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Do Antiepileptic Drugs Play a Role in Sudden Unexpected Death in Epilepsy?

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Abstract

Sudden unexpected death in epilepsy (SUDEP) accounts for approximately 2% of deaths in population-based cohorts of epilepsy, and up to 25% of deaths in cohorts of more severe epilepsy. When it occurs, SUDEP usually follows a generalised tonic-clonic seizure. Unresponsiveness, apnoea, and cardiac arrest occur in SUDEP, rather than the typical gradual recovery. The great majority of tonic-clonic seizures occur without difficulty and how the rare seizure associated with SUDEP differs from others is unknown.

Three mechanisms have been proposed for SUDEP: cardiac arrhythmia, neurogenic pulmonary oedema, and postictal suppression of brainstem respiratory centres leading to central apnoea. Recent studies have found that the incidence of SUDEP increases with the severity of epilepsy in the population studied. The duration of epilepsy, number of tonic-clonic seizures, mental retardation, and simultaneous treatment with more than two antiepileptic drugs are independent risk factors for SUDEP. Some studies have reported that carbamazepine use, carbamazepine toxicity, and frequent, rapid changes in carbamazepine levels, may be associated with SUDEP. Other evidence indicates that carbamazepine could potentially increase the risk for SUDEP by causing arrhythmia or by altering cardiac autonomic function. However, this evidence is tenuous and most studies have not found an association between the use of carbamazepine or any other individual antiepileptic drug and SUDEP.

There is little information regarding antiepileptic drugs other than phenytoin and carbamazepine. The incidence of SUDEP with gabapentin, tiagabine, and lamotrigine clinical development programmes is in the range found in other populations with refractory epilepsy. This suggests that these individual antiepileptic drugs are no more likely to cause SUDEP than antiepileptic drugs in general.

Best current evidence indicates that the risk of SUDEP can be decreased by aggressive treatment of tonic-clonic seizures with as few antiepileptic drugs as necessary to achieve complete control. At present there is no strong reason to avoid any particular antiepileptic drug. Further studies are needed to elucidate the potential role of individual antiepileptic drugs in SUDEP and establish clinical relevance, if any. These studies may be challenging to conduct and interpret because SUDEP is relatively uncommon and large numbers will be necessary to

narrow confidence intervals to determine the clinical relevance. Also adjustments will be needed to account for the potent risks associated with other independent factors.

Sudden unexpected death in epilepsy (SUDEP) has been recognised since the middle of the 19th century,[1,2] long before antiepileptic drugs were available. For many years SUDEP was considered rare and of interest mostly to forensic pathologists. Detailed patient follow-up that is required for US FDA submission of new antiepileptic drugs revealed a mortality rate higher than that expected in the general population or even the general population with epilepsy. Many of these deaths were sudden and unexplained even after complete autopsy. Regulatory authorities were required to consider the possibility that the antiepileptic drugs being evaluated were responsible for the deaths. This concern increased interest in SUDEP. Studies in the last decade have begun to clarify the incidence, aetiology, and risk factors for this entity. These studies have revealed that SUDEP is responsible for 18–25% of deaths among patients with medically-refractory epilepsy.[3,4] However, SUDEP appears to be relatively rare in population-based cohorts of epilepsy in which seizures are generally well controlled with medications. Only approximately 2% of deaths can be explained by SUDEP in this situation.[5] The potential role of antiepileptic drugs in the aetiology of SUDEP has also been examined in some of these studies. This review provides a general introduction to SUDEP and discusses the available information associating SUDEP with antiepileptic drugs. Where possible, the reviewer offers tentative conclusions.

1. Definition and Circumstances of Death

Early studies used a variety of definitions of SUDEP, making comparisons between these studies difficult. Recently, investigators have adopted more uniform definitions. Investigators in the UK have defined SUDEP as a "sudden, unexpected, witnessed or unwitnessed, nontraumatic and nondrowning death in patients with epilepsy with or without evidence for a seizure and excluding documented status epilepticus, in which postmortem examination does not reveal a toxicologic or anatomic cause for death".[6] North American investigators have required the following criteria: (i) the patient has epilepsy (recurrent unprovoked seizures); (ii) death occurs unexpectedly while the patient is in a reasonable state of health; (iii) death occurs over minutes; (iv) death occurs in benign circumstances while the patient is engaged in normal activities; and (v) no obvious cause of death, including status epilepticus is present.[7] Potential SUDEP cases have been divided into four categories: definite (other causes excluded by sufficient description of circumstances of death and autopsy with toxicologic screening); probable (no obvious cause of death but no autopsy); possible (SUDEP possible but information regarding circumstances of death insufficient); and not SUDEP (SUDEP unlikely because of circumstances at death or another cause of death established).[7] Because of low autopsy rates in the US, a working definition of SUDEP typically includes both definite and probable SUDEP.

