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Reducing the Risk of Sudden Unexpected Death in Epilepsy (SUDEP)

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Abstract

Purpose of Review Recent reports have highlighted an increase in the number of epilepsy-related deaths. Sudden unexpected death in epilepsy (SUDEP) is thought to be the number one cause of death in chronic epilepsy. This review provides a summary of the current evidence of how to communicate, stratify, and mitigate known risk factors for SUDEP.
Recent Findings There is now a clearer understanding of the possible pathological mechanisms that contribute to SUDEP. SUDEP is the culmination of multifactorial predisposing and precipitating factors and has been linked to particular candidate genes. A number of static and modifiable risk factors for SUDEP have been consistently identified. Recent guidance has emphasised the importance of communicating SUDEP risk to individuals at the earliest appropriate time.
Summary SUDEP risk assessment should be integral to the care of individuals with epilepsy. The use of evidence-based risk assessment tools may provide an opportunity to communicate identified risks in a person-centred holistic way. There is increasing evidence to support the use of wearable seizure monitoring devices to help reduce the frequency and impact of convulsive seizures, perhaps the number one risk factor for SUDEP.

Introduction

Epilepsy is a chronic neurological disorder characterised by a predisposition to seizure activity. The prevalence of epilepsy in the general population is anywhere between 0.6 and 1% depending upon sample population and methodological approach [1]. A diagnosis of epilepsy comes with increased rates of morbidity and mortality. At present, identification and stratification of risk in this population may not be optimally managed as rates of potentially avoidable deaths are higher than those of other chronic conditions [2]. The recent report published by Public Health England [3••] on deaths associated with neurological conditions in England 2001–2014 highlights an alarming trend. During this period, there was a significant increase in the age-standardised mortality rate (ASMR) associated with most neurological conditions. Specifically, there was a 70% increase in epilepsy-related deaths with steady increase in recent years. Increased mortality rates are related to a number of factors but sudden unexpected death in epilepsy (SUDEP) is the number one cause of death in chronic epilepsy [4].

SUDEP remains a diagnosis of exclusion; therefore, epidemiological investigation poses significant methodological challenges. As a result, incidence rates identified are wide ranging (0.09–9.3 per 1000 person-years). A unified definition of SUDEP [5] has been proposed in order help classify and standardise research methodologies moving forward. There is evidence to demonstrate that rates of SUDEP are in association with particular static and modifiable risk factors (Table 1).

Mechanism of action

The pathological pathway culminating in SUDEP is complex and multifactorial. There are a number of identified predisposing and precipitating factors that may be triggered in the peri-ictal period including cardiac arrhythmia, respiratory dysfunction, metabolic changes, and circulatory dysregulation [8]. Post-ictal cardiac arrhythmias have been associated with cases of near SUDEP [9] and the current evidence suggests that SUDEP cases may be characterised by a post-ictal apnoea followed by bradycardia progressing to asystole [10]. The MORTEMUS study [11] was a systematic retrospective review of cardiorespiratory death in epilepsy units worldwide. The response from 160 units identified 29 cardiorespiratory deaths including 16 cases of SUDEP and 9 cases of near SUDEP. The review of these deaths indicates compromise in both cardiac and respiratory functioning following a convulsive seizure. All 16 cases of SUDEP identified in this investigation experienced the same terminal pattern of apnoea followed by asystole.

Genetics

The pathological mechanisms suggested behind SUDEP have similarities with cases of sudden cardiac death (SCD). In fact, there may be an overlap between candidate genes for SCD and SUDEP [12]. Exome-based analysis has shown a specific association between long QT syndrome and SUDEP [13, 14]. Findings from animal models also suggest a possible role of dysfunction in genes linked to

Table 1. Risk factors associated with increased rates of SUDEP (adapted from Hesdorffer et al. 2011 [6]; Tomson et al. 2016 [7••])

Static risk factors
Male gender
Intellectual disability
Genotype
Age 20–40
Seizure onset < 16 years
Duration of epilepsy > 15 years
Modifiable risk factors
Treatment-resistant seizures
Nocturnal seizures
Absence of night surveillance
Sleeping in prone position
Seizure frequency (3 or more convulsions within 12 months)
Unclear compliance with treatment
Sub therapeutic AED levels
Sudden and frequent changes in AEDs
Alcohol misuse
Psychiatric co-morbidity

serotonin function and ion channels which have not yet been replicated in humans [15].

