Epilepsy module – evidence profile EPI1: Anti-seizure medicines for adults with established status epilepticus

WHO mhGAP guideline update: Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders

2023

World Health Organization

Contents

Mental Health Gap Action Programme (mhGAP) guideline for mental, neurological and substance use disorders, available at: https://www.who.int/publications/i/item/9789240084278

1 Background

Status epilepticus is a medical emergency which can lead to profound systemic and neurological damage, and is associated with significant short term and long term mortality. A staged treatment protocol for management of status epilepticus is usually recommended[1]. Randomized controlled trials show that benzodiazepines (intravenous lorazepam, intravenous diazepam or intramuscular midazolam) may be the most efficient treatment in early status epilepticus.[2,3] Approximately 30–40 % of all patients fail to respond to initial treatment with benzodiazepines (Benzodiazepine-resistant or established status epilepticus) and need further treatment with other intravenous anti-seizure medications.[4]

Traditionally intravenous phenytoin has been in benzodiazepine resistant status epilepticus, and is mentioned in most institutional protocols as the medication to be used if the patient is seizing despite the administration of first line benzodiazepine. However phenytoin may cause cardiac arrhythmias, hypotension, extravasation and purple glove syndrome. [5] The use of phenytoin is also limited by the speed of infusion, it needs to be infused at the rate of 1 mg/kg/min, so the infusion takes at least 20 minutes. In status epilepticus management, time is of the essence, as ongoing seizures lead to incremental brain injury. Fosphenytoin, a phenytoin pro-drug, is a useful alternative to phenytoin, as it can be administered at three times faster than phenytoin. However, higher cost and limited availability in low resource settings is an issue. Some of the older protocols also mention phenobarbital as an alternative to phenytoin, however there are concerns of increased respiratory distress if phenobarbital is administered after benzodiazepines. The advantages of phenobarbital include low cost and wide availability. Also it is an effective anti-seizure medication, and may work even after the failure of phenytoin. There is paucity of evidence on the efficacy and safety of phenobarbital in benzodiazepine resistant status epilepticus.

Recently, there has been use of intravenous formulations of other anti-epileptic drugs such as levetiracetam and valproate in benzodiazepine resistant status epilepticus. These drugs may offer advantages in terms of safety and improved tolerability, but availability and cost are an issue. Since the publication of WHO mhGAP guidelines in 2016, there have been many randomized controlled trials comparing levetiracetam with either phenytoin or fosphenytoin and a few RCTs comparing valproate with phenytoin/fosphenytoin and levetiracetam.[6-11] There is now adequate efficacy and safety data for levetiracetam, phenytoin, fosphenytoin and a reasonable amount of evidence for valproate in the setting of benzodiazepine resistant status epilepticus in adults. This question aims to identify and recommend the best treatment option in benzodiazepine resistant status epilepticus in adults for low and middle income countries.

2 Methodology

2.1. PICO question

Population/ Intervention / Comparison / Outcome (PICO)

Population: Adults presenting with established status epilepticus, i.e. seizures persisting after the first line agent (BZD-resistant status epilepticus)

Interventions:

- IV Phenytoin
- IV Fosphenytoin

- IV Levetiracetam
- IV Valproate
- IV Phenobarbital
- IV Lacosamide
- IV Diazepam infusion

Comparison: One intervention versus other(s)

Outcomes:
Critical
- Clinical seizure cessation within 60 minutes*
- Death
- Respiratory depression requiring intubation/ mechanical ventilation
- Cardiovascular adverse effects including hypotension and/or arrhythmias

Important
- Seizure freedom at 24 hours

***** Time points in different studies vary from 5 minutes to 60 minutes after start of infusion. In addition, variable infusion rates have been used.

Subgroups: None

2.2. Search strategy

Literature search was carried out by searching the following bibliographic databases: MEDLINE (1946–March 31, 2022) with in-process records and daily updates via Ovid; Embase+Embase Classic (1974–2022 week 12) via Ovid; and Cochrane Central Register of Controlled Trials – March 2022. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings) and Emtree Subject Headings (Embase), and keywords. Methodological filters were applied to limit the study types to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs) and controlled clinical trials. Conference abstracts were excluded from the search results. Date limits of 1990-current date and English language limits were also applied. See Appendix 1 for the detailed search strategy.

Inclusion and exclusion criteria for this review

Type of studies: Systematic reviews of randomized controlled trials. For primary studies, randomized controlled trials, quasi-randomized controlled trials, blinded or unblinded.

Types of participants:

Adults (including elderly adults) presenting with an acute seizure (hospital or community setting) and who continued to have seizures after the administration of intravenous benzodiazepines (lorazepam, diazepam or midazolam) and were subsequently treated with any of the following: intravenous phenytoin, fosphenytoin, levetiracetam, phenobarbital, valproate or lacosamide. The study population presenting *de novo* with a first convulsion and those with an established diagnosis of epilepsy. Any and all causes of the convulsive status epilepticus were included in the review.

Types of interventions:

In adults presenting with benzodiazepine-resistant status epilepticus, we included trials if they compared one treatment with another. Specific drugs included intravenous phenytoin, fosphenytoin, levetiracetam, phenobarbital, valproate and lacosamide. Systematic reviews were included if they evaluated any of these drugs in benzodiazepine resistant status epilepticus. Some systematic reviews have analysed phenytoin and fosphenytoin as one group. As many low and middle income countries may not have the availability and affordability of fosphenytoin, we tried to look for systematic reviews where in the use of phenytoin and fosphenytoin was analysed separately.

Types of outcome measures

- Clinical seizure cessation within 60 minutes*
- Death
- Respiratory depression requiring intubation/ mechanical ventilation
- Cardiovascular adverse effects including hypotension and/or arrhythmias
- Seizure freedom for 24 hours

***** Time points in different studies vary from 5 minutes to 60 minutes after start of infusion. In addition, variable infusion rates have been used.

2.3. Data collection and analysis

As the first stage in selecting relevant studies, records retrieved from the bibliographic databases and from other sources were recorded and assessed for eligibility by examining their titles and abstracts only. This assessment was performed in accordance with the inclusion and exclusion criteria developed a priori. The full text of articles found to be potentially relevant on the basis of their titles and abstracts was retrieved and examined in light of the same inclusion criteria in the second stage of study selection. Data from eligible studies were then extracted into pre-defined templates that included the characteristics of the study design and of the population, intervention, comparator and outcomes. Two members of the research team (SS and SA) independently assessed trials for inclusion. We also extracted the outcome data specified. Any disagreements were resolved by discussion. We included studies which enrolled only adults, or adults and children, if studies enrolling only adults were not available. In cases where no adult or adult-pediatric combined study was available, pediatric studies, if available were selected. The flow of articles throughout the search and up to the final cohort of included studies is depicted with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

2.4. Selection and coding of identified records

EndNote X9 was used to organize the citations obtained from the searches. A copy of the reference library (text format) of the included studies has been provided separately (as txt file).

2.5. Quality assessment

The methodological quality of each trial was assessed using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2) for the main outcome of seizure cessation within 60 minutes. The following criteria were assessed:

(1) Bias arising from the randomization process

(2) Bias due to deviations from intended interventions

(3) Bias due to missing outcome data
(4) Bias in measurement of the outcome
(5) Bias in selection of the reported result

2.6. Analysis of subgroups or subsets

No subgroup analysis was performed.

3 Results

3.1. List of systematic reviews and/or studies identified by the search process

3.1.1. INCLUDED IN GRADE TABLES/FOOTNOTES

1. Chamberlain JM, Kapur J, Shinnar S, Elm J, Holsti M, Babcock L, Rogers A, et al. Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial. Lancet. 2020 Apr 11;395(10231):1217-1224.Agarwal P, Kumar N, Chandra R, Gupta G, Antony AR, Garg N. Randomized study of intravenous valproate and phenytoin in status epilepticus. Seizure 2007; 16: 527–532

2. Su Y, Huang H, Jiang M, Pan S, Ding L, Zhang L, Jiang W, Zhuang X. Phenobarbital versus valproate for generalized convulsive status epilepticus in adults (2): A multicenter prospective randomized controlled trial in China (China 2-P vs. V). Epilepsy Res. 2021 Nov;177:106755.

3. Su Y, Liu G, Tian F, Ren G, Jiang M, Chun B, Zhang Y, Zhang Y, Ye H, Gao D, Chen W. Phenobarbital Versus Valproate for Generalized Convulsive Status Epilepticus in Adults: A Prospective Randomized Controlled Trial in China. CNS Drugs. 2016 Dec;30(12):1201-1207.

4. Chakravarthi S, Goyal MK, Modi M, Bhalla A, Singh P. Levetiracetam versus phenytoin in management of status epilepticus. J Clin Neurosci. 2015 Jun;22(6):959-63.

5. Burman RJ, Ackermann S, Shapson-Coe A, Ndondo A, Buys H, Wilmshurst JM. Comparison of Parenteral Phenobarbital vs. Parenteral Phenytoin as Second-Line Management for Pediatric Convulsive Status Epilepticus in a Resource-Limited Setting. Front Neurol. 2019 May 15;10:506.

6. Misra UK, Dubey D, Kalita J. Comparison of lacosamide versus sodium valproate in status epilepticus: A pilot study. Epilepsy Behav. 2017 Nov;76:110-113.

7. Chen WB, Gao R, Su YY, Zhao JW, Zhang YZ, Wang L, Ren Y, Fan CQ. Valproate versus diazepam for generalized convulsive status epilepticus: a pilot study. Eur J Neurol. 2011 Dec;18(12):1391-6.

3.1.2. EXCLUDED FROM GRADE TABLES/FOOTNOTES

Systematic reviews and meta-analyses

1. Prasad M, Krishnan PR, Sequeira R, Al-Roomi K. Anticonvulsant therapy for status epilepticus. Cochrane Database Syst Rev. 2014 Sep 10;9:CD003723.
   REASON FOR EXCLUSION: Review did not evaluate the specified population of our scoping question i.e. established status epilepticus (i.e. seizures persisting after the first line agent or Benzodiazepine-resistant status epilepticus). Although the authors included studies on premonitory, early, established, and refractory status epilepticus; ultimately the studies were not analysed based on the type of status epilepticus.

2. Angurana SK, Suthar R. Efficacy and Safety of Levetiracetam vs. Phenytoin as Second Line Antiseizure Medication for Pediatric Convulsive Status Epilepticus: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. J Trop Pediatr. 2021 May 17;67(2):fmab014.
   REASON FOR EXCLUSION: Meta-analysis focused on children. Phenytoin and Fosphenytoin clubbed under one group of phenytoin. As fosphenytoin may have a different efficacy profile, as it can be administered faster, and a different safety profile (as it is water soluble, and phenytoin is not), meta-analyses which separately analysed these drugs were preferred.

3. Feng Y, Chen Y, Jia Y, Wang Z, Wang X, Jiang L, Ai C, Li W, Liu Y. Efficacy and safety of levetiracetam versus (fos)phenytoin for second-line treatment of epilepticus: a meta-analysis of latest randomized controlled trials. Seizure. 2021 Oct;91:339-345.
   REASON FOR EXCLUSION: Meta-analysis included both pediatric and adult studies. Also included some studies, where-in levetiracetam and (fos)phenytoin were administered immediately after benzodiazepines, and not only in patients with benzodiazepine resistant status epilepticus.

4. DeMott JM, Slocum GW, Gottlieb M, Peksa GD. Levetiracetam vs. phenytoin as 2nd-line treatment for status epilepticus: A systematic review and meta- analysis. Epilepsy Behav. 2020 Oct;111:107286.
   REASON FOR EXCLUSION: Not focused on adults, studies on children also included. Also, Chamberlain 2020 study not included.