Circumstances of death are remarkably uniform in various studies. Between one-third and two-thirds of SUDEP cases are found dead in bed, often in prone position.[8-11] One-half to three-quarters die shortly after a witnessed seizure.[8,11-13] Indirect evidence of tonic-clonic seizures is found in many of the remaining patients. In continuously observed patients with SUDEP, a tonic-clonic seizure is typically followed by unresponsiveness, apnoea and pulselessness. Attempts to resuscitate are unsuccessful, even with advanced life support.[8,9,13] Tonic-clonic seizures preceding SUDEP do not appear to differ from the patient's usual seizures in severity or other characteristics. It must be emphasised that the great majority of patients tolerate the great majority of tonic-clonic seizures without difficulty. Au-

Table I. Incidence of sudden unexpected death in epilepsy in various epilepsy populations

Population type	Location/group studied	Incidence (/1000 patient-years)
Geographic population	Olmsted County, Minnesota, USA[5]	0.35
Large health provider cohort	Group Health Cooperative of Puget Sound, Tacoma, Washington, USA[3]	1.3
	Provincial Health Plan, Saskatchewan, Canada[15]	0.5
	Hospital admissions for epilepsy, Stockholm, Sweden[16]	1.5
Refractory epilepsy cohorts	3 epilepsy centres in Midwestern USA[4]	1.5
	Epilepsy centre, UK[17]	2.0
	Institutionalised youths, UK[18]	3.4
	Epilepsy centre, UK[19]	5.9
Antiepileptic drug[a] and medical device clinical development programmes	Lamotrigine[7]	2.8
	Gabapentin[20]	3.8
	Tiagabine[21]	3.3
	Vagal nerve stimulator[22]	4.1
Epilepsy surgery programmes	Pittsburgh, Pennsylvania, USA[23]	9.3
	Philadelphia, Pennsylvania, USA[24]	4.0

a Almost all patients were receiving multiple antiepileptic drugs.

topsies following SUDEP are unremarkable except for pulmonary oedema, which occurs in almost all cases.[8,9,14] There is generally little evidence of cardiovascular disease, although this may be in part due to exclusion criteria adopted by many investigators. Many studies exclude patients with evidence of significant cardiovascular disease at autopsy.

2. Incidence

To date, the only published population-based study (Olmsted County, Minnesota, USA) found a SUDEP incidence of 0.35 per 1000 patient years.[5] Sudden unexplained death was 24 times more likely in epilepsy patients than in the population without epilepsy.[5] SUDEP incidence appears to increase steadily with an increasing severity of epilepsy in the studied population (table I). SUDEP incidence in antiepileptic drug development programmes is in the range found in cohorts of patients with refractory epilepsy and somewhat less than the incidence in patients awaiting epilepsy surgery (table I). Almost all patients in drug development programmes were treated with multiple antiepileptic drugs.

3. Risk Factors

Uncontrolled case series,[8,9,12,25] typically collected at medical examiners' offices, suggested that SUDEP cases had more frequent seizures, more developmental delay, and more CNS lesions than the 'general population' with epilepsy. Virtually all patients experienced tonic-clonic seizures. Controlled studies[4,16] have demonstrated that the duration of epilepsy, frequency of generalised tonic-clonic seizures, and mental retardation, are independent risk factors for SUDEP. Tonic-clonic seizures rather than other seizure types appears to be the culprit; as few as 1–3 tonic-clonic seizures per year increases the risk of SUDEP.[4] The use of psychotropic drugs was shown to increase the risk of SUDEP in some[15,16] but not all[4] studies.

