EPI 2: First-line anti-epileptic medication for management of acute convulsive seizures, when intravenous access is available [2015]

SCOPING QUESTION: In adults with acute convulsive seizures, where intravenous access is available, which first-line anti-epileptic medication should be used to abort seizures when compared to comparator?

Back to Table of Contents

BACKGROUND

Acute convulsive seizures are a medical emergency in adults that commonly present in emergency rooms and require prompt recognition and management. Although most seizures self-terminate within 5 minutes, seizures that last longer than 5–10 minutes are at high risk of continuing for at least 30 minutes. Once a seizure lasts for >5-10 minutes, it is unlikely to stop spontaneously within the next few minutes and so intervention is indicated (Shinnar et al., 2001). The current operational definition of status epilepticus (SE) is ≥5 minutes of continuous seizures or ≥2 discrete seizures without complete recovery of consciousness in between (Lowenstein et al., 2001). The use of this operational definition allows for starting treatment early (within 5-10 minutes).

It is also recognized that for a majority of seizures occurring in the out-of-hospital settings it is virtually impossible to ascertain the onset, which makes it very difficult to determine even the approximate duration of the seizure. Therefore, the definition of SE has been expanded to include any patient who is brought convulsing to the emergency room (Lowenstein et al, 2001; Aldredge et al., 2001).

Immediate treatment of acute convulsive seizures or SE is crucial to prevent adverse neurologic and systemic consequences. Multiple protocols for management of acute convulsive seizures and SE are available (Mazurkiewicz-Bełdzińska et al., 2014; Hirsch et al., 2013; Claassen et al., 2012; Minicucci et al., 2006). It has been shown that the use of any protocol for SE management leads to a better outcome, as compared to when a protocol is not used (Tirupathi et al., 2009).

When selecting the most appropriate antiepileptic medications for seizure control, the pharmacokinetics of the intervention must also be considered. This includes, for example, the duration of action and the mode of administration. Diazepam has traditionally been the medication of choice for intravenous (IV) preparations of benzodiazepines. Recently, lorazepam is suggested as a preferred option in view of perceived better efficacy, reduced risk of respiratory depression and long duration of action (Appleton et al., 2008; Aneja, 2012). However, lorazepam needs refrigeration when stored, which may limit its use in low- and middle-income countries (LAMICs) in field settings (Anejja, 2012; Gottwald et al., 1999).

This scoping question aims incorporate new evidence on these interventions published since 2009 and to identify and recommend the best first-line treatment option in adults with acute convulsive seizures, where IV access is available in LAMICs.

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome (PICO)

- **Population:** Adults presenting with SE or acute convulsive seizures where IV access is available
- **Interventions:** IV diazepam, IV lorazepam, IV midazolam, IV phenobarbital, IV phenytoin
- **Comparison:** One intervention vs. another intervention
- **Outcomes:**
    - Critical – Non-cessation of seizures, death, requirement for ventilator support

Search strategy

To identify relevant systematic reviews, the following databases were searched: Medline, Embase, The Cochrane Library, BMJ Clinical Evidence and PsychINFO up to July 2014. The search strategy developed by McMaster University was adapted and applied as follows:

- (meta analysis [Publication Type] OR meta analysis [Title/Abstract] OR meta analysis [MeSH Terms] OR review[Publication Type] OR search*[Title/Abstract]).

The following additional terms were used: *(status epilepticus OR acute seizures) AND (midazolam OR diazepam OR lorazepam OR phenobarbital OR phenytoin)*.

In order to identify additional primary studies, the search strategy used in the Prasad et al.. (2005) Cochrane Review was replicated and applied as follows:

- (1) Cochrane Central Database of Controlled Trials (CENTRAL); (2) MEDLINE; (3) EMBASE.

The search terms used included the following text words: *(status epilepticus), (anti-epileptic therapy)* and names of the medication *(midazolam OR diazepam OR lorazepam OR phenobarbital OR phenytoin)* in combination with any of the above words. This search was supplemented by the following search strategy the McMaster University search strategy as follows:

- (randomized controlled trial [Publication Type] OR randomized[Title/Abstract] OR placebo[Title/Abstract]). The following additional terms were used: (status epilepticus OR acute seizures) AND (midazolam OR diazepam OR lorazepam OR phenobarbital OR phenytoin).

Inclusion and exclusion criteria for this review

Type of studies

- Randomized controlled trials (RCTs)

Types of participants

- Adults (> 18 years of age) presenting with an acute seizure (either hospital or community setting) and who received treatment with an IV anti-epileptic medication, irrespective of the duration of the presenting convulsion.
- These included those presenting *de novo* with a first convulsion and those with an established diagnosis of epilepsy. Any and all causes of the convulsion (including convulsive status epilepticus) were included in the review.
- In scenarios where studies on adults were not available, studies on children or studies with both adults and children enrolled were included.

Types of interventions

- In adults presenting with an acute seizure including status epilepticus, we included trials if they compared one treatment with another.
- Specific medication included intravenous benzodiazepines (diazepam, lorazepam and midazolam), intravenous phenytoin and phenobarbital.
- Combination therapies (e.g. diazepam plus phenytoin) were excluded.

