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Sudden unexpected death in epilepsy (SUDEP): what every neurologist should know

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ABSTRACT – This review aims to empower general neurologists to provide better informed person-centred advice on sudden unexpected death in epilepsy (SUDEP) to people with epilepsy in order to help keep them safe. Past and present evidence is consolidated in order to inform readers about SUDEP, and up-to-date insights into the epidemiology, diagnostic classification, pathophysiology, risk factors, influence of co-morbidity, and importance of sensitive person-centred communication are outlined. This review provides "fingertip" information to the practicing neurologist with regards to identifying and communicating risks for SUDEP and suggests practical measures for managing these risks in partnership with the patient.

Key words: SUDEP, risk factor, communication

Many people with epilepsy (PWE) receive their care from non-specialist physicians or neurologists and neuro-paediatricians without specific epilepsy expertise. Every physician caring for PWE needs to know the risks associated with epilepsy in order to provide appropriate counselling about how to reduce those risks. Reduced life expectancy is a major concern. Epilepsy is associated with a two to three-fold mortality increase when compared to the general population (Wicks and Fountain, 2012). This increased risk is partly due to co-morbidities and the aetiology underlying the epilepsy, and partly due to seizures (Duncan *et al*., 2006; Schuele *et al*., 2007).

Among the major causes of death related to epilepsy, which include accidents and status epilepticus, the most common is sudden unexpected death in epilepsy (SUDEP) (Sander and Bell, 2004). There is a clear need to develop strategies to identify those at increased risk and improve the management of PWE, with the aim of reducing premature mortality, in particular SUDEP.

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Box 1. Brief facts on SUDEP.

Definition
SUDEP is defined as sudden, unexpected, non-traumatic, non-drowning death in an individual with epilepsy, witnessed or unwitnessed, in which post-mortem examination does not reveal an anatomical or toxicological cause of death.

Causes
It is likely that there is no single explanation for all deaths, and different mechanisms may be involved. The vast majority of SUDEPs occur in the aftermath of a generalised tonic-clonic seizure. Witnessed recorded SUDEP cases involve postictal cardio-respiratory dysfunction with failure of arousal. The most important risk factor is a history of generalised tonic-clonic seizures.

Incidence
The risk of sudden unexpected deaths has been estimated to be 24 times higher in young persons with epilepsy than in the general population of the same age.
SUDEP incidence is estimated at 1 per 10,000 patient-years in newly diagnosed epilepsy in community-based studies and 1-2 per 1,000 patient-years in cross-sectional studies of patients with chronic epilepsy. A higher incidence, of 2-10 cases of SUDEP per 1,000 patient-years, is reported in studies of patients with treatment-resistant epilepsy.
The incidence in children is estimated to be lower than in other age groups; approximately 0.2 per 1,000 patient-years.

Further, as epilepsy is a chronic condition, PWE who have been in remission may experience relapses making them vulnerable to seizure-related death. This is also true for those who have had successful epilepsy surgery. It has been shown that the presence of pre-operative generalised seizures is a risk factor for late recurrence, thus a risk factor for SUDEP (Schwartz *et al*., 2006).
Although there are currently no established evidence-based prevention strategies (Maguire *et al*., 2016; McLean *et al*., 2016), this seminar will summarize available evidence and suggest how PWE may be counselled about SUDEP.

When is a death classified as SUDEP?

SUDEP is the sudden and unexpected death of a PWE when complete autopsy and toxicology does not identify a cause of death. Based on this definition, SUDEP is a diagnosis of exclusion (*box 1*). *Definite* SUDEP requires an autopsy to confirm no anatomical or toxicological cause. *Probable* SUDEP is applied when autopsy is not performed but the circumstances of death are otherwise very suggestive, and *possible* SUDEP is when autopsy is not performed and there is a potential competing cause of death. SUDEP Plus is used for cases which would otherwise fulfil the definition of SUDEP in the presence of another condition which could have contributed to the death (*e.g.* coronary insufficiency with no evidence of myocardial infarction or long-QT syndrome with no documented terminal primary ventricular arrhythmia). *Near*-SUDEP includes cases in which cardiorespiratory arrest is reversed by resuscitation efforts with subsequent survival for more than one hour (Nashef *et al*., 2012).
Generalised tonic-clonic seizures (GTCS) convey the greatest risk of SUDEP, though there are exceptions and SUDEP can rarely occur in the absence of a history of tonic-clonic seizures in patients presenting focal seizures with impaired awareness (Sperling *et al*., 1999; Langan *et al*., 2000) and in the absence of terminal seizures (Lhatoo *et al*., 2016).

