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Anticonvulsant therapy for status epilepticus (Review)

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[Intervention Review]

Anticonvulsant therapy for status epilepticus

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A B S T R A C T

Background

Status epilepticus is a medical emergency associated with significant mortality and morbidity that requires immediate and effective treatment.

Objectives

(1) To determine whether a particular anticonvulsant is more effective or safer to use in status epilepticus compared to another and compared to placebo.
(2) To delineate reasons for disagreement in the literature regarding recommended treatment regimens and to highlight areas for future research.

Search methods

For the latest update of this review, the following electronic databases were searched on 15/08/2013: the Cochrane Epilepsy Group's Specialized Register, CENTRAL *The Cochrane Library* July 2013, Issue 7, and MEDLINE (Ovid) 1946 to 15/08/2013.

Selection criteria

Randomised controlled trials of participants with premonitory, early, established or refractory status epilepticus using a truly random or quasi-random allocation of treatments were included.

Data collection and analysis

Two review authors independently selected trials for inclusion, assessed trial quality and extracted data.

Main results

Eighteen studies with 2755 participants were included. Few studies used the same interventions. Intravenous diazepam was better than placebo in reducing the risk of non-cessation of seizures (risk ratio (RR) 0.73, 95% confidence interval (CI) 0.57 to 0.92), requirement for ventilatory support (RR 0.39, 95% CI 0.16 to 0.94), or continuation of status epilepticus requiring use of a different drug or general anaesthesia (RR 0.73, 95% CI 0.57 to 0.92). Intravenous lorazepam was better than placebo for risk of non-cessation of seizures (RR 0.52, 95% CI 0.38 to 0.71) and for risk of continuation of status epilepticus requiring a different drug or general anaesthesia (RR 0.52, 95% CI 0.38 to 0.71). Intravenous lorazepam was better than intravenous diazepam for reducing the risk of non-cessation of seizures (RR 0.64, 95% CI 0.45 to 0.90) and had a lower risk for continuation of status epilepticus requiring a different drug or general anaesthesia (RR 0.63, 95% CI 0.45 to 0.88). Intravenous lorazepam was better than intravenous phenytoin for risk of non-cessation of seizures (RR 0.62, 95% CI 0.45 to 0.86). Diazepam gel was better than placebo gel in reducing the risk of non-cessation of seizures (RR 0.43 95% CI 0.30 to 0.62)

For pre-hospital treatment, intramuscular midazolam is at least as effective as (probably more effective than) intravenous lorazepam in control of seizures (RR1.16, 95% CI 1.06 to 1.27) and frequency of hospitalisation (RR 0.88, 95% CI 0.79 to 0.97) or intensive care admissions (RR 0.79, 95% CI 0.65 to 0.96). It was uncertain whether Intravenous valproate was better than intravenous phenytoin in reducing risk of non-cessation of seizures (RR 0.75, 95% CI 0.28 to 2.00). Both levetiracetam and lorazepam were equally effective in aborting seizures (RR 0.97, 95% CI 0.44 to 2.13). Results for other comparisons of anticonvulsant therapies were uncertain due to single studies with few participants.

The body of randomised evidence to guide clinical decisions is small. It was uncertain whether any anticonvulsant therapy was better than another in terms of adverse effects, due to few studies and participants identified. The quality of the evidence from the included studies is not strong but appears acceptable. We were unable to make judgements for risk of bias domains incomplete outcome reporting (attrition bias) and selective outcome reporting (selection bias) due to unclear reporting by the study authors.

Authors' conclusions

Intravenous lorazepam is better than intravenous diazepam or intravenous phenytoin alone for cessation of seizures. Intravenous lorazepam also carries a lower risk of continuation of status epilepticus requiring a different drug or general anaesthesia compared with intravenous diazepam. Both intravenous lorazepam and diazepam are better than placebo for the same outcomes. For pre hospital management, midazolam IM seemed more effective than lorazepam IV for cessation of seizures, frequency of hospitalisation and ICU admissions however,it was unclear whether the risk of recurrence of seizures differed between treatments. The results of other comparisons of anticonvulsant therapies versus each other were also uncertain. Universally accepted definitions of premonitory, early, established and refractory status epilepticus are required. Diazepam gel was better than placebo gel in reducing the risk of non-cessation of seizures. Results for other comparisons of anticonvulsant therapies were uncertain due to single studies with few participants.

PLAIN LANGUAGE SUMMARY

Anticonvulsant therapy for status epilepticus

Some patients develop abnormal excessive electrical activity of brain nerve cells. This is called seizure activity and may involve a small area of the brain or the whole brain, resulting in sudden dysfunction of the structures involved, such as shaking of the limbs. The seizure activity often results in jerky movements (convulsions) and usually lasts a few minutes. When there is either more than 30 minutes of continuous seizure activity; or there are two or more seizures in a row without recovery of full consciousness between two seizures, the condition is called status epilepticus, which is a medical emergency. Many drugs have been studied in the management of this condition. This review found that intravenous (injected into a vein) lorazepam is better than diazepam or phenytoin for immediate control of status epilepticus. In the treatment of serially occurring seizures, diazepam gel administered rectally is effective in controlling seizures. Intravenous lorazepam is better than intravenous diazepam or phenytoin for immediate control of status epilepticus. For pre-hospital treatment, intramuscular midazolam is as effective as (probably more effective than) intravenous lorazepam in control of seizures and frequency of hospitalisation or intensive care admissions. There is a need to conduct more studies on other drugs routinely used for this condition.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Lorazepam IV versus diazepam IV for status epilepticus

Lorazepam IV versus diazepam IV for status epilepticus

Patient or population: patients with status epilepticus
Settings:
Intervention: Lorazepam IV versus diazepam IV

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	**Corresponding risk**				
	Control	**Lorazepam IV versus diazepam IV**				
Non-cessation of seizures	Study population		**RR 0.64** (0.45 to 0.9)	264 (3 studies)	⊕⊕⊕⊖ **moderate** [1]	
	381 per 1000	244 per 1000 (171 to 343)				
	Moderate					
	219 per 1000	140 per 1000 (99 to 197)				
Requirement for ventilatory support	Study population		**RR 0.73** (0.36 to 1.49)	264 (3 studies)	⊕⊕⊖⊖ **low** [1,2,]	
	127 per 1000	93 per 1000 (46 to 189)				
	Moderate					
	125 per 1000	91 per 1000 (45 to 186)				
Adverse effects	Study population		See comment	264 (3 studies)	⊕⊖⊖⊖ **very low** [3,4]	Risks were calculated from pooled risk differences
	82 per 1000	51 per 1000 (-18 to 112)				
	Moderate					
	103 per 1000	64 per 1000				

		(-23 to 141)				
Continuation of status requiring a different drug or general anaesthesia	**Study population**		**RR 0.63** (0.45 to 0.88)	264 (3 studies)	⊕⊕⊕⊖ **moderate** [5]	
	388 per 1000	244 per 1000 (175 to 341)				
	Moderate					
	250 per 1000	158 per 1000 (112 to 220)				
Death	**Study population**		See comment	203 (2 studies)	⊕⊕⊕⊖ **moderate** [1]	Risks were calculated from pooled risk differences
	30 per 1000	51 per 1000 (-10 to 110)				
	Moderate					
	22 per 1000	37 per 1000 (-7 to 81)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. 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; **IV:** intravenous; **RR:** Risk ratio.

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] Of the three studies, one (Appleton 1995) used odd/even dates for randomisation, clearly incurring high risk of bias. Two studies did not conceal allocation, incurring high risk of bias (Mehta 2007; Misra 2011) . . Furthermore an additional eight studies (Agarwal 2007; Chamberlain 1997; Chen 2011; McCormick 1999; Pellock 1998; Rossetti 2011; Shaner 1988; Sreenath 2010) did not provide clear information regarding generation of random sequence and/or allocation concealment.Taken together, there is enough risk of bias to downgrade the quality of evidence.

[2] The summary effect estimate crosses the line of null effect, and hence is consistent with appreciable benefit as well as appreciable harm.

[3] No explanation was provided
.

[4] I SQUARE is 49%

[5] The summary effect is consistent with 100 fewer to 30 more patients having an adverse event

Summary of findings 2. Lorazepam IV versus diazepam plus phenytoin IV for status epilepticus

Lorazepam IV versus diazepam plus phenytoin IV for status epilepticus

Patient or population: patients with status epilepticus
Settings:
Intervention: Lorazepam IV versus diazepam plus phenytoin IV

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	**Corresponding risk**				
	Control	Lorazepam IV versus diazepam plus phenytoin IV				
Non-cessation of seizures	Study population		RD -0.04 (-0.35 to 0.26)	370 (2 studies)	⊕⊕⊝⊝ **low** [1,2,3]	
	227 per 1000	179 per 1000 (127 to 257)				
	Moderate					
	221 per 1000	175 per 1000 (124 to 250)				
Adverse effects	Study population		RR 0.85 (0.63 to 1.15)	370 (2 studies)	⊕⊕⊕⊝ **moderate** [1,3]	
	290 per 1000	246 per 1000 (182 to 333)				
	Moderate					
	281 per 1000	239 per 1000 (177 to 323)				
Deaths	See comment	See comment	Not estimable	178 (1)	See comment	Reported in a single study
Requirement of Ventilatory support	See comment	See comment	Not estimable	178 (1)	See comment	Reported in a single study

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. 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).

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] Even though one study did not have a clear concealment of allocation, this is possibly a lack of reporting. Lack of blinding in this study is unlikely to bias the outcome assessment as the outcomes are clearly detectable and objective.
[2] The I square is 95%.
[3] The number of events is small and confidence interval is wide.

Summary of findings 3. Diazepam gel versus placebo gel for status epilepticus

Diazepam gel versus placebo gel for status epilepticus

Patient or population: patients with status epilepticus
Settings:
Intervention: Diazepam gel versus placebo gel

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Diazepam gel versus placebo gel				
Non-cessation of seizures	Study population		RR 0.43 (0.3 to 0.62)	165 (2 studies)	⊕⊕⊕⊝ moderate [1,2]	
	716 per 1000	308 per 1000 (215 to 444)				
	Moderate					
	716 per 1000	308 per 1000 (215 to 444)				
Adverse effects	Study population		RR 1.5 (0.94 to 2.37)	165 (2 studies)	⊕⊕⊕⊝ moderate [1,2]	
	250 per 1000	375 per 1000 (235 to 592)				

Moderate		
248 per 1000	372 per 1000 (233 to 588)	

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*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. 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; **RR:** Risk ratio;

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.

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[1] One placebo-controlled study did not describe the method of sequence generation, but probably this is a limitation of writing style. Use of placebo will tend to limit any bias due to this.

[2] Only few events recorded.

BACKGROUND

Description of the condition

Status epilepticus is defined as a condition in which there is either more than 30 minutes of continuous seizure activity; or two or more sequential seizures without recovery of full consciousness between the seizures. Status epilepticus is a medical emergency. It is associated with an overall mortality of 8% in children and 30% in adults (Epilepsy Foundation of America 1993). An additional 5% to 10% of people experiencing this condition have permanent sequelae, such as a permanent vegetative state or cognitive difficulties. Approximately 12% to 30% of adults with a new diagnosis of epilepsy present in status epilepticus (Lowenstein 1998). Some authors, depending upon the duration of seizure activity, stipulate three stages of the condition: early, established and refractory. Early status epilepticus consists of the first 30 minutes of the epileptic state during which physiological mechanisms compensate for the greatly enhanced metabolic activity. Established status epilepticus is defined as the stage beyond 30 minutes, where the status continues despite early stage treatment. It is during this phase that physiological compensation mechanisms begin to fail. If seizures continue for 60 to 90 minutes after the initiation of therapy the stage of refractory status is said to have been reached. Status epilepticus may be convulsive (with limb stiffness and jerking) or non-convulsive (without limb stiffness and jerking). Though convulsive status epilepticus is associated with a higher mortality and morbidity than non-convulsive status epilepticus, both require prompt and effective treatment. However, the most effective treatment regimen is not clear from the literature. Different experts give different recommendations regarding the best treatment regimen for status epilepticus (Lowenstein 1998; Prasad 1995; Epilepsy Foundation of America 1993) and the evidence base of many of these recommendations is often unclear. We conducted a systematic review of all the randomised controlled trials that we could identify to summarise the existing evidence, to delineate the reasons for disagreements and to highlight areas requiring further research.

Description of the intervention

Several drugs are available as interventions to treat status epilepticus.

Interventions for the treatment of status epilepticus cover a range of drugs, some of which may be safe, while others may be associated with serious adverse events. As status epilepticus progresses sequentially through premonitory, early, established and refractory stages, accordingly, treatment starts with benzodiazepines but may, in appropriate situations, require anaesthetic agents. The need to terminate the status requires the use of such interventions that enter the brain rapidly, and have a long half-life to prevent recurrence of seizures. Diazepam, lorazepam and midazolam, being lipid soluble, enter the brain rapidly, but diazepam is rapidly taken up by fatty tissues and hence has a shorter redistribution half-life (one hour) compared to half-lives of midazolam (two hours) and lorazepam (14 hours). As a result, duration of action of diazepam is only 0.25 to 0.5 hour, whereas for lorazepam it is 12 to 24 hours. For long-term maintenance therapy, drugs that can be administered in both parenteral and oral routes are required, such as sodium valproate, phenytoin, phenobarbitone etc.

How the intervention might work

The mechanism of action varies from one drug to another. Benzodiazepines (diazepam, lorazepam, midazolam) mainly potentiate GABA induced chloride influx. The most important mechanism for phenobarbitone is GABA receptor mediated synaptic inhibition. Phenytoin has a stabiliSing influence on the neuronal membrane through prolongation of the inactivated state of voltage sensitive neuronal sodium channel. Sodium valproate acts through multiple mechanisms: frequency dependent prolongation of sodium channel inactivation, attenuation of calcium mediated transient currents, augmentation of GABA. Benzodiazepines have a relatively short duration of action, and hence for maintenance of action, phenytoin, sodium valproate, or phenobarbitone are used or added to benzodiazepines.

Why it is important to do this review

Status epilepticus is a medical emergency with a significant mortality, but like many acute medical emergencies it is a challenging topic for randomised controlled trials. A regularly updated systematic review is required to summarise current evidence in order to inform both treatment guidelines and the research agenda.

OBJECTIVES

The primary objective of the review was to synthesise the available evidence from randomised controlled trials (RCTs):

1. to determine whether a particular anticonvulsant is more effective or safer in controlling status epilepticus compared with another drug or placebo;
2. to delineate reasons for disagreements regarding recommended treatment and highlight areas for future research.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials using a truly random or quasi-random allocation of treatment were included in this review if they included people with premonitory, early, established or refractory status epilepticus (see below for definitions).

Types of participants

For a study to be included in the review, study participants were required to have premonitory or early stage status epilepticus or established status epilepticus. The premonitory phase was referred to as the period during which seizures became increasingly frequent or severe but the condition did not meet the definition of status epilepticus. Early status was defined as the first 30 minutes of seizure activity. Established status epilepticus was defined as a condition with either more than 30 minutes of continuous seizure activity or two or more sequential seizures without recovery of full consciousness between the seizures. If seizure activity remains uncontrolled for one to two hours, in spite of first-line treatment, then the participant is considered to be in refractory status epilepticus (Shorvon 2001).

Both convulsive as well as non-convulsive status epilepticus were considered for this review.

Types of interventions

Studies comparing any anticonvulsant drug against placebo or another anticonvulsant drug were included in the review. For the premonitory stage of status epilepticus, interventions included diazepam (intravenous or intrarectal); lorazepam (intravenous); paraldehyde (intramuscular or intrarectal) or midazolam (intravenous, intramuscular or intrarectal). For early or established status epilepticus, drug interventions included lorazepam; diazepam; phenytoin; fosphenytoin; lignocaine; paraldehyde or clonazepam. For refractory status epilepticus, thiopentone; propofol; pentobarbitone; isoflurane or etomidate were included.

Types of outcome measures

The outcomes considered depended on the stage of status epilepticus at which the treatment was tested. For the purpose of this review, our intention was to analyse treatment failure as the primary outcome. We intended to define treatment failure for the various stages as any of the following.

For premonitory stage

1. Development of status epilepticus or death.

For early or established status epilepticus

1. Death.
2. Continuation of status epilepticus requiring use of a different drug or general anaesthesia for control.
3. Long-term disabling sequelae, defined as persistent neurological deficits severe enough to require dependence on some other person for activities of daily living (walking, toileting, bathing, dressing and eating) at six months after randomisation.
4. Need for ventilatory support.
5. Incomplete recovery before discharge, defined as inability to attain pre-status epilepticus state at the time of discharge. This outcome was included because most people attain their pre-status epilepticus state before discharge and are not followed up subsequently. People who do not recover need to be followed up in order to judge recovery or persistent deficit.

We used the term 'non-cessation of seizures' rather than cessation of seizures (used in the various studies) to maintain uniformity since all the other outcomes were unfavourable outcomes. Some of the studies described data on continuation of status epilepticus requiring a different drug or general anaesthesia separately, hence this has been taken as a separate outcome for analysis.

For refractory status epilepticus

1. Death.
2. Long-term sequelae defined as dependence for activities of daily living (walking, toileting, bathing, dressing and eating) assessed at six months or beyond, but if studies reported only one or three months after onset, this was treated as a long-term outcome.

Other outcomes which were considered for separate analyses in this review

1. Complications such as infections; renal failure; respiratory failure.
2. Adverse effects of drugs. The following were considered in the safety analysis:

a. hypotension, defined as a systolic blood pressure below 90 mm Hg recorded while the drug was being administered or within 24 hours of the last dose;
b. respiratory depression, defined as the occurrence of apnoea or need for intubation;
c. cardiac arrest (diagnosed clinically) or bradyarrhythmias including heart block, documented on an electrocardiogram.

We intended to analyse outcomes separately and as a composite outcome (treatment failure) because the latter would have allowed more power. This was not possible because many participants had more than one outcome measured during the course of treatment and the studies presented the number of outcomes observed but not the number of participants having one or more of these outcomes. We also considered an analysis of the number of outcomes as a continuous variable but the studies did not present standard deviations for these data and, therefore, did not permit meta-analysis.

Search methods for identification of studies

This search was run for the original review in July 2005 and subsequent searches have been run in January 2010, January 2011, February 2012, and August 2013. For the initial review, the following databases were searched:

(1) Cochrane Epilepsy Group Specialized Register (December 2009);
(2) Cochrane Central Database of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, Issue 4) using the strategy outlined in Appendix 2;
(3) MEDLINE (1950 to December week 4, 2009) using the strategy outlined in Appendix 3;
In addition, we searched EMBASE (1966 - January 2003) for the original version of this review, but we no longer have access to this database.

For the most recent update of this review, we searched the following electronic databases for published trials:

(1) Cochrane Epilepsy Group Specialized Register (15 August 2013) using the strategy outlined in Appendix 1;
(2) Cochrane Central Database of Controlled Trials (CENTRAL) ,*The Cochrane Library* July 2013, Issue 7*)* using the strategy outlined in Appendix 2;
(3) MEDLINE (Ovid, 1946 to 15/08/2013) using the strategy outlined in Appendix 3.

We did not apply any language restrictions to our search.

All resulting titles and abstracts were scanned and any relevant articles were followed up.

Data collection and analysis

Two review authors (MP, PRK) independently selected the trials to be included in the review. Any disagreements were resolved by seeking an independent opinion of the third review author (KA-R).

The methodological quality of each trial was assessed by two review authors (MP, PRK). The following criteria were included: randomisation method; baseline comparability of the trial arms; blinding; and whether the published data permitted an intention-to-treat analysis. Data were independently extracted by two review authors and cross-checked. Data on the number of participants

with each outcome event, by allocated treatment group, were sought to allow an intention-to-treat analysis.

We assessed the risk of bias as low, high or unclear risk of bias. We evaluated the following characteristics using the Cochrane 'Risk of bias' tool.

1. Random sequence generation (selection bias).
2. Allocation concealment (selection bias).
3. Blinding of participants and personnel (performance bias).
4. Blinding of outcome assessment (detection bias).

The trials comparing the same drugs were combined, whereas those comparing different drugs were analysed separately.

Our intention was to carry out our primary analysis on the risk of treatment failure. However, it was not possible to extract data on this outcome because the same participants were probably counted more than once in the various outcomes presented in the studies. Clearly some individuals had more than one of the above outcomes. For example, a person might require anaesthesia and ventilation then recover incompletely and may have long-term disabling sequelae. Our intention was to carry out separate analyses for premonitory stage, early status epilepticus, established status epilepticus and refractory status epilepticus. However, the definitions used in the different studies were both variable (see Table 1) and often unclear.

Potential causes of heterogeneity were assessed by examining differences between trials in respect to trial design; participant population; intervention and outcome. We tested for heterogeneity between trial results for each outcome using a chi squared (Chi2) test. If the test for heterogeneity was statistically non-significant, then the results from the different trials were combined to obtain a summary estimate of effect (and the corresponding confidence interval (CI)) using a fixed-effect model. We used risk ratio (RR) as the measure of choice for our analyses, but for some outcomes there were zero events in all the arms of some studies. In such situations we used risk difference (RD) to ensure inclusion of the data in our meta-analysis. Using RR would exclude such studies from analysis because confidence intervals cannot be calculated around RR when there is a zero event in both the arms of the study.

Assessment of statistical heterogeneity was supplemented using the I2 statistic, which provides an estimate of the percentage of variability due to heterogeneity rather than a sampling error.

Interpretation of I2 for heterogeneity is as follows.

- 0% to 40%: may not be important.
- 30% to 60%: represents moderate heterogeneity.
- 50% to 90%: represents substantial heterogeneity.
- 75% to 100%: represents considerable heterogeneity.

R E S U L T S

Description of studies

Results of the search

In the original review, the search yielded 28 studies that could potentially be included. After close scrutiny, 10 studies met the inclusion criteria, and the remaining 18 were excluded. For the current update, the search yielded 27 studies that could potentially be included. 17 out of these 27 studies were excluded after screening the abstracts. The full texts of the remaining 10 studies were screened and out of those, eight met the inclusion criteria. The current update includes eight new studies (Agarwal 2007; Ahmad 2006; Chen 2011; Mehta 2007; Misra 2011; Rossetti 2011; Silbergleit 2012; Sreenath 2010).

Included studies

Eighteen studies are included with a total of 2755 participants. Of the 18 studies included in this review, five studied participants with premonitory status (Alldredge 2001; Cereghino 2002; Chamberlain 1997; Pellock 1998; Treiman 1998), one established (Shaner 1988), three refractory (Agarwal 2007; Mehta 2007; Singhi 2002), and one mixed status epilepticus (Leppik 1983). Two studies did not clearly define the status (Appleton 1995; McCormick 1999). This made it difficult to analyse studies according to type of status epilepticus. Ten studies included only adults (Alldredge 2001; Cereghino 2002; Leppik 1983; Pellock 1998; Shaner 1988; Treiman 1998; Chen 2011;Misra 2011; Rossetti 2011), and six only children (Appleton 1995; Chamberlain 1997; McCormick 1999; Singhi 2002;Ahmad 2006;Sreenath 2010). Two studies included both adults and children (Agarwal 2007; Silbergleit 2012) The type of status epilepticus included varied from study to study: twelve generalised tonic-clonic (Alldredge 2001; Appleton 1995; Shaner 1988; Treiman 1998;Agarwal 2007; Ahmad 2006; Chen 2011;Mehta 2007; Misra 2011; Rossetti 2011; Silbergleit 2012; Sreenath 2010); and three mixed (Cereghino 2002; Leppik 1983; Singhi 2002). Three studies (Chamberlain 1997; McCormick 1999; Pellock 1998) did not describe the type of status epilepticus. Time-since-onset of status epilepticus also was variable, from minutes to hours in the different studies.

Three studies had more than two arms: (four arms in two studies (Appleton 1995; Treiman 1998) and three in one (Alldredge 2001)). There was difficulty in data extraction in one of these (Appleton 1995), so that only two arms were included in our analysis. Three studies had placebo arms (Alldredge 2001; Cereghino 2002; Pellock 1998) all in premonitory status epilepticus, described by two authors as acute repetitive seizures (Cereghino 2002; Pellock 1998). Two studies compared intrarectal diazepam gel with placebo (Cereghino 2002; Pellock 1998); and one study had lorazepam, diazepam, and placebo arms (Alldredge 2001), with the interventions all administered intravenously. Eight studies compared two or more active drugs. All studies except three (two intrarectal and one intramuscular (IM) midazolam in one arm) used intravenous (IV) administration of drugs. Twenty different comparisons were available but only five (lorazepam versus diazepam, both administered intravenously; lorazepam versus diazepam plus phenytoin; diazepam plus phenytoin versus phenobarbitone, administered intravenously; diazepam intrarectal gel versus placebo gel, valproate versus diazepam intravenously) included more than one study to permit a meta-analysis. In three studies (Alldredge 2001; Cereghino 2002; Pellock 1998) drugs were administered in the prehospital phase.

All participants were followed up only during their hospital stay. No study had post-discharge follow-up. All studies had cessation of status epilepticus and adverse effects as outcomes. Death was an outcome in five comparisons. Other outcomes studied were requirement for ventilatory support (seven comparisons) and

continuation of status epilepticus requiring another drug or general anaesthesia (five comparisons).

Excluded studies

Eleven studies are now excluded from the review. The reasons for exclusion were: poor data presentation (three studies), publication of only the study protocol (one study), a non-randomised comparative clinical trial (one study), a case study with only one participant (one study), and participants not having status epilepticus (one study), poor randomisation method (one study), comparing two doses of the same drug (one study) (for details *see* Excluded studies).

Risk of bias in included studies

Six studies (Alldredge 2001; Cereghino 2002; Leppik 1983; Pellock 1998; Silbergleit 2012; Treiman 1998) used a similar-looking placebo or comparison drug. With similar-looking interventions and blinding the recruiting person and the person administering the intervention should not know the group to which the next participant is going to be assigned. Thus, the similarity in

appearance concealed the allocation in these studies. In addition, three studies (Rossetti 2011; Shaner 1988; Sreenath 2010) used sealed envelopes to conceal allocation in the randomisation process but whether the envelopes were opaque and serially numbered is unclear from the study reports. The rest of the studies (Agarwal 2007; Appleton 1995; Chamberlain 1997; Chen 2011; McCormick 1999; Mehta 2007; Misra 2011) did not mention any attempt to conceal randomisation. Studies with a similar-looking placebo or comparison drug were assumed to be blinded but nine studies (Ahmad 2006; Appleton 1995; Chen 2011; Mehta 2007; Misra 2011; Rossetti 2011; Shaner 1988; Singhi 2002; Sreenath 2010) did not have blinding of carers or outcome assessors. The follow-up was restricted to the period of the hospital admissions in all the studies.

Three studies (Appleton 1995; Leppik 1983; Shaner 1988) did not report the number of participants having the events; rather they counted the number of events in the arms. This made it difficult to extract data from these studies for meta-analysis.

