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EPI 3: Anti-epileptic medications for management of established status epilepticus [Updated 2015]

SCOPING QUESTION: In adults with established status epilepticus (i.e., seizures persisting after the first-line treatment with benzodiazepines [or benzodiazepines-resistant status epilepticus]), which anti-epileptic medications are associated with cessation of seizures and reduced adverse effects)?

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BACKGROUND

Status epilepticus (SE) is a medical emergency that can lead to profound systemic and neurological damage and is associated with significant short- and long-term mortality. SE is operationally defined as a convulsive seizure lasting ≥ 5 minutes or the occurrence of two or more discrete seizures between which there is incomplete recovery of consciousness (Lowenstein et al., 2001).

A staged treatment protocol for management of SE is usually recommended (Shorvon et al., 2008). Randomized controlled trials (RCTs) show that benzodiazepines (such as intravenous [IV] lorazepam, IV diazepam or intramuscular [IM] midazolam) may be the most efficient treatment in early SE (Chamberlain et al., 2014; Silbergleit et al., 2012). Approximately 30–40 % of all patients fail to respond to initial treatment with benzodiazepines (in established SE) and need further treatment with other IV antiepileptic medications (Silbergleit et al., 2012).

Traditionally, IV phenytoin or phenobarbital have been used in benzodiazepine-resistant SE. Both phenobarbital and phenytoin may cause cardiac arrhythmias, hypotension and respiratory depression (although the latter may be due to the prior administration of benzodiazepines) (Trinka, 2005). The use of these medications has been based on tradition and clinical experience rather than based on evidence. In recent years, use of IV formulations of other anti-epileptic medications, such as valproic acid (sodium valproic acid) in benzodiazepine-resistant SE has increased. 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. Some medications may offer advantages in terms of safety and improved tolerability, but availability and cost could also be an issue.

The evidence base for the use of these medications (including phenytoin, phenobarbital and valproic acid) in established SE is scant, but there is a dearth of high quality clinical trials in this area investigating the early stages of SE (that is, not yet established SE) (Shorvon, 2012). There are also feasibility and affordability issues, as well as the fact that IV valproic acid is not currently on the WHO Essential Medicines List (October 2013).²

In many settings, IV administration is not possible due to staff training restraints, time pressures or due to other resource constraints. The use of IM phenobarbital for established SE is not uncommon. It is for this reason that the use of IM phenobarbital will be evaluated as part of this evidence



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profile¹. This question aims to identify and recommend the best treatment option in benzodiazepine-resistant SE for low- and middle-income countries (LAMICs) and to incorporate evidence published since 2009.

PART 1: EVIDENCE REVIEW

Population/ Intervention / Comparison / Outcome (PICO)

- **Population:** Adults presenting with established SE (i.e., seizures persisting after the first-line agent [benzodiazepine-resistant SE])
- **Interventions:** IV phenytoin, IV valproic acid, IV phenobarbital, IM phenobarbital
- **Comparison:** One intervention vs. another intervention (head-to-head comparisons)
- **Outcomes:**
 - **Critical** – Cessation of seizures, death, adverse effects
 - **Important** – Recurrence of seizures within 24 hours

Search strategy

In order 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 the McMaster University was adapted and applied as follows to identify existing meta-analyses:

- (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 (phenytoin OR valproic acid OR phenobarbital)*.

In order to identify additional primary studies, the McMaster University search strategy was used again 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 (phenytoin OR valproic acid OR phenobarbital)*.

¹ Diazepam infusion, a route of administration sometimes included in treatment guidelines and delivered by specialists, was not included in this review given the focus on non-specialist settings.

² Intravenous valproic acid was included in the updated WHO Essential Medicines List (August 2015).



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Inclusion and exclusion criteria for this review

Type of studies

- Systematic reviews
- RCTs
- Quasi-randomized controlled trials, blinded or unblinded

Types of participants

- Adults (>18 years of age) presenting with an acute seizure (in a hospital or community setting) and who continued to have seizures after the administration of iIV benzodiazepines (including lorazepam, diazepam or midazolam) and who were subsequently treated with any of the following: intravenous phenytoin, phenobarbital, or valproic acid.
- Adults 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 that enrolled both adults and children were included.

