Appendix e-6. Evidence profile tables

Modified GRADE table indicating factors used to determine the overall confidence in the evidence - Incidence

Intervention	Outcome	Studies (first author, y)	Class	Effect size (95% CI)	Precision	Consistency	Directness	Plausibility	Reporting bias	Magnitude of effect	Dose response	Direction of bias	Comment
SUDEP incidence rates in childhood	SUDEP incidence	**1) Ackers, 2011[e11]** **2) Berg, 2013[e12]** **3) Nickels, 2012[e13]**	**I** **I** **I**	1) of 0.19 per 1,000 patient-years (95% CI 0.06–0.43). 2) 0.3 per 1000 patient-years (95% CI 0.2–0.6) 3) 0.22 per 1000 patient-years (95% CI 0.4–0.6).									**Three Class I articles** **Downgraded due to imprecision** **Moderate confidence**
SUDEP incidence with childhood onset epilepsy including adulthood	SUDEP incidence	**Sillanpää, 2013[e14]**	**I**	2.3/1,000 patient-years (95% CI 1.5–3.4).	**x**								**No downgrading Based on 1 Class I** **study Confidence** **moderate**
SUDEP incidence in the general population	SUDEP incidence	**1) Lhatoo, 2001[e15]** **2) Holst, 2013[e16]** **3) Aurlien, 2012[e17]** **4) Langan, 1998[e8]** **5) Tennis, 1995[e6]**	**I** **I** **I** **I** **I** **I**	1) 0.09/1,000 patient-years. 2) 0.41/1,000 person-years (95% CI 0.32–0.55). 3) 0.5/1,000 patient-years (95% CI 0.2–0.7). 4) 1.5/1,000 patient-years (95% CI 0.9–2.5). 5) 0.54/1,000 patient-years (95% CI 0.4–0.7). 6) 2.6/1,000 patient-years (95% CI 1.8–3.8).	**Downgraded in meta-analysis**								**With study above** **Included for incidence in adults** **Low confidence**

		6) Langan, 2002[e9]											**in evidence Downgraded twice 1) for meta-analysis 2) for imprecision**
Persons with epilepsy who were likely at some point difficult to treat	SUDEP incidence	**Derby, 1996[e7]**	**I**	1.5/1,000 person-years (95% CI, 0.8–2.7).									**Moderate confidence Based on one Class 1 study**
Pregnant women with epilepsy	SUDEP Incidence	**Edey, 2014[e10]**	**I**	0.79/ 1,000 pregnancies (95% CI 0.6–1.0).									**Moderate confidence Based on one Class 1 study**
					Downgraded								**For all 12 Class I studies, overall incidence Confidence low Downgraded because of meta-analysis**

													and imprecision

Modified GRADE table indicating factors used to determine the overall confidence in the evidence - Risk factors

Intervention/risk factor	Outcome	Studies (first author, y)	Class	Effect size (95% CI)	Precision	Consistency	Directness	Plausibility	Reporting bias	Magnitude of effect	Dose response	Direction of bias	Comment
Presence or absence of GTCs	**Increases SUDEP risk**	**Hesdorffer, 2011[e20]** **Hitiris, 2007[e21]**	**II** **II**	GTCS (OR 5.07, 95% CI 2.94–8.76, for 1–2 GTCS per y; OR 15.46, 95% CI 9.92–24.10, for >3 GTCS per y). OR 1.90, 95% CI 0.72–5.00).	\						**Upgraded**		**Second study does not exclude important effect encompassed by the first study Upgraded from moderate to high confidence because of dose response**
GTC frequency	**Increases SUDEP risk**	**Surges, 2010[e25]** **Hesdorffer, 2011[e20]**	**II** **II**	OR 1.044, 95% CI 1.00–1.09. OR 5.07, 95% CI 2.94–8.76, for 1–2 GTCS per y, and OR 15.46, 95% CI 9.92–24.10, for >3 GTCS per y.						**xx**			**High confidence Upgraded because of magnitude of effect (dose response is part of the question)**