Types of outcome measures

i. Non-cessation of seizures: The term 'non-cessation of seizures' was used rather than 'cessation of seizures' (which is used in the various studies) to be in consistent with Prasad et al.'s (2014) Cochrane Review on which the evidence profile is based. This outcome was used in the Cochrane Review to maintain uniformity with the other outcomes, which were unfavorable. The timeline for non-cessation of seizures have not been specified in the Cochrane Review and varies across studies.
ii. Death
iii. Requirement for ventilator support

Data collection and analysis

Two members of the research team independently assessed trials for inclusion. The methodological quality of each trial was assessed using the following criteria:

- Randomization method;
- Baseline comparability of the trial arms;
- Blinding; and
- Whether the published data permitted an intention-to-treat (ITT) analysis.

Data were independently extracted by two review authors and cross-checked. Data on the number of participants sought for each outcome event by allocated treatment group in order to allow for an ITT analysis.

Included in GRADE tables or footnotes

- Prasad M, Krishnan PR, Sequeira R, Al-Roomi K (2014). Anticonvulsant therapy for status epilepticus. Cochrane Database of Systematic Reviews.9:CD003723. doi:10.1002/14651858.CD003723.pub3

- Chamberlain JM, Okada P, Holsti M, Mahajan P, Brown KM, Vance C et al. (2014). Lorazepam vs diazepam for pediatric status epilepticus: a randomized clinical trial. The Journal of the American Medical Association.311(16):1652-1660. doi:10.1001/jama.2014.2625.

- Gathwala G, Goel M, Singh J, Mittal K (2012). Intravenous diazepam, midazolam and lorazepam in acute seizure control. Indian Journal of Pediatrics. 79(3):327-332. doi:10.1007/s12098-011-0505-y.

Excluded from GRADE tables and footnotes

Appleton R, Macleod S, Martland T (2008). Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. Cochrane Database of Systematic Reviews.3:CD001905.
REASON FOR EXCLUSION: Review is not focused on treatment in adults.

Sreenath TG, Gupta P, Sharma KK, Krishnamurthy S (2010). Lorazepam versus diazepam-phenytoin combination in the treatment of convulsive status epilepticus in children: a randomized controlled trial. European Journal of Paediatric Neurology. 14(2):162-168. doi:10.1016/j.ejpn.2009.02.004.
REASON FOR EXCLUSION: One of the interventions was a combination treatment, which was not the intervention of interest.

PICO Table

Population: Adults presenting with SE or acute convulsive seizures where IV access is available				**Relevant GRADE table**
Intervention	**Comparison**	**Outcome**	**Systematic review/study selected and justification for use**	
IV lorazepam	IV diazepam	Non-cessation of seizure	*Update of the Prasad et al. (2014) Cochrane Review meta-analysis, with inclusion of the following studies*: • Chamberlain et al. (2014) • Gathwala et al. (2012)	Table 1
		Death	*Update of the Prasad et al. 2014 Cochrane Review meta-analysis with inclusion of the following studies* • Chamberlain et al. 2014 • Gathwala et al. 2012	
		Requirement for ventilator support	*Update of the Prasad et al. (2014) Cochrane Review meta-analysis with inclusion of the following studies* • Chamberlain et al. 2014 • Gathwala et al. 2012	
IV lorazepam	IV phenytoin	Non-cessation of seizures	Recent and relevant Prasad et al.'s (2014) Cochrane Review	Table 2
		Death	None	
		Requirement for ventilator support	Recent and relevant Prasad et al.'s (2014) Cochrane Review	
IV lorazepam	IV phenobarbital	Non-cessation of seizures	Recent and relevant Prasad et al.'s (2014) Cochrane Review	Table 3
		Death	None	

		Adverse effects	Recent and relevant Prasad et al., 2014 (Cochrane review)	
IV phenobarbital	IV phenytoin	Non-cessation of seizures	Recent and relevant Prasad et al., 2014 (Cochrane review)	Table 4
		Death	Recent and relevant Prasad et al., 2014 (Cochrane review)	
		Adverse effects	Recent and relevant Prasad et al., 2014 (Cochrane review)	
IV lorazepam	IV midazolam	Non-cessation of seizures	Recent and relevant Prasad et al., 2014 (Cochrane review) Study included after Prasad et al. (2014) Cochrane Review and/or previous WHO mhGAP guidelines: • Gathwala et al. 2012	Table 5
		Death	None	
		Adverse effects	Recent and relevant Prasad et al.'s (2014) Cochrane Review	
IV diazepam	IV midazolam	Non-cessation of seizures	No systematic review Study: Gathwala et al. (2012)	Table 6
		Death	None	
		Adverse effects	No systematic review Study: Gathwala et al. (2012)	

Narrative description of the studies that were considered in the analysis

Included in this analysis is the Cochrane review (Prasad et al., 2014) and two RCTs conducted by Chamberlain et al. (2014) and Gathwala et al. (2012), both performed after the Cochrane Review. The Cochrane Review has a comprehensive search strategy and a clear assessment of bias.