Types of interventions

- In adults presenting with benzodiazepine SE, trials were included if they compared one treatment with another.
- Specific medications included IV phenytoin, phenobarbital and valproic acid. Systematic reviews were included if they evaluated any of these medications in benzodiazepine-resistant SE.

Types of outcome measures

1. Cessation of seizures
2. Death
3. Adverse effects
4. Recurrence of seizures within 24 hours

Data collection and analysis

Two members of the research team independently assessed trials for inclusion. Outcome data specified above was extracted by the research team and any disagreements on inclusion were resolved through discussion. The methodological quality of each trial was assessed using the following criteria:



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- 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 was sought on the number of participants with each outcome event by allocated treatment group in order to allow for an ITT analysis.

Included in GRADE tables or footnotes

- Agarwal P, Kumar N, Chandra R, Gupta G, Antony AR, Garg N (2007). Randomized study of intravenous valproic acid and phenytoin in status epilepticus. *Seizure*.16(6): 527–532.
- Malamiri RA, Ghaempanah M, Khosroshahi N, Nikkhah A, Bavarian B, Ashrafi MR (2012). Efficacy and safety of intravenous valproic acid versus phenobarbital in controlling convulsive status epilepticus and acute prolonged convulsive seizures in children: a randomised trial. *Eur J Paediatr Neurol* 2012;16(5):536–41. doi:10.1016/j.ejpn.2012.01.012.

Excluded from GRADE tables or footnotes

Brigo F, Storti M, Del Felice A, Fiaschi A, Bongiovanni LG (2012). IV Valproic acid in generalized convulsive status epilepticus: a systematic review. *European Journal of Neurology*. 19(9):1180-1191. doi:10.1111/j.1468-1331.2011.03606.x.

REASON FOR EXCLUSION: Review was focused on the use of IV valproic acid as first-line or second-line treatment. It did not focus on benzodiazepine-resistant SE, which is the condition of interest for the scoping question.

Liu X, Wu Y, Chen Z, Ma M, Su L (2012). A systematic review of randomized controlled trials on the therapeutic effect of intravenous valproic acid in status epilepticus. *International Journal of Neuroscience*. 122(6):277-283. doi:10.3109/00207454.2012.657376.

REASON FOR EXCLUSION: Review was focused on the use of IV valproic acid as first-line or second-line treatment. It did not focus on benzodiazepine-resistant SE, which is the condition of interest for the scoping question.

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

REASON FOR EXCLUSION: Review did not evaluate the population of interest for the current scoping question. Although the authors included studies on premonitory, early, established and refractory SE, ultimately the studies were not analyzed based on the type of SE.

Trinka E, Höfler J, Zerbs A, Brigo F (2014). Efficacy and safety of intravenous valproic acid for status epilepticus: a systematic review. *CNS Drugs*.28(7):623-39. doi:10.1007/s40263-014-0167-1.

REASON FOR EXCLUSION: Review was focused on the use of IV valproic as first-line or second -ine treatment. It did not focus on benzodiazepine-resistant SE, which is the condition of interest for the scoping question.

Yasiry Z and Shorvon SD (2014). The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: a meta-analysis of published studies. *Seizure*.23(3):167-174. doi:10.1016/j.seizure.2013.12.007.

REASON FOR EXCLUSION: It was not possible to GRADE this review as it did not use a meta-analytic synthesis of results. This paper is discussed in the additional evidence section.