5. Abdelgadir I, Hamud A, Kadri A, Akram S, Pullattayil A, Akobeng AK, Powell C. Levetiracetam for convulsive status epilepticus in childhood: systematic review and meta-analysis. Arch Dis Child. 2020 Oct 15
   REASON FOR EXCLUSION: Meta-analysis included only studies on children. Some studies which did not enroll benzodiazepine-resistant status epilepticus patients also enrolled

6. Liampas I, Siokas V, Brotis A, Zintzaras E, Stefanidis I, Dardiotis E. Intravenous sodium valproate in status epilepticus: review and Meta-analysis. Int J Neurosci. 2021 Jan;131(1):70-84.

REASON FOR EXCLUSION: Many studies in the review did not enroll benzodiazepine resistant patients. Also, Chamberlain 2020 not included.

7. Brigo F, Bragazzi N, Nardone R, Trinka E. Direct and indirect comparison meta-analysis of levetiracetam versus phenytoin or valproate for convulsive status epilepticus. Epilepsy Behav. 2016 Nov;64(Pt A):110-115.
   REASON FOR EXCLUSION: Several key recent studies such as Chamberlain 2020 not included, as studies published after this review.

8. Brigo F, Del Giovane C, Nardone R, Trinka E, Lattanzi S. Intravenous antiepileptic drugs in adults with benzodiazepine-resistant convulsive status epilepticus: A systematic review and network meta-analysis. Epilepsy Behav. 2019 Dec;101(Pt B):106466.
   REASON FOR EXCLUSION: Several key recent studies such as Chamberlain 2020 not included.

9. Hoshiyama E, Kumasawa J, Uchida M, Hifumi T, Moriya T, Ajimi Y, et al. Phenytoin versus other antiepileptic drugs as treatments for status epilepticus in adults: a systematic review and meta-analysis. Acute Med Surg. 2022 Jan 7;9(1):e717.
   REASON FOR EXCLUSION: Many studies in the review did not enroll benzodiazepine resistant patients.

10. Brigo F, Del Giovane C, Nardone R, Trinka E, Lattanzi S. Second-line treatments in benzodiazepine-resistant convulsive status epilepticus: An updated network meta-analysis including the ESET Trial - What did change? Epilepsy Behav. 2020 May;106:107035.
    REASON FOR EXCLUSION: Brief publication as letter to the editor. Several key analyses not available.

Randomized controlled trials

11. Nene D, Mundlamuri RC, Satishchandra P, Prathyusha PV, Nagappa M, Bindu PS, Raghavendra K, et al. Comparing the efficacy of sodium valproate and levetiracetam following initial lorazepam in elderly patients with generalized convulsive status epilepticus (GCSE): A prospective randomized controlled pilot study. Seizure. 2019 Feb;65:111-117.
    REASON FOR EXCLUSION: Study did not enroll benzodiazepine resistant patients. Patients were administered valproate or levetiracetam immediately after lorazepam administration.

12. Kapur J, Elm J, Chamberlain JM, Barsan W, Cloyd J, Lowenstein D, Shinnar S, et al. Randomized Trial of Three Anticonvulsant Medications for Status Epilepticus. N Engl J Med. 2019 Nov 28;381(22):2103-2113.
    REASON FOR EXCLUSION: Subsequent study Chamberlain 2020 reported separate outcomes for adults and children, with extended pediatric recruitment of this same group of patients. As we have already included Chamberlain 2020 for the review, Kapur 2019 was not included.

13. Amiri-Nikpour MR, Nazarbaghi S, Eftekhari P, Mohammadi S, Dindarian S, Bagheri M, Mohammadi H. Sodium valproate compared to phenytoin in treatment of status epilepticus. Brain Behav. 2018 Mar 23;8(5):e00951.
REASON FOR EXCLUSION: Seizure cessation outcome reported at 7 days.

14. Gujjar AR, Nandhagopal R, Jacob PC, Al-Hashim A, Al-Amrani K, Ganguly SS, Al- Asmi A. Intravenous levetiracetam vs phenytoin for status epilepticus and cluster seizures: A prospective, randomized study. Seizure. 2017 Jul;49:8-12.
REASON FOR EXCLUSION: Study did not enroll benzodiazepine resistant patients. Patients were administered phenytoin or levetiracetam immediately after benzodiazepine administration.

15. Shaner DM, McCurdy SA, Herring MO, Gabor AJ. Treatment of status epilepticus: a prospective comparison of diazepam and phenytoin versus phenobarbital and optional phenytoin. Neurology. 1988 Feb;38(2):202-7.
REASON FOR EXCLUSION: Study did not enroll benzodiazepine resistant patients. Patients were administered either diazepam + phenytoin or Phenobarbital as initial treatment.

16. Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med. 1998 Sep 17;339(12):792-8.
REASON FOR EXCLUSION: Study evaluated first line treatment for status epilepticus; did not enroll benzodiazepine resistant patients.

17. Misra UK, Kalita J, Patel R. Sodium valproate vs phenytoin in status epilepticus: a pilot study. Neurology. 2006 Jul 25;67(2):340-2.
REASON FOR EXCLUSION: Study evaluated valproate vs phenytoin as first line treatment for status epilepticus; did not enroll benzodiazepine resistant patients.

18. Sreenath TG, Gupta P, Sharma KK, Krishnamurthy S. Lorazepam versus diazepam-phenytoin combination in the treatment of convulsive status epilepticus in children: a randomized controlled trial. Eur J Paediatr Neurol. 2010
REASON FOR EXCLUSION: Study evaluated first line treatment for status epilepticus; did not enroll benzodiazepine resistant patients.

19. Gilad R, Izkovitz N, Dabby R, Rapoport A, Sadeh M, Weller B, Lampl Y. Treatment of status epilepticus and acute repetitive seizures with i.v. valproic acid vs phenytoin. Acta Neurol Scand. 2008 Nov;118(5):296-300.
REASON FOR EXCLUSION: Study evaluated valproate vs phenytoin as first line treatment for status epilepticus; did not enroll benzodiazepine resistant patients.

20. Mundlamuri RC, Sinha S, Subbakrishna DK, Prathyusha PV, Nagappa M, Bindu PS, et al. Management of generalized convulsive status epilepticus (SE): A prospective randomised controlled study of combined treatment with intravenous lorazepam with either phenytoin, sodium valproate or levetiracetam--Pilot study. Epilepsy Res. 2015 Aug;114:52-8.

REASON FOR EXCLUSION: Study did not enroll benzodiazepine resistant patients. Patients were administered phenytoin, valproate or levetiracetam along with IV lorazepam.

21. Abbaskhanian A, Sheidaee K, Charati JY. Comparison of the effect of continuous intravenous infusion of sodium valproate and midazolam on management of status epilepticus in children. Arch Pediatr. 2021 Nov;28(8):696-701.
    REASON FOR EXCLUSION: Study enrolled patients with refractory status epilepticus, i.e. seizures persisting despite first line benzodiazepine, and second-line phenytoin or Phenobarbital.

22. Chitsaz A, Mehvari J, Salari M, Gholami F, Najafi MR. A comparative assessment the efficacy of intravenous infusion of sodium valproate and phenytion in the treatment of status epilepticus. Int J Prev Med. 2013 May;4(Suppl 2):S216-21.
23. REASON FOR EXCLUSION: Study did not enroll benzodiazepine resistant patients. Patients were administered phenytoin or levetiracetam immediately after diazepam administration.

24. Mehta V, Singhi P, Singhi S. Intravenous sodium valproate versus diazepam infusion for the control of refractory status epilepticus in children: a randomized controlled trial. J Child Neurol. 2007 Oct;22(10):1191-7.
    REASON FOR EXCLUSION: Study enrolled patients with refractory status epilepticus.

25. Nazir M, Tarray RA, Asimi R, Syed WA. Comparative Efficacy of IV Phenytoin, IV Valproate, and IV Levetiracetam in Childhood Status Epilepticus. J Epilepsy Res. 2020 Dec 31;10(2):69-73.
    REASON FOR EXCLUSION: Study did not enroll benzodiazepine resistant patients. Also, outcomes reported at 24 hours.

26. Vignesh V, Rameshkumar R, Mahadevan S. Comparison of Phenytoin, Valproate and Levetiracetam in Pediatric Convulsive Status Epilepticus: A Randomized Double-blind Controlled Clinical Trial. Indian Pediatr. 2020 Mar 15;57(3):222-227.
    REASON FOR EXCLUSION: Study enrolled only children.

27. Malamiri RA, Ghaempanah M, Khosroshahi N, Nikkhah A, Bavarian B, Ashrafi MR. Efficacy and safety of intravenous sodium valproate 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.
    REASON FOR EXCLUSION: Study enrolled only children.

28. Dalziel SR, Borland ML, Furyk J, Bonisch M, Neutze J, Donath S, et al. Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomized controlled trial. Lancet. 2019 May 25;393(10186):2135-2145.
    REASON FOR EXCLUSION: Study enrolled only children.

29. Lyttle MD, Rainford NEA, Gamble C, Messahel S, Humphreys A, Hickey H, et al. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open- label, randomised trial. Lancet. 2019 May 25;393(10186):2125-2134.
REASON FOR EXCLUSION: Study enrolled only children.

30. Noureen N, Khan S, Khursheed A, Iqbal I, Maryam M, Sharib SM, et al. Clinical Efficacy and Safety of Injectable Levetiracetam Versus Phenytoin as Second-Line Therapy in the Management of Generalized Convulsive Status Epilepticus in Children: An Open-Label Randomized Controlled Trial. J Clin Neurol. 2019 Oct;15(4):468-472.
REASON FOR EXCLUSION: Study enrolled only children.

31. Wani G, Imran A, Dhawan N, Gupta A, Giri JI. Levetiracetam versus phenytoin in children with status epilepticus. J Family Med Prim Care. 2019 Oct 31;8(10):3367-3371.
REASON FOR EXCLUSION: Study enrolled only children. Also, study did not enroll benzodiazepine resistant patients. Patients were administered phenytoin or levetiracetam immediately after midazolam administration.

32. Handral A, Veerappa BG, Gowda VK, Shivappa SK, Benakappa N, Benakappa A. Levetiracetam versus Fosphenytoin in Pediatric Convulsive Status Epilepticus: A Randomized Controlled Trial. J Pediatr Neurosci. 2020 Jul-Sep;15(3):252-256.
REASON FOR EXCLUSION: Study enrolled only children.

33. Nalisetty S, Kandasamy S, Sridharan B, Vijayakumar V, Sangaralingam T, Krishnamoorthi N. Clinical Effectiveness of Levetiracetam Compared to Fosphenytoin in the Treatment of Benzodiazepine Refractory Convulsive Status Epilepticus. Indian J Pediatr. 2020 Jul;87(7):512-519.
REASON FOR EXCLUSION: Study enrolled only children.

34. Senthilkumar CS, Selvakumar P, Kowsik M. Randomized controlled trial of levetiracetam versus fosphenytoin for convulsive status epilepticus in children. Int J Pediatr Res 2018; 5(4): 237-242.
REASON FOR EXCLUSION: Study enrolled only children.

35. Khajeh A, Yaghoubinia F, Yaghoubi S, Fayyazi A, Miri Aliabad G. Comparison of the Effect of Phenobarbital versus Sodium Valproate in Management of Children with Status Epilepticus. Iran J Child Neurol. 2018 Fall;12(4):85-93.
REASON FOR EXCLUSION: Study enrolled only children.

