*Epilepsia*, 54(Suppl. S2):23–28, 2013
doi: 10.1111/epi.12180



# Prevention of sudden unexpected death in epilepsy: A realistic goal?

***Philippe Ryvlin, †Lina Nashef, and ‡Torbjörn Tomson**

***Department of Functional Neurology and IDEE, Neurological Hospital, Hospices Civils de Lyon and TIGER, CRNL (INSERM U1028, CNRS 5292), University Claude Bernard Lyon-1, Lyon, France; †Department of Neurology, King's College Hospital, London, United Kingdom; and ‡Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden**

## Summary

**Sudden unexpected death in epilepsy (SUDEP) represents one of the most severe consequences of drug-resistant epilepsy, for which no evidence-based prevention is available. Development of effective prevention will depend on the following: (1) better understanding of the pathophysiology of SUDEP to define the most appropriate targets of intervention, and (2) identification of risk factors for SUDEP that would allow for the design of feasible clinical trials to test targeted interventions in high-risk populations. The most important known risk factor is the occurrence and frequency of generalized tonic–clonic seizure (GTCS), a seizure type that triggers the majority of witnessed SUDEP. Therefore, one likely way to prevent SUDEP is to minimize the risk of GTCS with optimal medical management and patient education. However, whether one might prevent SUDEP in patients with refractory epilepsy by using more frequent review of antiepileptic treatment and earlier referral for presurgical evaluation, remains to be seen. Another hypothetical strategy to prevent SUDEP is to reduce the risk of GTCS-induced postictal respiratory distress. This might be achieved by using lattice pillow, providing nocturnal supervision, reinforcing interictal serotoninergic tone, and lowering opiate- or adenosine-induced postictal brainstem depression. Promising interventions can be tested first on surrogate markers, such as postictal hypoxia in epilepsy monitoring units (EMUs), before SUDEP trials can be implemented. EMU safety should also be improved to avoid SUDEP occurrence in that setting. Finally, the development of ambulatory SUDEP prevention devices should be encouraged but raises a number of unsolved issues.**

**KEY WORDS: Epilepsy, Seizure, Death, Sudden unexpected death in epilepsy, Prevention.**

Sudden unexpected death in epilepsy (SUDEP) represents the main epilepsy-related cause of death, with high life-time prevalence in patients with uncontrolled seizure (Shorvon & Tomson, 2011). Indeed, >20% of patients with childhood-onset epilepsy who fail to achieve long-term seizure freedom will die of SUDEP within 40 years of follow-up (Sillanpaa & Shinnar, 2010). These figures, together with the devastating impact of the sudden loss of young adults, should make prevention of SUDEP a priority for the epilepsy community. So far, however, we lack evidence for the effectiveness of any intervention aimed at preventing SUDEP. The development of effective interventions is hampered by our incomplete understanding of the pathophysiology of SUDEP. It is therefore important to first consider the current state of knowledge of the mechanisms leading to SUDEP before exploring the most relevant directions which could lead to realistic and timely progress in SUDEP prevention.

## Targeting the Appropriate Patients for Future Clinical Trials

The highest SUDEP incidence has so far been reported in patients undergoing presurgical evaluation or having failed epilepsy surgery, with rates up to 9.3/1,000 patient-year (Dasheiff, 1991). According to this highest but possibly overestimated figure (other studies have reported lower rates around 6/1,000 patient-years in comparable

Address correspondence to Philippe Ryvlin, Unité 301, Hôpital Neurologique, 59 bd Pinel, 69003 Lyon, France. E-mail: ryvlin@cermep.fr

populations; Nilsson et al., 2003), to demonstrate that a 6-month–duration intervention reduces the incidence of SUDEP by 50% will require a sample size of about 12,000 patients. Such studies raise obvious major feasibility issues. Two alternative approaches may be considered. The first is to establish if there is a clear relationship in epidemiologic studies between SUDEP and other adverse consequences of seizures, such as serious injuries or emergency department attendances and thus provide surrogate end points and increased power. The second is to apply simple population–based interventions in well-defined communities with preexisting validated SUDEP registers.