PICO Table

| Population: In adults with established SE (that is, with seizures persisting after the first-line agent (benzodiazepine-resistant SE)) | | | | | |
|---|-------------------|------------------------------------|--|--|-----------------------------|
| Intervention | Comparison | Outcome | Systematic reviews/ RCTs identified | Justification for review and/or study use | Relevant GRADE Table |
| IV phenytoin | IV phenobarbital | Seizure cessation | None | N/A | N/A |
| | | Death | None | | |
| | | Adverse effects | None | | |
| | | Seizure recurrence within 24 hours | None | | |
| IV phenytoin | No control group | Seizure cessation | Yasiry and Shorvon (2014) | Recent review summarising relevant observational studies with good search strategy, however it can't be evaluated using GRADE methodology. | N/A |
| IV phenytoin | IV valproic acid | Seizure | Agarwal et al. | No systematic review available, only RCT | Table 1 |

| | | | | | |
|------------------|------------------|------------------------------------|--|--|---------|
| | | cessation | (2007) | | |
| | | Death | Agarwal et al. (2007) | No systematic review available, only RCT | |
| | | Adverse effects | Agarwal et al. (2007) | No systematic review available, only RCT | |
| | | Seizure recurrence within 24 hours | Agarwal et al. (2007) | No systematic review available, only RCT | |
| IV valproic acid | IV phenobarbital | Seizure cessation | Malamiri et al. (2012) | No systematic review available, only RCT | Table 2 |
| | | Death | None | No systematic review available, only RCT | |
| | | Adverse effects | Malamiri et al. (2012) | No systematic review available, only RCT | |
| | | Seizure recurrence within 24 hours | Malamiri et al. (2012) | No systematic review available, only RCT | |
| IV valproic acid | No control group | Seizure cessation | Yasiry and Shorvon (2014) | Recent review summarising relevant observational studies with good search strategy, however it can't be evaluated using GRADE methodology. | N/A |
| IV phenobarbital | No control group | Seizure cessation | Yasiry and Shorvon (2014) | Recent review summarising relevant observational studies with good search strategy, however it can't be evaluated using GRADE methodology. | N/A |
| IM phenobarbital | Placebo | | Crawley et al. (2000) White et al. (1988) | No systematic review available, only RCTs | N/A |

Narrative description of the studies that were considered in the analysis

Yasiry and Shorvon (2014) is a systematic evaluation of the published evidence-base for the efficacy of five anti-epileptic medications (specifically, lacosamide, levetiracetam, valproic acid, phenytoin and phenobarbital) in benzodiazepine-resistant SE. Lacosamide and levetiracetam have not been included in this evidence profile. The authors identified 27 studies and 22 of these were included in the meta-analysis. The papers included in the meta-analysis consisted of one randomized double-blinded trial, five open-label trials, 18 case series and three case reports, which describe a total

| Death (assessed with proportion) | | | | | | | | | | | | |
|---|-------------------|----------------------|---------------------------------------|--------------------------------------|---------------------------|------|-----------|------------|----------------------------------|---|------------------|----------|
| 1 | Randomized trials | Serious ¹ | No serious inconsistency | No serious indirectness ³ | Very serious ⁶ | None | 4/50 (8%) | 4/50 (8%) | RR 1 (0.27 to 3.78) ⁵ | 0 fewer per 1000 (from 58 fewer to 222 more) | ⊕○○○ VERY LOW | CRITICAL |
| | | | | | | | | 0% | | - | | |
| Adverse effects (assessed with proportions) | | | | | | | | | | | | |
| 1 | Randomized trials | Serious ¹ | No serious inconsistency | No serious indirectness ³ | Very serious ⁶ | None | 4/50 (8%) | 8/50 (16%) | RR 0.50 (0.16 to 1.56) | 80 fewer per 1000 (from 134 fewer to 90 more) | ⊕○○○ VERY LOW | CRITICAL |
| | | | | | | | | 0% | | - | | |
| Seizure recurrence within 24 hours (assessed with proportion of patients) | | | | | | | | | | | | |
| 1 | Randomized trials | Serious ¹ | No serious inconsistency ² | No serious indirectness ³ | Very serious ⁷ | None | 0/50 (0%) | 0/50 (0%) | - | - | ⊕○○○ VERY LOW | CRITICAL |
| | | | | | | | | 0% | | - | | |

¹ Method of randomization not clear; no allocation concealment; no blinding.

² Single study.

³ Study enrolled both adults and children.

⁴ Wide confidence intervals.

⁵ RR and CI calculated by research team.