The American Academy of Neurology (AAN) has published practice guidance on the importance of communicating the risk of SUDEP to individuals diagnosed with epilepsy [16••], which is consistent with recommendations from the National Institute for Health and Care Excellence (NICE) clinical guideline 137 [17]. However, to date, there is no systematic plan on how to deliver this discussion and assess risk in a person-centred way both initially and over time though evidence of the importance and mechanisms to do so is emerging [18–20].

Reducing SUDEP risk

In order to reduce risk, measures need to be put in place, targeted specifically at known risk factors. These measures may be wide ranging and include both pharmacological and non-pharmacological intervention. A Cochrane review investigating measures for the prevention of SUDEP demonstrates that to date, there is a paucity of robust evidence available to support risk reduction interventions. However, there are some positive findings [21••].

Risk assessment and communication

The SUDEP and Seizure Safety Checklist [22] is a freely available evidence-based risk assessment tool in the UK. The aim of this 'Checklist' is to help clinicians adopt a person-centred approach to risk assessment and communication. Using the Checklist will help facilitate risk discussion in a positive framework focused on empowering the individual to help modify risk factors. Known modifiable risk factors can be identified and the Checklist used to educate individuals on lifestyle changes that may help reduce some of the risks and promote safety [20].

The SUDEP and Seizure Safety Checklist (https://sudep.org/checklist) was developed from current available literature of known SUDEP-associated risk factors [22]. The Checklist has demonstrated validity of the identified risk factors in a case-control study design [23••]. The Checklist has also been trialled in a telehealth pilot in a high-risk population within a large primary care service over a 12-month period [24]. The use of the Checklist led to the identification of a number of people with epilepsy that required interventions to reduce risk that may have otherwise been missed. This was then further explored at another primary care site which further highlighted the use of the Checklist in identifying modifiable risk factors that have previously gone unrecognised [20]. These investigations demonstrate the importance of tools like the Checklist in motivating risk assessment and facilitating discussion in order to share the burden of risk modification across all aspects of care. The use of the Checklist in specialist epilepsy centres has led to a reduction in risk scores. The Checklist was administered prospectively to 259 individuals consecutively attending both an epilepsy specialist neurology clinic and an ID epilepsy clinic and scores compared. For those individuals considered at highest risk, there was a significant reduction in risk scores at a 12-month follow-up [25].

The SUDEP and Seizure Safety Checklist has been transformed into a free to download (in the UK) mobile phone app, EpSMon (Epilepsy self-monitor—www.epsmon.com) [26]. This provides an accessible platform for people with epilepsy to undertake a self-administered questionnaire every 3 months. The app provides advice around risk reduction and may make recommendations for the individuals to seek advice from their medical practitioner [24].

There are other instruments available to help assess collective risk factors for SUDEP in a systematic evidence-based way including the SUDEP-7 Inventory [27]. This inventory focuses heavily on seizures and associated electrophysiological changes as possible biomarkers for SUDEP. There may be scopes to consider the utility of using an assessment tool focused primarily on seizure control to complement the Checklist which considers individuals' holistic needs and wider risk variables [20].

Modifiable risk factors

Seizure-related factors

It has been consistently shown that convulsive seizures are potentially the key modifiable risk factor for SUDEP [16••]. In fact, having a high seizure frequency of any seizure time may be a significant risk factor [28]. It is therefore important to maximise seizure control and reduce the number of convulsive seizure to less than three per year [6]. Unfortunately, for people with treatment-resistant epilepsy, improving seizure control is not straightforward. There has been association drawn between number of AEDs prescribed and SUDEP risk [29]. It has also been demonstrated that individuals with uncertain

Table 2. Seizure monitoring devices and SUDEP risk (adapted and updated from Jory et al. 2016 [39••])

