



Sometimes, More Is More: Antiseizure Medication polytherapy Is Associated With Decreased SUDEP Risk

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Pharmacologic Treatment and SUDEP risk: A Nationwide, Population-Based, Case-Control Study

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Objective: We conducted a nationwide case-control study in Sweden to test the hypothesis that antiepileptic drugs (AEDs) mono- or polytherapy, adherence, antidepressants, neuroleptics, β -blockers, and statins are associated with sudden unexpected death in epilepsy (SUDEP) risk. **Methods:** Included were 255 SUDEP cases and 1148 matched controls. Information on clinical factors and medications came from medical records and the National Patient and Prescription Registers. The association between SUDEP and medications was assessed by odds ratios (ORs) with 95% CIs adjusted for potential risk factors including type of epilepsy, living conditions, comorbidity, and frequency of generalized tonic-clonic seizures (GTCS). **Results:** Polytherapy, especially taking 3 or more AEDs, was associated with a substantially reduced risk of SUDEP (OR: 0.31, 95% CI: 0.14-0.67). Combinations including lamotrigine (OR: 0.55, 95% CI: 0.31-0.97), valproic acid (OR: 0.53, 95% CI: 0.29-0.98), and levetiracetam (OR: 0.49, 95% CI: 0.27-0.90) were associated with reduced risk. No specific AED was associated with increased risk. Regarding monotherapy, although numbers were limited, the lowest SUDEP risk was seen in users of levetiracetam (0.10, 95% CI: 0.02-0.61). Having nonadherence mentioned in the medical record was associated with an OR of 2.75 (95% CI: 1.58-4.78). Statin use was associated with a reduced SUDEP risk (OR: 0.34, 95% CI: 0.11-0.99) but selective serotonin reuptake inhibitor use was not. **Conclusion:** These results provide support for the importance of medication adherence and intensified AED treatment for patients with poorly controlled GTCS in the effort to reduce SUDEP risk and suggest that comedication with statins may reduce risk.


Commentary

Every patient who dies of sudden unexpected death in epilepsy (SUDEP) leaves one major question unanswered; why this patient, rather than any of the other numerous poorly controlled patients in a typical epilepsy practice? Due to the relative scarce nature of these tragic events and lack of reliable physiological, biochemical, or imaging biomarkers, rarely does a patient who we consciously identify as high risk succumb to SUDEP; death appears bewilderingly random, unpredictable, and seemingly impossible to prevent.

The numerous previous studies in SUDEP do not necessarily assuage the practitioner of this apparent randomness. There is general agreement about the overwhelming importance of one characteristic—that poorly controlled generalized tonic-clonic seizures (GTCS), particularly nocturnal events, are strongly associated with the risk of SUDEP. All of the risk factors with sufficient evidence identified by The American Academy of Neurology SUDEP practice guideline of 2017¹ involve GTCS; their presence, increasing frequency, failure to control them adequately, and lack supervision when one occurs all contribute to SUDEP. Two dozen other risk factors

have been identified and have at least conflicting evidence in support, including male sex, use of anxiolytic drugs, intellectual disability, extratemporal epilepsy, substance use, heart rate variability, postictal generalized EEG suppression on EEG, postictal prone position, and others. The most disconcerting of these are related to antiseizure medications (ASMs)—that the number of ASMs used and lamotrigine use in women have been associated with an increased risk of SUDEP. Some of these risk assessments come from earlier retrospective case-control² or cohort³ studies. Although there were concerns that some ASMs may be proarrhythmic, there is general agreement that ASM polytherapy was a proxy of uncontrolled GTCS, rather than a direct independent contributor of SUDEP, and that this association is not present when analyses adjusted for the presence of GTCS.⁴ In fact, one convincing study by Ryvlin et al demonstrated that the risk of SUDEP decreased in patients who were in the active treatment arm of placebo-controlled randomized ASM trials; as these pharmaceutical trials were designed to add on ASM versus placebo to existing ASM regimen, all of these patients were on polytherapy.⁵





Sveinsson et al⁶ advance this concept further in the current case–control study that is based on the Swedish National Patient and Prescription Register database. The study design and cohort may be familiar to readers as the authors have published a well-regarded study using the identical cohort in 2019 in identifying the clinical risk factors in SUDEP.⁷ Both studies depend on a carefully constructed cohort utilizing the Swedish National Patient Register, a comprehensive dataset of all hospitalized and hospital-based ambulatory patients. The authors identified 255 SUDEP patients (cases) and 1148 matched control patients (controls) over a period of 5 years between 2006 and 2011. For each case, the 5 epilepsy controls alive at the time were selected, matched for sex. The data were then evaluated using 3 statistical models, adjusting for (1) sex only, (2) addition of duration/type of epilepsy, sharing bedroom, intellectual disability, substance/alcohol use, and education; (3) all of the previous, plus history/frequency of GTCS and nocturnal GTCS in the past year.

