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

Maguire MJ, Jackson CF, Marson AG, Nevitt SJ

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[Intervention Review]

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

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ABSTRACT

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 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 refractory 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); 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

We searched the following databases: Cochrane Epilepsy Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL, Issue 11, 2015) via the Cochrane Register of Studies Online (CRSO); MEDLINE (Ovid, 1946 onwards); SCOPUS (1823 onwards); PsycINFO (EBSCOhost, 1887 onwards); CINAHL Plus (EBSCOhost, 1937 onwards); ClinicalTrials.gov; and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP). We used no language restrictions. The date of the last search was 12 November 2015. 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 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: 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 582 records from the databases and search strategies. We found 10 further records by searching other resources (hand-searching). We removed 211 duplicate records and screened 381 records (title and abstract) for inclusion in the review. We excluded 364 records based on the title and abstract and assessed 17 full-text articles. We excluded 15 studies: eight studies did not assess interventions to prevent SUDEP; five studies measured sensitivity of devices to detect GTCS but did not directly measure SUDEP; and two studies assessed risk factors for SUDEP but not interventions for preventing SUDEP. One listed study is awaiting classification.

We included one case-control study at serious risk of bias within a qualitative analysis in this review. This study of 154 cases of SUDEP and 616 controls ascertained a protective effect for the presence of nocturnal supervision (unadjusted odds ratio (OR) 0.34, 95% confidence interval (CI) 0.22 to 0.53) and when a supervising person shared the same bedroom or when special precautions, for example a listening device, were used (unadjusted OR 0.41, 95% CI 0.20 to 0.82). This effect was independent of seizure control. Non-SUDEP deaths; changes to anxiety, depression, and quality of life; and number of hospital attendances were not reported.

Authors' conclusions

We found very low-quality evidence of a preventative effect for nocturnal supervision against 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 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, however exactly why SUDEP occurs is currently unknown. However, 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

The aim of this review was to examine the effectiveness of treatments designed to prevent SUDEP.

Methods

The last search for trials for this review was performed in November 2015. We searched electronic databases and contacted experts in the area to find relevant randomised or non-randomised (observational) studies for the review. Our 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.

Results

Out of 592 records found in our searches, we were able to include one observational study. We found several studies that measured how sensitive devices are at detecting GTCS at night, but these studies did not measure SUDEP and so were not relevant to this review.

The one included study identified 154 people who had experienced SUDEP and then compared them to 616 people with epilepsy who had not experienced SUDEP. The study found that fewer people experienced SUDEP who had a supervising person sharing a bedroom with them or who used special precautions such as regular checking throughout the night or a listening device used than those who did not use these measures of supervision.

This study did not provide any information on number of other deaths not related to SUDEP; changes in anxiety, depression, and quality of life; and number of hospital attendances.

Quality of the evidence

We judged the quality of the evidence from this review to be very low as the only included study was not randomised, and information about supervision measures to prevent SUDEP was not available for 40% of the people with epilepsy who did not experience SUDEP.

Conclusions

We found very limited, low-quality 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.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

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

Patient or population: Cases of SUDEP and matched controls
Settings: Retrospective case-control study
Intervention: Nocturnal supervision or special precautions to prevent SUDEP
Comparison: No intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality 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	See comment	See comment	**OR** 0.34 (95% CI 0.22 to 0.53)	468 (1 study)	⊕◯◯◯ **very low**[1]	109 deaths out of 278 in the no intervention group and 34 deaths out of 190 deaths in the intervention group. Assumed and corresponding risks not calculated due to study design (case-control)
Number of deaths due to SUDEP: Special precautions compared to no special precautions	See comment	See comment	**OR** 0.41 (95% CI 0.20 to 0.82)	331 (1 study)	⊕◯◯◯ **very low**[1]	109 deaths out of 278 in the no intervention group and 11 deaths out of 53 deaths in the intervention group. Assumed and corresponding risks not calculated due to study design (case-control)

Number of other deaths (unrelated to SUDEP)	Not reported	Not reported	NA	NA	NA
Change in mean depression and anxiety scores	Not reported	Not reported	NA	NA	NA
Clinically important change in quality of life	Not reported	Not reported	NA	NA	NA
Number of hospital attendances for seizures	Not reported	Not reported	NA	NA	NA

*The basis for the **assumed risk** is the event rate in the control group. The **corresponding risk** (and its 95% confidence interval) 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; **RR:** risk ratio; **SUDEP:** Sudden Unexpected Death in Epilepsy

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

[1]Quality of the evidence automatically started at 'low' due to observation design of the included study. Downgraded once to 'very low' due to serious risk of bias, mainly due to a large amount of missing data in the control group.

