Treatments for the prevention of Sudden Unexpected Death in Epilepsy (SUDEP)

Review information

Review type: Intervention

Authors

Melissa J Maguire[1], Cerian F Jackson[2], Anthony G Marson[2,3,4], Sarah J Nevitt[5]

[1]Department of Neurology, Leeds General Infirmary, Leeds, UK
[2]Department of Molecular and Clinical Pharmacology, Institute of Translational Medicine, University of Liverpool, Liverpool, UK
[3]The Walton Centre NHS Foundation Trust, Liverpool, UK
[4]Liverpool Health Partners, Liverpool, UK
[5]Department of Biostatistics, University of Liverpool, Liverpool, UK

Citation example: Maguire MJ, Jackson CF, Marson AG, Nevitt SJ. Treatments for the prevention of Sudden Unexpected Death in Epilepsy (SUDEP). Cochrane Database of Systematic Reviews 2020 , Issue 3 . Art. No.: CD011792. DOI: 10.1002/14651858.CD011792.pub3 .

Contact person

Melissa J Maguire

Consultant Neurologist
Department of Neurology
Leeds General Infirmary
Great George Street
Leeds
UK

E-mail: maguirem@doctors.org.uk
E-mail 2: melissajmaguire@hotmail.com

Dates

Assessed as Up-to-date: 4 February 2019
Date of Search: 4 February 2019
Next Stage Expected: 4 February 2021
Protocol First Published: Issue 7 , 2015
Review First Published: Issue 7 , 2016
Last Citation Issue: Issue 3 , 2020

What's new

Date	Event	Description
4 February 2019	New citation: conclusions not changed	Conclusions are unchanged
4 February 2019	Updated	Searches updated 4 February 2019; 3 new studies have been included (Radhakrishnan 2018; Shankar 2016; van der Lende 2018)

History

Date	Event	Description
26 April 2017	Amended	Declarations of interest section updated.

Abstract

Background

This is an updated version of the original Cochrane Review, published in 2016, Issue 7.

Sudden Unexpected Death in Epilepsy (SUDEP) is defined as sudden, unexpected, witnessed or unwitnessed, non-traumatic or non-drowning death of people with epilepsy, with or without evidence of a seizure, excluding documented status epilepticus and in whom postmortem examination does not reveal a structural or toxicological cause for death. SUDEP has a reported incidence of 1 to 2 per 1000 patient-years and represents

the most common epilepsy-related cause of death. The presence and frequency of generalised tonic-clonic seizures (GTCS), male sex, early age of seizure onset, duration of epilepsy, and polytherapy are all predictors of risk of SUDEP. The exact pathophysiology of SUDEP is currently unknown, although GTCS-induced cardiac, respiratory, and brainstem dysfunction appears likely. Appropriately chosen antiepileptic drug treatment can render around 70% of patients free of all seizures. However, around one-third will remain drug-resistant despite polytherapy. Continuing seizures place patients at risk of SUDEP, depression, and reduced quality of life. Preventative strategies for SUDEP include reducing the occurrence of GTCS by timely referral for presurgical evaluation in people with lesional epilepsy and advice on lifestyle measures; detecting cardiorespiratory distress through clinical observation and seizure, respiratory, and heart rate monitoring devices; preventing airway obstruction through nocturnal supervision and safety pillows; reducing central hypoventilation through physical stimulation and enhancing serotonergic mechanisms of respiratory regulation using selective serotonin reuptake inhibitors (SSRIs); and reducing adenosine and endogenous opioid-induced brain and brainstem depression.

Objectives

To assess the effectiveness of interventions in preventing SUDEP in people with epilepsy by synthesising evidence from randomised controlled trials of interventions and cohort and case-control non-randomised studies.

Search methods

For the latest update we searched the following databases without language restrictions: Cochrane Register of Studies (CRS Web, 4 February 2019); MEDLINE (Ovid, 1946 to 1 February 2019); SCOPUS (1823 to 4 February 2019); PsycINFO (EBSCOhost, 1887 to 4 January 2019); CINAHL Plus (EBSCOhost, 1937 to 4 February 2019); ClinicalTrials.gov (5 February 2019); and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP, 5 February 2019). We checked the reference lists of retrieved studies for additional reports of relevant studies and contacted lead study authors for any relevant unpublished material. We identified any grey literature studies published in the last five years by searching: Zetoc database; ISI Proceedings; International Bureau for Epilepsy (IBE) congress proceedings database; International League Against Epilepsy (ILAE) congress proceedings database; abstract books of symposia and congresses, meeting abstracts, and research reports.

Selection criteria

We aimed to include randomised controlled trials (RCTs), quasi-RCTs, and cluster-RCTs; prospective non-randomised cohort controlled and uncontrolled studies; and case-control studies of adults and children with epilepsy receiving an intervention for the prevention of SUDEP. Types of interventions included: early versus delayed pre-surgical evaluation for lesional epilepsy; educational programmes; seizure-monitoring devices; safety pillows; nocturnal supervision; selective serotonin reuptake inhibitors (SSRIs); opiate antagonists; and adenosine antagonists.

Data collection and analysis

We aimed to collect data on study design factors and participant demographics for included studies. The primary outcome of interest was the number of deaths from SUDEP. Secondary outcomes included: number of other deaths (unrelated to SUDEP); change in mean depression and anxiety scores (as defined within the study); clinically important change in quality of life, that is any change in quality of life score (average and endpoint) according to validated quality of life scales; and number of hospital attendances for seizures.

Main results

We identified 1277 records from the databases and search strategies. We found 10 further records by searching other resources (handsearching). We removed 469 duplicate records and screened 818 records (title and abstract) for inclusion in the review. We excluded 785 records based on the title and abstract and assessed 33 full-text articles. We excluded 29 studies: eight studies did not assess interventions to prevent SUDEP; eight studies were review articles, not clinical studies; five studies measured sensitivity of devices to detect GTCS but did not directly measure SUDEP; six studies assessed risk factors for SUDEP but not interventions for preventing SUDEP; and two studies did not have a control group.

We included one cohort study and three case-control studies of serious to critical risk of bias. The 6-month prospective cohort study observed no significant effect of providing patients with SUDEP information on drug compliance and quality of life, anxiety and depression levels. The study was too short and with no deaths observed in either group to determine a protective effect. Two case control studies reported a protective effect for nocturnal supervision against SUDEP. However due to significant heterogeneity, the results could not be combined in meta-analysis. One study of 154 SUDEP cases and 616 controls reported an unadjusted odds ratio (OR) of 0.34 (95% CI 0.22 to 0.53; $P < 0.0001$). The same study demonstrated the protective effect was independent of seizure control, suggesting that nocturnal supervision is not just a surrogate marker of seizure control. The second case-control study of 48 SUDEP cases and 220 controls reported an unadjusted OR of 0.08 (95% CI 0.02 to 0.27; $P < 0.0001$). The third case-control study of residential care centre patients who were already receiving physical checks more than 15 minutes apart throughout the night did not report any protective effect for additional nocturnal supervision (physical checks < 15 minutes apart; use of listening devices; dormitory setting; and use of bed sensors). However the same study did ascertain a difference between centres: the residential centre with the lowest level of supervision had the highest incidence of SUDEP. The case-control

studies did not report on quality of life or depression and anxiety scores.

Authors' conclusions

We found limited, very low-certainty evidence that supervision at night reduces the incidence of SUDEP. Further research is required to identify the effectiveness of other current interventions — for example seizure detection devices, safety pillows, SSRIs, early surgical evaluation, educational programmes, and opiate and adenosine antagonists — in preventing SUDEP in people with epilepsy.

Plain language summary

Treatments to prevent Sudden Unexpected Death in Epilepsy (SUDEP)

Background

Sudden Unexpected Death in Epilepsy (SUDEP) is defined as sudden, unexpected, witnessed or unwitnessed, non-traumatic or non-drowning death of people with epilepsy, with or without evidence of an epileptic seizure, and for whom a postmortem examination reveals no other cause of death. SUDEP is the most common epilepsy-related cause of death, with around 1 to 2 deaths per 1000 patients per year. Frequent seizures, in particular convulsive seizures (termed generalised tonic clonic seizures (GTCS)) , male gender, young age of first seizure, long duration of epilepsy, and taking multiple antiepileptic drugs are all thought to increase the risk for SUDEP; exactly why SUDEP occurs is currently unknown, however, though it is thought to be related to heart failure, breathing difficulties, and brain damage following GTCS.

With the correct antiepileptic treatment regimen around 70% of people with epilepsy can become free of all seizures. However, around one-third of people with epilepsy will continue to have seizures despite taking multiple antiepileptic drugs. Continuing seizures place patients at risk of SUDEP and can be associated with depression and lower quality of life. Strategies to try to prevent SUDEP include reducing the number of GTCS a patient has (by considering epilepsy surgery or making lifestyle changes), examining for heart and breathing problems during and following seizures, supervising patients at night or using safety pillows to prevent breathing difficulties. Drugs that increase the brain chemical serotonin and reduce the brain chemicals adenosine and opioids may also help prevent breathing difficulties.

Objective

To examine the effectiveness of treatments designed to prevent SUDEP.

Methods

We searched electronic databases and contacted experts in the area to find relevant randomised or non-randomised (observational) studies for the review. Outcomes of interest were: number of deaths due to SUDEP; number of other deaths not related to SUDEP; changes in anxiety, depression, and quality of life; and number of hospital attendances.

The evidence is current to February 2019.

Results

Out of 818 records found in our searches, we were able to include four observational studies. We found several studies that measured how sensitive devices are at detecting GTCS at night, but these studies did not measure SUDEP and so weren't relevant to this review.

Three studies investigated whether having a supervising person sharing a bedroom with the patient and using special precautions such as regular checking throughout the night or a listening device prevented SUDEP. Two of the three studies which included 202 people who had died of SUDEP and 836 people with epilepsy who were alive found these measures did prevent SUDEP. The third study of 60 SUDEP deaths and 240 controls looked at whether increasing night-time supervision for patients in two residential units above regular checks to include bed monitors and listening devices prevented SUDEP. This study did not show any additional preventative effect. However the same study did show that the centre with the most SUDEP deaths had the lowest level of supervision. The studies did not report on changes in anxiety, depression, quality of life and number of hospital attendances.

The fourth study looked at the effect of giving information to people with epilepsy about SUDEP and whether it improved the taking of antiepileptic medication and the impact on mood and anxiety. The study followed patients up for six months after being given the information (or not) and did not demonstrate any effect on the taking of medication or mood and anxiety. There were no deaths in the study so the effect of giving information and impact on risk of SUDEP is unknown.

Certainty of the evidence

We judged the certainty of the evidence from this review to be very low as the included studies were not randomised, and information about supervision measures to prevent SUDEP was not available in up to 40% of the people within the studies who did not experience SUDEP.

Conclusions

We found limited, very low-certainty evidence that supervision at night prevents SUDEP. Further research is

needed to identify if other treatments, such as seizure detection devices, safety pillows, and drug interventions working on serotonin, adenosine, and opiate levels in the brain are effective in preventing SUDEP in people with epilepsy.

Background

This is an updated version of the original Cochrane Review, published in the *Cochrane Database of Systematic Reviews (*2016, Issue 7; Maguire 2016).

Description of the condition

Sudden Unexpected Death in Epilepsy (SUDEP) is defined as sudden, unexpected, witnessed or unwitnessed, non-traumatic or non-drowning death of people with epilepsy, with or without evidence of a seizure, excluding documented status epilepticus, and in whom postmortem examination does not reveal a structural or toxicological cause for death.

SUDEP has a reported incidence of 1 to 2 per 1000 patient-years and represents the most common epilepsy-related cause of death (Shorvon 2011). Other deaths related to epilepsy include non-recovery from status epilepticus, seizure-related accidents, and suicide. SUDEP claims the lives of young adults, causing devastation to families. Its prevention is of paramount importance. Discussions around SUDEP are often difficult for patients and health professionals, although patients should be given and have access to information on SUDEP. Evidence from a UK-based study suggests that SUDEP is not commonly discussed with patients and families (Morton 2006). The highest SUDEP incidence reported in patients undergoing presurgical evaluation or having previously failed surgery was 9.3 per 1000 patient-years (Dasheiff 1991). A pooled meta-analysis of four case-control studies ascertained that the presence and frequency of generalised tonic-clonic seizures (GTCS) was the strongest predictor of risk of SUDEP. For example, compared with patients with no GTCS, patients having three or more GTCS per month had an odds ratio greater than 15. Male gender, age of onset of epilepsy of under 16 years old, duration of epilepsy for over 15 years, and polytherapy are also significant predictors of risk for SUDEP (Hesdorffer 2011; Hesdorffer 2012).

The exact pathophysiology of SUDEP is currently unknown, although GTCS-induced cardiac, respiratory, and brainstem dysfunction appears likely (Langan 2000).

Information has been gleaned from rare monitored cases of SUDEP, and demonstrates severe postictal electroencephalogram (EEG) suppression.

In the retrospective **Mort**ality in **E**pilepsy **M**onitoring **U**nit **S**tudy (MORTEMUS) of 16 SUDEP cases and nine near-SUDEP cases, available cardiorespiratory data were analysed in 10 monitored cases of SUDEP. The study ascertained a consistent pattern of changes that initially began with rapid breathing (18 to 50 breaths per minute) immediately following a GTCS and followed within three minutes by postictal generalised EEG suppression, terminal apnoea, and severe bradycardia with subsequent cardiac arrest. In this study the cardiorespiratory collapse was terminal in one-third of patients. In the remaining two-thirds, there appeared to be a transient restoration of cardiac function but with abnormal respiratory effort potentially aggravated by the prone position, leading eventually to terminal apnoea and terminal asystole. There were less consistent patterns of cardiorespiratory change in five of nine monitored near-SUDEP cases. In these cases, postictal apnoea followed by asystole, ictal asystole, ventricular fibrillation, and postictal cardiorespiratory arrest were observed. The study highlighted a potential window for lifesaving intervention, in that those patients who received cardiopulmonary resuscitation within three minutes (seven near-SUDEP cases) were successfully resuscitated. The study suggested improved supervision within epilepsy-monitoring units, particularly nocturnal supervision (Ryvlin 2013a).

Ictal hypoxia, dysfunction in subcortical and brainstem networks controlling electrogenesis, and the release of adenosine and endogenous opioids within the brain and brainstem following a GTCS have been proposed as mechanisms to explain the above clinical findings (Nashef 2009). Seizure-related arrhythmias were originally proposed as a mechanism for SUDEP, but many believe this to be a self-limiting process (Schuele 2010). There are, however, cases of death of patients exhibiting rare sodium and potassium channelopathies, although the exact circumstances of death are uncertain (Tu 2011).

Appropriately chosen antiepileptic drug treatment can render around 70% of people with epilepsy free of all seizures. However, around one-third of people with epilepsy will remain drug-resistant despite polytherapy. Continuing seizures place patients at risk of SUDEP, depression, and reduced quality of life. Preventative strategies for SUDEP are therefore of paramount importance.

Description of the intervention

Experts within the field of SUDEP believe it results from a multifactorial neurovegetative breakdown. Thus any preventative intervention must target contributing factors (Ryvlin 2013b). These include:

1. reducing the occurrence of GTCS by timely referral for presurgical evaluation in people with lesional epilepsy and advice on lifestyle measures (e.g. concordance with optimal antiepileptic drug treatment);
2. enhancing the ability to detect cardiorespiratory distress through clinical observation and seizure, respiratory, and heart rate monitoring devices;

3. preventing airway obstruction through nocturnal supervision and safety pillows;
4. reducing central hypoventilation through physical stimulation and enhancing serotonergic mechanisms of respiratory regulation using selective serotonin reuptake inhibitors (SSRIs);
5. reducing adenosine and endogenous opioid-induced brain and brainstem depression.

How the intervention might work

1. Patients with a surgical epileptogenic target should be referred for presurgical evaluation since targeted surgery may improve the likelihood of successful seizure control. Whilst studies report a greater risk of SUDEP in patients who have failed surgery, it is unclear whether the surgery itself is preventative for SUDEP or whether risk differences relate to the underlying pathologic process (Ryvlin 2006). Patient education is important in ensuring compliance with treatment and should include discussion of lifestyle factors that may adversely affect seizure control and drug effectiveness (e.g. sleep deprivation, stress, and excess alcohol). Similarly a care plan for seizure clusters and discussions around contraception, pregnancy, gastrointestinal disorders, and any other medications that may affect antiepileptic drug treatment are all important discussion points. This may be delivered through formal educational programmes, advice leaflets, or verbal consultation.
2. Seizure-monitoring devices, which include bed sensors, fall alarms, and tracking devices, range from technology worn at the wrist that detects seizures via changes in vibrations to more sophisticated multimodal systems monitoring movements and vital signs, including heart rate, via a sensitive bed mat. These systems alert a carer or parent to potential seizure activity, which in turn may prevent SUDEP.
3. Safety pillows, which have small holes, are thought to reduce postictal respiratory distress and thus SUDEP when the person is face down on the pillow in a prone position (Devinsky 2012). One retrospective study reported that around 71% of people who died of SUDEP were in the prone position, suggesting position may play a significant role in the condition (Kloster 1999). People in postictal hypoxic coma will not be able to correct their position and are thus at risk of respiratory failure. The utility of oxygen therapy following a seizure is used in most epilepsy monitoring units and has been shown to prevent SUDEP in a mouse model of seizure-induced SUDEP by reducing the risk of respiratory distress (Venit 2004).
4. Nocturnal supervision would allow turning of the person from a prone to a recovery position, reducing the risk of respiratory distress and reducing central hypoventilation. One case-control study found that nocturnal supervision was protective against SUDEP (Langan 2005). Serotonergic nuclei within the lower brainstem play an important role in regulating respiratory function, particularly in the context of recurrent hypoxia. Abnormalities of these nuclei are documented in sudden infant death and also in mice models of SUDEP (Uteshev 2010). The SSRI fluoxetine has been shown to prevent apnoea in these mice models. A clinical retrospective study ascertained that people undergoing videotelemetry and taking an SSRI were significantly less likely to have ictal/postictal hypoxia than those not taking an SSRI (Bateman 2010). Another study observed the effect of peri-ictal nursing interventions (supplemental oxygen, oropharyngeal suction, and patient repositioning) on respiratory dysfunction and postictal EEG suppression. It showed a reduced duration of hypoxaemia and EEG suppression with early peri-ictal interventions (Seyal 2013).
5. Inhibitors of adenosine and opiate substances may prevent SUDEP by reducing the severity of postictal EEG depression and brainstem dysfunction. Caffeine, an antagonist of adenosine receptors, is potentially pro-convulsant. However naloxone, an opiate receptor antagonist, has not been demonstrated to have a pro-convulsant effect and thus may have a use in preventing SUDEP.