Please refer to Figure 1 and Figure 2.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
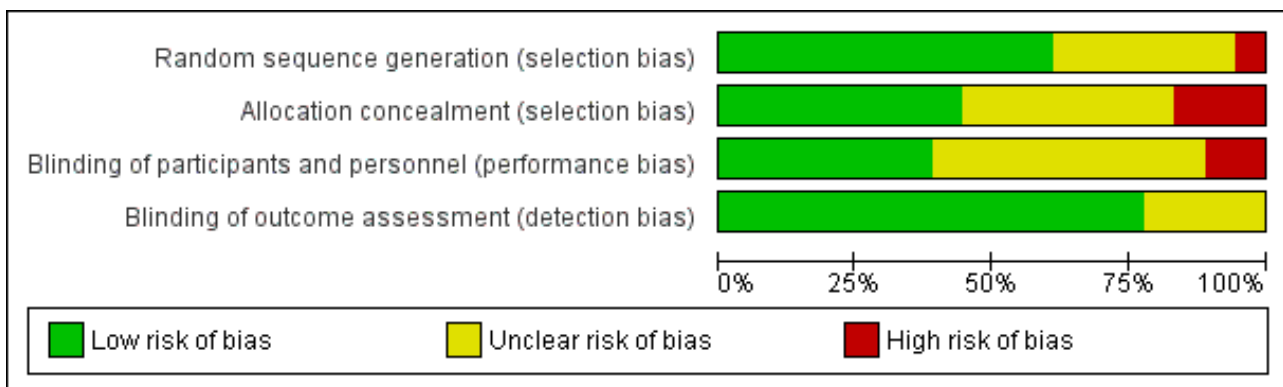
Figure 2. **'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.**

Effects of interventions

See: **Summary of findings for the main comparison** Lorazepam IV versus diazepam IV for status epilepticus; **Summary of findings 2** Lorazepam IV versus diazepam plus phenytoin IV for status epilepticus; **Summary of findings 3** Diazepam gel versus placebo gel for status epilepticus

All disagreements were resolved through discussion. Poor data presentation encountered included studies not mentioning the total number of participants studied, or presenting only the number of outcomes observed rather than the number of participants with the outcomes.

The data extraction was difficult because of heterogeneity in the definition of status epilepticus (see Table 1) and the type of data presented. Very few studies used the same interventions. We could combine data from eleven studies over five different outcomes. Even here, the definitions used by different authors varied and we assumed that the type of participants were similar. We presented the rest of the studies separately.

The results are presented according to the comparisons used.

Comparison 1: Lorazepam IV versus diazepam IV

There were three studies with 289 participants (Alldredge 2001; Appleton 1995; Leppik 1983). The outcome of death was available in two studies (203 participants). There was no statistically significant difference in deaths between the two groups (5/103 versus 3/100 participants; risk difference (RD) 0.02, 95% confidence interval (CI) -0.04 to 0.08). Compared with diazepam, lorazepam had statistically significant lower risk of non-cessation of seizures (32/130 versus 51/134 participants; risk ratio (RR) 0.64, 95% CI 0.45 to 0.90) and of continuation of status epilepticus requiring a different drug or general anaesthesia (32/130 participants versus 52/134; RR 0.63, 95% CI 0.45 to 0.88).

There was a statistically non-significant trend favouring lorazepam for reducing requirement for ventilatory support (12/130 versus 17/134 participants; RR 0.73, 95% CI 0.36 to 1.49) and adverse effects (7/130 versus 11/134 participants; RD -0.03, 95% CI -0.10 to 0.03).

Comparison 2: Lorazepam IV versus placebo IV

There was one study (Alldredge 2001) with 137 participants. Compared with placebo, lorazepam had a statistically significant lower risk of non-cessation of seizures (27/66 versus 56/71 participants; RR 0.52, 95% CI 0.38 to 0.71) and of continuation of status epilepticus requiring a different drug or general anaesthesia (27/66 versus 56/71 participants; RR 0.52, 95% CI 0.38 to 0.71). There was a statistically non-significant but strong trend favouring lorazepam for the following outcomes: death (5/66 versus 11/71 participants; RR 0.49, 95% CI 0.18 to 1.33); requirement for ventilatory support (7/66 versus 16/71 participants; RR 0.47, 95% CI 0.21 to 1.07) and adverse effects (7/66 versus 16/71 participants; RR 0.47, 95% CI 0.21 to 1.07).

Comparison 3: Lorazepam IV versus diazepam plus phenytoin IV

There were two studies (Sreenath 2010, Treiman 1998) with 370 participants. The outcome of non-cessation of seizures and adverse effects were available in both studies. There was a statistically non-

significant trend favouring lorazepam for both non-cessation of seizures (34/187 versus 42/183 participants; RD -0.04, CI -0.35 to 0.26) and adverse effects (46/187 versus 53/183 participants; RR 0.85, 95% CI 0.63 to 1.15). The outcome of death and requirement of ventilatory support were available in one study. There was no statistically significant difference for the outcome of death (0/88 versus 0/90 participants and requirement of ventilatory support (0/88 versus 0/90).

Comparison 4: Lorazepam IV versus phenobarbitone IV

A single study (Treiman 1998) with 188 participants showed no statistically significant difference in the risk of non-cessation of seizures (34/97 versus 38/91 participants; RR 0.84, 95% CI 0.58 to 1.21) or adverse effects (42/97 versus 46/91 participants; RR 0.86, 95% CI 0.63 to 1.16) between the two drugs.

Comparison 5: Lorazepam IV versus phenytoin IV

There was only one study (Treiman 1998) with 198 participants. Risk of non-cessation of seizures was less with lorazepam compared with phenytoin (34/97 versus 57/101, RR 0.62, 95% CI 0.45 to 0.86). There was no statistically significant difference between the two groups regarding adverse effects (42/97 versus 44/101, RR 0.99, 95% CI 0.72 to 1.37).

Comparison 6: Midazolam IV versus lorazepam IV

There was a single small study (McCormick 1999) with 27 participants. This study reported a statistically non-significant trend favouring midazolam regarding the following outcomes: non-cessation of seizures (1/15 versus 4/12 participants; RR 0.20, 95% CI 0.03 to 1.56); requirement for ventilatory support (1/15 versus 2/12 participants; RR 0.40, 95% CI 0.04 to 3.90) and adverse effects (1/15 versus 2/12 participants; RR 0.40, 95% CI 0.04 to 3.90) and continuation of status epilepticus requiring a different drug or general anaesthesia (1/15 versus 4/12 participants; RR 0.20, 95% CI 0.03 to 1.56).

Comparison 7: Midazolam IV versus diazepam IV

There was a single study (Singhi 2002) with 40 participants. There was no statistically significant difference between the two groups regarding the following outcomes: non-cessation of seizures (3/21 versus 2/19 participants; RR 1.36, 95% CI 0.25 to 7.27); requirement for ventilatory support (11/21 versus 9/19 participants; RR 1.11, 95% CI 0.59 to 2.07) and adverse effects (8/21 versus 9/19 participants; RR 0.80, 95% CI 0.39 to 1.66). There was a statistically non-significant trend favouring diazepam for the outcome of death (8/21 versus 2/19 participants; RR 3.62, 95% CI 0.87 to 14.97).

Comparison 8: Midazolam IM versus diazepam IV

A small single study (Chamberlain 1997) of 24 participants showed no statistically significant difference between the two groups for the following outcomes: non-cessation of seizures (1/13 versus 1/11 participants; RR 0.85, 95% CI 0.06 to 12.01); requirement for ventilatory support (1/13 versus 1/11 participants; RR 0.85, 95% CI 0.06 to 12.01); adverse effects (1/13 versus 1/11 participants; RR 0.85, 95% CI 0.06 to 12.01) and continuation of status epilepticus requiring a different drug or general anaesthesia (1/13 versus 1/11 participants; RR 0.85, 95% CI 0.06 to 12.01).

Comparison 9: Diazepam IV versus placebo IV

One hundred and thirty nine participants in a single study (Alldredge 2001) were analysed. Most of the outcomes significantly favoured diazepam: non-cessation of seizures (39/68 versus 56/71 participants; RR 0.73, 95% CI 0.57 to 0.92); death (3/68 versus 11/71 participants; RR 0.28, 95% CI 0.08 to 0.98); requirement for ventilatory support (6/68 versus 16/71 participants; RR 0.39, 95% CI 0.16 to 0.94) and continuation of status requiring a different drug or general anaesthesia (39/68 versus 56/71 participants; RR 0.73, 95% CI 0.57 to 0.92). There was a non-significant trend favouring diazepam for adverse effects (7/68 versus 16/71 participants; RR 0.46, 95% CI 0.20 to 1.04).

Comparison 10: Diazepam gel versus placebo gel

There were two studies (Cereghino 2002; Pellock 1998) with a total of 165 participants. The risk of non-cessation of seizures was significantly less with diazepam gel compared with placebo gel (24/77 versus 63/88 participants; RR 0.43, 95% CI 0.30 to 0.62). For adverse effects there was a strong but statistically non-significant trend towards the placebo gel (29/77 versus 22/88 participants; RR 1.50, 95% RR 0.94 to 2.37).

Comparison 11: Leviteracetam IV versus Lorazepam IV

There was one study (Misra 2011) with a total of 79 participants. Both levetiracetam and lorazepam were equally effective in aborting seizures (9/38 versus 10/41, RR 0.97, 95% CI 0.44 to 2.13).

Comparison 12: Diazepam plus phenytoin IV versus phenobarbitone IV

There were two studies (Shaner 1988; Treiman 1998) with a total of 222 participants. For the outcomes of death and requirement for ventilatory support, data were available in only one study (36 participants). There was no statistically significant difference between the two groups for the following outcomes: requirement for ventilatory support (6/18 versus 6/18 participants; RR 1.00, 95% CI 0.40 to 2.52); adverse effects (57/113 versus 55/109 participants, RR 1.00, 95% CI 0.77 to 1.30) and death (0/18 versus 0/18 participants; RD 0.00, 95% CI -0.10 to 0.10). For non-cessation of seizures, the test for heterogeneity was significant and the type of status epilepticus studied was different, hence the two studies were analysed separately for this outcome. There was a weak statistically non-significant trend favouring phenobarbitone in one of the studies (Shaner 1988) (8/18 versus 2/18 participants; RR 4.00, 95% CI 0.98 to 16.30). In the other larger study (Treiman 1998), there was no statistically significant difference between the two groups for non-cessation of seizures (42/95 versus 38/91 participants; RR 1.06, 95% CI 0.76 to 1.47).

Comparison 13: Diazepam plus phenytoin IV versus phenobarbitone IV (premonitory status)

The was a single study (Treiman 1998) with 196 participants. There was no statistically significant difference between the two groups for cessation of seizures (42/95 versus 38/91 RR 1.06, 95% CI 0.76 to 1.47).

Comparison 14: Diazepam plus phenytoin IV versus phenytoin IV

There was a single study (Treiman 1998) with 196 participants. The study reported a statistically non-significant trend favouring diazepam plus phenytoin for non-cessation of seizures (42/95 versus 57/101 participants; RR 0.78, 95% CI 0.59 to 1.04). There was no statistically significant difference between the two groups for adverse effects (48/95 versus 44/101 participants; RR 1.16, 95% CI 0.86 to 1.56).

Comparison 15: Phenobarbitone IV versus phenytoin IV

There was a single study (Treiman 1998) with 186 participants. There was a statistically non-significant trend favouring phenobarbitone for non-cessation of seizures (38/91 versus 51/95 participants; RR 0.78, 95% CI 0.57 to 1.06). There was no statistically significant difference between the two groups for adverse effects (46/91 versus 44/95 participants; RR 1.09, 95% CI 0.81 to 1.47).

Comparison 16: Lorazepam intranasal versus paraldehyde IM

There was a single study (Ahmad 2006) with 160 participants. There was no statistically significant difference between two groups for cessation of seizures (60/80 versus 49/80 participants; RR 1.22, 95% CI 0.99 to 1.52). There was no statistically significant difference between two groups for deaths (15/80 versus 13/80 participants; RR 1.15, 95% CI 0.59 to 2.27).

Comparison 17:Valproate IV versus Phenytoin IV

There was one study (Agarwal 2007) with a total of 100 participants. The study reported a statistically non-significant trend favouring Intravenous valproate for reducing risk of non-cessation of seizures (6/50 versus 8/50, RR 0.75, 95% CI 0.28 to 2.00).

Comparison 18: Midazolam IM versus lorazepam IV

There was a single study (Silbergleit 2012) with 893 participants. The study reported a statistically significant difference favouring midazolam for cessation of seizures (329/448 versus 282/445; RR 1.16, 95% CI 1.06 to 1.27), for requirement for intensive care unit (ICU) admission (128/448 versus 161/445 participants; RR 0.79, 95% CI 0.65 to 0.96), and for requirement for hospitalisation (258/448 versus 292/445 participants; RR 0.88, 95% CI 0.79 to 0.97).There was no statistically significant difference between the two groups for following outcomes: endotracheal Intubation (63/448 versus 64/445 participants; RR 0.98, 95% CI 0.71 to 1.35); recurrence of seizures (51/448 versus 47/445 participants; RR 1.08, 95% CI 0.74 to 1.57); adverse effects (16/448 versus 18/445 participants; RR 0.88, 95% CI 0.46 to 1.71): for ICU stay (mean difference (MD) 1.60, 95% CI -0.23 to 3.43, P =0.09); and length of hospital stay (MD 1.20, 95% CI -0.24 to 2.64, P =0.10).

Comparison 19: Valproate IV versus diazepam IV infusion

There were two studies (Chen 2011; Mehta 2007) with 106 participants. There was a statistically non-significant trend favouring diazepam for non-cessation of seizures (19/50 versus 19/56; RR 1.16, 95% CI 0.71 to 1.89). There was a statistically significant difference between the two groups for the adverse effect of hypotension (0/50 versus 12/56, RR 0.08, 95% CI 0.01 to 0.58)

Comparison 20: Propofol IVversus barbiturates IV

There was a single study (Rossetti 2011) with 23 participants. There was no statistically significant difference between the two groups in any of the following outcomes: refractory status epilepticus (RSE) controlled with first course of drug (6/14 versus 2/9 participants; RR 1.93, 95% CI 0.49 to 7.54); RSE treated subsequently (4/8 versus 5/7 participants; RR 0.70, 95% CI 0.30 to 1.62); thrombotic/embolic

complication (0/14 versus 0/9 participants); mortality (6/14 versus 3/9 participants; RR 1.29, 95% CI 0.43 to 3.88); functional outcome at three weeks (5/14 versus 3/9 participants; RR 1.07, 95% CI 0.34 to 3.42); infection requiring antibiotics (7/14 versus 6/9 participants; RR 0.75, 95% CI 0.37 to 1.51).

DISCUSSION

Our review demonstrated that there are few reported randomised studies on drug interventions used in status epilepticus. Considering that the condition is relatively frequent in neurological practice, it is surprising that we found only 18 studies with analysable data. For status epilepticus, carrying out randomised controlled trials (RCTs) in the emergency situation may be difficult; particularly when the patient is unconscious, which makes getting rapid consent to join a trial difficult. This review highlights the need to conduct more randomised studies in status epilepticus.

The review has demonstrated several areas requiring attention in future research in status epilepticus. A universally acceptable definition of premonitory, early, established and refractory status needs to be agreed upon and used consistently by investigators. Agreement on the definition of outcomes and method of data presentation is also desirable to facilitate meta-analysis. In particular, reports should provide the number of participants having each outcome and the denominator in analyses should be the number of participants rather than the number of episodes of status epilepticus.

The time frame required of the administration of interventions would be an important element for study/comparison in the future. A table has been added depicting the time since onset of status to administration of drug and since administration of drug to cessation of seizures as reported for drugs in respective studies (Table 2).

Summary of main results

Even with limited data, the results may be summarised as follows.

1. Diazepam was better than placebo for cessation of seizures: there was a lower risk of requirement for ventilatory support and continuation of status epilepticus requiring a different drug or general anaesthesia with diazepam.
2. Lorazepam was better than placebo for cessation of seizures and carried a lower risk for continuation of status epilepticus requiring a different drug or general anaesthesia.
3. Lorazepam was better than diazepam for cessation of seizures and had a lower risk for continuation of status epilepticus requiring a different drug or general anaesthesia.
4. Lorazepam was better than phenytoin for cessation of seizures.

5. For pre hospital treatment, midazolam IM was as effective and probably better than lorazepam IV for cessation of seizures, frequency of hospitalisation and ICU admissions but not for risk of recurrence of seizures.

No definitive conclusions were possible with other comparisons. However, statistically non-significant trends were found for the following.

1. Lorazepam IV versus diazepam IV - trend favouring lorazepam for ventilatory support and adverse effects.

2. Lorazepam IV versus placebo - trend favouring lorazepam for death, requirement for ventilatory support and adverse effects.
3. Lorazepam IV versus diazepam plus phenytoin IV - trend favouring lorazepam for cessation of seizures and adverse effects.
4. Midazolam versus lorazepam IV - trend favouring midazolam for cessation of seizures, need for ventilatory support, adverse effects and continuation of status epilepticus requiring a different drug or general anaesthesia.
5. Midazolam versus diazepam IV - trend favouring diazepam for reduced number of deaths.
6. Diazepam versus placebo gel - trend towards fewer adverse effects with placebo gel.
7. Diazepam plus phenytoin versus phenytoin IV - trend favouring diazepam plus phenytoin for cessation of seizures.
8. Phenobarbitone versus phenytoin IV - trend favouring phenobarbitone for cessation of seizures.

Overall completeness and applicability of evidence

Considering the frequency and seriousness of the condition, the body of randomised evidence available to guide clinical decisions is small. The only clinically applicable conclusions appear to favour lorazepam or midazolam as initial treatment of status epilepticus. Of these, adequate evidence is available only in favour of midazolam IM. However, this result is applicable only for pre hospital treatment. Once a patient has reached hospital, the intravenous (IV) route is the preferred route, for which evidence seems to favour lorazepam.

Quality of the evidence

The quality of evidence is not strong, but appears acceptable.

Potential biases in the review process

Several criteria to assess risk of bias could not be assessed because of unclear reporting by the authors. Attempts to contact the authors for clarification did not succeed. This may have underestimated/overestimated the risk of bias in the studies.

Agreements and disagreements with other studies or reviews

Seperate systematic reviews for drugs like levetiracetam have appeared in literature but their results lack precision because of the small number of studies and events.

AUTHORS' CONCLUSIONS

Implications for practice

Lorazepam is better than diazepam or phenytoin for cessation of seizures and carries a lower risk of continuation of status epilepticus that requires use of a different drug or general anaesthesia. Both lorazepam and diazepam (IV or gel form) are better than placebo for the same outcomes. For pre hospital treatment, midazolam IM seemed more effective than lorazepam IV for cessation of seizures, frequency of hospitalisation and ICU admissions. However, it was unclear whether the risk of recurrence of seizures differed between treatments. The results of other comparisons of anticonvulsant therapies versus each other were also uncertain.

Implications for research

The review has demonstrated several areas requiring attention in future research in the treatment of status epilepticus. Investigators need to develop and use universally acceptable definitions of premonitory, early, established and refractory status epilepticus. Agreement on the definition of outcomes and method of data presentation is also desirable to facilitate meta-analysis. In particular, investigators should report the number of participants having each outcome, with one participant included only once in a study. Where counts of seizure episodes are presented, then the standard deviation of the counts should be provided to facilitate meta-analysis.

A practical difficulty in conducting RCTs in status epilepticus is obtaining consent, because participants are unconscious or not in a state to provide it. Taking consent from next of kin is one option. Such an approach has been used in RCTs with participants experiencing head injury and stroke.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Agarwal 2007

Methods	Randomised parallel group design
Participants	Patients refractory to IV Diazepam
Interventions	Group A; IV Valproate 20 mg/kg loading dose @ 40 mg/min
	Group B; IV Phenytoin 20 mg/kg @ max. 50 mg/min after dilution with normal saline
Outcomes	SE controlled, recurrence in 12 h and 24 h, mortality, left against medical advice, hypotension, respiratory depression, mild elevation of SGPT
Notes	Study conducted in India

Agarwal 2007 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described

Ahmad 2006

Methods	Parallel group, randomised
Participants	Children, mean age 19 years, 55% male, setting: tertiary hospital
Interventions	Arm 1: Intranasal Lorazepam 100 microgram/kg
	Arm 2: IM Paraldehyde 0.2 mL/kg
Outcomes	Cessation of seizures within 10 minutes of administration of drug
	Deaths in hospital
Notes	Study from Malawi, single centre. Funded by UK college of Emergency Medicine

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocked randomisation by computer-generated random number table
Allocation concealment (selection bias)	Low risk	Allocations were sealed in unmarked identical envelopes. Investigators were masked to these allocations before the point of patient treatment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Lack of blinding may have affected institution of co-intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Even though not blinded, outcomes such as seizure activity determination is unlikely to be subject to bias in detection

Alldredge 2001

Methods	Randomised parallel group design
Participants	Adult patients with out-of-hospital status epilepticus treated by paramedics. Mean age: 50 yrs, male 63%. Setting: pre hospital treatment by paramedics of Dept of public health, San Francisco, USA
Interventions	Experimental = diazepam (5 mg) or lorazepam (2 mg), IV, pre hospital Control = matching placebo
Outcomes	Cessation of status on arrival to hospital Requirement for ventilatory support on arrival to hospital Status of recovery (neurological outcome) at discharge from hospital Mortality in hospital Complications during transfer Adverse effects of drugs
Notes	Study conducted in USA. Funded by NIH, single-centre study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (selection bias)	Low risk	Randomisation by computer-generated sequence of random numbers
Allocation concealment (selection bias)	Low risk	Coded kits with identical content were used
Blinding of participants and personnel (perfor- mance bias) All outcomes	Low risk	Double blind, placebo-controlled trial
Blinding of outcome as- sessment (detection bias) All outcomes	Low risk	Double blind, placebo-controlled trial

Appleton 1995

Methods	Randomised, parallel group design
Participants	Children (mean age: 5.2 years), male 58%. Emergency services of a tertiary hospital for children
Interventions	Arm 1 = diazepam 0.3 - 0.4 mg/kg IV/rectal, single dose Arm 2 = lorazepam 0.05 - 0.1 mg/kg IV/rectal, single dose
Outcomes	(I) the time taken for the initial (presenting) convulsion to stop after administration of the drug; (2) the numbers of doses required to treat the initial convulsion: (3) the use of additional anti-epileptic drugs to terminate the initial convulsion; (4) the total number of seizures occurring in the first 24 hours of admission: and (5) the development of respiratory depression, (6) ICU admission, and (6) adverse effects
Notes	Study conducted in UK, No mention of funding source

Risk of bias

Appleton 1995 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomised based on date of admission; odd date = diazepam, even date = lorazepam
Allocation concealment (selection bias)	High risk	No concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Even though not blinded, outcomes such as seizure activity determination, requirement of another antiepileptic drug and number of doses are unlikely to be subject to bias in detection

Cereghino 2002

Methods	Randomised parallel group, placebo-controlled trials
Participants	Adults.(mean 28 years), male 57%. Home treatment by caregivers
Interventions	Experimental = diazepam gel 0.2 mg/kg Control = identical placebo gel both administered through rectal route No. of doses: single (study 003), three (0, 4 and 12 hours in study 001)
Outcomes	Cessation of seizures and adverse events over 12 (in study 003) to 24 hours (study 001)
Notes	Study conducted in USA, multi-centric. Two studies (labelled 001 and 003) have been jointly reported in this report

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised by computer-generated code
Allocation concealment (selection bias)	Low risk	Placebo-controlled trial
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blinded study
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blinded study

Chamberlain 1997

Methods	Randomised parallel group
Participants	Birth to age of 18 years.
Interventions	Arm 1 = midazolam 0.2 mg/kg IM Arm 2 = diazepam 0.3 mg/kg IV
Outcomes	Cessation of seizures Requirement for ventilatory support Adverse effects
Notes	Study conducted in USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not described
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described

Chen 2011

Methods	Randomised, parallel group design
Participants	Adults (mean age 41 years). Male 55%. Setting: University hospital
Interventions	Arm 1: Diazepam bolus 0.2 mg/kg @ 5 mg/min followed by infusion @ 4 mg/hr initially for 3 min and then increased every 3 min by 1 microgram/kg/min Arm 2: Valproate loading dose of 30 mg/kg began @ 6 mg/kg per min followed by a continuous infusion at @ 1–2 mg/kg per h Route: IV
Outcomes	Effective control of seizures at 24 hours Deaths in-hospital Recovery to baseline at three months Neurological sequelae at three months Post SE symptomatic epilepsy at three months

Chen 2011 *(Continued)*

Notes	Study conducted in China, single centre

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation using random number table
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Lack of blinding may have affected institution of co-intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Even though not blinded, outcomes such as seizure activity determination is unlikely to be subject to bias in detection

Leppik 1983

Methods	Randomised, placebo-controlled, parallel group design
Participants	Adults (mean age 53 years), male 71%. Setting: University hospitals
Interventions	Arm 1 = lorazepam 2 mg IV Arm 2 = diazepam 5 mg IV One or two doses to achieve seizure control
Outcomes	Cessation of seizures after first dose Recovery at discharge Mortality in hospital Requirement for ventilatory support Complications Adverse effects Patients followed up until discharge from hospital
Notes	Study conducted in USA, multi-centric (three centres)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly numbered identical kits
Allocation concealment (selection bias)	Low risk	Randomly numbered identical kits
Blinding of participants and personnel (performance bias)	Low risk	Double blinded

Leppik 1983 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blinded

McCormick 1999

Methods	Randomised parallel group design
Participants	1 month to 15 years of age.
Interventions	Arm 1 = midazolam 0.2 mg/kg IV Arm 2 = lorazepam 0.1 mg/kg IV
Outcomes	Cessation of seizures Requirement for ventilatory support Complications Adverse effects
Notes	Study conducted in USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	There is no mention of 'blinding' in the abstract (full paper not found in our extensive search), but the short period of observation in this study may not be liable to bias in performance of the participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Even though there was no blinding, the outcome measures are unlikely to be susceptible to high degree of bias

Mehta 2007

Methods	An open-label, randomised controlled trial
Participants	Children, 5 months to 12 years of age, with refractory convulsive status epilepticus. Mean age in Valproate group-36.3 months and Diazepam group-44.5 months
Interventions	Valproate: LoadIng dose: 30 mg/kg diluted 1:1 in normal saline from 2 to 5 mins followed by infusion @ 5 mg/kg/hour continued until seizure-free period of 6 hours was reached and then reduced @ 1 mg/kg/ hour every 2 hours. Maintenance dose: 10 mg/kg IV every 8 hours Diazepam: 10 microgram/kg/min increased every 5 min by 10 mircogram/kg/min

Outcomes	Control of RSE, time interval for control, dose required to control RSE, breakthrough seizures, respiratory depression, hypotension
Notes	Study conducted in India

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation method
Allocation concealment (selection bias)	High risk	No concealment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Open-label study
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Even though not blinded, outcomes such as seizure activity determination and occurrence of adverse events are unlikely to be subject to bias in detection

Misra 2011

Methods	Randomised, open-label study
Participants	Adult patients, mean age for Lorazepam group 38.90 and Levetiracetam group 39.16 years Consecutive patients with either convulsive SE or subtle convulsive SE were recruited
Interventions	Levetiracetam: 20 mg/kg IV over 15 min Lorazepam: 0.1 mg/kg IV over 2-4 min
Outcomes	Control of seizure, adverse events such as hypotension, respiratory failure, pneumonia, UTI, ventilatory need, days of ventilation, hepatitis, rash, agitation, thrombocytopenia and deaths
Notes	Study conducted in India