Knowledge of SUDEP risk factors has recently advanced thanks to the pooled analysis of four major case–control studies performed by the Subcommission on Mortality of the ILAE Commission on Epidemiology (Hesdorffer et al., 2011, 2012). As previously suggested, the presence and frequency of generalized tonic–clonic seizures (GTCS; either primary or secondary generalized) was found to represent the main risk factor, with an odds ratio of >15 for patients with three or more GTCS per month (Hesdorffer et al., 2012). A few other risk factors proved significant, but with odds ratios <2, including male gender, age of onset of epilepsy <16 years, duration of epilepsy >15 years, and polytherapy (Hesdorffer et al., 2011). However, when adjustments were made for the number of GTCS, neither polytherapy nor the use of specific antiepileptic drugs (AEDs) such as lamotrigine or carbamazepine, was associated with an increased risk of SUDEP (Hesdorffer et al., 2012).

How these figures translate into incidence of SUDEP in specific populations remains unknown. In the pooled analysis discussed above, cases and controls were mixed populations of patients seen at epilepsy centers and community-based cohorts of prevalent epilepsy (Hesdorffer et al., 2011), both of which demonstrate comparable SUDEP rates between 1 and 2/1,000 patient-years (Shorvon & Tomson, 2011). About 12% of the controls had more than three GTCS per year (Hesdorffer et al., 2011). Extrapolating from the data reported in this analysis, one would suspect that the subgroup of patients with $\geq 3$ GTCS/year would have an annual rate of SUDEP grossly ranging from 5 to 18/1,000 patient-years, thus raising the same feasibility issue for clinical trials as described above for patients with surgical failure.

Therefore, we still need to characterize populations with greater risk of SUDEP to test the impact of potentially preventive interventions. This will require further epidemiologic studies in well-selected and phenotyped populations combining previously identified predictors (nonidiopathic refractory epilepsy with an early age of onset affecting young adults with frequent GTCS), coupled with the identification of novel and independent risk factors that could more directly reflect the pathophysiology of SUDEP (nocturnal seizures, prolonged postictal electroencephalography [EEG] suppression, ictal/postictal hypoxemia, depression, and/or other biomarkers of serotoninergic dysfunction, and so on). Such studies should be a priority in the field.

## Targeting the Mechanisms Leading to SUDEP

A better understanding of SUDEP pathophysiology should help identify mechanisms to be targeted by preventive interventions, as well as patients with sufficiently high SUDEP risk to allow feasible clinical trials. While still debated, the mechanisms leading to SUDEP seem to be usually triggered by a GTCS (Langan et al., 2000; Tomson et al., 2008). Exceptions, for which monitored evidence is lacking, might include rare channelopathies responsible for both epilepsy and cardiac predisposition to sudden death, or non–seizure-related arrhythmic sudden cardiac deaths, and from partial seizures triggering ictal malignant arrhythmias. In the rare patients with a known mutation of *SCN5A* or *KCNH2* genes or family history of *SCN1A* mutation who died of SUDEP, information regarding the circumstances of death was either lacking or suggested that patients died in bed unwitnessed or after a convulsion (Hindocha et al., 2008; Aurlien et al., 2009; Tu et al., 2011). The only reported malignant arrhythmia triggered by a partial seizure and which did not spontaneously resolve, was a successfully resuscitated near-SUDEP (Espinosa et al., 2009). In fact, ictal asystole, hitherto considered a potential cause of SUDEP, is now believed by many to be generally a self-limiting process, whereby secondary brain hypoxia aborts the ictal discharge and its related central neurovegetative dysfunction, leading to restoration of normal cardiac activity (Schuele et al., 2010).

Following GTCS, the pattern observed in the rare monitored cases of SUDEP typically combines severe postictal EEG suppression, which does not recover until death, hypopnea and irregular breathing followed by apnea, and electrocardiography (ECG) abnormalities including bradycardia and terminal asystole (Nashef & Ryvlin, 2009). A number of issues, however, remain unanswered: (1) does the severity of immediate postictal EEG suppression differ between SUDEP and following GTCS in general? what is the contribution of brain hypoxia to the occurrence and persistence of EEG flattening? (2) how adequate is the often observed postictal respiratory effort preceding apnea? and if not, what are the primary mechanism(s) contributing to impaired ventilation (hypoventilation with ineffective irregular respiratory muscle contraction, neurogenic pulmonary edema, obstructive apnea promoted by upper airway muscle hypotonia and the prone position)? (3) similarly, how good is cardiac output during periods of altered cardiac rhythm and abnormal QRS complex observed before terminal asystole?