Why it is important to do this review

SUDEP has devastating consequences for patients and families. Various devices and interventions are available to people with epilepsy that are thought to reduce the risk of SUDEP. However, no robust evidence is available to confirm this preventative effect. A systematic review of the literature base will inform patients and healthcare professionals on treatment policy and prevention of SUDEP.

Objectives

To assess the effectiveness of interventions in preventing SUDEP in people with epilepsy by synthesising evidence from randomised controlled trials of interventions and cohort and case-control non-randomised studies.

Methods

Criteria for considering studies for this review

Types of studies

We considered the following types of studies for inclusion.

1. Randomised controlled trials (RCTs), quasi-RCTs, and cluster-RCTs
2. Prospective non-randomised cohort controlled and uncontrolled studies
3. Case-control studies

The rationale for including non-randomised studies was that given the relatively low incidence rate of SUDEP, an RCT would need to recruit a very large sample in order to show evidence of a preventative effect. Non-randomised studies, including case-control designs, are better at addressing the question of effectiveness in

SUDEP prevention given their ability to include larger populations for longer treatment periods.

Types of participants

We included participants who satisfied each of the following criteria.

1. Any age
2. Diagnosis of epilepsy (any type)
3. Receiving an intervention for prevention of SUDEP

Types of interventions

1. Early versus delayed presurgical evaluation for lesional epilepsy
2. Educational programmes
3. Seizure-monitoring devices
4. Safety pillows
5. Nocturnal supervision
6. SSRIs
7. Opiate antagonists
8. Adenosine antagonists

Intervention group: patients who received an intervention in preventing SUDEP.

Control group(s): patients who received a placebo, comparative intervention, or no intervention in preventing SUDEP.

Types of outcome measures

Primary outcomes

1. Number of deaths from SUDEP

Secondary outcomes

1. Number of other deaths (unrelated to SUDEP)
2. Change in mean depression and anxiety scores (as defined within the study)
3. Clinically important change in quality of life: any change in quality of life score (average and endpoint) according to validated quality of life scales
4. Number of hospital attendances for seizures

Search methods for identification of studies

Electronic searches

Searches were run for the original review on 16 December 2014 and subsequent searches were run in November 2015, September 2017, and February 2019. For the latest update we searched the following databases.

1. Cochrane Register of Studies (CRS Web, 4 February 2019), using the search strategy shown in Appendix 1.
2. MEDLINE (Ovid, 1946 to 1 February 2019), using the search strategy shown in Appendix 2.
3. SCOPUS (1823 to 4 February 2019), using the search strategy shown in Appendix 3.
4. PsycINFO (EBSCOhost, 1887 to 4 February 2019), using the search strategy shown in Appendix 4.
5. CINAHL Plus (EBSCOhost, 1937 to 4 February 2019), using the search strategy shown in Appendix 5.
6. ClinicalTrials.gov (5 February 2019), using the search strategy shown in Appendix 6.
7. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP, 5 January 2019), using the search strategy shown in Appendix 7.

The Cochrane Epilepsy Group Specialized Register and the Cochrane Central Register of Controlled Trials (CENTRAL) are both now included in the Cochrane Register of Studies (CRS Web). We used no language restrictions.

Searching other resources

We checked the reference lists of retrieved studies for additional reports of relevant studies. We also contacted lead study authors for any relevant unpublished material or missing data from included studies. We identified duplicate studies by screening reports according to title, authors' names, location, and medical institute, omitting any duplicated studies.

We identified any grey literature studies published in the last five years by searching:

1. Zetoc database;
2. ISI Proceedings;
3. International Bureau for Epilepsy (IBE) congress proceedings database;
4. International League Against Epilepsy (ILAE) congress proceedings database;
5. Abstract books of symposia and congresses, meeting abstracts, and research reports.

Data collection and analysis

Selection of studies

Two review authors (CFJ, MJM) reviewed the titles and abstracts of the studies identified by the electronic

searches and removed studies that did not meet the inclusion criteria. The same two review authors then reviewed the full-text reports to determine eligibility. We discussed any disagreements, consulting a third review author (SJN) if necessary. In the event of multiple reports deriving from one study, we linked the reports together.

Data extraction and management

Two review authors (MJM, SJN) independently completed data extraction using a pre-standardised data extraction form for the included studies.

We extracted the following information.

Methods

1. Year of publication
2. Number of study centres
3. Language
4. Industry funding
5. Study design (RCT, prospective cohort study, case-control study)
6. Blinding
7. Type of control group (placebo, comparative, no treatment)
8. Sample size
9. Follow-up period
0. Intervention type
1. Dose range of drug intervention
2. Inclusion and exclusion criteria

Participants

1. Age range
2. Number of male/female participants
3. Duration of epilepsy
4. Mean age of onset of epilepsy
5. Current number of antiepileptic drugs (AEDs)
6. Epilepsy type (focal, generalised, unclassified)
7. Seizure types (GTCS, focal onset seizures)
8. Baseline mean depression score or severity
9. Baseline mean seizure frequency/month

Outcomes

1. Number of participants experiencing each outcome recorded per treatment group
2. Number of dropouts

Assessment of risk of bias in included studies

Two review authors (SJN, MJM) independently assessed the risk of bias for the included studies.

Due to the observational design, we assessed risk of bias for non-randomised studies using the ROBINS-I tool (Sterne 2016). This tool considers seven domains of bias: two domains of bias pre-intervention (bias due to confounding and bias in selection of participants into the study); one domain of bias at intervention (bias in the measurement of interventions); and four domains of bias post intervention (bias due to departures from intended interventions, bias due to missing data, bias in measurement of outcomes, and bias in selection of the reported result). We planned to perform a separate 'Risk of bias' assessment for each outcome of interest in the study.

Important confounders of interest in this Cochrane Review included:

1. proportion of males;
2. proportion of participants with generalised seizures;
3. mean age of onset of epilepsy;
4. mean duration of epilepsy;
5. epilepsy type;
6. mean concomitant AEDs;
7. baseline seizure frequency (including baseline GTCS frequency);
8. baseline depression score.

Each domain of bias contained signalling questions to facilitate judgements of risk of bias. The response options for the signalling questions were: yes; probably yes; probably no; no; and no information. We have specified the signalling questions for each domain in Appendix 8.

The 'Risk of bias' judgement options for each domain were:

1. low risk of bias: the study is comparable to a well-performed randomised trial with regard to this domain;
2. moderate risk of bias: the study is sound for a non-randomised study with regard to this domain but cannot be considered comparable to a well-performed randomised trial;
3. serious risk of bias: the study has some important problems in this domain;
4. critical risk of bias: the study is too problematic in this domain to provide any useful evidence on the effects of

intervention;
5. no information on which to base a judgement about risk of bias for this domain.

We have presented guidance for an overall risk of bias for a study based on outcomes from 'Risk of bias' judgements of each domain in Table 1.

We would have examined all domains of the current Cochrane 'Risk of bias' assessment tool for RCTs (Higgins 2011). We would have made an overall summary judgement of risk of bias for each study per outcome, followed by an overall judgement per outcome across studies.

We planned to incorporate the 'Risk of bias' judgement into the analysis by performing a sensitivity analysis including only studies rated as being at low risk of bias. We will perform such an analysis in future updates if additional studies are included in the review.

Measures of treatment effect

For binary outcomes (number of SUDEP deaths, number of non-SUDEP deaths, number of hospital attendances) we planned to present results as risk ratios with 95% confidence intervals (CIs) for RCTs and non-randomised cohort studies, and odds ratios with 95% CIs for case-control studies.

For continuous outcomes (mean change in depression score, mean change in quality of life score) we planned to present results as mean differences or standardised mean differences with 95% CIs.

Unit of analysis issues

There were no unit of analysis issues in any of the included studies. In the event of unit of analysis issues occurring across the included studies in future updates (e.g. cluster randomised or repeated measures), we would:

1. determine whether the methods in such studies were conducted appropriately;
2. combine extracted effect sizes from such studies through a generic inverse variance meta-analysis.

Dealing with missing data

For future updates of the review, we intend to search for missing statistics from studies by contacting the study authors. In the event of the data being unavailable, we will attempt to determine whether or not the data are missing at random and the possible impact of missing data on analysis.

Assessment of heterogeneity

We did not perform meta-analysis in the review due to the heterogeneity in the reporting of results in two of the included studies.

If we are able to perform meta-analysis in future updates of the review, we will assess clinical heterogeneity by comparing the distribution of important participant factors between studies (age, proportion of males, proportion with generalised seizures, epilepsy type, duration of epilepsy, mean concomitant AEDs, baseline seizure frequency, baseline depression score) and trial factors (study design, type of control group). We will assess statistical heterogeneity by using the I^2 statistic, with an I^2 value equal to or greater than 75% indicating considerable heterogeneity, 50% to 90% indicating substantial heterogeneity, and 30% to 60% indicating moderate heterogeneity. If the I^2 value is equal to or greater than 75%, we will make an a priori decision not to perform a meta-analysis; the Cochrane Review will then take a narrative form, and we will discuss all comparisons according to the findings presented within the studies. Where possible, we will use meta-regression techniques to investigate possible sources of heterogeneity.

Assessment of reporting biases

For future updates of the review, we will investigate outcome reporting bias using the Outcome Reporting Bias in Trials (ORBIT) classification system, allocating studies a letter from A to I if selective outcome reporting bias is suspected (Kirkham 2010). Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Higgins 2011). Funnel plots can be used in investigating reporting biases but are of limited power to detect small-study effects. We will not use funnel plots for outcomes where there are 10 or fewer studies, or where all studies are of similar sizes.

Data synthesis

We did not perform meta-analysis in the review due to the heterogeneity in the reporting of results in two of the included studies.

If we are able to perform meta-analysis in future updates of the review, we will synthesise data using the risk ratio, odds ratio, mean difference, or standardised mean difference values depending on the measures used in both the controlled and uncontrolled studies. We will carry out a sensitivity analysis to check for differences between a random-effects model and fixed-effect model in influencing conclusions. If differences between the models exist, we intend to report outcomes based on the random-effects model, which incorporates an assumption that the different studies are estimating different, yet related, intervention effects.

For controlled studies, we intended to perform meta-analysis using the Mantel-Haenszel method for dichotomous outcomes and the inverse variance method for continuous outcomes. For uncontrolled studies, we

would have used the inverse variance method for continuous outcomes in meta-analysis.

We aimed to combine data for outcomes for the same intervention. We would not combine data from randomised controlled and uncontrolled studies or from studies of prospective and retrospective designs.

We expected to perform the following comparisons of intervention group versus controls for:

1. number of SUDEP deaths;
2. number of non-SUDEP deaths;
3. number of hospital attendances;
4. change in depression score;
5. change in quality of life score.

We would have stratified each comparison by type of intervention to ensure appropriate combination of study data.

Subgroup analysis and investigation of heterogeneity

If we are able to perform meta-analysis for future updates of the review, we will stratify subgroup analyses by type of intervention and duration of intervention. For investigation of heterogeneity, please see the Assessment of heterogeneity section.

Sensitivity analysis

If we are able to perform meta-analysis for future updates of the review, in the event of identifying any inconsistencies or peculiarities we will perform sensitivity analysis using only studies considered to be at low risk of bias. We will compare the results from this second meta-analysis with the reports from the initial analysis, which would include all studies.

Summary of findings and assessment of the certainty of the evidence

We have included the following outcomes in Summary of findings table 1: number of SUDEP deaths; number of non-SUDEP deaths; depression and anxiety scores; quality of life; and number of hospital attendances. We assessed the certainty of each outcome using the GRADE approach (Guyatt 2008).

Results

Description of studies

Results of the search

From searches conducted up to February 2019, we identified 1277 records from the databases and search strategies outlined in Electronic searches. We found 10 further records by searching other resources (handsearching). We removed 469 duplicate records and screened 818 records (title and abstract) for inclusion in the review. We excluded 785 records based on the title and abstract and assessed 33 full-text articles for inclusion in the review. We excluded 29 studies from the review (see Excluded studies below) and included four studies (Langan 2005; Radhakrishnan 2018; Shankar 2016; van der Lende 2018).

See Figure 1 for a PRISMA study flow diagram.

Included studies

Of studies that met the inclusion criteria we identified one prospective cohort study (Radhakrishnan 2018), and three case-control studies (Langan 2005; Shankar 2016; van der Lende 2018).

Participants (cohort study)

Radhakrishnan 2018 recruited consecutive people with epilepsy (PWE) aged over 15 years with a duration of epilepsy of at least one month from a tertiary care teaching hospital in Northern India.

In total, 121 PWE were recruited to the intervention group (116 PWE retained to 6 months for analysis, 81 males and 35 females, mean age 25.8 years) and 110 PWE were recruited to the control group (106 retained to 6 months for analysis, 76 males and 30 females, mean age 27.6 years). PWE in intervention and control groups were balanced in terms of characteristics (age, duration of epilepsy, gender, education, type of epilepsy, family history of epilepsy, seizure frequency, number of antiepileptic drugs, intelligence quotient, neuroimaging findings and socioeconomic classification) and baseline scores of drug adherence, quality of life, anxiety and depression outcome measures.

Caregivers of the PWE were also recruited; and for PWE with an intelligence quotient (IQ) of less than 80, caregivers completed outcome measures on behalf of the PWE. No information is given, however, about how many caregivers were recruited with PWE and characteristics of caregivers.

Participants (case-control studies)

Langan 2005 included 154 cases in which postmortem examination between 1989 to 1998 had been performed and a diagnosis of SUDEP, as per the operational definition outlined above, had been made. Cases were identified through coroner reports, the British Neurologic Surveillance Unit, and the UK support charity Epilepsy Bereaved. Each case had four controls with epilepsy, matched for age and geographical area and identified through the Medical Research Council (MRC) General Practice Research Framework. The cases included 97 men and 57 women

with a mean age of 32 years. Demographic details for controls were not reported.

Shankar 2016 included 48 SUDEP cases aged between 2 and 82 years at death, identified from all 93 epilepsy and epilepsy-associated deaths which occurred in the UK county of Cornwall between 2004 and 2012, as recorded by the Cornwall Coroner. Controls were 220 outpatients attending epilepsy clinics within Cornwall. The cases included 33 men and 15 women with a mean age of 42.5 years. The controls included 115 men and 105 women with a mean age of 42.7 years. No further demographic details were reported for either the cases or the controls.

van der Lende 2018 included 60 SUDEP cases which occurred in individuals under the age of 60 (mean age 39.3 years, 42 males and 18 females) at two epilepsy residential care facilities in the Netherlands and the UK between 1987 and 2014. Four controls per case were matched on age (± 5 years) and residential unit. The controls were 132 males and 66 females, mean age 40 years. Characteristics of SUDEP cases and controls were mostly similar (epilepsy aetiology, epilepsy duration, seizure types, number of antiepileptic drugs and use of benzodiazepines). SUDEP cases had a higher frequency of convulsive seizures ($P = 0.001$), however, particularly nocturnal convulsive seizures ($P < 0.001$), and a higher intelligence quotient compared with controls ($P = 0.005$).

Interventions (cohort study)

Radhakrishnan 2018 was initiated in January 2016 as single arm design (pre-test/post-test design) with all participants receiving the intervention (SUDEP information and standard epilepsy care) for six months. A control group was added to the trial design in September 2017 due to concerns over bias. The control group were recruited according to the same eligibility criteria and received only standard epilepsy care for six months and the SUDEP information was provided to the control group at the end of the study period. Outcomes measured were within-group changes from baseline to six months' drug adherence, quality of life, anxiety and depression. No cases of SUDEP during the study are reported.

Interventions (case-control studies)

In Langan 2005, supervision at night was one of several factors listed as assessment variables between groups. This was defined as the presence in the bedroom of an individual of normal intelligence and at least 10 years old or the use of special precautions. Special precautions involved regular checks throughout the night or the use of a listening device.

In Shankar 2016, night surveillance was one of 17 factors listed as assessment variables between groups, but the number of cases and controls receiving or not receiving these interventions was not reported.

In van der Lende 2018, nocturnal supervision was an assessment variable between groups. Grades of nocturnal supervision were defined as follows.

- Grade 1: no central acoustic or listening device and sleeping alone and physical checks more than 15 minutes apart.
- Grade 2: central acoustic or listening device, having a roommate, having a physical check at least every 15 minutes.
- Grade 3: central acoustic or listening device and dormitory; central acoustic or listening device and additional device (e.g. bed motion sensor/video monitoring); central acoustic or listening device and having a physical check at least every 15 minutes.

Within the residential facilities, all individuals were physically checked by carers (one carer to every 14 residents) at least once or twice a night and additional checks were performed on a need basis. Therefore for the purposes of this review, we define Grade 1 as no additional intervention (i.e. 'no additional nocturnal supervision') and Grades 2 and 3 combined as 'additional nocturnal supervision'.

All of these retrospective case-control studies also considered other factors that were not relevant to this review; see Characteristics of included studies for details. Depression treatment (including SSRIs) and presence of anxiolytic medication were also examined as risk factors in Shankar 2016; however 'anxiolytic medication' was not clearly defined and we interpreted 'depression treatment' to really be defined as the association between clinical depression and SUDEP (rather than the use of interventions for depression to prevent against SUDEP). We did not therefore judge 'depression treatment' or 'anxiolytic medication' to be relevant interventions for this review.

Excluded studies

We excluded 29 studies. Eight studies did not assess interventions to prevent SUDEP (Almeida 2010; Annegers 1998; Annegers 2000; Bateman 2010; Fisher 2010; NCT00986310; Nilsson 2001; Ryvlin 2011); eight studies were review articles rather than clinical studies (Asadi-Pooya 2009; DeGiorgio 2019; Devinsky 2018; Purnell 2018; Ryvlin 2018b; Schachter 2006; Scorza 2011; Verma 2015); six studies assessed risk factors for SUDEP but not interventions for preventing SUDEP (DeGiorgio 2008; Kang 2017; Schmuely 2016; Seymour 2012; Sveinsson 2018; Terra 2012); five studies measured sensitivity of devices to detect GTCS but did not directly measure SUDEP (Beniczky 2013; Narechania 2013; NCT00101933; Seyal 2013; Van Poppel 2013); and two studies did not have a control group (NCT00736424; Ryvlin 2018a).

Risk of bias in included studies

We rated risk of bias across each domain and then made an overall risk of bias judgement for the included studies (Langan 2005; Radhakrishnan 2018; Shankar 2016; van der Lende 2018). We rated all three of the case-control studies as having an overall serious risk of bias (Langan 2005; Shankar 2016; van der Lende 2018); and Radhakrishnan 2018, the prospective cohort study, as having an overall critical risk of bias (see Table 1 for guidance of how we rated the overall risk of bias in the studies and see Table 2, Table 3, Table 4 and Table 5 for responses to signalling questions).

