] of these, resuscitative measures were attempted but were not successful. Three victims survived admission to a hospital after their seizures and collapse, but were found pulseless 2 to 4 hours later. In 7 cases, no seizure was witnessed, but these victims were discovered at autopsy to have acute tongue lacerations consistent with seizure bites. About half of the 60 victims in whom cause of death was not directly related to seizure activity showed evidence of having had a seizure close to the time of death.

INTERVENTION: N/A

Lip, G. Y., & Brodie, M. J. (1992). Sudden death in epilepsy: an avoidable outcome? *J R Soc Med*, 85(10), 609-611.

In a retrospective survey of mortality among the first 1000 unselected patients referred to the Epilepsy Research Unit at the Western Infirmary in Glasgow between 1985 and 1990, a total of 18 deaths were identified. Three patients had committed suicide and one each had died of status epilepticus in hospital, a subdural haematoma and a myocardial infarction. The remaining 12 deaths (67%) were sudden (median age 32 years; range 22-68 years). Poor seizure control and poor compliance with antiepileptic drug therapy were recorded in only three (25%) of these patients. There was a change in antiepileptic drug regimen in five (28%) in the month before death. Only two (17%) underwent postmortem examination. In nine of the 12 patients dying suddenly, the primary cause of death was not listed as epilepsy but as asphyxia (3), aspiration (2) and one each of ischaemic heart disease, myocardial infarction, asystole and drowning (in the bath). 'Status epilepticus' was assumed to have been responsible for the other three deaths, two of which were unwitnessed. Sudden death in people with epilepsy is an entity of great concern. Appropriate death certification and mandatory postmortem examination are essential to provide a truer picture of this neglected phenomenon.

NHMRC: IV

QUALITY: Poor

OUTCOME: analysis of 18 deaths from first 1000 patients referred to epilepsy research unit raising questions of sample representativeness. One patients had witnessed generalised seizure prior to death, nine patients found in bed or bedroom and two patients collapsed suddenly without having had a seizure.

INTERVENTION: N/A

Nashef, L., Fish, D. R., Sander, J. W., & Shorvon, S. D. (1995). Incidence of sudden unexpected death in an adult outpatient cohort with epilepsy at a tertiary referral centre. *J Neurol Neurosurg Psychiatry*, 58(4), 462-464.

Overall mortality, incidence of sudden unexpected death, and cause of death were determined in 601 adult outpatients with epilepsy at a tertiary referral centre. The patients were followed up from 1990 to 30 June 1993. There were 24 deaths among the 601 patients (1849 patient years) with a standardised mortality ratio of 5.1 (95% confidence interval 3.3-7.6) of which 14 were related to epilepsy. Underlying disease of which epilepsy was a symptom accounted for four deaths only. An incidence of sudden deaths (including seizure related) was of the order of 1:200/year. In conclusion, excess mortality in chronic epilepsy is more likely to be related to the epilepsy itself than to underlying pathology. The relatively high incidence of sudden deaths found in this hospital based cohort has important implications for patient management.

NHMRC: IV

QUALITY: Poor – no comparison group

OUTCOME: Analysis of 601 patients from a hospital outpatient department with diagnosed epilepsy: follow up for three years. A total of 24 patients died during the follow up period, representing an overall mortality of 1:77 per year and an standardised mortality ratios of 5.1 (95% confidence interval (95% CI) 3-3-7 6). At least 14 deaths (58%) were considered to be related to epilepsy. There were 11 unexpected sudden deaths: evidence suggesting a seizure was found in seven of 11 cases.

INTERVENTION: N/A

Nashef, L., Walker, F., Allen, P., Sander, J. W., Shorvon, S. D., & Fish, D. R. (1996). Apnoea and bradycardia during epileptic seizures: relation to sudden death in epilepsy. *J Neurol Neurosurg Psychiatry*, 60(3), 297-300.

OBJECTIVE: To record non-invasively ictal cardiorespiratory variables. METHODS: Techniques employed in polysomnography were used in patients with epilepsy undergoing EEG-video recording at a telemetry unit. RESULTS: Apnoea (> 10, range > 10-63, mean 24 s) was seen in 20 of 47 clinical seizures (three secondary generalised, 16 complex partial, and one tonic) and 10 of 17 patients. Apnoea was central in 10 patients, but obstructive apnoea was also recorded in three of 10. Oxyhaemoglobin saturation (SpO₂) dropped to less than 85% in 10 seizures (six patients). An increase in heart rate was common (91% of seizures). Bradycardia/sinus arrest was documented in four patients (mean maximum RR interval 5.36, range 2.8-8.6 s) but always in the context of a change in respiratory pattern. CONCLUSION: Ictal apnoea was often seen. The occurrence of bradycardia in association with apnoea suggests the involvement of cardiorespiratory reflexes. Similar mechanisms may operate in cases of sudden death in epilepsy.