⁶ Very few events; wide CI crossing 1.

⁷ No events.

Table 2. IV valproic acid vs. IV phenobarbital for treatment of adults with benzodiazepine-resistant SE

Author: S Sharma

Question: Should IV valproate vs IV phenobarbital be used for adults with benzodiazepine-resistant SE?

Bibliography: Malamiri RA, Ghaempanah M, Khosroshahi N, Nikkhah A, Bavarian B, Ashrafi MR (2012). Efficacy and safety of intravenous valproic acid versus phenobarbital in controlling convulsive status epilepticus and acute prolonged convulsive seizures in children: a randomised trial. Eur J Paediatr Neurol 2012;16(5):536–41. doi:10.1016/j.ejpn.2012.01.012.

| Quality assessment | | | | | | | No. of patients | | Effect | | Quality | Importance |
|--|-------------------|-------------------------|---------------------------------------|----------------------|-----------------------------|----------------------|------------------|------------------|------------------------|---|------------------|------------|
| No. of studies | Design | Risk of bias | Inconsistency | Indirectness | Imprecision | Other considerations | IV valproic acid | IV phenobarbital | Relative (95% CI) | Absolute | | |
| Seizure cessation (assessed with proportion of patients) | | | | | | | | | | | | |
| 1 | Randomized trials | No serious risk of bias | No serious inconsistency ¹ | Serious ² | Very serious ^{3,4} | None | 27/30 (90%) | 23/30 (76.7%) | RR 1.17 (0.93 to 1.48) | 130 more per 1000 (from 54 fewer to 368 more) | ⊕○○○ VERY LOW | CRITICAL |
| | | | | | | | | 0% | | - | | |

| Adverse effects (assessed with proportion of patients with adverse effects) | | | | | | | | | | | | |
|---|-----------------------|-------------------------|---------------------------------------|----------------------|-----------------------------|------|--------------|---------------|-------------------------------------|--|---------------|----------|
| 1 | Randomized trials | No serious risk of bias | No serious inconsistency | Serious ² | Very serious ^{3,4} | None | 7/30 (23.3%) | 22/30 (73.3%) | RR 0.32 (0.16 to 0.63) | 499 fewer per 1000 (from 271 fewer to 616 fewer) | ⊕○○○ VERY LOW | CRITICAL |
| | | | | | | | | 0% | | - | | |
| Seizure recurrence within 24 hours (assessed with proportion of patients with seizure recurrence) | | | | | | | | | | | | |
| 1 | Randomized trials | No serious risk of bias | No serious inconsistency ¹ | Serious ² | Very serious ⁵ | None | 4/27 (14.8%) | 12/23 (52.2%) | RR 0.28 (0.11 to 0.76) ⁶ | 376 fewer per 1000 (from 125 fewer to 464 fewer) | ⊕○○○ VERY LOW | CRITICAL |
| | | | | | | | | 0% | | - | | |
| Death | | | | | | | | | | | | |
| 0 | No evidence available | | | | | None | - | - | - | - | | CRITICAL |
| | | | | | | | | 0% | | - | | |

¹ Single study.

² Study on children.

³ Wide confidence interval crossing 1.

⁴ Total number of patients 60; very few events.

⁵ Total number of patients 60.

⁶ RR and CI calculated by research team.

Additional Evidence not included in GRADE tables

Phenytoin for Benzodiazepine-resistant SE in adults

In the Yasiry and Shorvon (2014) review, eight studies on the use of phenytoin reporting 294 episodes of SE were included. The meta-analysis was performed on a combination of different study designs, including randomized (Agarwal et al., 2007), quasi-randomized (Ogutut et al., 2003) and observational retrospective studies (Alvarez et al., 2011; Ismail et al., 2012; Franzoni et al., 2006; Miyahara et al., 2009; Tiamkao et al., 2009; Brevoord et al., 2005). The Agarwal et al. (2007) RCT has already been mentioned Grade Table 1. The rest were observational studies.