Based on available information, including those collected within MORTEMUS (MORTality in Epilepsy Monitoring Unit Study), one can speculate on the most likely mechanisms of SUDEP. Apnea is already present during GTCS, and might be responsible for significant hypoxemia in some cases, contributed to by ventilation-perfusion inequality (Bateman et al., 2008; Seyal et al., 2010). A GTCS-induced release of endogenous opioids and adenosine within the brain and brainstem, believed to be instrumental in seizure termination, may then be responsible for postictal EEG suppression and central neurovegetative dysfunction translating into both respiratory and cardiac abnormalities. Respiratory abnormalities, which might be aggravated by the prone position, will include central hypopnea and apnea, neurogenic pulmonary edema, impaired gas transfer, as well as upper airways hypotonia, all of which might worsen brainstem hypoxia and associated cardiorespiratory failure. This vicious cycle is likely to be further aggravated by cerebral hypoperfusion secondary to bradycardia and transient asystole. Terminal asystole is usually observed after terminal apnea. Therefore, the three main contributing and interrelated factors, that is, cardiac, respiratory, and brainstem dysfunctions, appear both entangled and reciprocally aggravating. This might account for the variations observed in the duration and sequence of events leading to SUDEP in monitored patients.

Overall, rather than depending on one single or primary factor, SUDEP in most cases appears likely to result from a GTCS-induced global and multifactorial neurovegetative breakdown. Prevention might in turn target a number of contributing factors, with the aims of: (1) reducing the occurrence of GTCS with optimal treatment), (2) detecting postictal cardiorespiratory distress (seizure, $SpO_2$, ECG monitor), (3) reducing the risk of upper airways partial obstruction and postictal respiratory distress (lattice pillow, supervision, $O_2$), (4) reducing central hypoventilation through physical stimulation, (5) reducing endogenous opioid and/or adenosine mediated postictal brain and brainstem depression, and (6) reinforcing serotonin-related respiratory rescue mechanisms (SSRI).

## Potential Interventions for Preventing SUDEP

### More appropriate and more effective antiepileptic treatment

The strong epidemiologic and pathophysiologic link between seizures, and more specifically GTCS, and SUDEP, suggests that efforts to minimize the risk of seizures should translate into lower rate of SUDEP. A number of general recommendations for optimizing epilepsy therapy deserve to be emphasized in this context, including:

**1** *Optimal choice of AED regimen*, based on an accurate diagnosis of the epilepsy syndrome to avoid on the one hand, undiagnosed and untreated active epilepsy, and on the other hand, misclassified and mistreated idiopathic generalized epilepsy using aggravating narrow spectrum AEDs. A further and controversial issue is if specific monotherapies or polytherapy can carry an increased SUDEP risk. Regarding monotherapy, a few reports have suggested that lamotrigine and carbamazepine could be associated with a higher risk of SUDEP (Timmings, 1993; Langan et al., 2005; Aurlien et al., 2010). However, these findings were not confirmed by the pooled analysis of case–controlled studies discussed above (Hesdorffer et al., 2012). This analysis also demonstrated that the previously reported association between polytherapy and risk of SUDEP reflected higher frequency of GTCS in patients with greater number of AEDs, and vanished after adjusting for seizure frequency (Hesdorffer et al., 2012). In fact, a meta-analysis of all double-blind randomized placebo controlled trials performed in adult patients with refractory epilepsy showed that patients receiving an add-on AED had a sevenfold lower risk of SUDEP (0.9/1,000 patient-years) than those receiving placebo on top of their baseline AED treatment (6.9/1,000 patient-years; Ryvlin et al., 2011). Although these findings cannot readily translate into clinical recommendations, they suggest that review of treatment in patients with refractory epilepsy might have a beneficial impact on the risk of SUDEP.

**2** *Patients' education* to promote adherence to treatment, avoidance of seizure triggering factors (lack of sleep, alcohol, medications lowering seizure threshold, abrupt AED changes), and appropriate reaction to seizure clusters (rescue medication), missed medication (redosing), or to any other situations that could lower AEDs levels (gastrointestinal disorders, pregnancy, or prescription of other drugs such as oral contraceptive in patients treated with lamotrigine; (Devinsky, 2012).