Bias due to confounding

Cohort study

We judged Radhakrishnan 2018 to be at critical risk of bias due to confounding. The outcomes measured within the study were subjective (drug adherence, quality of life, depression and anxiety) which could be influenced by a range of factors, including confounding factors. However most analyses do not control or adjust for any confounders. For the outcome drug adherence, regression analysis was performed to characterise 'predictors of adherence' but only in the subgroup of participants who demonstrated improved drug adherence. We consider that it is inappropriate to exclude participants without improved drug adherence from an analysis of predictors of adherence.

Case-control studies

We judged Langan 2005 and van der Lende 2018 to be at moderate risk and Shankar 2016 to be at serious risk of bias due to confounding. For all three studies, the objective of the study was to examine a range of factors associated with SUDEP, therefore confounding is inevitable. However, van der Lende 2018 performed a multivariable analysis adjusting for convulsive seizure frequency (an important confounder) and Langan 2005 performed multivariable analyses and assessed variables independently of seizure frequency, but did not report on control of other potential confounders (types of seizures, history of depression) between groups. Shankar 2016 presented only univariable analyses as "low numbers and missing data" which prevented a multivariable analysis, and we judged that the univariable analyses reported are likely to be confounded.

Bias in selection of participants into the study

Cohort study

We judged Radhakrishnan 2018 to be at low risk of bias in the selection of participants into the study. Although the control group was added to the study design 18 months after the start of the study and therefore characteristics and outcomes of participants within the intervention group who had completed the 6-month study period would have been known, it is stated that recruitment into both groups was "consecutive" and that the control group was recruited using the same inclusion criteria — selection should not, therefore, have been influenced.

Case-control studies

We judged Langan 2005 to be at low risk and Shankar 2016 and van der Lende 2018 to be at moderate risk of bias for selection of participants into the study. In Langan 2005 and Shankar 2016, the selection of SUDEP cases was clearly described; and controls were randomly selected from the eligible population and matched for sex and geographical location in Langan 2005. In Shankar 2016, however, controls were selected consecutively but it was unclear why cases and controls were considered over separate, non-overlapping time periods and whether any selection bias could have occurred. Also in van der Lende 2018, it was unclear how many individuals were reviewed when establishing SUDEP cases and exactly how matched controls were selected from the residential facilities and whether any selection bias could have occurred.

Bias in classification of interventions

Cohort study

We judged Radhakrishnan 2018 to be at moderate risk of bias in classification of the intervention. As the control group was added to the study design 18 months after the start of the study and therefore characteristics and outcomes of participants within the intervention group who had completed the 6-month study period would have been known, it is unclear whether both groups (intervention and control) or only the control group were recruited to following the addition of the control group (i.e. whether the intervention groups were defined by the time point).

Case-control studies

We judged Langan 2005 and Shankar 2016 to be at moderate risk of bias in classification of the intervention as it is possible that intervention status was recorded after outcome and provided by a relative (rather than the case) for the SUDEP cases in both studies, which could be a source of bias. In van der Lende 2018, where 'grades' of nocturnal supervision were considered as the intervention, it is likely that the 'grades of intervention' were defined for this study rather than defined at the start of the intervention and it is also unclear whether the grades could have changed over time during the time period of the study; for example if an individual had additional measures of nocturnal supervision some nights and no additional measures other nights, which grade would the individual be classified as? It is also possible that classification of the grade of intervention may have been affected by knowledge of case or control status; for example, more detailed records regarding interventions

received may have been recorded for residents who died compared to residents who did not. Therefore we judged van der Lende 2018 to be at serious risk of bias in measurement of the intervention.

Bias due to deviations from intended interventions

Cohort study

We judged Radhakrishnan 2018 to be at critical risk of bias for deviations from intended interventions. Participants for whom depression and anxiety was detected in the intervention group did not receive 'reinforcement' SUDEP information at subsequent clinics. As one of the aims of the study was to examine the impact of providing SUDEP information on anxiety and depression, this deviation will have directly impacted upon the outcome.

Case-control studies

We judged Langan 2005 to be at moderate risk and Shankar 2016 and van der Lende 2018 to be at serious risk of bias for deviations from intended interventions. In all three studies, the intervention of interest to this review was not intended to be the only 'intervention' in the study, adherence to the intervention was not reported, switching may have occurred, and co-interventions may have been present. In Shankar 2016, furthermore, very limited information about the interventions was available and the number of cases and controls receiving or not receiving the interventions was not reported. In van der Lende 2018, it was also not clear whether the 'grades' of intervention could have changed during the time period of the study (see 'Bias in classification of interventions' above).

Bias due to missing data

Cohort study

We judged Radhakrishnan 2018 to be at low risk of bias due to missing data. Outcome data was available for 96% of recruited participants in the intervention and control groups, and it appears that the few missing patients were lost to follow-up or did not complete all of the outcome measures to be included in analysis at the end of the 6-month study period.

Case-control studies

We judged van der Lende 2018 to be at moderate risk of bias due to missing data. Around 20% of included cases and controls were excluded from analysis due to missing data and no reasons were given for the missing data. As the amount of missing data is relatively small and balanced across cases and controls, it is unlikely conclusions would have been changed by this missing data.

We judged Langan 2005 and Shankar 2016 to be at serious risk of bias due to missing data. In Langan 2005, there was a large proportion of missing data for the outcome "nocturnal supervision", with around 40% missing data for controls, and an imbalance of missing data between cases and controls. In Shankar 2016, "low numbers and missing data" prevented a multivariable analysis; it is not, however, stated which data were missing and how many participants were included in the analysis of each factor related to SUDEP.

Bias in measurement of outcomes

Cohort study

We judged Radhakrishnan 2018 to be at moderate risk of bias for measurement of the outcome. Outcomes of the study were subjective and measured by questionnaires administered directly to participants. As participants would have been aware of their intervention status when completing the questionnaires, their intervention status may have influenced their responses.

Case-control studies

We judged Langan 2005 and Shankar 2016 to be at low risk of bias for measurement of the outcome, since the objective outcome measurement (SUDEP or no SUDEP) was established before intervention status. We judged van der Lende 2018 to be at moderate risk of bias as although the outcome measurement is 'Objectives', it was unclear exactly how cases and controls were selected into the study and whether intervention status (i.e. the 'grades' of interventions) was classified before or after outcome status was established.

Bias in selection of the reported result

Cohort study

We judged Radhakrishnan 2018 to be at critical risk of bias due to selection of the reported result. Mostly within-group analyses only are reported and no between-group analyses are reported for the secondary outcomes. As noted in 'Bias due to deviations from intended interventions' above, inconsistent delivery of the intervention to participants with anxiety and depression detected at baseline will have directly impacted on the results for these outcomes. In addition a regression analysis was performed to examine characteristics which predict adherence but only in the subgroup of participants with improved adherence. This is clearly not an appropriate analysis.

Case-control studies

We judged all three of the studies to be at moderate risk of bias due to selection of the reported result. In Langan 2005 and van der Lende 2018, results of only a single multivariable model were reported, and it is unclear if

results would have been different for other multivariable models. Furthermore for van der Lende 2018, it was unclear if results would have been different if 'grade of intervention' could have been classified differently. In Shankar 2016, it was unclear how the factors analysed were selected and if other factors were considered or if alternative analyses had been conducted.

Effects of interventions

See Summary of findings table 1 for a summary of the findings of the review. We judged all evidence to be of very low certainty due to the retrospective, observational design of the included studies and serious risk of bias, mainly relating to confounding, missing data and lack of reported information regarding selection into the study, control groups and classification of intervention status.

Primary outcome: number of deaths from SUDEP

Cohort study

The prospective cohort study did not measure the number of deaths from SUDEP as an outcome and no deaths (all cause) were reported during the study (Radhakrishnan 2018). However, the 6-month duration of this study was likely too short to measure the direct impact of the interventions on the number of deaths from SUDEP.

Case-control studies

All three included case-control studies contributed data to this outcome. All studies examined the association of a range of factors to SUDEP; factors (interventions) relevant to this review were nocturnal supervision and special precautions in Langan 2005: and nocturnal supervision in Shankar 2016 and in van der Lende 2018.

In Langan 2005, all 154 SUDEP cases had data for the presence or absence of the intervention, but data for the presence or absence of the intervention was reported for only 367 out of 616 (60%) of controls. In Shankar 2016, it is not reported how many of the 48 SUDEP cases and 220 control participants had data for the presence or absence of the intervention; unadjusted odds ratios are presented without details of the number of participants contributing to each analysis. In van der Lende 2018, data for the presence or absence of the intervention was reported for 48 out of 60 SUDEP cases (80%) and 163 out of 198 controls (82%). Furthermore, due to the setting of van der Lende 2018 (epilepsy residential facilities), all participants had some level of nocturnal supervision and for the purposes of this review we are comparing additional measures of nocturnal supervision to no additional measures of nocturnal supervision.

Due to this heterogeneity in the setting of the studies and in the reporting of results, we have not combined the results for nocturnal supervision. The association between SUDEP and each intervention in each study is presented narratively below.

Langan 2005 presented results such that odds ratio (OR) less than 1 indicates that the intervention is protective against SUDEP (i.e. fewer cases of SUDEP occurred when the intervention was present compared to when the intervention was absent), while Shankar 2016 and van der Lende 2018 presented results such that OR greater than 1 indicates that the intervention is protective against SUDEP.

For consistency of interpretation, for the results presented in this review we assume that OR less than 1 indicates that the intervention is protective against SUDEP, and therefore we have inverted the direction of the results for Shankar 2016 and van der Lende 2018 (but we have reported results by grade of nocturnal supervision using the original direction as reported by van der Lende 2018).

Nocturnal supervision compared to no nocturnal supervision

Langan 2005 found a protective effect for the presence of nocturnal supervision (adjusted OR from multivariable logistic regression 0.40, 95% confidence interval (CI) 0.20 to 0.80). This effect was independent of seizure control (see Characteristics of included studies for details of variables adjusted for).

Based on the number of cases and controls reported with nocturnal supervision, we calculated unadjusted ORs. We still found a protective effect in unadjusted analysis: OR 0.34, 95% CI 0.22 to 0.53; $P < 0.0001$; Analysis 1.1).

Shankar 2016 also reported a protective effect for the presence of nocturnal supervision: unadjusted OR 0.08, 95% CI 0.02 to 0.27; $P < 0.0001$; Analysis 1.2).

van der Lende 2018 found no significant effect of additional nocturnal supervision compared to no additional nocturnal supervision on SUDEP (unadjusted OR 0.76, 95% CI 0.40 to 1.46; $P = 0.41$; Analysis 1.3).

van der Lende 2018 reported three grades of nocturnal supervision (see Included studies for definitions). Results for SUDEP cases and controls by grade are reported in Table 6; the authors concluded no significant difference between grade of nocturnal supervision (adjusted for number of nocturnal convulsive seizures).

Special precautions compared to no special precautions

Langan 2005 found a protective effect when a supervising person shared the same bedroom or when special precautions, for example a listening device, were used (adjusted OR from multivariable logistic regression 0.10, 95% CI 0.00 to 0.30). This effect was independent of seizure control (see Characteristics of included studies for details of variables adjusted for).

Based on the number of cases and controls reported with special precautions, we calculated unadjusted ORs. We still found a protective effect in unadjusted analysis: OR 0.41, 95% CI 0.20 to 0.82; P = 0.01; Analysis 1.4).

Secondary outcomes

Cohort study

The prospective cohort study reported change in mean depression and anxiety scores and change in quality of life but did not report any deaths (unrelated to SUDEP) or number of hospital attendances for seizures (Radhakrishnan 2018).

Change in depression and anxiety scores

Radhakrishnan 2018 measured the change in depression and change in anxiety from baseline to six months by the Patient Health Questionnaire (PHQ-9) and by the Hamilton Anxiety Rating Scale (HAM-A) respectively. Within-group changes only were reported; no between-group (i.e. the intervention group compared to the control group) changes were available. Within-group changes are reported in Table 7. Radhakrishnan 2018 concluded that there was no significant change in anxiety and depression scores after 6 months of follow-up in either group.

Change in quality of life score

Radhakrishnan 2018 measured the change in quality of life from baseline to six months, measured by Quality of Life in Epilepsy-31 (QOLIE-31) or the Quality of Life in Epilepsy for Adolescents (QOLIE-AD-48). Within-group changes only were reported; no between-group (i.e. the intervention group compared to the control group) changes were available. Within-group changes for the QOLIE-31 are reported in Table 7 (QOLIE-AD-48 results were not reported). Radhakrishnan 2018 concluded that there was no significant change in quality of life scores after six months of follow-up in either group.

Case-control studies

The three case-control studies did not report our secondary outcomes 'number of other deaths (unrelated to SUDEP)', 'change in mean depression and anxiety scores (as defined within the study)', 'clinically important change in quality of life', and 'number of hospital attendances for seizures' (Langan 2005; Shankar 2016; van der Lende 2018).

Discussion

Summary of main results

We found one cohort study and three case-control studies of serious to critical risk of bias. The 6-month cohort study reported no significant effect on drug compliance or on quality of life, anxiety and depression levels when providing patients with SUDEP information compared to no information. The study was of too short duration, with no deaths observed in either group, to determine a protective effect (Radhakrishnan 2018). Two case-control studies reported a protective effect for nocturnal supervision against SUDEP (Langan 2005; Shankar 2016). In one study the protective effect was independent of seizure control, suggesting that nocturnal supervision is not just a surrogate marker of seizure control (Langan 2005). This is important since additional results within the same study highlighted increased risk for SUDEP with higher frequency of convulsive seizures, although not beyond 50 seizures in the previous three months. The control of such seizures may be important in SUDEP prevention. The third case-control study within two residential care settings where patients were already receiving physical checks more than 15 minutes apart throughout the night did not report any protective effect for additional nocturnal supervision (physical checks < 15 minutes apart, use of listening devices, dormitory setting and use of bed sensors) (van der Lende 2018). However the same study did ascertain a difference between centres: the centre with the lowest level of supervision had the highest incidence of SUDEP. The case-control studies did not report on quality of life or depression and anxiety scores.

Overall completeness and applicability of evidence

This review highlights a significant deficiency within the evidence base for clinical studies of preventative interventions against SUDEP. Many seizure-monitoring devices are available for purchase for patients and carers, some of which have been shown to be effective at detecting GTCS (Beniczky 2013; Narechania 2013; NCT00101933; Seyal 2013; Van Poppel 2013). These devices may be marketed in such a way as to suggest a preventative effect against SUDEP; this has not been borne out in the literature and requires much more extensive clinical investigation. We made contact with several commercial companies manufacturing seizure-monitoring devices (Cyberonics Inc, Emfit Ltd, Medtronic, Medpage Ltd, and Epi-Care) in order to obtain any unpublished information relating to this review, but we were unsuccessful.

No information has been reported on the effectiveness of other interventions (safety pillows, SSRIs, inhibitors of adenosine and opiate substances) in preventing SUDEP.

Certainty of the evidence

The evidence we have obtained is limited by being from four non-randomised studies, including three case-control studies with an observational design and an overall serious to critical risk of bias across the studies.

There is also the possible risk of publication bias given that none of the device companies contacted were willing to share unpublished information on their devices.

We judged the certainty of the limited evidence available for this review to be very low (Summary of findings table 1), mainly due to risks of bias relating to confounding, missing data and lack of reported information regarding selection into the study, control groups and classification of intervention status, deviations from the intended interventions and selection of the reported results, including inappropriate analysis methods.

Potential biases in the review process

There is a possible risk of publication bias in this review given that unpublished data were not made available by device companies. It is also possible that despite the exhaustive searches carried out in this review, we have not identified other sources of unpublished data. This can be more of an issue for reviews including observational study designs such as this review.

We have carried out a quality assessment of the single included study appropriate to the observational study design.

Agreements and disagreements with other studies or reviews

There are no other available reviews examining the preventative effect of interventions other than antiepileptic drugs in the prevention of SUDEP in people with epilepsy.

Authors' conclusions

Implications for practice

This review provides very low certainty evidence of a preventative effect of nocturnal supervision against SUDEP. As most SUDEP deaths are unwitnessed, timely supervision and administration of first aid post seizure recovery are paramount. Clearly this, as well as the practical steps to be taken in providing such supervision, needs to be discussed with carers of people who have frequent uncontrolled nocturnal seizures. Specific recommendations as to the best form of nocturnal supervision in preventing SUDEP risk requires further research.

This review has highlighted an overall deficiency in the literature base on the effectiveness of a wide range of interventions in the prevention of SUDEP in people with epilepsy. We did not include antiepileptic drugs as an intervention in this review, although a systematic review of placebo-controlled trials of adjunctive antiepileptic drugs ascertained lower rates of definite or probable SUDEP in the active treatment arm (OR 0.17, 95% CI 0.05 to 0.57; P = 0.0046). The same review concluded that treatment with adjunctive medication may have reduced the incidence of definite or probable SUDEP by more than seven times compared with placebo in people with previously uncontrolled seizures (Ryvlin 2011). This information supports the consideration of further trials of antiepileptic drugs in patients who fail to achieve remission on trials of monotherapy, provided patients are compliant.

Over the years several seizure-monitoring devices have been marketed for private purchase by patients and carers. These devices have varying sensitivities in their capacity to detect seizures, and thus prompt early intervention. Some companies may have marketed devices on the basis of SUDEP, given the risk with nocturnal tonic-clonic seizures; however a preventative effect has not been borne out from our review of the literature base.

We have identified one report of the effects of providing SUDEP information to patients with epilepsy. This short-duration study did not provide any evidence of a protective effect against SUDEP or ascertain a significant improvement in drug compliance or change in anxiety and depression levels. The American Academy of Neurology practice guidelines, National Institute of Clinical Excellence guidelines and the Scottish Intercollegiate Guidelines Network (SIGN) all advise discussion of tailored information about SUDEP (Harden 2017; NICE 2012; SIGN 2015). There is also evidence that patients and families wish to be informed of the risk of SUDEP (Tonberg 2015). There is, however, no consensus as to the form or content of the information, particularly given the uncertain pathophysiology and the lack of evidence base around preventative measures as encountered in this review.

We have not identified any reported evidence of a preventative effect for other interventions purported to reduce the risk of SUDEP via preventing airway obstruction or cardiorespiratory arrest, or both.

Implications for research

Despite the clinical importance of SUDEP in epilepsy and the greater risk with more frequent nocturnal seizures, our understanding of the exact pathophysiology of the event is currently unknown. This makes advancing research into preventative interventions against SUDEP more challenging. Any research observing preventative effects against SUDEP would require observational designs recruiting large numbers of patients with long durations of follow-up given the small number of cases per year of SUDEP. Whilst not impossible, these studies often require significant funding resources. An interesting area to examine would be the utility of SSRIs both as an antiepileptic and as a preventative intervention for SUDEP. Three small observational studies have demonstrated an antiepileptic effect with SSRIs, although sample sizes were small and the duration of treatment ranged between four and 14 months (Favale 1995; Favale 2003; Specchio 2004).