NHMRC: IV

QUALITY: Poor – small sample

OUTCOME: Analysis of 47 seizures in 17 patients. Apnoea (> 10 s) was documented in 10 patients: duration ranged from >10 to 63 seconds with a mean of 24 seconds. SpO₂ dropped to less than 85% in 10 seizures (six patients) in association with apnoea. Transient bradycardia/sinus arrest was documented in four patients. Increase in heart rate occurred in 91% of seizures (39 of 41) including patients with later ictal bradycardia.

INTERVENTION: N/A

Opeskin, K., & Berkovic, S. F. (2003). Risk factors for sudden unexpected death in epilepsy: a controlled prospective study based on coroners cases. *Seizure*, 12(7), 456-464.

We performed a controlled prospective study of pathologically verified sudden unexpected death in epilepsy (SUDEP) in a coronial setting, to identify risk factors. We prospectively studied coronial deaths of

people with epilepsy in Vic., Australia, during a 21-month period. Fifty SUDEP and 50 subjects with epilepsy who died of other causes (controls) were collected sequentially. Clinical data was obtained shortly after death from questionnaires completed by treating doctors, discussion with family members and coronial files, including police reports of death, autopsy and toxicology reports. Factors assessed were age, sex, duration of epilepsy, type of seizure(s), seizure frequency, symptomatic epilepsy, including post-traumatic epilepsy, presence of structural brain lesion, idiopathic epilepsy, mental retardation, psychiatric illness, including dementia, recent stressful life event, particular antiepileptic drugs (AEDs) and AED polytherapy, compliance with AED treatment, psychotropic drug prescription, alcohol and other substance abuse, place of death and evidence of terminal seizure. The SUDEP group was characterised by younger age and higher proportion found dead in bed and with evidence of terminal seizure compared to controls. The profile of patients at risk for SUDEP are young people with epilepsy. They are most likely to die in sleep and our data support the view that SUDEP is a seizure-related event. This, taken in conjunction with the finding that there was no increased risk associated with a particular AED in monotherapy or multiple AEDs suggests that attempts to better treat patients' epilepsy with AEDs might decrease the risk of SUDEP. Although the literature suggests that SUDEP is more frequent in patients with severe epilepsy, we did not find a correlation with seizure frequency suggesting that other clinical indices may be more important.

NHMRC: III-3

QUALITY: Poor

OUTCOME: Cases = police reports of death were searched for subjects with a history of epilepsy (n = 50). Controls = patients with a history of epilepsy who died from other causes (n = 50). Cases and controls were collected sequentially and not matched in any way other than for assessment period. Questionnaires were sent to treating doctors requesting information shortly after the death. Evidence of terminal seizure was significantly more common in the SUDEP group (44% vs 16%, $p < 0.002$). Six SUDEPs were witnessed and seizure occurred in all of these. Three deaths in the control group were witnessed and a seizure was witnessed in one of these. There was no significant difference between the number of witnessed deaths, and the number of seizures in witnessed deaths in the SUDEP group versus control group.

INTERVENTION: N/A

Opeskin, K., Harvey, A. S., Cordner, S. M., & Berkovic, S. F. (2000). Sudden unexpected death in epilepsy in Victoria. *J Clin Neurosci*, 7(1), 34-37.

Sudden unexpected death in epilepsy (SUDEP) refers to sudden unexpected death in patients with epilepsy in whom autopsy fails to reveal an anatomic or toxicological cause of death. The purpose of this study was to examine associated factors and mechanisms relating to SUDEP in Victoria. The study was a retrospective study based on data from questionnaires completed by treating doctors and coronial files including police reports of death, autopsy and toxicology reports. The deaths were of people with epilepsy in Victoria that were referred to the coroner between 1991 and 1997. There were 15,751 coronial autopsies of which 357 had epilepsy and 50 (14%) were SUDEPs. The SUDEP rate was approximately 1 per 3000 epileptics per year. This study suggested the following associations: young age, tonic-clonic seizures, seizure frequency greater than 10/year, duration of epilepsy greater than 10 years, mental retardation, psychiatric disease and alcohol abuse. Antiepileptic drug (AED) compliance was rated by treating doctors as good in 24 cases. One or more postmortem AED drug levels was subtherapeutic in 30 of 50 cases. Only 5 were receiving psychotropic drugs; only 1 of these was receiving more than one of these drugs. A history of recent unusually stressful life event was present in only 4 cases. At least 11 showed evidence of terminal seizure, and the majority of events occurred in sleep. These observations support the hypothesis that seizures are the mechanism of many cases of SUDEP. The associations observed were largely in agreement with previous studies. However, seizure frequency was greater and duration of epilepsy greater than most previous studies. The role of factors such as AED compliance,