The first analysis (see GRADE Table 1: lorazepam vs. diazepam) included the following evidence from the Prasad et al. (2014) Cochrane Review:

- Two studies in adults (Alldredge et al., 2001; and Leppik et al., 1983);
  - Alldredge et al. (2001) is a randomized, blinded study of treatment of adults with out-of-hospital SE treated by paramedics with either diazepam or lorazepam.
  - Leppik et al. (1983) is a randomized, blinded study of lorazepam vs. diazepam in adults.

The research team for this evidence profile performed meta-analyses on these two studies for the outcomes of non-cessation of seizures and requirement of ventilator support. The meta-analyses were performed based on the methodology of the Prasad et al. (2014) Cochrane Review. Heterogeneity between trial results for each outcome was tested using a chi-squared 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. In these situations risk difference (RD) was used to ensure inclusion of the meta-analyses data. For the outcome of death, the Prasad et al. (2014) Cochrane Review was used (Analysis 1.5) because deaths were reported only in these two studies.

The next three analyses (see GRADE Tables 2, 3 and 4) are all based on a randomized, blinded study (Treiman et al., 1998) of four treatments for convulsive SE (including IV lorazepam, IV phenobarbital, IV diazepam plus phenytoin, phenytoin alone). The analyses from the Prasad et al. (2014) Cochrane Review were incorporated into the GRADE tables (Analysis 5.1, 4.1, 15.1).

The fifth analysis (GRADE Table 5) is based on a single randomized open label study (McCormick et al., 1999) of IV midazolam vs. IV lorazepam in SE. The data from the Gathwala et al. (2012) study are mentioned as a footnote to the GRADE table.

The last analysis (GRADE Table 6 on IV midazolam vs. IV diazepam) is based on the Gathwala et al. (2012) study.

The objective of the Gathwala et al. (2012) study was to test the hypothesis that lorazepam has better efficacy and safety than diazepam for treating pediatric SE. The authors led a double-blind, randomized clinical trial involving patients aged 3 months to younger than 18 years with convulsive SE presenting to 1 of 11 US academic pediatric emergency departments that were eligible. There were 273 patients in total with 140 randomized to diazepam and 133 to lorazepam. Patients received either 0.2 mg/kg of diazepam or 0.1 mg/kg of lorazepam intravenously, with half of this dose repeated at 5 minutes if necessary. If SE continued at 12 minutes, fosphenytoin was administered. The primary efficacy outcome was cessation of SE by 10 minutes without recurrence within 30 minutes. The primary safety outcome was the performance of assisted ventilation. Secondary outcomes included rates of seizure recurrence and sedation and times to cessation of SE and return to baseline mental status. Outcomes were measured 4 hours after study medication administration. The authors found that cessation of SE for 10 minutes without recurrence within 30 minutes occurred in 101 of 140 (72.1%) in the diazepam group and 97 of 133 (72.9%) in the lorazepam group, with an absolute efficacy difference of 0.8% (95% CI, −11.4% to 9.8%). There were 26 patients in each group who required assisted ventilation (16.0% given diazepam and 17.6% given lorazepam; absolute risk difference, 1.6%; 95% CI, −9.9% to 6.8%). There were no statistically significant differences in secondary outcomes except that lorazepam patients were more likely to be sedated (66.9% vs 50%, respectively; absolute risk difference, 16.9%; 95% CI, 6.1% to 27.7%).

GRADE Tables

Table 1. IV lorazepam vs. IV diazepam for treatment of acute convulsive seizures where IV access is available

Author: S Sharma
Question: Should IV lorazepam vs. IV diazepam be used for treatment of adults presenting with acute convulsive seizures where IV administration is indicated?
Bibliography: Prasad M, Krishnan PR, Sequeira R, Al-Roomi K (2014). Anticonvulsant therapy for status epilepticus. Cochrane Database of Systematic Reviews.9:CD003723. doi:10.1002/14651858.CD003723.pub3.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV lorazepam	IV diazepam	Relative (95% CI)	Absolute		
Non-cessation of seizures (assessed with risk ratio [RR])												
2	Randomized trials	No serious risk of bias	No serious inconsistency[1]	No serious indirectness	Serious[2]	None	31/103 (30.1%)	46/100 (46%)	RR 0.68 (0.48 to 0.96)	147 fewer per 1000 (from 18 fewer to 239 fewer)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Requirement for ventilator support (assessed with risk ratio)												
2	Randomized trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	11/103 (10.7%)	10/100 (10%)	RR 1.06 (0.47 to 2.38)	6 more per 1000 (from 53 fewer to 138 more)	⊕⊕⊕O MODERATE	CRITICAL
								0%		-		
Death (assessed with risk difference [RD])												
2	Randomized trials	Serious[3]	No serious inconsistency	Serious	Serious[4]	Reporting bias	5/103 (4.9%)	3/100 (3%)	RD 0 (-0.04 to 0.08)	30 fewer per 1000 (from 28 fewer to 31 fewer)	⊕OOO VERY LOW	CRITICAL
								0%		-		

[1] I^2=0.
[2] Wide confidence intervals.
[3] Sample size, though large, is not sufficient for an estimate of death.
[4] Very few number of events.