4. Pathogenesis

Understanding the pathogenesis of SUDEP is necessary to elucidate any potential contributions of antiepileptic drugs. Three potential mechanisms have been proposed. Initial reports speculated that fatal cardiac arrhythmia may cause SUDEP (see the review by Jay and Leestma[26]). The catecholamine surge associated with tonic-clonic seizures may induce subtle cardiac lesions. Catecholamine surges

may also induce ventricular ectopic activity. Ventricular ectopic activity may also be increased by sleep, psychotropic medications, and some antiepileptic drugs, perhaps explaining some of the associations observed in clinical studies.[8,9,15,16,26] Finally animal models have demonstrated that both interictal and ictal discharges increase the risk of cardiac arrhythmia.[27] However, this potential mechanism has been challenged because serious arrhythmia is rare when heart rhythm is monitored during epileptic seizures[28,29] and because animal models of SUDEP suggest that arrhythmia is not the primary cause of death.[30,31]

Pulmonary oedema is frequently observed at autopsy in persons with SUDEP.[8,9,14] This has led to the proposal that neurogenic pulmonary oedema causes SUDEP.[8,14] Neurogenic pulmonary oedema does occur rarely after epileptic seizures (see the review by Archibald and Armstrong[32]). Hypothalamic stimulation, which may occur during a seizure, increases pulmonary vascular permeability.[33] However, the extent of pulmonary oedema observed in autopsies and in the animal model of SUDEP is not thought sufficient to account for death in most cases.[31,34]

The mechanism currently favoured by many argues that a profound central apnoea following generalised tonic-clonic seizures is the primary cause of death; pulmonary oedema and arrhythmia are thought to be secondary to the apnoea.[17,34,35] This hypothesis is supported by the animal model of SUDEP,[31] and by observations that apnoea is common following epileptic seizures.[36] Furthermore, a review of rare cases of SUDEP recorded during video-electroencephalography (EEG) monitoring[37,38] suggests that severe postictal cerebral suppression inhibits brainstem mediated respiratory drive resulting in apnoea, arrhythmia, and death. An obstructive component may exacerbate the apnoea and perhaps this accounts for the finding that many patients with SUDEP are found dead in bed in the prone position.

5. Sudden Unexpected Death in Epilepsy (SUDEP) and Antiepileptic Drugs

5.1 SUDEP and Compliance with Antiepileptic Drug Treatment

The earlier SUDEP series, based at medical examiner's offices consistently demonstrated low postmortem antiepileptic drug blood levels.[8-10] These uncontrolled observations were interpreted as representing non-compliance with antiepileptic drug treatment. One recent controlled study found that postmortem sub-therapeutic antiepileptic drug levels were significantly more common in SUDEP cases than in epilepsy patients who had died of other causes[39] while another study[40] found no difference. It is not clear whether postmortem antiepileptic drug measurements reflect the situation at time of death because continuing metabolism, alteration in protein binding, and redistribution may alter serum antiepileptic drug concentrations. Studies in New Zealand White rabbits demonstrated that whole blood phenytoin concentrations drop 45% in the 72 hours postmortem while carbamazepine levels remain stable.[41] There is also reason to believe that concentrations of valproic acid (valproate) and phenobarbital (phenobarbitone) decrease postmortem[41] although this phenomenon has not been studied *per se*. Because of these concerns, recent studies have compared premortem antiepileptic drug levels in SUDEP patients and controls. The number of patients with sub-therapeutic antiepileptic drug levels during the last visit prior to SUDEP did not differ in the two groups.[4,42] Serial premortem antiepileptic drug determinations did not reveal a pattern of non-compliance among SUDEP patients either.[42] Therefore, the best data available suggests that antiepileptic drug non-compliance is not a risk factor for SUDEP.

5.2 SUDEP and the Number of Antiepileptic Drugs Used

Earlier uncontrolled series reported that SUDEP patients were treated with multiple antiepileptic

drugs more often than epilepsy patients in general.[8-10] A controlled study also found that simultaneous treatment with more than one antiepileptic drug was associated with SUDEP.[15] These authors speculated that the number of antiepileptic drugs used was a surrogate for the severity of epilepsy although they were unable to assess the severity of epilepsy in their patients and so could not directly address this question. Two subsequent cohort-based case-controlled studies[4,16] have reported that treatment with more than two antiepileptic drugs is a risk factor for SUDEP even after adjustment for the number of seizures experienced.