The overall risk of bias was serious. Agarwal et al.'s (2007) randomization method was not clear, allocation concealment not mentioned and the trial was not blinded. Ogutu et al. (2003) led a quasi-randomized study with no allocation concealment. Alvarez et al. (2011) led a retrospective study with baseline prognostic variables (i.e., etiology) that was different in the 3 groups (i.e., baseline confounding). Brevoord et al. (2005), Franzoni et al. (2006), Ismail et al. (2012) and Miyahara et al. (2009) demonstrated a high risk of bias because there were no comparators and all were retrospective studies. Tiamkao et al. (2009) studied adults (>15 years) with benzodiazepine-resistant SE in whom valproic acid was used either as first-line or second-line treatment. The study was not meant to be comparative, but seizure cessation in the phenytoin group was also mentioned. The sample size was small and uneven, with just 12 participants in the valproic acid group and 37 patients in phenytoin group.

As well, there was serious indirectness in many of the included RCTs. Ogutu et al. (2003) included children with severe falciparum malaria and SE; Ismail et al. (2012) included children with febrile SE; and Miyahara et al. (2009) included cases with progressive myoclonic epilepsy. The meta-analysis of the pooled effect sizes showed a mean efficacy of 50.2% (95% CI: 34.2– 66.1%). Heterogeneity via I^2 was calculated to be 16.45%.

Valproic acid for adults with benzodiazepine-resistant SE

In the Yasiry and Shorvon (2014) review, there were eight studies describing treatment with IV valproic acid in 250 benzodiazepine-resistant episodes that were included in the meta-analysis. The meta-analysis was performed on a combination of different study designs, randomized (Agarwal et al., 2007; Malamiri et al., 2012) with different comparators (including phenytoin in Agarwal et al. (2007) and phenobarbital in Malamiri et al. [2012]), as well observational studies (Alvarez et al., 2011; Chang et al. (2010); Tiamkao et al., 2009; Olsen et al., 2007; Yu et al., 2003; Chen et al., 2009). Three of the eight studies were in adults (Alvarez et al., 2011; Tiamkao et al., 2009; Olsen et al., 2007) and Chen et al. (2009) was on children and adults with SE resistant to IV diazepam and IM phenobarbital. Heterogeneity calculated via I^2 was 12.73%. The meta-analysis yielded a mean effect size for the efficacy of valproic acid of 75.7% (95% CI: 63.7–84.8%).

Phenobarbital for adults with benzodiazepine-resistant SE

The Yasiry and Shorvon (2014) review also two studies reporting treatment of IV phenobarbital in 42 episodes of benzodiazepine-resistant SE. Of these, the Malamiri et al. (2012) study was a randomized open label study of valproic acid vs. phenobarbital in children with benzodiazepine-resistant SE, which has been covered in GRADE Table 2. The other included Kokwaro et al. (2003), an observational study of 12 children with severe falciparum malaria and convulsions. I^2 was 0% due to the number of studies taken. The meta-analysis revealed a mean efficacy of 73.6% (95% CI: 58.3–84.8%).



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IM phenobarbital as an alternative to IV anti-epileptic medications in children with benzodiazepine-resistant SE

IM phenobarbital was considered given its widespread use in resource-restricted settings in the treatment of established SE. In October 2014, an additional search for evidence was conducted (see Appendix 1). Non-GRADEd evidence includes two RCTs (Crawley et al., 1992; White et al., 1988) and four non-controlled studies (Kokwaro et al., 2003; Kuile et al., 1992; Murri et al., 1992; Sternowsky et al., 1981).

The two RCTs identified by the search (Crawley et al., 1992; White et al., 1988) reported the tolerability and the effects on seizure frequency among a total of 388 children being admitted with cerebral malaria when given one dose of IM phenobarbital vs. placebo. IM phenobarbital alone was tolerated across both studies. The use of IM phenobarbital, as well as three or more doses of diazepam, was found to greatly increase the risk of respiratory depression and death in the Crawley et al. (1992) study (which notably used 20 mg/kg as opposed to 3.5 mg/kg in the White et al. (1988) study). Seizure frequency across both studies decreased significantly with the use of IM phenobarbital. The quality of these two studies is low mainly due to their size (in terms of low number of participants and events) and the indirectness of the study population (i.e., benzodiazepine-resistant convulsive SE vs. cerebral malaria). Furthermore, the optimum dose cannot be concluded from only two RCTs.