Epidemiology of SUDEP

In the UK, SUDEP accounts for approximately 500 of the 1,200 epilepsy-related deaths a year (Shankar *et al*., 2013). It has been more difficult to estimate the number of SUDEPs in the USA. A large population-based study of PWE (Ficker *et al*., 1998) reported an estimated incidence of SUDEP of 0.35 cases per 1,000 person-years of follow-up while another reported 2.7 per 1,000 person-years (Leestma *et al*., 1989). Other studies (Neuspiel and Kuller, 1985; Donner *et al*., 2001; Hitiris et *al*., 2007) in North America have shown differences possibly due to variation in patient selection criteria and methods of study and analysis (Tomson *et al*., 2016).
The risk of SUDEP is about 1 in 10,000 person-years in population-based studies of newly diagnosed epilepsy and 1 in 1,000 person-years in people with chronic epilepsy. SUDEP risk, however, increases with less well controlled epilepsy to 1 in 200-300 person-years in cohorts seen in specialist centres and up to almost 1 in 100 person-years in those with severe treatment-resistant epilepsy, being particularly high among those with uncontrolled tonic-clonic seizures (Tomson *et al*., 2005). SUDEP risk is in general lower in children, at around 0.2 per 1,000 children with epilepsy (Donner *et al*., 2001; Ackers, 2011; Berg *et al*., 2013), but no studies have evaluated SUDEP rates in sub-populations of children with epilepsy. In the US, the public health burden of SUDEP in terms of life-years lost is estimated to be second only to stroke among neurological conditions (Devinsky *et al*., 2016). The cumulative risk of SUDEP in a population-based follow-up study of 40 years was estimated to be 7-12% (Sillanpää and Shinnar, 2010).

SUDEP pathophysiology

The majority of reported witnessed SUDEP cases occurred in conjunction with a GTCS. Current evidence, drawn from deaths occurring in epilepsy monitoring units, suggests that the final terminal pathway involves severe compromise of centrally mediated cardiopulmonary function as a result of the seizure, with terminal apnoea usually preceding asystole (Ryvlin *et al*., 2013). That approximately 80% of all SUDEP cases appear to be unwitnessed suggests that witnessed seizures are less likely to be fatal (Nashef *et al*., 1998). It is, however, not known why one specific seizure is fatal when the PWE may have previously had numerous apparently similar non-fatal seizures, nor why only some individuals with treatment-resistant epilepsy die of SUDEP. While some differences may relate to modifiable environmental or treatment-related factors, there may also be genetic susceptibility (Goldman *et al*., 2016; Nashef and Sander, 2016).

Most SUDEPs are unwitnessed, with the deceased often found in bed, more often in the prone position than would be expected by chance (Kloster and Engelskjon, 1999), and with evidence suggestive of a seizure in the majority of cases (Nashef *et al*., 1998).

Modifiable risk factors for SUDEP

Case-control studies have identified clinical factors associated with increased SUDEP risk among PWE (Tomson *et al*., 2016). By far the most important clinical risk factor is frequency of GTCS, but nocturnal seizures, early age at epilepsy onset (before the age of 16 years), male gender, and long duration of epilepsy (over 15 years) have been identified as additional risk factors. Lack of antiepileptic drug treatment has also been associated with increased SUDEP risk, while the presence of someone capable of providing assistance at night was reported as protective in one case control study (Langan *et al*., 2005).