PICO Table

Population: In adults with established status epilepticus, i.e. seizures persisting after the first line agent (i.e. Benzodiazepine-resistant status epilepticus)				
Intervention	**Comparison**	**Outcome**	**RCTs identified**	**Comment**
IV Phenytoin	IV Levetiracetam	Clinical seizure cessation within 60 min	Chakravarti 2015	Cardiovascular adverse effects not reported in the study
		Death		
		Respiratory depression requiring intubation/ mechanical ventilation		
		Cardiovascular adverse effects including hypotension and/or arrhythmias		
		Seizure freedom for 24 hours		
IV Levetiracetam	IV Fosphenytoin	Clinical seizure cessation	Chamberlain 2020	Seizure recurrence outcome reported at 12 hours
		Death		
		Respiratory depression requiring intubation/ mechanical ventilation		
		Cardiovascular adverse effects including hypotension and/or arrhythmias		
		Seizure freedom for 24 hours		
IV Phenobarbital	IV Phenytoin	Clinical seizure cessation	Burman 2019	No deaths reported in either arm. Cardiovascular adverse effects were very few (0 in PHB group, and 2 in PHT group)
		Death		
		Respiratory depression requiring intubation/ mechanical ventilation		
		Cardiovascular adverse effects including hypotension and/or arrhythmias		
		Seizure freedom for 24 hours		
IV Phenytoin	IV Valproate	Clinical seizure cessation	Agarwal 2007	
		Need for intubation		
		Death		
		Respiratory depression requiring intubation/ mechanical ventilation		

Population: In adults with established status epilepticus, i.e. seizures persisting after the first line agent (i.e. Benzodiazepine-resistant status epilepticus)				
		Cardiovascular adverse effects including hypotension and/or arrhythmias		
		Seizure freedom for 24 hours		
IV Fosphenytoin	IV Valproate	Clinical seizure cessation	Chamberlain 2020	Seizure recurrence outcome reported at 12 hours
		Death		
		Respiratory depression requiring intubation/ mechanical ventilation		
		Cardiovascular adverse effects including hypotension and/or arrhythmias		
		Seizure freedom for 24 hours		
IV valproate	IV Phenobarbital	Seizure cessation within 60 min after start of infusion	Su 2016 Su 2021	Meta-analysis done by us
		Death		
		Respiratory depression requiring intubation/ mechanical ventilation		
		Cardiovascular adverse effects including hypotension and/or arrhythmias		
		Seizure freedom for 24 hours		
IV valproate	IV Levetiracetam	Clinical seizure cessation	Chamberlain 2020	Seizure recurrence outcome reported at 12 hours
		Death		
		Respiratory depression requiring intubation/ mechanical ventilation		
		Cardiovascular adverse effects including hypotension and/or arrhythmias		
		Seizure freedom for 24 hours		
IV Valproate	IV Lacosamide	Seizure cessation within 60 min after start of infusion	Misra 2017	
		Death		
		Respiratory depression requiring intubation/ mechanical ventilation		
		Cardiovascular adverse effects including hypotension and/or		

Population: In adults with established status epilepticus, i.e. seizures persisting after the first line agent (i.e. Benzodiazepine-resistant status epilepticus)				
		arrhythmias		
		Seizure freedom for 24 hours		
IV Valproate	IV Diazepam Infusion	Seizure cessation within 60 min after start of infusion	Chen 2011	
		Death		
		Respiratory depression requiring intubation/ mechanical ventilation		
		Cardiovascular adverse effects including hypotension and/or arrhythmias		
		Seizure freedom for 24 hours		

Remarks

No prior meta-analysis or systematic review was found suitable for the purpose of this evidence profile. We included studies which enrolled only adults, or adults and children, if studies enrolling only adults were not available. In cases where no adult or adult-pediatric combined study was available, pediatric studies, if available were selected. Only single studies were available for most comparisons. Two studies were available for the valproate-phenobarbital comparisons; Su 2016 and Su 2021. We performed the meta-analysis of these two studies for the purpose of our review.

3.2. Narrative description of studies that contributed to GRADE analysis

Eight randomised controlled trials were identified to study comparisons between the anti-epileptic drugs.

1. The Chamberlain (2020) study was a multi-centric randomized double-blind controlled trial comparing the efficacy and safety of levetiracetam, fosphenytoin or valproate in patients with benzodiazepine resistant status epileptcus (ESETT study). This was an extension of the Kapur 2019 ESETT study, reporting the results of extended enrolment of children in the trial, and comparing the efficacy and safety of the use of levetiracetam, fosphenytoin, and valproate in different age groups (children (2-<18 years), young adults (18-65 years), and older adults (>65 years).
2. The Agarwal (2007) study was a randomized open-label trial of valproate versus phenytoin in patients (adults and children) with status epilepticus which did not respond to first-line intravenous diazepam.
3. The Su (2016) study was a randomized open-label trial comparing the valproate versus Phenobarbital in adults with generalized status epilepticus which did not respond to first-line intravenous diazepam.
4. The Su (2021) study was a multi-centric randomized open-label trial comparing the valproate versus Phenobarbital in adults with generalized status epilepticus which did not respond to first-line intravenous diazepam.
5. The Chakravarthi (2015) study was a randomized open-label trial of levetiracetam versus phenytoin in adults with status epilepticus which did not respond to first-line intravenous benzodiazepines.
6. The Burman (2019) study was a randomized open-label trial of Phenobarbital versus phenytoin in children with status epilepticus which did not respond to first-line intravenous benzodiazepines. This study was included as there was no adult study available for this comparison.
7. The Misra (2017) study was a randomized open-label trial of lacosamide versus valproate in adults with status epilepticus which did not respond to first-line intravenous benzodiazepines.
8. The Chen (2011) study was a randomized open-label trial of valproate versus diazepam infusion in adults with status epilepticus which did not respond to first-line intravenous diazepam.

3.3. Grading the Evidence

GRADE Tables

Table 1

Author(s): Suvasini Sharma
Question: Should Phenytoin vs Levetiracetam be used in adults with benzodiazepine resistant status epilepticus?
Setting: secondary or tertiary care
Bibliography: Chakravarthi S, Goyal MK, Modi M, Bhalla A, Singh P. Levetiracetam versus phenytoin in management of status epilepticus. J Clin Neurosci. 2015 Jun;22(6):959-63.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phenytoin	Levetiracetam	Relative (95% CI)	Absolute (95% CI)		
Seizure cessation within 60 minutes (assessed with: Clinical assessment)												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	15/22 (68.2%)	13/22 (59.1%)	**RR 1.058** (0.664 to 1.685)	**34 more per 1,000** (from 199 fewer to 405 more)	⨁⨁◯◯ Low	CRITICAL
Death												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phenytoin	Levetiracetam	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	very serious[c]	none	2/22 (9.1%)	2/22 (9.1%)	**RR 1.000** (0.154 to 6.470)	**0 fewer per 1,000** (from 77 fewer to 497 more)	⨁◯◯◯ Very low	CRITICAL

Respiratory depression needing intubation or mechanical ventilation

1	randomised trials	serious[a]	not serious	not serious	very serious[c]	none	6/22 (27.3%)	4/22 (18.2%)	**RR 1.50** (0.49 to 4.59)	**91 more per 1,000** (from 93 fewer to 653 more)	⨁◯◯◯ Very low	CRITICAL

Seizure freedom for 24 hours

1	randomised trials	serious[a]	not serious	not serious	very serious[c]	none	6/22 (27.3%)	9/22 (40.9%)	**RR 0.940** (0.391 to 2.256)	**25 fewer per 1,000** (from 249 fewer to 514 more)	⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations

a. Randomization was done using a simple random sampling method in which the patients were assigned to either LEV or PHT depending on the order of recruitment into the study. Odd numbered patients received PHT (n = 22; group A) and those with even numbers were administered LEV (n = 22; group B)

b. Wide CIs crossing 1

c. Very wide CIs crossing 1

Table 2

Author(s): Suvasini Sharma
Question: Should Levetiracetam vs Fosphenytoin be used in adults with benzodiazepine resistant status epilepticus?
Setting: Secondary or Tertiary care
Bibliography: Chamberlain JM, Kapur J, Shinnar S, Elm J, Holsti M, Babcock L, Rogers A, et al. Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial. Lancet. 2020 Apr 11;395(10231):1217-1224.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levetiracetam	Fosphenytoin	Relative (95% CI)	Absolute (95% CI)		
Seizure cessation within 60 minutes												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	38/90 (42.2%)	31/70 (44.3%)	**RR 0.96** (0.67 to 1.38)	**18 fewer per 1,000** (from 146 fewer to 168 more)	⨁⨁⨁◯ Moderate	CRITICAL
Death												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levetiracetam	Fosphenytoin	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	very serious[b]	none	6/90 (6.7%)	3/71 (4.2%)	**RR 2.30** (0.68 to 9.06)	**55 more per 1,000** (from 14 fewer to 341 more)	⨁⨁◯◯ Low	CRITICAL

Respiratory depression requiring intubation/ mechanical ventilation

1	randomised trials	not serious	not serious	not serious	serious[a]	none	26/90 (28.9%)	18/71 (25.4%)	**RR 1.14** (0.68 to 1.91)	**35 more per 1,000** (from 81 fewer to 231 more)	⨁⨁⨁◯ Moderate	CRITICAL

Cardiovascular adverse effects including hypotension and/or arrhythmias

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levetiracetam	Fosphenytoin	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	very serious[b]	none	2/90 (2.2%)	3/71 (4.2%)	**RR 0.526** (0.090 to 3.060)	**20 fewer per 1,000** (from 38 fewer to 87 more)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations
a. Wide CIs crossing 1
b. very wide CIs crossing 1

Table 3

Author(s): Suvasini Sharma
Question: Should Phenobarbital vs Phenytoin be used in adults with benzodiazepine resistant status epilepticus?
Setting: Secondary or tertiary care
Bibliography: Burman RJ, Ackermann S, Shapson-Coe A, Ndondo A, Buys H, Wilmshurst JM. Comparison of Parenteral Phenobarbital vs. Parenteral Phenytoin as Second-Line Management for Pediatric Convulsive Status Epilepticus in a Resource-Limited Setting. Front Neurol. 2019 May 15;10:506.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phenobarbital	Phenytoin	Relative (95% CI)	Absolute (95% CI)		
Seizure cessation within 60 minutes												
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	31/36 (86.1%)	15/33 (45.5%)	**RR 1.840** (1.275 to 2.845)	**382 more per 1,000** (from 125 more to 839 more)	⨁⨁◯◯ Low	CRITICAL
Respiratory depression requiring intubation/ mechanical ventilation												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Phenobarbital	Phenytoin	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	5/36 (13.9%)	14/33 (42.4%)	**RR 0.327** (0.530 to 4.035)	**286 fewer per 1,000** (from 199 fewer to 1,000 more)	⨁⨁◯◯ Low	CRITICAL

Seizure freedom for 24 hours

1	randomised trials	not serious	not serious	serious[a]	serious[b]	none	32/36 (88.9%)	28/33 (84.8%)	**RR 1.048** (0.870 to 1.260)	**41 more per 1,000** (from 110 fewer to 221 more)	⨁⨁◯◯ Low	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations
a. This study was performed in children
b. Wide CIs

Table 4

Author(s): Suvasini Sharma
Question: Should Valproate vs Phenytoin be used in adults with benzodiazepine resistant status epilepticus?
Setting: Secondary or tertiary care
Bibliography: Agarwal P, Kumar N, Chandra R, Gupta G, Antony AR, Garg N. Randomized study of intravenous valproate and phenytoin in status epilepticus. Seizure 2007; 16: 527–532

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Valproate	Phenytoin	Relative (95% CI)	Absolute (95% CI)		
Seizure cessation within 60 minutes												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	44/50 (88.0%)	42/50 (84.0%)	**RR 1.05** (0.89 to 1.23)	**42 more per 1,000** (from 92 fewer to 193 more)	⨁◯◯◯ Very low	CRITICAL
Death												
1	randomised trials	serious[a]	not serious	serious[b]	very serious[d]	none	4/50 (8.0%)	4/50 (8.0%)	**RR 1.00** (0.27 to 3.78)	**0 fewer per 1,000** (from 58 fewer to 222 more)	⨁◯◯◯ Very low	CRITICAL
Respiratory depression requiring intubation/ mechanical ventilation												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Valproate	Phenytoin	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	serious[b]	serious[e]	none	0/50 (0.0%)	2/50 (4.0%)	not estimable		⨁◯◯◯ Very low	CRITICAL