BACKGROUND

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 patients 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 MORTality in Epilepsy Monitoring Unit Study (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). However, there are 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 refractory 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 anti-epileptic 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 hypoxemia 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 proconvulsant. However, naloxone, an opiate receptor antagonist, has not been demonstrated to have a proconvulsant 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

We searched the following databases (search date 12 November 2015).

1. Cochrane Epilepsy Group Specialized Register
2. Cochrane Central Register of Controlled Trials (CENTRAL, Issue 11, 2015) via the Cochrane Register of Studies Online (CRSO)
3. MEDLINE (Ovid, 1946 onwards)
4. SCOPUS (1823 onwards)
5. PsycINFO (EBSCOhost, 1887 onwards)
6. CINAHL Plus (EBSCOhost, 1937 onwards)
7. ClinicalTrials.gov
8. World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)

We have presented the proposed search strategy for MEDLINE is in Appendix 1, which we modified for use with the other databases. 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. 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 prestandardised data extraction form for one included study.

We extracted the following information.

Methods

- Year of publication
- Number of study centres
- Language
- Industry funding

- Study design (RCT, prospective cohort study, case-control study)
- Blinding
- Type of control group (placebo, comparative, no treatment)
- Sample size
- Follow-up period
- Intervention type
- Dose range of drug intervention
- Inclusion and exclusion criteria

Participants

- Age range
- Number of male/female participants
- Duration of epilepsy
- Mean age of onset of epilepsy
- Current number of anti-epileptic drugs (AEDs)
- Epilepsy type (focal, generalised, unclassified)
- Seizure types (GTCS, focal onset seizures)
- Baseline mean depression score or severity
- Baseline mean seizure frequency/month

Outcomes

- Number of participants experiencing each outcome recorded per treatment group
- Number of dropouts

Assessment of risk of bias in included studies

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

Due to the observational design, we assessed risk of bias for non-randomised studies using the ACROBAT-NRSI tool recently developed by members of the Cochrane Bias Methods Group and Cochrane Non-Randomised Studies Methods Group (ACROBAT-NRSI 2014). This tool is an extension of the existing tool for assessing risk of bias in randomised trials (Higgins 2011), and 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 postintervention (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 performed 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 2.

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 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 the single included study. In the event of unit of analysis issues occurring across the included studies in future updates (for example 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 as only a single study was included.

For future updates of the review if we are able to perform meta-analysis, 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 as only a single study was included.

For future updates of the review if we are able to perform meta-analysis, 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 use 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 stratify each comparison by type of intervention to ensure appropriate combination of study data.

Summary of findings and quality of the evidence (GRADE)

We included the following outcomes in a 'Summary of findings' table: number of SUDEP deaths, number of non-SUDEP deaths, depression and anxiety scores, quality of life, and number of hospital attendances, and assessed each outcome using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (Guyatt 2008).

Subgroup analysis and investigation of heterogeneity

For future updates of the review if we are able to perform meta-analysis, 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

For future updates of the review if we are able to perform meta-analysis, 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.