Figure 1. New meta-analysis performed on non-cessation of seizures outcome with IV lorazepam vs. IV diazepam (using studies on adults)

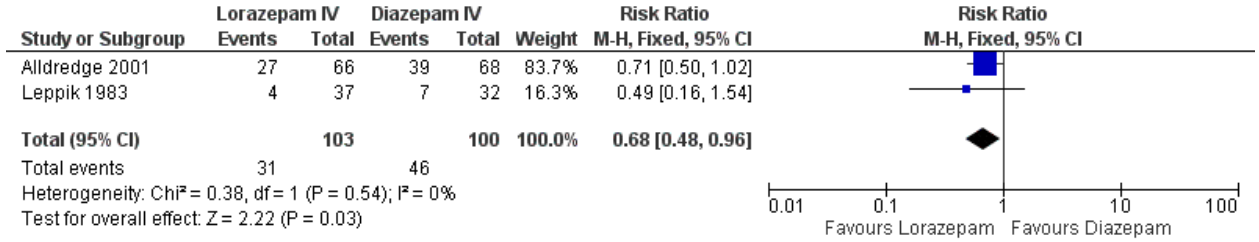

Figure 2. New meta-analysis performed on need for ventilator support with IV lorazepam vs. IV diazepam (using studies on adults)

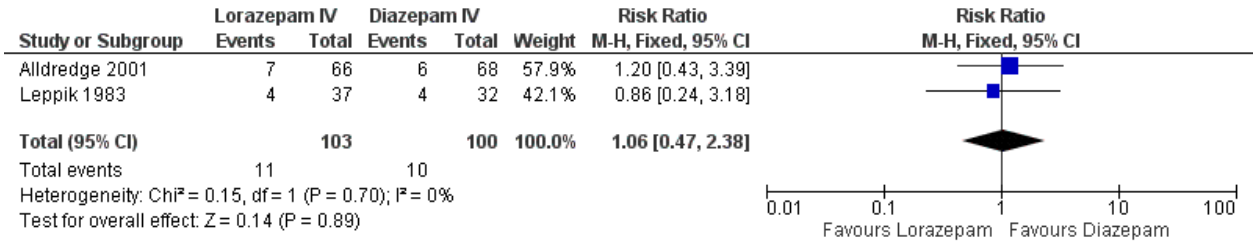

Table 2. IV lorazepam vs. IV phenytoin for treatment of acute convulsive seizures when IV access is available

Author: S Sharma
Question: Should IV lorazepam vs. IV phenytoin be used for treatment of adults presenting with acute convulsive seizures where IV access is available?
Bibliography: Prasad M, Krishnan PR, Sequeira R, Al-Roomi K (2014). Anticonvulsant therapy for status epilepticus. Cochrane Database of Systematic Reviews.9:CD003723. doi:10.1002/14651858.CD003723.pub3. *(Analysis 5.1)*

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV lorazepam	IV phenytoin	Relative (95% CI)	Absolute		
Non-cessation of seizures (assessed with risk ratio)												
1	Randomized trials	No serious risk of bias	No serious inconsistency[1]	No serious indirectness	Serious[2]	Reporting bias[3]	34/97 (35.1%)	57/101 (56.4%)	RR 0.62 (0.45 to 0.86)	214 fewer per 1000 (from 79 fewer to 310 fewer)	⊕⊕OO LOW	CRITICAL
								0%		-		
Requirement for ventilator support												
0	No evidence available					none	-	-	-	-		CRITICAL
								0%		-		
Death												
0	No evidence available					none	-	-	-	-		CRITICAL
								0%		-		

[1] Single study.
[2] Wide confidence intervals.
[3] No other studies available on this comparison.

Table 3. IV lorazepam vs IV phenobarbital for the treatment of acute convulsive seizures where IV access is available

Author: S Sharma
Question: Should IV lorazepam vs IV phenobarbital be used for treatment of adults presenting with acute convulsive seizures where IV access is available?
Bibliography: Prasad M, Krishnan PR, Sequeira R, Al-Roomi K (2014). Anticonvulsant therapy for status epilepticus. Cochrane Database of Systematic Reviews.9:CD003723. doi:10.1002/14651858.CD003723.pub3. *(Analysis 4.1)*

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV lorazepam	IV phenobarbital	Relative (95% CI)	Absolute		
Non-cessation of seizures (assessed with Risk ratio)												
1	Randomized trials	No serious risk of bias	No serious inconsistency[1]	No serious indirectness	Serious[2]	Reporting bias[3]	34/97 (35.1%)	38/91 (41.8%)	RR 0.84 (0.58 to 1.21)	67 fewer per 1000 (from 175 fewer to 88 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Requirement for ventilator support												
0	No evidence available					None	-	-	-	-		CRITICAL
								0%		-		
Death												
0	No evidence available					None	-	-	-	-		CRITICAL
								0%		-		

[1] Only 1 study.
[2] Wide confidence intervals.
[3] No other studies available on this comparison.