Cardiovascular adverse effects including hypotension and/or arrhythmias

1	randomised trials	serious[a]	not serious	serious[b]	serious[e]	none	0/50 (0.0%)	6/50 (12.0%)	not estimable		⨁◯◯◯ Very low	CRITICAL

Seizure freedom for 24 hours

1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	38/50 (76.0%)	34/50 (68.0%)	**RR 1.118** (0.874 to 1.430)	**80 more per 1,000** (from 86 fewer to 292 more)	⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations

a. Method of randomization not clear, no allocation concealment
b. study includes both adults and children
c. Wide CIs
d. Very wide CIs crossing 1
e. very few events, RR could not be calculated

Table 5

Author(s): Suvasini Sharma
Question: Should Fosphenytoin vs Valproate be used in adults with benzodiazepine resistant status epilepticus?
Setting: Secondary or Tertiary Care
Bibliography: Chamberlain JM, Kapur J, Shinnar S, Elm J, Holsti M, Babcock L, Rogers A, et al. Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial. Lancet. 2020 Apr 11;395(10231):1217-1224.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fosphenytoin	Valproate	Relative (95% CI)	Absolute (95% CI)		
Seizure cessation within 60 minutes												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	31/71 (43.7%)	35/76 (46.1%)	**RR 0.948** (0.662 to 1.358)	**24 fewer per 1,000** (from 156 fewer to 165 more)	⨁⨁⨁◯ Moderate	CRITICAL
Death												
1	randomised trials	not serious	not serious	not serious	very serious[b]	none	3/71 (4.2%)	1/76 (1.3%)	**RR 3.210** (0.342 to 30.130)	**29 more per 1,000** (from 9 fewer to 383 more)	⨁⨁◯◯ Low	CRITICAL
Respiratory depression requiring intubation/ mechanical ventilation												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fosphenytoin	Valproate	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	18/71 (25.4%)	16/76 (21.1%)	**RR 1.204** (0.662 to 2.173)	**43 more per 1,000** (from 71 fewer to 247 more)	⨁⨁⨁◯ Moderate	CRITICAL

Cardiovascular adverse effects including hypotension and/or arrhythmias

1	randomised trials	not serious	not serious	not serious	very serious[c]	none	3/71 (4.2%)	0/76 (0.0%)	not estimable		⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations
a. Wide CIs
b. Very wide CIs crossing 1
c. RR not calculable; very few events

Table 6

Author(s): Suvasini Sharma
Question: Should Levetiracetam vs Valproate be used in adults with benzodiazepine resistant status epilepticus?
Setting: Secondary or tertiary care
Bibliography: Chamberlain JM, Kapur J, Shinnar S, Elm J, Holsti M, Babcock L, Rogers A, et al. Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial. Lancet. 2020 Apr 11;395(10231):1217-1224.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levetiracetam	Valproate	Relative (95% CI)	Absolute (95% CI)		
Seizure cessation within 60 minutes												
1	randomised trials	not serious	not serious	not serious	serious[a]	none	38/90 (42.2%)	35/76 (46.1%)	**RR 0.977** (0.690 to 1.383)	**11 fewer per 1,000** (from 143 fewer to 176 more)	⨁⨁⨁◯ Moderate	CRITICAL
Death												
1	randomised trials	not serious	not serious	not serious	very serious[b]	none	6/90 (6.7%)	1/76 (1.3%)	**RR 5.07** (0.64 to 41.10)	**54 more per 1,000** (from 5 fewer to 528 more)	⨁⨁◯◯ Low	CRITICAL
Respiratory depression requiring intubation/ mechanical ventilation												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levetiracetam	Valproate	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	not serious	not serious	not serious	serious[a]	none	26/90 (28.9%)	16/76 (21.1%)	**RR 1.372** (0.780 to 2.360)	**78 more per 1,000** (from 46 fewer to 286 more)	⨁⨁⨁◯ Moderate	CRITICAL
Cardiovascular adverse effects including hypotension and/or arrhythmias												
1	randomised trials	not serious	not serious	not serious	serious[c]	none	2/90 (2.2%)	0/76 (0.0%)	not estimable		⨁⨁⨁◯ Moderate	CRITICAL

CI: confidence interval; **RR:** risk ratio

Explanations
a. Wide CIs crossing 1
b. Very wide CIs crossing 1
c. Very few events, RR not calculated

Table 7

Author(s): Suvasini Sharma
Question: Should Lacosamide vs Valproate be used in adults with benzodiazepine resistant status epilepticus?
Setting: Secondary or tertiary care
Bibliography: Misra UK, Dubey D, Kalita J. Comparison of lacosamide versus sodium valproate in status epilepticus: A pilot study. Epilepsy Behav. 2017 Nov;76:110-113.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lacosamide	Valproate	Relative (95% CI)	Absolute (95% CI)		
Seizure cessation within 60 minutes												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	21/33 (63.6%)	23/33 (69.7%)	**RR 0.930** (0.649 to 1.280)	**49 fewer per 1,000** (from 245 fewer to 195 more)	⊕⊕◯◯ Low	CRITICAL
Death												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	10/33 (30.3%)	12/33 (36.4%)	**RR 0.83** (0.41 to 1.65)	**62 fewer per 1,000** (from 215 fewer to 236 more)	⊕⊕◯◯ Low	CRITICAL
Respiratory depression requiring intubation/ mechanical ventilation												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lacosamide	Valproate	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	16/33 (48.5%)	16/33 (48.5%)	**RR 1.000** (0.608 to 1.649)	**0 fewer per 1,000** (from 190 fewer to 315 more)	⨁⨁◯◯ Low	CRITICAL
Cardiovascular adverse effects including hypotension and/or arrhythmias												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	2/33 (6.1%)	0/33 (0.0%)	not estimable		⨁⨁◯◯ Low	CRITICAL
Seizure freedom for 24 hours												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	15/33 (45.5%)	20/33 (60.6%)	**RR 0.750** (0.472 to 1.193)	**152 fewer per 1,000** (from 320 fewer to 117 more)	⨁⨁◯◯ Low	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations
a. No mention of allocation concealment
b. Wide CIs crossing 1 c. Very few events. RR not estimable

Table 8

Author(s): Suvasini Sharma
Question: Should Diazepam infusion vs Valproate be used in adults with benzodiazepine resistant status epilepticus?
Setting: Secondary or tertiary care
Bibliography: Chen WB, Gao R, Su YY, Zhao JW, Zhang YZ, Wang L, Ren Y, Fan CQ. Valproate versus diazepam for generalized convulsive status epilepticus: a pilot study. Eur J Neurol. 2011 Dec;18(12):1391-6.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diazepam infusion	Valproate	Relative (95% CI)	Absolute (95% CI)		
Seizure cessation within 60 minutes												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	20/36 (55.6%)	15/30 (50.0%)	**RR 1.11** (0.70 to 1.73)	**55 more per 1,000** (from 150 fewer to 365 more)	⨁⨁◯◯ Low	CRITICAL
Death												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diazepam infusion	Valproate	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	2/36 (5.6%)	5/30 (16.7%)	**RR 0.33** (0.06 to 1.59)	**112 fewer per 1,000** (from 157 fewer to 98 more)	⨁⨁◯◯ Low	CRITICAL
Respiratory depression requiring intubation/ mechanical ventilation												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	2/36 (5.6%)	0/30 (0.0%)	not estimable		⨁⨁◯◯ Low	CRITICAL
Cardiovascular adverse effects including hypotension and/or arrhythmias												
1	randomised trials	serious[a]	not serious	not serious	serious[c]	none	2/36 (5.6%)	0/30 (0.0%)	not estimable		⨁⨁◯◯ Low	CRITICAL
Seizure freedom for 24 hours												
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	15/36 (41.7%)	12/30 (40.0%)	**RR 1.042** (0.581 to 1.868)	**17 more per 1,000** (from 168 fewer to 347 more)	⨁⨁◯◯ Low	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations
a. No mention of allocation concealment
b. Wide CIs crossing 1
c. Very few events, RR not estimable

Table 9
Author(s): Suvasini Sharma
Question: Should Valproate vs Phenobarbital be used in adults with benzodiazepine resistant status epilepticus?
Setting: Secondary or tertiary care

Bibliography:
Su Y, Huang H, Jiang M, Pan S, Ding L, Zhang L, Jiang W, Zhuang X. Phenobarbital versus valproate for generalized convulsive status epilepticus in adults (2): A multicenter prospective randomized controlled trial in China (China 2-P vs. V). Epilepsy Res. 2021 Nov;177:106755.

Su Y, Liu G, Tian F, Ren G, Jiang M, Chun B, Zhang Y, Zhang Y, Ye H, Gao D, Chen W. Phenobarbital Versus Valproate for Generalized Convulsive Status Epilepticus in Adults: A Prospective Randomized Controlled Trial in China. CNS Drugs. 2016 Dec;30(12):1201-1207.

New meta-analysis performed for Valproate versus Phenobarbital in adults with benzodiazepine resistant status epilepticus

	Valproate		Phenobarbital			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI
Su 2016	16	36	30	37	50.3%	0.55 [0.37, 0.82]
Su 2021	23	36	28	33	49.7%	0.75 [0.57, 1.00]
Total (95% CI)		**72**		**70**	**100.0%**	**0.65 [0.51, 0.82]**
Total events	39		58			

Heterogeneity: Chi² = 1.73, df = 1 (P = 0.19); I² = 42%
Test for overall effect: Z = 3.54 (P = 0.0004)

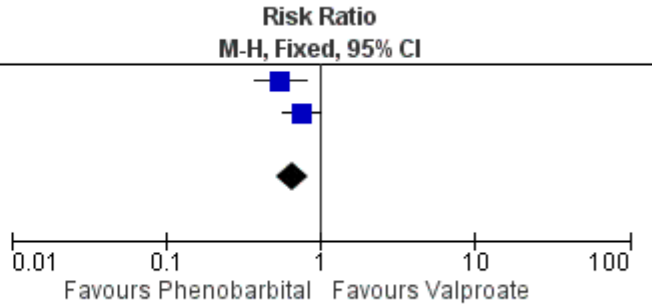

Fig 1: Forest plot for Valproate versus Phenobarbital, Outcome: Seizure cessation within 60 min