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number tables were used
Allocation concealment (selection bias)	High risk	No concealment
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label study

Misra 2011 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Even though not blinded, outcomes such as seizure activity determination and occurrence of adverse events are unlikely to be subject to bias in detection

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Pellock 1998

Methods	Randomised, placebo-controlled, parallel group design
Participants	Adult patients Premonitory status Patients given the drug at home by caregivers
Interventions	Experimental = diazepam 0.2 mg/kg intrarectal Control = placebo gel intrarectal
Outcomes	Cessation of seizures Complications Adverse effects
Notes	Study conducted in USA

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not described
Allocation concealment (selection bias)	Low risk	Placebo-controlled
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind placebo-controlled
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blind placebo-controlled

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Rossetti 2011

Methods	Randomisation was stratified by institution, using blocks with sealed envelopes
Participants	Adults (older than 16 years) Male 43.4%, Median age: Propofol 57 years, Barbiturates 64 years
Interventions	Barbiturate arm: Pentobarbital (USA): bolus of 5 mg/kg IV, then titration toward burst-suppression or, if no EEG available, toward 2 mg/kg/h until EEG was available OR Thiopental (Switzerland): bolus of 2 mg/kg IV, then titration toward burst-suppression or, if no EEG available, toward 4 mg/kg/h until EEG was available Propofol arm: Propofol (USA and Switzerland): bolus of 2 mg/kg, then titration toward burst-suppression or, if no EEG available, toward 5 mg/kg/h until EEG was available

Rossetti 2011 *(Continued)*

	In each arm, a BDZ was administered at low dose (lorazepam: 4 mg/24 h, or clonazepam 2 mg/24 h) throughout the study period, to reduce required doses of study drugs
Outcomes	Efficacy (RSE controlled, mortality, functional outcome)
	Tolerability (thrombotic/embolic complications, infections, hypotension)
	Follow-up: three months
	Outcomes assessed at one week, three weeks and three months
Notes	Multi-centre trial carried out in USA and Switzerland

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Sealed envelopes have been used but it is not clearly mentioned whether they were opaque and serially numbered
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	The participants were not blinded but there is no clear description of co-intervention bias due to this
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The study is described as single blinded, and outcome measures are unlikely to be subject to bias

Shaner 1988

Methods	Randomisation by sealed envelopes No blinding
Participants	Patients aged over 15 years
Interventions	Arm 1 = diazepam 2 - 20 mg IV + phenytoin 6 - 18 mg/kg IV based on initial drug levels Arm 2 = phenobarbitone 10 - 30 mg/kg IV
Outcomes	Cessation of seizures Requirement for ventilatory support Mortality Complications Adverse effects
Notes	Study from California

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The method of sequence generation not given

Shaner 1988 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Sealed envelopes have been used but it is not clearly mentioned whether they were opaque and serially numbered
Blinding of participants and personnel (performance bias) All outcomes	High risk	There was no blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Even though there was no blinding, the outcome measures are unlikely to be susceptible to high degree of bias

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Silbergleit 2012

Methods	Randomised parallel group design
Participants	Adults and children (mean age 43 years); male 55%, pre hospital treatment by paramedics
Interventions	Arm 1: Midazolam IM 10 mg (for weight > 40 kg) and 5 mg (for weight 13 - 40 kg)
	Arm 2: Lorazepam IV 4 mg (for weight > 40 kg) and 2 mg (for weight 13 - 40 kg)
Outcomes	Cessation of seizures
	Requirement of endotracheal Intubation
	Requirement of hospitalisation
	ICU Admissions
	Recurrence of seizure
	Hypotension
	IM Injection site complication
	IV injection site complication
	Length of ICU stay
	Length of hospital stay
	All outcomes measured in hospital. Follow-up till discharge from hospital
Notes	Multi-centric study by university hospitals, funded by US National Institute of Neurological Disorders and Stroke

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation by 'double-dummy strategy'
Allocation concealment (selection bias)	Low risk	Randomisation by 'double-dummy strategy' in which each kit was randomly assigned at the central pharmacy to contain either group

Silbergleit 2012 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double blind, randomised trial
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double blind, randomised trial

Singhi 2002

Methods	Randomised parallel group design
Participants	Children (mean 3.75 years), male 78%, university hospital intensive care setting
Interventions	Arm 1 = midazolam 0.2 mg/kg bolus followed by 2-10 microgram/kg/min infusion Arm 2 = diazepam 0.01 - 0.1 mg/kg/min infusion Route of administration: IV
Outcomes	Cessation of seizures Recovery at discharge and during follow-up Mortality Complications Adverse effects Out-patient follow-up period: not specified
Notes	Study from India, single centre, no mention of any funding source

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation in blocks of six by sealed envelopes
Allocation concealment (selection bias)	Low risk	The random assignment was kept sealed in an envelope by a faculty member not directly involved in the study
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Lack of blinding may have affected institution of co-intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Even though not blinded, outcomes such as seizure activity determination are unlikely to be subject to bias in detection

Sreenath 2010

Methods	Randomised parallel group design

Sreenath 2010 *(Continued)*

Participants	Children (mean age seven years), male 57%, university hospital setting
Interventions	Arm 1: IV Diazepam 0.2 mg/kg (repeated once, if seizure uncontrolled) and IV Phenytoin 18 mg/kg after 15-30 min
	Arm 2: IV Lorazepam 0.1 mg/kg (repeated once, if seizure uncontrolled)
Outcomes	Cessation of seizures
	Requirement of different drug/GA
	Requirement of ventilatory support
	Long-term disabling sequelae
	Deaths
	Adverse effects
	Follow-up only in hospital, period: 18 hours
Notes	Study carried out in India, single centre. Funding source not mentioned

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used computer-generated random numbers
Allocation concealment (selection bias)	Unclear risk	Used sealed envelopes but no mention of whether they were opaque and serially numbered
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Lack of blinding may have affected institution of co-intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Even though not blinded, outcomes such as seizure activity determination is unlikely to be subject to bias in detection

Treiman 1998

Methods	Randomised parallel group design
Participants	Adults (mean age 59 years), male 82%. Setting: University hospitals and Veterans Affairs medical centres
Interventions	Arm 1 = lorazepam IV (Intravenous: 0.1 mg/kg) Arm 2 = phenobarbitone IV (15mg/kg) Arm 3 = diazepam (0.15 mg/kg) + phenytoin IV (18 mg/kg) Arm 4 = phenytoin IV (18 mg/kg)
Outcomes	Cessation of seizures at 20 minutes and no recurrence for next 40 minutes
	Discharged alive at 30 days

Treiman 1998 *(Continued)*

	Adverse effects over 12 hours
Notes	Study from USA, multi-centric

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Method of sequence generation not described in details but in view of identical kits for the different arms, risk of bias is considered low
Allocation concealment (selection bias)	Low risk	Identical and numbered kits were used
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical kits would blind the participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessment would be blinded as identical kits were used

BDZ: benzodiazepine
EEG: electroencephalogram
GA: general anaesthesia
ICU: intensive care unit
IM: intramuscular injection
IV: administered intravenously
RSE: refractory status epilepticus
SE: status epilepticus
SGPT: serum glutamic-pyruvic transaminase
UTI: urinary tract infection

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

Study	Reason for exclusion
Andermann 1994	Data analysis not possible due to inadequate information.
Czapinski 1995	Data analysis not possible due to inadequate information.
Lowenstein 2001	This paper provides only details of the study design and methodology of an already included study (Alldredge 2001).
Mahmoudian 2006	This was not a truly randomised study as the allocation was made on the basis of odd or even date of entry into the study. Authors, even in their full paper, did not present the number of patients in each arm of the study and did not respond to emails sent to them for data required to enter into RevMan.
Osborn 1987	Study population did not include patients with status epilepticus.
Remy 1992	This study compares two different doses of the same drug (intrarectal diazepam gel), and hence does not meet the inclusion criteria.
Scott 1998	This study is an abstract of same study excluded (see Scott 1999).

Study	Reason for exclusion
Scott 1999	Only counts of number of seizures in each group are given; the data can be analysed neither as dichotomous nor as continuous variable.
Sorel 1981	Comparative clinical trial.
Taverner 1958	Only one participant in the trial.
Van Gestel 2005	The study was not randomised.

DATA AND ANALYSES

Comparison 1. Lorazepam IV versus diazepam IV

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non-cessation of seizures	3	264	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.45, 0.90]
2 Requirement for ventilatory support	3	264	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.36, 1.49]
3 Adverse effects	3	264	Risk Difference (M-H, Fixed, 95% CI)	-0.03 [-0.10, 0.03]
4 Continuation of status requiring a different drug or general anaesthesia	3	264	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.45, 0.88]
5 Death	2	203	Risk Difference (M-H, Fixed, 95% CI)	0.02 [-0.04, 0.08]

Analysis 1.1. Comparison 1 Lorazepam IV versus diazepam IV, Outcome 1 Non-cessation of seizures.

Study or subgroup	Lorazepam IV n/N	Diazepam IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Alldredge 2001	27/66	39/68		76.3%	0.71[0.5,1.02]
Appleton 1995	1/27	5/34		8.79%	0.25[0.03,2.03]
Leppik 1983	4/37	7/32		14.91%	0.49[0.16,1.54]
Total (95% CI)	**130**	**134**		**100%**	**0.64[0.45,0.9]**
Total events: 32 (Lorazepam IV), 51 (Diazepam IV)					
Heterogeneity: Tau²=0; Chi²=1.32, df=2(P=0.52); I²=0%					
Test for overall effect: Z=2.56(P=0.01)					

Favours Lorazepam 0.005 0.1 1 10 200 Favours Diazepam
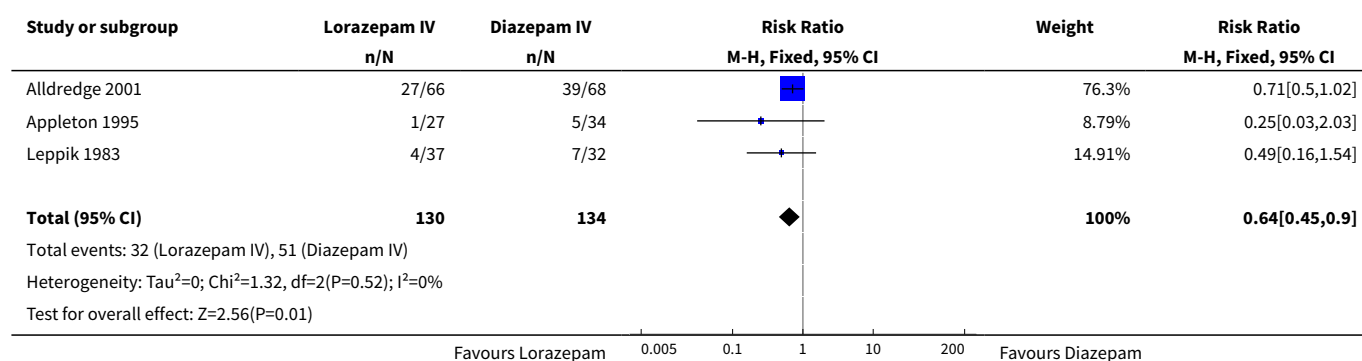
Analysis 1.2. Comparison 1 Lorazepam IV versus diazepam IV, Outcome 2 Requirement for ventilatory support.

Study or subgroup	Lorazepam IV n/N	Diazepam IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Alldredge 2001	7/66	6/68		36.05%	1.2[0.43,3.39]
Appleton 1995	1/27	7/34		37.79%	0.18[0.02,1.37]
Leppik 1983	4/37	4/32		26.16%	0.86[0.24,3.18]
Total (95% CI)	**130**	**134**		**100%**	**0.73[0.36,1.49]**
Total events: 12 (Lorazepam IV), 17 (Diazepam IV)					
Heterogeneity: Tau²=0; Chi²=2.78, df=2(P=0.25); I²=28.13%					
Test for overall effect: Z=0.87(P=0.38)					

Favours Lorazepam   0.01 0.1 1 10 100   Favours Diazepam

Analysis 1.3. Comparison 1 Lorazepam IV versus diazepam IV, Outcome 3 Adverse effects.

Study or subgroup	Lorazepam IV n/N	Diazepam IV n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
Alldredge 2001	7/66	7/68		50.98%	0[-0.1,0.11]
Appleton 1995	0/27	0/34		22.91%	0[-0.06,0.06]
Leppik 1983	0/37	4/32		26.12%	-0.12[-0.25,-0]
Total (95% CI)	**130**	**134**		**100%**	**-0.03[-0.1,0.03]**
Total events: 7 (Lorazepam IV), 11 (Diazepam IV)					
Heterogeneity: Tau²=0; Chi²=3.61, df=2(P=0.16); I²=44.64%					
Test for overall effect: Z=0.95(P=0.34)					

Favours Lorazepam   -0.5 -0.25 0 0.25 0.5   Favours Diazepam

Analysis 1.4. Comparison 1 Lorazepam IV versus diazepam IV, Outcome 4 Continuation of status requiring a different drug or general anaesthesia.

Study or subgroup	Lorazepam IV n/N	Diazepam IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Alldredge 2001	27/66	39/68		74.71%	0.71[0.5,1.02]
Appleton 1995	1/27	5/34		8.61%	0.25[0.03,2.03]
Leppik 1983	4/37	8/32		16.68%	0.43[0.14,1.3]
Total (95% CI)	**130**	**134**		**100%**	**0.63[0.45,0.88]**
Total events: 32 (Lorazepam IV), 52 (Diazepam IV)					
Heterogeneity: Tau²=0; Chi²=1.68, df=2(P=0.43); I²=0%					
Test for overall effect: Z=2.68(P=0.01)					

Favours Lorazepam   0.01 0.1 1 10 100   Favours Diazepam
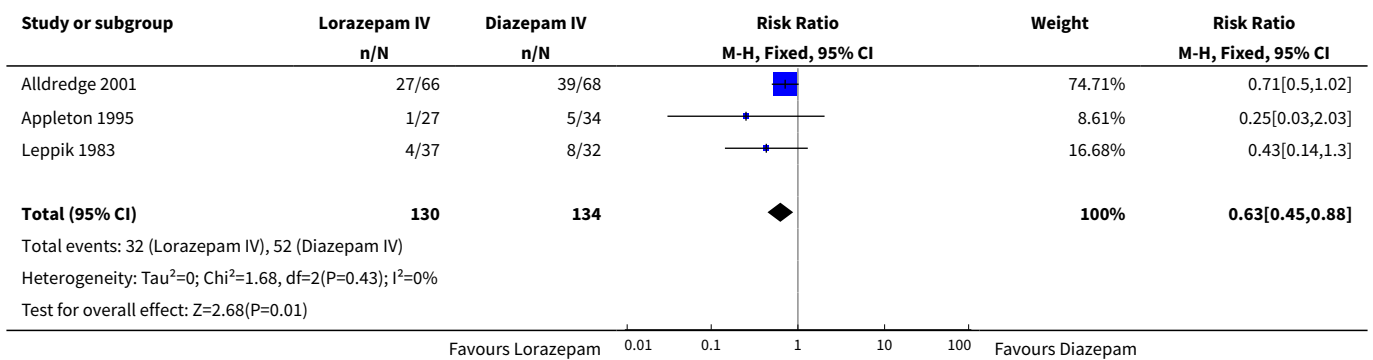
Analysis 1.5. Comparison 1 Lorazepam IV versus diazepam IV, Outcome 5 Death.
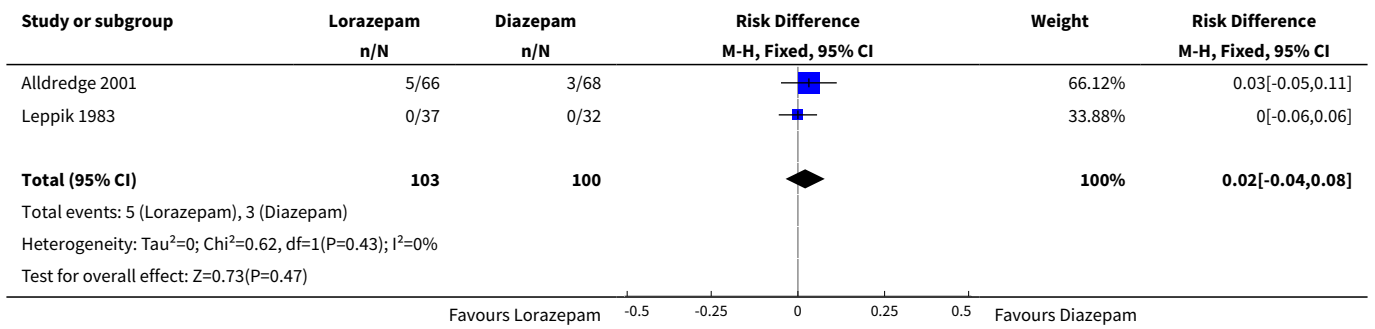
Study or subgroup	Lorazepam n/N	Diazepam n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
Alldredge 2001	5/66	3/68		66.12%	0.03[-0.05,0.11]
Leppik 1983	0/37	0/32		33.88%	0[-0.06,0.06]
Total (95% CI)	**103**	**100**		**100%**	**0.02[-0.04,0.08]**
Total events: 5 (Lorazepam), 3 (Diazepam)					
Heterogeneity: Tau²=0; Chi²=0.62, df=1(P=0.43); I²=0%					
Test for overall effect: Z=0.73(P=0.47)					

Favours Lorazepam -0.5 -0.25 0 0.25 0.5 Favours Diazepam

Comparison 2. Lorazepam IV versus placebo IV

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non-cessation of seizures	1	137	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.38, 0.71]
2 Requirement for ventilatory support	1	137	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.21, 1.07]
3 Adverse effects	1	137	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.21, 1.07]
4 Continuation of status requiring a different drug or general anaesthesia	1	137	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.38, 0.71]
5 Death	1	137	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.18, 1.33]

Analysis 2.1. Comparison 2 Lorazepam IV versus placebo IV, Outcome 1 Non-cessation of seizures.

Study or subgroup	Lorazepam IV n/N	Placebo IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Alldredge 2001	27/66	56/71		100%	0.52[0.38,0.71]
Total (95% CI)	**66**	**71**		**100%**	**0.52[0.38,0.71]**
Total events: 27 (Lorazepam IV), 56 (Placebo IV)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.1(P<0.0001)					

Favours Lorazepam 0.1 0.2 0.5 1 2 5 10 Favours Placebo

Analysis 2.2. Comparison 2 Lorazepam IV versus placebo IV, Outcome 2 Requirement for ventilatory support.

Study or subgroup	Lorazepam IV n/N	Placebo IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Alldredge 2001	7/66	16/71		100%	0.47[0.21,1.07]
Total (95% CI)	**66**	**71**		**100%**	**0.47[0.21,1.07]**
Total events: 7 (Lorazepam IV), 16 (Placebo IV)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.8(P=0.07)					

Favours Lorazepam 0.1 0.2 0.5 1 2 5 10 Favours Placebo

Analysis 2.3. Comparison 2 Lorazepam IV versus placebo IV, Outcome 3 Adverse effects.

Study or subgroup	Lorazepam IV n/N	Placebo IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Alldredge 2001	7/66	16/71		100%	0.47[0.21,1.07]
Total (95% CI)	**66**	**71**		**100%**	**0.47[0.21,1.07]**
Total events: 7 (Lorazepam IV), 16 (Placebo IV)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.8(P=0.07)					

Favours Lorazepam 0.1 0.2 0.5 1 2 5 10 Favours Placebo
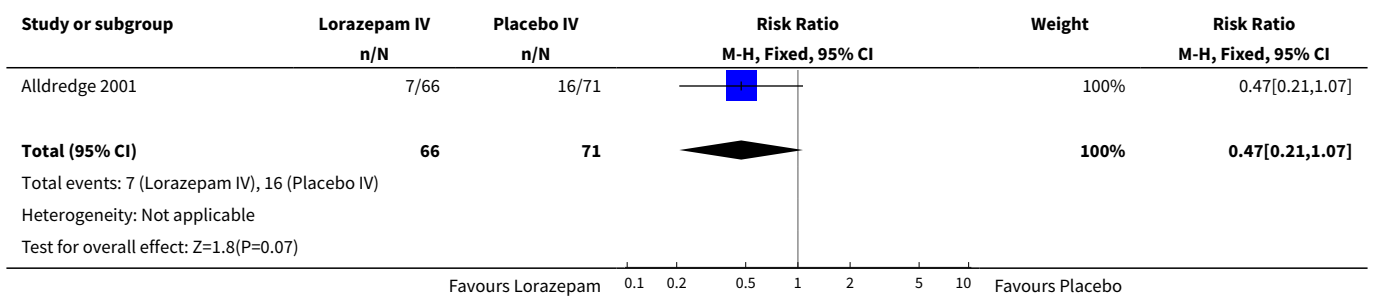
Analysis 2.4. Comparison 2 Lorazepam IV versus placebo IV, Outcome 4 Continuation of status requiring a different drug or general anaesthesia.

Study or subgroup	Lorazepam IV n/N	Placebo IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Alldredge 2001	27/66	56/71		100%	0.52[0.38,0.71]
Total (95% CI)	**66**	**71**		**100%**	**0.52[0.38,0.71]**
Total events: 27 (Lorazepam IV), 56 (Placebo IV)					
Heterogeneity: Not applicable					
Test for overall effect: Z=4.1(P<0.0001)					

Favours Lorazepam 0.1 0.2 0.5 1 2 5 10 Favours Placebo
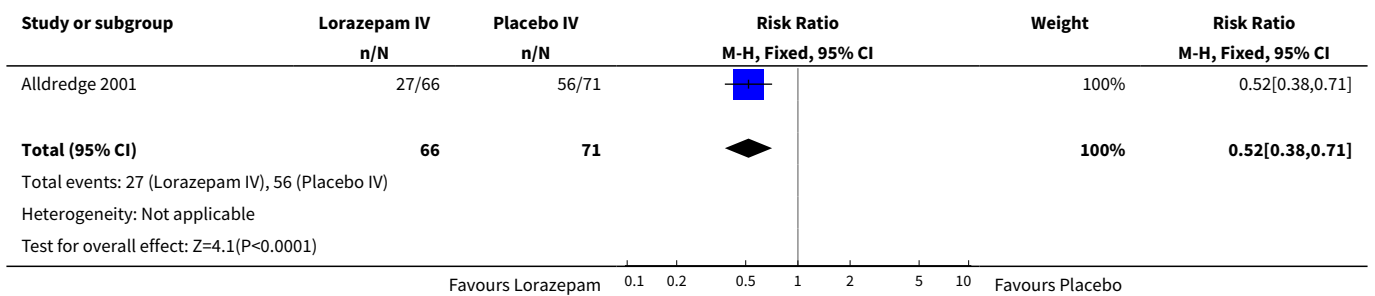
Analysis 2.5. Comparison 2 Lorazepam IV versus placebo IV, Outcome 5 Death.
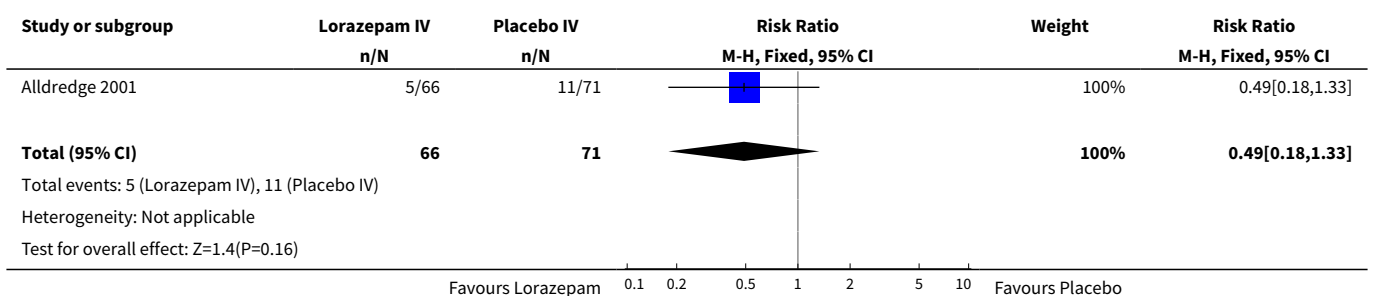
Study or subgroup	Lorazepam IV n/N	Placebo IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Alldredge 2001	5/66	11/71		100%	0.49[0.18,1.33]
Total (95% CI)	**66**	**71**		**100%**	**0.49[0.18,1.33]**
Total events: 5 (Lorazepam IV), 11 (Placebo IV)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.4(P=0.16)					

Favours Lorazepam 0.1 0.2 0.5 1 2 5 10 Favours Placebo

Comparison 3. Lorazepam IV versus diazepam plus phenytoin IV

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Non-cessation of seizures	2	370	Risk Difference (M-H, Random, 95% CI)	-0.04 [-0.35, 0.26]
2 Adverse effects	2	370	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.63, 1.15]
3 Deaths	1	178	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Requirement of Ventilatory support	1	178	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 Lorazepam IV versus diazepam plus phenytoin IV, Outcome 1 Non-cessation of seizures.

Study or subgroup	Lorazepam IV	DZP+Phenytoin IV	Risk Difference	Weight	Risk Difference
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Sreenath 2010	0/90	0/88		52.53%	0[-0.02,0.02]
Treiman 1998	34/97	42/95		47.47%	-0.09[-0.23,0.05]
Total (95% CI)	**187**	**183**		**100%**	**-0.04[-0.35,0.26]**
Total events: 34 (Lorazepam IV), 42 (DZP+Phenytoin IV)					
Heterogeneity: Tau²=0.05; Chi²=18.79, df=1(P<0.0001); I²=94.68%					
Test for overall effect: Z=0.28(P=0.78)					

Favours Lorazepam -1 -0.5 0 0.5 1 Favours DZP+DPH

Analysis 3.2. Comparison 3 Lorazepam IV versus diazepam plus phenytoin IV, Outcome 2 Adverse effects.

Study or subgroup	Lorazepam	DZP+Phenytoin	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Sreenath 2010	4/90	5/88		9.44%	0.78[0.22,2.82]
Treiman 1998	42/97	48/95		90.56%	0.86[0.63,1.16]
Total (95% CI)	**187**	**183**		**100%**	**0.85[0.63,1.15]**
Total events: 46 (Lorazepam), 53 (DZP+Phenytoin)					
Heterogeneity: Tau²=0; Chi²=0.02, df=1(P=0.89); I²=0%					
Test for overall effect: Z=1.07(P=0.29)					

Favours Lorazepam 0.1 0.2 0.5 1 2 5 10 Favours DZP+DPH
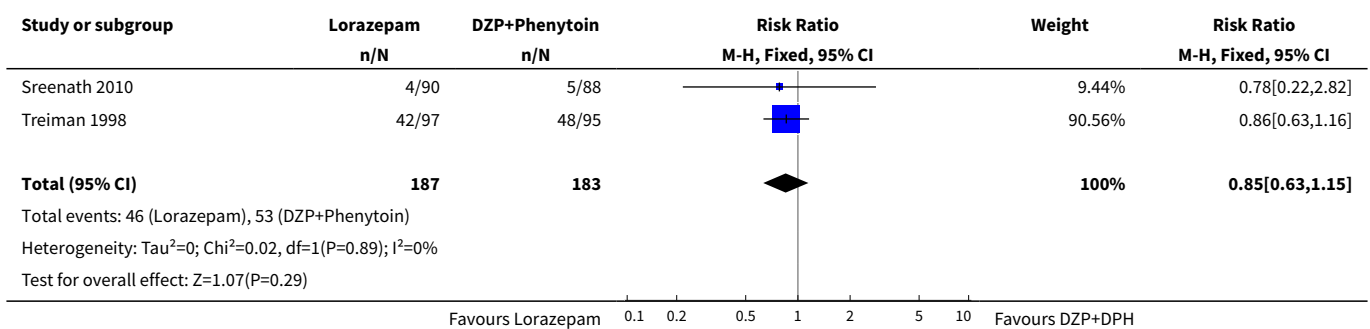
Analysis 3.3. Comparison 3 Lorazepam IV versus diazepam plus phenytoin IV, Outcome 3 Deaths.