Walczak et al.[4] followed a large prospectively enrolled cohort of patients from three epilepsy centres in the upper Midwestern USA. While this cohort probably had somewhat more severe seizures than that found in the community, virtually all patients were intensively studied and the diagnosis of epilepsy was secure. In this cohort, simultaneous treatment with more than two antiepileptic drugs increased the risk of SUDEP by 3–4 times, after adjustment for the number of seizures of any type or the number of tonic-clonic seizures.

Nilsson et al.[16] studied a cohort of all patients discharged from a Stockholm, Sweden county hospital with a diagnosis of seizures between 1980 and 1989. This population was probably more reflective of those patients who had epilepsy in the community. They found that simultaneous treatment with more than two antiepileptic drugs increased the risk of SUDEP by approximately nine times, after adjustment for the number of seizures of any type, age at onset of epilepsy, type of epilepsy, and the number of antiepileptic drug dosage changes.

Thus, two large, epidemiologically sound studies of complementary populations have found that treatment with multiple antiepileptic drugs increases the risk of SUDEP after some adjustment for seizure type and severity. It is not clear whether the number of seizures, type of seizures, age of onset, and type of epilepsy are a complete reflection of epilepsy severity. Other factors such as mental retardation, structural lesions, and psychosocial measures may also be important. The physiological impact of individual seizures varies widely and ideally should be incorporated into a measure of seizure severity. Scales to measure this exist, but would be impossible to administer prospectively to a sufficiently large cohort. The number of SUDEP cases in the two cohorts was also relatively small and adjustments were made *post hoc* based on available information in at least one of the studies.[4] Despite this, the findings are remarkably consistent and attempts to adjust for seizure and epilepsy severity are reasonable, leading this reviewer to conclude that simultaneous treatment with more than two antiepileptic drugs is an independent risk factor for SUDEP.

5.3 SUDEP and Individual Antiepileptic Drugs

The question then arises whether any individual antiepileptic drug or combination of antiepileptic drugs is associated with SUDEP. Unfortunately much less information is available to answer this question. Older antiepileptic drugs (phenytoin, phenobarbital, and valproic acid) used in the earlier SUDEP case series appeared to reflect general practice and no single antiepileptic drug appeared to predominate.

Neither contemporary cohort based studies[3,4] nor contemporary medical examiner series[12,40] have found any particular antiepileptic drug to be associated with SUDEP. SUDEP was noted in drug development programmes for lamotrigine,[7] tiagabine,[21] and gabapentin.[20] Initially, there was concern that these antiepileptic drugs may be responsible. However, the SUDEP incidence in these antiepileptic drug development programmes was in the general range found in cohorts of patients with severe epilepsy (table I). These comparisons have led to the conclusion that the higher SUDEP incidence in clinical development programmes (relative to an unselected cohort of patients with epilepsy) is due to the severity of the epilepsy rather than to the antiepileptic drugs.[7,22] Patients treated with add-on lamotrigine had somewhat lower SUDEP rates than patients treated with add-on placebo in the lamotrigine clinical development programme,[7] which provides further support for this conclusion. These comparisons do not rule out the possibility that

antiepileptic drugs in general, rather than epilepsy, are responsible for SUDEP because patients treated with a particular antiepileptic drug were compared with patients treated with other antiepileptic drugs. These comparisons do provide evidence that the particular antiepileptic drug studied is not associated with SUDEP any more often than antiepileptic drugs in general.

There are theoretical reasons to suspect that carbamazepine may be more likely to cause SUDEP than other antiepileptic drugs (see sections 6.1 and 6.2). Consequently, several reports have analysed the possibility that carbamazepine use is associated with SUDEP. Carbamazepine was implicated in a small series of 14 SUDEP patients at an epilepsy centre in Cardiff, Wales. Eighty-five percent of SUDEP cases had been treated with carbamazepine while only 38% of the remaining patients without SUDEP followed at that centre had been treated with carbamazepine.[17] However, three larger controlled studies found that the use of carbamazepine was equally likely in SUDEP cases and control subjects.[4,12,16] Furthermore, a cohort-based study[3] found that carbamazepine use in SUDEP cases was less likely than in the cohort from which the cases had been drawn. None of these series adjusted for other known risk factors for SUDEP, therefore the possibility that carbamazepine varied systematically with other known risk factors cannot be excluded.