In the digital world, a novel app (EpSMon; www.sudep.org/epilepsy-self-monitor) has been developed to monitor seizures, medication, and overall well-being to provide a more personalised approach to managing risk of SUDEP, which could fluctuate over the course of time. This will provide ample opportunity to collect prospective annual data nationwide linking clinical factors, interventions, and antiepileptic drugs to overall SUDEP risk so that better-quality and more uniform information can be gathered about how to prevent SUDEP.

Acknowledgements

This review update was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to Cochrane Epilepsy. The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service, or the Department of Health.

We thank Cochrane Epilepsy for their support in the development of the protocol and this review.

We, and the Cochrane Epilepsy Group, are grateful to the following peer reviewers for their time and comments: Peter Hennessey, Danial Sayyad, Jack Wilkinson.

Contributions of authors

Melissa J Maguire developed the protocol, screened studies for inclusion, performed data extraction and quality opinion, and contributed to the writing of review results and discussion for this update.

Sarah J Nevitt developed the protocol, consulted on 'Risk of bias' assessment tools, performed data extraction and quality opinion, and contributed to the writing of review results and discussion for this update.

Declarations of interest

Melissa J Maguire: none known.

Cerian F Jackson: none known.

Anthony G Marson: a consortium of pharmaceutical companies (GSK, EISAI, UCB Pharma) funded the National Audit of Seizure Management in Hospitals (NASH) through grants paid to the University of Liverpool. Professor Tony Marson is part funded by the Applied Research Collaboration North West Coast (ARC NWC).

Sarah J Nevitt: none known.

Differences between protocol and review

The previous version of the review used the ACROBAT-NRSI 2014 tool for risk of bias assessment of the included case control study. At the time of the review update, this tool has been adapted and is now the ROBINS-I tool (Sterne 2016). For the update, all four included studies have therefore been assessed according to the signalling questions and risk of bias domains of the ROBINS-I tool.

Published notes

Characteristics of studies

Characteristics of included studies

Langan 2005

Methods	Case-control study performed in the UK
Participants	154 SUDEP cases aged between 16 and 50 years at death, identified between 1989 to 1998 through coroner reports, the British Neurologic Surveillance Unit, and the UK support charity Epilepsy Bereaved. Each case had 4 controls with epilepsy (total of 616 controls), matched for age and geographical area and identified through the Medical Research Council (MRC) General Practice Research Framework. The cases included 97 men and 57 women with a mean age of 32 years. Demographic details for controls were not reported, but it was stated that controls were age matched within 5 years of cases.
Interventions	Supervision at night was 1 of several factors listed as assessment variables between groups (see 'Outcomes' below for details of other factors not relevant to this review). This was defined as the presence of an individual of normal intelligence and at least 10 years old in the bedroom or the use of special precautions. Special precautions involved regular checks throughout the night or the use of a listening device.
Outcomes	Association of case or control status with factors including supervision at night and use of special precautions (other factors not relevant to this review: duration of epilepsy, seizure type and control including changes in seizure severity, treatment history and compliance, recent antiepileptic drug withdrawal, concomitant use of psychotropic medication, family history of sudden death, learning disability, electroencephalogram changes, history of drug or alcohol abuse, presence of other medical conditions, level of attendance at doctor or hospital appointments).
Notes	Analyses were based on data available retrospectively, therefore not all cases and controls contributed to each factor.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Bias due to confounding	Unclear risk	**Moderate risk of bias:** The objective of the study means that confounding is inevitable. The study assessed variables independently of seizure frequency, but did not report on control of other potential confounders (types of seizures, history of depression) between groups.
Bias in selection of participants into the study	Low risk	**Low risk of bias:** Controls were randomly selected from the eligible population and matched for age and geographical location.
Bias in measurement of interventions	Unclear risk	**Moderate risk of bias:** For cases, it is possible that intervention status was recorded after outcome and provided by a relative (rather than the case), which could be a source of bias.
Bias due to departures from intended interventions	Unclear risk	**Moderate risk of bias:** The intervention of interest to this review was not intended to be the only 'intervention' in the study. Switching may therefore have occurred, and co-interventions may have been present.
Bias due to missing data	High risk	**Serious risk of bias:** There was a large proportion of missing data for the variable nocturnal supervision, with around 40% missing data for controls, and an imbalance of missing data between cases and controls
Bias in measurement of outcomes	Low risk	**Low risk of bias:** The objective outcome measurement was established before intervention status.
Bias in selection of the reported result	Unclear risk	**Moderate risk of bias:** Results for 1 multivariable model reported, and unclear if results would have been different for other multivariable models.

Radhakrishnan 2018

Methods	Prospective cohort study with a pre-test/post-test design conducted at a tertiary care teaching hospital in Northern India
Participants	Consecutive people with epilepsy (PWE) aged over 15 years with a duration of epilepsy of at least 1 month were recruited; 119 inpatients and 112 outpatients Mean (standard deviation) age of PWE included in analysis: intervention group = 25.80 (8.19) years; control group = 27.59 (8.43) years Mean (standard deviation) duration of epilepsy included in analysis: intervention group = 14.82 (7.91) years; control group = 16.78 (8.41) years Caregivers of the PWE were also recruited but no information is given about how many caregivers were recruited with PWE and characteristics of caregivers
Interventions	Intervention group: SUDEP information plus standard epilepsy care for 6 months (n = 121 recruited, n = 116 available for post-test analysis) Control group: standard epilepsy care only for 6 months (n = 110, n = 106 available for post-test analysis) After completion of study period, control group also received SUDEP information.
Outcomes	Primary outcome 1. Change in antiepileptic drug adherence from baseline to 6 months, measured by Modified Morisky Medication Adherence Scale (MMAS) Secondary outcomes 1. Change in quality of life from baseline to 6 months, measured by Quality of Life in Epilepsy-31 (QOLIE-31) or Quality of life in Epilepsy for Adolescents (QOLIE-AD-48) 2. Change in anxiety from baseline to 6 months, measured by Hamilton Anxiety Rating Scale (HAM-A) 3. Change in depression from baseline to 6 months, measured by Patient Health Questionnaire (PHQ-9)
Notes	The study was initiated in January 2016 as single arm design with all participants receiving the intervention (SUDEP information and standard epilepsy care) for 6 months. A control group was added to the trial design in September 2017 due to concerns over bias. The control group were recruited according to the same eligibility criteria and received only standard epilepsy care for 6 months. PWE in intervention and control groups were balanced in terms of characteristics (age, duration of epilepsy, gender, education, type of epilepsy, family history of epilepsy, seizure frequency, number of antiepileptic drugs, intelligence quotient, neuroimaging findings and socioeconomic classification) and baseline scores of MMAS, QOLIE-31 or QOLIE-AD-48, HAM-A and PHQ-9. Within-group (pre-test/post-test in the intervention and control groups) only are made, no statistical comparisons of the intervention and control groups post-test are made.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Bias due to confounding	High risk	**Critical risk of bias**: subjective outcomes are measured in this study which could be influenced by factors, including confounding factors. However most analyses do not control or adjust for any confounders. A regression analysis is performed to examine which characteristics 'predictors of adherence' in the subgroup of participants with improved drug adherence. It is not appropriate to exclude those without improved drug adherence from an analysis of predictors of adherence.
Bias in selection of participants into the study	Low risk	**Low risk of bias**: the control group was added to the study design 18 months after the start of the study, therefore characteristics and outcomes of participants within the intervention group who had completed the 6-month study period would have been known and a period effect could in theory be present. However, it is stated that recruitment into both groups was "consecutive" and that the control group was recruited using the same inclusion criteria, therefore selection should not have been influenced.
Bias in measurement of interventions	Unclear risk	**Moderate risk of bias**: the control group was added to the study design 18 months after the start of the study, therefore characteristics and outcomes of participants within the intervention group who had completed the 6-month study period would have been known. It is unclear whether both groups (intervention and control) or only the control group were recruited to following the addition of the control group (i.e. whether the intervention groups were defined by the time point).
Bias due to departures from intended interventions	High risk	**Critical risk of bias**: participants for whom depression and anxiety was detected in the intervention group did not receive 'reinforcement' SUDEP information at subsequent clinics. As 1 of the aims of the study was examine the impact of providing the SUDEP information on anxiety and depression, this deviation will have directly impacted upon the outcome.
Bias due to missing data	Low risk	**Low risk of bias**: outcome data available for 96% of recruited participants in the intervention and control groups and it appears that the few missing patients were lost to follow-up or did not complete all of the outcome measures to be included in analysis at the end of the 6-month study period.
Bias in measurement of outcomes	Unclear risk	**Moderate risk of bias**: outcomes of the study were subjective and measured by questionnaires administered directly to participants. As participants would have been aware of their intervention status when completing the questionnaires, their intervention status may have influenced their responses.
Bias in selection of the reported result	High risk	**Critical risk of bias**: mostly within-group analyses only are reported and no between-group analyses are reported for the secondary outcomes. A regression analysis is performed to examine which characteristics 'predictors of adherence' in the subgroup of participants with improved adherence only which is not an appropriate analysis.

Shankar 2016

Methods	Case-control study performed in the UK
Participants	48 SUDEP cases aged between 2 and 82 years at death, identified from all 93 epilepsy and epilepsy-associated deaths which occurred in Cornwall (UK) between 2004 and 2012, as recorded by the Cornwall Coroner. Controls were 220 outpatients attending epilepsy clinics within Cornwall. The cases included 33 men and 15 women with a mean age of 42.5 years The controls included 115 men and 105 women with a mean age of 42.7 years
Interventions	Night surveillance was 1 of 17 factors listed as assessment variables between groups (see 'Outcomes' below for details of other factors not relevant to this review)
Outcomes	Association of case or control status with factors including Night surveillance (Other factors not relevant to this review: sleeping in a prone position, unclear treatment history, generalised tonic-clonic epilepsy, increasing seizure frequency, compliance issues, alcohol problems, subtherapeutic AED levels, epilepsy duration over 15 years, early onset epilepsy, frequent AED changes, presence of anxiolytic medication, depression treatment, intellectual disability, male gender, carbamazepine treatment, increasing seizure frequency).
Notes	Very little information provided (other than age and gender) of the cases and controls, and justification of the factors examined.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Bias due to confounding	High risk	**Serious risk of bias:** the objective of the study means that confounding is inevitable and no multivariable analysis was conducted. Therefore the univariable analyses reported are likely to be confounded.
Bias in selection of participants into the study	Unclear risk	**Moderate risk of bias:** selection of cases clearly described. Controls selected consecutively but unclear why cases and controls were considered over separate, non-overlapping time periods and whether any selection bias could have occurred.
Bias in measurement of interventions	Unclear risk	**Moderate risk of bias:** for cases, it is possible that intervention status was recorded after outcome and provided by a relative (rather than the case), which could be a source of bias.
Bias due to departures from intended interventions	High risk	**Serious risk of bias:** Intervention of interest to us was not intended to be the only 'intervention' in the study. No information is given regarding the interventions, adherence to the intervention, and co-interventions may have been present.
Bias due to missing data	High risk	**Serious risk of bias:** "Low numbers and missing data" prevented a multivariable analysis; however it is not stated which data were missing and how many participants were included in the analysis of each factor related to SUDEP.
Bias in measurement of outcomes	Low risk	**Low risk of bias:** the objective outcome measurement was established before intervention status
Bias in selection of the reported result	Unclear risk	**Moderate risk of bias:** unclear how the factors analysed were selected and if other factors were considered or if alternative analyses had been conducted

van der Lende 2018

Methods	Nested case–control study in two epilepsy residential care facilities in the Netherlands and the UK
Participants	60 SUDEP cases under the age of 60 years, which occurred at two epilepsy residential care facilities in the Netherlands and the UK (Stichting Epilepsie Instellingen Nederland (SEIN) and Chalfont Centre for Epilepsy (CCE)) between 1987 and 2014. 4 controls per case were matched on age (±5 years) and residential unit, with the date of death of the SUDEP cases uses as an index date for matching controls. The cases were 42 males and 18 females, mean age 39.3 years. The controls were 132 males and 66 females, mean age 40 years.
Interventions	Nocturnal supervision was 1 of 5 listed as assessment variables between groups (see 'Outcomes' below for details of other factors not relevant to this review).
Outcomes	Association of case or control status with factors including nocturnal supervision. (Other factors not relevant to this review: having convulsive seizures, frequency of convulsive seizures, having nocturnal convulsive seizures, frequency of nocturnal convulsive seizures).
Notes	Characteristics of SUDEP cases and controls were mostly similar (epilepsy etiology, epilepsy duration, seizure types, number of antiepileptic drugs and use of benzodiazepines). However SUDEP cases had a higher frequency of convulsive seizures ($P = 0.001$), particularly nocturnal convulsive seizures ($P < 0.001$), and a higher intelligence quotient compared with controls ($P = 0.005$).

Risk of bias table

Bias	Authors' judgement	Support for judgement
Bias due to confounding	Unclear risk	**Moderate risk of bias:** the objective of the study means that confounding is inevitable; however from the information available, it seems that confounders were measured fairly accurately and an appropriate adjusted analysis adjusting for convulsive seizure frequency (an important confounder) was performed.
Bias in selection of participants into the study	Unclear risk	**Moderate risk of bias:** unclear how many participants were reviewed when establishing SUDEP cases and exactly how matched controls were selected from the residential facilities. Unclear if any selection bias could have been present.
Bias in measurement of interventions	High risk	**Serious risk of bias:** likely that the 'grades of intervention' were defined for this study rather than at the start of the intervention, unclear whether the grades could have changed over time and it is possible that classification of the grade of intervention may have been affected by knowledge of case or control status.
Bias due to departures from intended interventions	High risk	**Serious risk of bias:** intervention of interest to us was not necessarily intended to be the only 'intervention' in the study. No information is given regarding adherence to the intervention, the consistency of the intervention and whether the 'grade' of the intervention could have changed over time and co-interventions may have been present.
Bias due to missing data	Unclear risk	**Moderate risk of bias:** around 20% of included cases and controls were excluded from analysis due to missing data but as the amount of missing data is relatively small and balanced across cases and controls, it is unlikely conclusions would have been changed by this missing data.
Bias in measurement of outcomes	Unclear risk	**Moderate risk of bias:** objective outcome measurement, but unclear exactly how cases and controls were selected into the study and whether intervention status was determined after outcome status.
Bias in selection of the reported result	Unclear risk	**Moderate risk of bias:** results for 1 multivariable model reported, unclear if results would have been different for other multivariable models or if 'grade of intervention' could have been classified differently.

Footnotes

SUDEP: Sudden Unexpected Death in Epilepsy

Due to different options for the 'Risk of bias' judgement in the non-randomised studies tool (Sterne 2016), we have assigned 'critical serious risk of bias' and 'serious risk of bias' as 'high risk of bias' and 'moderate risk of bias' as 'unclear risk of bias' in the table above. See the 'Support for judgement' column for more information and Table 2, Table 3, Table 4 and Table 5 for full quality assessments with signalling questions.

Characteristics of excluded studies

Almeida 2010

Reason for exclusion	Did not assess interventions to prevent SUDEP

Annegers 1998

Reason for exclusion	Did not assess interventions to prevent SUDEP

Annegers 2000

Reason for exclusion	Did not assess interventions to prevent SUDEP

Asadi-Pooya 2009

Reason for exclusion	Review article, not a clinical study

Bateman 2010

Reason for exclusion	Did not assess interventions to prevent SUDEP

Beniczky 2013

Reason for exclusion	Measured sensitivity of devices to detect generalised tonic-clonic seizures but did not directly measure SUDEP

DeGiorgio 2008

Reason for exclusion	Assessed risk factors for SUDEP but not interventions for preventing SUDEP

DeGiorgio 2019

Reason for exclusion	Review article, not a clinical study

Devinsky 2018

Reason for exclusion	Review article, not a clinical study

Fisher 2010

Reason for exclusion	Did not assess interventions to prevent SUDEP

Kang 2017

Reason for exclusion	Assessed risk factors for SUDEP but not interventions for preventing SUDEP

Narechania 2013

Reason for exclusion	Measured sensitivity of devices to detect generalised tonic-clonic seizures but did not directly measure SUDEP

NCT00101933

Reason for exclusion	Measured sensitivity of devices to detect generalised tonic-clonic seizures but did not directly measure SUDEP

NCT00736424

Reason for exclusion	All participants had neuro-stimulation, no control group

NCT00986310

Reason for exclusion	Did not assess interventions to prevent SUDEP

Nilsson 2001

Reason for exclusion	Did not assess interventions to prevent SUDEP

Purnell 2018

Reason for exclusion	Review article, not a clinical study

Ryvlin 2011

Reason for exclusion	Did not assess interventions to prevent SUDEP

Ryvlin 2018a

Reason for exclusion	All participants had vagus nerve stimulation, no control group

Ryvlin 2018b

Reason for exclusion	Review article, not a clinical study

Schachter 2006

Reason for exclusion	Review article, not a clinical study

Schmuely 2016

Reason for exclusion	Assessed risk factors for SUDEP but not interventions for preventing SUDEP

Scorza 2011

Reason for exclusion	Review article, not a clinical study

Seyal 2013

Reason for exclusion	Measured sensitivity of devices to detect generalised tonic–clonic seizures but did not directly measure SUDEP

Seymour 2012

Reason for exclusion	Assessed risk factors for SUDEP but not interventions for preventing SUDEP

Sveinsson 2018

Reason for exclusion	Assessed risk factors for SUDEP but not interventions for preventing SUDEP

Terra 2012

Reason for exclusion	Assessed risk factors for SUDEP but not interventions for preventing SUDEP

Van Poppel 2013

Reason for exclusion	Measured sensitivity of devices to detect generalised tonic–clonic seizures but did not directly measure SUDEP

Verma 2015

Reason for exclusion	Review article, not a clinical study

Footnotes

SUDEP: Sudden Unexpected Death in Epilepsy

Characteristics of studies awaiting classification

Footnotes

Characteristics of ongoing studies

Footnotes

Summary of findings tables

1 Interventions for compared with no intervention for preventing Sudden Unexpected Death in Epilepsy (SUDEP)

Interventions for compared with no intervention for preventing Sudden Unexpected Death in Epilepsy (SUDEP)

Patient or population: cases of SUDEP and matched controls (number of deaths due to SUDEP) and consecutive people with epilepsy from a tertiary care teaching hospital in Northern India (change in mean depression and anxiety scores and change in quality of life)

Settings: outpatients and patients within an epilepsy residential facility (number of deaths due to SUDEP), inpatients and outpatients from a tertiary care teaching hospital in Northern India (change in mean depression and anxiety scores and change in quality of life).