Study or subgroup	DZP-Phenytoin n/N	Lorazepam n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Sreenath 2010	0/88	0/90			Not estimable
Total (95% CI)	**88**	**90**			**Not estimable**
Total events: 0 (DZP-Phenytoin), 0 (Lorazepam)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours experimental 0.01 0.1 1 10 100 Favours control
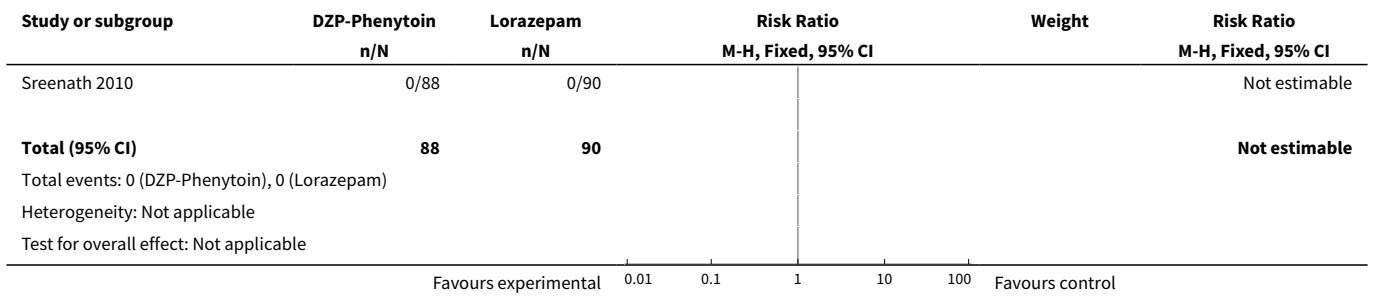
Analysis 3.4. Comparison 3 Lorazepam IV versus diazepam plus phenytoin IV, Outcome 4 Requirement of Ventilatory support.
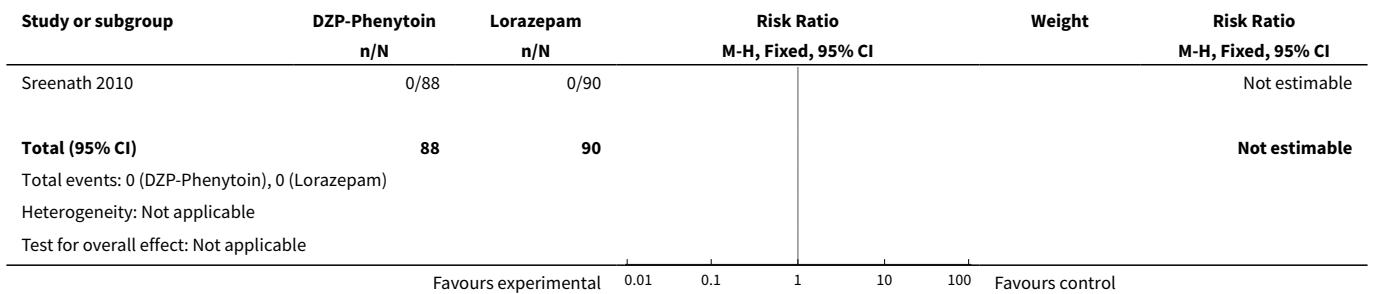
Study or subgroup	DZP-Phenytoin n/N	Lorazepam n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Sreenath 2010	0/88	0/90			Not estimable
Total (95% CI)	**88**	**90**			**Not estimable**
Total events: 0 (DZP-Phenytoin), 0 (Lorazepam)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours experimental 0.01 0.1 1 10 100 Favours control

Comparison 4. Lorazepam IV versus phenobarbitone IV

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non-cessation of seizures	1	188	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.58, 1.21]
2 Adverse effects	1	188	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.63, 1.16]

Analysis 4.1. Comparison 4 Lorazepam IV versus phenobarbitone IV, Outcome 1 Non-cessation of seizures.

Study or subgroup	Lorazepam IV n/N	Phenobarbitone IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Treiman 1998	34/97	38/91		100%	0.84[0.58,1.21]
Total (95% CI)	**97**	**91**		**100%**	**0.84[0.58,1.21]**
Total events: 34 (Lorazepam IV), 38 (Phenobarbitone IV)					
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%					
Test for overall effect: Z=0.94(P=0.35)					

Favours Lorazepam 0.1 0.2 0.5 1 2 5 10 Favours Phenobarb
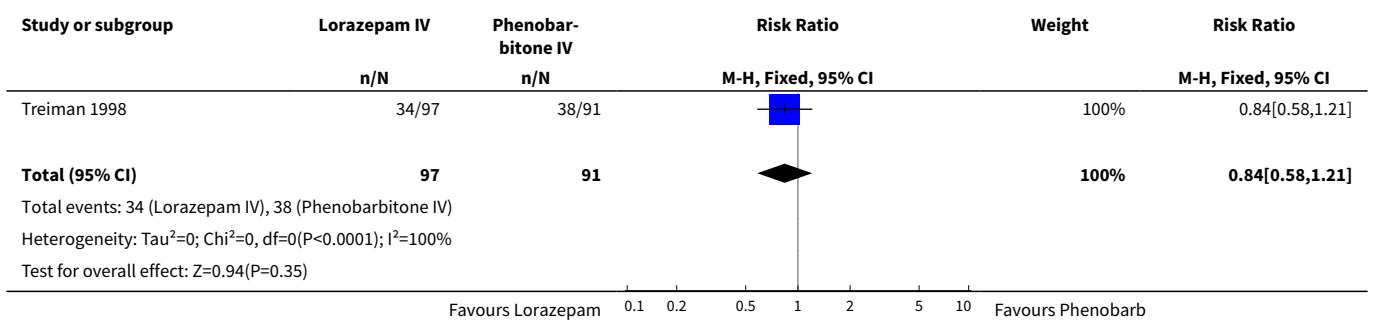
Analysis 4.2. Comparison 4 Lorazepam IV versus phenobarbitone IV, Outcome 2 Adverse effects.
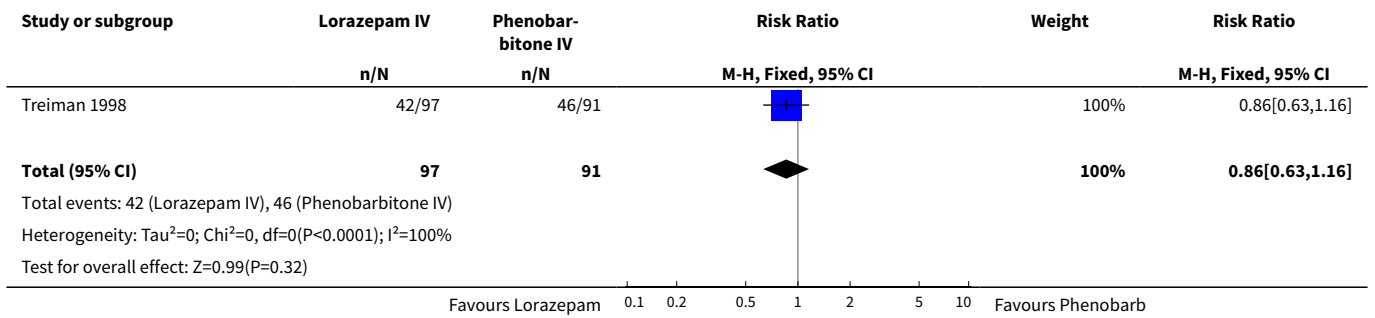
Study or subgroup	Lorazepam IV	Phenobar- bitone IV	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Treiman 1998	42/97	46/91		100%	0.86[0.63,1.16]
Total (95% CI)	**97**	**91**		**100%**	**0.86[0.63,1.16]**
Total events: 42 (Lorazepam IV), 46 (Phenobarbitone IV)					
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%					
Test for overall effect: Z=0.99(P=0.32)					

Favours Lorazepam 0.1 0.2 0.5 1 2 5 10 Favours Phenobarb

Comparison 5. Lorazepam IV versus phenytoin IV

Outcome or subgroup title	No. of studies	No. of partici- pants	Statistical method	Effect size
1 Non-cessation of seizures	1	198	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.45, 0.86]
2 Adverse effects	1	198	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.72, 1.37]

Analysis 5.1. Comparison 5 Lorazepam IV versus phenytoin IV, Outcome 1 Non-cessation of seizures.

Study or subgroup	Lorazepam IV	Phenytoin IV	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Treiman 1998	34/97	57/101		100%	0.62[0.45,0.86]
Total (95% CI)	**97**	**101**		**100%**	**0.62[0.45,0.86]**
Total events: 34 (Lorazepam IV), 57 (Phenytoin IV)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.91(P=0)					

Favours Lorazepam 0.1 0.2 0.5 1 2 5 10 Favours DPH
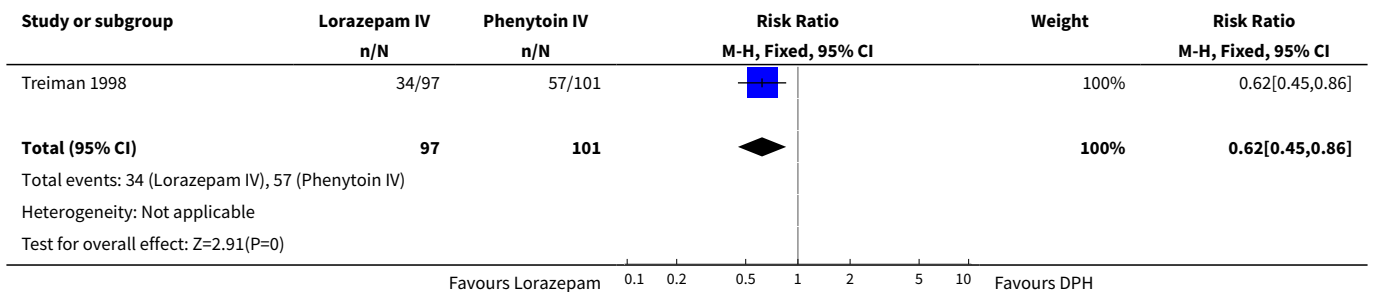
Analysis 5.2. Comparison 5 Lorazepam IV versus phenytoin IV, Outcome 2 Adverse effects.
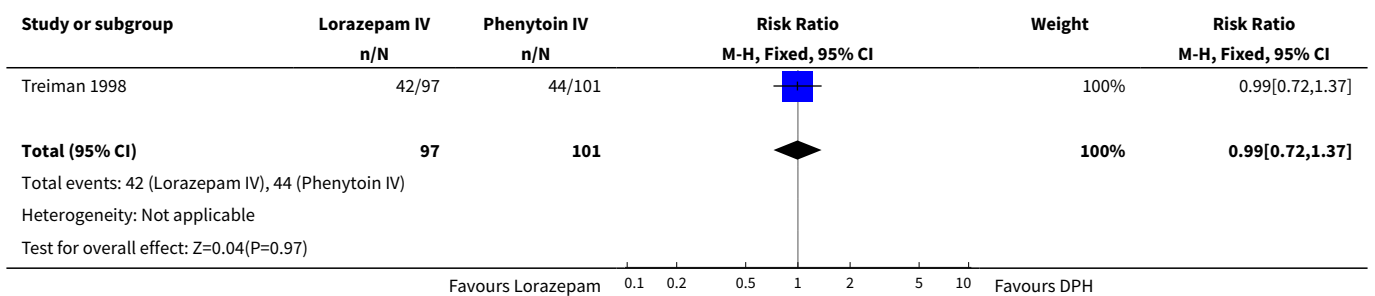
Study or subgroup	Lorazepam IV	Phenytoin IV	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Treiman 1998	42/97	44/101		100%	0.99[0.72,1.37]
Total (95% CI)	**97**	**101**		**100%**	**0.99[0.72,1.37]**
Total events: 42 (Lorazepam IV), 44 (Phenytoin IV)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.04(P=0.97)					

Favours Lorazepam 0.1 0.2 0.5 1 2 5 10 Favours DPH

Comparison 6. Midazolam IV versus lorazepam IV

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non-cessation of seizures	1	27	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.03, 1.56]
2 Requirement for ventilatory support	1	27	Risk Ratio (M-H, Fixed, 95% CI)	0.4 [0.04, 3.90]
3 Adverse effects	1	27	Risk Ratio (M-H, Fixed, 95% CI)	0.4 [0.04, 3.90]
4 Continuation of status requiring a different drug or general anaesthesia	1	27	Risk Ratio (M-H, Fixed, 95% CI)	0.2 [0.03, 1.56]

Analysis 6.1. Comparison 6 Midazolam IV versus lorazepam IV, Outcome 1 Non-cessation of seizures.

Study or subgroup	Midazolam IV n/N	Lorazepam IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
McCormick 1999	1/15	4/12		100%	0.2[0.03,1.56]
Total (95% CI)	**15**	**12**		**100%**	**0.2[0.03,1.56]**

Total events: 1 (Midazolam IV), 4 (Lorazepam IV)

Heterogeneity: Not applicable

Test for overall effect: Z=1.53(P=0.12)

Favours Midazolam 0.01 0.1 1 10 100 Favours Lorazepam
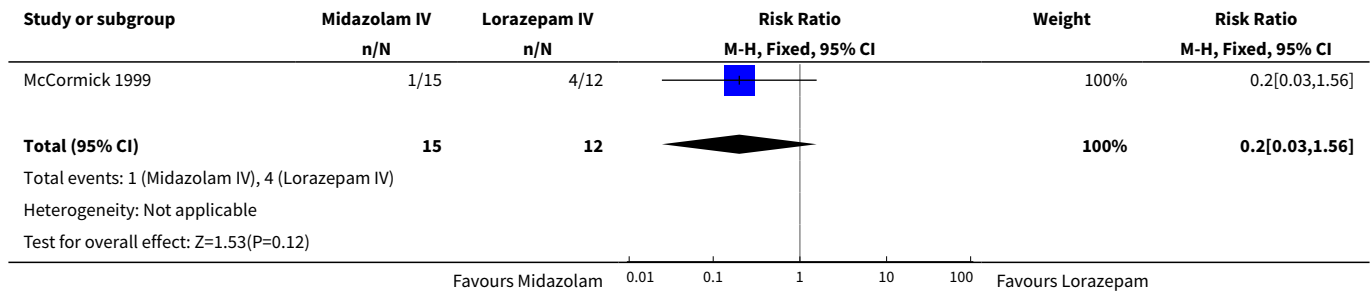
Analysis 6.2. Comparison 6 Midazolam IV versus lorazepam IV, Outcome 2 Requirement for ventilatory support.

Study or subgroup	Midazolam IV n/N	Lorazepam IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
McCormick 1999	1/15	2/12		100%	0.4[0.04,3.9]
Total (95% CI)	**15**	**12**		**100%**	**0.4[0.04,3.9]**

Total events: 1 (Midazolam IV), 2 (Lorazepam IV)

Heterogeneity: Not applicable

Test for overall effect: Z=0.79(P=0.43)

Favours Midazolam 0.01 0.1 1 10 100 Favours Lorazepam
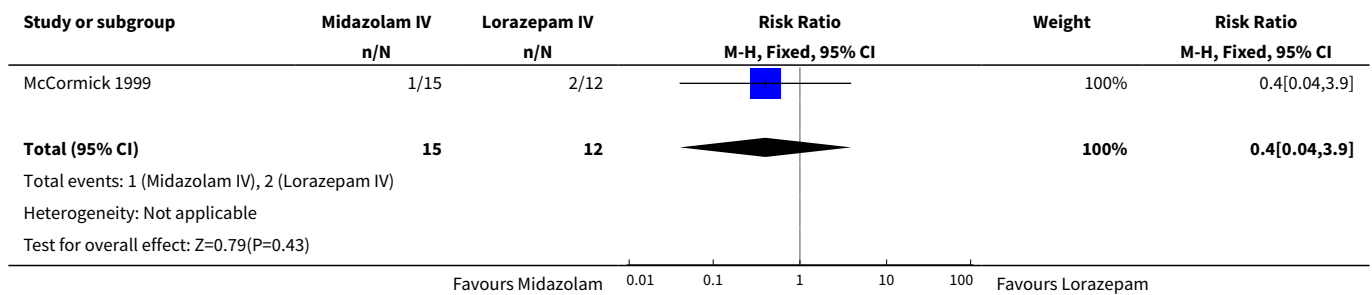
Analysis 6.3. Comparison 6 Midazolam IV versus lorazepam IV, Outcome 3 Adverse effects.

Study or subgroup	Midazolam IV n/N	Lorazepam IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
McCormick 1999	1/15	2/12		100%	0.4[0.04,3.9]

Favours Midazolam 0.01 0.1 1 10 100 Favours Lorazepam

Study or subgroup	Midazolam IV n/N	Lorazepam IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total (95% CI)	15	12		100%	0.4[0.04,3.9]
Total events: 1 (Midazolam IV), 2 (Lorazepam IV)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.79(P=0.43)					

Favours Midazolam 0.01 0.1 1 10 100 Favours Lorazepam

Analysis 6.4. Comparison 6 Midazolam IV versus lorazepam IV, Outcome 4 Continuation of status requiring a different drug or general anaesthesia.

Study or subgroup	Midazolam IV n/N	Lorazepam IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
McCormick 1999	1/15	4/12		100%	0.2[0.03,1.56]
Total (95% CI)	15	12		100%	0.2[0.03,1.56]
Total events: 1 (Midazolam IV), 4 (Lorazepam IV)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.53(P=0.12)					

Favours Midazolam 0.01 0.1 1 10 100 Favours Lorazepam
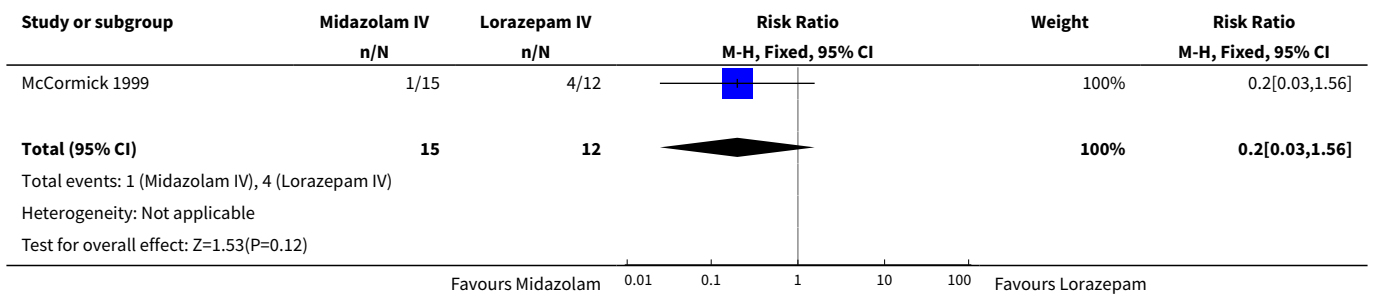
Comparison 7. Midazolam IV versus diazepam IV

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non-cessation of seizures	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.25, 7.27]
2 Requirement for ventilatory support	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.59, 2.07]
3 Adverse effects	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.39, 1.66]
4 Death	1	40	Risk Ratio (M-H, Fixed, 95% CI)	3.62 [0.87, 14.97]

Analysis 7.1. Comparison 7 Midazolam IV versus diazepam IV, Outcome 1 Non-cessation of seizures.

Study or subgroup	Midazolam IV n/N	Diazepam IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Singhi 2002	3/21	2/19		100%	1.36[0.25,7.27]
Total (95% CI)	21	19		100%	1.36[0.25,7.27]
Total events: 3 (Midazolam IV), 2 (Diazepam IV)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.36(P=0.72)					

Favours Midazolam 0.01 0.1 1 10 100 Favours Diazepam
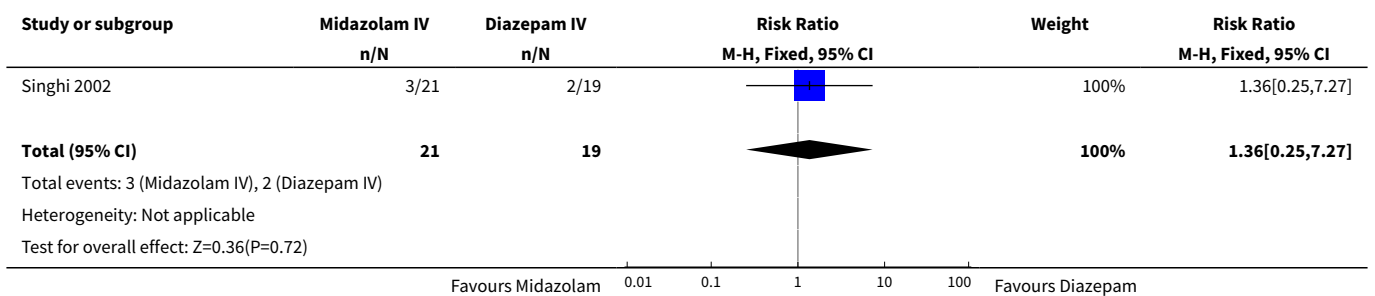
Analysis 7.2. Comparison 7 Midazolam IV versus diazepam IV, Outcome 2 Requirement for ventilatory support.

Study or subgroup	Midazolam IV n/N	Diazepam IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Singhi 2002	11/21	9/19		100%	1.11[0.59,2.07]
Total (95% CI)	**21**	**19**		**100%**	**1.11[0.59,2.07]**
Total events: 11 (Midazolam IV), 9 (Diazepam IV)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.32(P=0.75)					

Favours Midazolam 0.1 0.2 0.5 1 2 5 10 Favours Diazepam
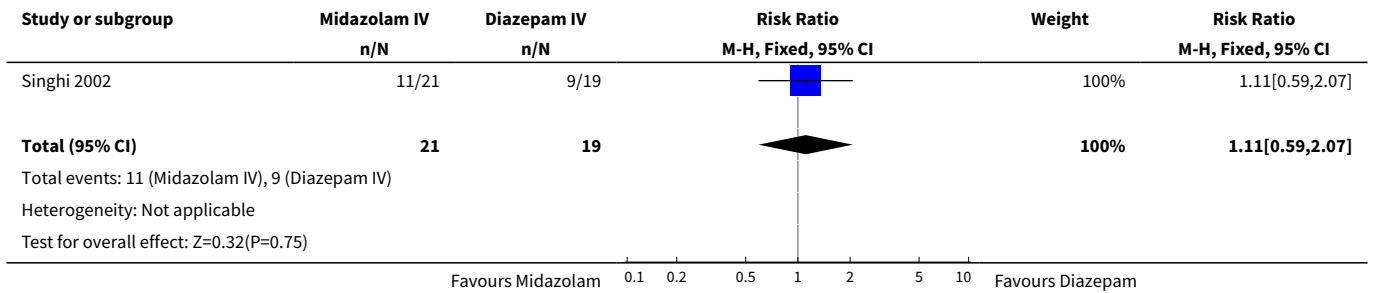
Analysis 7.3. Comparison 7 Midazolam IV versus diazepam IV, Outcome 3 Adverse effects.

Study or subgroup	Midazolam IV n/N	Diazepam IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Singhi 2002	8/21	9/19		100%	0.8[0.39,1.66]
Total (95% CI)	**21**	**19**		**100%**	**0.8[0.39,1.66]**
Total events: 8 (Midazolam IV), 9 (Diazepam IV)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.59(P=0.55)					

Favours Midazolam 0.1 0.2 0.5 1 2 5 10 Favours Diazepam
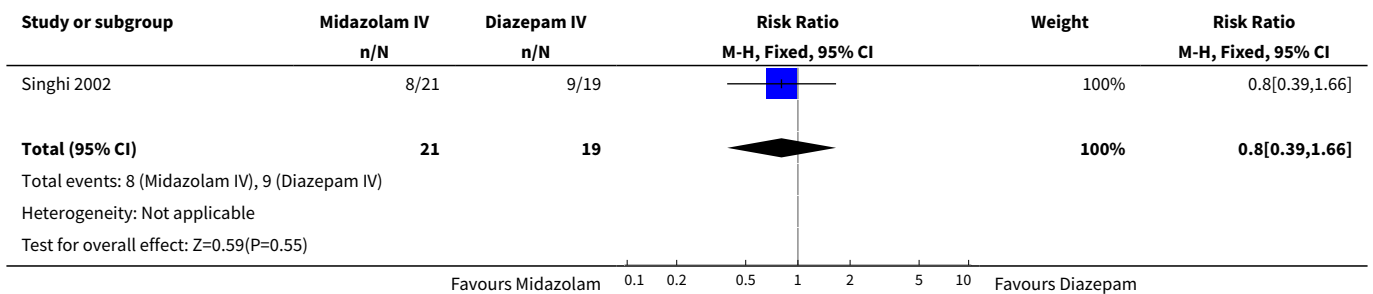
Analysis 7.4. Comparison 7 Midazolam IV versus diazepam IV, Outcome 4 Death.
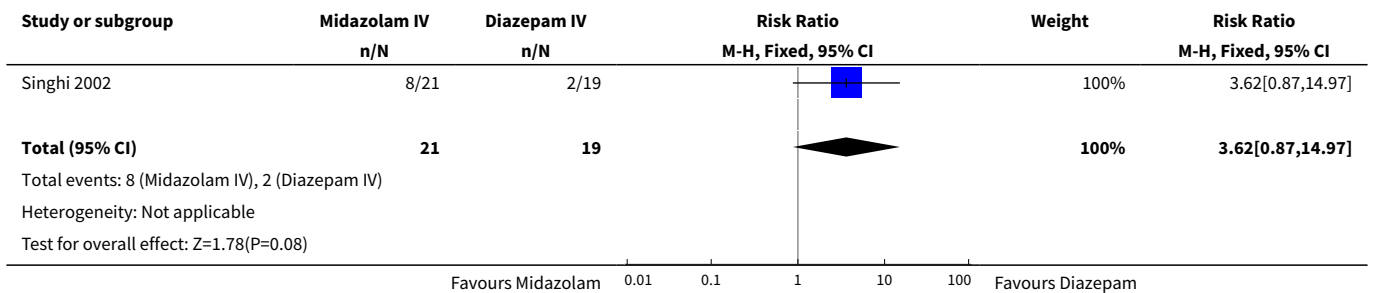
Study or subgroup	Midazolam IV n/N	Diazepam IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Singhi 2002	8/21	2/19		100%	3.62[0.87,14.97]
Total (95% CI)	**21**	**19**		**100%**	**3.62[0.87,14.97]**
Total events: 8 (Midazolam IV), 2 (Diazepam IV)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.78(P=0.08)					

Favours Midazolam 0.01 0.1 1 10 100 Favours Diazepam

Comparison 8. Midazolam IM versus diazepam IV

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non-cessation of seizures	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.06, 12.01]
2 Requirement for ventilatory support	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.06, 12.01]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3 Adverse effects	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.06, 12.01]
4 Continuation of status requiring a different drug or general anaesthesia	1	24	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.06, 12.01]

Analysis 8.1. Comparison 8 Midazolam IM versus diazepam IV, Outcome 1 Non-cessation of seizures.