Further analyses have explored the possibility that toxic concentrations of carbamazepine may be associated with SUDEP. One study found that toxic carbamazepine concentrations at last visit were equally likely in SUDEP cases and controls.[4] A recent analysis comparing postmortem antiepileptic drug levels in SUDEP cases and controls did not find toxic carbamazepine concentrations in any of the cases.[40] However, a more detailed analysis by Nilsson et al.[42] found that the risk of SUDEP was increased 9-fold with toxic carbamazepine concentrations at the time of last visit, after adjusting for age and seizure frequency. The risk was increased further to >26 times the reference, after adjusting for age, seizure frequency, and the number of antiepileptic drug dose changes in the last year. SUDEP risk was not increased with therapeutic carbamazepine concentrations at the last visit, irrespective of how many antiepileptic drug dose changes had been made. SUDEP risk was also increased 9-fold with low carbamazepine concentrations at last visit, but only when more than one antiepileptic drug dose change had been made in the last year. In contrast, phenytoin concentrations at last visit were not associated with SUDEP even after all of the above adjustments. The authors concluded that frequent changes of carbamazepine dose with concentrations outside of therapeutic range were an independent risk factor for SUDEP after adjustment for seizure severity.

6. Possible Mechanisms Implicating Antiepileptic Drugs in SUDEP

6.1 Antiepileptic Drugs and Arrhythmia

Phenytoin has been used as an antiarrhythmic drug in the past, particularly to normalise the prolonged refractory period of the atrioventricular node caused by digoxin therapy. Bradyarrhythmias have been reported infrequently, occasionally evolving to asystole and death, usually in elderly patients treated for cardiac disorders, and almost exclusively with intravenous treatment (see the review by Tomson and Kennebäck[43]). To my knowledge only one case of arrhythmia has been attributed to oral phenytoin use.[44] The almost exclusive occurrence of arrhythmia with intravenous use has led to the conclusion that the solvent used in the older phenytoin intravenous formulation or the rapid increase in phenytoin concentration associated with intravenous use was responsible for the arrhythmia.

Bradyarrhythmias, including atrioventricular block and asystole, have been reported somewhat more frequently with oral administration of carbamazepine even at relatively low doses. Bradyarrhythmia almost always occurred in patients older than 40 years, usually with pre-existing conduction abnormalities (see reviews by Tomson and Kennebäck[43] and Kasarkis et al.[45]). However, arrhythmias detected during 24-hour ECG monitoring were equally likely in elderly patients treated with carba-

mazepine and in age-matched controls.[46] Initiation of carbamazepine did not induce changes in measures of cardiac conduction in another small study.[47] Phenobarbital does not decrease cardiac conduction,[48] nor does intravenous valproic acid induce ECG abnormalities, even when rapidly administered to elderly patients with cardiac rhythm disturbances.[49-52] To my knowledge, the risk of arrhythmias with the use of other antiepileptic drugs has not been studied.

In summary, antiepileptic drugs rarely cause bradyarrhythmias; when they do so it is usually in elderly patients with pre-existing cardiac conduction defects. It is therefore unlikely that direct antiepileptic drug effects on cardiac conduction are responsible for SUDEP.

6.2 Antiepileptic Drugs and Alteration of Cardiac Autonomic Function

Functional and anatomic studies have indicated that interictal autonomic cardiac function is abnormal in epilepsy patients treated with antiepileptic drugs. Separating the effects of epilepsy from the effects of antiepileptic drugs has been difficult but there is some evidence that carbamazepine has an independent effect. Many other factors can affect measures of cardiac autonomic function. The possibility that these other confounders (e.g. generalised anxiety or non-antiepileptic medications) may differ in epilepsy and control subjects has not been addressed. This issue, together with the different procedures used, makes comparisons between studies and the drawing of any conclusions difficult.

The single study comparing autonomic cardiac control in a group of newly diagnosed untreated epilepsy patients and a group of controls found no differences.[53] Multiple studies have found alterations of autonomic cardiac control in treated patients with chronic epilepsy.[53-56] These alterations appeared more significant in epilepsy patients treated with carbamazepine than in those treated with other antiepileptic drugs,[53-56] although carbamazepine alone clearly did not account for all autonomic changes in a study that attempted to separate the effects of epilepsy and carbamazepine statistically.[55] Carbamazepine administration appeared to increase sympathetic autonomic activity in control patients without epilepsy.[55] Phenytoin, valproic acid, phenobarbital and vigabatrin did not appear to influence cardiac autonomic activity in epilepsy patients[48,53,54] although the power to exclude effects in these studies has been limited.