Frequency of seizures of any type	**Increases SUDEP risk**	**Lhatoo, 2010[e26]** **Walscak, 2001[e23]** **Nilsson, 1999[e24]** **Aurlien, 2012[e27]** Nested case-control study (19 cases and 89 controls). Investigators found that seizure frequency of more than 1/wk was associated with an increased SUDEP risk: OR adjusted for age and gender 3.0 (95% CI 0.97–9.2; *p* = 0.057).	**II** **II** **II** **II** **II**	No difference in SUDEP risk. GTCS frequency was associated with an increased SUDEP risk (OR 7.0 [2.0–24.2]); however, the frequency of all seizures was not associated with an increased risk (OR 1.1 [0.3–4.0]). Investigators compared 3–12 seizures per y with 2 or fewer seizures per y and reported an RR for SUDEP of 4.64 (95% CI 1.22–17.63). Seizure frequency of more than one per wk was associated with an increased SUDEP risk: OR adjusted for age and gender 3.0 (95% CI 0.97–9.2).	x								**Imprecision** **across** **studies** **leads to** **no conclusion**

Seizure occurrence vs prolonged seizure freedom	**Increases SUDEP risk**	**Sillanpää, 2013**[e14] **Hitiris, 2007**[e21] **Nilsson, 1999**[e24]	**I** **II** **II**	5.1 (95% CI 1.5–17.3). 2.02 (95% CI 1.11–3.81; *p* = 0.001, adjusted by guideline panel *p* = 0.007 for multiple comparisons). RR of 23.20 (95% CI 3.16–170.28).									**Moderate confidence**

Highly refractory epilepsy	**Increases SUDEP risk**	**Racoosin, 2001[e29]** **Tomson, 2013[e30]**	**I** **I**	There were 52 SUDEP occurrences in 13,617.1 patient-years, which results in an incidence rate of 3.82/1,000 patient-years (95% CI 3.50–4.14). Also evaluated were 3 monotherapy initiation trials wherein participants had newly diagnosed epilepsy and were not taking any concomitant AEDs. For these studies in 982.5 patient-years, there were no SUDEP occurrences, yielding a rate of 0/1,000 patient-years (95% CI 0.00–3.69 by Poisson analysis for rare events). For participants in clinical trials of LTG (not including placebo or active control arms), the incidence rates in studies of newly diagnosed epilepsy (2 SUDEP cases per 2,484 people with newly diagnosed epilepsy, resulting in an incidence rate per patient-y of 2.2 [95% CI 0.38–7.4]) did not differ from that of refractory epilepsy studies (2 SUDEP cases per 1,695 people in refractory trials, yielding an incidence rate per patient-years of 2.5 [95% CI 0.42–8.2]). In this analysis, the rate ratio of SUDEP for add-on trials vs monotherapy	x								**Because of considerable imprecision across and within studies, no conclusion can be made**

				trials was 1.5 (95% CI 0.3–8.5).									
AED monotherapy or no therapy vs monotherapy	**Increases SUDEP risk**	**Hesdorffer, 2012[e31]** **Derby, 1996[e7]**	**II** **II**	OR 1.87 (95% CI 0.93–3.75) SUDEP risk was increased by GTCS frequency and not use of a specific AED or number of AEDs, including taking no AEDs or taking 1 or more AEDs. SUDEP risk for those who had received 3 concurrent AED prescriptions compared with the risk for those who received 1 prescription showed no difference, yielding a SUDEP risk of 0.4 (95% CI 0.1–3.5).	**x**								**Both studies are imprecise; therefore, there is insufficient evidence to make a conclusion**
Specific AED	**Increases SUDEP risk**	**Hesdorffer, 2012[e31]**	**II**	**No increased risk; detailed data not provided.**									**Low**

Lamotrigine	**Increases SUDEP risk**	**Tomson, 2013[e30]**	**I**	The overall, unadjusted rate of SUDEP for LTG was 2.2 events per 1,000-patient-years (95% CI 0.70–5.4). In the LTG arms relative to comparator arms, adjusted for length of exposure and trial, SUDEP risk rates were the following: placebo controlled, OR 0.22 (95% CI 0.00–3.14; *p* = 0.26); active comparator, OR 2.18 (95% CI 0.17–117; *p* = 0.89); and placebo controlled crossover, OR 1.08 (95% CI 0.00–42.2; *p* = 1.0).	x								**Because of imprecision in the study, no conclusion can be made.**
Lamotrigine in women	**Increases SUDEP risk**	**Tomson, 2013[e30]** **Aurlien, 2012[e27]** **Hesdorffer, 2012[e31]**	**I** **II** **II**	SUDEP incidence to be 2.0 (0.42–8.2) for women taking LTG vs 2.5 (0.34–6.6) for men taking LTG. Increased SUDEP risk in women, resulting in an OR of 8.9 (95% CI 1.9–42.1). No difference in SUDEP rates between the genders for those taking LTG.									Low confidence in the evidence based on 1 Class II study, with an additional Class I study and a Class II study with insufficient information to assess precision.
Change in therapy vs no change in therapy	**Increases SUDEP risk**	**Ryvlin, 2011[e32]**	**I**	OR of 0.17 (95% CI 0.05–0.57; *p* = 0.0046), indicating that add-on AEDs are protective against SUDEP.									Moderate