Intervention: interventions to prevent SUDEP (nocturnal supervision and special precautions for number of deaths due to SUDEP and SUDEP information for change in mean depression and anxiety scores and change in quality of life)

Comparison: no intervention (including usual care or standard epilepsy care for all outcomes)

Outcomes	Illustrative comparative risks* (95% CI)[a]		Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No intervention	Intervention to prevent SUDEP				
Number of deaths due to SUDEP: nocturnal supervision compared to no supervision	A protective effect for the presence of nocturnal supervision against SUDEP was found in 2 studies, including from an analysis adjusted for other factors (adjusted OR 0.40, 95% CI 0.20 to 0.80)		NA	up to 203 SUDEP cases up to 533 controls (2 case–control studies)	⊕⊖⊖⊖ **very low**[b]	1 study: 109 deaths out of 278 in the no intervention group and 34 deaths out of 190 deaths in the intervention group. The other study did not report how many of the cases and controls received an intervention or not, only an odds ratio for the association of the intervention and SUDEP was reported.
Number of deaths due to SUDEP: additional nocturnal supervision compared to no additional supervision	No significant effect of additional nocturnal supervision compared to no additional nocturnal supervision on SUDEP		**OR 0.76** (0.40 to 1.46)[c]	48 SUDEP cases 163 controls (1 case–control study)	⊕⊖⊖⊖ **very low**[b]	There was also no significant difference between grade of nocturnal supervision (adjusted for number of nocturnal convulsive seizures) and the effect on SUDEP
Number of deaths due to SUDEP: special precautions compared to no special precautions	A protective effect for the presence of nocturnal supervision against SUDEP was found including from an analysis adjusted for other factors (adjusted OR 0.10, 95% CI 0.00 to 0.30)		**OR 0.41** (0.20 to 0.82)[c]	155 SUDEP cases 176 controls (1 case control study)	⊕⊖⊖⊖ **very low**[b]	109 deaths out of 278 in the no intervention group and 11 deaths out of 53 deaths in the intervention group
Number of other deaths (unrelated to SUDEP)	Outcome not reported				NA	

Change in mean depression and anxiety scores Follow-up: 6 months	There was no significant change from baseline in anxiety and depression scores after 6 months of follow-up in either the intervention or control group	NA	222 participants (1 cohort study)	⊕⊖⊖⊖ **very low**[d]	Depression was measured by the Patient Health Questionnaire (PHQ-9) and anxiety was measured by the Hamilton Anxiety Rating Scale (HAM-A). Within-group changes only were reported; no between-group (i.e. the intervention group compared to the control group) changes were available.
Clinically important change in quality of life Follow-up: 6 months	There was no significant change from baseline in quality of life scores after 6 months of follow-up in either the intervention or control group	NA	215 participants (1 cohort study)	⊕⊖⊖⊖ **very low**[d]	Quality of life was measured by the Quality of Life in Epilepsy-31 (QOLIE-31) and by the Quality of life in Epilepsy for Adolescents (QOLIE-AD-48); results were not reported for the 7 participants who completed the QOLIE-AD-48. Within-group changes only were reported; no between-group (i.e. the intervention group compared to the control group) changes were available.
Number of hospital attendances for seizures	Outcome not reported			NA	

*The basis for the **assumed risk** is the event rate in the control group. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **NA:** not applicable; **OR:** odds ratio; **SUDEP:** Sudden Unexpected Death in Epilepsy

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

Footnotes

a. Assumed and corresponding risks not calculated due to study design (case-control)

b. Quality of the evidence automatically started at 'low' due to the retrospective, observational design of the included studies. Downgraded once to 'very low' due to serious risk of bias, mainly relating to confounding, missing data and lack of reported information regarding selection into the study, control groups and classification of intervention status.

c. Unadjusted odds ratio. OR < 1 indicates that the intervention is protective against SUDEP

d. Certainty of the evidence automatically started at 'low' due to the retrospective, observational design of the included studies. Downgraded to 'very low' due to critical risk of bias relating to confounding, deviations from the intended interventions and selection of the reported results, including inappropriate analysis methods.

Additional tables

1 Guidance for making a single 'Risk of bias' judgement for an outcome based on 'Risk of bias' judgements for the 7 domains of the ROBINS-I

'Risk of bias' judgement for the outcome	Criteria (based on 7 'Risk of bias' domains)
Low risk of bias (the study is comparable to a well-performed randomised trial)	The study is judged to be at low risk of bias for all domains
Moderate risk of bias (the study appears to provide sound evidence for a non-randomised study but cannot be considered comparable to a well-performed randomised trial)	The study is judged to be at low or moderate risk of bias for all domains
Serious risk of bias (the study has some important problems)	The study is judged to be at serious risk of bias in at least 1 domain, but not at critical risk of bias in any domain
Critical risk of bias (the study is too problematic to provide any useful evidence on the effects of intervention)	The study is judged to be at critical risk of bias in at least 1 domain
No information on which to base a judgement about risk of bias	There is no clear indication that the study is at serious or critical risk of bias, and there is a lack of information in 1 or more key domains of bias (a judgement is required for this)

Footnotes

2 Responses to ROBINS-I signalling questions and 'Risk of bias' judgements for Langan 2005

Question	Signalling question response	Description
Bias due to confounding		
1.1 Is there potential for confounding of the effect of intervention in this study?	Y	Aim of the study was to explore variables that may influence the factors associated with SUDEP. The 'intervention' of interest to us is 1 of those variables, so confounding is inevitable
1.2. If Y or PY to 1.1 Was the analysis based on splitting participants' follow up time according to intervention received?	NA	Case-control study, cases and controls were retrospectively examined over the same period of time
1.4. Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains?	PY	Multivariable logistic regression, but variables that were not significant in the model are not reported in the results
1.5. If Y or PY to 1.4: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	PY	Variables taken from a Medical Research Council (MRC) database/coroners' records/interviews with bereaved families. Probably fairly accurate
1.6. Did the authors control for any post- intervention variables that could have been affected by the intervention?	PN	Intervention is given over a period of time, and variables are also measured over a period of time with probable overlap
1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	NA	Case-control study, cases and controls were examined over the same period of time
'Risk of bias' judgement	**Moderate**	The objective of the study means that confounding is inevitable; however from the limited information available, it seems that an appropriate adjusted analysis was performed
Bias in selection of participants into the study		

Question	Signalling question response	Description
2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	N	Case-control study, therefore selection was based on outcome (SUDEP or no SUDEP), not based on any participants characteristics and not related to the intervention
2.4 Do start of follow-up and start of intervention coincide for most participants?	PN	Cases and controls are examined over a fixed period and it is not stated when any interventions were started for the cases and controls, unlikely that interventions were started at the beginning of the time period of interest for most participants
2.5 If N or PN to 2.4 Were adjustment techniques used that are likely to correct for the presence of selection biases?	PN	Controls were randomly sampled from a national database so unlikely that any selection bias was presented, therefore adjustment techniques probably not required
'Risk of bias' judgement	**Low**	Random sample of controls used and no evidence of any selection bias
Bias in classification of interventions		
3.1 Were intervention groups clearly defined?	Y	Clear whether a participant had any of the listed supervision, but data for the controls missing
3.2 Was the information used to define intervention groups recorded at the start of the intervention?	PY	For controls, likely recorded at the time of intervention (continuous intervention over a period of time). For cases, this information may have been recorded following the outcome and information provided by a relative rather than the case (deceased)
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	PN	For controls, likely recorded at the time of intervention (continuous intervention over a period of time). For cases, this information may have been recorded following the outcome and information provided by a relative rather than the case (deceased)
'Risk of bias' judgement	**Moderate**	For cases, it is possible that intervention status was recorded after outcome, which could be a source of bias
Bias due to deviations from intended interventions (aim for this study is to assess the effect of starting and adhering to intervention)		
4.3. Were important co-interventions balanced across intervention groups?	N	Number of AEDs and current use of carbamazepine not balanced across cases and controls
4.4. Was the intervention implemented successfully for most participants?	NI	No information given but possible that intervention could be disrupted (e.g. person supervised leaves the room) or devices fail
4.5. Did study participants adhere to the assigned intervention regimen?	NI	No information given regarding adherence to the interventions
4.6. If N or PN to 4.3, 4.4 or 4.5 Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	N	Adherence to the intervention is not mentioned or taken account of in analysis
'Risk of bias' judgement	**Moderate**	Intervention of interest to us was not intended to be the only 'intervention' in the study. No information is given regarding adherence to the intervention, and co-interventions may have been present

Question	Signalling question response	Description
Bias due to missing data		
5.1 Were outcome data available for all, or nearly all, participants?	Y	Participants selected based on outcome status (case-control study)
5.2 Were participants excluded due to missing data on intervention status?	Y	A lot of missing data for the controls for intervention status
5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Y	Data also missing for controls for other variables
5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across cases and controls?	N	A lot of missing data for controls, mostly complete for cases
5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	N	Participants and variables with missing data excluded from analysis
'Risk of bias' judgement	**Serious**	A large proportion of missing data for outcome status and an imbalance of missing data across cases and controls
Bias in measurement of outcomes		
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	N	Cases were those who had experienced SUDEP, controls had not experienced SUDEP
6.2 Were outcome assessors aware of the intervention received by study participants?	N	By design, cases and controls established first and then variable information including intervention status extracted afterwards
6.3 Were the methods of outcome assessment comparable across intervention groups?	N	By design, cases and controls established first and then variable information including intervention status extracted afterwards
6.4 Were any systematic errors in measurement of the outcome related to intervention received?	N	Cases were those who had experienced SUDEP, controls had not experienced SUDEP, therefore very unlikely that any errors related to measurement of the outcome occurred
'Risk of bias' judgement	**Low**	Objective outcome measurement established before intervention status
Bias in selection of the reported result		
Is the reported effect estimate likely to be selected, on the basis of the results, from...		
7.1 ...multiple outcome *measurements* within the outcome domain?	N	A single and clearly defined outcome, SUDEP or no SUDEP.
7.2 ...multiple *analyses* of the intervention-outcome relationship?	PN	Multivariable analysis performed, unclear exactly how many variables were included in the model and whether results would have been different for the intervention-outcome relationship if other non-significant variables had been retained in the model
7.3 ...different *subgroups?*	N	No subgroups reported
'Risk of bias' judgement	**Moderate**	Results for 1 multivariable model reported, unclear if results would have been different for other multivariable models

Footnotes

Abbreviations: Y: yes; PY: probably yes; PN: probably no; N: no; NI: no information

AEDs: antiepileptic drugs
SUDEP: Sudden Unexpected Death in Epilepsy

3 Responses to ROBINS-I signalling questions and 'Risk of bias' judgements for Shankar 2016

Question	Signalling question response	Description
Bias due to confounding		
1.1 Is there potential for confounding of the effect of intervention in this study?	Y	Aim of the study was to explore variables that may influence the factors associated with SUDEP. The 'intervention' of interest to us is 1 of those variables, so confounding is inevitable
1.2. If Y or PY to 1.1 Was the analysis based on splitting participants' follow up time according to intervention received?	PN	Case-control study, cases and controls were retrospectively examined over completely different periods of time. The rationale for this is unclear but is unlikely to be due to any of the interventions of interest
1.4. Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains?	N	Univariable analysis only used (odds ratios calculated for having a specific factor in those who died from SUDEP compared to controls.) The authors stated that "low numbers and missing data" prevented a multivariable analysis.
1.6. Did the authors control for any post- intervention variables that could have been affected by the intervention?	N	Univariable analysis only used (odds ratios calculated for having a specific factor in those who died from SUDEP compared to controls.) The authors stated that "low numbers and missing data" prevented a multivariable analysis. No variables controlled for (pre- or post-intervention)
1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	N	Case-control study, no variables controlled for (pre- or post-intervention)
'Risk of bias' judgement	**Serious**	The objective of the study means that confounding is inevitable and no multivariable analysis was conducted. Therefore the univariable analyses reported are likely to be confounded
Bias in selection of participants into the study		
2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	PN	Case-control study, therefore selection was based on outcome (SUDEP or no SUDEP). Selection of cases clearly described Not completely clear how the controls were selected (e.g. how the time period that consecutive controls were chosen was selected), but it does not appear to be related to participants characteristics or any interventions.
2.4 Do start of follow-up and start of intervention coincide for most participants?	PN	Cases and controls are examined over a fixed time periods and it is not stated when any interventions were started for the cases and controls, unlikely that interventions were started at the beginning of the time period of interest for most participants
2.5 If N or PN to 2.4 Were adjustment techniques used that are likely to correct for the presence of selection biases?	PN	Not completely clear how the controls were selected and why cases and controls were considered over separate, non-overlapping time periods. No apparent adjustments made for any selection biases.
'Risk of bias' judgement	**Moderate**	Selection of cases clearly described. Controls selected consecutively but unclear why cases and controls were considered over separate, non-overlapping time periods and whether any selection bias could have occurred

Question	Signalling question response	Description
Bias in classification of interventions		
3.1 Were intervention groups clearly defined?	PY	Presumably presence or absence of the intervention or factor, but unclear how the intervention and factor groups were measured.
3.2 Was the information used to define intervention groups recorded at the start of the intervention?	PY	For controls, likely recorded at the time of intervention (continuous intervention over a period of time). For cases, this information may have been recorded following the outcome and information provided by a relative rather than the case (deceased)
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	PY	For controls, likely recorded at the time of intervention (continuous intervention over a period of time). For cases, this information may have been recorded following the outcome and information provided by a relative rather than the case (deceased)
'Risk of bias' judgement	**Moderate**	For cases, it is possible that intervention status was recorded after outcome and provided by a relative (rather than the case), which could be a source of bias
Bias due to deviations from intended interventions (aim for this study is to assess the effect of starting and adhering to intervention)		
4.3. Were important co-interventions balanced across intervention groups?	NI	No information provided regarding the number of cases and controls receiving the interventions, only odds ratios for having a specific factor in those who died from SUDEP compared to controls presented
4.4. Was the intervention implemented successfully for most participants?	NI	No information provided regarding the number of cases and controls receiving the interventions, only odds ratios for having a specific factor in those who died from SUDEP compared to controls presented
4.5. Did study participants adhere to the assigned intervention regimen?	NI	No information provided regarding the number of cases and controls receiving the interventions, only odds ratios for having a specific factor in those who died from SUDEP compared to controls presented
4.6. If N or PN to 4.3, 4.4 or 4.5 Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	N	Adherence to the intervention is not mentioned or taken account of in analysis
'Risk of bias' judgement	**Serious**	Intervention of interest to us was not intended to be the only 'intervention' in the study. No information is given regarding the interventions, adherence to the intervention, and co-interventions may have been present.
Bias due to missing data		
5.1 Were outcome data available for all, or nearly all, participants?	Y	Participants selected based on outcome status (case-control study)
5.2 Were participants excluded due to missing data on intervention status?	NI	it does not appear that any participants were excluded from the study completely due to missing data regarding interventions, but numbers of participants included in the analysis of each factor related to SUDEP is not provided so unclear how much data was missing on intervention status

Question	Signalling question response	Description
5.3 Were participants excluded due to missing data on other variables needed for the analysis?	NI	"Low numbers and missing data" prevented a multivariable analysis, however it is not stated which data was missing and how many participants were included in the analysis of each factor related to SUDEP
5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	NI	"Low numbers and missing data" prevented a multivariable analysis, however it is not stated which data was missing and how many participants were included in the analysis of each factor related to SUDEP
5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	N	No examination of whether results are robust to missing data
'Risk of bias' judgement	**Serious**	"Low numbers and missing data" prevented a multivariable analysis, however it is not stated which data was missing and how many participants were included in the analysis of each factor related to SUDEP
Bias in measurement of outcomes		
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	N	Cases were those who had experienced SUDEP, controls had not experienced SUDEP
6.2 Were outcome assessors aware of the intervention received by study participants?	N	By design, cases and controls established first and then variable information including intervention status extracted afterwards
6.3 Were the methods of outcome assessment comparable across intervention groups?	N	By design, cases and controls established first and then variable information including intervention status extracted afterwards
6.4 Were any systematic errors in measurement of the outcome related to intervention received?	N	Cases were those who had experienced SUDEP, controls had not experienced SUDEP, therefore very unlikely that any errors related to measurement of the outcome occurred
'Risk of bias' judgement	**Low**	Objective outcome measurement established before intervention status
Bias in selection of the reported result		
Is the reported effect estimate likely to be selected, on the basis of the results, from...		
7.1 ...multiple outcome *measurements* within the outcome domain?	N	A single and clearly defined outcome, SUDEP or no SUDEP.
7.2 ...multiple *analyses* of the intervention-outcome relationship?	NI	Unclear how the factors analysed were selected and if other factors were considered or if alternative analyses had been conducted
7.3 ...different *subgroups?*	N	No subgroups reported
'Risk of bias' judgement	**Moderate**	Unclear how the factors analysed were selected and if other factors were considered or if alternative analyses had been conducted

Footnotes

Abbreviations: Y: yes; PY: probably yes; PN: probably no; N: no; NI: no information
AEDs: antiepileptic drugs
SUDEP: Sudden Unexpected Death in Epilepsy

4 Responses to ROBINS-I signalling questions and 'Risk of bias' judgements for Radhakrishnan 2018

Question	Signalling question response	Description
Bias due to confounding		
1.1 Is there potential for confounding of the effect of intervention in this study?	Y	Intervention and control groups appear balanced for participant characteristics and baseline outcome measures. However, outcomes measured are drug adherence, quality of life, depression and anxiety which are all subjective outcomes which could be influenced by a range of factors, including confounding factors.
1.2. If Y or PY to 1.1: Was the analysis based on splitting participants' follow-up time according to intervention received?	PN	Participants were followed up for the same amount of time in both groups (6 months) and it does not appear that interventions could be switched during this time.
1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	N	Most analyses do not control or adjust for any confounders. A single regression analysis is performed to examine which characteristics 'predictors of adherence' in the subgroup of participants with improved adherence only which is not an appropriate analysis
1.6. Did the authors control for any post- intervention variables that could have been affected by the intervention?	N	No post-intervention variables controlled for in any of the analyses
1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	N	Most analyses do not control or adjust for any confounders. A regression analysis is performed to examine which characteristics 'predictors of adherence' in the subgroup of participants with improved drug adherence. It is not appropriate to exclude those without improved drug adherence from an analysis of predictors of adherence.
'Risk of bias' judgement	**Critical**	Subjective outcomes are measured in this study which could be influenced by a range of factors, including confounding factors. However most analyses do not control or adjust for any confounders. A univariate regression analysis is performed to examine which characteristics 'predictors of adherence' in the subgroup of participants with improved drug adherence. It is not appropriate to exclude those without improved drug adherence from an analysis of predictors of adherence.
Bias in selection of participants into the study		
2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	PN	The control group was added to the study design 18 months after the start of the study, therefore characteristics and outcomes of participants within the intervention group who had completed the 6-month study period would have been known and a period effect could in theory be present. However, it is stated that recruitment into both groups was 'consecutive' and that the control group was recruited using the same inclusion criteria, therefore selection should not have been influenced.
2.4. Do start of follow-up and start of intervention coincide for most participants?	Y	From the information provided, it appears that the intervention was started on recruitment to the study. The control (standard epilepsy care) would have started before the study
'Risk of bias' judgement	**Low**	The control group was added to the study design 18 months after the start of the study, therefore characteristics and outcomes of participants within the intervention group who had completed the 6-month study period would have been known and a period effect could in theory be present. However, it is stated that recruitment into both groups was "consecutive" and that the control group was recruited using the same inclusion criteria, therefore selection should not have been influenced.