Study or subgroup	Midazolam IM n/N	Diazepam IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Chamberlain 1997	1/13	1/11		100%	0.85[0.06,12.01]
Total (95% CI)	**13**	**11**		**100%**	**0.85[0.06,12.01]**

Total events: 1 (Midazolam IM), 1 (Diazepam IV)
Heterogeneity: Not applicable
Test for overall effect: Z=0.12(P=0.9)

Favours Midazolam 0.01 0.1 1 10 100 Favours Diazepam
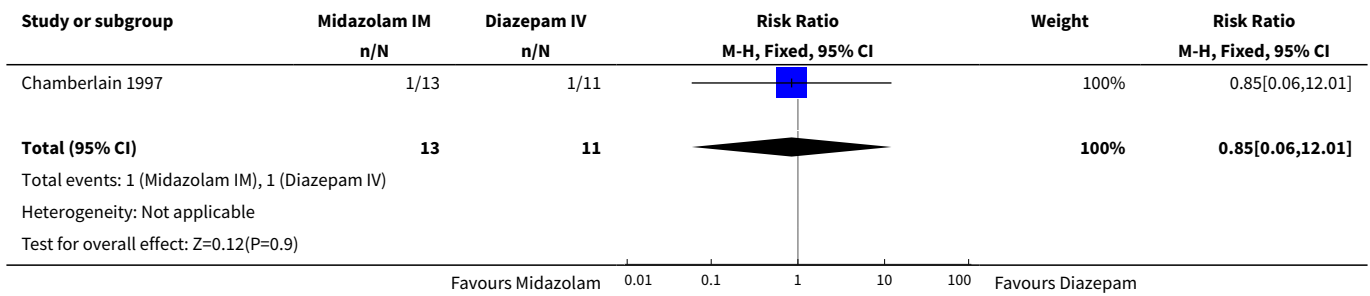
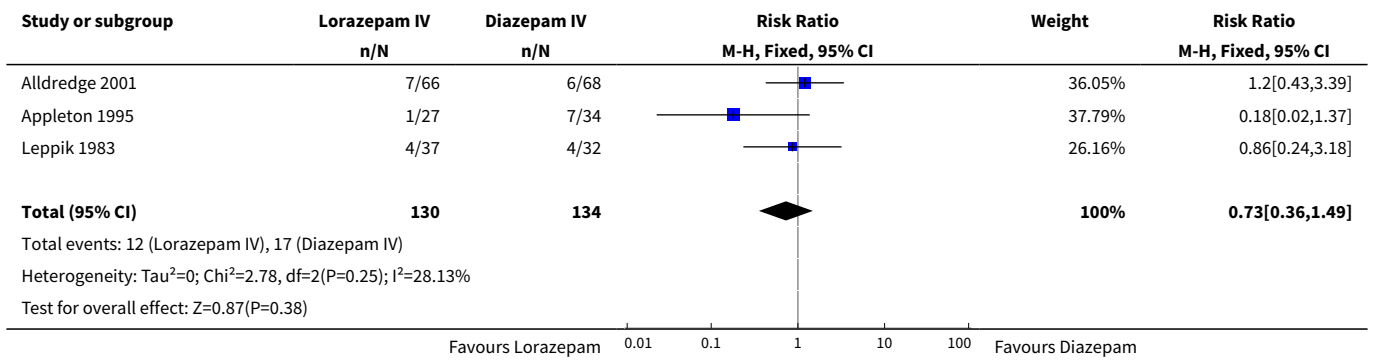### Analysis 8.2. Comparison 8 Midazolam IM versus diazepam IV, Outcome 2 Requirement for ventilatory support.

Study or subgroup	Midazolam IM n/N	Diazepam IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Chamberlain 1997	1/13	1/11		100%	0.85[0.06,12.01]
Total (95% CI)	**13**	**11**		**100%**	**0.85[0.06,12.01]**

Total events: 1 (Midazolam IM), 1 (Diazepam IV)
Heterogeneity: Not applicable
Test for overall effect: Z=0.12(P=0.9)

Favours Midazolam 0.01 0.1 1 10 100 Favours Diazepam
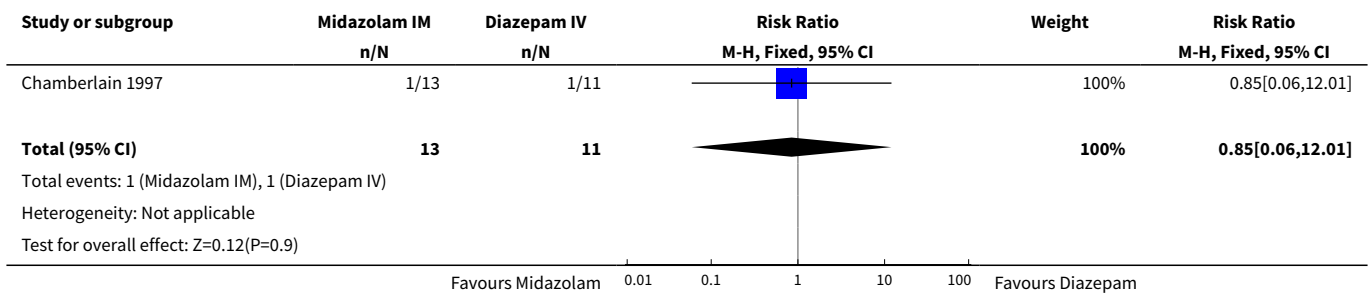
Analysis 8.3. Comparison 8 Midazolam IM versus diazepam IV, Outcome 3 Adverse effects.

Study or subgroup	Midazolam IM n/N	Diazepam IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Chamberlain 1997	1/13	1/11		100%	0.85[0.06,12.01]
Total (95% CI)	**13**	**11**		**100%**	**0.85[0.06,12.01]**

Total events: 1 (Midazolam IM), 1 (Diazepam IV)
Heterogeneity: Not applicable
Test for overall effect: Z=0.12(P=0.9)

Favours Midazolam 0.01 0.1 1 10 100 Favours Diazepam
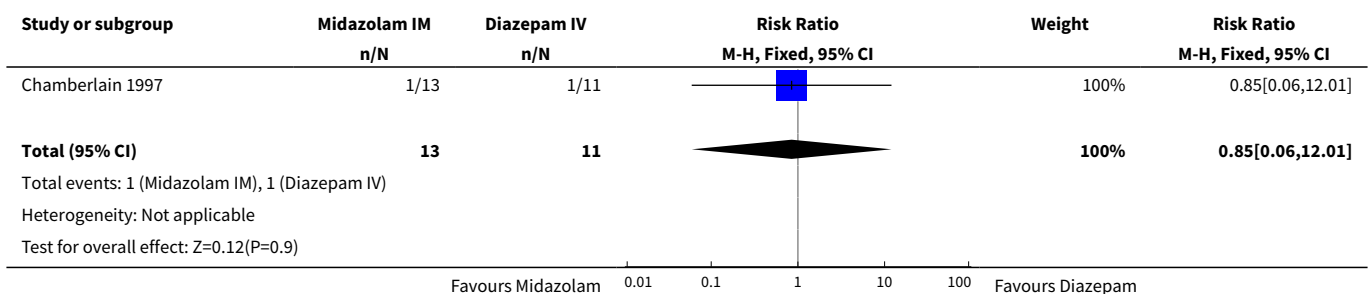
Analysis 8.4. Comparison 8 Midazolam IM versus diazepam IV, Outcome 4 Continuation of status requiring a different drug or general anaesthesia.

Study or subgroup	Midazolam IM n/N	Diazepam IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Chamberlain 1997	1/13	1/11		100%	0.85[0.06,12.01]
Total (95% CI)	**13**	**11**		**100%**	**0.85[0.06,12.01]**
Total events: 1 (Midazolam IM), 1 (Diazepam IV)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.12(P=0.9)					

Favours Midazolam 0.01   0.1   1   10   100   Favours Diazepam
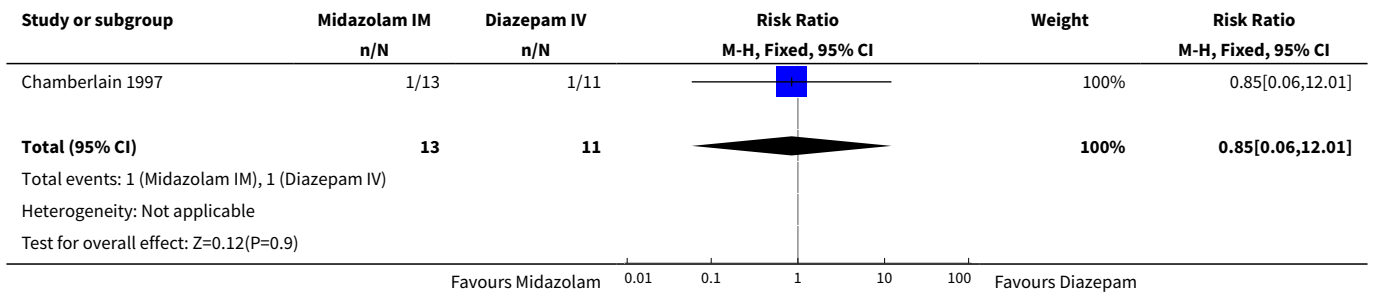
Comparison 9. Diazepam IV versus placebo IV

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non-cessation of seizures	1	139	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.57, 0.92]
2 Requirement for ventilatory support	1	139	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.16, 0.94]
3 Adverse effects	1	139	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.20, 1.04]
4 Continuation of status requiring a different drug or general anaesthesia	1	139	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.57, 0.92]
5 Death	1	139	Risk Ratio (M-H, Fixed, 95% CI)	0.28 [0.08, 0.98]

Analysis 9.1. Comparison 9 Diazepam IV versus placebo IV, Outcome 1 Non-cessation of seizures.

Study or subgroup	Diazepam IV n/N	Placebo IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Alldredge 2001	39/68	56/71		100%	0.73[0.57,0.92]
Total (95% CI)	**68**	**71**		**100%**	**0.73[0.57,0.92]**
Total events: 39 (Diazepam IV), 56 (Placebo IV)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.63(P=0.01)					

Favours Diazepam 0.1   0.2   0.5   1   2   5   10   Favours Placebo
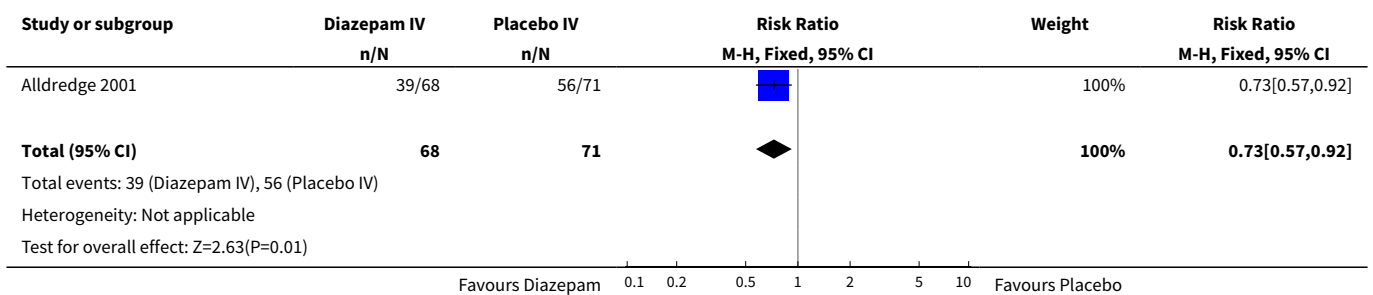
Analysis 9.2. Comparison 9 Diazepam IV versus placebo IV, Outcome 2 Requirement for ventilatory support.

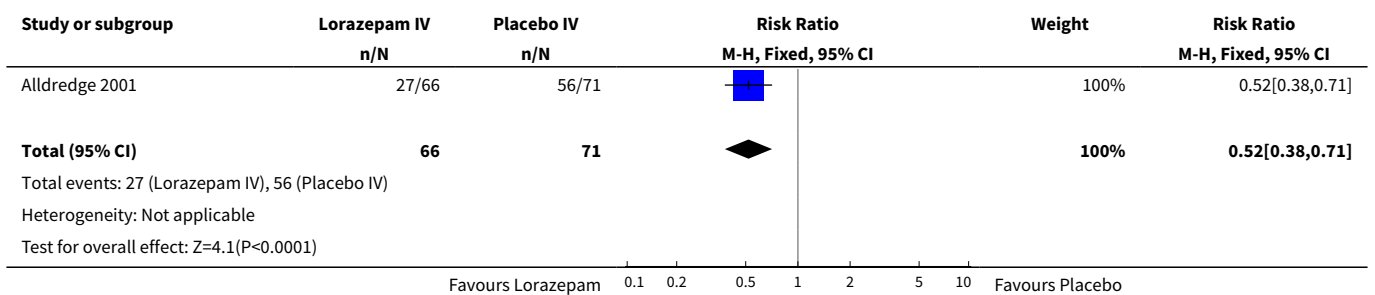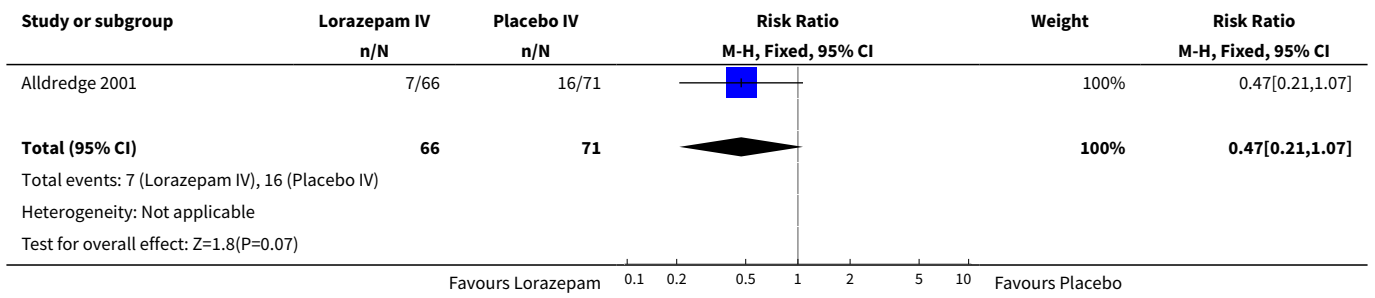| Study or subgroup	Diazepam IV n/N	Placebo IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Alldredge 2001	6/68	16/71		100%	0.39[0.16,0.94]
Total (95% CI)	**68**	**71**		**100%**	**0.39[0.16,0.94]**
Total events: 6 (Diazepam IV), 16 (Placebo IV)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.09(P=0.04)					

Favours Diazepam 0.1 0.2 0.5 1 2 5 10 Favours Placebo
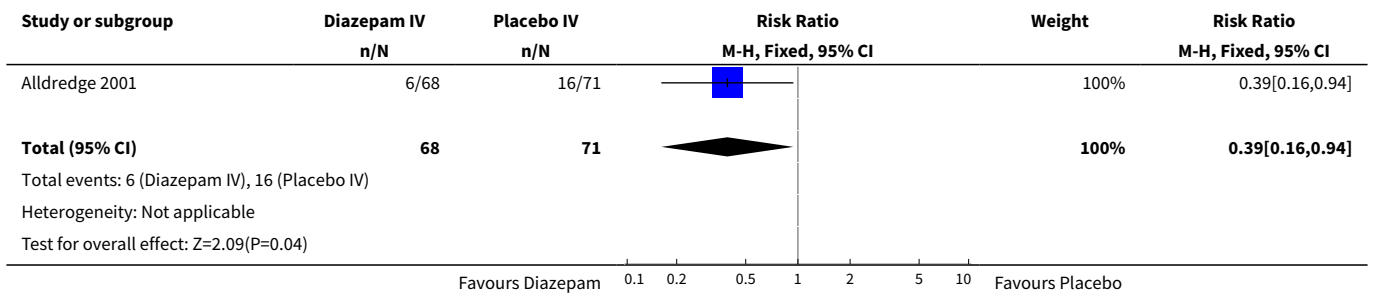
Analysis 9.3. Comparison 9 Diazepam IV versus placebo IV, Outcome 3 Adverse effects.

Study or subgroup	Diazepam IV n/N	Placebo IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Alldredge 2001	7/68	16/71		100%	0.46[0.2,1.04]
Total (95% CI)	**68**	**71**		**100%**	**0.46[0.2,1.04]**
Total events: 7 (Diazepam IV), 16 (Placebo IV)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.86(P=0.06)					

Favours Diazepam 0.1 0.2 0.5 1 2 5 10 Favours Placebo
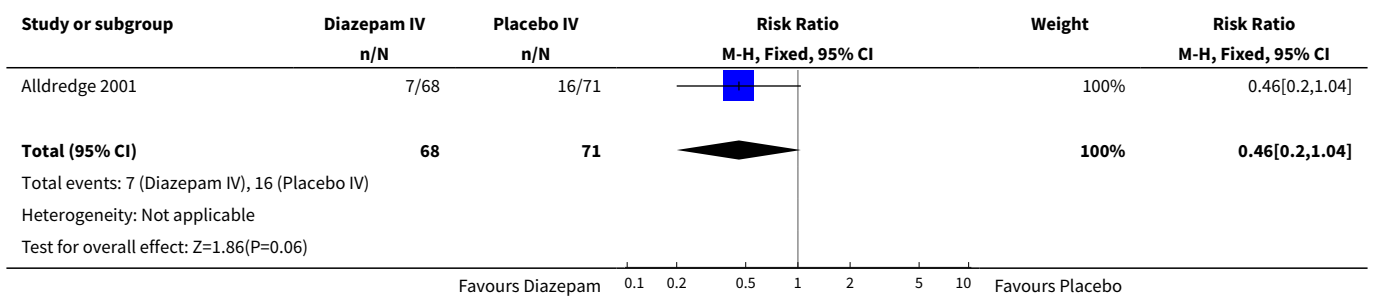
Analysis 9.4. Comparison 9 Diazepam IV versus placebo IV, Outcome 4 Continuation of status requiring a different drug or general anaesthesia.
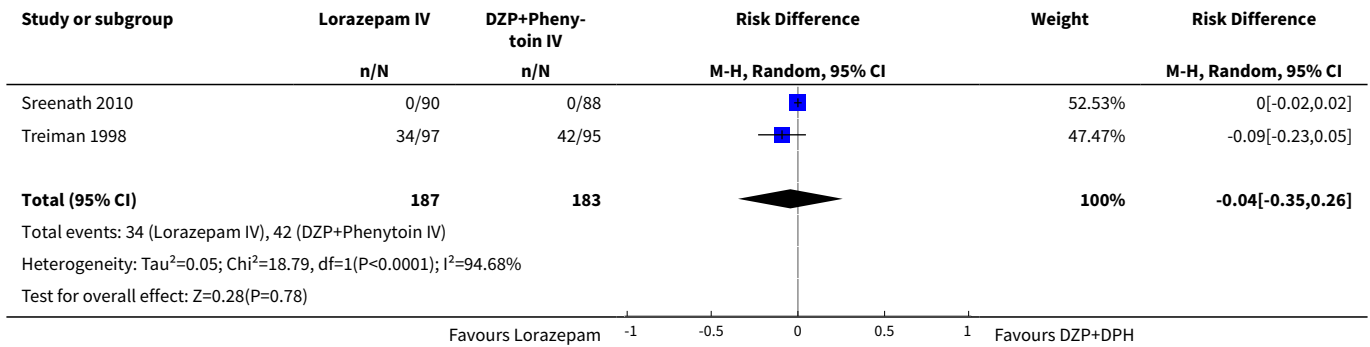
Study or subgroup	Diazepam IV n/N	Placebo IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Alldredge 2001	39/68	56/71		100%	0.73[0.57,0.92]
Total (95% CI)	**68**	**71**		**100%**	**0.73[0.57,0.92]**
Total events: 39 (Diazepam IV), 56 (Placebo IV)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.63(P=0.01)					

Favours Diazepam 0.1 0.2 0.5 1 2 5 10 Favours Placebo
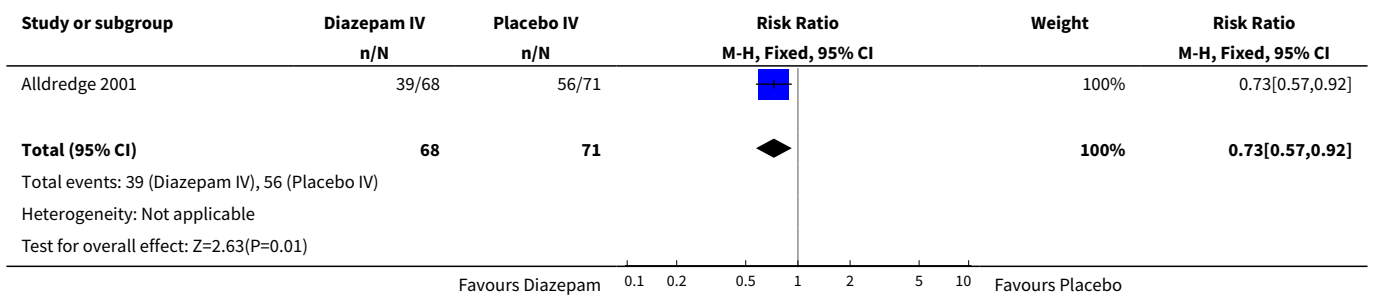
Analysis 9.5. Comparison 9 Diazepam IV versus placebo IV, Outcome 5 Death.

Study or subgroup	Diazepam IV n/N	Placebo IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Alldredge 2001	3/68	11/71		100%	0.28[0.08,0.98]
Total (95% CI)	**68**	**71**		**100%**	**0.28[0.08,0.98]**
Total events: 3 (Diazepam IV), 11 (Placebo IV)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2(P=0.05)					

Favours Diazepam 0.01 0.1 1 10 100 Favours Placebo
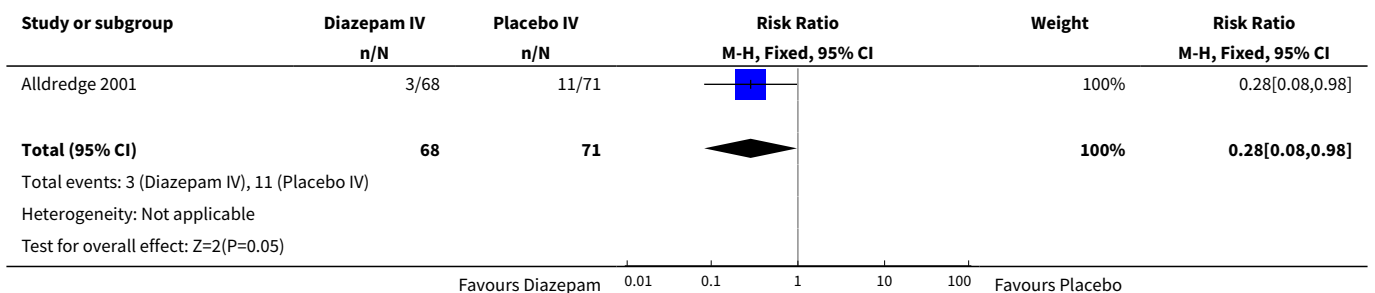
Comparison 10. Diazepam gel versus placebo gel

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non-cessation of seizures	2	165	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.30, 0.62]
2 Adverse effects	2	165	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [0.94, 2.37]

Analysis 10.1. Comparison 10 Diazepam gel versus placebo gel, Outcome 1 Non-cessation of seizures.

Study or subgroup	Diazepam gel n/N	placebo gel n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Cereghino 2002	9/31	28/39		42.25%	0.4[0.23,0.73]
Pellock 1998	15/46	35/49		57.75%	0.46[0.29,0.72]
Total (95% CI)	**77**	**88**		**100%**	**0.43[0.3,0.62]**

Total events: 24 (Diazepam gel), 63 (placebo gel)

Heterogeneity: Tau²=0; Chi²=0.1, df=1(P=0.75); I²=0%

Test for overall effect: Z=4.56(P<0.0001)

Favours Diazepam gel 0.1 0.2 0.5 1 2 5 10 Favours placebo gel

Analysis 10.2. Comparison 10 Diazepam gel versus placebo gel, Outcome 2 Adverse effects.
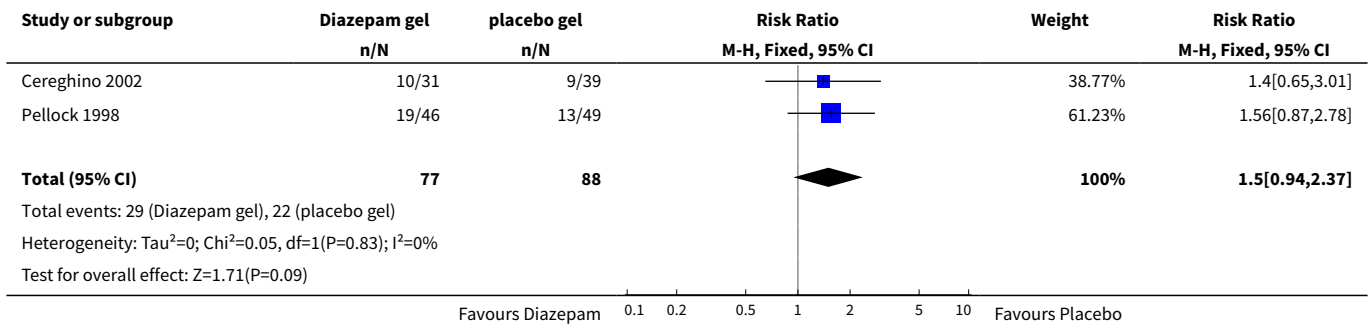
Study or subgroup	Diazepam gel n/N	placebo gel n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Cereghino 2002	10/31	9/39		38.77%	1.4[0.65,3.01]
Pellock 1998	19/46	13/49		61.23%	1.56[0.87,2.78]
Total (95% CI)	**77**	**88**		**100%**	**1.5[0.94,2.37]**

Total events: 29 (Diazepam gel), 22 (placebo gel)

Heterogeneity: Tau²=0; Chi²=0.05, df=1(P=0.83); I²=0%

Test for overall effect: Z=1.71(P=0.09)

Favours Diazepam 0.1 0.2 0.5 1 2 5 10 Favours Placebo

Comparison 11. Levetiracetam versus lorazepam IV

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non-cessation of seizure	1	79	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.44, 2.13]
2 Siezure recurrence at 1-24 h	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.27, 1.54]
3 Hypotension	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.05, 0.96]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Respiratory failure	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.19, 1.12]
5 Death	1	44	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.51, 2.00]
6 Ventilatory need	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.13, 0.99]

Analysis 11.1. Comparison 11 Levetiracetam versus lorazepam IV, Outcome 1 Non-cessation of seizure.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Misra 2011	9/38	10/41		100%	0.97[0.44,2.13]
Total (95% CI)	**38**	**41**		**100%**	**0.97[0.44,2.13]**
Total events: 9 (Experimental), 10 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.07(P=0.94)					

Favours Levetiracetam 0.01 0.1 1 10 100 Favours Lorazepam
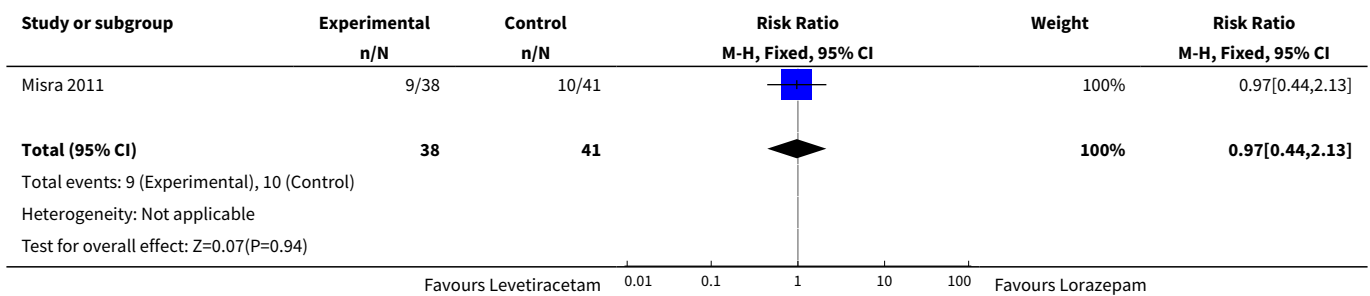
Analysis 11.2. Comparison 11 Levetiracetam versus lorazepam IV, Outcome 2 Siezure recurrence at 1-24 h.