RESULTS

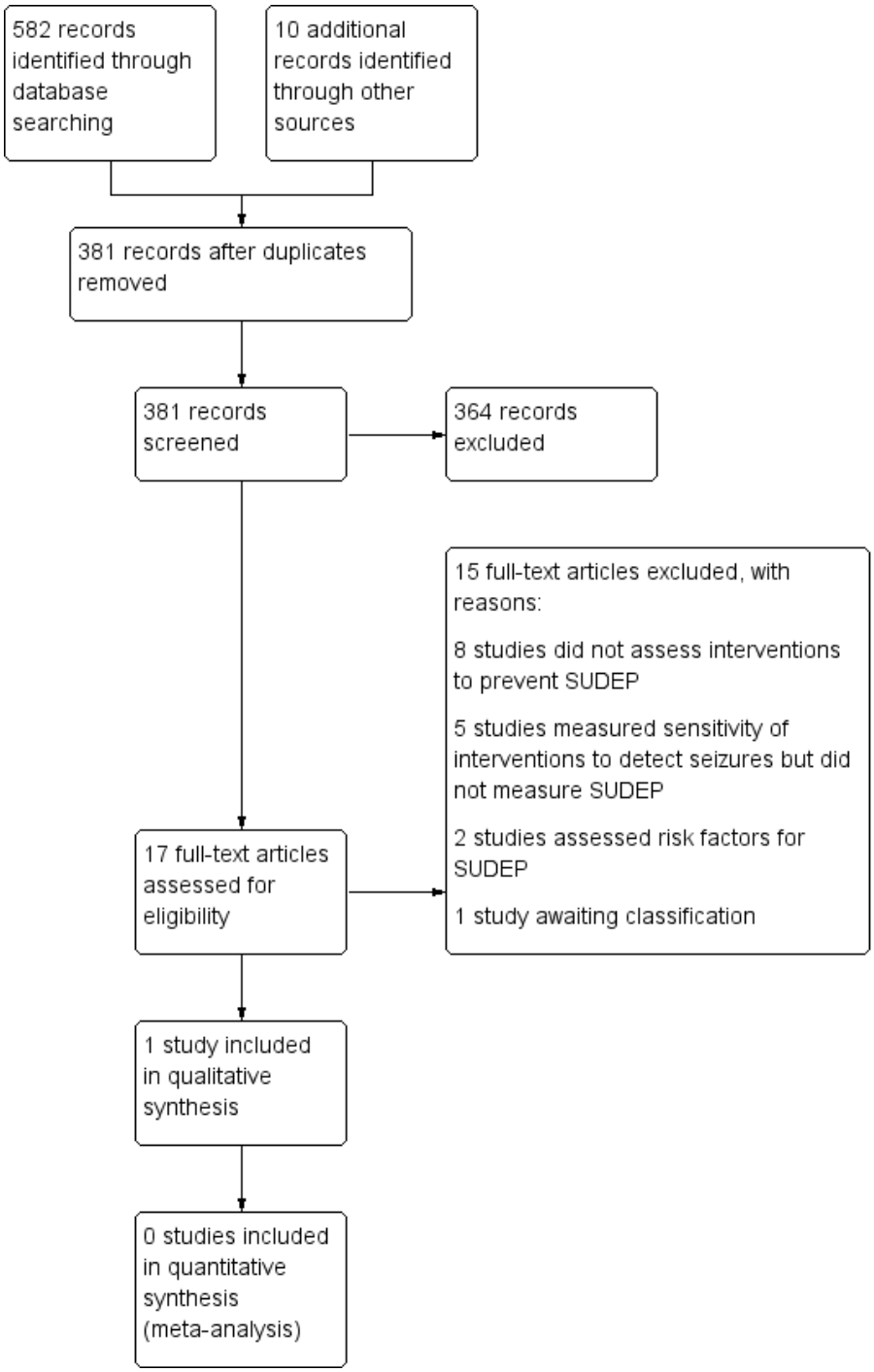
Description of studies

Results of the search

We identified 582 records from the databases and search strategies outlined in Electronic searches. We found 10 further records by searching other resources (handsearching). We removed 211 duplicate records and screened 381 records (title and abstract) for inclusion in the review.

We excluded 364 records based on the title and abstract and assessed 17 full-text articles for inclusion in the review. We excluded 15 studies from the review (see Excluded studies below), listed one study as awaiting classification (see Studies awaiting classification), and included one case-control study (Langan 2005). See Figure 1 for a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) study flow diagram.

Figure 1. Study flow diagram.



Included studies

We identified one case-control study that met the inclusion criteria (Langan 2005).

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.

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. This retrospective study considered other factors that were not relevant to this review; see Characteristics of included studies for details.

The cases included 97 men and 57 women with a mean age of 32 years. Demographic details for controls were not reported.

We listed one study (NCT00736424 2014), available only as a ClinicalTrials.gov registration, as awaiting classification. The study is listed as completed, but no results are available. The aim of the study was to "to collect patient data that may be pooled with other data to estimate the SUDEP rate in people with refractory epilepsy receiving bilateral deep brain stimulation of the anterior nucleus of the thalamus." We hope to make contact with study authors to clarify design and results of this study for future updates of this review.

Excluded studies

We excluded 15 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), 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 assessed risk factors for SUDEP but not interventions for preventing SUDEP (DeGiorgio 2008; Seymour 2012).

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 study (Langan 2005). We rated the study as having an overall serious risk of bias (see Table 1 for 'Risk of bias' summary and Table 2 for responses to signalling questions).

Confounding

We reported the study as having a moderate risk of bias for confounding. 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.