[2015]

Table 4. IV phenobarbital vs. IV phenytoin for treatment of acute convulsive seizures where IV access is available

Author: S Sharma
Question: Should IV phenobarbital vs. IV phenytoin be used for treatment of adults presenting with acute convulsive seizures where IV access is available?
Bibliography: Prasad M, Krishnan PR, Sequeira R, Al-Roomi K (2014). Anticonvulsant therapy for status epilepticus. Cochrane Database of Systematic Reviews.9:CD003723. doi:10.1002/14651858.CD003723.pub3. *(Analysis 15.1)*

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**IV phenobarbital**	**IV phenytoin**	**Relative (95% CI)**	**Absolute**		
Non-cessation of seizures (assessed with risk ratio)												
1	Randomized trials	No serious risk of bias	No serious inconsistency[1]	No serious indirectness	Serious[2]	Reporting bias[3]	38/91 (41.8%)	51/95 (53.7%)	RR 0.78 (0.57 to 1.06)	118 fewer per 1000 (from 231 fewer to 32 more)	⊕⊕OO LOW	CRITICAL
								0%		-		
Requirement for ventilator support												
0	No evidence available					None	-	-	-	-		CRITICAL
								0%		-		
Death												
0	No evidence available					None	-	-	-	-		CRITICAL
								0%		-		

[1] Single study.
[2] Wide confidence intervals.
[3] No other studies available on this comparison.

[2015]

Table 5. IV midazolam vs. IV lorazepam for treatment of acute convulsive seizures where IV access is available

Author: S Sharma
Question: Should IV midazolam vs. IV lorazepam be used for treatment of adults with acute convulsive seizures where IV access is available?
Bibliography: 1) Prasad M, Krishnan PR, Sequeira R, Al-Roomi K (2014). Anticonvulsant therapy for status epilepticus. Cochrane Database of Systematic Reviews.9:CD003723. doi:10.1002/14651858.CD003723.pub3.; 2) Gathwala G, Goel M, Singh J, Mittal K (2012). Intravenous diazepam, midazolam and lorazepam in acute seizure control. Indian Journal of Pediatrics.79(3):327-332. doi:10.1007/s12098-011-0505-y.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV midazolam	IV lorazepam	Relative (95% CI)	Absolute		
Non-cessation of seizures (assessed with risk ratio)												
1	Randomized trials	Serious[1]	No serious inconsistency[2]	Serious[3]	Very serious[4]	None	1/15 (6.7%)	4/12 (33.3%)	RR 0.20 (0.03 to 1.56)	267 fewer per 1000 (from 323 fewer to 187 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Requirement for ventilator support (assessed with Risk ratio)												
1	Randomized trials	Serious[1]	No serious inconsistency[2]	No serious indirectness	Very serious[4]	None	1/15 (6.7%)	2/12 (16.7%)	RR 0.40 (0.04 to 3.9)	100 fewer per 1000 (from 160 fewer to 483 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Death												
0	No evidence available					None	-	-	-	-		CRITICAL
								0%		-		

[1] Only abstract available; allocation concealment not clear, likely open label.
[2] Only one study.
[3] Study of children only.
[4] Sample size of 27 patients. Wide confidence intervals. Very few events.

Table 6. IV diazepam vs. IV midazolam for treatment of children with acute convulsive seizures where IV access is available

Author: S Sharma
Question: Should IV diazepam vs. IV midazolam be used for treatment of children with acute convulsive seizures where IV access is available?
Bibliography: Gathwala G, Goel M, Singh J, Mittal K (2012). Intravenous diazepam, midazolam and lorazepam in acute seizure control. Indian Journal of Pediatrics.79(3):327-332. doi:10.1007/s12098-011-0505-y.

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV diazepam	IV midazolam	Relative (95% CI)	Absolute		
Non-cessation of seizures (assessed with risk ratio)												
1	Randomized trials	Serious[1]	No serious inconsistency[2]	Serious[3]	Very serious[4]	Reporting bias[5]	3/40 (7.5%)	1/40 (2.5%)	RR 3.0 (0.33 to 27.63)[6]	50 more per 1000 (from 17 fewer to 666 more)	⊕OOO VERY LOW	CRITICAL
								0%		-		
Requirement for ventilator support (assessed with risk ratio)												
1	Randomized trials	Serious[1]	No serious inconsistency[2]	Serious[3]	Very serious[7]	Reporting bias[5]	1/40 (2.5%)	0/40 (0%)	-	-	⊕OOO VERY LOW	CRITICAL
								0%		-		
Death												
0	No evidence available					None	-	-	-	-		CRITICAL
								0%		-		

[1] Open label study, allocation concealment not mentioned.
[2] Single study.
[3] Study in children.
[4] Sample size of 40 in each group; very few events; wide confidence intervals crossing 1.
[5] No other studies comparing IV diazepam vs. IV midazolam as first-line therapy for acute seizures in children available.
[6] RR and CI calculated by research team.
[7] Sample size of 40 in each group, with only one event.