Preventive measures are directed at potentially modifiable risk factors although there have been no studies to show that modifications of risk factors result in a reduction in SUDEP incidence. Such studies would face major methodological and ethical challenges (Tomson *et al*., 2016). Despite the lack of direct evidence, it is likely that there are measures that can be taken to reduce the risk of SUDEP.

As stated, the most established risk factor for SUDEP is uncontrolled tonic-clonic seizures (Tomson *et al*., 2008 ; Surges *et al*., 2009; Tomson *et al*., 2016; Shankar *et al*., 2016). If the seizure frequency is higher, the risk of SUDEP is greater. Compared to being free from GTCS, having 1-2 GTCS per year was associated with a five-fold increased risk of SUDEP, and three or more GTCS per year a 15-fold increase (Hesdorffer *et al*., 2011). It is therefore imperative that ongoing seizures or any increase in seizure frequency or shift from non-generalised to GTCS be closely reviewed and managed with proactive measures, including treatment optimisation and referral to specialised services. There is a paucity of studies correlating changes in seizure severity to SUDEP. The limited evidence (Shankar *et al*., 2014) suggests a possible association. This area would benefit from further systematic study.

A study which pooled data from randomised placebo-controlled trials in patients with refractory epilepsy showed that treatment with adjunctive AEDs at efficacious doses may have reduced the incidence of definite or probable SUDEP by more than seven times compared with placebo in patients with previously uncontrolled seizures. This provides evidence that, at least in a clinical trial setting, active treatment review and management in patients with refractory epilepsy may reduce SUDEP rates (Ryvlin *et al*., 2011).

While nocturnal seizures may carry a lower risk of accidental injury, they are a risk factor for SUDEP (Lamberts *et al*., 2012). The reported protective effect of sharing a room with someone capable of providing assistance has already been referred to (Langan *et al*., 2005). Evidence from the MORTEMUS study (Ryvlin *et al*., 2013) demonstrated that delayed resuscitation, when events occur outside of daytime hours, was noted in all SUDEP cases, indicating that at least some of the risk associated with nocturnal seizures relates to lack of supervision (Sander, 2013). Thus, noting and managing nocturnal seizures needs to be part of the standard assessment at epilepsy care visits, including discussing ways to improve night time supervision for persons with frequent nocturnal GTCS. Practical measures, such as co-habiting with a friend or a relative and the use of audio monitors if seizures are uncontrolled, can be considered. There is, however, very limited and poor-quality evidence for most personal-use devices which are claimed to monitor and protect PWE in the community (Jory *et al*., 2016).

It may be hypothesized that successful epilepsy surgery can reduce SUDEP risk in association with a reduction in seizure frequency (Sperling *et al*., 2005). Refractory PWE who did not undergo surgery had a six-fold increased rate of death compared to those who underwent epilepsy surgery. Post-surgery, the operated PWE had a standardised mortality rate equal to the general population (Sperling *et al*., 2005). Pregnant women with epilepsy are also at risk of SUDEP (Saving Mothers Lives, 2011).

Comorbidities and SUDEP risk

Whether comorbidities such as cardiac and respiratory conditions, including obstructive sleep apnoea,

have an impact on SUDEP risk is unknown. However, inadequately managed sleep apnoea is associated with increased seizure frequency, as is sleep deprivation from any other cause.

Intellectual disability (ID) is common among PWE. It is estimated that around 25% of PWE have ID (De Boer *et al.*, 2008). There have been suggestions of over-representation of SUDEP in ID populations (Kiani *et al.*, 2013), but data are conflicting (Shankar *et al.*, 2016; Young *et al.*, 2015). This group is particularly challenging with a high proportion being treatment resistant. Difficulties with communication may make informed choice difficult. The clinician thus needs to have an appreciation of ID-specific issues, as applied to epilepsy. There is an urgent need for studies assessing the role of ID and other comorbidities of epilepsy in SUDEP risk.