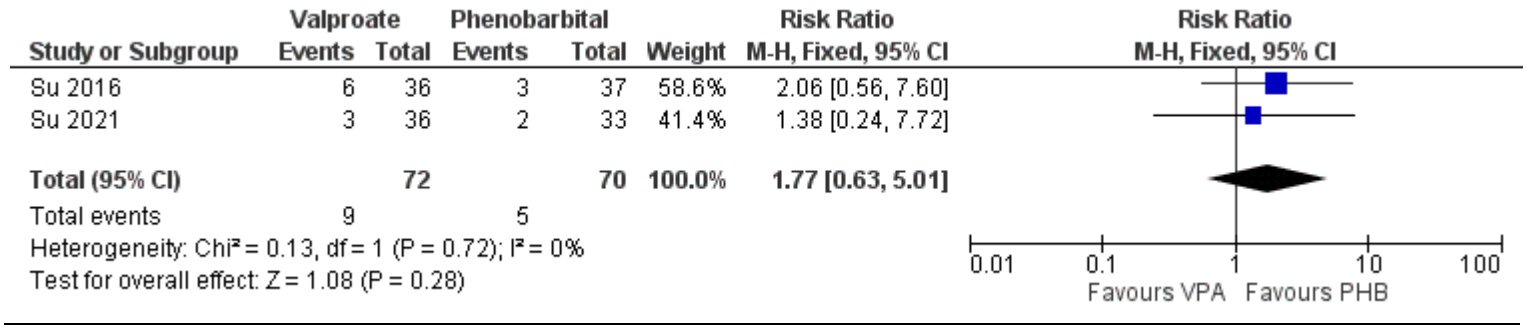

Fig 2: Forest plot for Valproate versus Phenobarbital, Outcome: Death

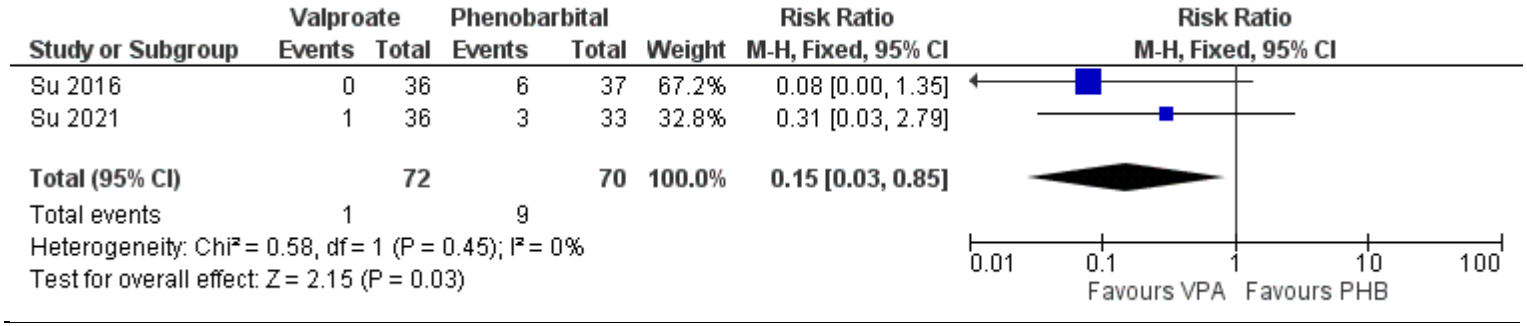

Fig 3: Forest plot for Valproate versus Phenobarbital, Outcome: Respiratory depression requiring intubation/ mechanical ventilation

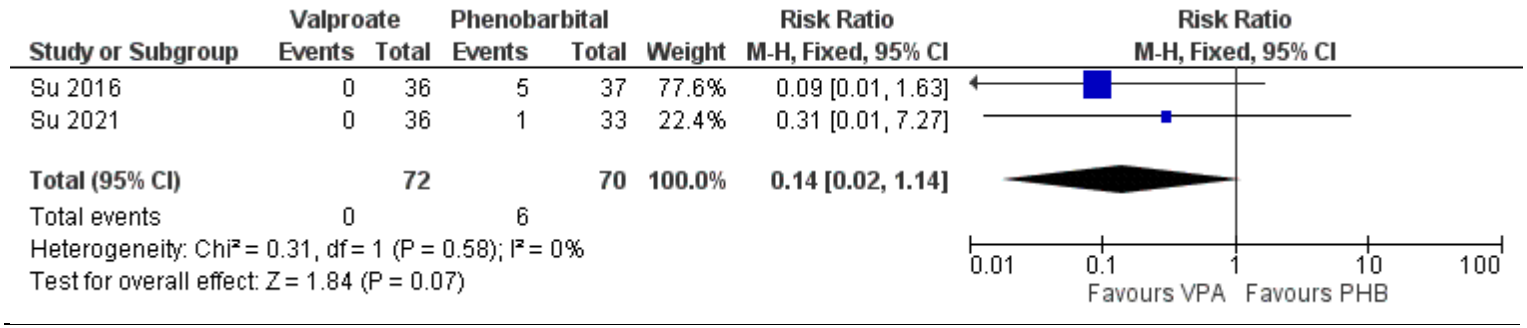

Fig 4: Forest plot for Valproate versus Phenobarbital, Outcome: Cardiovascular adverse effects including hypotension and/or arrhythmias

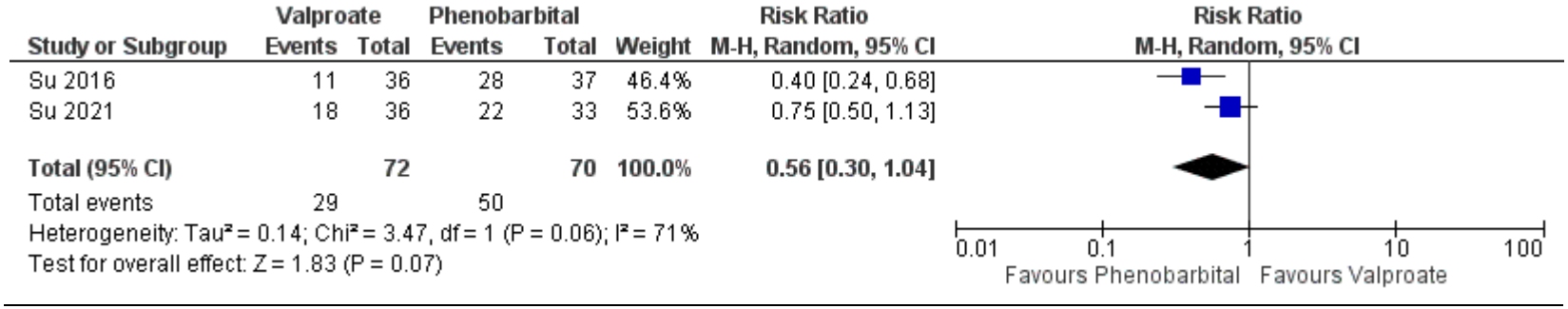

Fig 5: Forest plot for Valproate versus Phenobarbital, Outcome: Seizure freedom for 24 hours

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Valproate	Phenobarbital	Relative (95% CI)	Absolute (95% CI)		
Seizure cessation within 60 minutes												
2	randomised trials	serious[a]	serious[b]	not serious	not serious	none	39/72 (54.2%)	58/70 (82.9%)	**RR 0.65** (0.51 to 0.82)	**290 fewer per 1,000** (from 406 fewer to 149 fewer)	⨁⨁◯◯ Low	CRITICAL
Death												
2	randomised trials	serious[a]	not serious	not serious	very serious[c]	none	9/72 (12.5%)	5/70 (7.1%)	**RR 1.77** (0.63 to 5.01)	**55 more per 1,000** (from 26 fewer to 286 more)	⨁◯◯◯ Very low	CRITICAL
Respiratory depression requiring intubation/ mechanical ventilation												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Valproate	Phenobarbital	Relative (95% CI)	Absolute (95% CI)		
2	randomised trials	serious[a]	not serious	not serious	serious[d]	none	1/72 (1.4%)	9/70 (12.9%)	**RR 0.15** (0.03 to 0.85)	**109 fewer per 1,000** (from 125 fewer to 19 fewer)	⨁⨁◯◯ Low	CRITICAL

Cardiovascular adverse effects including hypotension and/or arrhythmias

2	randomised trials	serious[a]	not serious	not serious	serious[e]	none	0/72 (0.0%)	6/72 (8.3%)	**RR 0.14** (0.02 to 1.14)	**72 fewer per 1,000** (from 82 fewer to 12 more)	⨁⨁◯◯ Low	CRITICAL

Seizure freedom for 24 hours

2	randomised trials	serious[a]	serious[f]	not serious	serious[d]	none	29/72 (40.3%)	50/70 (71.4%)	**RR 0.56** (0.30 to 1.04)	**314 fewer per 1,000** (from 500 fewer to 29 more)	⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations
a. No mention of allocation concealment in Su 2021 study
b. I-squared 42%
c. Very wide CIs crossing 1
d. Wide CIs
e. Wide CIs crossing 1
f. I squared 71%

3.4. Additional evidence not mentioned in GRADE tables

Nil

4 From Evidence to Recommendations

4.1. Summary of comparisons considered

	Diazepam infusion	Fosphenytoin	Lacosamide	Levetiracetam	Phenobarbital	Phenytoin	Valproate
Diazepam infusion	-						2022*
Fosphenytoin		-		2022			2022
Lacosamide			-				2022
Levetiracetam		2022		-		2022	2022
Phenobarbital					-	2022	2015, 2022
Phenytoin				2022	2022	-	2015, 2022
Valproate	2022*		2022	2022	2015, 2022	2015, 2022	-

* available during the 2015 review, but not included as the scope was defined to exclude comparison of a continuous infusion with a bolus medication.

The above table summarises the comparisons that were considered in the current evidence review (2022), and also the previous evidence review (2015) on which the current mhGAP recommendations are based.

4.2. Summary of findings

Outcome	Comparisons								
	Phenytoin vs Levetiracetam	**Levetiracetam Vs Fosphenytoin**	**Phenobarbital Vs Phenytoin**	**Valproate Vs Phenytoin**	**Fosphenytoin Vs Valproate**	**Levetiracetam Vs Valproate**	**Lacosamide Vs Valproate**	**Diazepam infusion Vs Valproate**	**Valproate Vs Phenobarbital**
Seizure cessation within 60 min	1 study RR 1.058 (0.664 to 1.685) No difference	1 study RR 0.96 (0.67 to 1.38) No difference	1 study RR 1.840 (1.275 to 2.845) Favors phenobarbital	1 study RR 1.05 (0.89 to 1.23) No difference	1 study RR 0.948 (0.662 to 1.358) No difference	1 study RR 0.977 (0.690 to 1.383) No difference	1 study RR 0.930 (0.649 to 1.280) No difference	1 study RR 1.11 (0.70 to 1.73) No difference	2 studies RR 0.65 (0.51 to 0.82) Favors Phenobarbital
Summary of quality of evidence	Low	Moderate	Low	Very low	Moderate	Moderate	Low	Low	Low
Death	1 study RR 1.000 (0.154 to 6.470) No difference	1 study RR 2.30 (0.68 to 9.06) - No difference	Not reported	1 study RR 1.00 (0.27 to 3.78) No difference	1 study RR 3.210 (0.342 to 30.130) No difference	1 study RR 5.07 (0.64 to 41.10) No difference	1 study RR 0.83 (0.41 to 1.65) - No difference	1 study RR 0.33 (0.06 to 1.59) No difference	2 studies RR 1.77 (0.63 to 5.01) No difference
Summary of quality of evidence	Very low	Low	NA	Very low	Low	Low	Low	Low	Very Low
Respiratory depression	1 study RR 1.50 (0.49 to 4.59) No difference	1 study RR 1.14 (0.68 to 1.91) No difference	1 study RR 0.327 (0.530 to 4.035)	1 study Very few events, RR not estimable[a]	1 study RR 1.204 (0.662 to 2.173)	1 study RR 1.372 (0.780 to 2.360)	1 study RR 1.000 (0.608 to 1.649) No	1 study RR not estimable[f]	2 studies RR 0.15 (0.03 to 0.85) Favors Valproate

Outcome	Comparisons								
			No difference		No difference	No difference	difference		
Summary of quality of evidence	Very low	Moderate	Low	Very low	Moderate	Moderate	Low	Low	Low
Cardiovascular adverse effects	Not reported	1 study RR 0.526 (0.090 to 3.060) Favors Levetiracetam	Not reported	1 study RR not estimable[b]	1 study RR not estimable[c]	1 study RR not estimable[d]	1 study RR not estimable[e]	1 study RR not estimable[g]	2 studies RR 0.14 (0.02 to 1.14)Favors Valproate
Summary of quality of evidence	NA	Low	NA	Very low	Low	Low	Low		Low
Seizure freedom for 24 hours	1 study RR 0.940 (0.391 to 2.256) No difference	Not reported	1 study RR 1.048 No difference	1 study RR 1.118 (0.874 to 1.430) No difference	Not reported	Not reported	1 study RR 0.750 (0.472 to 1.193) No difference	1 study RR 1.042 (0.581 to 1.868) No difference	2 studies RR 0.56 (0.30 to 1.04) No difference
Summary of quality of evidence	Very low	NA	Low	Very low	NA	NA	Low	Very Low	Very low
Any other adverse events reported	2/22 had adverse drug reactions in phenytoin arm but type not clarified	Nil	Nil	Nil	Nil	Nil	Nil	3 patients in Valproate arm had raised ammonia with normal transaminases and 1 patient in Valproate arm had bone marrow	Su 2021-6/33 in Phenobarbital arm and 3/36 in Valproate arm had raised transaminases, decreased RBC/WBC- 4/33 in Phenobarbital arm, 1/36 in

Outcome	Comparisons								
								suppression	Valproate arm; gastric retention- 2/33 in Phenobarbital arm, increased aPTT- 2/33 in Phenobarbital Arm Su 2016: 6 showed transient hyperammonemia in VPA group without hepatic injury, 4/37 in Valproate arm had raised transaminases

[a] Very few events. 0/50 in Valproate arm, and 2/50 in phenytoin arm

[b] Very few events. 0/50 in Valproate arm, 6/50 in phenytoin arm

[c] Very few events. 3/71 in Fosphenytoin arm, 0/76 in Valproate arm

[d.] Very few events. 2/90 in Levetiracetam arm, 0/76 in Valproate arm.