The four non-controlled studies (Kokwaro et al., 2003; Kuile et al., 1992; Murri et al., 1992; Sternowsky et al., 1981), which varied in their study populations (12 children with malaria, 20 children with malaria, 390 adults and children aged 10-65 years old with head injury and 41 children with simple febrile seizures, respectively), investigated the tolerance of IM phenobarbital and its prophylactic effects on seizure frequency. There were no notable adverse effects, apart from a tendency of phenobarbital to deepen coma or render patients sleepy that was identified in the Kuile et al. (1992) study (where just 11 children received the intervention) or to experience respiratory depression (with 1 child in Kokwaro et al. (2003) study). The optimum dose cannot be concluded from these studies, although the Kokwaro et al. (2003) study showed that a 15 mg/kg loading dose of phenobarbital followed by two maintenance doses of 5 mg/kg achieved the expected therapeutic plasma concentrations of 10-130 mg/kg in children with severe falciparum malaria and SE.



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PART 2: FROM EVIDENCE TO RECOMMENDATIONS

Evidence to recommendation table

| | |
|---|---|
| Benefits | <p>From comparative studies, the evidence is inconclusive to determine if there is a clinically important difference in efficacy between IV phenytoin, phenobarbital and valproic acid for the treatment of benzodiazepine-resistant SE in adults. This statement is based on low quality evidence from two RCTs (total n=160).</p> <p>However in the meta-analysis of non-randomized studies, a high proportion (between 50% and 75%) of patients treated with valproic acid, phenytoin and phenobarbital showed clinically-relevant improvement. Individual performance of the medications as assessed in the systematic review estimated efficacy of phenobarbital as 73.6% (95% CI: 58.3-84.8%), phenytoin 50.2% (95% CI: 34.266.1%) and valproic acid 75.7% (95% CI: 63.7-84.8%). However, the evidence is of very low quality, with serious risk of bias and serious indirectness.</p> <p>The completion of a literature search showed evidence of significant decreases in seizure frequency with the use of IM phenobarbital in children with cerebral malaria. A non-controlled study found that among adults with head injury, IM phenobarbital is prophylactically effective and is tolerated by patients.</p> |
| Harms | <p>The risk of adverse effects and seizure recurrence within 24 hours is higher in patients who are administered phenobarbital vs. valproic acid.</p> <p>There was only one comparative study reporting on deaths in IV use of the aforementioned medications, which was of very low quality. The evidence is inconclusive and so it is not possible to determine if there is a clinically important difference in the occurrence of death with the use of these pharmacological interventions.</p> |
| Summary of the quality of evidence | There is an overall low quality of available evidence. |

| Value and preferences | |
|--|---|
| In favour | <p>SE is a medical emergency associated with substantial mortality and so its control is of critical importance. An additional percentage of persons experiencing this condition have permanent sequelae, such as a permanent vegetative state or cognitive difficulties.</p> <p>Adults treated for established SE require monitoring and may require ventilator support; therefore, secondary care is necessary.</p> <p>Advantages of valproic acid include lesser risk of cardiorespiratory side effects. Valproic acid is a broad-spectrum medication active against all types of seizures; therefore, it may be a good agent for maintenance therapy after the acute control of seizures in idiopathic generalized epilepsy or when the type of seizure/epilepsy syndrome is not clear.</p> |
| Against | <p>Valproic acid has the risk of hepatotoxicity and pancreatitis.</p> <p>Phenobarbital carries the risk of sedation and respiratory depression, which may be increased if it is used after benzodiazepines.</p> <p>Phenytoin has associated risks of arrhythmia and hypotension and can be difficult to administer in certain settings.</p> |
| Uncertainty or variability? | <p>There is no variability in the value and preference for a specific kind of treatment intervention across different settings.</p> |
| Feasibility (including resource use considerations) | <p>The IV forms of phenytoin and phenobarbital are included on the WHO Essential Medicines List. However, IV valproic acid is not included.</p> <p>Despite the inclusion of two of the treatments discussed in this evidence profile, many LAMICs face serious issues with access to medicines, particularly for phenobarbital, which is a controlled medication. Many LAMICs face complete stock-outs for long periods of time.</p> <p>The cost of IV valproic acid is relatively high and may not be an affordable option in LAMICs with health care resource constraints.</p> |