Selection bias

We reported the study as having a low risk of bias for selection. Controls were randomly selected from the eligible population and matched for sex and geographical location.

Bias in measurement of intervention

We reported the study as having a moderate risk of bias in measurement of the intervention. It is possible that intervention status for cases was recorded after outcome, which could be a source of bias.

Bias due to departures from intended interventions

We reported the study as having a moderate risk of bias for departures from intended interventions. 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.

Missing data

We reported the study as having a serious risk of bias for missing data. 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.

Bias in measurement of outcomes

We reported the study as having a low risk of bias for measurement of outcome, since the objective outcome measurement was established before intervention status.

Selective reporting

We reported the study as having a moderate risk of bias for selective reporting, as results of only a single multivariable model were reported, and it is unclear if results would have been different for other multivariable models.

Effects of interventions

See: **Summary of findings for the main comparison** Interventions for compared with no intervention for preventing Sudden Unexpected Death in Epilepsy (SUDEP)
See Summary of findings for the main comparison for a summary of the findings and quality of evidence of the review.

Primary outcome: number of deaths from SUDEP

Data was available for all cases, but only 367 out of 616 (60%) of controls for this outcome.
We found a protective effect for the presence of nocturnal supervision (adjusted odds ratio (OR) 0.40, 95% confidence interval (CI) 0.20 to 0.80) and when a supervising person shared the same bedroom or when special precautions, for example a listening device, were used (adjusted OR 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 nocturnal supervision or special precautions, we calculated unadjusted ORs. We still found a protective effect for both measures in unadjusted analysis: nocturnal supervision (OR 0.34, 95% CI 0.22 to 0.53; Analysis 1.1) and special precautions (OR 0.41, 95% CI 0.20 to 0.82; Analysis 1.2).

Secondary outcomes

Langan 2005 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.

DISCUSSION

Summary of main results

We found one case-control study at serious risk of bias that reported a protective effect for nocturnal supervision against SUDEP (Langan 2005). This protective effect was independent of seizure control, suggesting that nocturnal supervision is not just a surrogate marker of seizure control. 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.
We found no other randomised or non-randomised studies assessing the effectiveness of other interventions in preventing SUDEP in people with epilepsy.

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 unfortunately has not been borne out in the literature and requires much more extensive clinical investigation. We made contact with several commercial companies (Cyberonics Inc, Emfit Ltd, Medtronic, Medpage Ltd, and Epi-Care) manufacturing seizure-monitoring devices in order to obtain any unpublished information relating to this review, but 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.

Quality of the evidence

The evidence we have obtained is limited by being from only a single study with an observational design and an overall serious risk of bias. 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 quality of the limited evidence available for this review to be very low (Summary of findings for the main comparison).

Potential biases in the review process

There is a possible risk of publication bias in this review given that unpublished data was not made available by device companies. It is also possible that despite the exhaustive searches carried out in this review other sources of unpublished data have not been identified. 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 anti-epileptic drugs in the prevention of SUDEP in people with epilepsy.

AUTHORS' CONCLUSIONS

Implications for practice

This review provides very low-quality 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, need to be discussed with carers of people who have frequent uncontrolled nocturnal seizures.

This review has sadly 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 anti-epileptic drugs as an intervention in this review, although a systematic review of placebo-controlled trials of adjunctive anti-epileptic 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 considering further trials of anti-epileptic 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 misleadingly 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 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 anti-epileptic and as a preventative intervention for SUDEP. Three small observational studies have demonstrated an anti-epileptic 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) has recently 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 would provide ample opportunity to collect prospective annual data nationwide linking clinical factors, interventions, and anti-epileptic drugs to overall SUDEP risk so that better-quality and more uniform information can be gathered about how to prevent SUDEP.

(https://www.sudep.org/epilepsy-self-monitor).

ACKNOWLEDGEMENTS

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REFERENCES

References to studies included in this review

Langan 2005 *{published data only}*
Langan Y, Nashef L, Sander JW. Case-control study of SUDEP. *Neurology* 2005;**64**(7):1131–3.

References to studies excluded from this review

Almeida 2010 *{published data only}*
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.

Annegers 1998 *{published data only}*
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.

Annegers 2000 *{published data only}*
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.

Bateman 2010 *{published data only}*
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.

Beniczky 2013 *{published data only}*
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.

DeGiorgio 2008 *{published data only}*
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.

Fisher 2010 *{published data only}*
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**:899–908.