Question	Signalling question response	Description
Bias in classification of interventions		
3.1 Were intervention groups clearly defined?	Y	Intervention group receive SUDEP information plus standard epilepsy care and control group receive standard epilepsy care only
3.2 Was the information used to define intervention groups recorded at the start of the intervention?	PY	The control group was added to the study design 18 months after the start of the study, therefore characteristics and outcomes of participants within the intervention group who had completed the 6-month study period would have been known. It is unclear whether both groups (intervention and control) or only the control group were recruited to following the addition of the control group (i.e. whether the intervention groups were defined by the time point).
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	PY	The control group was added to the study design 18 months after the start of the study, therefore characteristics and outcomes of participants within the intervention group who had completed the 6-month study period would have been known. It is unclear whether both groups (intervention and control) or only the control group were recruited to following the addition of the control group (i.e. whether the intervention groups were defined by the time point).
'Risk of bias' judgement	**Moderate**	The control group was added to the study design 18 months after the start of the study, therefore characteristics and outcomes of participants within the intervention group who had completed the 6-month study period would have been known. It is unclear whether both groups (intervention and control) or only the control group were recruited to following the addition of the control group (i.e. whether the intervention groups were defined by the time point).
Bias due to deviations from intended interventions (aim for this study is to assess the effect of assignment to intervention)		
4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Y	Both groups received 'standard epilepsy care' but it was not described what was involved in this control intervention and whether this intervention was given consistently across all participants. Within the intervention group, all participants were given detailed information on SUDEP at baseline, delivered by a senior doctor and an epilepsy expert. However, only participants who did not have depression and anxiety detected at baseline received a 'reinforcement' intervention at subsequent clinical visits, therefore intervention was delivered inconsistently.
4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Y / PY / PN / N / NI / NA	Unclear whether there was any imbalance in the 'standard epilepsy care' received by both groups as no information on this intervention is provided. Participants for whom depression and anxiety was detected in the intervention group did not receive 'reinforcement' SUDEP information at subsequent clinics. As 1 of the aims of the study was examine the impact of providing the SUDEP information on anxiety and depression, this deviation will have directly impacted upon the outcome.

Question	Signalling question response	Description
'Risk of bias' judgement	**Critical**	Participants for whom depression and anxiety was detected in the intervention group did not receive 'reinforcement' SUDEP information at subsequent clinics. As 1 of the aims of the study was examine the impact of providing the SUDEP information on anxiety and depression, this deviation will have directly impacted upon the outcome.
Bias due to missing data		
5.1 Were outcome data available for all, or nearly all, participants?	Y	Outcome data available for 116 out of 121 participants in the intervention group (96%) and 106 out of 110 participants in the control group (96%)
5.2 Were participants excluded due to missing data on intervention status?	PN	It appears that the few missing patients were lost to follow-up or did not complete the outcome measures to be included in analysis at the end of the 6-month study period
5.3 Were participants excluded due to missing data on other variables needed for the analysis?	PN	It appears that the few missing patients were lost to follow-up or did not complete all of the outcome measures to be included in analysis at the end of the 6-month study period
'Risk of bias' judgement	**Low**	Outcome data available for 96% of recruited participants in the intervention and control groups and it appears that the few missing patients were lost to follow-up or did not complete all of the outcome measures to be included in analysis at the end of the 6-month study period
Bias in measurement of outcomes		
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Y	Participants and personnel involved in the study would have been aware of their intervention status and all outcomes measures collected are subjective
6.2 Were outcome assessors unaware of the intervention received by study participants?	NI	Aside from participants who completed questionnaires for outcome measures and were aware of their intervention status, it is unclear who other outcome assessors were (e.g. individuals conducting statistical analysis) and if any of these outcome assessors were blinded
6.3 Were the methods of outcome assessment comparable across intervention groups?	PY	Questionnaires were administered to all participants in the intervention and control groups, no apparent differences in the outcome assessment
6.4 Were any systematic errors in measurement of the outcome unrelated to intervention received?	PN	It is possible that questionnaires could have been completed incorrectly which would have impacted on the measurement of outcomes but no evidence that this occurred systematically in the study
'Risk of bias' judgement	**Moderate**	Outcomes of the study were subjective and measured by questionnaires administered directly to participants. As participants would have been aware of their intervention status when completing the questionnaires, their intervention status may have influenced their responses
Bias in selection of the reported result		
Is the reported effect estimate likely to be selected, on the basis of the results, from...		

Question	Signalling question response	Description
7.1. ... multiple outcome measurements within the outcome domain?	PN	It appears that outcomes have been measured according to the validated questionnaires used within the studies, no evidence that multiple outcome measurements have been made
7.2 ...multiple *analyses* of the intervention-outcome relationship?	PY	Within-group analyses (pre-test/post-test differences in the intervention and control group respectively) only are conducted for most outcomes. A between-group (intervention vs control group) analysis is reported only for the primary outcome and it is unclear why such an analysis is not reported for the secondary outcomes
7.3 ...different subgroups?	Y	A regression analysis is performed to examine which characteristics 'predictors of adherence' in the subgroup of participants with improved adherence only which is not an appropriate analysis
'Risk of bias' judgement	**Critical**	Mostly within-group analyses only are reported and no between-group analyses are reported for the secondary outcomes. A regression analysis is performed to examine which characteristics 'predictors of adherence' in the subgroup of participants with improved adherence only which is not an appropriate analysis

Footnotes

5 Responses to ROBINS-I signalling questions and 'Risk of bias' judgements for van der Lende 2018

Question	Signalling question response	Description
Bias due to confounding		
1.1 Is there potential for confounding of the effect of intervention in this study?	Y	Aim of the study was to explore variables that may influence the factors associated with SUDEP. The 'intervention' of interest to us is 1 of those variables, so confounding is inevitable
1.2. If Y or PY to 1.1 Was the analysis based on splitting participants' follow up time according to intervention received?	NA	Case-control study, cases and controls were retrospectively examined over the same period of time (1987 to 2014).
1.4. Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains?	PY	Multivariable logistic regression, which includes grade of supervision and number of nocturnal convulsive seizures. No other potential confounding variables appear to be included in the model but demographics and clinical characteristics of cases and controls are fairly similar other than frequency of convulsive seizures which seems to be the most important confounding factor therefore analysis may be sufficient.
1.5. If Y or PY to 1.4: Were confounding domains that were adjusted for measured validly and reliably by the variables available in this study?	PY	Data extracted from records of the epilepsy residential facilities and medical records. Probably fairly accurate but some data is missing for seizure variables and nocturnal supervision
1.6. Did the authors control for any post- intervention variables that could have been affected by the intervention?	PN	Intervention is given over a period of time, and variables are also measured over a period of time with probable overlap
1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	NA	Case-control study, cases and controls were examined over the same period of time in the same residential facilities (date of death of SUDEP cases used as an index date for matching cases).

Question	Signalling question response	Description
'Risk of bias' judgement	**Moderate**	The objective of the study means that confounding is inevitable, however from the information available, it seems that an appropriate adjusted analysis was performed
Bias in selection of participants into the study		
2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	N	Case-control study, therefore selection was based on outcome (SUDEP or no SUDEP), not based on any participants characteristics and not related to the intervention
2.4 Do start of follow-up and start of intervention coincide for most participants?	PN	Cases and controls are examined over a fixed period (1987 to 2014) and it is not stated when any interventions were started for the cases and controls. It is unlikely that interventions were started at the beginning of the time period of interest for most participants
2.5 If N or PN to 2.4 Were adjustment techniques used that are likely to correct for the presence of selection biases?	PN	Unclear exactly how controls were selected from the residential facilities, it is only stated that the controls were matched. It is also unclear how many deaths with reviewed to result in 60 SUDEP cases and unclear if any adjustment was performed to correct for selection bias
'Risk of bias' judgement	**Moderate**	Unclear how many participants were reviewed when establishing SUDEP cases and exactly how matched controls were selected from the residential facilities. Unclear if any selection bias could have been present
Bias in classification of interventions		
3.1 Were intervention groups clearly defined?	PY	Clear definitions of the grades of interventions and number of participants in each 'grade' group in the cases and controls clearly defined but intervention available for only around 80% of cases and controls and not explicitly stated why 20% of cases and controls are not included in analyses (e.g. due to missing data for grade of intervention).
3.2 Was the information used to define intervention groups recorded at the start of the intervention?	N	Likely that the 'grades' of intervention were defined for the purposes of this study. Level of nocturnal intervention within the residential facilities changed over the period of time of the study. It is unclear whether cases and controls could have been classified as a number of 'grades' at different points during the study and how the 'grade' used in the analysis was determined.
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	PN	It is likely that nocturnal supervision was recorded for all residents of the facilities, regardless of case or control status, however the level of detail recorded and therefore the grade of intervention classified may have been greater for individuals who died than those who did not.
'Risk of bias' judgement	**Serious**	Likely that the 'grades of intervention' were defined for this study rather than at the start of the intervention, unclear whether the grades could have changed over time and it is possible that classification of the grade of intervention may have been affected by knowledge of case or control status.
Bias due to deviations from intended interventions (aim for this study is to assess the effect of starting and adhering to intervention)		

Question	Signalling question response	Description
4.3. Were important co-interventions balanced across intervention groups?	N	Convulsive seizure frequency and intelligence quotient were not balanced across cases and controls.
4.4. Was the intervention implemented successfully for most participants?	NI	No information given but possible that intervention could be disrupted (e.g. person supervised leaves the room) or devices fail. It is also unclear whether cases and controls could have been classified as a number of 'grades' at different points during the study and how the 'grade' used in the analysis was determined.
4.5. Did study participants adhere to the assigned intervention regimen?	NI	No information given regarding adherence or consistency of the interventions
4.6. If N or PN to 4.3, 4.4 or 4.5 Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	N	Adherence to or consistency of the intervention is not mentioned or taken account of in analysis
'Risk of bias' judgement	**Serious**	Intervention of interest to us was not necessarily intended to be the only 'intervention' in the study. No information is given regarding adherence to the intervention, the consistency of the intervention and whether the 'grade' of the intervention could have changed over time and co-interventions may have been present
Bias due to missing data		
5.1 Were outcome data available for all, or nearly all, participants?	Y	Participants selected based on outcome status (case-control study)
5.2 Were participants excluded due to missing data on intervention status?	Y	20% of cases and controls were excluded from analysis due to missing data on 'grade' of intervention
5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Y	Data also missing for cases and controls for other variables which would have lead to exclusions from analysis
5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across cases and controls?	PY	Proportions of missing data similar across cases and controls but no reasons given for missing data.
5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	PY	No analyses performed to account for missing data, however amount of missing data is relatively small and balanced across cases and controls, therefore unlikely conclusions would have been changed by this missing data
'Risk of bias' judgement	**Moderate**	Around 20% of included cases and controls were excluded from analysis due to missing data but as the amount of missing data is relatively small and balanced across cases and controls, therefore unlikely conclusions would have been changed by this missing data
Bias in measurement of outcomes		
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	N	Cases were those who had experienced SUDEP, controls had not experienced SUDEP

Question	Signalling question response	Description
6.2 Were outcome assessors aware of the intervention received by study participants?	PN	It is likely that cases and controls were established first and then variable information to classify the information status was extracted afterwards but not completely clear.
6.3 Were the methods of outcome assessment comparable across intervention groups?	PN	It is likely that cases and controls were established first and then variable information to classify the information status was extracted afterwards but not completely clear.
6.4 Were any systematic errors in measurement of the outcome related to intervention received?	PN	Cases were those who had experienced SUDEP, controls had not experienced SUDEP, therefore very unlikely that any errors related to measurement of the outcome occurred. However it is not clear exactly how the cases and controls were selected into the study from all residents
'Risk of bias' judgement	**Moderate**	Objective outcome measurement, but unclear exactly how cases and controls were selected into the study and whether intervention status was determined after outcome status
Bias in selection of the reported result		
Is the reported effect estimate likely to be selected, on the basis of the results, from...		
7.1 ...multiple outcome *measurements* within the outcome domain?	PN	A single and clearly defined outcome, SUDEP or no SUDEP but unclear exactly how the cases and controls were selected
7.2 ...multiple *analyses* of the intervention-outcome relationship?	PN	Multivariable analysis performed with 2 variables, unlikely other analyses were performed. Unclear if different classifications of 'grade of intervention' could have been analysed
7.3 ...different *subgroups?*	N	No subgroups reported
'Risk of bias' judgement	**Moderate**	Results for 1 multivariable model reported, unclear if results would have been different for other multivariable models or if 'grade of intervention' could have been classified differently.

Footnotes

Abbreviations: Y: yes; PY: probably yes; PN: probably no; N: no; NI: no information

AEDs: antiepileptic drugs
SUDEP: Sudden Unexpected Death in Epilepsy

6 Grades of nocturnal supervision and association with SUDEP in van der Lende 2018

Nocturnal Supervision	SUDEP cases	Controls	Odds Ratio (95% CI)[a]
Grade 1	28/48 (58%)	84/163 (52%)	0.73 (0.15 to 3.46), P = 0.693
Grade 2	16/48 (33%)	73/163 (45%)	0.37 (0.08 to 1.83), P = 0.225
Grade 3	4/48 (8%)	6/163 (4%)	Reference

Footnotes

Abbreviations: CI: confidence interval; P: P value; SUDEP: Sudden Unexpected Death in Epilepsy

a. Odds ratios calculated from a multivariable logistic regression model with grade of supervision corrected for epilepsy severity (number of nocturnal convulsive seizures).

7 Within-group changes from baseline to 6 months in depression, anxiety and quality of life in Radhakrishnan 2018

Outcome (measure)	Group	N	Pre-test score (Mean (95% CI))	Post-test score (Mean (95% CI))	P value
Depression (PHQ-9)	SUDEP information	116	2.99 (2.38 to 3.59)	2.70 (2.14 to 3.26)	0.105
	Control	106	3.17 (2.53 to 3.81)	2.82 (2.24 to 3.40)	0.080
Anxiety (HAM-A)	SUDEP information	116	7.19 (6.16 to 8.21)	6.68 (5.71 to 7.65)	0.119
	Control	106	6.76 (5.88 to 7.64)	6.21 (5.31 to 7.11)	0.387
Quality of life (QOLIE-31)[a]	SUDEP information	111	68.06 (65.35 to 70.77)	68.05 (65.70 to 70.40)	0.991
	Control	104	69.97 (67.59 to 72.34)	68.19 (65.85 to 70.53)	0.161

Footnotes

a. Results were not reported for the 7 participants (5 in the SUDEP information group and 2 in the control group who completed the QOLIE-AD-48)

CI: Confidence interval; HAM-A: Hamilton Anxiety Rating Scale; PHQ-9: Patient Health Questionnaire; QOLIE-31: Quality of Life in Epilepsy-31; QOLIE-AD-48: Quality of life in Epilepsy for Adolescents; SUDEP: Sudden Unexpected Death in Epilepsy

References to studies

Included studies

Langan 2005

[CRSSTD: 5479618]

Langan Y, Nashef L, Sander JW. Case-control study of SUDEP. Neurology 2005;64(7):1131-3. [CRSREF: 5479619; PubMed: 15824334]

Radhakrishnan 2018

[CRSSTD: 13184310]

Radhakrishnan DM, Ramanujam B, Srivastava P, Dash D, Tripathi M. Effect of providing sudden unexpected death in epilepsy (SUDEP) information to persons with epilepsy (PWE) and their caregivers-Experience from a tertiary care hospital. Acta Neurologica Scandinavica 2018;138(5):417-24. [CRSREF: 13184311; DOI: 10.1111/ane.12994; PubMed: 29984404]

Shankar 2016

[CRSSTD: 13184312]

Shankar R, Walker M, McLean B, Laugharne R, Ferrand F, Hanna J, et al. Steps to prevent SUDEP: the validity of risk factors in the SUDEP and seizure safety checklist: a case control study. Journal of Neurology 2016;236(9):1840-6. [CRSREF: 13184313; DOI: 10.1007/s00415-016-8203-3; PubMed: 27334909]

van der Lende 2018

[CRSSTD: 13184314]

van der Lende M, Hesdorffer DC, Sander JW, Thijs RD. Nocturnal supervision and SUDEP risk at different epilepsy care settings. Neurology 2018;91(16):e1508-e18. [CRSREF: 13184315; DOI: 10.1212/WNL.0000000000006356; PubMed: 30242018]

Excluded studies

Almeida 2010

[CRSSTD: 5479620]

Almeida AG, Nunes ML, Palmini ALF, Costa JC. Incidence of SUDEP in a cohort of patients with refractory epilepsy: the role of surgery and lesion localization. Arquivos de Neuro-Psiquiatria 2010;68(6):898-902. [CRSREF: 5479621]

Annegers 1998

[CRSSTD: 5479622]

Annegers JF, Coan SP, Hauser WA, Leestma J, Duffell W, Tarver B. Epilepsy, vagal nerve stimulation by the NCP system, mortality, and sudden, unexpected, unexplained death. Epilepsia 1998;39(2):206-12. [CRSREF: 5479623]

Annegers 2000

[CRSSTD: 5479624]

Annegers JF, Coan SP, Hauser WA, Leestma J. Epilepsy, vagal nerve stimulation by the NCP system, all-cause mortality, and sudden, unexpected, unexplained death. Epilepsia 2000;41(5):549-53. [CRSREF: 5479625]

Asadi-Pooya 2009

[CRSSTD: 13184316]

Asadi-Pooya AA, Sperling MR. Clinical features of sudden unexpected death in epilepsy. Journal of Clinical Neurophysiology 2009;26(5):297-301. [CRSREF: 13184317]

Bateman 2010

[CRSSTD: 5479626]

Bateman LM, Li CS, Lin TC, Seyal M. Serotonin reuptake inhibitors are associated with reduced severity of ictal hypoxemia in medically refractory partial epilepsy. Epilepsia 2010;51(10):2211-4. [CRSREF: 5479627]

Beniczky 2013

[CRSSTD: 5479628]