[e]. Very few events. 2/33 in Lacosamide arm, 0/33 in Valproate arm

[f]. Very few events. 2/36 in Diazepam infusion arm, 0/30 in Valproate arm

g. Very few events. 2/36 in Diazepam infusion arm, 0/30 in Valproate arm

4.3. Evidence to decision

Table 4: Evidence to decision table
Please note * indicates evidence from overarching qualitative review by Gronholm et al, 2023.

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Priority of the problem	Is the problem a priority? The more serious a problem is, the more likely it is that an option that addresses the problem should be a priority (e.g., diseases that are fatal or disabling are likely to be a higher priority than diseases that only cause minor distress). The more people who are affected, the more likely it is that an option that addresses the problem should be a priority.			
	• Are the consequences of the problem serious (that is, severe or important in terms of the potential benefits or savings)? • Is the problem urgent? • Is it a recognised priority (such as based on a political or policy decision)? [Not relevant when an individual patient perspective is taken]	☐ No ☐ Probably no ☐ Probably yes ☒ **Yes** ☐ Varies ☐ Don't know	Status epilepticus is a medical emergency with resultant mortality in nearly 30% of affected adults and significant neurological and systemic morbidity. Timely control of status is of paramount importance to improve the outcomes.	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Desirable Effects	How substantial are the desirable anticipated effects? The larger the benefit, the more likely it is that an option should be recommended.			
	• Judgments for each outcome for which there is a desirable effect • How substantial (large) are the desirable anticipated effects (including health and other benefits) of the option (taking into account the severity or importance of the desirable consequences and the number of people affected)?	☐ Trivial ☐ Small ☒ **Moderate** ☐ Large ☐ Varies ☐ Don't know	From comparative studies, there is low/moderate quality evidence that there is no clinically important difference in efficacy between intravenous fosphenytoin, levetiracetam, and valproate for the treatment of benzodiazepine resistant status epilepticus in adults. There is low quality evidence that Phenobarbital may be better than Valproate in the treatment of benzodiazepine resistant status epilepticus in adults. • For the following comparisons, RR(95% CIs) indicated no difference in seizure cessation within 60 mins by group (levetiracetam vs phenytoin; levetiracetam vs fosphenytoin; valproate vs phenytoin; fosphenytoin vs valproate; levetiracetam vs valproate; lacosamide vs valproate). A favourable effect was seen for phenobarbital (vs phenytoin RR	Adults treated for established status epilepticus require monitoring and may require ventilatory support; thus secondary care is necessary. The following drugs phenytoin, fosphenytoin, levetiracetam or valproate are equally effective for seizure cessation in adults with benzodiazepine resistant status epilepticus. Phenobarbital is also likely an effective alternative agent. Another factor of concern is the speed of administration. Levetiracetam, Fosphenytoin and Valproate can be administered within 10 minutes, whereas Phenytoin and

CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
		1.840 (95% CI: 1.275, 2.845); vs valproate RR 0.65(95% CI: 0.51, 0.82). • For death, the evidence was mixed with a favourable effect seen for fosphenytoin (vs levetiracetam) RR 2.30 (95% CI: 0.68, 9.06); valproate (vs fosphenytoin) RR 3.21 (95% CI: 0.34, 30.13); levetiracetam (vs valproate) RR 5.07(95% CI: 0.64, 41.10); lacosamide (vs valproate RR 0.83 (95% CI: 0.41, 1.65); diazepam infusion (vs valproate) RR 0.33 (95% CI: 0.06, 1.59); valproate (vs phenobarbital) RR 1.77(0.63, 5.01) • For respiratory depression, one comparison favoured levetiracetam (vs phenytoin RR 1.50 (95% CI: 0.49, 4.59). Three comparisons favoured valproate (vs fosphenytoin RR 1.21 (95% CI: 0.66, 2.17); (vs levetiracetam RR 1.37 (95% CI: 0.78 to 2.36); (vs	Phenobarbital need to be infused over 20 minutes. Time is of the essence while treating status epilepticus. Advantages of levetiracetam and valproate include lesser risk of adverse effects as compared to fosphenytoin. Both Levetiracetam and Valproate are broad spectrum drugs active against all types of seizures, and hence may be a good agent for maintenance therapy after the acute control of seizures in adults with genetic generalized epilepsy or when the type of seizure/ epilepsy syndrome is not clear.

CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
		phenobarbital RR 0.15 (95% CI: 0.03, 0.85)). One comparison favoured phenobarbital (vs phenytoin) RR: 0.14(0.02,1.14) • For cardiovascular adverse effects, one comparison favoured levetiracetam (vs phenytoin RR 0.53(95% CI: 0.09, 3.06). One comparison favoured valproate vs phenobarbital RR 0.65 (95% CI: 0.11, 3.75) • For seizure freedom at 24 hours, the evidence was mixed with no difference seen by group in four comparisons (levetiracetam vs phenytoin; phenobarbital vs phenytoin; valproate vs phenytoin; diazeparm infusion vs valproate). One comparison favoured valproate (vs lacosamide RR 0.75 (95% CI: 0.42 to 1.19). One comparison favoured phenobarbital (vs valproate RR 0.56 (95% CI: 0.30 to 1.04)	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Undesirable Effects	How substantial are the undesirable anticipated effects? The greater the harm, the less likely it is that an option should be recommended.			
	• Judgments for each outcome for which there is an undesirable effect • How substantial (large) are the undesirable anticipated effects (including harms to health and other harms) of the option (taking into account the severity or importance of the adverse effects and the number of people affected)?	☐ Large ☐ Moderate ☐ Small ☐ Trivial ☒ **Varies** ☐ Don't know	There is low to moderate quality evidence that the safety profile of levetiracetam was better than fosphenytoin, in terms of lesser cardiovascular adverse events. There is low quality evidence that Phenobarbital has higher risk of respiratory depression and cardiovascular adverse effects as compared to valproate.	Valproate has the risk of hepatotoxicity, and is contra-indicated in patients with liver disease, which may not be evident when the patient is brought convulsing and needs emergency treatment. Phenobarbital and diazepam infusion carry the risk of sedation and respiratory depression, which may be increased if they are used after benzodiazepines. Phenotyoin has associated risks of arrhythmia and hypotension and can be difficult to administer in adults with co-morbid cardiac conditions. Valproate has been associated with hepatic side effects, in terms of raised transaminases and

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
				elevated ammonia levels. Most trials excluded women known to be pregnant. Seizures in pregnant women can be due to eclampsia which requires different treatment. Fosphenytoin or levetiracetam may be a better choice for women with epilepsy who have status epilepticus.
Certainty of evidence	What is the overall certainty of the evidence of effects? The less certain the evidence is for critical outcomes (those that are driving a recommendation), the less likely that an option should be recommended (or the more important it is likely to be to conduct a pilot study or impact evaluation, if it is recommended).			
	• What is the overall certainty of this evidence of effects, across all of the outcomes that are critical to making a decision? • See GRADE guidance regarding detailed judgments about the quality of evidence or certainty in estimates of effects	☐ Very low ☒ **Low** ☐ Moderate ☐ High ☐ No included studies	• There is low to moderate quality evidence that there is no clinically important difference in efficacy between intravenous fosphenytoin/phenytoin, levetiracetam or valproate for the treatment of benzodiazepine-resistant status epilepticus in adults. • There is low quality evidence that phenobarbital may be more effective than valproate in the	