Power spectral analysis of heart rate variability has been advanced as a means to separately analyse parasympathetic and sympathetic cardiac autonomic activity[57] although the utility of this measure has been debated.[58] Studies utilising this measure have found decreased sympathetic tone[48,56,59] and decreased parasympathetic modulation[48,56,59] in epilepsy patients. Decreased parasympathetic modulation was significantly more common with carbamazepine treatment[56,59] and this was broadly consistent with noncomputerised analysis of ECG RR intervals in previous studies.[53-55]

Autonomic cardiac activity in epilepsy patients during carbamazepine withdrawal was analysed in two studies. Hennessy et al.[60] studied power spectral analysis of heart rate variability in 12 patients undergoing carbamazepine withdrawal during video-EEG monitoring. They reported that abrupt cessation of therapeutic carbamazepine levels was associated with evidence of increased sympathetic cardiac activity in 10 out of 12 patients with intractable epilepsy; 1 out of 12 patients had an increase in preventricular contractions.[60] Kennebäck et al.[61] reported that the abrupt cessation of toxic carbamazepine levels was associated with a significant reduction in heart rate variability in a pattern known to predict mortality after myocardial infarction.[61] Furthermore, in 3 of 10 patients, premature ventricular contractions increased beyond a threshold typically associated with more malignant arrhythmias.[61] A power spectral measurement of heart rate variability similar to that employed by Hennessy et al.[60] did not show changes to suggest elevated sympathetic function; in fact a measure of cardiac sympathetic function significantly decreased during the withdrawal period.[61] Differences in the methods of computing the power spectral measures of heart rate variability, other methodological differences, or the

older age of the patients in Kennebäck et al.[61] may account for the different findings.

Single photon emission computed tomography with iodine-123 metaiodobenzylguanidine allows for the anatomic examination of cardiac sympathetic innervation. *In vivo* examination of epilepsy patients reveals that there is decreased cardiac uptake of this radioligand.[59] This most likely indicates postganglionic sympathetic denervation and raises the possibility of denervation hypersensitivity. However, a mild tonic increase in central sympathetic outflow, perhaps due to interictal epileptiform activity could also result in these findings.[59] Cardiac uptake of this radioligand did not differ in patients treated with carbamazepine and those treated with lamotrigine.[59]

If cardiac sympathetic postganglionic denervation hypersensitivity does in fact occur in epilepsy patients, the risk of fatal arrhythmia during the massive sympathetic output of a generalised tonic-clonic seizure may in fact be higher. The autonomic nervous system changes associated with carbamazepine use, especially with abrupt large fluctuations in carbamazepine concentrations may play an important additional role. These mechanistic speculations are consistent with the clinical findings of Nilsson et al.[42] These authors found that SUDEP is strongly associated with the interaction between number of antiepileptic dose changes and carbamazepine concentrations outside the therapeutic range.

This reviewer believes that the above thoughts regarding mechanisms are tentative and not yet convincing, however, they are worthy of further study. The results of Nilsson et al.,[42] while methodologically and statistically sound, are based on only five patients in whom carbamazepine levels were supratherapeutic but not particularly high. The confidence intervals were correspondingly wide so the clinical significance of these findings is unclear. Two other studies have not found an association between carbamazepine toxicity and SUDEP.[4,40] although both studies probably had less power to detect such an association.

Nilsson et al.[42] compared the risk of SUDEP in patients treated with carbamazepine and those treated with phenytoin. The increased risks attributed to some aspects of carbamazepine treatment may, in fact, reflect a protective effect of phenytoin rather than a deleterious effect of carbamazepine. Phenytoin may exert a protective effect by its antiarrhythmic properties or by other mechanisms.[62,63] Finally, it is not clear whether the decreased parasympathetic modulation apparently associated with carbamazepine treatment is harmful. Indeed, Druschky et al.[59] have suggested that decreased parasympathetic modulation may 'counter-regulate sympathetic cardiac dysfunction' and thus help prevent SUDEP. In this reviewer's opinion, further clinical observations implicating carbamazepine toxicity in SUDEP, a better understanding of the phenomena underlying heart rate variability, and a thorough understanding of the effect of carbamazepine on cardiac autonomic function are necessary before any role for carbamazepine toxicity in SUDEP can be accepted.