Narechania 2013 *{published data only}*
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.

NCT00101933 *{published data only}*
NCT00101933. SANTE - Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy. http://ClinicalTrials.gov/show/NCT00101933 (accessed 10 December 2015).

NCT00986310 *{published data only}*
NCT00986310. Efficacy of fluoxetine in reducing ictal hypoventilation in patients with partial epilepsy. http://clinicaltrials.gov/show/NCT00986310 (accessed 10 December 2015).

Nilsson 2001 *{published data only}*
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.

Ryvlin 2011 *{published data only}*
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. *The Lancet Neurology* 2011;**10**(11):961–8.

Seyal 2013 *{published data only}*
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.

Seymour 2012 *{published data only}*
Seymour N, Granbichler CA, Polkey CE, Nashef L. Mortality after temporal lobe epilepsy surgery. *Epilepsia* 2012;**53**(2):267–71.

Van Poppel 2013 *{published data only}*
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.

References to studies awaiting assessment

NCT00736424 2014 *{published data only}*
NCT00736424. Brain stimulation for epilepsy long term follow-up (SUDEP). http://clinicaltrials.gov/show/NCT00736424.

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 http://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. *The 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.

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]

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 http://www.cochrane-handbook.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.

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. *The 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. *The Lancet* 2011;**378**(9808):2028–38.

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.

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.

References to 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. [DOI: 10.1002/14651858.CD011792]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

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 was not reported, but it was stated that controls were age matched within 5 years of cases
Interventions	Supervision at night was one 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 anti-epileptic 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 ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Bias due to confounding	Unclear risk	**MODERATE RISK OF BIAS**: 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

Langan 2005 (*Continued*)

Bias in measurement of interventions	Unclear risk	**MODERATE RISK OF BIAS**: It is possible that intervention status for cases was recorded after outcome, 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

SUDEP: Sudden Unexpected Death in Epilepsy
Due to different options for the 'Risk of bias' judgement in the non-randomised studies tool (ACROBAT-NRSI 2014), we have assigned '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 for full quality assessment with signalling questions.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Almeida 2010	Did not assess interventions to prevent SUDEP
Annegers 1998	Did not assess interventions to prevent SUDEP
Annegers 2000	Did not assess interventions to prevent SUDEP
Bateman 2010	Did not assess interventions to prevent SUDEP

(*Continued*)

Beniczky 2013	Measured sensitivity of devices to detect generalised tonic-clonic seizures but did not directly measure SUDEP
DeGiorgio 2008	Assessed risk factors for SUDEP but not interventions for preventing SUDEP
Fisher 2010	Did not assess interventions to prevent SUDEP
Narechania 2013	Measured sensitivity of devices to detect generalised tonic-clonic seizures but did not directly measure SUDEP
NCT00101933	Measured sensitivity of devices to detect generalised tonic-clonic seizures but did not directly measure SUDEP
NCT00986310	Did not assess interventions to prevent SUDEP
Nilsson 2001	Did not assess interventions to prevent SUDEP
Ryvlin 2011	Did not assess interventions to prevent SUDEP
Seyal 2013	Measured sensitivity of devices to detect generalised tonic-clonic seizures but did not directly measure SUDEP
Seymour 2012	Assessed risk factors for SUDEP but not interventions for preventing SUDEP
Van Poppel 2013	Measured sensitivity of devices to detect generalised tonic-clonic seizures but did not directly measure SUDEP

SUDEP: Sudden Unexpected Death in Epilepsy

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT00736424 2014

Methods	Observational case series at 5 sites across the USA and Canada
Participants	People diagnosed with refractory epilepsy
Interventions	Bilateral neuro-stimulation of the anterior nucleus of the thalamus
Outcomes	Rate of SUDEP No other outcome measures provided
Notes	Study listed as completed, no results available

SUDEP: Sudden Unexpected Death in Epilepsy

DATA AND ANALYSES

Comparison 1. Use of interventions compared to no interventions to prevent SUDEP

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nocturnal supervision compared to no supervision	1	468	Odds Ratio (M-H, Fixed, 95% CI)	0.34 [0.22, 0.53]
2 Special precautions compared to no special precautions	1	331	Odds Ratio (M-H, Fixed, 95% CI)	0.41 [0.20, 0.82]

Analysis 1.1. Comparison 1 Use of interventions compared to no interventions to prevent SUDEP, Outcome 1 Nocturnal supervision compared to no supervision.