psychotropic drug prescription and recent unusually stressful life event is less clear. This highlights the need for case-control studies of risk factors for SUDEP.

NHMRC:IV

QUALITY: Poor – no comparison group

OUTCOME: Retrospective study based on data from questionnaires completed by treating doctors. There were 15 751 coronial autopsies between April 1971 and December 1997 of which 357 were epileptic deaths. Of these 357 epileptic deaths 50 (14%) were SUDEPs (sudden unexpected deaths where autopsy failed to reveal an anatomic or toxicologic cause of death). At least 11 of the 50 cases showed evidence of a terminal seizure. Death was observed in 2 of the 50 SUDEP cases. In one of these cases the deceased had a generalised tonic-clonic seizure and died. In the other case the deceased was found gasping for air without apparent convulsion. Additionally, 10 cases showed evidence of terminal seizure in the form of bitten lip or tongue, urinary incontinence, body half on or half off bed or 'wrapped up' in sheets. In an additional 5 cases a seizure was observed within a few hours before death.

INTERVENTION: N/A

Pollanen, M. S., & Kodikara, S. (2012). Sudden unexpected death in epilepsy: a retrospective analysis of 24 adult cases. *Forensic Sci Med Pathol*, 8(1), 13-18. doi: 10.1007/s12024-011-9263-4

Sudden unexpected death in epilepsy is a common form of seizure-related death but is poorly appreciated by the medical profession. A number of risk factors have been identified in this context including male gender, young adult age group (20-40 years), poor compliance with antiepileptic drugs, polytherapy, and presence of neuropathological lesions. In addition it has been noted that most of the victims sustained an unwitnessed collapse at home. In this paper, we describe a retrospective review of 24 adult cases of sudden unexpected death in epilepsy. The study recognizes two risk factors; poor compliance with anti-epileptic monotherapy and an age between 20 and 29 years. All the victims were found dead at home and only one had a witnessed collapse. Our study shows a variety of neuropathological findings as the etiology. The completeness of the autopsy findings for all the cases is a strength compared to some of the other studies.

NHMRC: IV

QUALITY: Poor – no comparison group

OUTCOME: Analysis of 24 cases of sudden unexpected death in epilepsy. Twenty-three were found dead (96%) while only one had a witnessed collapse (4%). Six individuals had bitten tongues (25%).

INTERVENTION: N/A

Stecker, E. C., Reinier, K., Uy-Evanado, A., Teodorescu, C., Chugh, H., Gunson, K., . . . Chugh, S. S. (2013). Relationship between seizure episode and sudden cardiac arrest in patients with epilepsy: a community-based study. *Circ Arrhythm Electrophysiol*, 6(5), 912-916. doi: 10.1161/circep.113.000544

BACKGROUND: Among patients with epilepsy, sudden cardiac arrest (SCA) is a major cause of death. It is commonly thought that SCA in epilepsy occurs after a seizure, though the strength of evidence supporting this is limited. We sought to evaluate the relationship between seizures and SCA in patients with epilepsy.

METHODS AND RESULTS: From the ongoing Oregon Sudden Unexpected Death Study, cases of SCA identified using prospective, multisource ascertainment (Portland metropolitan area, Oregon; population approximately 1 million; February 1, 2002, to March 1, 2012) were evaluated for history of epilepsy. In the subset with witnessed SCA, clinical presentations were analyzed for evidence of seizure activity immediately before the event as well as lifetime clinical history, including nature of seizures before SCA.