Additional evidence not found in GRADE tables

A second meta-analysis was run to highlight the evidence for IV lorazepam vs. IV diazepam among adults and children. For children only, there was no difference found between these two interventions. For adults and children combined, the results from the meta-analysis represented in Figure 3 and 4 below show that lorazepam is more effective than diazepam for the control of seizures only. This result should be considered, as it has implications on the clinical management of seizures in adults and children with active seizures.

Figure 3. Meta-analysis: Effectiveness of IV lorazepam vs. IV diazepam on control of seizures in adults and children combined

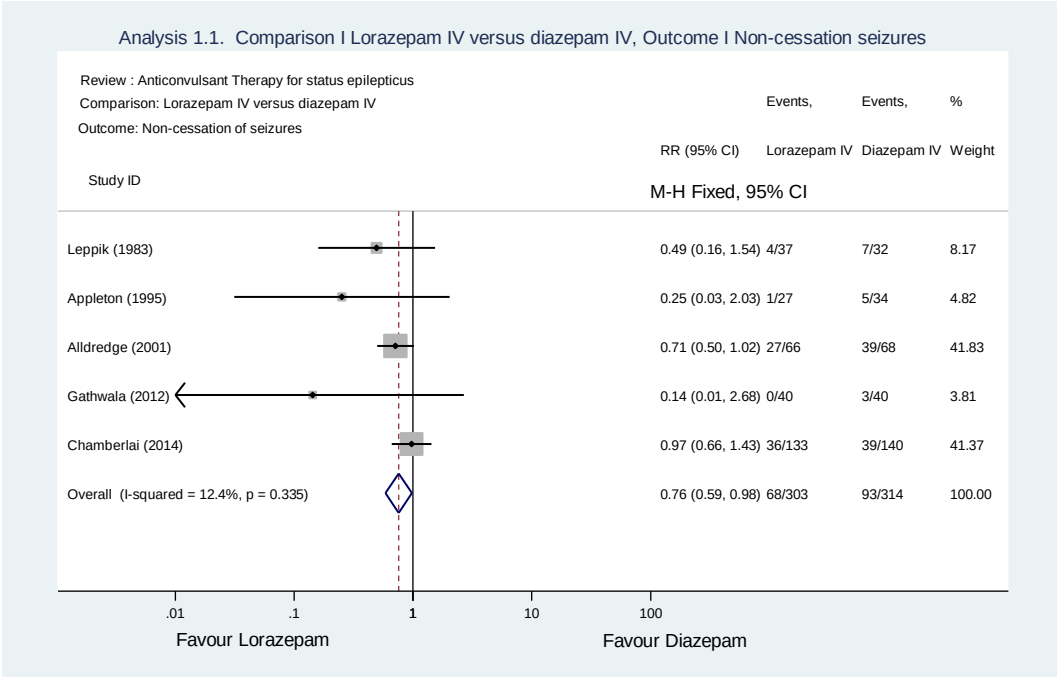

Figure 4. Result details from meta-analysis on effectiveness of IV lorazepam vs. IV diazepam

Study	RR	[95% Conf.	Interval]	% Weight
Leppik (1983)	0.494	0.159	1.536	8.17
Appleton (1995)	0.252	0.031	2.030	4.82
Alldredge (2001)	0.713	0.500	1.017	41.83
Gathwala (2012)	0.143	0.008	2.679	3.81
Chamberlai (2014)	0.972	0.661	1.429	41.37
M-H pooled RR	0.758	0.588	0.978	100.00

Heterogeneity chi-squared = 4.57 (d.f. = 4) p = 0.335
I-squared (variation in RR attributable to heterogeneity) = 12.4%

Test of RR=1 : z= 2.13 p = 0.033

This meta-analysis comparing IV lorazepam vs. IV diazepam for the cessation of seizures among adults and children with active convulsive seizures indicates that IV lorazepam is more effective than IV diazepam (RR= 0.76 [95% CI 0.59 to 0.98]). There is a minor amount of heterogeneity among the studies, which is within acceptable limits so as not to affect the consistency of the included studies (I^2=12.4%).

Figures 5 and 6 detail the results from the meta-analysis conducted by the research team of IV lorazepam vs. IV diazepam on the requirement for ventilator support outcome. The meta- analysis found that among adults and children with active convulsive seizures, the overall pooled effect was not found to be significant (p=0.607), which reveals a confidence interval which crosses the line of no effect (RR= 0.90 [95% CI 0.59 to 1.36]). There is no heterogeneity among the studies. This result indicates that the interventions are not different for the outcome of respiratory depression requiring ventilator support.