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

Comparison: 1 Use of interventions compared to no interventions to prevent SUDEP

Outcome: 1 Nocturnal supervision compared to no supervision

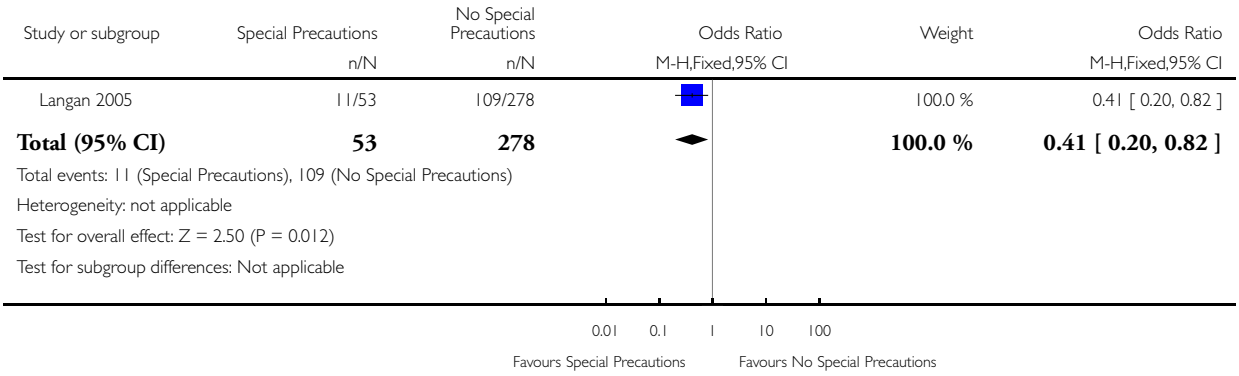
Study or subgroup	Supervision n/N	No supervision n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Langan 2005	34/190	109/278		100.0 %	0.34 [0.22, 0.53]
Total (95% CI)	**190**	**278**		**100.0 %**	**0.34 [0.22, 0.53]**
Total events: 34 (Supervision), 109 (No supervision)					
Heterogeneity: not applicable					
Test for overall effect: Z = 4.81 (P < 0.00001)					
Test for subgroup differences: Not applicable					

Analysis 1.2. Comparison 1 Use of interventions compared to no interventions to prevent SUDEP, Outcome 2 Special precautions compared to no special precautions.

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

Comparison: 1 Use of interventions compared to no interventions to prevent SUDEP

Outcome: 2 Special precautions compared to no special precautions



ADDITIONAL TABLES

Table 1. Guidance for making a single 'Risk of bias' judgement for an outcome based on 'Risk of bias' judgements for the 7 domains

'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

Table 1. Guidance for making a single 'Risk of bias' judgement for an outcome based on 'Risk of bias' judgements for the 7 domains (*Continued*)

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)

Table 2. Responses to ACROBAT-NRSI signalling questions and 'Risk of bias' judgements for Langan 2005 (case-control study)

Question	Signalling question response	Description	Bias due to con
Bias due to confounding			
1.1 Is confounding of the effect of intervention unlikely in this study?	N	Aim of the study was to explore variables that may influence the factors associated with SUDEP. The 'intervention' of interest to us is one of those variables, so confounding is inevitable	
1.4. Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains?	PY	Multivariate 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 avoid adjusting for postintervention variables?	PN	Intervention is given over a period of time, and variables are also measured over a period of time with probable overlap	
'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			**Bias in selection**
For case-control studies: **2.4** Were the controls sampled from the population that gave rise to the cases, or using another method that avoids selection bias?	Y	Controls were randomly sampled from a national database	
'Risk of bias' judgement	**Low**	Random sample of controls used	

Table 2. Responses to ACROBAT-NRSI signalling questions and 'Risk of bias' judgements for Langan 2005 (case-control study) (*Continued*)

Bias in measurement of interventions			**Bias in measure**
3.1 Is intervention status well defined?	Y	Clear whether a participant had any of the listed supervision, but data for the controls missing	
3.2 Was information on intervention status recorded at the time of 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 Was information on intervention status unaffected 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 departures from intended interventions			**Bias due to dep**
4.1. Were the critical co-interventions balanced across intervention groups?	N	Number of AEDs and current use of carbamazepine not balanced across cases and controls	
4.2. Were numbers of switches to other interventions low?	NI	Unclear how long participants had used interventions or whether they had switched between interventions	
4.3. Was implementation failure minor?	NI	No information given but possible that intervention could be disrupted (e.g. person supervised leaves the room) or devices fail	
'Risk of bias' judgement	**Moderate**	Intervention of interest to us was not intended to be the only 'intervention' in the study. Switching therefore may have occurred, and co-interventions may have been present	
Bias due to missing data			**Bias due to mis**
For case-control studies: **5.1** Was outcome status reasonably complete for those in whom it was sought?	Y	Participants chosen based on outcome status	