Given the importance of seizure control for SUDEP risk reduction, patient counselling should include a discussion of seizure provoking factors, such as alcohol, sleep deprivation and non-adherence to treatment, and the need to avoid these. Excessive or harmful use of alcohol is a documented trigger for seizures in PWE (Shankar *et al.*, 2016) and alcohol or substance abuse should be explored in relevant settings. Poor adherence to AED medication has been associated with significantly increased overall mortality, though SUDEP was not specifically analysed (Faught *et al.*, 2008; Ostler *et al.*, 2015; Ridsdale, 2015).

As triggers may provoke seizures in some but not others, an individualised assessment of seizure triggers is needed (*box 2*). It is important that PWE recognise the risks to their safety and make informed choices around treatment adherence.

Box 2. Suggested script for a first discussion on SUDEP in a clinical setting.

Epilepsy is a common medical condition that affects people to different degrees. Many people find that their epilepsy does not get in the way of their everyday life, and up to 70 in every 100 people with epilepsy have seizures that are fully controlled by medication. There are, however, risks to physical health and the potential for life-threatening situations with epilepsy. Injuries can result from seizures, and death can occur from drowning and from accidental injury although the risk is small and to some extent avoidable. Rarely, a person with epilepsy may die suddenly and unexpectedly, usually from a severe seizure which affects vital functions; this is known as SUDEP.

It is estimated that SUDEP affects 1 in 10,000 people with newly diagnosed epilepsy every year, and 1 in 1,000 people with chronic epilepsy. It is not possible to accurately predict who will be affected by SUDEP. However, potential risk factors which increase the risk of SUDEP have been identified. For the vast majority of seizures, the individual recovers fully. Relevant factors include the severity of the seizure in question, whether someone is present to provide assistance, and the position the person is in during and immediately after the seizure.

Check on patients'/carers' understanding and look to consider person-centred risk factors and how the individuals concerned can help reduce their risk.

A video example of conducting a structured assessment is found here: https://www.youtube.com/watch?v=Z9KHQvsapAc

SUDEP in children

Like adults, children with epilepsy are at a significantly increased risk of death compared to the general population. The majority of premature mortality in children with epilepsy is not seizure related, most often due to respiratory illness in association with severe neurological disability, chronic epilepsy, and comorbid conditions.

SUDEP is the most common cause of seizure-related death also in children, however, compared with adults, rates are considerably lower in children, affecting approximately 0.2 to 0.3 per 1,000 children with epilepsy per year (Donner *et al.*, 2001; Ackers *et al.*, 2011; Berg *et al.*, 2013). The majority of reported SUDEP deaths occur after the age of 20 years (Thurman *et al.*, 2014). When SUDEP does occur in childhood, many of the risk factors previously identified appear to be present, including treatment-resistant GTCS and nocturnal seizures. The limited studies examining risk factors specific for SUDEP in children identify developmental delay and drug-resistant epilepsy as important factors (Callenbach *et al.*, 2001; Donner *et al.*, 2001; Weber *et al.*, 2005). Mortality is an important consideration in the childhood-onset epileptic encephalopathies because of the combination of severe drug-resistant seizures and developmental delay. Dravet syndrome, most often associated with mutations in the sodium channel-encoding gene *SCN1A*, has been specifically associated with an increased risk of SUDEP, although it is not clear if a specific genetic mutation confers an increased risk beyond the already mentioned factors (Skluzacek *et al.*, 2011). The situation is similar in other conditions such as isodicentric chromosome 15 syndrome.

While the literature regarding specific paediatric risk factors for SUDEP is sparse, there is a relatively strong literature on the wishes of parents regarding SUDEP risk disclosure. Qualitative and quantitative research supports the finding that parents of children with epilepsy want to be informed of SUDEP risk

Table 1. Suggested SUDEP discussion pathway for a recently diagnosed PWE.