**3** *Timely referral to presurgical evaluation*, with the view that successful curative treatment should offer the most effective protection against SUDEP. Although this conclusion is supported by studies showing higher risk of SUDEP in patients who failed surgery as compared to those who achieved seizure freedom (Sperling et al., 1999; Salanova et al., 2002; Sperling et al., 2005), we still lack definite proof that this difference primarily reflects the impact of epilepsy surgery, rather than preexisting biologic differences between the two groups (Ryvlin et al., 2006). For instance, patients failing temporal lobe surgery might have epilepsy involving extratemporal brain regions controlling cardiorespiratory functions, leading to increased risk of SUDEP (Ryvlin & Kahane, 2003). This hypothesis supports improving the delineation and surgical management of patients whose epileptogenic zone could represent a risk factor for SUDEP, such as the insular cortex (Ryvlin, 2006).

**Reducing the risk of postictal respiratory failure**

**1** *Lattice pillows* have been proposed to reduce the contribution of the prone position to postictal respiratory distress and thus SUDEP (Devinsky, 2012). Although having the face down in the pillow might not necessarily result in major airways obstruction, the observation that more SUDEP patients are found prone than expected by chance, with 71% found prone in one study (Kloster & Engelskjøn, 1999), suggests that this environmental factor plays a significant role, in as much as patients in postictal coma are unable to correct their position in response to hypoxemia (Nashef et al., 1998). The impact of sleep position upon the risk of sudden infant death syndrome also emphasizes the potential role of such intervention. However, no study has evaluated the benefit of using lattice pillows in epilepsy. It would be worth comparing the impact of using lattice, standard, and no pillow upon ictal/postictal $SpO_2$ measurements in an epilepsy monitoring unit (EMU) setting.

**2** *Nocturnal supervision* was found to be protective of SUDEP in one case–control study (Langan et al., 2005), a finding supported by another observational study (Nashef et al., 1995). The development of seizure-detecting devices enable more effective night time supervision, but also raises the issue of false-positive/false-negative detection rates as well as that of the risk/benefit balance of such intervention on patients' quality of life. The decision to apply such measures needs to be individualized according to patient preference, seizure profile (nocturnal, generalized, frequency), and overall risk of SUDEP, with the knowledge that seizure-detecting devices have not been demonstrated to reduce the risk of SUDEP. Although most SUDEP cases are unwitnessed, one must also be aware that the intervention of a witness does not necessarily preclude the occurrence of SUDEP, as illustrated by video recording of patients who died in the EMU while being supervised. Turning the patient from prone to recovery position during the early postictal phase might be sufficient to reverse respiratory distress in some cases, but more active resuscitation procedures are likely to be needed in others. Therefore, families aiming at organizing nocturnal supervision for a relative at significant risk of SUDEP should be educated in order to react promptly and efficiently to ictal/postictal cardiorespiratory distress.

**3** *Supervision in EMUs* raises similar issues, despite the fact that SUDEP in EMUs are extremely rare and its contribution to all SUDEPs in society is minimal. Nevertheless, one could rightly consider that such events should not occur at all in a dedicated medical environment with staff supposedly trained to anticipate the consequences of seizures and GTCS, particularly that the latter are often promoted by tapering AEDs. Therefore, physicians and nurses face clear- cut responsibilities in managing SUDEP prevention in EMUs. The MORTEMUS study points to major weaknesses in the general organization of EMU safety with often inadequate supervision, especially at night. Observations from MORTEMUS support the development of safety guidelines in EMUs, with two priorities: (1) systematic monitoring of ECG and $SpO_2$ with appropriate alarm system in all patients undergoing long-term video-EEG monitoring, (2) organization of specific emergency code in EMUs, (3) education of EMU staff to quickly identify ictal/postictal cardiorespiratory distress and start appropriate cardiopulmonary resuscitation.

**4** *Postictal $O_2$ therapy* is being used systematically in some EMUs, without any evidence that this procedure reduces the risk of postictal respiratory distress or SUDEP. However, in a mice model of seizure-induced SUDEP, $O_2$ therapy proved extremely efficacious to prevent death (Venit et al., 2004). Although it remains difficult to extrapolate such experimental findings to humans, it appears reasonable to provide $O_2$ therapy in patients with postictal decreased $SpO_2$ or respiratory distress. Studies are also warranted of the impact of postictal $O_2$ therapy on various outcomes, including the duration of postictal EEG suppression and clinical state.