Only 34% of patients with history of epilepsy and a witnessed arrest had evidence of seizure activity before the arrest. Rates of survival to hospital discharge after attempted resuscitation were 2.7% in patients with history of epilepsy versus 11.9% for patients without epilepsy (P=0.014). Patients with epilepsy had a significantly lower rate of presentation with ventricular tachycardia/ventricular fibrillation

as opposed to pulseless electrical activity/asystole (epilepsy, 26%; no epilepsy, 44%; $P=0.002$), despite nearly identical response times. CONCLUSIONS: In the majority (66%) of epilepsy patients, there was no relationship between seizure and SCA, implying that SCA in epilepsy patients often may not involve seizure as a trigger. The significantly worse rate of survival from SCA in epilepsy patients warrants urgent investigation.

NHMRC: III-3

QUALITY: Fair

OUTCOME: 2417 patients with sudden cardiac arrest identified during 10-year follow-up, 106 (4.4%) had a history of epilepsy and 2311 (95.6%) did not have epilepsy. Resuscitation was attempted in 75 (71%) patients with epilepsy and 1710 (74%) patients without epilepsy ($P=0.52$). The rate of survival to hospital discharge was 2.7% among resuscitated patients with epilepsy and 11.9% among those without epilepsy ($P=0.014$). This difference occurred in the setting of significantly lower rates of presentation with ventricular tachycardia (VT) or ventricular fibrillation (VF) among patients with epilepsy (epilepsy, 26%; no epilepsy, 44%; $P=0.002$) as opposed to presentation with bradycardia/asystole (epilepsy, 47%; no epilepsy, 30%; $P=0.002$). These differences in presenting arrhythmia were observed despite nearly identical response times (epilepsy, 6.8 ± 3.6 minutes; no epilepsy, 6.9 ± 3.6 minutes; $P=0.84$) and identical rates of return of spontaneous circulation (both groups, 36%; $P=0.91$). When restricted to only witnessed arrests, a trend remained for more frequent bradycardia among patients with epilepsy (31% versus 19%, $P=0.06$), though not for other presenting arrhythmias. Witnessed arrest with bystander information was present in 32 (30%) patients with epilepsy. Of these, 11 (34%) demonstrated some seizure-like activity in the period shortly before arrest. Among 50 randomly selected patients without epilepsy, 5 (10%) exhibited seizure-like activity at the time of cardiac arrest ($P=0.01$).

INTERVENTION: N/A

Walczak, T. S., Leppik, I. E., D'Amelio, M., Rarick, J., So, E., Ahman, P., . . . Hauser, W. A. (2001). Incidence and risk factors in sudden unexpected death in epilepsy: a prospective cohort study *Neurology*, 56(4), 519-525.

OBJECTIVE: To determine incidence of and risk factors for sudden unexpected death in epilepsy (SUDEP). METHODS: Three epilepsy centers enrolled 4,578 patients and prospectively followed these patients for 16,463 patient-years. The cohort was screened for death annually. Deaths were investigated to determine whether SUDEP occurred. Potential risk factors were compared in SUDEP cases and in controls enrolled contemporaneously at the same center. RESULTS: Incidence of SUDEP was 1.21/1,000 patient-years and was higher among women (1.45/1,000) than men (0.98/1,000). SUDEP accounted for 18% of all deaths. Occurrence of tonic-clonic seizures, treatment with more than two anticonvulsant medications, and full-scale IQ less than 70 were independent risk factors for SUDEP. The number of tonic-clonic seizures was a risk factor only in women. The presence of cerebral structural lesions and use of psychotropic drugs at the last visit were not risk factors for SUDEP in this cohort. Subtherapeutic anticonvulsant levels at the last visit were equally common in the two groups. No particular anticonvulsant appeared to be associated with SUDEP. CONCLUSIONS: These results support the idea that tonic-clonic seizures are an important proximate cause of SUDEP. This information creates a risk profile for SUDEP that may help direct preventative efforts.

NHMRC: III-3

QUALITY: Fair

OUTCOME: Prospective study of patients from three different epilepsy centres to track sudden and unexpected death from epilepsy. Mortality rate of 2.4% (111/4578): 9% ($n=10$) deaths due to definite SUDEP, 9% ($n=10$) deaths due to probable SUDEP, 7.2% ($n=8$) deaths due to possible SUDEP, 70.2% ($n=78$) deaths not related to SUDEP and 5 patients in whom cause of death was not able to be determined. Overall, 25.5% of deaths were related to SUDEP: while generalised seizures and number of tonic-clonic

seizures were risk factors for SUDEP, the number of patients who suffered a seizure *immediately* before death was not reported.
INTERVENTION: N/A