



## SUDEP: What Are the Risk Factors? Do Seizures or Antiepileptic Drugs Contribute to an Increased Risk?

### Do Antiepileptic Drugs or Generalized Tonic–Clonic Seizure Frequency Increase SUDEP Risk? A Combined Analysis.

Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, Langan Y, Walczak TS, Beghi E, Brodie MJ, Hauser WA, for the ILAE Commission on Epidemiology (Subcommission on Mortality). *Epilepsia* 2012;53(2):249–252.

**PURPOSE:** In an analysis of four case–control studies of sudden unexpected death in epilepsy (SUDEP), we found that yearly frequency of generalized tonic–clonic seizures (GTCS) and antiepileptic drug (AED) polytherapy were associated with an increased risk for SUDEP. The prior analysis, however, did not evaluate AEDs and GTCS frequency concurrently. **METHODS:** We combined data from the three case-control studies with information on the frequency of GTCS and AED therapy, that is, carbamazepine, phenytoin, valproic acid, and other AED therapy. Number of AEDs was also considered. Lamotrigine and GTCS frequency were considered separately in two of the case–control studies. Logistic regression analysis was used to evaluate GTCS frequency, each of the AEDs, and number of AEDs. Adjusted analysis of the different AEDs accounted for study, age at death, gender, and GTCS frequency. **KEY FINDINGS:** In crude analysis, GTCS frequency, AED polytherapy, and number of AEDs were associated with an increased risk for SUDEP. Analysis of individual AEDs and of number of AEDs, adjusting for GTCS frequency, revealed no increased risk associated with AEDs as monotherapy, polytherapy, or total number. GTCS frequency remained strongly associated with an increased risk for SUDEP. **SIGNIFICANCE:** Our findings—that none of the AEDs considered were associated with increased SUDEP risk as monotherapy or as polytherapy when GTCS frequency was taken into account—provide a consistent message that number of GTCS increases SUDEP risk and not AEDs. These results suggest that prevention of SUDEP must involve increased efforts to decrease GTCS frequency in order to avert the occurrence of this devastating epilepsy outcome.

### Sudden Unexpected Death in Epilepsy: People With Nocturnal Seizures May Be at Highest Risk.

Lamberts RJ, Thijs RD, Laffan A, Langan Y, Sander JW. *Epilepsia* 2012;53(2):253–257.

**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.

### Commentary

Although sudden unexpected death in epilepsy (SUDEP) is one of the most frequent causes of death among patients with epilepsy (1), risk factors identifying those most at risk have not been clarified. Currently, epilepsy and seizure severity factors including generalized tonic seizures (GTCS) are most commonly associated with SUDEP (1–4). In addition, studies suggest that antiepileptic drug



(AED) therapy and, in particular, carbamazepine and lamotrigine may also contribute (2, 5) to the risk of SUDEP. As most unwitnessed SUDEP deaths occur in or by a bed, it has been suggested that nocturnal seizures may be associated with a higher risk of SUDEP (6). This is supported by ictal recordings of SUDEP occurring during sleep (7). Further study is needed to explore whether these factors increase the risk of SUDEP.

Two recent studies (Hesdorffer et al. and Lamberts et al.) investigated risk factors associated with SUDEP. Hesdorffer and colleagues followed up on results from a prior analysis of four case-control studies (2) of SUDEP, finding that yearly frequency of GTCS and AED polytherapy was associated with an increased risk for SUDEP. They combined data from three case-control studies (1, 3, 4) of risk factors for SUDEP. These studies all had information on GTCS frequency per year and AED therapy. Cases were subjects with well-defined SUDEP criteria. Controls were people living with epilepsy. Cases and controls with a history of heart disease were excluded. The analysis by Hesdorffer et al. included 216 cases and 831 controls. Yearly GTCS frequency was associated with an increased risk of SUDEP in the crude and adjusted analysis. Although polytherapy was associated with an increased risk in the crude analysis, after adjustment for multiple factors including GTCS and gender, it was no longer independently associated with an increased risk. Similarly, there was no association with any of the studied AEDs as monotherapy (lamotrigine, carbamazepine, valproate). A separate analysis of male and female subjects did not find a significant association between lamotrigine and SUDEP. Of interest, monotherapy appeared to be protective. Lamberts and colleagues assessed whether those with sleep-related SUDEP were more likely to have nocturnal seizures and whether diurnal or nocturnal seizure patterns differed between those who died secondary to SUDEP compared with controls. Seizure patterns were classified in 154 autopsy-confirmed SUDEP cases and 616 age- and sex-matched controls living with epilepsy as diurnal (exclusively during the day) and nocturnal (exclusively at night). SUDEP cases were classified as witnessed or unwitnessed as well as being sleep related or not. The time of death was defined as occurring within one of six hour periods. Most SUDEP cases were unwitnessed (86%), and most cases were sleep related (58%). If the SUDEP case was sleep related, it was more likely to be unwitnessed. Among the cases, seizure patterns were nocturnal in 36% and diurnal in 32%. Among controls 17% had a nocturnal pattern and 58% had a diurnal pattern. Those who died during sleep were more likely to have nocturnal seizures than those who died while awake. Most who died suddenly had a nocturnal seizure pattern, whereas the majority of controls had an exclusive diurnal seizure pattern. Sleep-related SUDEP occurred most frequently in the early morning, whereas non-sleep-related death occurred most frequently between 8 am and 12 pm and 4 pm and 8 pm.

The results of Hesdorffer and colleagues suggest that GTCS frequency is a significant predictive factor for risk of SUDEP. These findings support that SUDEP is a seizure-related event. Postulated mechanisms for SUDEP include respiratory failure, cardiac arrhythmia, or cerebral electrical shutdown. Future basic and clinical research should continue to focus on potential sequelae of GTCS that may predispose patients with epilepsy to an increased risk of SUDEP. In addition, control of GTCS should be considered as integral to reducing the risk of SUDEP. The impact of AED therapy on SUDEP risk is an evolving story. Prior studies have suggested an

increased risk in association with specific AEDs such as lamotrigine and carbamazepine. Indeed, a recent nested case-control study from Norway (8) found that the incidence of SUDEP was significantly higher among female patients with epilepsy who were treated with lamotrigine, and a significantly higher proportion of female SUDEP cases were taking lamotrigine when compared with controls. Although population based, the numbers in this study are small (26 cases of SUDEP). The data from Hesdorffer et al. do not support an independent risk of either AED polytherapy or individual AEDs after controlling for GTCS frequency. As the authors suggest, all studies investigating risk factors associated with SUDEP need to carefully control for GTCS frequency. The Norwegian population-based study discussed above did not control for GTCS frequency.

Although prior studies suggest that nocturnal seizures are associated with a higher risk of SUDEP, the association between nocturnal seizures and SUDEP risk had previously not been well studied. The results from Lamberts and colleagues support that nocturnal seizures are an independent risk factor for SUDEP. In their analysis, the authors controlled for history of GTCS as well as number of GTCS in the last 3 months. Their data clarify that SUDEP is a sleep-related and unwitnessed event. In their study, most sleep-related SUDEP cases occurred between the hours of 4 am and 8 am, which interestingly is similar to published data regarding sudden cardiac death and sudden infant death syndrome.

Taken together, these studies support the association between SUDEP and GTCS frequency and nocturnal seizures. Identification of these risk factors will direct future research to understand the mechanisms of SUDEP. Understanding the risk factors associated with an increased risk of SUDEP is necessary in directing research efforts at predicting who is at risk as well as preventing one of the most frequent causes of death in patients with epilepsy.

by Alison M. Pack, MD, MPH

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