CRITERIA, QUESTIONS	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
		treatment of benzodiazepine-resistant status epilepticus in adults. • There is low to moderate quality evidence that the safety profile of levetiracetam was better than fosphenytoin, in terms of lesser cardiovascular adverse events. There is low to moderate quality evidence that the safety profile of valproate was better than phenytoin or fosphenytoin, in terms of less requirement for intubation and lesser cardiovascular side effects. However, valproate has been associated with hepatic side effects, in terms of raised transaminases and elevated ammonia levels. • There is low quality evidence that phenobarbital has higher risk of respiratory depression and cardiovascular adverse effects as compared to valproate.	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Values	Is there important uncertainty about or variability in how much people value the main outcomes? The more likely it is that differences in values would lead to different decisions, the less likely it is that there will be a consensus that an option is a priority (or the more important it is likely to be to obtain evidence of the values of those affected by the option). Values in this context refer to the relative importance of the outcomes of interest (how much people value each of those outcomes). These values are sometimes called 'utility values'.			
	• Is there important uncertainty about how much people value each of the main outcomes? • Is there important variability in how much people value each of the main outcomes?	☐ Important uncertainty or variability ☐ Possibly important uncertainty or variability ☐ Probably no important uncertainty or variability ☒ **No important uncertainty or variability**	Treatment of status epilepticus is a medical emergency and potentially lifesaving. • The qualitative systematic review (Gronholm et al., 2023) also assessed values, resources, cost effectiveness, health equity quality and non-discrimination, feasibility and human rights related factors in mental health care and mental health services. • Overall, the studies reviewed highlighted importance and recognition of importance of mental health interventions and the outcomes of those interventions on people's mental health and wellbeing. The utility value could be limited by certain factors and barriers present in the health systems. For instance, low awareness, poor funding and	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			poor political buy-in, or other social barriers. Social networks or raising awareness can facilitate adoption and recognition of mental health issues and the perceived value of the interventions.	
Balance of effects	Does the balance between desirable and undesirable effects favor the intervention or the comparison? The larger the desirable effects in relation to the undesirable effects, taking into account the values of those affected (i.e. the relative value they attach to the desirable and undesirable outcomes) the more likely it is that an option should be recommended.			
	• Judgments regarding each of the four preceding criteria • To what extent do the following considerations influence the balance between the desirable and undesirable effects: - How much less people value outcomes that are in the future compared to outcomes that occur now (their discount rates)? - People's attitudes towards undesirable effects (how risk averse they are)? - People's attitudes towards desirable effects (how risk seeking they are)?	☐ Favors the comparison ☐ Probably favors the comparison ☐ Does not favor either the intervention or the comparison ☐ Probably favors the intervention ☐ Favors the intervention ☒ **Varies** ☐ Don't know	• The following drugs phenytoin, fosphenytoin, levetiracetam or valproate are equally effective for seizure cessation in adults with benzodiazepine resistant status epilepticus. • Phenobarbital is also likely an effective alternative agent. • Advantages of levetiracetam and valproate include lesser risk of adverse effects as compared to fosphenytoin. • Both Levetiracetam and Valproate are broad spectrum drugs active against all types of seizures, and hence may be a good agent for maintenance	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			therapy after the acute control of seizures in adults with genetic generalized epilepsy or when the type of seizure/ epilepsy syndrome is not clear • Another factor of concern is the speed of administration. Levetiracetam, Fosphenytoin and Valproate can be administered within 10 minutes, whereas Phenytoin and Phenobarbital need to be infused over 20 minutes. Time is of the essence while treating status epilepticus.	
Resources required	How large are the resource requirements (costs)? The greater the cost, the less likely it is that an option should be a priority. Conversely, the greater the savings, the more likely it is that an option should be a priority.			
	• How large is the difference in each item of resource use for which fewer resources are required? • How large is the difference in each item of resource use for which more resources are required? • How large an investment of resources would the option require or save?	☐ Large costs ☐ Moderate costs ☐ Negligible costs and savings ☐ Moderate savings ☐ Large savings ☐ Varies ☒ **Don't know**	No reviews examining resources were identified.	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Certainty of evidence of required resources	What is the certainty of the evidence of resource requirements (costs)?			
	• Have all-important items of resource use that may differ between the options being considered been identified? • How certain is the evidence of differences in resource use between the options being considered (see GRADE guidance regarding detailed judgments about the quality of evidence or certainty in estimates)? • How certain is the cost of the items of resource use that differ between the options being considered? • Is there important variability in the cost of the items of resource use that differ between the options being considered?	☐ Very low ☐ Low ☐ Moderate ☐ High ☒ **No included studies**	No reviews examining resources were identified.	
Cost effectiveness	Does the cost-effectiveness of the intervention favor the intervention or the comparison? The greater the cost per unit of benefit, the less likely it is that an option should be a priority.			
	• Judgments regarding each of the six preceding criteria • Is the cost effectiveness ratio sensitive to one-way sensitivity analyses? • Is the cost effectiveness ratio sensitive to multivariable sensitivity analysis? • Is the economic evaluation on which the cost effectiveness estimate is based reliable? • Is the economic evaluation on which the cost effectiveness estimate is based applicable to the setting(s) of interest?	☐ Favors the comparison ☐ Probably favors the comparison ☐ Does not favor either the intervention or the comparison ☐ Probably favors the intervention ☐ Favors the intervention	No reviews examining cost effectiveness identified.	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
		☐ Varies ☒ **No included studies**		
Health equity, equality and non-discrimination	What would be the impact on health equity, equality and non-discrimination? (WHO INTEGRATE) Health equity and equality reflect a concerted and sustained effort to improve health for individuals across all populations, and to reduce avoidable systematic differences in how health and its determinants are distributed. Equality is linked to the legal principle of non-discrimination, which is designed to ensure that individuals or population groups do not experience discrimination on the basis of their sex, age, ethnicity, culture or language, sexual orientation or gender identity, disability status, education, socioeconomic status, place of residence or any other characteristics. All recommendations should be in accordance with universal human rights standards and principles. The greater the likelihood that the intervention increases health equity and/or equality and that it reduces discrimination against any particular group, the greater the likelihood of a general recommendation in favor of this intervention.			

	• How are the condition and its determinants distributed across different population groups? Is the intervention likely to reduce or increase existing health inequalities and/or health inequities? Does the intervention prioritise and/or aid those furthest behind?
	• How are the benefits and harms of the intervention distributed across the population? Who carries the burden (e.g. all), who benefits (e.g. a very small sub-group)?
	• How affordable is the intervention for individuals, workplaces or communities?
	• How accessible - in terms of physical as well as informational access - is the intervention across different population groups?
	• Is there any suitable alternative to addressing the condition, does the intervention represent the only available option? Is this option proportionate to the
		☐ Reduced
		☐ Probably reduced
		☐ Probably no impact
		☒ **Probably increased**
		☐ Increased
		☐ Varies
		☐ Don't know
			• There was no direct evidence to evaluate impact on health equity, equality and non-discrimination.
			• The qualitative review (Gronholm et al., 2023) noted considerations for ensuring mental, neurological and substance use interventions are equitable, equally available and non-discriminatory:
			• Accessibility, physical/practical considerations
			  • Time & travel constraints
			  • Accessibility, informational barriers
			  • Affordability - treatment costs
				Phenobarbital is a controlled medicine which limits access.

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

	need, and will it be subject to periodic review?		• These factors may be exacerbated for certain groups:
			  • People with low education/literacy (e.g., written instructions, psychoeducation materials)
			  • Women - travel restrictions, stronger stigma/shame, caregiving responsibilities
			  • Low resource settings - affordability/cost considerations exacerbated.	

Feasibility	Is the intervention feasible to implement? The less feasible (capable of being accomplished or brought about) an option is, the less likely it is that it should be recommended (i.e. the more barriers there are that would be difficult to overcome).			
	• Can the option be accomplished or brought about? • Is the intervention or option sustainable? • Are there important barriers that are likely to limit the feasibility of implementing the intervention (option) or require consideration when implementing it?	☐ No ☐ Probably no ☒ **Probably yes** ☐ Yes ☐ Varies ☐ Don't know	There was no direct evidence to evaluate feasibility to implement the interventions. • The anticonvulsants IV phenytoin, phenobarbital and valproate were on the EML at the time of this review. IV levetiracetam has recently been added. • Health worker training in safe	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			administration and monitoring is also necessary and the feasibility of this is a consideration.	
Human rights and sociocultural acceptability	Is the intervention aligned with human rights principles and socio-culturally acceptable? (WHO INTEGRATE) This criterion encompasses two distinct constructs: The first refers to an intervention's compliance with universal human rights standards and other considerations laid out in international human rights law beyond the right to health (as the right to health provides the basis of other criteria and sub-criteria in this framework). The second, sociocultural acceptability, is highly time-specific and context-specific and reflects the extent to which those implementing or benefiting from an intervention as well as other relevant stakeholder groups consider it to be appropriate, based on anticipated or experienced cognitive and emotional responses to the intervention. The greater the sociocultural acceptability of an intervention to all or most relevant stakeholders, the greater the likelihood of a general recommendation in favor of this intervention.			
	• Is the intervention in accordance with universal human rights standards and principles? • Is the intervention socio-culturally acceptable to patients/beneficiaries as well as to those implementing it? To which extent do patients/beneficiaries value different non-health outcomes? • Is the intervention socio-culturally acceptable to the public and other relevant stakeholder groups? Is the intervention sensitive to sex, age, ethnicity, culture or language, sexual orientation or gender identity, disability status, education, socio-economic status, place of residence or any other relevant characteristics? • How does the intervention affect an individual's, population group's or organization's autonomy, i.e. their ability to make a competent, informed and voluntary decision? • How intrusive is the intervention, ranging from low intrusiveness (e.g. providing information) to intermediate intrusiveness (e.g. guiding choices) to	☐ No ☐ Probably no ☐Probably yes ☒ **Yes** ☐ Varies ☐ Don't know	There was no direct evidence to evaluate alignment with human rights principle and socio -cultural acceptability. The qualitative review (Gronholm et al., 2023) noted several considerations which would impact the right to health and access to healthcare. (e.g., stigma and discrimination and lack of confidentiality could affect the help -seeking among service users). • The importance of socio-cultural acceptability of mental, neurological and substance use interventions was clearly expressed. Pre-intervention considerations that consider cultural and social aspects	

CRITERIA, QUESTIONS		JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

	high intrusiveness (e.g. restricting or eliminating choices)? Where applicable, are high intrusiveness and/or impacts on the privacy and dignity of concerned stakeholders justified?		improve the acceptability of implemented interventions.
			• When interventions were perceived as appropriate for the culture and target group, the content and medium of the intervention received more positive feedback from service users and caregivers. Also, considerations of age, sex and language have been highlighted as important to acceptability and accessibility.
			• Mitigating steps to improve sociocultural acceptability include:
			  • To train health workers in non-judgemental care
			  • Facilitate the use of indigenous/ local phrases and terms to increase acceptability, accessibility and fidelity.	

4.4. Summary of judgements

Table 5: Summary of judgements

Priority of the problem	- Don't know	- Varies		- No	- Probably No	- Probably Yes	✓ **Yes**
Desirable effects	- Don't know	- Varies		- Trivial	- Small	✓ **Moderate**	- Large
Undesirable effects	- Don't know	✓ **Varies**		- Large	- Moderate	- Small	- Trivial
Certainty of the evidence	- No included studies			- Very low	✓ **Low**	- Moderate	- High
Values				- Important uncertainty or variability	- Possibly important uncertainty or variability	- Probably no important uncertainty or variability	✓ **No important uncertainty or variability**
Balance of effects	- Don't know	✓ **Varies**	- Favours comparison	- Probably favours comparison	- Does not favour either	- Probably favours intervention	- Favours intervention
Resources required	✓ **Don't know**	- Varies	- Large costs	- Moderate costs	- Negligible costs or savings	- Moderate savings	- Large savings
Certainty of the evidence on required resources	✓ **No included studies**			- Very low	- Low	- Moderate	- High
Cost–effectiveness	✓ **No included studies**	- Varies	- Favours comparison	- Probably favours comparison	- Does not favour either	- Probably favours intervention	- Favours intervention
Equity, equality and non-discrimination	- Don't know	- Varies	- Reduced	Probably reduced	- Probably no impact	✓ **Probably increased**	- Increased
Feasibility	- Don't know	- Varies		- No	- Probably No	✓ **Probably Yes**	- Yes
Human rights and socio-cultural acceptability	- Don't know	- Varies		- No	- Probably No	- Probably Yes	✓ **Yes**

✓Indicates category selected, -Indicates category not selected

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12) Gronholm PC, Makhmud A, Barbui C, et al Qualitative evidence regarding the experience of receiving and providing care for mental health conditions in non-specialist settings in low-income and middle-income countries: a systematic review of reviews. BMJ Ment Health 2023;26:e300755.

Appendix I: mhGAP process note

mhGAP Guideline Update: Notes on process for identifying level of evidence review required v2_0 (13/12/2021)

This document is intended to provide guidance to focal points on the level of evidence review required as part of the evidence retrieval process for the mhGAP guideline update process. As a general rule, the update process should be informed by existing high quality systematic reviews.
The process for evidence retrieval and synthesis is fully outlined in chapter 8 of the WHO handbook for guideline development
https://apps.who.int/iris/handle/10665/145714.

Three main categories of evidence review are proposed in this document:

1) Existing relevant, up to date, high quality systematic review(s) provide the evidence required. **An existing systematic review is sufficient to prepare the evidence summaries**. It may be possible to include more than one systematic review for the same PICO, as different reviews may match different outcomes of a PICO. However, if more than one systematic review is available for the same PICO outcome, one review should be selected, based on quality, relevance, search comprehensiveness and date of last update. The selection process should be transparently reported, with justification of choices.
2) Existing high quality systematic reviews are either out of date or do not fully address the PICO, though it is considered that the review can be updated to meet these requirements. **An update of an existing systematic review is required before the evidence summaries can be prepared**. The update process may require addition of new studies published after the review, or inclusion of outcomes not covered by the existing reviews.
3) Existing systematic reviews are either not of sufficiently high quality or cannot be updated to fully address the PICO. **A new systematic review is required before the evidence summaries can be prepared**

Figure 1 below details the process to identify which level of evidence review is required to support the evidence retrieval process for a PICO.