1. Include in an early appointment, with a clinician or specialist nurse, an offer to discuss the recent diagnosis of epilepsy and its implications. Invite the patient to bring along a family member or friend.
2. Ensure the patient is comfortable and give enough time for questions and discussion.
3. Explore the understanding of the diagnosis of epilepsy and its particular relevance to them. Establish what they know about possible risk issues arising from epilepsy.
4. If a relative or friend witnessed the person's seizure, ask what their thoughts were.
5. Enquire sensitively if the patient is familiar with any direct adverse outcomes of epilepsy.
6. Ask if they have come across the term SUDEP (Sudden Unexpected Death in Epilepsy).
7. Enquire if they would be interested in knowing more.
8. Explain the entity including that this is usually related to the after-effects of a severe seizure, putting a strain on breathing and heart function.
9. Offer reassurance that it is a rare event which perhaps occurs in the range of 1/10,000 person-years among new-onset cases, though the risk can be considerably higher; 1/1,000 in chronic epilepsy, and even higher in poorly controlled epilepsy with ongoing convulsions.
10. Put this risk in context of other risks we take in our daily lives.
11. Cover core risk factors listed in *table 1*, systematically allowing the patient/carer or companion to clarify any item.
12. Highlight other indirect factors which could impact on seizure control (*table 1*), tailoring the discussion to the individual patient.
13. Ask the patient and/or carer to reflect on what they have learnt from the consultation including, where appropriate, positive measures to minimise his/her risk.
14. Encourage reflecting and planning on how the PWE will recognise a change in individual risk and what action to take.
15. Provide relevant information or sources: www.sudep.org; sudepaware.org; www.epilepsy.com; www.sudepglobalconversation.com.
16. Record the discussion including the PWE's attitude towards self-management of risk with a view to informing future discussions.
17. Re-visit risk factors briefly in future appointments and consider using tools such as the SUDEP and seizure safety checklist (https://www.sudep.org/checklist).

(Gayatri *et al*., 2010; Ramachandrannair *et al*., 2013). Health care providers are therefore encouraged to discuss this risk with families and young persons, where appropriate. SUDEP risk discussion can be incorporated into a general discussion about safety in the context of seizures and is also appropriate at times when young persons are having difficulty with treatment concordance, are contemplating surgical referral for epilepsy surgery, or facing lifestyle changes, such as moving out of the family home. When SUDEP risk is lower, such as the case with fully controlled seizures or absence seizures, a discussion of risk can offer reassurance to the family. When risk is higher, families can be counselled on how to mitigate that risk by reducing seizure burden and improving seizure safety, with the use of audio devices, improved treatment adherence, and referral to specialised epilepsy clinics for comprehensive assessment and treatment.

SUDEP communication and the role of the neurologist

Routine clinical epilepsy care should include a comprehensive person-centred risk assessment and communication of all identified risks, with a focus on modifiable or avoidable risk. It may be difficult to identify the appropriate time to address SUDEP with PWE and their families. While some advocate discussion at the first clinic visit, others recognize this may be

Table 2. Key points when discussing SUDEP with your patient.

Direct SUDEP risk factors	Potential indirect factors which may affect seizure control
Generalised tonic-clonic seizures >2/year	
Nocturnal seizures and lack of surveillance	Excessive use of alcohol (other substances).
Early age at epilepsy onset, *i.e.* before the age of 16	Non-adherence with AEDs.
Treatment resistance defined as absence of 5-year terminal remission.	Sleep deprivation and irregular sleep pattern.
Long duration of epilepsy of over 15 years	Prescribed drug changes likely to result in worsening or loss of seizure control.