Total number of AEDs ever used	**Increases SUDEP risk**	**Langan, 2005[e22]** **Tennis, 1995[e6]**	**II** **II**	OR was (1–2 AEDs, OR = 1 (referent); (3–4 AEDs, OR = 1.3 0. (95% CI 0.6–2.8); more than 4 AEDs, OR = 3.1 (95% CI 1.4–7.0); 0 AEDs, OR = 21.7 (95% CI 4.4–106); AED number unknown, OR = 8 (95% CI 2.7–25.6). Poisson regression showed a 1.7-fold increase in SUDEP risk for each increment in maximum number of AEDs used.									It is possible that lack of AED treatment in epilepsy is associated with an increased SUDEP risk (low confidence in the evidence, 1 Class II study). It is possible that epilepsy treatment with a higher number of AEDs is associated with an increased SUDEP risk (low confidence in the evidence from 2 Class II studies downgraded to low from moderate because of uncertainty that the total number of AEDs ever used is a surrogate for more refractory epilepsy).
Frequent changes in AEDs	**Increases SUDEP risk**	**Surges, 2010[e25]**	**II**	Changing AEDs 3–5 times in 1 y compared with not making changes, adjusted for seizure frequency, was associated with an RR of 9.32 (95% CI 1.95–44.50) (study authors used conditional multiple logistic regression analysis).									**Low confidence**
Lack of therapeutic drug monitoring	**Increases SUDEP risk**	**Nilsson, 2001[e33]**	**II**	RR 3.7 (95% CI 1.0–13.1) for outpatients who had no TDM compared with those who had 13 TDMs during the 2 y of observation, adjusted for age, gender, seizure frequency, number of AEDs concomitantly consumed, number of AED dosage changes per y, and number of outpatient visits per y.	x								**Because of imprecision, the data are insufficient to support a conclusion.**

AEDs within recommended range	**Decreases SUDEP risk**	**Hesdorffer, 2011[e20]** **Walczak, 2001[e23]**	**II** **II**	In the first case-control study, investigators reported no association with CBZ, VPA, or PHT levels. The second case-control study (20 cases and 80 controls) reported no difference in the proportion of people with AED levels within the recommended reference range between SUDEP cases and controls. No statistical detail was provided in these studies regarding this risk factor.									**Because of insufficient detail, no conclusion can be made.**
Nocturnal seizures	**Increases SUDEP risk**	**Lamberts, 2012[e34]**	**II**	OR 3.9,95% CI 2.5–6.0; $p < 0.01$ after adjustment for several SUDEP-associated factors.									**Low confidence**
Nocturnal supervision	**Decreased SUDEP risk**	**Langan, 2005[e22]**	**II**	OR 0.4 (95% CI 0.2–0.8).						X			**Upgraded to moderate confidence because of magnitude of effect**

Epilepsy syndrome	**Alteration of SUDEP risk associated with a syndrome**	**Sillanpää, 2013[e14]** **Lhatoo, 2010[e26]** **Aurlien, 2012[e27]** **Hesdorffer, 2011[e20]**	**1** **II** **II** **II**	Not having a localization-related epilepsy is associated with an increased SUDEP risk with adjusted HR of 3.0 (95% CI 1.2–7.6). No difference. No difference. Idiopathic generalized epilepsy is associated with a lower SUDEP risk compared with all other seizure types, with an OR of 0.69 (95% CI 0.49–0.98). Compared with women without idiopathic generalized epilepsy, women with idiopathic generalized epilepsy were protected from developing SUDEP (OR 0.16; 95% CI 0.04–0.57).	x	x							**Studies are inconsistent and imprecise; therefore, no conclusion can be made.**