6.3 Antiepileptic Drugs and the Intensity of Postictal Cerebral Inhibition

A third possible mechanism extends the idea that postictal inhibition of cerebral activity blunts brainstem-mediated airway protective reflexes and respiratory drive, leading to apnoea, secondary arrhythmia, and death. Treatment with multiple antiepileptic drugs or certain individual antiepileptic drugs could conceivably further exacerbate this inhibition, especially in individuals with a generalised encephalopathy.[4] At this point there are no animal or human data to support this idea and it remains entirely speculative.

7. Conclusions, Clinical Implications, and Further Studies

Consistent evidence indicates that the simultaneous use of more than two antiepileptic drugs increases the risk of SUDEP. The clinical relevance of the risk posed by polytherapy is not entirely clear and the risk associated with polytherapy is probably less than the risk associated with even infrequent tonic-clonic seizures.[4,16] In this reviewer's opinion, current knowledge has not associated any particular

antiepileptic drug with SUDEP. The associations between carbamazepine toxicity and SUDEP are tenuous and their clinical relevance is uncertain. There does not appear to be any reason to avoid carbamazepine, even in patients with multiple risks for SUDEP. It is reasonable to avoid abrupt carbamazepine withdrawal, especially in the setting of carbamazepine toxicity although even here the association with SUDEP is tenuous.

These conclusions have implications for the treatment of patients with epilepsy. Every effort should be made to control tonic-clonic seizures with less than three antiepileptic drugs. Using as few antiepileptic drugs as possible decreases cost, minimises adverse effects and decreases the likelihood of medication interactions so this has long been the standard of practice. The association between SUDEP and antiepileptic polytherapy is a further reason to use only as many antiepileptic drugs as are needed. The great majority of tonic-clonic seizures can be controlled with less than three antiepileptic drugs provided that antiepileptic drugs with complementary mechanisms and pharmacokinetic properties are used. Unfortunately, it is easier to add antiepileptic drugs than to withdraw them, so unnecessary polypharmacy is still too common in the treatment of chronic epilepsy.

Appropriate antiepileptic drug trials can usually be completed within 2 years. If epilepsy is not controlled within this time interval, it is unlikely to be ever completely controlled with antiepileptic drugs alone.[64] An evaluation by a centre specialising in epilepsy is appropriate at this point to confirm the diagnosis of epilepsy and consider other treatment options. Successful epilepsy surgery reduces all-causes mortality and probably reduces SUDEP in medically refractory epilepsy.[24] There is tenuous evidence that the vagal nerve stimulator may reduce SUDEP in this population although this requires confirmation.[22] Resective epilepsy surgery results in complete seizure control in 60–80% of patients with intractable epilepsy, while complete seizure control is rare with vagal nerve stimulation.[65-67] Vagal nerve stimulation should therefore be used only when resective epilepsy surgery is not indicated.

Further studies are necessary to confirm that antiepileptic polytherapy is associated with SUDEP, to assess the possibility that any individual antiepileptic drug is associated with excessive risk and to address the potential mechanisms discussed above. Studies of SUDEP risk among patients treated with the newer antiepileptic drugs in large epilepsy cohorts are especially needed. Addressing these issues will be challenging for the following reasons. SUDEP is relatively uncommon in the general population. It is now clear that the risk of SUDEP associated with antiepileptic drug therapy will require adjustment to account for the potent risks associated with other independent factors. Studies of selected populations with severe epilepsy will probably be necessary to accumulate the number of SUDEP cases necessary to answer these questions. Comparing the incidence of SUDEP in epilepsy patients using a given antiepileptic drug to sudden death rates in patients using the same antiepileptic drug for other conditions (e.g. depression, migraine, pain) may be helpful. However, adjustment will be necessary because mortality may differ in epilepsy and the other medical conditions. Large numbers will also be necessary to narrow confidence intervals and determine the clinical relevance of these observations. Future studies may reveal that any association between individual antiepileptic drugs and SUDEP may be statistically valid but not clinically relevant.

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