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| | |
|------------------------------------|---|
| Uncertainty or variability? | There is variability with regards to the feasibility of the treatment options discussed here. The costs associated with acquisition of medication are higher, but the resource intensity of managing the side effects of phenytoin and phenobarbital is high. |
|------------------------------------|---|

Recommendation and remarks

Recommendation

In adults with established status epilepticus, i.e. seizures persisting after two doses of benzodiazepines, either intravenous valproic acid, intravenous phenobarbital or intravenous phenytoin can be used with appropriate monitoring.

Intravenous valproic acid is preferred over intravenous phenobarbital or intravenous phenytoin because of its superior risk-benefit profile. The choice of these medications depends on local resource settings, including availability and facilities for monitoring.

Where intravenous infusion may not be feasible, intramuscular phenobarbital remains an option, with appropriate monitoring. Phenytoin and valproic acid should not be given intramuscularly.

Rationale: Status epilepticus is a medical emergency associated with substantial mortality and so its control is of critical importance. Although the quality of the evidence is very low, the benefits of intravenous phenytoin, phenobarbital and valproic acid outweigh their harms with no clinically relevant differences between individual interventions in direct comparisons in management of established status epilepticus. Advantages of valproic acid include lesser risk of cardiorespiratory side effects. Valproic acid is a broad-spectrum medication active against all types of seizures, and hence may be a good agent for maintenance therapy after the acute control of seizures in idiopathic generalized epilepsy or when the type of seizure/ epilepsy syndrome is not clear. However, valproic acid has the risk of hepatotoxicity and pancreatitis. Phenobarbital carries the risk of sedation and respiratory depression, which may be increased if it is used after benzodiazepines. Phenytoin carries the risk of arrhythmia and hypotension and difficulties in administration.

Remarks

The above medications are initiated when seizures persist after two doses of benzodiazepines.



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The choice of the medication can be affected by a number of factors, for example, the availability, cost and side effect profile of each.

Judgements about the strength of a recommendation

| Factor | Decision |
|----------------------------------|---|
| Quality of the evidence | <input type="checkbox"/> High <input type="checkbox"/> Moderate <input type="checkbox"/> Low <input checked="" type="checkbox"/> Very low |
| Balance of benefits versus harms | <input checked="" type="checkbox"/> Benefits clearly outweigh harms <input type="checkbox"/> Benefits and harms are balanced <input type="checkbox"/> Potential harms clearly outweigh potential benefits |
| Values and preferences | <input checked="" type="checkbox"/> No major variability <input type="checkbox"/> Major variability |
| Resource use | <input type="checkbox"/> Less resource-intensive <input type="checkbox"/> More resource-intensive <input checked="" type="checkbox"/> N/A – The costs associated with acquisition of medication is higher, but the resource intensity of managing the side effects of phenytoin and phenobarbital is high. |
| Strength | CONDITIONAL |



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OTHER REFERENCES

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.

Crawley J, Waruiru C, Mithwani S, Mwangi I, Watkins W, Ouma D, Winstanley P, Peto T, Marsh K (2000). Effect of phenobarbital on seizure frequency and mortality in childhood cerebral malaria: a randomised, controlled intervention study. *Lancet*.355(9205):701-706.

Kokwaro GO, Ogutu BR, Mucohi SN, Otieno GO, Newton JC (2003). Pharmacokinetics and clinical effect of phenobarbital in children with severe falciparum malaria and convulsions. *British Journal of Clinical Pharmacology*.56(4):453-457.

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ⁱ Confidence interval (CI)

ⁱⁱ Relative risk (RR)