Figure 5. Meta-analysis: Effectiveness of IV lorazepam vs. IV diazepam on requirement for ventilator support in adults and children

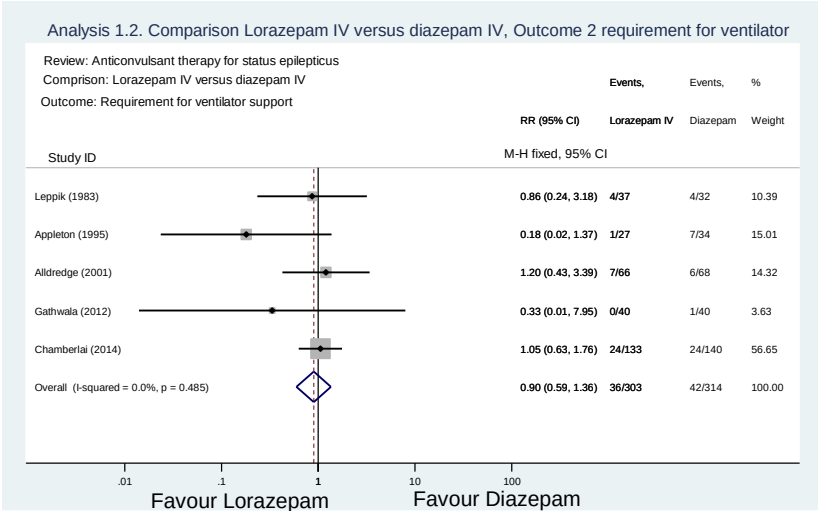

Figure 6. Result details from meta-analysis on effectiveness of IV lorazepam vs. IV diazepam on requirement for ventilator support outcome

Study	RR	[95% Conf.	Interval]	% Weight
Leppik (1983)	0.865	0.235	3.182	10.39
Appleton (1995)	0.180	0.024	1.374	15.01
Alldredge (2001)	1.202	0.426	3.389	14.32
Gathwala (2012)	0.333	0.014	7.945	3.63
Chamberlai (2014)	1.053	0.630	1.759	56.65
M-H pooled RR	0.897	0.594	1.355	100.00

Heterogeneity chi-squared = 3.45 (d.f. = 4) p = 0.485
I-squared (variation in RR attributable to heterogeneity) = 0.0%

Test of RR=1 : z= 0.51 p = 0.607

PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Summary of evidence table

	Comparisons					
Outcome	IV lorazepam vs. IV diazepam *(Number of studies, RR or RD [95% CI], quality)*	IV lorazepam vs. IV phenytoin *(Number of studies, RR [95% CI], quality)*	IV lorazepam vs. IV phenobarbital *(Number of studies, RR [95% CI], quality)*	IV phenobarbital vs. IV phenytoin *(Number of studies, RR [95% CI], quality)*	IV midazolam vs. IV lorazepam *(Number of studies, RR [95% CI], quality)*	IV diazepam vs. IV midazolam *(Number of studies, RR [95% CI], quality)*
Non-cessation of seizures	2 studies, RR 0.68 (0.48 to 0.96) Favours lorazepam, MODERATE quality	1 study in adults, RR 0.62 (0.45 to 0.86) Favours lorazepam, LOW quality	1 study in adults, RR 0.84 (0.58 to 1.21) No difference, LOW quality	1 study in adults, RR 0.78 (0.57 to 1.06) No difference, LOW quality	2 studies in children, RR 0.20 (0.03 to 1.56) No difference, VERY LOW quality	1 study in children, RR 3.0 (0.33 to 27.63) No difference, VERY LOW quality
Requirement for ventilator support	2 studies, RR 1.06 (0.47 to 2.38) No difference, MODERATE quality	Not reported	Not reported	Not reported	2 studies in children, RR 0.40 (0.04 to 3.9) No difference, VERY LOW quality	1 study in children, VERY LOW quality
Death	2 studies, RD 0.02 (-0.04 to 0.08). No difference, VERY LOW quality	Not reported	Not reported	Not reported	Not reported	Not reported

NOTE: *When IV lorazepam is compared with IV diazepam for seizure cessation among children and adults with active convulsive seizures, lorazepam is found to be more effective (RR 0.76 [95% CI 0.59-0-58]). There is no difference in these medications among adults and children with active convulsive for the outcome of respiratory depression.*

Evidence to recommendation table

Benefits	From the available evidence, IV lorazepam appears to be more effective than IV diazepam in the treatment of acute convulsive seizures in adults. When these medications are compared among adults and children for seizure cessation, IV lorazepam appears to be more effective in adults. There is no difference among children only.

	The evidence is inconclusive and so it is not possible to determine if there is a clinically important difference between: a) IV lorazepam and IV phenobarbital; b) IV lorazepam and IV midazolam; and c) IV diazepam and IV midazolam.
Harms	The evidence is inconclusive and so it is not possible to determine if there is a clinically important difference in the requirement of ventilator support or death with the use of these pharmacological interventions. Phenobarbital and phenytoin are associated with significant and life threatening side-effects.
Summary of the quality of evidence	The available evidence is MODERATE to VERY LOW quality.

Value and preferences	
In favour	Control of acute convulsive seizures is of critical importance. They are associated with substantial morbidity and mortality. An additional percentage of people experiencing this condition have permanent sequelae, such as a permanent vegetative state or cognitive difficulties.
Against	Potential complications of treatment of convulsive seizures with the benzodiazepines or phenobarbital include hypotension and respiratory arrest. People treated for acute convulsive seizures may require monitoring and may require ventilator support; therefore, secondary care is necessary. Sedative effects of benzodiazipines may interfere with neurological examination

Uncertainty or variability?	There is no variability in terms of the value of these interventions and treatment preferences.