**5** *Serotoninergic drug*, including selective serotonin reuptake inhibitor (SSRI), might offer a way to decrease the risk of postictal central apnea. Lower brainstem serotoninergic nuclei play an important role in the regulation of respiration (Richter et al., 2003), in particular when recurrent hypoxia leads to a specific plasticity phenomenon called long-term facilitation (Ling et al., 2001; Mahamed & Mitchell, 2008). Abnormalities of brainstem serotoninergic nuclei have been described in sudden infant death syndrome (SIDS) (Paterson et al., 2006), as well as in mice models of SUDEP (Uteshev et al., 2010; Faingold et al., 2011a). Accordingly, fluoxetine was shown to prevent the occurrence of fatal apnea in these models (Tupal & Faingold, 2006; Faingold et al., 2011b). These experimental data prompted a retrospective study looking at the association between SSRI treatment and pulse oximetry in patients undergoing video-EEG monitoring (Bateman et al., 2010). Ictal/postictal hypoxemia was significantly less frequent in patients receiving SSRI than in those without such treatment (Bateman et al., 2010). Two double-blind randomized placebo-controlled trials are underway to confirm this finding, but whatever the outcome, the relevance for SUDEP prevention remains to be shown.

**6** *Inhibitors of opiate and adenosine receptors* might also contribute, thereby reducing the severity of postictal EEG and neurovegetative dysfunction (Shen et al., 2010). However, this therapeutic strategy carries the risk of aggravating the duration, frequency or severity of seizures, as illustrated by the proconvulsant effect of caffeine, a potent antagonist of adenosine receptors (Shapira et al., 1985). Conversely, naltrexone, an opioid receptor antagonist, is used long term in patients with addiction (Tiihonen et al., 2012), without a known effect on

seizure threshold even in patients with alcohol dependence (Volpicelli et al., 1992; Krystal et al., 2001), offering a potential future avenue for SUDEP prevention.

### Development of ambulatory SUDEP prevention devices

According to the highly successful experience using pacemakers and implantable defibrillators accumulated over decades in the prevention of sudden cardiac death, one might wish to develop comparable systems for preventing SUDEP. However, in addition to the general difficulties posed by patient selection and SUDEP clinical trials already addressed, this strategy faces major challenges, including:

**1** Which abnormality should trigger the intervention? Detection of bradycardia or asystole would represent an easier and more robust option than that of hypoxemia, but which of these two options will result in the most timely intervention is not known.

**2** Which type of intervention might prove effective in resuscitating patients with seizure-induced cardiorespiratory arrest? standard cardiac pacing should prevent brain hypoperfusion but might fail to reverse the fatal consequences of respiratory failure and related hypoxia. Whether phrenic nerve stimulation might overcome this problem is unknown.

## Conclusion

Prevention of SUDEP remains a major clinical challenge for the epilepsy community, but also an active field of scientific development with many potential diagnostic and therapeutic innovations. With present knowledge, the most obvious action is to aim for improved control of GTCS, by optimized use of AEDs as well as early referral of suitable patients for surgery. It is also likely on present evidence that GTCSs occurring when assistance is at hand are less likely to be fatal. As discussed above, the difficulties of assessing the effectiveness of interventions in appropriate clinical trials is a major hindrance for the development and implementation of novel strategies. Significant progress seems achievable but requires collaborative efforts to identify populations at high risk of SUDEP and thus allow implementation of feasible and informative clinical trials. The successful public campaigns that resulted in marked reduction of the incidence of SIDS can serve as an inspiration for the application of simple interventions as well as innovative methods to assess their effectiveness.

## Disclosure

PR has received speaker or consultant fees from UCB pharma, EISAI, GSK, Cyberonics, and Medtronic. LN has received consultancy honoraria and/or attended international meetings supported by GSK, Eisai, and UCB Pharma. TT has received speaker's honoraria or research funding from Bial, Eisai, GSK, UCB, Sanofi-Aventis, Novartis, and has also served as consultant for GSK in a blinded adjudication of SUDEP events. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

## References

Aurlien D, Leren TP, Taubøll E, Gjerstad L. (2009) New SCN5A mutation in a SUDEP victim with idiopathic epilepsy. *Seizure* 18:158–160.

Aurlien D, Larsen JP, Gjerstad L, Taubøll E. (2010) Increased risk of sudden unexpected death in epilepsy in females using lamotrigine: a nested, case–control study. *Epilepsia* 53:258–266.