Table 2. Responses to ACROBAT-NRSI signalling questions and 'Risk of bias' judgements for Langan 2005 (case-control study) (*Continued*)

For case-control studies: **5.2** Were data on intervention status reasonably complete?	N	A lot of missing data for the controls for intervention status
5.3 Are data reasonably complete for other variables in the analysis?	N	Data also missing for controls for other variables
For case-control studies: **5.4 If N or PN to 5.1, 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 N or PN to 5.1, 5.2, or 5.3: Were appropriate statistical methods used to account for 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		**Bias in measure**
For case-control studies: **6.1** Was the definition of case status (and control status, if applicable) based on objective criteria?	Y	Cases were those who had experienced SUDEP, controls had not experienced SUDEP
For case-control studies: **6.2** Was the definition of case status (and control status, if applicable) applied without knowledge of the intervention received?	Y	Cases and controls established first and then variable information including intervention status extracted afterwards
'Risk of bias' judgement	**Low**	Objective outcome measurement established before intervention status
Bias in selection of the reported result		**Bias in selection**
Is the reported effect estimate unlikely to be selected, on the basis of the results, from...		*Is the reported effe of the results, fro*

Table 2. Responses to ACROBAT-NRSI signalling questions and 'Risk of bias' judgements for Langan 2005 (case-control study) (*Continued*)

For case-control studies: **7.1** ...multiple *definitions of the intervention*?	Y	A clear definition of the intervention(s) given for this study
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?	Y	No subgroups reported
'Risk of bias' judgement	**Moderate**	Results for one multivariable model reported, unclear if results would have been different for other multivariable models

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

APPENDICES

Appendix 1. MEDLINE search strategy

We have based this search strategy on the Cochrane Highly Sensitive Search Strategy for identifying randomised trials (Lefebvre 2011).
1. exp Death, Sudden/
2. exp Epilepsy/
3. exp Seizures/
4. (epilep$ or seizure$ or convuls$).tw.
5. 2 or 3 or 4
6. exp *Pre-Eclampsia/ or exp *Eclampsia/
7. 5 not 6
8. 1 and 7
9. (sudden AND unexp* AND death AND epilep*).tw.
10. SUDEP.tw.
11. 8 or 9 or 10
12. (randomized controlled trial or controlled 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. exp animals/ not humans.sh.
17. 15 not 16
18. (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 validation studies).pt.

19. ((clinical or comparative or evaluation or multicenter or multicentre or validation) adj2 (study or studies or trial?)).tw.
20. exp case-control studies/ or exp cohort studies/ or exp cross-sectional studies/
21. (("before and after" or "before-and-after" or case$ or cohort 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 (method or procedure or study or studies or trial?)).tw.
22. 18 or 19 or 20 or 21
23. 22 not case reports.pt.
24. exp animals/ not humans.sh.
25. 23 not 24
26. 17 or 25
27. 11 and 26

Appendix 2. Signalling questions for 7 'Risk of bias' domains of the ACROBAT-NRSI

Bias due to confounding		**Bias due to con**
1.1 Is confounding of the effect of intervention unlikely in this study?	Y / PY / PN / N / NI	
If Y or PY 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 or PY to 1.1, and no further sig*
For cohort-type studies: **1.2. If N or PN to 1.1:** Were participants analysed according to their initial intervention group throughout follow-up?	Y / PY / PN / N / NI / NA	
If Y or PY to 1.2, answer questions 1.4 to 1.6, which relate to baseline confounding		*If Y or PY to 1.2,*
For cohort-type studies: **1.3 If N or PN to 1.2:** Were intervention discontinuations or switches unlikely to be related to factors that are prognostic for the outcome?	Y / PY / PN / N / NI / NA	
If Y or PY to 1.3, answer questions 1.4 to 1.6, which relate to baseline confounding *If N or PN to 1.1 and 1.2 and 1.3, answer questions 1.7 and 1.8, which relate to time-varying confounding*		*If Y or PY to 1.3,* *If N or PN to 1.1* *confounding*
1.4. Did the authors use an appropriate analysis method that adjusted for all the critically important confounding domains?	Y / PY / PN / N / NI / NA	
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?	Y / PY / PN / N / NI / NA	
1.6. Did the authors avoid adjusting for postintervention variables?	Y / PY / PN / N / NI / NA	