Monitoring device	Function	Evidence	Study(s)
Audio monitor	Can be used to detect sound and provide surveillance in a less restrictive manner.	Has a high sensitivity (0.81) and moderate positive predictive value (0.40) but shows a high interpatient variability	Arends J et al. 2016 [40]
Pressure sensor mat	Can be placed under a normal mattress (not pressure relief), has built in sensors to detect movement	Variable convulsive seizure detection rate, 0–89%	Narechania et al. 2013 [41]; Van Poppel et al. 2013 [42]; Fulton et al. 2013 [43]
		Low specificity (high false positive rates) due to movement differentiation challenges	Carlson et al. 2009 [44]
Video monitor	The use of video monitoring is practical and easily accessible, but needs consideration of privacy issues and best interests if individual lacks capacity	There is evidence that observed movements correlate with caregiver reporting	Shankar et al. 2013 [45]
		To date, video monitoring is unproven with EEG comparison	Cuppens et al. 2012 [46]
Accelerometer	Detect changes in velocity and motion. Can be integrated into widely available devices including smart phones or watches	Sensitivity 87–95%, high levels of false positive results have been reported (small study designs)	Lockman et al. 2011 [47]; Beniczky et al. 2013 [48]; Cuppens et al. 2014 [49]
Physiological parameters	Seizures are associated with autonomic dysfunction.	A multi-centre assessment of wearable multi-modal seizure detecting devices show good tolerability in everyday wear with high sensitivity (up to 100%) and improved specificity	Onorati et al. 2017 [50]
	Electrodermal activity, heart rate, heart rate variability, ECG morphology, and oxygen saturation can all be measured and monitored by wearable devices.	ECG monitoring of seizure activity has shown good sensitivity.	Masse et al. 2010 [51]
	The wearable apnea detection device (WADD) is suitable for home use and detects spontaneous apnoea with an integrated finger cuff plethysmograph	The technology is available to combine a portable ECG system with photoplethysmography	Vandecasteele et al. 2017 [52]
		A small pilot group showed good tolerability, with sensitivity of	Rodriguez-Villegas et al. 2014 [53]

Table 2. (Continued)

Monitoring device	Function	Evidence	Study(s)
		88.6% and specificity of 99.6%.	
Electromyography (EMG)	Measures the motor manifestations of seizures. Can be developed into wearable portable devise for seizure monitoring in future	High sensitivity and specificity when compared to video EEG in detecting convulsive seizures.	Cavazos et al. 2015 [54]; Graves et al. 2017 [55]
Smart devices and applications (apps)	Platform for risk assessment and communication easily accessible, sensor technology can be incorporated into device and specific seizure algorithms developed for apps	Embrace by Empathica is a smart watch platform that uses electrodermal monitoring, accelerometer technology, heart rate monitoring, and temperature to detect convulsive seizures. This device has received FDA approval for use. The device has been tested against the gold standard of video EEG and found comparable. The Epi-watch designed for the Apple i-watchallows individuals to monitor their seizures and provides data from biosensor in order to help identify potential trigger factors to help modify risk	Poh et al. 2012 [56] Picard et al. 2017 [57] https://blog.empatica.com/embrace-is-now-an-fda-approved-medical-device-bf506d991b1c https://www.hopkinsmedicine.org/epiwatch#app Ge et al. 2017 [58]
Baroreflex sensitivity	Baroreflex sensitivity (BRS) is a reliable biomarker for autonomic function, which has shown dysregulation following bilateral convulsive seizures.	A small sample of 26 seizures of 26 individuals demonstrated impaired BRS following a bilateral convulsive seizure indicating autonomic dysregulation which may be linked to cardiovascular problems prior to SUDEP. These changes were not observed in a control group ($n = 19$) with focal seizures	Hampel et al. 2016 [59] Hampel et al. 2017 [60]

treatment history or prescribed no AEDs have an increased risk of SUDEP [22]. Introducing new AEDs or adjunctive treatment for individuals with refractory seizures may significantly reduce the incidence of SUDEP when compared to placebo [30].

Nocturnal seizures, particularly of a convulsive nature, may confer an independent risk of SUDEP [31]. There is evidence to suggest that nocturnal supervision may be protective for those at risk [11, 30]. This supervision may be in the form of remote monitoring devices [21••]. There is evidence of a correlation between sleeping in the prone position and cases of SUDEP [32, 33]. Managing this risk may be complicated by the fact that individuals may become prone following a convulsive seizure, again highlighting the importance of nocturnal monitoring for those at high risk.