Bateman LM, Li CS, Seyal M. (2008) Ictal hypoxemia in localization-related epilepsy: analysis of incidence, severity and risk factors. *Brain* 131:3239–3245.

Bateman LM, Li CS, Lin TC, Seyal M. (2010) Serotonin reuptake inhibitors are associated with reduced severity of ictal hypoxemia in medically refractory partial epilepsy. *Epilepsia* 51:2211–2214.

Dasheiff RM. (1991) Sudden unexpected death in epilepsy: a series from an epilepsy surgery program and speculation on the relationship to sudden cardiac death. *J Clin Neurophysiol* 8:216–222.

Devinsky O. (2012) Sudden, unexpected death in epilepsy. *N Engl J Med* 365:1801–1811.

Espinosa PS, Lee JW, Tedrow UB, Bromfield EB, Dworetzky BA. (2009) Sudden unexpected near death in epilepsy: malignant arrhythmia from a partial seizure. *Neurology* 72:1702–1703.

Faingold CL, Randall M, Mhaskar Y, Uteshev VV. (2011a) Differences in serotonin receptor expression in the brainstem may explain the differential ability of a serotonin agonist to block seizure-induced sudden death in DBA/2 vs. DBA/1 mice. *Brain Res* 1418:104–110.

Faingold CL, Tupal S, Randall M. (2011b) Prevention of seizure-induced sudden death in a chronic SUDEP model by semichronic administration of a selective serotonin reuptake inhibitor. *Epilepsy Behav* 22:186–190.

Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, Langan Y, Walczak TS, Beghi E, Brodie MJ, Hauser A; ILAE Commission on Epidemiology; Subcommission on Mortality. (2011) Combined analysis of risk factors for SUDEP. *Epilepsia* 52:1150–1159.

Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, Langan Y, Walczak TS, Beghi E, Brodie MJ, Hauser WA; ILAE Commission on Epidemiology (Subcommission on Mortality). (2012) Do antiepileptic drugs or generalized tonic-clonic seizure frequency increase SUDEP risk? A combined analysis. *Epilepsia* 53:249–252.

Hindocha N, Nashef L, Elmslie F, Birch R, Zuberi S, Al-Chalabi A, Crotti L, Schwartz PJ, Makoff A. (2008) Two cases of sudden unexpected death in epilepsy in a GEFS+ family with an SCN1A mutation. *Epilepsia* 49:360–365.

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

Krystal JH, Cramer JA, Krol WF, Kirk GF, Rosenheck RA; Veterans Affairs Naltrexone Cooperative Study 425 Group. (2001) Naltrexone in the treatment of alcohol dependence. *N Engl J Med* 345:1734–1739.

Langan Y, Nashef L, Sander JW. (2000) Sudden unexpected death in epilepsy: a series of witnessed deaths. *J Neurol Neurosurg Psychiatry* 68:211–213.

Langan Y, Nashef L, Sander JW. (2005) Case–control study of SUDEP. *Neurology* 64:1131–1133.

Ling L, Fuller DD, Bach KB, Kinkead R, Olson EB Jr, Mitchell GS. (2001) Chronic intermittent hypoxia elicits serotonin-dependent plasticity in the central neural control of breathing. *J Neurosci* 21:5381–5388.

Mahamed S, Mitchell GS. (2008) Simulated apnoeas induce serotonin-dependent respiratory long-term facilitation in rats. *J Physiol* 586:2171–2181.

Nashef L, Ryvlin P. (2009) Sudden unexpected death in epilepsy (SUDEP): update and reflections. *Neurol Clin* 27:1063–1074.

Nashef L, Fish DR, Garner S, Sander JWAS, Shorvon SD. (1995) Sudden death in epilepsy: a study of incidence in a young cohort with epilepsy and learning difficulty. *Epilepsia* 36:1187–1194.

Nashef L, Garner S, Sander JWAS, Fish DR, Shorvon SD. (1998) Circumstances of death in sudden death in epilepsy: interviews of bereaved relatives. *J Neurol Neurosurg Psychiatry* 64:349–352.

Nilsson L, Ahlbom A, Farahmand BY, Tomson T. (2003) Mortality in a population-based cohort of epilepsy surgery patients. *Epilepsia* 44:575–581.