Study or subgroup	Levetiracetam n/N	Lorazepam n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Misra 2011	6/29	10/31		100%	0.64[0.27,1.54]
Total (95% CI)	**29**	**31**		**100%**	**0.64[0.27,1.54]**
Total events: 6 (Levetiracetam), 10 (Lorazepam)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.99(P=0.32)					

Favours Levetiracetam 0.01 0.1 1 10 100 Favours Lorazepam
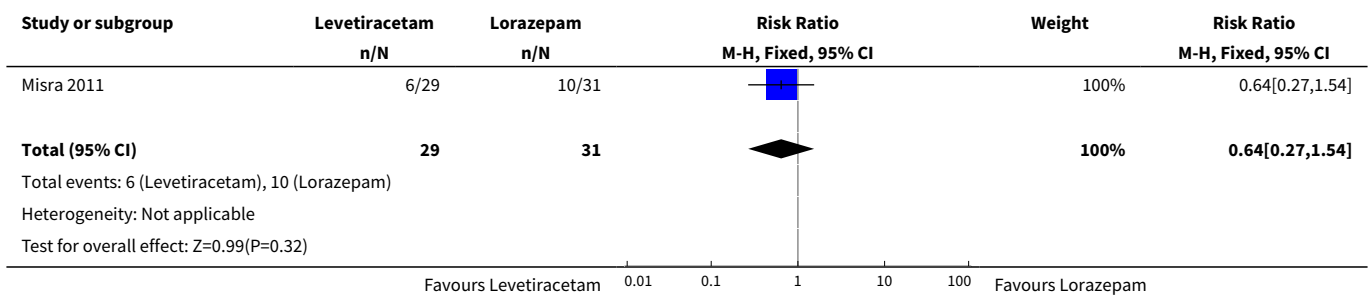
Analysis 11.3. Comparison 11 Levetiracetam versus lorazepam IV, Outcome 3 Hypotension.

Study or subgroup	Levetiracetam n/N	Lorazepam n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Misra 2011	2/23	8/21		100%	0.23[0.05,0.96]
Total (95% CI)	**23**	**21**		**100%**	**0.23[0.05,0.96]**
Total events: 2 (Levetiracetam), 8 (Lorazepam)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.02(P=0.04)					

Favours Levetiracetam 0.01 0.1 1 10 100 Favours Lorazepam
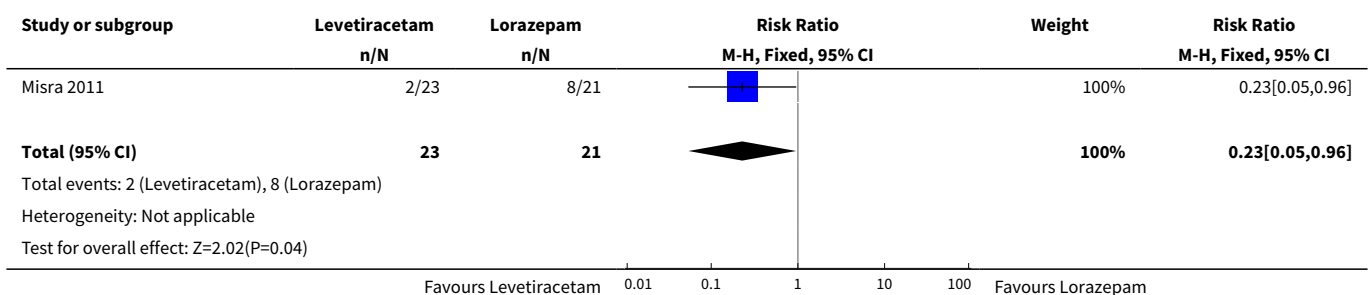
Analysis 11.4.   Comparison 11 Levetiracetam versus lorazepam IV, Outcome 4 Respiratory failure.

Study or subgroup	Levetiracetam n/N	Lorazepam n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Misra 2011	5/23	10/21		100%	0.46[0.19,1.12]
Total (95% CI)	**23**	**21**		**100%**	**0.46[0.19,1.12]**
Total events: 5 (Levetiracetam), 10 (Lorazepam)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.72(P=0.09)					

Favours Levetiracetam 0.01 0.1 1 10 100 Favours Lorazepam
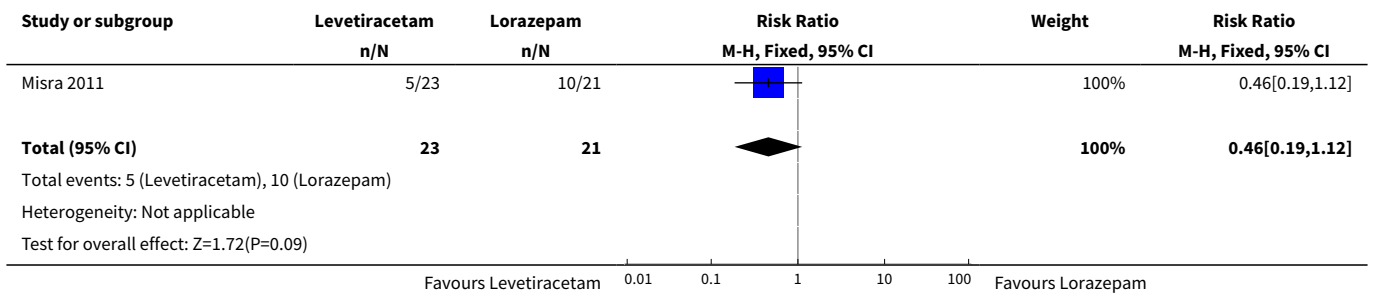
Analysis 11.5.   Comparison 11 Levetiracetam versus lorazepam IV, Outcome 5 Death.

Study or subgroup	Levetiracetam n/N	Lorazepam n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Misra 2011	10/23	9/21		100%	1.01[0.51,2]
Total (95% CI)	**23**	**21**		**100%**	**1.01[0.51,2]**
Total events: 10 (Levetiracetam), 9 (Lorazepam)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.04(P=0.97)					

Favours Levetiracetam 0.01 0.1 1 10 100 Favours Lorazepam
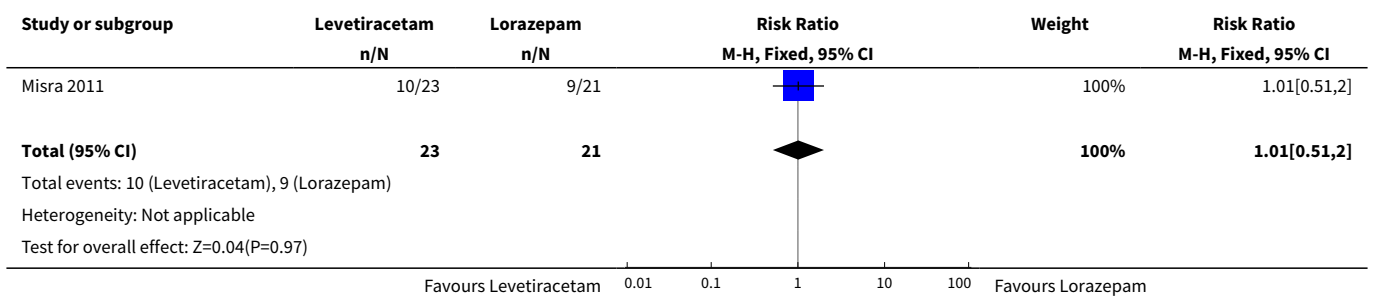
Analysis 11.6.   Comparison 11 Levetiracetam versus lorazepam IV, Outcome 6 Ventilatory need.
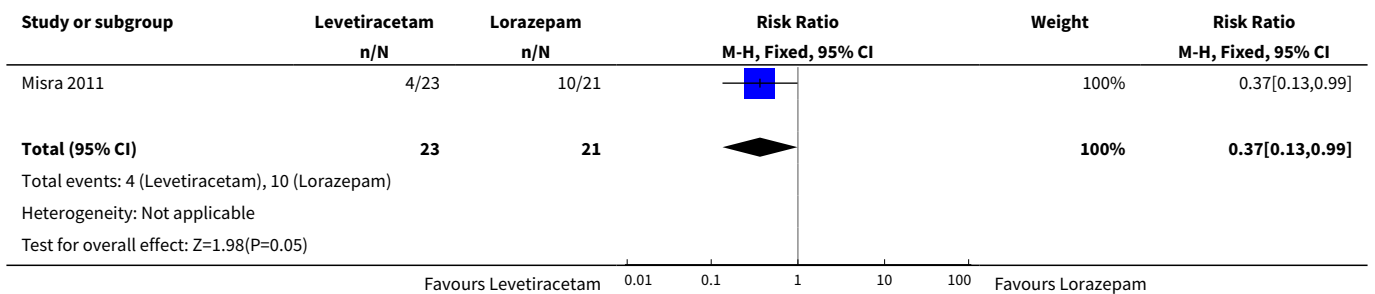
Study or subgroup	Levetiracetam n/N	Lorazepam n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Misra 2011	4/23	10/21		100%	0.37[0.13,0.99]
Total (95% CI)	**23**	**21**		**100%**	**0.37[0.13,0.99]**
Total events: 4 (Levetiracetam), 10 (Lorazepam)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.98(P=0.05)					

Favours Levetiracetam 0.01 0.1 1 10 100 Favours Lorazepam

Comparison 12.   Diazepam plus phenytoin IV versus phenobarbitone IV

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non-cessation of seizures	1	36	Risk Ratio (M-H, Fixed, 95% CI)	4.0 [0.98, 16.30]
2 Adverse effects	2	222	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.77, 1.30]
3 Requirement for ventilatory support	1	36	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.40, 2.52]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4 Death	1	36	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.10, 0.10]

Analysis 12.1. Comparison 12 Diazepam plus phenytoin IV versus phenobarbitone IV, Outcome 1 Non-cessation of seizures.

Study or subgroup	Di-azepam-PHT IV n/N	Phenobar-bitone IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Shaner 1988	8/18	2/18		100%	4[0.98,16.3]
Total (95% CI)	**18**	**18**		**100%**	**4[0.98,16.3]**

Total events: 8 (Diazepam-PHT IV), 2 (Phenobarbitone IV)
Heterogeneity: Not applicable
Test for overall effect: Z=1.93(P=0.05)

Favours Diazepam-PHT 0.01 0.1 1 10 100 Favours Phenobarb
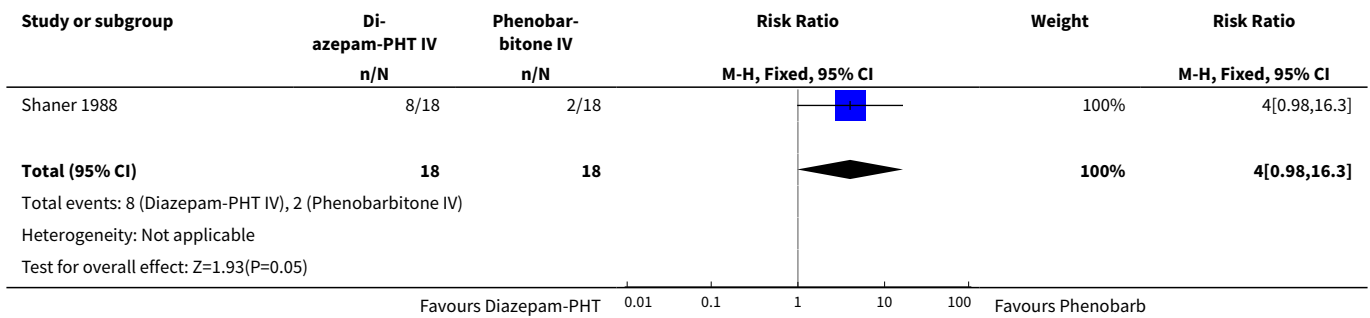
Analysis 12.2. Comparison 12 Diazepam plus phenytoin IV versus phenobarbitone IV, Outcome 2 Adverse effects.

Study or subgroup	Di-azepam-PHT IV n/N	Phenobar-bitone IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Shaner 1988	9/18	9/18		16.07%	1[0.52,1.92]
Treiman 1998	48/95	46/91		83.93%	1[0.75,1.33]
Total (95% CI)	**113**	**109**		**100%**	**1[0.77,1.3]**

Total events: 57 (Diazepam-PHT IV), 55 (Phenobarbitone IV)
Heterogeneity: Tau²=0; Chi²=0, df=1(P=1); I²=0%
Test for overall effect: Z=0(P=1)

Favours Diazepam-PHT 0.1 0.2 0.5 1 2 5 10 Favours Phenobarb
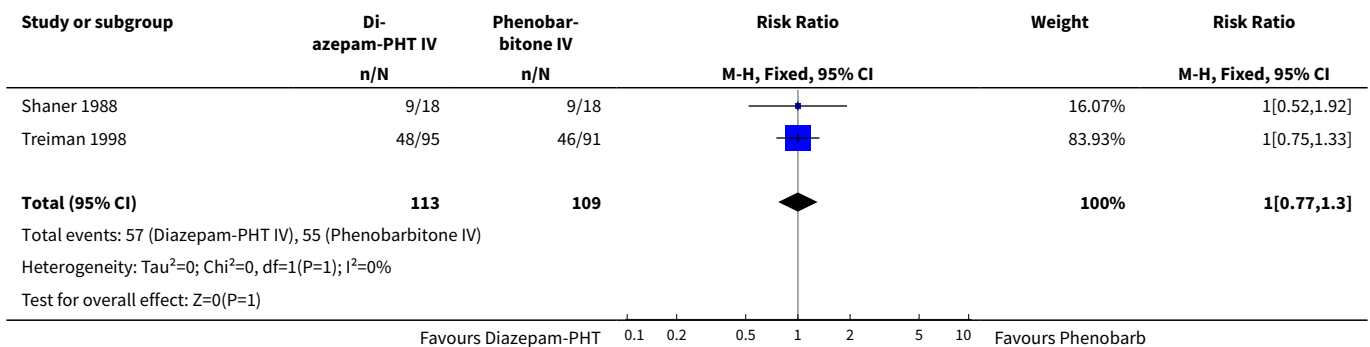
Analysis 12.3. Comparison 12 Diazepam plus phenytoin IV versus phenobarbitone IV, Outcome 3 Requirement for ventilatory support.

Study or subgroup	Di-azepam-PHT IV n/N	Phenobar-bitone IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Shaner 1988	6/18	6/18		100%	1[0.4,2.52]
Total (95% CI)	**18**	**18**		**100%**	**1[0.4,2.52]**

Total events: 6 (Diazepam-PHT IV), 6 (Phenobarbitone IV)
Heterogeneity: Not applicable
Test for overall effect: Not applicable

Favours Diazepam-PHT 0.1 0.2 0.5 1 2 5 10 Favours Phenobarb
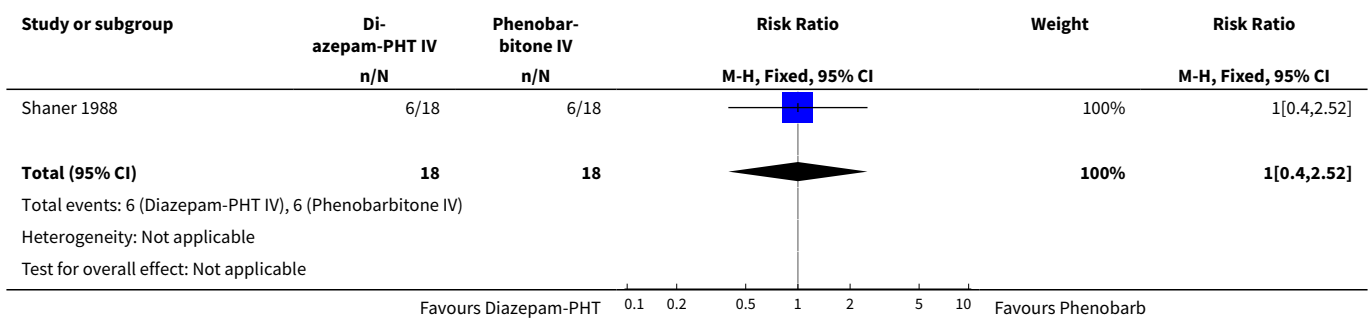
Analysis 12.4. Comparison 12 Diazepam plus phenytoin IV versus phenobarbitone IV, Outcome 4 Death.
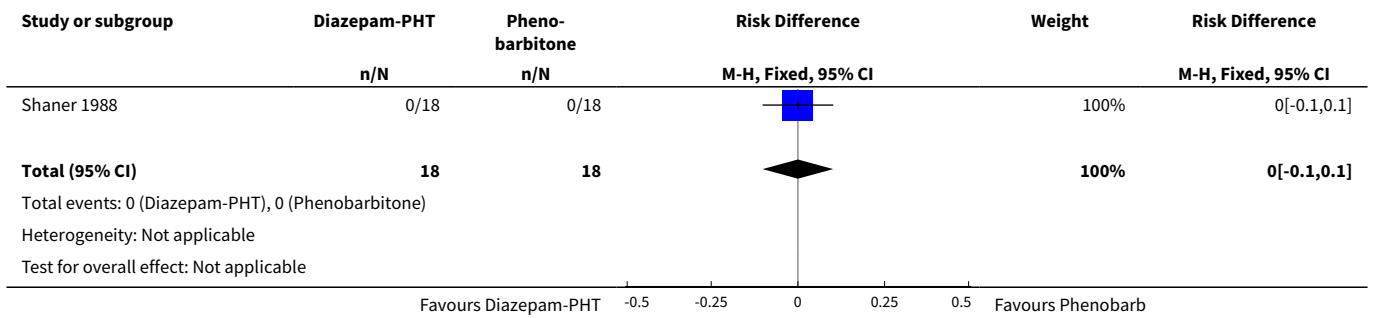
Study or subgroup	Diazepam-PHT n/N	Pheno-barbitone n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
Shaner 1988	0/18	0/18		100%	0[-0.1,0.1]
Total (95% CI)	**18**	**18**		**100%**	**0[-0.1,0.1]**
Total events: 0 (Diazepam-PHT), 0 (Phenobarbitone)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours Diazepam-PHT -0.5 -0.25 0 0.25 0.5 Favours Phenobarb

Comparison 13. Diazepam plus phenytoin IV versus phenobarbitone IV (premonitory status)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Non-cessation of seizures	1	186	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.76, 1.47]

Analysis 13.1. Comparison 13 Diazepam plus phenytoin IV versus phenobarbitone IV (premonitory status), Outcome 1 Non-cessation of seizures.
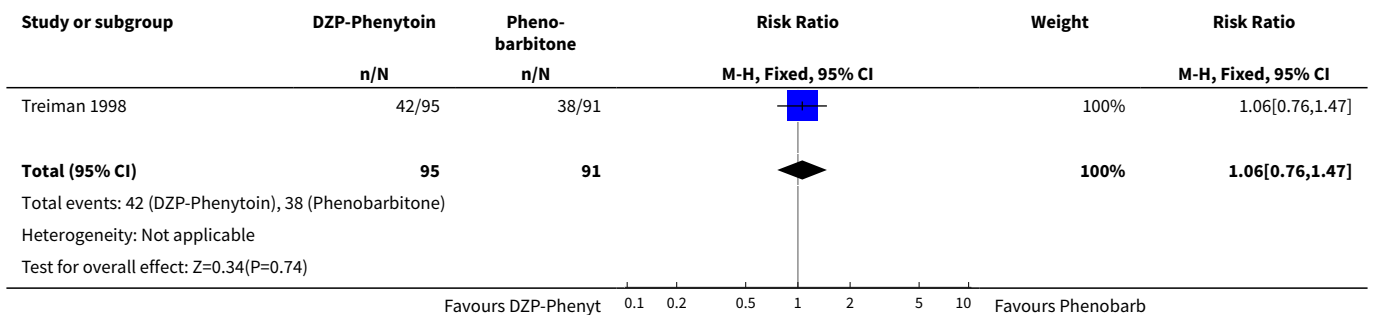
Study or subgroup	DZP-Phenytoin n/N	Pheno-barbitone n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Treiman 1998	42/95	38/91		100%	1.06[0.76,1.47]
Total (95% CI)	**95**	**91**		**100%**	**1.06[0.76,1.47]**
Total events: 42 (DZP-Phenytoin), 38 (Phenobarbitone)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.34(P=0.74)					

Favours DZP-Phenyt 0.1 0.2 0.5 1 2 5 10 Favours Phenobarb

Comparison 14. Diazepam plus phenytoin IV versus phenytoin IV

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Non-cessation of seizures	1	196	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.59, 1.04]
2 Adverse effects	1	196	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.86, 1.56]

Analysis 14.1. Comparison 14 Diazepam plus phenytoin IV versus phenytoin IV, Outcome 1 Non-cessation of seizures.

Study or subgroup	DZP+Phenytoin n/N	Phenytoin n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Treiman 1998	42/95	57/101		100%	0.78[0.59,1.04]
Total (95% CI)	**95**	**101**		**100%**	**0.78[0.59,1.04]**
Total events: 42 (DZP+Phenytoin), 57 (Phenytoin)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.69(P=0.09)					

Favours DZP+DPH 0.1 0.2 0.5 1 2 5 10 Favours DPH
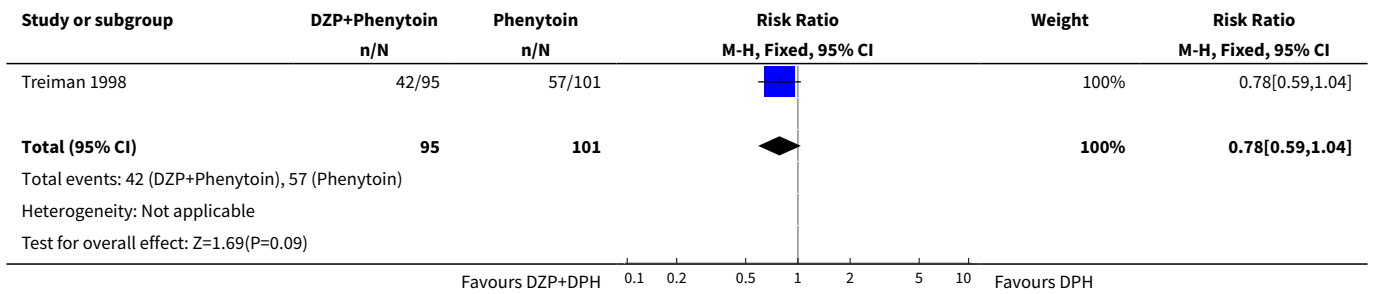
Analysis 14.2. Comparison 14 Diazepam plus phenytoin IV versus phenytoin IV, Outcome 2 Adverse effects.
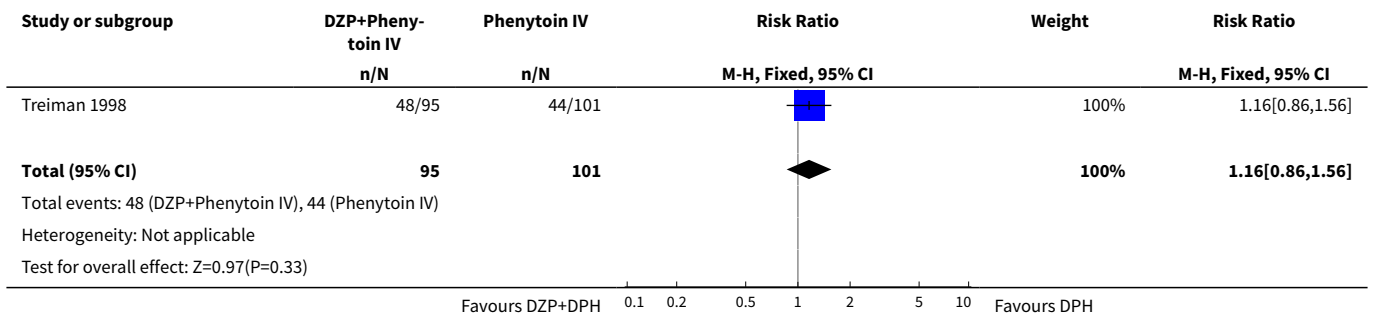
Study or subgroup	DZP+Phenytoin IV n/N	Phenytoin IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Treiman 1998	48/95	44/101		100%	1.16[0.86,1.56]
Total (95% CI)	**95**	**101**		**100%**	**1.16[0.86,1.56]**
Total events: 48 (DZP+Phenytoin IV), 44 (Phenytoin IV)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.97(P=0.33)					

Favours DZP+DPH 0.1 0.2 0.5 1 2 5 10 Favours DPH

Comparison 15. Phenobarbitone IV versus phenytoin IV

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non-cessation of seizures	1	186	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.57, 1.06]
2 Adverse effects	1	186	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.81, 1.47]

Analysis 15.1. Comparison 15 Phenobarbitone IV versus phenytoin IV, Outcome 1 Non-cessation of seizures.