MRI abnormality	**Altering SUDEP risk**	**Walzcak, 2001[e23]** **Nilsson, 1999[e24]** **Surges, 2010[e25]** **Lhatoo, 2010[e26]** **Aurlien, 2012[e27]**	**II** **II** **II** **II** **II**	OR of 0.7 (95% CI 0.2–2.3). RR of 1.38,95% CI 0.52–3.65. Decreased SUDEP risk with MRI abnormality showing OR = 0.11 (95% CI 0.01–0.88). OR of 1.5 (95% CI 0.36–6.32). Pathology on CT or MRI were not risk factors; however, the 95% CIs are broad (0.9–17.6).		x							**Conflicting evidence; therefore no conclusion can be made.**
Intellectual disability	**Increased SUDEP risk**	**Derby, 1996[e7]** **Hesdorffer, 2011[e20]** **Tennis, 1995[e6]**	**II** **II** **II**	RR of 1.4 (95% CI 0.3–8.0). OR of 1.38 (95% CI 0.91–2.09). Hospitalization for intellectual disability was associated with increased risk (minimum incidence density ratio = 1.2 and maximum incidence density ratio = 1.8).	x								**Downgraded from moderate to low confidence because of imprecision**

Gender	**Association of gender with SUDEP risk**	**Tennis, 1995[e6]** **Hesdorffer, 2011[e20]** **Racoosin, 2001[e29]** **Aurlien, 2012[e27]** **Lhatoo, 2010[e26]**	**II** **II** **II** **II** **II**	Male gender was associated with increased risk (minimum incidence density ratio 1.4 and maximum incidence density ratio 1.8). Male gender and increased risk that results in an OR of 1.42 (95% CI 1.07–1.88). 3.0% deaths attributed to SUDEP were reported in women (95% CI 1.8%–4.8%) and 4.4% deaths attributed to SUDEP in men (95% CI 3.2%–6.2%). Increased SUDEP in women with OR is 0.71 (95% CI 0.26–1.98). Increased SUDEP in men OR is 1.15 (95% CI 0.27–4.92).	X								**Downgraded from moderate to low confidence because of to imprecision that male gender is associated with increased SUDEP risk**

Age at onset	**Age associated with SUDEP risk**	**Sillanpää, 2010[e28]** **Lhatoo, 2010[e26]** **Hesdorffer, 2011[e20]** **Aurlien, 2012[e27]**	**I** **II** **II** **II**	Age at epilepsy onset of less than 2 y compared with children with onset at older ages did not have increased SUDEP risk (HR 1.9; 95% CI 0.7−5.2; $p = 0.20$). In a Class II case-control study (10 cases, 30 controls), investigators reported no difference in age at onset (cases mean age at onset 13.1 y [SD 7.8; range 2–28], controls mean age at onset 10.7 y [SD 8.6; range 1–31]; $p = 0.91$). In a Class II case-control study, investigators compared people with an epilepsy onset age between younger than 16 y and 1660 y and found a 1.72-fold increased SUDEP risk in the younger age group (95% CI 1.23–2.40); those with onset after age 60 y were 60% less likely to have SUDEP, but this was not significant. In a Class II nested case-control study (19 cases, 89 controls), investigators reported no increased risk with epilepsy onset before age 16 y in cases compared with controls (OR 0.6 [95% CI 0.2–1.9]).		xx							**Evidence is conflicting; therefore, no conclusion can be made.**

Duration of epilepsy	**Longer duration increases SUDEP risk**	**Hesdorffer, 2011[e20]** **Racoosin, 2001[e29]** **Aurlien, 2012[e27]** **Lhatoo, 2010[e26]**	**II** **II** **II** **II**	Duration of epilepsy for more than 15 y compared with less than or equal to 15 y was associated with an increased SUDEP risk that results in an OR of 1.95 (95% CI 1.45–2.63). From a clinical trials database in which there were 52 SUDEP occurrences in 13,617.1 patient-years, investigators reported that a duration of epilepsy of <5 y to more than 20 y was not significant. Rates ranged from 5.1% (95 % CI 1.9%–13.5%) in persons with epilepsy of more than 5 years' duration to 2.6% (95% CI 1.5%–4.5%) for epilepsy of more than 20 years' duration. In a nested case-control study (19 cases, 89 controls), investigators reported no difference in SUDEP risk with duration of epilepsy more than 10 y (OR 1.0 [95% CI 0.3–3.0]). In a case-control study, investigators reported on 10 cases and 30 controls who had undergone video-EEG monitoring, and found no difference in SUDEP risk with duration of epilepsy (p = 0.7810).	x	x							**Downgraded from moderate confidence to insufficient evidence because of imprecision and conflicting evidence.**