The most significant finding is the confirmation that polytherapy was not associated with an increase in SUDEP; on the contrary, it was associated with a significant reduction in the risk. None of the previously identified concerning risk factors, such as the increased risk with the overall number of ASMs used or risks imparted by a particular ASM (such as lamotrigine use in women), were associated with increased risk. This finding, in conjunction with the previous Ryvlin study, should put to rest any lingering concerns regarding ASM polytherapy; it would in fact be reasonable to conclude that control of GTCS, however transient with polytherapy, can decrease SUDEP risk.

This study is not without significant limitations; due to its retrospective nature, heavily relying on patient charts and a drug registry, it is inherently prone to biases and limitations of any such chart review studies. Whether similar results will eventually be seen in prospectively collected cohorts remains to be seen. The number of patients on zero ASMs, both in the cases and controls, is surprisingly high, at 18% and 23%, respectively. Previous case–control studies have reported far lower values, at least less than 50% of what is reported for this study. One may be concerned about the possibility that nonepilepsy patients were inadvertently included as determination of mild cases of epilepsy can be challenging under any circumstances, and even more so with record review. However, the more likely explanation is that the authors used ASM dispensation records to determine treatment, and it is certainly possible that such a high number of patients were not fully compliant. The effects of GTCS were controlled through statistical modeling; an initial matching for known confounders, including presence, frequency, and nocturnal nature of GTCS, would have been a more effective design, but may not have been possible.

There are several other intriguing secondary results from this study, including the finding was that levetiracetam was associated with a lowered risk of SUDEP, whether either as monotherapy or part of a polytherapy regimen. To my knowledge, this was the first time this was reported; there are no known inherent reasons related to the mechanism, off-target

effects, or efficacy against GTCS that could explain these results, and further studies are needed to examine this unexpected effect. One may suspect this may be due to the fact that levetiracetam, due to its ease of use, superior safety profile, and ability to be initiated at a therapeutic dose, is frequently an early ASM choice (though the authors of the study inform me that during the study period, it was not typically used first line in Sweden) and more likely to be switched out in poorly controlled patients.


Other important medication hypotheses regarding SUDEP were examined in this study. Although there has been much interest in the role of serotonin depletion as a risk factor,⁸ the authors did not find that the use of selective serotonin reuptake inhibitors decreased the risk of SUDEP. There was a decreased risk of SUDEP with the use of statins in this study; a previous study had reported decreased risk of developing epilepsy with the use statins in patients with coronary artery disease.⁹ It remains to be determined whether statins have an independent mechanistic effect to explain this result or whether this reflects more attentive care in general, but this opens up the possibility of another medication intervention. Lastly, surprisingly, the level of care (tertiary care epilepsy centers, neurologists, non-specialists) did not affect SUDEP risk, though this may have been confounded by the probability that more complex, difficult to treat patients were more likely to be followed at dedicated epilepsy clinics.

This cohort (comprising both of their studies) points to a number of other potentially actionable measures, aside from ASM polytherapy, that may lower the risk of SUDEP. The risk of imparted by substance and alcohol use should not be underestimated, as is the dangers of medication nonadherence. Proper night-time supervision, though difficult to arrange organically, may confer significant protection. A method through systematic review of these risk factors has been proposed using a SUDEP and seizure safety checklist.¹⁰ While neither this tool nor any other proposed biomarkers can identify patients at high risk of SUDEP with any reasonable specificity, decreasing the risk of SUDEP will require vigilance and action beyond just medications.

In summary, despite the results of this study, the benefits and drawbacks of polytherapy should be carefully assessed. Polytherapy magnifies all of the problems associated with ASM monotherapy; patients will experience more side effects, there will be more medication interactions, cost of treatment will rise, dosing errors will proliferate, and compliance will be more difficult. Nevertheless, decreasing GTCS with polytherapy, particularly with new ASMs as they become available, should be attempted proactively. Although SUDEP deaths will remain random and unpredictable, this may be one further small step toward a comprehensive effort toward prevention.

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