Study or subgroup	Phenobarbitone IV n/N	Phenytoin IV n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Treiman 1998	38/91	51/95		100%	0.78[0.57,1.06]
Total (95% CI)	**91**	**95**		**100%**	**0.78[0.57,1.06]**
Total events: 38 (Phenobarbitone IV), 51 (Phenytoin IV)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.61(P=0.11)					

Favours Phenobarb 0.5 0.7 1 1.5 2 Favours DPH
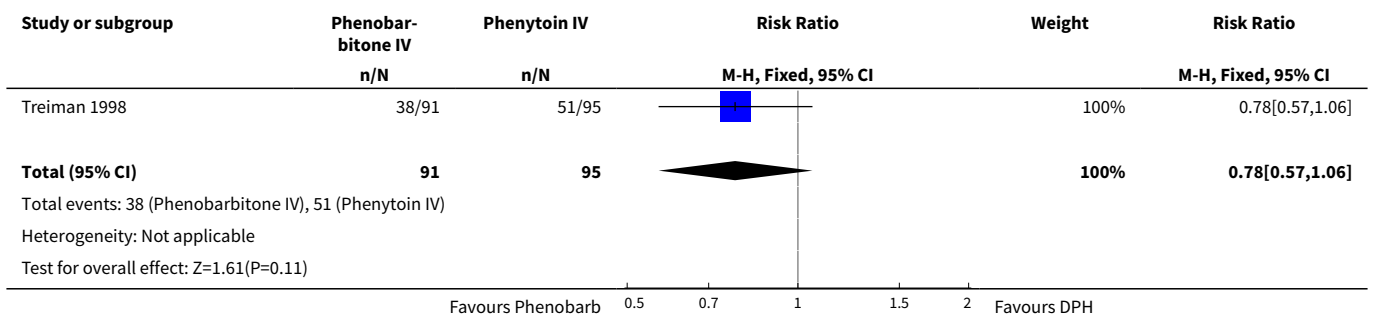
Analysis 15.2. Comparison 15 Phenobarbitone IV versus phenytoin IV, Outcome 2 Adverse effects.

Study or subgroup	Phenobar-bitone IV	Phenytoin IV	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Treiman 1998	46/91	44/95		100%	1.09[0.81,1.47]
Total (95% CI)	**91**	**95**		**100%**	**1.09[0.81,1.47]**
Total events: 46 (Phenobarbitone IV), 44 (Phenytoin IV)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.58(P=0.56)					

Favours Phenobarb 0.1 0.2 0.5 1 2 5 10 Favours DPH
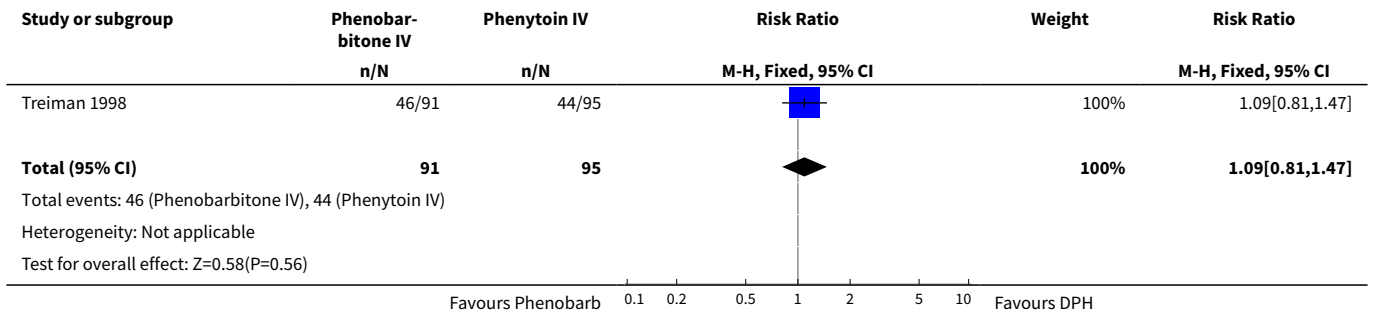
Comparison 16. Lorazepam intranasal versus paraldehyde IM

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Cessation of seizures	1	160	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.99, 1.52]
2 Deaths	1	160	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.59, 2.27]

Analysis 16.1. Comparison 16 Lorazepam intranasal versus paraldehyde IM, Outcome 1 Cessation of seizures.

Study or subgroup	Lorazepam	Paraldehyde	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Ahmad 2006	60/80	49/80		100%	1.22[0.99,1.52]
Total (95% CI)	**80**	**80**		**100%**	**1.22[0.99,1.52]**
Total events: 60 (Lorazepam), 49 (Paraldehyde)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.84(P=0.07)					

Favours experimental 0.01 0.1 1 10 100 Favours control
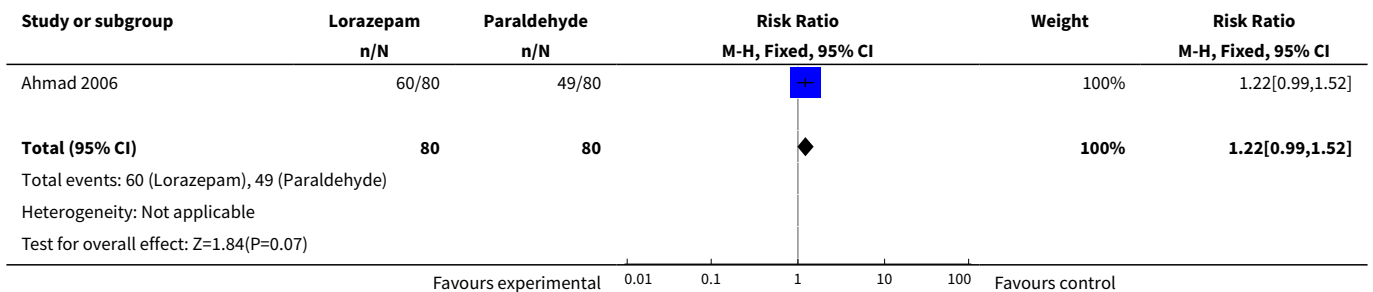
Analysis 16.2. Comparison 16 Lorazepam intranasal versus paraldehyde IM, Outcome 2 Deaths.
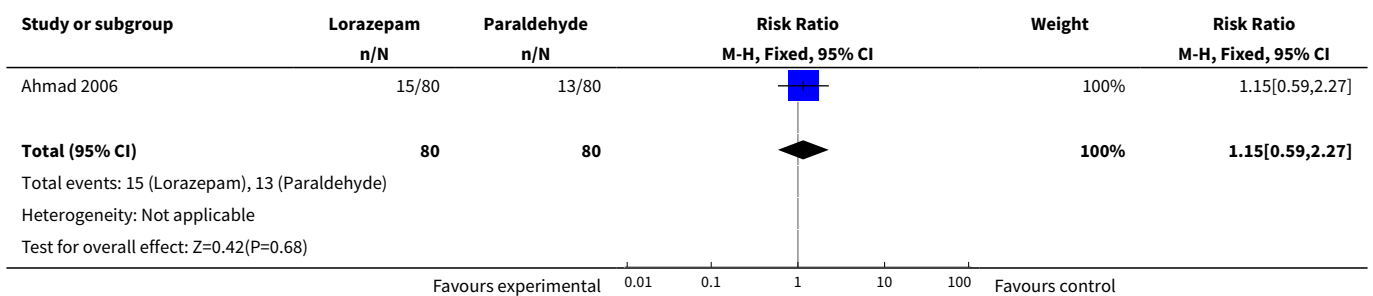
Study or subgroup	Lorazepam	Paraldehyde	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Fixed, 95% CI		M-H, Fixed, 95% CI
Ahmad 2006	15/80	13/80		100%	1.15[0.59,2.27]
Total (95% CI)	**80**	**80**		**100%**	**1.15[0.59,2.27]**
Total events: 15 (Lorazepam), 13 (Paraldehyde)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.42(P=0.68)					

Favours experimental 0.01 0.1 1 10 100 Favours control

Comparison 17. Valproate versus phenytoin IV

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Non-cessation of seizure	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.28, 2.00]
2 Adverse effects	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.16, 1.55]
3 Deaths	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.26, 3.78]

Analysis 17.1. Comparison 17 Valproate versus phenytoin IV, Outcome 1 Non-cessation of seizure.

Study or subgroup	Valproate n/N	Phenytoin n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Agarwal 2007	6/50	8/50		100%	0.75[0.28,2]
Total (95% CI)	**50**	**50**		**100%**	**0.75[0.28,2]**

Total events: 6 (Valproate), 8 (Phenytoin)
Heterogeneity: Not applicable
Test for overall effect: Z=0.57(P=0.57)

Favours Valproate 0.01 0.1 1 10 100 Favours Phenytoin
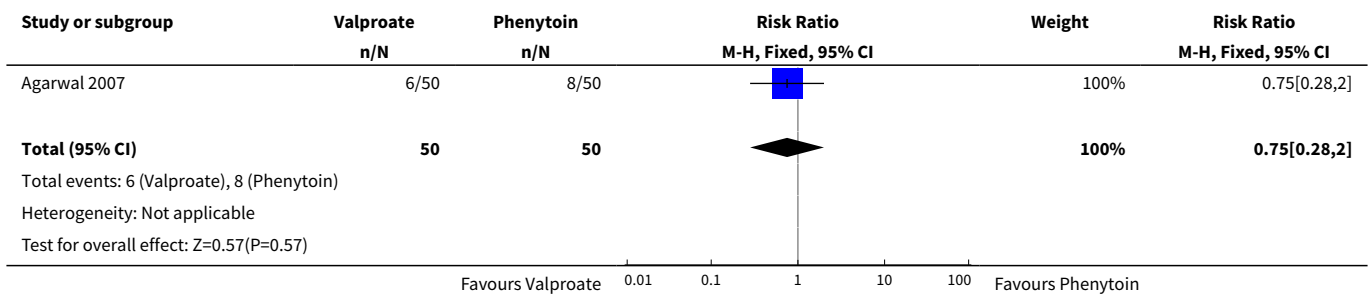
Analysis 17.2. Comparison 17 Valproate versus phenytoin IV, Outcome 2 Adverse effects.

Study or subgroup	Valproate n/N	Phenytoin n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Agarwal 2007	4/50	8/50		100%	0.5[0.16,1.55]
Total (95% CI)	**50**	**50**		**100%**	**0.5[0.16,1.55]**

Total events: 4 (Valproate), 8 (Phenytoin)
Heterogeneity: Not applicable
Test for overall effect: Z=1.2(P=0.23)

Favours Valproate 0.01 0.1 1 10 100 Favours Phenytoin
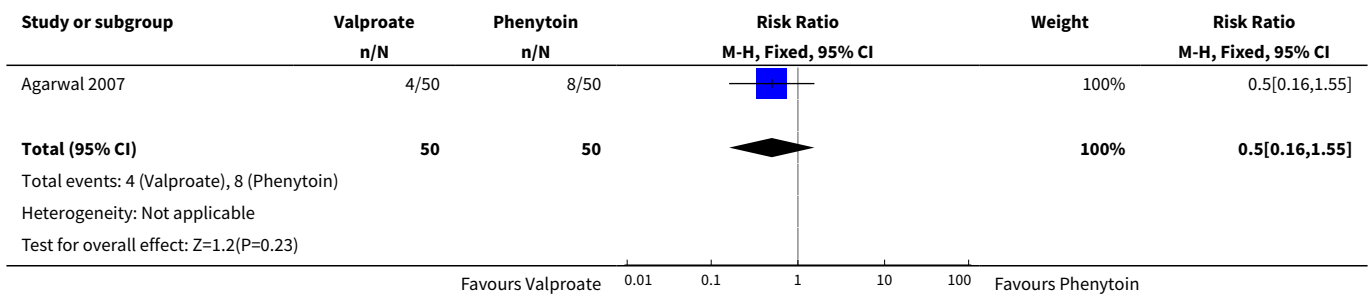
Analysis 17.3. Comparison 17 Valproate versus phenytoin IV, Outcome 3 Deaths.
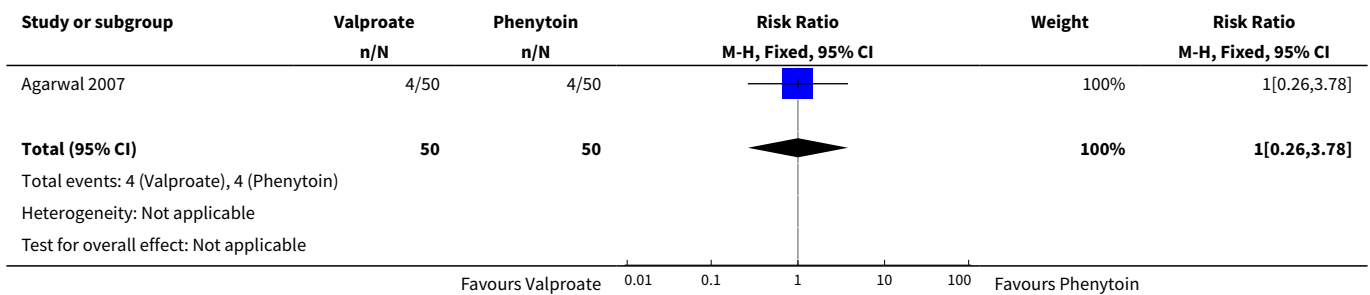
Study or subgroup	Valproate n/N	Phenytoin n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Agarwal 2007	4/50	4/50		100%	1[0.26,3.78]
Total (95% CI)	**50**	**50**		**100%**	**1[0.26,3.78]**

Total events: 4 (Valproate), 4 (Phenytoin)
Heterogeneity: Not applicable
Test for overall effect: Not applicable

Favours Valproate 0.01 0.1 1 10 100 Favours Phenytoin

Comparison 18. Midazolam IM versus lorazepam IV

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Cessation of seizures	1	893	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.06, 1.27]
2 Endotracheal Intubation	1	893	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.71, 1.35]
3 Requirement of Hospitali-sation	1	893	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.79, 0.97]
4 ICU Admissions	1	893	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.65, 0.96]
5 Recurrence of seizure	1	893	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.74, 1.57]
6 Adverse effects	1	893	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.46, 1.71]
7 Length of ICU stay	1	278	Mean Difference (IV, Fixed, 95% CI)	1.60 [-0.23, 3.43]
8 Length of Hospital stay	1	536	Mean Difference (IV, Fixed, 95% CI)	1.20 [-0.24, 2.64]

Analysis 18.1. Comparison 18 Midazolam IM versus lorazepam IV, Outcome 1 Cessation of seizures.

Study or subgroup	Midazolam n/N	Lorazepam n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Silbergleit 2012	329/448	282/445		100%	1.16[1.06,1.27]
Total (95% CI)	**448**	**445**		**100%**	**1.16[1.06,1.27]**
Total events: 329 (Midazolam), 282 (Lorazepam)					
Heterogeneity: Not applicable					
Test for overall effect: Z=3.21(P=0)					

Favours midazolam 0.01 0.1 1 10 100 Favours lorazepam
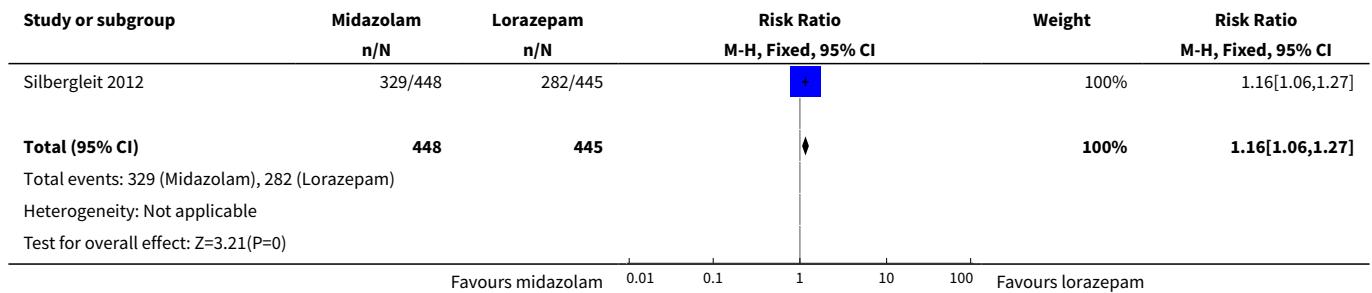
Analysis 18.2. Comparison 18 Midazolam IM versus lorazepam IV, Outcome 2 Endotracheal Intubation.

Study or subgroup	Midazolam n/N	Lorazepam n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Silbergleit 2012	63/448	64/445		100%	0.98[0.71,1.35]
Total (95% CI)	**448**	**445**		**100%**	**0.98[0.71,1.35]**
Total events: 63 (Midazolam), 64 (Lorazepam)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.14(P=0.89)					

Favours midazolam 0.01 0.1 1 10 100 Favours lorazepam
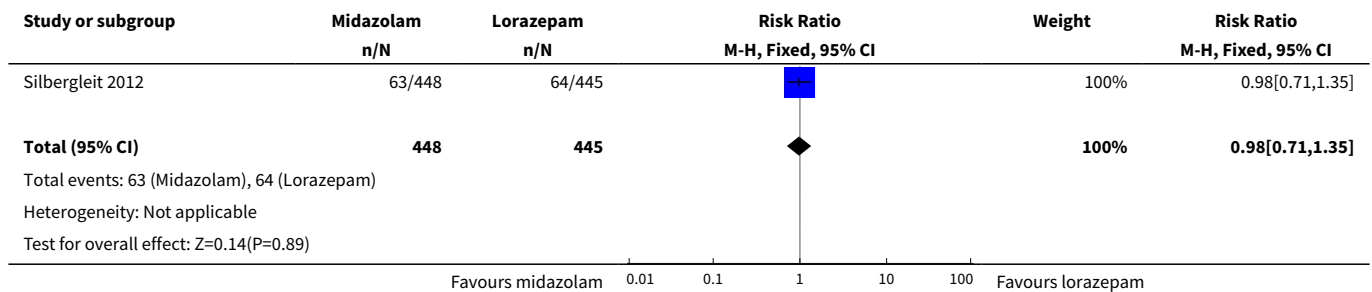
Analysis 18.3.   Comparison 18 Midazolam IM versus lorazepam IV, Outcome 3 Requirement of Hospitalisation.

Study or subgroup	Midazolam n/N	Lorazepam n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Silbergleit 2012	258/448	292/445		100%	0.88[0.79,0.97]
Total (95% CI)	**448**	**445**		**100%**	**0.88[0.79,0.97]**
Total events: 258 (Midazolam), 292 (Lorazepam)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.46(P=0.01)					

Favours midazolam 0.01 0.1 1 10 100 Favours lorazepam
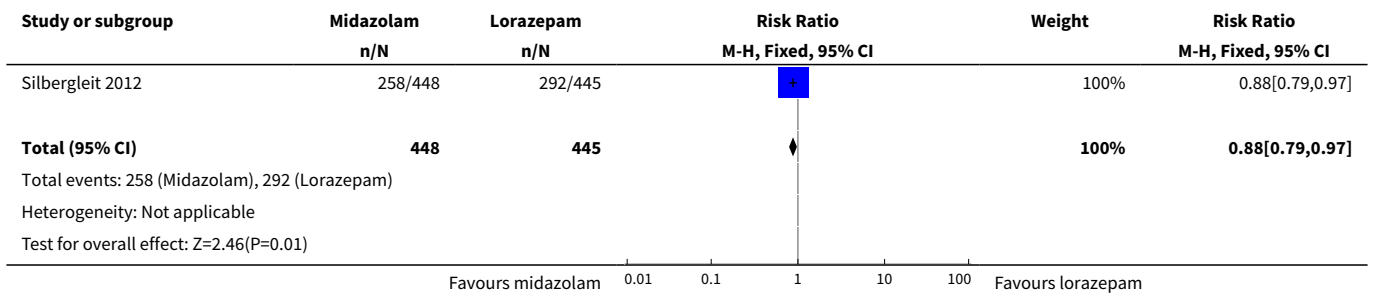
Analysis 18.4.   Comparison 18 Midazolam IM versus lorazepam IV, Outcome 4 ICU Admissions.

Study or subgroup	Midazolam n/N	Lorazepam n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Silbergleit 2012	128/448	161/445		100%	0.79[0.65,0.96]
Total (95% CI)	**448**	**445**		**100%**	**0.79[0.65,0.96]**
Total events: 128 (Midazolam), 161 (Lorazepam)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.42(P=0.02)					

Favours midazolam 0.01 0.1 1 10 100 Favours lorazepam
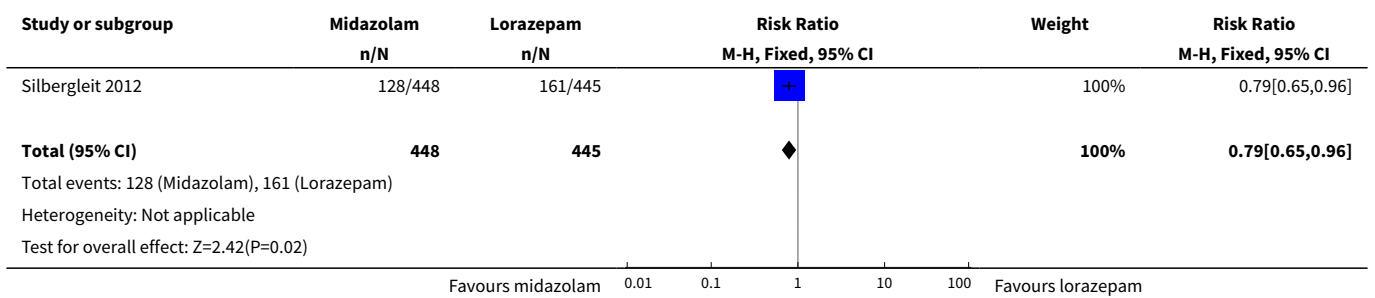
Analysis 18.5.   Comparison 18 Midazolam IM versus lorazepam IV, Outcome 5 Recurrence of seizure.

Study or subgroup	Midazolam n/N	Lorazepam n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Silbergleit 2012	51/448	47/445		100%	1.08[0.74,1.57]
Total (95% CI)	**448**	**445**		**100%**	**1.08[0.74,1.57]**
Total events: 51 (Midazolam), 47 (Lorazepam)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.39(P=0.69)					

Favours experimental 0.01 0.1 1 10 100 Favours control
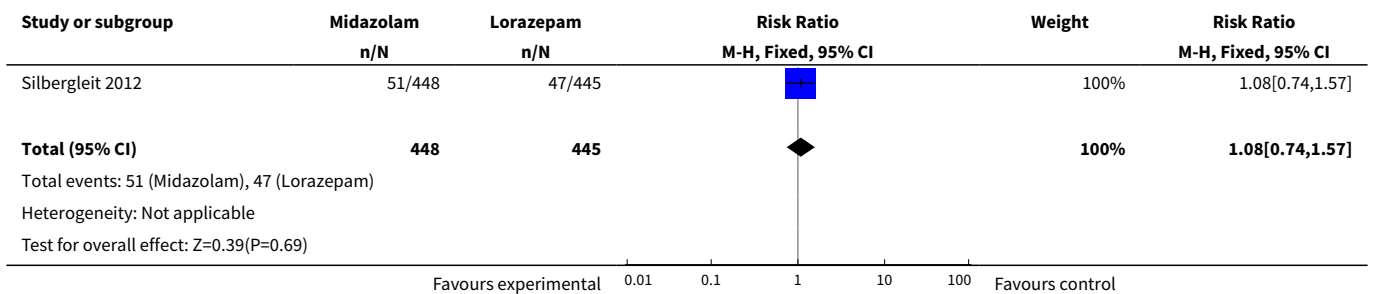
Analysis 18.6.   Comparison 18 Midazolam IM versus lorazepam IV, Outcome 6 Adverse effects.

Study or subgroup	Midazolam n/N	Lorazepam n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Silbergleit 2012	16/448	18/445		100%	0.88[0.46,1.71]
Total (95% CI)	**448**	**445**		**100%**	**0.88[0.46,1.71]**
Total events: 16 (Midazolam), 18 (Lorazepam)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.37(P=0.71)					

Favours experimental 0.01 0.1 1 10 100 Favours control
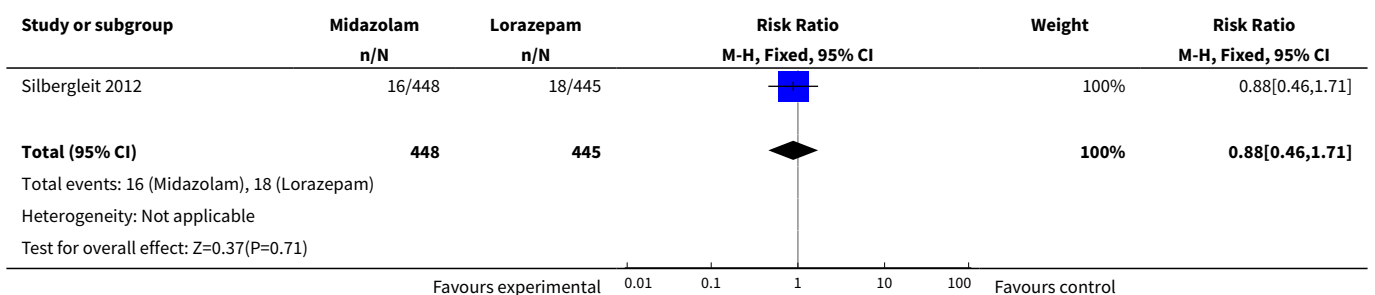
Analysis 18.7. Comparison 18 Midazolam IM versus lorazepam IV, Outcome 7 Length of ICU stay.

Study or subgroup	Midazolam		Lorazepam		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Silbergleit 2012	123	5.7 (9.5)	155	4.1 (4.7)		100%	1.6[-0.23,3.43]
Total ***	**123**		**155**			**100%**	**1.6[-0.23,3.43]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.71(P=0.09)							

Favours experimental -100 -50 0 50 100 Favours control
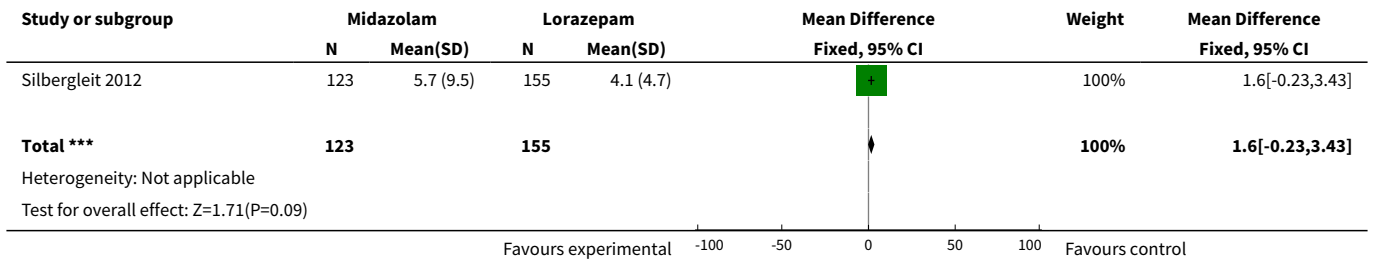
Analysis 18.8. Comparison 18 Midazolam IM versus lorazepam IV, Outcome 8 Length of Hospital stay.