(*Continued*)

1.7. Did the authors use an appropriate analysis method that adjusted for all the critically 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 adjusted 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	**Bias in selection**
2.1. Was selection into the study unrelated to intervention or unrelated to outcome?	Y / PY / PN / N / NI
For cohort-type studies: **2.2.** Do start of follow-up and start of intervention coincide for most participants?	Y / PY / PN / N / NI
2.3. If N or PN to 2.1 or 2.2: Were adjustment techniques used that are likely to correct for the presence of selection biases?	Y / PY / PN / N / NI / NA
For case-control studies: **2.4** Were the controls sampled from the population that gave rise to the cases, or using another method that avoids selection bias?	Y / PY / PN / N / NI
'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 measurement of interventions	**Bias in measure**
3.1 Is intervention status well defined?	Y / PY / PN / N / NI
3.2 Was information on intervention status recorded at the time of intervention?	Y / PY / PN / N / NI
3.3 Was information on intervention status unaffected by knowledge of the outcome or risk of the outcome?	Y / PY / PN / N / NI

(*Continued*)

'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 departures from intended interventions	**Bias due to dep**
4.1. Were the critical co-interventions balanced across intervention groups?	Y / PY / PN / N / NI
4.2. Were numbers of switches to other interventions low?	Y / PY / PN / N / NI
4.3. Was implementation failure minor?	Y / PY / PN / N / NI
For cohort-type studies: **4.4. If N or PN to 4,1, 4.2, or 4.3:** Were adjustment techniques used that are likely to correct for these issues?	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	**Bias due to mis**
For cohort-type studies: **5.1** Are outcome data reasonably complete? *For case-control studies:* **5.1** Was outcome status reasonably complete for those in whom it was sought?	Y / PY / PN / N / NI
For cohort-type studies: **5.2** Was intervention status reasonably complete for those in whom it was sought? *For case-control studies:* **5.2** Were data on intervention status reasonably complete?	Y / PY / PN / N / NI
5.3 Are data reasonably complete for other variables in the analysis?	Y / PY / PN / N / NI
For cohort-type studies: **5.4 If N or PN to 5.1, 5.2, or 5.3:** Are the proportion of participants and reasons for missing data similar across interventions? *For case-control studies:*	Y / PY / PN / N / NI / NA

(*Continued*)

5.4 If N or PN to 5.1, 5.2, or 5.3: Are the proportion of participants and reasons for missing data similar across cases and controls?	
5.5 If N or PN to 5.1, 5.2, or 5.3: Were appropriate statistical methods used to account for 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	**Bias in measure**
For cohort-type studies: **6.1** Was the outcome measure objective? *For case-control studies:* **6.1** Was the definition of case status (and control status, if applicable) based on objective criteria?	Y / PY / PN / N / NI
For cohort-type studies: **6.2** Were outcome assessors unaware of the intervention received by study participants? *For case-control studies:* **6.2** Was the definition of case status (and control status, if applicable) applied without knowledge of the intervention received?	Y / PY / PN / N / NI
For cohort-type studies: **6.3** Were the methods of outcome assessment comparable across intervention groups?	Y / PY / PN / N / NI
For cohort-type studies: **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	**Bias in selection**
Is the reported effect estimate unlikely to be selected, on the basis of the results, from...	*Is the reported eff results, from...*

(*Continued*)

For cohort-type studies: **7.1.** ...multiple outcome *measurements* within the outcome domain? *For case-control studies:* **7.1** ...multiple *definitions of the intervention*?	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

Abbreviations: Y
NI: no informat

WHAT'S NEW

Last assessed as up-to-date: 12 November 2015.

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

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.

Cerian F Jackson developed the protocol, screened studies for inclusion, and provided feedback on drafts of the review.

Anthony G Marson supervised the protocol and provided expert feedback on drafts of the review.

Sarah J Nolan 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.

DECLARATIONS OF INTEREST

Melissa J Maguire: none known.

Cerian F Jackson: none known.

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Sarah J Nolan: none known.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There were no differences between the published protocol and the review.

INDEX TERMS

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