difficult. Most agree, however, that discussing SUDEP, as well as other seizure-related risk factors and risk management, sometime early in the course of the patient's epilepsy is important. A proposed pathway (*table 1* table 1) is shown, and the key points to discuss are listed in *table 2* table 2. *Table 3* summarises the benefits and risks of having this discussion. Given the sensitivity of the discussion, there is the potential for some PWE to become distressed by it (Tonberg *et al*., 2015). *Box 1* lists key facts related to SUDEP to use along with *box 2* for a discussion on this sensitive issue.
A fatal accident inquiry into the SUDEP deaths of two young women in Scotland, UK (Scotland Judiciary, 2016) showed neither had been advised of the risk of SUDEP by their doctor. There was no recorded SUDEP discussion. The judge concluded that their deaths might have been avoided had they been informed of the risks and taken precautions to minimise these risks. In his report, the judge made a series of recommendations. These include the recommendation that the majority of people with epilepsy should be told about SUDEP when first diagnosed. Any decision not to do this should be noted in medical records (http://www.scotland-judiciary.org.uk/).
Although surveys have not shown this to be commonly carried out (Waddell *et al*., 2013), it is now considered best practice to conduct a person-centred discussion of SUDEP preferably at an early appointment. If such a discussion is deemed inappropriate, it is important for the reasons to be recorded and a plan made to identify when and by whom the topic would be re-visited. The onus is on the PWE's responsible direct clinical team (nurse, doctor, *etc*.) who have competency in epilepsy care to discuss the risks of SUDEP along with other

Table 3. Positive reasons and concerns when discussing SUDEP.

Discussing SUDEP: positive reasons	Discussing SUDEP: concerns
The patient's right to know about his/her condition.	This might dismay and distress patients.
In circumstances of low risk, discussion may ease patient fear and anxiety.	Increased patient fear and anxiety resulting in a move from leading a 'normal life' to a 'risk averse' life.
Supports patient empowerment and identifies key areas for patients to focus and work on.	Might lead to a false sense of security in those at a lower risk.
Encourages epilepsy self-management and effective collaboration during treatment between clinician and patient. The aim is to prevent seizures and minimise risk of SUDEP.	Cultural and ethnic differences in attitudes need to be considered.
Supports a relationship of trust between clinician and patient.	Based on cultural and ethnic issues, this could be seen as the professional abdicating responsibility.
Guidelines recommend SUDEP discussion as part of comprehensive care.	
Structured discussion provides evidence of quality of patient care and sense of direction of treatment management.	
Following guideline recommendations reduces clinician and corporate risk in case of an adverse outcome.	

epilepsy-related risks. The clinical practice guidance in the UK from The National Institute of Clinical Excellence (NICE) (Clinical Guideline 137, NICE) has clearly addressed this.

However, despite patient expectations and practice guidelines, there remain barriers to meaningful discussions of SUDEP with PWE (Waddell *et al*., 2013). Principal among them is a lack of clarity about how to have a structured and patient-centred conversation. The risk of SUDEP can initially be included in the discussion when other risks related to epilepsy are addressed and when the importance of preventing seizures by avoiding triggers and through successful treatment is discussed. This can be backed up by general patient information leaflets, many of which address SUDEP. A possible model (Brown *et al*., 2013; Shankar *et al*., 2013, 2014, 2015a, 2016) is to incorporate a brief semi-structured risk assessment in routine clinical practice, such as the SUDEP and seizure safety checklist (https://www.sudep.org/checklist) (SUDEP, 2016). This can be a catalyst for open discussion and could help guide treatment by identifying areas for modification of risk status, supporting clinician interventions, and providing a better understanding of those risk factors which lie within the control of the patient.

SUDEP and premature mortality in epilepsy have become a major focus in the epilepsy community (Devinsky *et al*., 2016; Tomson *et al*., 2016). Leading experts and advocacy organizations call for systemic strategies to reduce mortality. While there has been much progress in understanding and managing epilepsy as a condition, it is increasingly recognised that systematic person-centred communication of risk (Shankar *et al*., 2015b) remains a neglected area. The physician has a critical role in patient education, to encourage epilepsy self-management and ensure that PWE are fully informed of the risks of epilepsy and how to modify those risks. It is only with clearly communicated and accurate information about epilepsy that PWE can make informed decisions to reduce their risk of mortality in epilepsy. □

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

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TEST YOURSELF

(1) How high is the incidence of SUDEP in people with newly diagnosed epilepsy?

(2) What are the direct and indirect risk factors for SUDEP?

(3) How would you look to assess person-centred SUDEP risk in adults/children and communicate it?

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".