Study or subgroup	Midazolam		Lorazepam		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Silbergleit 2012	251	6.7 (10)	285	5.5 (6.4)		100%	1.2[-0.24,2.64]
Total ***	**251**		**285**			**100%**	**1.2[-0.24,2.64]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=1.63(P=0.1)							

Favours experimental -100 -50 0 50 100 Favours control
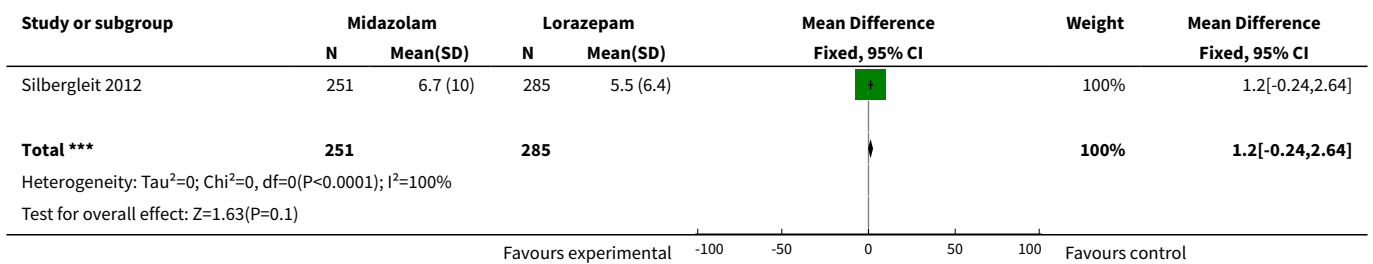
Comparison 19. Valproate IV versus diazepam IV infusion

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Non-cessation of seizure	2	106	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.71, 1.89]
2 Hypotension	2	106	Risk Ratio (M-H, Fixed, 95% CI)	0.08 [0.01, 0.58]
3 Relapse of seizure	1	35	Risk Ratio (M-H, Fixed, 95% CI)	0.8 [0.23, 2.83]
4 Respiratory depression	1	40	Risk Ratio (M-H, Fixed, 95% CI)	0.05 [0.00, 0.76]

Analysis 19.1. Comparison 19 Valproate IV versus diazepam IV infusion, Outcome 1 Non-cessation of seizure.

Study or subgroup	Valproate n/N	Diazepam n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Chen 2011	15/30	16/36		82.9%	1.13[0.67,1.88]
Mehta 2007	4/20	3/20		17.1%	1.33[0.34,5.21]
Total (95% CI)	**50**	**56**		**100%**	**1.16[0.71,1.89]**
Total events: 19 (Valproate), 19 (Diazepam)					
Heterogeneity: Tau²=0; Chi²=0.05, df=1(P=0.82); I²=0%					

Favours Valproate 0.01 0.1 1 10 100 Favours Diazepam

Study or subgroup	Valproate n/N	Diazepam n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=0.6(P=0.55)					

Favours Valproate 0.01 0.1 1 10 100 Favours Diazepam

Analysis 19.2. Comparison 19 Valproate IV versus diazepam IV infusion, Outcome 2 Hypotension.

Study or subgroup	Valproate n/N	Diazepam n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Chen 2011	0/30	2/36		17.84%	0.24[0.01,4.79]
Mehta 2007	0/20	10/20		82.16%	0.05[0,0.76]
Total (95% CI)	**50**	**56**		**100%**	**0.08[0.01,0.58]**
Total events: 0 (Valproate), 12 (Diazepam)					
Heterogeneity: Tau²=0; Chi²=0.64, df=1(P=0.42); I²=0%					
Test for overall effect: Z=2.5(P=0.01)					

Favours Valproate 0.01 0.1 1 10 100 Favours Diazepam
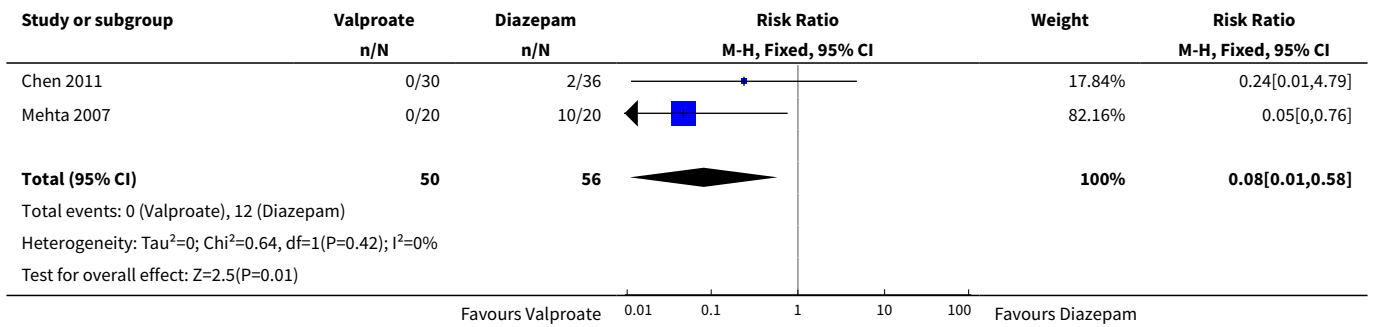
Analysis 19.3. Comparison 19 Valproate IV versus diazepam IV infusion, Outcome 3 Relapse of seizure.

Study or subgroup	Valproate n/N	Diazepam n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Chen 2011	3/15	5/20		100%	0.8[0.23,2.83]
Total (95% CI)	**15**	**20**		**100%**	**0.8[0.23,2.83]**
Total events: 3 (Valproate), 5 (Diazepam)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.35(P=0.73)					

Favours Valproate 0.01 0.1 1 10 100 Favours Diazepam
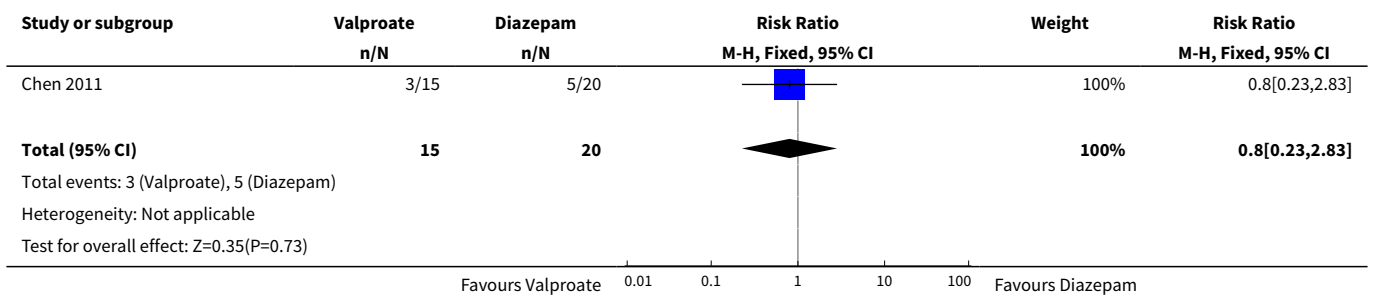
Analysis 19.4. Comparison 19 Valproate IV versus diazepam IV infusion, Outcome 4 Respiratory depression.

Study or subgroup	Valproate n/N	Diazepam n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Mehta 2007	0/20	10/20		100%	0.05[0,0.76]
Total (95% CI)	**20**	**20**		**100%**	**0.05[0,0.76]**
Total events: 0 (Valproate), 10 (Diazepam)					
Heterogeneity: Not applicable					
Test for overall effect: Z=2.15(P=0.03)					

Favours Valproate 0.01 0.1 1 10 100 Favours Diazepam
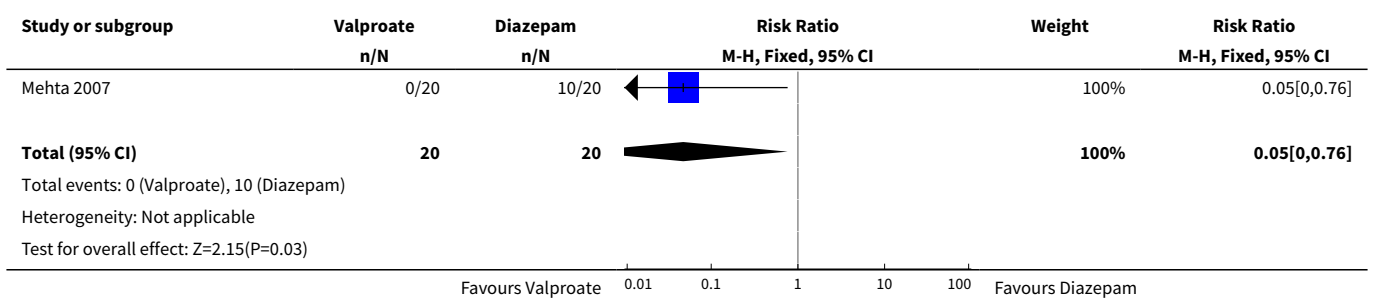
Comparison 20. Propofol IV versus barbiturates IV

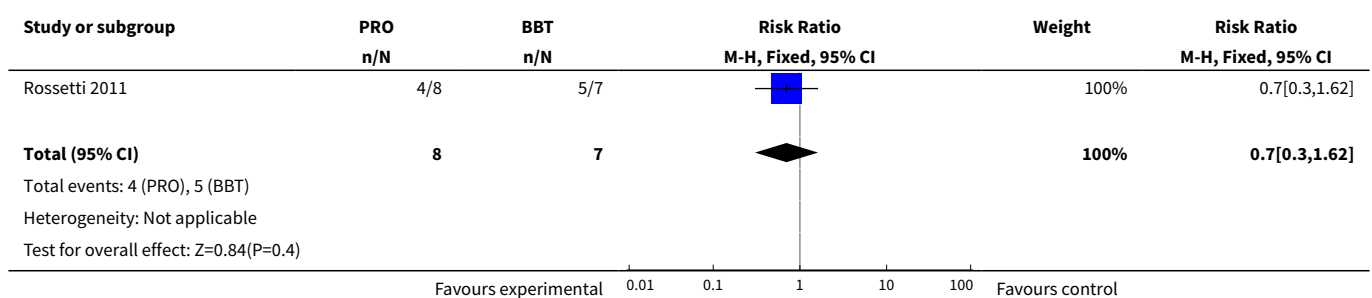| Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 RSE controlled with first course of drug	1	23	Risk Ratio (M-H, Fixed, 95% CI)	1.93 [0.49, 7.54]
2 RSE treated subsequently	1	15	Risk Ratio (M-H, Fixed, 95% CI)	0.7 [0.30, 1.62]
3 Thrombotic/embolic complications	1	23	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Mortality	1	23	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.43, 3.88]
5 Functional outcome at 3 weeks	1	23	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.34, 3.42]
6 Infections requiring antibiotics	1	23	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.37, 1.51]

Analysis 20.1. Comparison 20 Propofol IV versus barbiturates IV, Outcome 1 RSE controlled with first course of drug.

Study or subgroup	PRO n/N	BBT n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Rossetti 2011	6/14	2/9		100%	1.93[0.49,7.54]
Total (95% CI)	**14**	**9**		**100%**	**1.93[0.49,7.54]**

Total events: 6 (PRO), 2 (BBT)

Heterogeneity: Not applicable

Test for overall effect: Z=0.94(P=0.35)

Favours experimental 0.01 0.1 1 10 100 Favours control
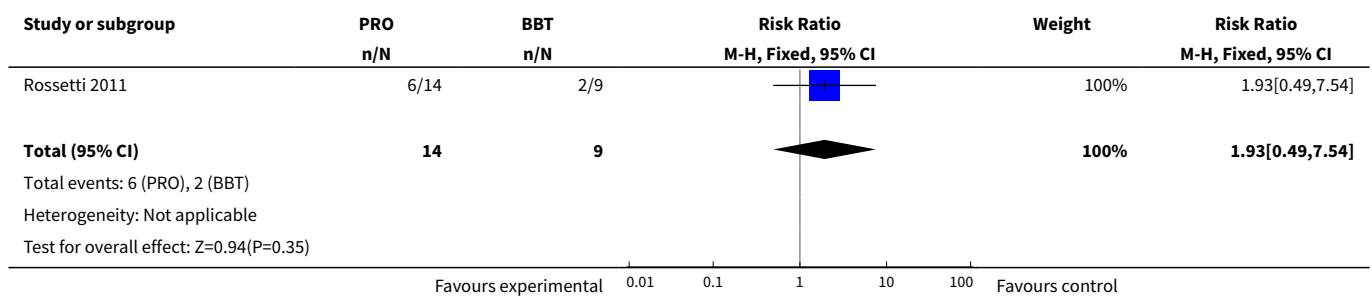
Analysis 20.2. Comparison 20 Propofol IV versus barbiturates IV, Outcome 2 RSE treated subsequently.

Study or subgroup	PRO n/N	BBT n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Rossetti 2011	4/8	5/7		100%	0.7[0.3,1.62]
Total (95% CI)	**8**	**7**		**100%**	**0.7[0.3,1.62]**

Total events: 4 (PRO), 5 (BBT)

Heterogeneity: Not applicable

Test for overall effect: Z=0.84(P=0.4)

Favours experimental 0.01 0.1 1 10 100 Favours control

Analysis 20.3. Comparison 20 Propofol IV versus barbiturates IV, Outcome 3 Thrombotic/embolic complications.

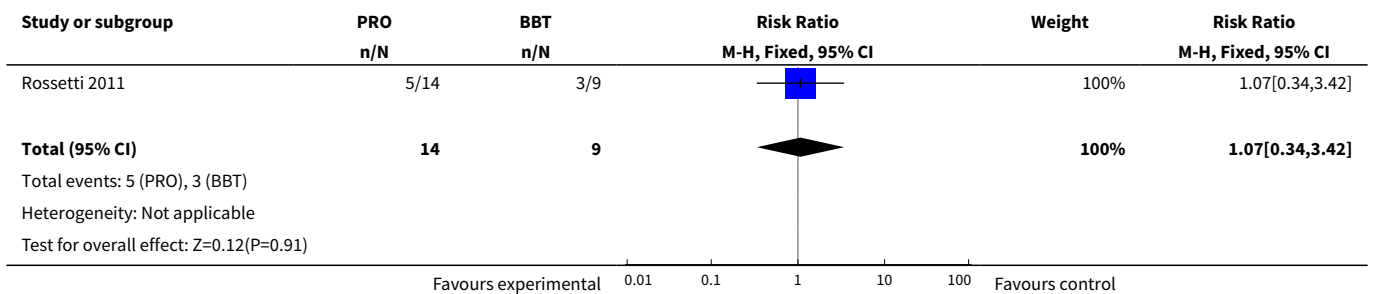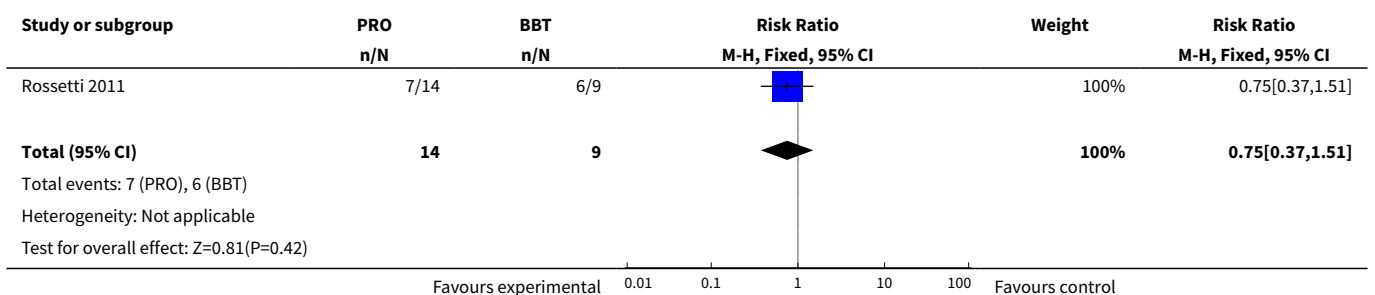| Study or subgroup	PRO n/N	BBT n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Rossetti 2011	0/14	0/9			Not estimable
Total (95% CI)	**14**	**9**			**Not estimable**
Total events: 0 (PRO), 0 (BBT)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Favours experimental 0.01 0.1 1 10 100 Favours control
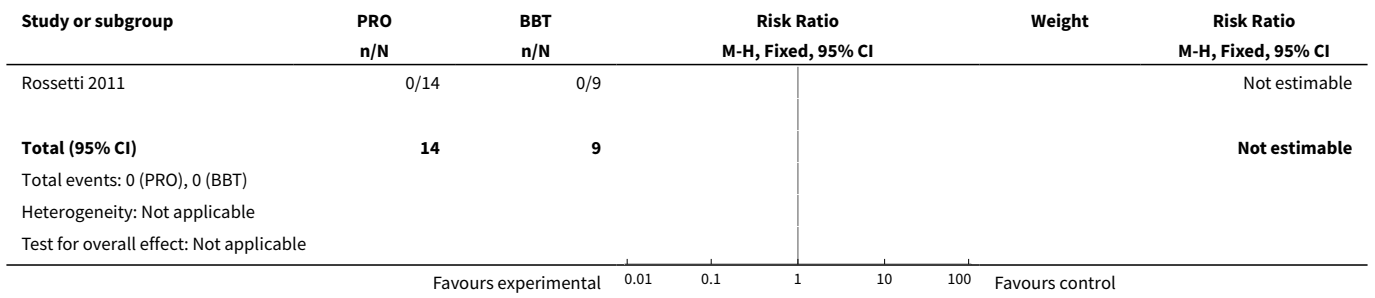
Analysis 20.4. Comparison 20 Propofol IV versus barbiturates IV, Outcome 4 Mortality.

Study or subgroup	PRO n/N	BBT n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Rossetti 2011	6/14	3/9		100%	1.29[0.43,3.88]
Total (95% CI)	**14**	**9**		**100%**	**1.29[0.43,3.88]**
Total events: 6 (PRO), 3 (BBT)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.45(P=0.66)					

Favours experimental 0.01 0.1 1 10 100 Favours control
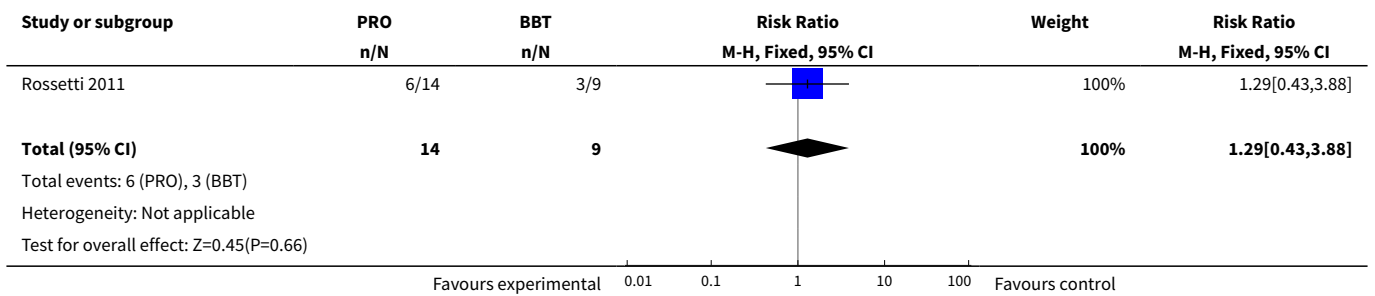
Analysis 20.5. Comparison 20 Propofol IV versus barbiturates IV, Outcome 5 Functional outcome at 3 weeks.

Study or subgroup	PRO n/N	BBT n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Rossetti 2011	5/14	3/9		100%	1.07[0.34,3.42]
Total (95% CI)	**14**	**9**		**100%**	**1.07[0.34,3.42]**
Total events: 5 (PRO), 3 (BBT)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.12(P=0.91)					

Favours experimental 0.01 0.1 1 10 100 Favours control

Analysis 20.6. Comparison 20 Propofol IV versus barbiturates IV, Outcome 6 Infections requiring antibiotics.

Study or subgroup	PRO n/N	BBT n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Rossetti 2011	7/14	6/9		100%	0.75[0.37,1.51]
Total (95% CI)	**14**	**9**		**100%**	**0.75[0.37,1.51]**
Total events: 7 (PRO), 6 (BBT)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.81(P=0.42)					

Favours experimental 0.01 0.1 1 10 100 Favours control

ADDITIONAL TABLES

Table 1. Definitions of status epilepticus followed in various studies

Study	Definition
Alldredge 2001	Continuous or repeated seizure activity > 5 minutes without recovery of consciousness.
Leppik 1983 (mixed)	(a) Generalised tonic-clonic status: three or more generalised tonic-clonic seizures in one hour; two or more generalised seizures in rapid succession without recovery of consciousness; (b) absence status: confusional state with generalised 3 Hz spike wave pattern on EEG; (c) complex partial status: confusional state, clinical seizure or both with focal EEG abnormality; (d) elementary status: partial seizures without loss of consciousness.
Pellock 1998 (premonitory)	Acute repetitive seizures (no definition).
Remy 1991 (mixed)	Successive partial seizures for at least 20 minutes or two generalised tonic-clonic seizures within 20 minutes.
Shaner 1988 (established/mixed)	Generalised convulsive status epilepticus: (a) a history of 30 minutes of continuous generalised convulsive seizures and witnessed generalised seizures in the emergency room; (b) a history of 30 minutes of recurrent generalised convulsive seizures but failure to attain baseline mental status between seizures and witnessed generalised seizures in the emergency room; (c) a history of 3 or more generalised convulsive seizures in one hour in patients with obtundation prior to the onset of status epilepticus and witnessed generalised convulsive seizures in the emergency room; (d) uncertain history of seizures but generalised convulsive seizures continuously for more than 5 minutes as witnessed in the emergency room.
Singhi 2002 (refractory)	Motor seizures uncontrolled after 2 doses of diazepam and phenytoin infusion.
McCormick 1999 (unclear)	No definition.
Chamberlain 1997 (premonitory)	Motor seizures of at least 10 minutes duration.
Appleton 1995 (unclear)	No definition.
Treiman 1998 (premonitory)	Overt generalised convulsive status: two or more generalised convulsions or continuous convulsive activity > 10 minutes.
Cereghino 2002 (premonitory)	Multiple seizures of complex partial or generalised type within an observation period between 12 - 24 hours.
Misra 2011	Two or more convulsive seizures without full recovery of consciousness between the seizures or continuous convulsions lasting for more than five minutes.
Mehta 2007	30 minutes of continuous seizure activity or two or more sequential seizures without full recovery of consciousness between seizures.
Chen 2011	More than five minutes of continuous seizures or two or more discrete seizures between which there is incomplete recovery of consciousness.
Agarwal 2007	Continuous, generalized, convulsive seizure lasting greater than 5 minutes, or two or more seizures during which patient does not return to baseline consciousness.
Ahmad 2006	Generalized convulsions continuing for minimum of five minutes.

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Table 1. Definitions of status epilepticus followed in various studies *(Continued)*

Rossetti 2011	Continuous, generalized, convulsive seizure lasting greater than 5 minutes, or two or more seizures during which patient does not return to baseline consciousness.
Silbergleit 2012	Continuous convulsions for longer than five minutes or having convulsions at the time of treatment after having intermittent seizures without regaining consciousness for longer than five minutes.
Sreenath 2010	Continuous convulsive activity lasting for 5 minutes or more.

Table 2.   Time elapsed

	Lorazepam IV	Di-azepam-pheny-toin IV	Diazepam IV	Paraldehyde IM	Valproate IV	Levetirac-etam IV	Midazolam IV infusion	Midazolam IM
Time since onset of status to administration of drug (min)			30 (10-441) (Mehta 2007) 31.3 (16.8-45.8) (Alldredge 2001)	120 (35.5-252) (Ahmad 2006)	30 (5.5-147) (Mehta 2007)			
Time since administration of drug to seizure cessation (min)	0.3 (0.25-0.38) (Sreenath 2010) 7.5 (4.5-11.5) (Ahmad 2006) 1.6 (Silbergleit 2012)	0.3 (0.255-0.4) (Sreenath 2010)	15.8 (2.8-28.8) (Singhi 2002) (for RSE)	8 (5-21) (Ahmad 2006)	-	-	15.9 (6.3-25.5) (Singhi 2002) (for RSE)	3.3 (Silbergleit 2012)

IM: intramuscular injection
IV: administered intravenously
RSE: refractory status epilepticus

A P P E N D I C E S

Appendix 1. Cochrane Epilepsy Group Specialized Register search strategy

#1 diazepam or lorazepam or paraldehyde or midazolam or phenytoin or fosphenytoin or lignocaine or clonazepam or thiopentone or propofol or pentobarbitone or isoflurane or etomidate

#2 MeSH DESCRIPTOR Anticonvulsants Explode All WITH AD AE AG AN AI BL CF CS CH CL CT DU EC HI IM IP ME PK PD PO RE ST SD TU TO UR

#3 #1 OR #2

#4 MeSH DESCRIPTOR Status Epilepticus Explode All WITH BL CF CI CL CO CN DI DH DT EC EM EN EP EH ET GE HI IM ME MI MO NU PS PA PP PC PX RA RI RT RH SU TH US UR VE VI

#5 "status epilepticus"

#6 #4 OR #5

#7 #3 AND #6

Appendix 2. CENTRAL search strategy

#1   diazepam OR lorazepam OR paraldehyde OR midazolam

#2   phenytoin or fosphenytoin

#3   lignocaine or clonazepam

#4   thiopentone or propofol or pentobarbitone or isoflurane or etomidate

#5   MeSH descriptor Anticonvulsants explode all trees

#6   (#1 OR #2 OR #3 OR #4 OR #5)

#7   MeSH descriptor Status Epilepticus explode all trees

#8   (status epilepticus)

#9   (#7 OR #8)

#10   (#6 AND #9)

Appendix 3. MEDLINE search strategy

This strategy is based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials published in Lefebvre 2009.

1. randomized controlled trial.pt.

2. controlled clinical trial.pt.

3. randomized.ab.

4. placebo.ab.

5. clinical trials as topic.sh.

6. randomly.ab.

7. trial.ti.

8. 7 or 5 or 2 or 6 or 1 or 4 or 3

9. exp animals/ not humans.sh.

10. 8 not 9

11. exp Status Epilepticus/

12. status epilepticus.tw.

13. 11 or 12

14. (diazepam or lorazepam or paraldehyde or midazolam).tw.

15. (phenytoin or fosphenytoin or lignocaine or paraldehyde or clonazepam).tw.

16. (thiopentone or propofol or pentobarbitone or isoflurane or etomidate).tw.

17. *Anticonvulsants/

18. 14 or 15 or 16 or 17

19. 10 and 13 and 18

WHAT'S NEW

Date	Event	Description
15 August 2013	New search has been performed	Searches updated.
15 August 2013	New citation required but conclusions have not changed	Eight new studies have been added. Conclusions remain the same.

HISTORY

Protocol first published: Issue 3, 2002
Review first published: Issue 4, 2005

Date	Event	Description
23 February 2012	New search has been performed	Searches updated 23 February 2012.
16 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

MP was primarily responsible for the update of the review.
Selection of studies for inclusion, conducted quality assessment, data extraction, entry to Revman (MP).
Creation of risk of bias table for each study (including those included in the first version of the review) and summary of finding tables using GRADEPRO (MP).
Duplicate selection of studies for the update, data extraction and commented on the final draft of the review (PK).
Contributed to the first version of the review and commented on the final draft of the review (RS, LA-R).

DECLARATIONS OF INTEREST

None known.

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External sources

- No sources of support supplied

I N D E X   T E R M S

Medical Subject Headings (MeSH)

Anticonvulsants [*therapeutic use]; Diazepam [therapeutic use]; Injections, Intravenous; Lorazepam [therapeutic use]; Midazolam [therapeutic use]; Phenobarbital [therapeutic use]; Phenytoin [therapeutic use]; Randomized Controlled Trials as Topic; Status Epilepticus [*drug therapy]

MeSH check words

Humans