Paterson DS, Trachtenberg FL, Thompson EG, Belliveau RA, Beggs AH, Darnall R, Chadwick AE, Krous HF, Kinney HC. (2006) Multiple serotonergic brainstem abnormalities in sudden infant death syndrome. *JAMA* 296:2124–2132.

Richter DW, Manzke T, Wilken B, Ponimaskin E. (2003) Serotonin receptors: guardians of stable breathing. *Trends Mol Med* 9:542–548.

Ryvlin P. (2006) Avoid falling into the depths of the insular trap. *Epileptic Disord* 8(Suppl. 2):37–56.

Ryvlin P, Kahane P. (2003) Does epilepsy surgery lower the mortality of drug-resistant epilepsy. *Epilepsy Res* 56:105–120.

Ryvlin P, Montavont A, Kahane P. (2006) Sudden unexpected death in epilepsy: from mechanisms to prevention. *Curr Opin Neurol* 19:194–199.

Ryvlin P, Cucherat M, Rheims S. (2011) Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials. *Lancet Neurol* 10:961–968.

Salanova V, Markand O, Worth R. (2002) Temporal lobe epilepsy surgery: outcome, complications, and late mortality rate in 215 patients. *Epilepsia* 43:170–174.

Schuele SU, Bermeo AC, Alexopoulos AV, Burgess RC. (2010) Anoxia-ischemia: a mechanism of seizure termination in ictal asystole. *Epilepsia* 51:170–173.

Seyal M, Bateman LM, Albertson TE, Lin TC, Li CS. (2010) Respiratory changes with seizures in localization-related epilepsy: analysis of periictal hypercapnia and airflow patterns. *Epilepsia* 51: 1359–1364.

Shapira B, Zohar J, Newman M, Drexler H, Belmaker RH. (1985) Potentiation of seizure length and clinical response to electroconvulsive therapy by caffeine pretreatment: a case report. *Convuls Ther* 1:58–60.

Shen HY, Li T, Boison D. (2010) A novel mouse model for sudden unexpected death in epilepsy (SUDEP): role of impaired adenosine clearance. *Epilepsia* 51:465–468.

Shorvon S, Tomson T. (2011) Sudden unexpected death in epilepsy. *Lancet* 378:2028–2038.

Sillanpaa M, Shinnar S. (2010) Long-term mortality in childhood-onset epilepsy. *N Engl J Med* 363:2522–2529.

Sperling MR, Feldman H, Kinman J, Liporace JD, O'Connor MJ. (1999) Seizure control and mortality in epilepsy. *Ann Neurol* 46: 45–50.

Sperling MR, Harris A, Nei M, Liporace JD, O'Connor MJ. (2005) Mortality after epilepsy surgery. *Epilepsia* 46(Suppl. 11):49–53.

Tiihonen J, Krupitsky E, Verbitskaya E, Blokhina E, Mamontova O, Föhr J, Tuomola P, Kuoppasalmi K, Kiviniemi V, Zwartau E. (2012) Naltrexone implant for the treatment of polydrug dependence: a randomized controlled trial. *Am J Psychiatry* 169:531–536.

Timmings PL. (1993) Sudden unexpected death in epilepsy: a local audit. *Seizure* 2:287–290.

Tomson T, Nashef L, Ryvlin P. (2008) Sudden unexpected death in epilepsy: current knowledge and future directions. *Lancet Neurol* 7:1021–1031.

Tu E, Bagnall RD, Duflou J, Semsarian C. (2011) Post-mortem review and genetic analysis of sudden unexpected death in epilepsy (SUDEP) cases. *Brain Pathol* 21:201–208.

Tupal S, Faingold CL. (2006) Evidence supporting a role of serotonin in modulation of sudden death induced by seizures in DBA/2 mice. *Epilepsia* 47:21–26.

Uteshev VV, Tupal S, Mhaskar Y, Faingold CL. (2010) Abnormal serotonin receptor expression in DBA/2 mice associated with susceptibility to sudden death due to respiratory arrest. *Epilepsy Res* 88:183–188.

Venit EL, Shepard BD, Seyfried TN. (2004) Oxygenation prevents sudden death in seizure-prone mice. *Epilepsia* 45:993–996.

Volpicelli JR, Alterman AI, Hayashida M, O'Brien CP. (1992) Naltrexone in the treatment of alcohol dependence. *Arch Gen Psychiatry* 49:876–880.