Table 3. Managing SUDEP risk: desirable standards of care (adapted from Watkins et al. 2018 [65])

Seizure frequency	Maximise seizure control (GTC and nocturnal seizures) with pharmacological and non-pharmacological treatment. Aim for less than 3 seizures pre year.
Collateral risk	Work collaboratively with patient, families, and caregivers to deliver person-centred risk reduction. Including advocating nocturnal supervision where indicated.
Access to care	Ensure equitable access to appropriate specialist review and reasonable adjustments for people with ID.
Co-morbidities	Detailed assessment of physical and psychological co-morbidities including genetic testing, and liaison with relevant specialists.

Non-pharmacological interventions

Maximising seizure control needs consideration of all treatment options. For individuals who undergo epilepsy surgery, achieving seizure freedom reduces mortality rates [34]. Vagus nerve stimulation (VNS) has also been shown to have some impact on lowering SUDEP rates in a high-risk treatment-resistant population [35, 36]. A recent large-scale review of SUDEP cases in a treatment-resistant population has shown that treatment with VNS is associated with a significantly lower SUDEP risk on long-term follow-up [37]. There is also emerging evidence for newer therapies including responsive nerve stimulation (RNS) which suggest there may be a role in reducing seizure frequency and therefore reducing risk of SUDEP [38].

Seizure monitoring devices

There are a wide range of seizure surveillance devices available with varying evidence to support their efficacy with a recurrent problem of high rates of false positive alerts (Table 2). With advancements in technology and accessibility of smart devices, individuals may soon be able to participate in monitoring their risk on an individual basis. This will aid communication between individuals, primary care, and specialist services. However, the evidence is limited to suggest that the use of any of these devices will reduce the risk of SUDEP [21••, 39••].

Co-morbidities

The unified SUDEP diagnostic criteria give consideration for other physical co-morbidities that may have played a role in a death [5]. The concept is labelled as SUDEP *plus* [5]. As a result, a diagnosis of SUDEP should now be considered even in the presence of other physical illness that may have influenced or been influenced by seizure activity [61]. It is therefore important to ensure that individuals with multiple morbidities have their conditions optimally managed.

The evidence around the role of co-morbid psychological disorders as a risk factor for SUDEP remains conflicted, with a previous systematic review identifying no association with increased risk [62]. However, more recently, a nationwide Swedish cohort study has demonstrated that any psychiatric co-morbidity significantly increases the risk of SUDEP [63]. Therefore, as with physical co-morbidities, it is important that individual's psychological health is assessed and treated appropriately. There is some evidence from animal models that selective serotonin reuptake inhibitors (SSRIs), a first-line treatment in depression and anxiety disorders, may reduce risk of SUDEP [64].

Conclusion

The aetiology of SUDEP is likely multifactorial in nature with a wide range of confounding factors that may play a role with predisposing and precipitating effects.

The desirable standards of care for managing SUDEP risk have been set out with a holistic approach to care (Table 3). It is important that in accordance with guidance from NICE clinical guidelines 137 [17] and the AAN [16••], individuals are provided with accessible information on SUDEP at the earliest appropriate time. All healthcare professional involved in epilepsy management should work collaboratively in order to optimise seizure management as frequency of convulsive seizures is perhaps the most important factor in SUDEP risk. Clinicians should be advocating the need for nocturnal surveillance for those people at high risk, weighing up the impact this may have on an individual's privacy [65].

For individuals with treatment-resistant seizures, management should be optimised with AEDs with consideration of potential side effects. Where appropriate, individuals should be considered for non-pharmacological interventions including VNS and epilepsy surgery. Epilepsy is a complex neurological disorder that affects all aspects of an individual's life. The impact is often far wider than that of seizures alone with biological, psychological, and social influences. Therefore, managing epilepsy and associated risks should be done in a holistic person-centred way to identify and modify any static and modifiable risk factors. This should include the assessment and management of physical and psychological co-morbidities.

Compliance with Ethical Standards

Conflict of Interest

Rohit Shankar is a stakeholder of the 'SUDEP and Seizure Safety Checklist'. Rohit Shankar is a principal developer and key stakeholder of EpSMon. Rohit Shankar has received institutional and research support and personal fees from LivaNova, UCB, Eisai, Special Products, Bial and Desitin.
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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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