Extratemporal lobe epilepsy	**Increased risk**	**Lhatoo, 2010[e26]**	**II**	Nonlateralizable onset vs temporal onset was a risk factor with an OR of 7.94 (95% CI 3.13–20.15).									**Low confidence**
Heart rate variability	**Increased risk**	**Surges, 2010[e25]**	**II**	Investigators reported no difference between cases and controls, adjusted for seizure clustering. Multiple aspects of cardiac rhythm were assessed across groups, with in general narrow CIs surrounding the differences.									**Low confidence in evidence against heart rate variability carrying any risk for SUDEP**
Vagus nerve stimulator	**Decreases SUDEP risk**	**Granbichler, 2015[e35]** **Annegers, 2000[e36]**	**I** **II**	SUDEP rates did not differ in comparison with less than 2 y of use (3.4/1,000 patient-years; 95% CI 0.7–10) to more than 2 y of use (3.3/1,000 patient-years; 95% CI 1.3–6.8). Rate of SUDEP was 5.5/1,000 patient-years over the first 2 years, but only 1.7/1,000 patient-years thereafter, resulting in an RR of 2.72 (95% CI 0.6–12.8) (rate calculated per 1,000 patient-years because primary data were unavailable).	x								**Because of considerable imprecision in both articles, the evidence is not sufficient to support a conclusion.**

Use of psychotropic drugs	**Increases SUDEP risk**	**Nilsson, 1999[e24]** **Tennis, 1995[e6]** **Walzcak, 2001[e23]**	**II** **II** **II**	No significant increased SUDEP risk associated with antipsychotics (RR 2.14 [95% CI 0.90–5.10]) but found an increased SUDEP risk for anxiolytics (RR 3.00 [95% CI 1.16–7.76]). No difference No difference in SUDEP risk (OR 1.6 [95% CI 0.4–5.6]).	x								**No conclusion because of imprecision; an important effect cannot be ruled out. Confidence in evidence is low that anxiolytics increase risk.**
Epilepsy surgery	**Decreases SUDEP risk**	**Hesdorffer, 2011[e20]**	**II**	No difference in SUDEP risk (OR 1.6 [95% CI 0.4–5.6]).									**Low confidence**
Comorbid mental health disorders	**Increases SUDEP risk**	**Hesdorffer, 2011[e20]**	**II**	Comorbid mental health disorder was not associated with an increased SUDEP risk (OR 0.63, 95% CI 0.31–1.28).	x								**Insufficient evidence because of imprecision**
Alcohol abuse	**Increases SUDEP risk**	**Hesdorffer, 2011[e20]**	**II**	Investigators reported that alcohol abuse was not associated with an increased SUDEP risk (OR 1.63 [95% CI 0.99–2.66]).	x								**Insufficient evidence because of imprecision**

Lung disease	**Increases SUDEP risk**	**Hesdorffer, 2011[e20]**	**II**	Investigators found that lung disease was not associated with an increased SUDEP risk (OR 0.77 [95% CI 0.40–1.48]).	x								**Insufficient evidence because of imprecision**

Postictal EEG suppression	**Increases SUDEP risk**	**Lhatoo, 2010[e26]** **Surges, 2011[e38]**	**II** **II**	In a case-control study[e26] (10 cases and 30 controls), investigators reported from epilepsy monitoring unit data that PGES was seen in 15/30 (50%) seizures in case patients who later died of SUDEP and 35/92 (38%) control seizures. After adjustment for age, gender, and age at epilepsy onset, OR analysis of all seizures indicated significantly elevated odds of SUDEP for patients with PGES durations of >50 seconds ($p < 0.05$). Beyond 80 seconds, the odds were quadrupled ($p < 0.005$). For generalized motor seizures, the odds of SUDEP were significantly elevated with PGES durations of >20 seconds ($p < 0.05$). Each 10-second epoch of PGES up to >90 seconds, which was the longest duration evaluated, was associated with an increasing SUDEP risk, although this analysis is imprecise because of small numbers of cases. PGES occurred in 4/17 patients who died of SUDEP and 3/19 controls, resulting in an OR of 1.6 (95% CI 0.3–8.7). The duration of PGES did not correlate with SUDEP.	**XX**								**When seizure type is controlled for in GTCS vs other seizure types, PGES is not clearly associated with SUDEP; however, a clinically important effect cannot be ruled out on the basis of wide CIs. Therefore, the evidence is insufficient to support or refute that postictal EEG suppression affects SUDEP risk (2 Class II studies).**

Abbreviations: AEDs = antiepilepsy drugs; CBZ = carbamazepine; GTCS = generalized tonic-clonic seizures; HR = hazard ratio; LTG = lamotrigine; OR = odds ratio; PGES = postictal generalized EEG suppression; PHT = phenytoin; RR = relative risk; SUDEP = sudden unexpected death in epilepsy; TDM = therapeutic drug monitoring; VPA = sodium valproate.