Beniczky S, Polster T, Kjaer TW, Hjalgrim H. Detection of generalized tonic-clonic seizures by a wireless wrist accelerometer: a prospective, multicenter study. Epilepsia 2013;54(4):e58-61. [CRSREF: 5479629]

DeGiorgio 2008

[CRSSTD: 5479630]

DeGiorgio CM, Miller PR, Meymi SK. Do N-3 fatty acids improve risk factors associated with sudden death in epilepsy (SUDEP)? A pilot randomized crossover trial. Epilepsia 2008;49(Suppl 7):76, Abstract no: 1.176. [CRSREF: 5479631]

DeGiorgio 2019

[CRSSTD: 13184318]

DeGiorgio CM, Curtis A, Hertling D, Moseley BD. Sudden unexpected death in epilepsy: risk factors, biomarkers, and prevention. Acta Neurologica Scandinavica 2019;139(3):220-30. [CRSREF: 13184319; DOI: 10.1111/ane.13049; PubMed: 30443951]

Devinsky 2018

[CRSSTD: 13184320]

Devinsky O, Friedman D, Besag FMC. Nocturnal monitoring in epilepsy: Evidence mounts. Neurology 2018; 91(16):731-2. [CRSREF: 13184321]

Fisher 2010

[CRSSTD: 5479632]

Fisher R, Salanova V, Witt T, Worth R, Henry T, Gross R, et al. Electrical stimulation of the anterior nucleus of thalamus for treatment of refractory epilepsy. Epilepsia 2010;51(5):899-908. [CRSREF: 5479633; DOI: 10.1111/j.1528-1167.2010.02536.x; PubMed: 20331461]

Kang 2017

[CRSSTD: 13184322]

Kang JY, Rabiei AH, Myint L, Nei M. Equivocal significance of post-ictal generalized EEG suppression as a marker of SUDEP risk. Seizure 2017;48:28-32. [CRSREF: 13184323]

Narechania 2013

[CRSSTD: 5479634]

Narechania AP, Garic II, Sen-Gupta I, Macken MP, Gerard EE, Schuele SU. Assessment of a quasi-piezoelectric mattress monitor as a detection system for generalized convulsions. Epilepsy & Behavior 2013;28(2):172-6. [CRSREF: 5479635]

NCT00101933

[CRSSTD: 5479636]

NCT00101933. SANTE - Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy. http://ClinicalTrials.gov/show/NCT00101933 (accessed 10 December 2015). [CRSREF: 5479637]

NCT00736424

[CRSSTD: 13184324]

NCT00736424. Brain stimulation for epilepsy long term follow-up (SUDEP). http://clinicaltrials.gov/show/NCT00736424. [CRSREF: 13184325]

NCT00986310

[CRSSTD: 5479638]

NCT00986310. Efficacy of fluoxetine in reducing ictal hypoventilation in patients with partial epilepsy. http://clinicaltrials.gov/show/NCT00986310 (accessed 10 December 2015). [CRSREF: 5479639]

Nilsson 2001

[CRSSTD: 5479640]

Nilsson L, Bergman U, Diwan V, Farahmand BY, Persson PG, Tomson T. Antiepileptic drug therapy and its management in sudden unexpected death in epilepsy: a case-control study. Epilepsia 2001;42(5):667-73. [CRSREF: 5479641]

Purnell 2018

[CRSSTD: 13184326]

Purnell BS, Thijs RD, Buchanan GF. Dead in the Night: Sleep-Wake and Time-Of-Day Influences on Sudden Unexpected Death in Epilepsy. Frontiers in neurology 2018;9:1079. [CRSREF: 13184327; DOI: 10.3389/fneur.2018.01079; PubMed: 30619039]

Ryvlin 2011

[CRSSTD: 5479642]

Ryvlin P, Cucherat M, Rheims S. 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 Neurology 2011;10(11):961-8. [CRSREF: 5479643]

Ryvlin 2018a

[CRSSTD: 13184328]

Ryvlin P, So EL, Gordon CM, Hesdorffer DC, Sperling MR, Devinsky O, et al. Long-term surveillance of SUDEP in drug-resistant epilepsy patients treated with VNS therapy. Epilepsia 2018;59(3):562-72. [CRSREF: 13184329]

Ryvlin 2018b

[CRSSTD: 13184330]

Ryvlin P, Ciumas C, Wisniewski I, Beniczky S. Wearable devices for sudden unexpected death in epilepsy prevention. Epilepsia 2018;59(Suppl1):61-6. [CRSREF: 13184331]

Schachter 2006

[CRSSTD: 13184332]

Schachter SC. Therapeutic effects of vagus nerve stimulation in epilepsy and implications for sudden unexpected death in epilepsy. Clinical Autonomic Research 2006;16(1):29-32. [CRSREF: 13184333]

Schmuely 2016

[CRSSTD: 13184334]

Shmuely S, Surges R, Sander JW, Thijs RD. Prone sleeping and SUDEP risk: the dynamics of body positions in nonfatal convulsive seizures. Epilepsy & Behavior 2016;62:176-9. [CRSREF: 13184335; DOI: 10.1016/j.yebeh.2016.06.017; PubMed: 27490904]

Scorza 2011

[CRSSTD: 13184336]

Scorza FA, Cysneiros RM, de Albuquerque M, Scattolini M, Arida RM. Sudden unexpected death in epilepsy: an important concern. Clinics (Sao Paulo, Brazil) 2011;66(Suppl 1):65-9. [CRSREF: 13184337; DOI: 10.1590/s1807-59322011001300008; PubMed: 21779724]

Seyal 2013

[CRSSTD: 5479644]

Seyal M, Bateman LM, Li CS. Impact of peri-ictal interventions on respiratory dysfunction, postictal EEG suppression, and postictal immobility. Epilepsia 2013;54(2):377-82. [CRSREF: 5479645]

Seymour 2012

[CRSSTD: 5479646]

Seymour N, Granbichler CA, Polkey CE, Nashef L. Mortality after temporal lobe epilepsy surgery. Epilepsia 2012; 53(2):267-71. [CRSREF: 5479647]

Sveinsson 2018

[CRSSTD: 13184338]

Sveinsson O, Andersson T, Carlsson S, Tomson T. Circumstances of SUDEP: a nationwide population-based case series. Epilepsia 2018;59(5):1074-82. [CRSREF: 13184339]

Terra 2012

[CRSSTD: 13184340]

Terra VC, Sakamoto AC, Machado HR, Martins LD, Cavalheiro EA, Arida RM, et al. Do pets reduce the likelihood of

sudden unexplained death in epilepsy? Seizure 2012;21(8):649-51. [CRSREF: 13184341]

Van Poppel 2013

[CRSSTD: 5479648]

Van Poppel K, Fulton SP, McGregor A, Ellis M, Patters A, Wheless J. Prospective study of the Emfit movement monitor. Journal of Child Neurology 2013;28(11):1434-6. [CRSREF: 5479649]

Verma 2015

[CRSSTD: 13184342]

Verma A, Kumar A. Sudden unexpected death in epilepsy: some approaches to prevent it. Journal of neuropsychiatry and clinical neurosciences 2015;27(1):e28-31. [CRSREF: 13184343; DOI: 10.1176/appi.neuropsych.13120366; PubMed: 25716492]

Studies awaiting classification

Ongoing studies

Other references

Additional references

ACROBAT-NRSI 2014

Sterne JAC, Higgins JPT, Reeves BC on behalf of the development group for ACROBAT-NRSI. A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NRSI), Version 1.0.0, 24 September 2014. Available from www.riskofbias.info (accessed 5 January 2015).

Dasheiff 1991

Dasheiff RM. Sudden unexpected death in epilepsy: a series from an epilepsy surgery program and speculation on the relationship to sudden cardiac death. Journal of Clinical Neurophysiology 1991;8(2):216-22.

Devinsky 2012

Devinsky O. Sudden, unexpected death in epilepsy. New England Journal of Medicine 2012;365(19):1801-11.

Favale 1995

Favale E, Rubino V, Mainardi P, Lunardi G, Albano C. Anticonvulsant effect of fluoxetine in humans. Neurology 1995;45(10):1926-7.

Favale 2003

Favale E, Audenino D, Cocito L, Albano C. The anticonvulsant effect of citalopram as an indirect evidence of serotonergic impairment in human epileptogenesis. Seizure 2003;12(5):316-8.

Guyatt 2008

Guyatt GH, Oxman AD, Vist G, Kunz R, Flack-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336(7650):924-6.

Harden 2017

Harden C, Tomson T, Gloss D, Buchhalter J, Cross JH, Donner E, et al. Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors: report of the guideline development, dissemination, and implementation subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 2017;88(17):1674-80. [DOI: 10.1212/WNL.0000000000003685; PubMed: 28438841]

Hesdorffer 2011

Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, Langan Y, et al. Combined analysis of risk factors for SUDEP. Epilepsia 2011;52(6):1150-9.

Hesdorffer 2012

Hesdorffer DC, Tomson T, Benn E, Sander JW, Nilsson L, Langan Y, et al. Do antiepileptic drugs or generalized tonic-clonic seizure frequency increase SUDEP risk? A combined analysis. Epilepsia 2012;53(2):249-52.

Higgins 2011

Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928. [DOI: 10.1136/bmj.d5928; PubMed: 22008217]

Kirkham 2010

Kirkham JJ, Swan KM, Altman DG, Gamble C, Dodd S, Smyth R, et al. The impact of outcome reporting bias in randomised controlled trials on a cohort of systematic reviews. BMJ 2010;340:c365. [DOI: 10.1136/bmj.c365]

Kloster 1999

Kloster R, Engelskjøn T. Sudden unexpected death in epilepsy (SUDEP): a clinical perspective and a search for risk factors. Journal of Neurology, Neurosurgery, and Psychiatry 1999;67(4):439-44.

Langan 2000

Langan Y, Nashef L, Sander JW. Sudden unexpected death in epilepsy: a series of witnessed deaths. Journal of Neurology, Neurosurgery, and Psychiatry 2000;68(2):211-3.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from handbook.cochrane.org/.

Morton 2006

Morton B, Richardson A, Duncan S. Sudden unexpected death in epilepsy (SUDEP): don't ask, don't tell? Journal of Neurology, Neurosurgery, and Psychiatry 2006;77(2):199-202.

Nashef 2009

Nashef L, Ryvlin P. Sudden unexpected death in epilepsy (SUDEP): update and reflections. Neurologic Clinics 2009;27(4):1063-74.

NICE 2012

National Institute of Clinical Excellence. Epilepsies: diagnosis and management. www.nice.org.uk/guidance/cg137 (accessed prior to 4 March 2020).

Ryvlin 2006

Ryvlin P, Montavont A, Kahane P. Sudden unexpected death in epilepsy: from mechanisms to prevention. Current Opinion in Neurology 2006;19(2):194-9.

Ryvlin 2013a

Ryvlin P, Nashef L, Lhatoo SD, Bateman LM, Bird J, Bleasel A, et al. Incidence and mechanisms of cardiorespiratory arrests in epilepsy monitoring units (MORTEMUS): a retrospective study. Lancet Neurology 2013;12(10):966-77.

Ryvlin 2013b

Ryvlin P, Nashef L, Tomson T. Prevention of sudden unexpected death in epilepsy: a realistic goal? Epilepsia 2013;54(Suppl 2):23-8.

Schuele 2010

Schuele SU, Bermeo AC, Alexopoulos AV, Burgess RC. Anoxia-ischemia: a mechanism of seizure termination in ictal asystole. Epilepsia 2010;51(1):170-3.

Shorvon 2011

Shorvon S, Tomson T. Sudden unexpected death in epilepsy. Lancet 2011;378(9808):2028-38.

SIGN 2015

Scottish Intercollegiate Guidelines Network. Diagnosis and management of epilepsy in adults: a national clinical guideline. SIGN guideline 143. www.sign.ac.uk/sign-143-diagnosis-and-management-of-epilepsy-in-adults (accessed prior to 4 March 2020.

Specchio 2004

Specchio LM, Iudice A, Specchio N, La Neve A, Spinelli A, Galli R, et al. Citalopram as treatment of depression in patients with epilepsy. Clinical Neuropharmacology 2004;27(3):133-6.

Sterne 2016

Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919. [DOI: 10.1136/bmj.i4919; PubMed: 27733354]

Tonberg 2015

Tonberg A, Harden J, McLellan A, Duncan S. A qualitative study of the reactions of young adults with epilepsy to SUDEP disclosure, perceptions of risks, views on the timing of disclosure, and behavioural change. Epilepsy & Behavior 2015;42:98-106. [DOI: 10.1016/j.yebeh.2014.11.018; PubMed: 25506792]

Tu 2011

Tu E, Bagnall RD, Duflou J, Semsarian C. Post-mortem review and genetic analysis of sudden unexpected death in epilepsy (SUDEP) cases. Brain Pathology 2011;21(2):201-8.

Uteshev 2010

Uteshev VV, Tupal S, Mhaskar Y, Faingold CL. Abnormal serotonin receptor expression in DBA/2 mice associated

with susceptibility to sudden death due to respiratory arrest. Epilepsy Research 2010;88(2-3):183-8.

Venit 2004

Venit EL, Shepard BD, Seyfried TN. Oxygenation prevents sudden death in seizure-prone mice. Epilepsia 2004; 45(8):993-6.

Other published versions of this review

Maguire 2015

Maguire MJ, Jackson CF, Marson AG, Nolan SJ. Treatments for the prevention of Sudden Unexpected Death in Epilepsy (SUDEP). Cochrane Database of Systematic Reviews 2015, Issue 7. Art. No.: CD011792 DOI: 10.1002/14651858.CD011792.

Maguire 2016

Maguire MJ, Jackson CF, Marson AG, Nevitt SJ. Treatments for the prevention of Sudden Unexpected Death in Epilepsy (SUDEP). Cochrane Database of Systematic Reviews 2016, Issue 7. Art. No.: CD011792 DOI: 10.1002/14651858.CD011792.pub2.

Classification pending references

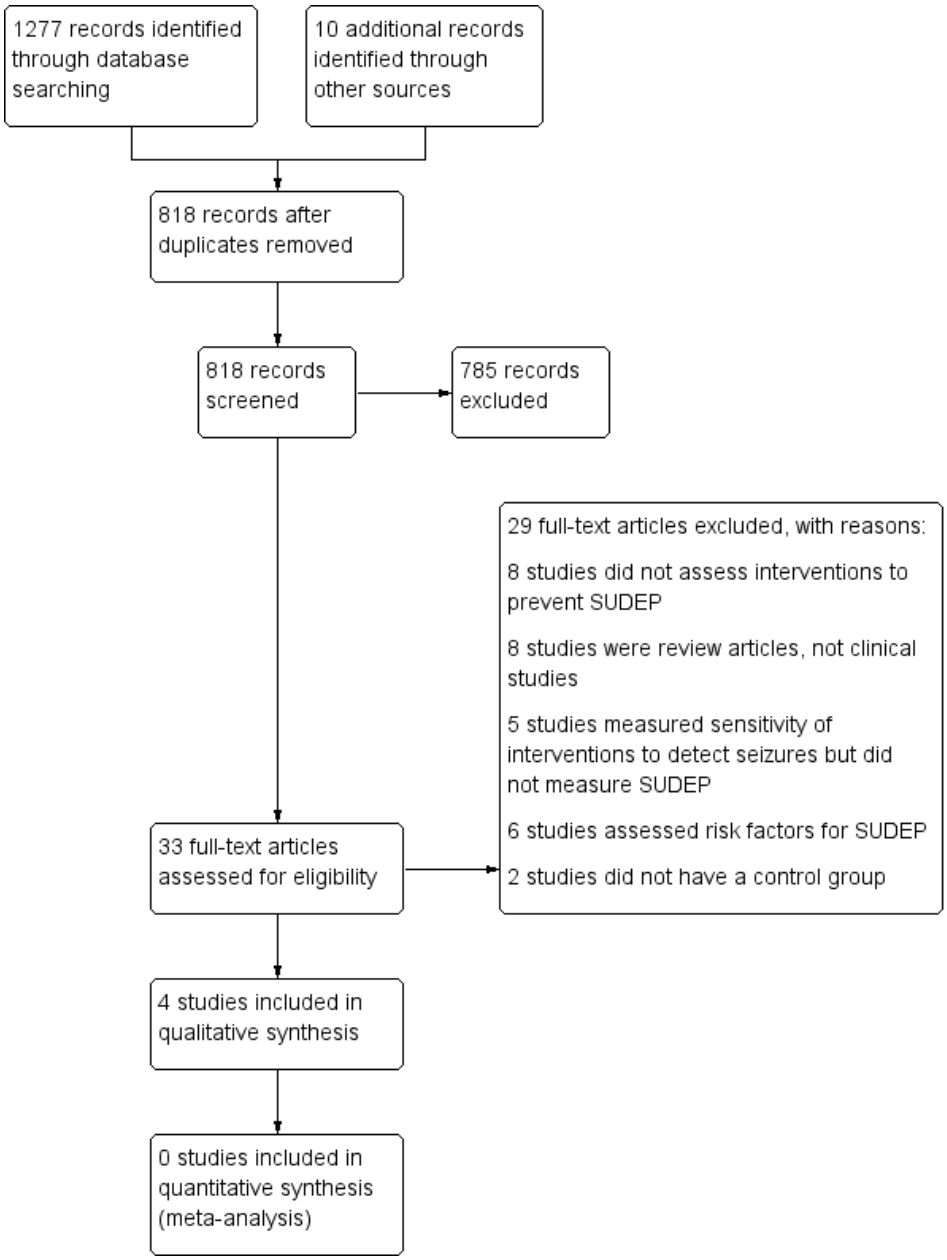
Data and analyses

1 Use of interventions compared to no interventions to prevent SUDEP

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 Nocturnal supervision compared to no supervision	1		Odds Ratio(M-H, Fixed, 95% CI)	No totals
1.2 Nocturnal supervision compared to no supervision (odds ratio only available)	1		Odds Ratio(IV, Fixed, 95% CI)	No totals
1.3 Additional nocturnal supervision compared to no additional nocturnal supervision	1		Odds Ratio(M-H, Fixed, 95% CI)	No totals
1.4 Special precautions compared to no special precautions	1		Odds Ratio(M-H, Fixed, 95% CI)	No totals

Figures

Figure 1



Caption

Study flow diagram.