Feasibility (including resource use considerations)	Both IV lorazepam and IV diazepam are included in the WHO Essential Medicine List. IV midazolam is also included, but under the section on preoperative medication and sedation for short-term procedures and not under anti-epileptics. IV lorazepam and IV midazolam may not be easily available in LAMICs. Another concern is the temperature stability of lorazepam. Lorazepam experiences degradation with high temperatures and hence needs refrigeration (Gottwald et al., 1999; McMullan et al., 2014). This may limit its use in LAMICs in field settings.
Uncertainty or variability?	There is variability in feasibility with regards to the availability of the medications across different health care settings.

Recommendation and remarks

Recommendation

In adults presenting with acute convulsive seizures where intravenous access is available, either intravenous lorazepam or diazepam can be administered to terminate the seizure. Intravenous lorazepam (if available) may be preferred over intravenous diazepam because of slightly superior benefit-risk profile.

Rationale: Although the quality of the evidence is low, the benefits of anti-epileptic medications outweigh their harms with

intravenous lorazepam appearing to be more effective than intravenous diazepam for management of acute convulsive seizures in adults. Control of acute convulsive seizures is of critical importance as they are associated with substantial morbidity and mortality. Both intravenous lorazepam and diazepam are included in WHO Model Essential Medicine List.

Remarks

Intravenous lorazepam may not be available in many low-and middle-income country settings.
In field settings, where the environmental temperatures are high and refrigeration is not available, intravenous diazepam may be preferable over lorazepam because of its better stability at higher environmental temperatures.
No recommendation can be made regarding intravenous midazolam, phenobarbital and phenytoin due to insufficient evidence.

Judgements about the strength of a recommendation

Factor	Decision
Quality of the evidence	□ High □ Moderate □ Low **X Very low**
Balance of benefits versus harms	**X Benefits clearly outweigh harms** □ Benefits and harms are balanced □ Potential harms clearly outweigh potential benefits
Values and preferences	**X No major variability** □ Major variability
Resource use	□ Less resource-intensive **X More resource-intensive**
Strength	**CONDITIONAL**

OTHER REFERENCES

Alldredge BK, Gelb AM, Isaacs SM, Corry MD, Allen F, Ulrich S, Gottwald MD, O'Neil N, Neuhaus JM, Segal MR, Lowenstein DH (2001). A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. New England Journal of Medicine.345(9):631-637.

Aneja S (2012). Benzodiazepines for acute management of seizures. Indian J Pediatr. 79(3):381-2. doi:10.1007/s12098-012-0702-3.

Appleton R, Macleod S, Martland T (2008). Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. Cochrane Database Systematic Review.3:CD001905

Claassen J, Silbergleit R, Weingart SD, Smith WS (2012). Emergency neurological life support: status epilepticus. Neurocritical Care.17(Suppl.1):S73-8.

Gottwald MD, Akers LC, Liu PK, Orsulak PJ, Corry MD, Bacchetti P, Fields SM, Lowenstein DH, Alldredge BK (1999). Prehospital stability of diazepam and lorazepam. American Journal of Emergency Medicine.17(4):333-7.

Hirsch LJ and Gaspard N (2013). Status epilepticus. Continuum (Minneap Minn).19(3 Epilepsy):767-794. doi:10.1212/01.CON.0000431395.16229.5a.

Lowenstein DH, Alldredge BK, Allen F, Neuhaus J, Corry M, Gottwald M, O'Neil N, Ulrich S, Isaacs SM, Gelb A (2001). The prehospital treatment of status epilepticus (PHTSE) study: design and methodology. Controlled Clinical Trials.22(3):290-309.

Mazurkiewicz-Bełdzińska M, Szmuda M, Zawadzka M, Matheisel A (2014). Current treatment of convulsive status epilepticus - a therapeutic protocol and review. Anaesthesiology Intensive Therapy.46(4):293-300. doi:10.5603/AIT.2014.0048.

McMaster search strategy: http://hiru.mcmaster.ca/hiru/HIRU_Hedges_MEDLINE_Strategies.aspx.

McMullan JT, Jones E, Barnhart B, Denninghoff K, Spaite D, Zaleski E, Silbergleit R (2014). Degradation of benzodiazepines after 120 days of EMS deployment. Prehospital Emergency Care.18(3):368-374. doi:10.3109/10903127.2013.869642.

Minicucci F, Muscas G, Perucca E, Capovilla G, Vigevano F, Tinuper P (2006). Treatment of status epilepticus in adults: guidelines of the Italian Leagueagainst Epilepsy. Epilepsia.47(Suppl.5):9-15.

Shinnar S, Berg AT, Moshe SL, Shinnar R (2001). How long do new-onset seizures in children last? Annals of Neurology.49(5):659-664.
Tirupathi S, McMenamin JB, Webb DW (2009). Analysis of factors influencing admission to intensive care following convulsive status epilepticus in children. Seizure.18(9):630-633. doi:10.1016/j.seizure.2009.07.006.