Sources of support

Internal sources

- No sources of support provided

External sources

- National Institute for Health Research (NIHR), UK

Feedback

Appendices

1 CRS Web search strategy

1. SUDEP AND INSEGMENT
2. MeSH DESCRIPTOR Death, Sudden Explode All AND INSEGMENT
3. (sudden or unexp*) NEAR4 death AND INSEGMENT
4. #2 OR #3
5. MESH DESCRIPTOR Epilepsy EXPLODE ALL AND INSEGMENT
6. MESH DESCRIPTOR Seizures EXPLODE ALL AND INSEGMENT

7. (epilep* OR seizure* OR convuls*):AB,KW,MC,MH,TI AND INSEGMENT

8. #5 OR #6 OR #7 AND INSEGMENT

9. #4 AND #8

10. #1 OR #9

11. SUDEP AND CENTRAL:TARGET

12. MeSH DESCRIPTOR Death, Sudden Explode All AND CENTRAL:TARGET

13. (sudden or unexp*) NEAR4 death AND CENTRAL:TARGET

14. #12 OR #13 AND CENTRAL:TARGET

15. MESH DESCRIPTOR Epilepsy EXPLODE ALL AND CENTRAL:TARGET

16. MESH DESCRIPTOR Seizures EXPLODE ALL AND CENTRAL:TARGET

17. (epilep* OR seizure* OR convuls*):AB,KW,MC,MH,TI AND CENTRAL:TARGET

18. #15 OR #16 OR #17 AND CENTRAL:TARGET

19. #14 AND #18 AND CENTRAL:TARGET

20. #11 OR #19 AND CENTRAL:TARGET

21. #10 OR #20

2 MEDLINE search strategy

We have based this search strategy on the Cochrane Highly Sensitive Search Strategy for identifying randomised trials (Lefebvre 2011).

1. SUDEP.tw.

2. exp Death, Sudden/

3. ((sudden or unexp$) adj4 death).tw.

4. 2 or 3

5. exp Epilepsy/ or epilep$.tw.

6. exp Seizures/

7. (seizure$ or convuls$).ti.

8. 5 or 6 or 7

9. exp *Pre-Eclampsia/ or exp *Eclampsia/

10. 8 not 9

11. 1 or (4 and 10)

12. (randomized controlled trial or controlled clinical trial or pragmatic clinical trial).pt. or (randomi?ed or placebo or randomly).ab.

13. clinical trials as topic.sh.

14. trial.ti.

15. 12 or 13 or 14

16. (clinical trial or clinical trial phase i or clinical trial phase ii or clinical trial phase iii or clinical trial phase iv or comparative study or evaluation studies or multicenter study or observational study or validation studies).pt.

17. ((clinical or comparative or controlled or evaluation or multicenter or multi-center or multicentre or multi-centre or validation) adj3 (study or studies or trial?)).tw,hw.

18. epidemiologic studies/ or exp case-control studies/ or exp cohort studies/ or exp controlled before-after studies/ or exp cross-sectional studies/ or exp historically controlled study/ or exp interrupted time series analysis/

19. (cohort$ or (case$ adj3 (comparison$ or control$ or series))).tw,hw.

20. epidemiologic methods/

21. limit 20 to yr=1966-1989

22. (("before and after" or "before-and-after" or case$ or cross?section$ or "cross section$" or "follow up" or "follow-up" or longitudinal or observation$ or prospective or "record-linkage" or "record linkage" or retrospective or "time-series" or "time series") adj2 (analy$ or investigat$ or method or procedure or study or studies or trial?)).tw,hw.

23. ("quasi-experiment$" or quasiexperiment$ or "quasi experiment$" or "quasi random$" or "quasi-random$" or quasirandom$ or "quasi control$" or "quasi-control$" or quasicontrol$).ti,ab,hw.

24. (time points adj3 (over or multiple or three or four or five or six or seven or eight or nine or ten or eleven or twelve or month$ or hour? or day? or "more than")).ab.

25. (control adj3 (area or cohort? or compare? or condition or design or group? or intervention? or participant? or study)).ab. not (controlled clinical trial or randomized controlled trial).pt.

26. (control year? or experimental year? or control period? or experimental period?).ti,ab.

27. ((strategy or strategies) adj2 (improv$ or education$)).ti,ab.

28. ((single or doubl$ or tripl$ or treb$) adj3 (blind$ or mask$)).tw.

29. ("4 arm" or "four arm").tw,hw.

30. 16 or 17 or 18 or 19 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29

31. 15 or 30

32. exp animals/ not humans.sh.

33. 31 not 32

34. 33 not case reports.pt.

35. 11 and 34

36. remove duplicates from 35

3 SCOPUS search strategy

((((TITLE-ABS-KEY(SUDEP OR "Sudden Unexplained Death in Epilepsy" OR "Sudden Unexpected Death in Epilepsy")) OR ((TITLE-ABS-KEY(death W/4 (sudden OR unexp*))) AND ((TITLE-ABS-KEY(epilep* OR "infantile spasm" OR "ring chromosome 20" OR "R20" OR "myoclonic encephalopathy" OR "pyridoxine dependency") OR (TITLE-ABS-KEY(syndrome) W/2 (aicardi OR angelman OR doose OR dravet OR janz OR jeavons OR "landau kleffner" OR "lennox gastaut" OR ohtahara OR panayiotopoulos OR rasmussen OR rett OR "sturge weber" OR tassinari OR "unverricht lundborg" OR west)) OR TITLE(seizure OR convuls*) OR (TITLE-ABS-KEY(lafora*) W/4 (disease OR epilep*) AND NOT (TITLE(dog OR canine) OR INDEXTERMS(dog OR canine)))) AND NOT (TITLE(*eclampsia) OR INDEXTERMS(*eclampsia))))) AND ((TITLE-ABS((randomiz* OR randomis* OR controlled OR placebo OR blind* OR unblind* OR "parallel group" OR crossover OR "cross over" OR cluster OR "head to head") W/4 (analy* OR investigat* OR method OR procedure OR study OR studies OR trial))) OR (((TITLE-ABS(("before and after" OR cohort OR comparative OR "cross section*" OR "follow up" OR longitudinal OR multicenter OR observation* OR prospective OR quasicontrol* OR "quasi control*" OR quasiexperiment* or "quasi experiment*" OR quasirandom* OR "quasi random*" OR "record linkage" OR retrospective OR "time series") W/4 (analy* OR investigat* OR method OR procedure OR study OR studies OR trial))) OR (TITLE-ABS(case* W/3 (comparison* OR control* OR series))) OR (TITLE-ABS((clinical OR epidemiologic OR evaluation OR validation) PRE/3 (study OR studies OR trial))) OR (ABS("time points" W/3 (over OR multiple OR three OR four OR five OR six OR seven OR eight OR nine OR ten OR eleven OR twelve OR month OR hour OR day OR "more than"))) OR (ABS(control W/3 (area OR cohort OR compare* OR condition OR design OR group OR intervention OR participant OR study))) OR (TITLE-ABS("control year" OR "experimental year" OR "control period" OR "experimental period")) OR (TITLE-ABS((strategy OR strategies) W/2 (improv* OR education*)))) OR (TITLE-ABS-KEY((single OR doubl* OR tripl* OR treb*) PRE/3 (blind* OR mask*))) OR (TITLE-ABS-KEY("4 arm" OR "four arm"))))) AND NOT (TITLE(animal* OR mouse OR mice OR rat OR dog OR canine) AND NOT TITLE(human* OR patient OR child* OR infant* OR adolescen* OR adult OR elderly OR man OR men OR male OR wom?n OR female))) AND NOT (TITLE(case PRE/0 (report OR study OR studies)))

4 PsycINFO search strategy

S22 S6 AND S21

S21 S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20

S20 "4 arm" OR "four arm"

S19 (single OR doubl* OR tripl* OR treb*) W3 (blind* OR mask*)

S18 AB ((strategy OR strategies) W2 (improv* OR education*))

S17 TI ((strategy OR strategies) W2 (improv* OR education*))

S16 AB ("control year" OR "experimental year" OR "control period" OR "experimental period")

S15 TI ("control year" OR "experimental year" OR "control period" OR "experimental period")

S14 AB (control W3 (area OR cohort OR compare* OR condition OR design OR group OR intervention OR participant OR study))

S13 AB ("time points" W3 (over OR multiple OR three OR four OR five OR six OR seven OR eight OR nine OR ten OR eleven OR twelve OR month OR hour OR day OR "more than"))

S12 AB ((clinical OR epidemiologic OR evaluation OR validation) W2 (study OR studies OR trial))

S11 TI ((clinical OR epidemiologic OR evaluation OR validation) W2 (study OR studies OR trial))

S10 TI (case* W3 (comparison* OR control* OR series)) OR AB (case* W3 (comparison* OR control* OR series))

S9 AB (("before and after" OR cohort OR comparative OR controlled OR "cross section*" OR "follow up" OR longitudinal OR multicenter OR observation* OR prospective OR quasicontrol* OR quasi-control* OR quasiexperiment* or quasi-experiment* OR quasirandom* OR "record linkage" OR retrospective OR "time series") W3 (analy* OR investigat* OR method OR procedure OR study OR studies OR trial))

S8 TI (("before and after" OR cohort OR comparative OR controlled OR "cross section*" OR "follow up" OR longitudinal OR multicenter OR observation* OR prospective OR quasicontrol* OR quasi-control* OR quasiexperiment* or quasi-experiment* OR quasirandom* OR "record linkage" OR retrospective OR "time series") W3 (analy* OR investigat* OR method OR procedure OR study OR studies OR trial))

S7 TI ((randomiz* OR randomis* OR controlled OR placebo OR blind* OR unblind* OR "parallel group" OR crossover OR cross-over OR cluster OR "head to head") N2 (analy* OR method OR procedure OR study OR studies OR trial)) OR AB ((randomiz* OR randomis* OR controlled OR placebo OR blind* OR unblind* OR "parallel group" OR crossover OR cross-over OR cluster OR "head to head") N2 (analy* OR method OR procedure OR study OR studies OR trial))

S6 S1 OR (S2 AND S5)

S5 S3 OR S4

S4 MM "Epilepsy" OR MM "Epileptic Seizures" OR MM "Lennox Gastaut Syndrome" OR MM "Grand Mal Seizures" OR MM "Petit Mal Seizures" OR MM "Status Epilepticus"

S3 epilep* OR seizure*

S2 (sudden or unexp*) N4 death

S1 "Sudden Unexplained Death in Epilepsy" OR "Sudden Unexpected Death in Epilepsy" OR SUDEP

5 CINAHL search strategy

S24 S8 AND S23

S23 S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22

S22 "4 arm" OR "four arm"

S21 (single OR doubl* OR tripl* OR treb*) W3 (blind* OR mask*)

S20 AB ((strategy OR strategies) W2 (improv* OR education*))

S19 TI ((strategy OR strategies) W2 (improv* OR education*))

S18 AB ("control year" OR "experimental year" OR "control period" OR "experimental period")

S17 TI ("control year" OR "experimental year" OR "control period" OR "experimental period")

S16 AB (control W3 (area OR cohort OR compare* OR condition OR design OR group OR intervention OR participant OR study))

S15 AB ("time points" W3 (over OR multiple OR three OR four OR five OR six OR seven OR eight OR nine OR ten OR eleven OR twelve OR month OR hour OR day OR "more than"))

S14 AB ((clinical OR epidemiologic OR evaluation OR validation) W2 (study OR studies OR trial))

S13 TI ((clinical OR epidemiologic OR evaluation OR validation) W2 (study OR studies OR trial))

S12 TI (case* W3 (comparison* OR control* OR series)) OR AB (case* W3 (comparison* OR control* OR series))

S11 AB (("before and after" OR cohort OR comparative OR controlled OR "cross section*" OR "follow up" OR longitudinal OR multicenter OR observation* OR prospective OR quasicontrol* OR quasi-control* OR quasiexperiment* or quasi-experiment* OR quasirandom* OR "record linkage" OR retrospective OR "time series") W3 (analy* OR investigat* OR method OR procedure OR study OR studies OR trial))

S10 TI (("before and after" OR cohort OR comparative OR controlled OR "cross section*" OR "follow up" OR longitudinal OR multicenter OR observation* OR prospective OR quasicontrol* OR quasi-control* OR quasiexperiment* or quasi-experiment* OR quasirandom* OR "record linkage" OR retrospective OR "time series") W3 (analy* OR investigat* OR method OR procedure OR study OR studies OR trial))

S9 TI ((randomiz* OR randomis* OR controlled OR placebo OR blind* OR unblind* OR "parallel group" OR crossover OR cross-over OR cluster OR "head to head") N2 (analy* OR method OR procedure OR study OR studies OR trial)) OR AB ((randomiz* OR randomis* OR controlled OR placebo OR blind* OR unblind* OR "parallel group" OR crossover OR cross-over OR cluster OR "head to head") N2 (analy* OR method OR procedure OR study OR studies OR trial))

S8 S1 OR (S4 AND S7)

S7 S5 OR S6

S6 MM ("Epilepsy+") OR (MM "Seizures")

S5 epilep* OR seizure*

S4 S2 OR S3

S3 (sudden or unexp*) N4 death

S2 (MH "Death, Sudden+")

S1 "Sudden Unexplained Death in Epilepsy" OR "Sudden Unexpected Death in Epilepsy" OR SUDEP

6 ClinicalTrials.gov search strategy

SUDEP OR (death AND (sudden OR unexplained OR unexpected)) | Epilepsy

7 ICTRP search strategy

SUDEP OR sudden AND death AND epilepsy OR unexp* AND death AND epilepsy

8 Signalling questions for the seven 'Risk of bias' domains of the ROBINS-I tool

Bias due to confounding	
1.1 Is there potential for confounding of the effect of intervention in this study? *If N/PN to 1.1: the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered* *If Y/PY to 1.1: determine whether there is a need to assess time-varying confounding*	Y/PY/PN/N
1.2. If Y or PY to 1.1: Was the analysis based on splitting participants' follow up time according to intervention received? *If N/PN to 1.2, answer questions relating to baseline confounding (1.4 to 1.6)* *If Y/PY to 1.2, go to question 1.3.*	Y/PY/PN/N/NI/NA
1.3 Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? *If N/PN to 1.3, answer questions relating to baseline confounding (1.4 to 1.6)* *If Y/PY to 1.3, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)*	Y/PY/PN/N/NI/NA
1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding domains?	Y/PY/PN/N/NI/NA
1.5. If Y or PY to 1.4: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Y/PY/PN/N/NI/NA
1.6. Did the authors control for any post- intervention variables that could have been affected by the intervention?	Y/PY/PN/N/NI/NA
1.7. Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding?	Y/PY/PN/N/NI/NA
1.8. If Y or PY to 1.7: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Y/PY/PN/N/NI/NA
'Risk of bias' judgement	**Low/Moderate/Serious/Critical/NI**
OPTIONAL 1.9: What is the predicted direction of bias due to confounding?	Favours experimental/Favours comparator/Unpredictable
Bias in selection of participants into the study	
2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? *If N/PN to 2.1: go to 2.4*	Y/PY/PN/N/NI

2.2. If Y/PY to 2.1: Were the post- intervention variables that influenced selection likely to be associated with intervention?	Y/PY/PN/N/NI/NA
2.3. If Y/PY to 2.2: Were the postintervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?	Y/PY/PN/N/NI/NA
2.4. Do start of follow-up and start of intervention coincide for most participants?	Y/PY/PN/N/NI
2.5. If Y/PY to 2.2 and 2.3, or N/PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Y/PY/PN/N/NI/NA
'Risk of bias' judgement	**Low/Moderate/Serious/Critical/NI**
OPTIONAL 2.5: What is the predicted direction of bias due to selection of participants into the study?	Favours experimental/Favours comparator/Towards null/Away from null/Unpredictable
Bias in classification of interventions	
3.1 Were intervention groups clearly defined?	Y/PY/PN/N/NI
3.2 Was the information used to define intervention groups recorded at the start of the intervention?	Y/PY/PN/N/NI
3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Y/PY/PN/N/NI
'Risk of bias' judgement	**Low/Moderate/Serious/Critical/NI**
OPTIONAL 3.4: What is the predicted direction of bias due to measurement of outcomes or interventions?	Favours experimental/Favours comparator/Towards null/Away from null/Unpredictable
Bias due to deviations from intended interventions *If your aim for this study is to assess the effect of assignment to intervention, answer questions 4.1 and 4.2* *If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions 4.3 to 4.6*	
4.1. Were there deviations from the intended intervention beyond what would be expected in usual practice?	Y/PY/PN/N/NI
4.2. If Y/PY to 4.1: Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	Y/PY/PN/N/NI/NA
4.3. Were important co-interventions balanced across intervention groups?	Y/PY/PN/N/NI
4.4. Was the intervention implemented successfully for most participants?	Y/PY/PN/N/NI
4.5. Did study participants adhere to the assigned intervention regimen?	Y/PY/PN/N/NI
4.6. If N/PN to 4.3, 4.4 or 4.5: Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Y/PY/PN/N/NI/NA
'Risk of bias' judgement	**Low/Moderate/Serious/Critical/NI**
OPTIONAL 4.5: What is the predicted direction of bias due to departures from the intended interventions?	Favours experimental/Favours comparator/Towards null/Away from null/Unpredictable
Bias due to missing data	

5.1 Were outcome data available for all, or nearly all, participants?	Y/PY/PN/N/NI
5.2 Were participants excluded due to missing data on intervention status?	Y/PY/PN/N/NI
5.3 Were participants excluded due to missing data on other variables needed for the analysis?	Y/PY/PN/N/NI
5.4 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	Y/PY/PN/N/NI/NA
5.5 If PN/N to 5.1, or Y/PY to 5.2 or 5.3: Is there evidence that results were robust to the presence of missing data?	Y/PY/PN/N/NI/NA
'Risk of bias' judgement	**Low/Moderate/Serious/Critical/NI**
OPTIONAL 5.6: What is the predicted direction of bias due to missing data?	Favours experimental/Favours comparator/Towards null/Away from null/Unpredictable
Bias in measurement of outcomes	
6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Y/PY/PN/N/NI
6.2 Were outcome assessors unaware of the intervention received by study participants?	Y/PY/PN/N/NI
6.3 Were the methods of outcome assessment comparable across intervention groups?	Y/PY/PN/N/NI
6.4 Were any systematic errors in measurement of the outcome unrelated to intervention received?	Y/PY/PN/N/NI
'Risk of bias' judgement	**Low/Moderate/Serious/Critical/NI**
OPTIONAL 6.5: What is the predicted direction of bias due to measurement of outcomes?	Favours experimental/Favours comparator/Towards null/Away from null/Unpredictable
Bias in selection of the reported result *Is the reported effect estimate likely to be selected, on the basis of the results, from...*	
7.1. ... multiple outcome measurements within the outcome domain?	Y/PY/PN/N/NI
7.2 ...multiple *analyses* of the intervention-outcome relationship?	Y/PY/PN/N/NI
7.3 ...different subgroups?	Y/PY/PN/N/NI
'Risk of bias' judgement	**Low/Moderate/Serious/Critical/NI**
OPTIONAL 7.4: What is the predicted direction of bias due to selection of the reported result?	Favours experimental/Favours comparator/Towards null/Away from null/Unpredictable
Abbreviations: Y: yes; PY: probably yes; PN: probably no; N: no; NI: no information; NA: not applicable	