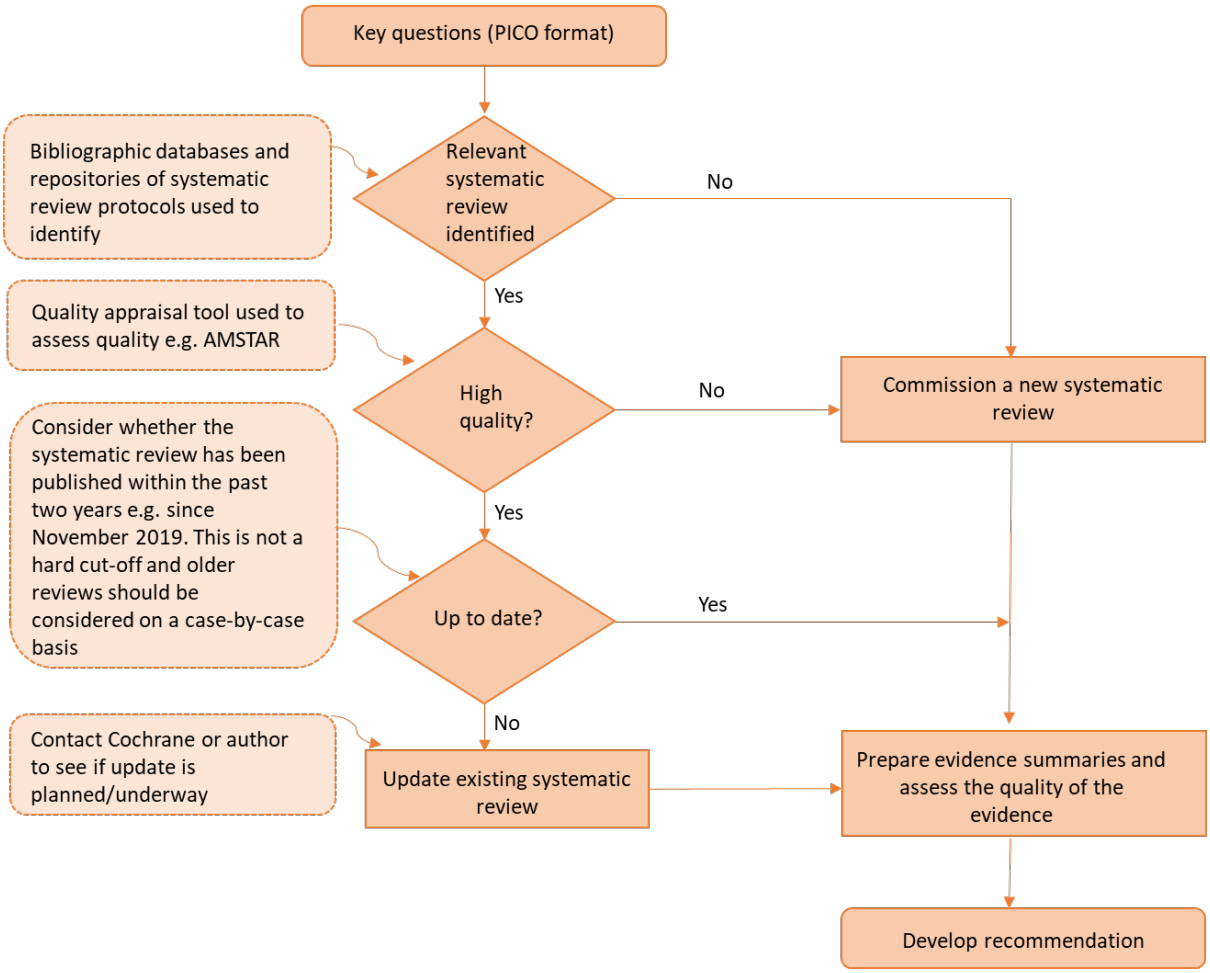

Figure 1: Is a new systematic review needed

All key questions are currently in PICO format as presented in the Appendix of the planning proposal PICOs. Subsequent steps include the following:

1. **Identify and evaluate existing systematic reviews**: Identify one or more systematic review(s) to address each PICO question. Existing systematic reviews will inform the guideline development process, whether or not a new systematic review or an update of an existing review is required, and the evidence review team will detail existing systematic reviews in each case. The method for identifying existing systematic reviews should be fully detailed in the evidence summary and include the following sources:
    a. Search of bibliographic databases, such as PubMed/Medline, EMBASE, PsychINFO, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHIL, Scopus, African Index Medicus, Index Medicus for the Eastern Mediterranean Region, Index Medicus for the South-East Asian Region, Latin American and Caribbean Health Sciences Literature, and Western Pacific Region Index Medicus.
    b. Search of repositories of systematic reviews protocols, including PROSPERO, Open Science Framework (OSF), and Cochrane.
2. **Assess if systematic review is up to date:** It is preferred that identified systematic reviews have been published within the past two years e.g. since

November 2019. This is not a hard cut-off and older reviews should be considered on a case-by-case basis, particularly those covering the time period since the last update of the mhGAP guideline in 2015. It is acknowledged that COVID has led to a pausing of many mental health research activities over the past two years, and this may also impact the availability of systematic reviews within the preferred two year period. For any reviews that fall outside the two year period, the guideline methodologist will advise on suitability.

3. **Appraise quality of systematic review:** Use the AMSTAR-2 quality appraisal tool to assess the quality of the identified systematic review(s) https://amstar.ca/docs/AMSTAR-2.pdf . This includes consideration of the extent to which the PICO is fully addressed by the systematic review(s) identified.

By following the process outlined in figure 1, and steps 1-3 above, the FP and evidence review team will have sufficient evidence to assess which of the three main categories of evidence review apply to each PICO under consideration:

1) Existing systematic reviews are sufficient to prepare the evidence summaries
2) An update of an existing systematic review is required before the evidence summaries can be prepared
3) A new systematic review is required before the evidence summaries can be prepared

Appendix II: Search terms used to identify systematic reviews

Detailed Search Strategy for the systematic literature search

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <1946 to March 31, 2022> Search update run April 1, 2022

#	Searches	Results
1	exp Status Epilepticus/	9127
2	(status epilepticus or absence status or petit mal status or chronic progressive epilepsia partialis continua or epilepsia partialis continua or kojevnikov* epileps* or kojewnikow* syndrome?).tw,kf.	14352
3	1 or 2	15583
4	Phenytoin/	13691
5	(antisacer or difenin or dihydan or dilantin or diphenylhydantoin? or epamin or epanutin or fenitoin or hydantol or phenytoin).tw,kf.	15234
6	Levetiracetam/	2531
7	(etiracetam or keppra or levetiracetam or "alpha ethyl 2 oxo 1 pyrrolidineacetamide").tw,kf.	4528
8	Valproic Acid/	13405
9	(valproate or convulsofin or depakene or depakine or depakote or dipropyl acetate or divalproex or ergenyl or magnesium valproate or propylisopropylacetic acid or valproic acid or vupral).tw,kf.	19341
10	exp phenobarbital/ or primidone/	18722
11	(gardenal or hysteps or luminal or phenemal or phenobarbital or phenobarbitone or phenylbarbital or phenylethylbarbituric acid or apo primidone or desoxyphenobarbital or liskantin or misodine or mizodin or mylepsinum or mysoline or primaclone or primidon holsten or primidone or resimatil or sertan).tw,kf.	70216
12	or/4-11	111859
13	Status Epilepticus/mo [Mortality]	387
14	treatment outcome/	1094312
15	Recurrence/	193909
16	Death/	18915
17	exp mortality/	416872
18	"Drug-Related Side Effects and Adverse Reactions"/	35487
19	adverse effects.fs.	1890760
20	(adverse effect? or adverse event? or safe or safety or effective* or death? or mortalit* or outcome?).tw,kf.	5740667
21	(seizure? adj5 (cessation? or recurren* or reduce? or reducing or reduction)).tw,kf.	13493
22	or/13-21	7587199
23	randomized controlled trial.pt.	562881
24	controlled clinical trial.pt.	94772

25	randomi#ed.ab.	664173
26	placebo.ab.	226817
27	clinical trials as topic.sh.	199635
28	randomly.ab.	378990
29	trial.ti.	259297
30	or/23-29	1478070
31	exp animals/ not humans.sh.	4980498
32	30 not 31	1361515
33	(systematic review or meta-analysis).pt.	264314
34	meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/	299533
35	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw.	263262
36	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw.	13566
37	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw.	33863
38	(data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw.	34493
39	(handsearch* or hand search*).ti,ab,kf,kw.	10368
40	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw.	31594
41	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf,kw.	11005
42	(meta regression* or metaregression*).ti,ab,kf,kw.	12187
43	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	398388
44	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.	289051
45	(cochrane or (health adj2 technology assessment) or evidence report).jw.	20694
46	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw.	15807
47	(outcomes research or relative effectiveness).ti,ab,kf,kw.	10511
48	((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf,kw.	3892
49	(multi* adj3 treatment adj3 comparison*).ti,ab,kf,kw.	271
50	(mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf,kw.	174
51	umbrella review*.ti,ab,kf,kw.	908
52	(multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.	13
53	(multiparamet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.	17
54	(multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.	11
55	or/33-54	591151
56	32 or 55	1805021
57	3 and 12 and 22 and 56	193

58	limit 57 to english language	188
59	limit 58 to ez=20211228-20220331	5
60	limit 58 to ed=20211228-20220331	2
61	59 or 60	7

Embase Classic+Embase <1947 to 2022 Week 12> Search run April 1, 2022

#	Searches	Results
1	exp epileptic state/	26530
2	(status epilepticus or absence status or petit mal status or chronic progressive epilepsia partialis continua or epilepsia partialis continua or kojevnikov* epileps* or kojewnikow* syndrome?).tw,kf.	23111
3	1 or 2	30086
4	phenytoin/	68262
5	(antisacer or difenin or dihydan or dilantin or diphenylhydantoin? or epamin or epanutin or fenitoin or hydantol or phenytoin).tw,kf.	25637
6	Levetiracetam/	11562
7	(etiracetam or keppra or levetiracetam or "alpha ethyl 2 oxo 1 pyrrolidineacetamide").tw,kf.	9698
8	Valproic Acid/	69125
9	(valproate or convulsofin or depakene or depakine or depakote or dipropyl acetate or divalproex or ergenyl or magnesium valproate or propylisopropylacetic acid or valproic acid or vupral).tw,kf.	31350
10	exp phenobarbital/ or primidone/	72156
11	(gardenal or hysteps or luminal or phenemal or phenobarbital or phenobarbitone or phenylbarbital or phenylethylbarbituric acid or apo primidone or desoxyphenobarbital or liskantin or misodine or mizodin or mylepsinum or mysoline or primaclone or primidon holsten or primidone or resimatil or sertan).tw,kf.	102098
12	or/4-11	244799
13	exp epileptic state/co [Complication]	921
14	treatment outcome/	915496
15	recurrent disease/	200701
16	death/	326439
17	exp mortality/	1300370
18	adverse drug reaction/	270720
19	(adverse effect? or adverse event? or safe or safety or effective* or death? or mortalit* or outcome?).tw,kf.	8086425
20	adverse effects.fs.	0
21	(seizure? adj5 (cessation? or recurren* or reduce? or reducing or reduction)).tw,kf.	21347
22	or/13-21	9032100
23	randomized controlled trial.pt.	0
24	controlled clinical trial.pt.	0
25	randomized controlled trial.sh.	703270
26	controlled clinical trial.sh.	465674
27	randomi#ed.ab.	959470

28	placebo.ab.	333893
29	clinical trials as topic.sh.	2
30	randomly.ab.	503720
31	trial.ti.	361952
32	or/23-31	1900795
33	exp animals/ not humans.sh.	30466526
34	32 not 33	130007
35	(systematic review or meta-analysis).pt.	0
36	meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/	519232
37	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw.	323043
38	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw.	15986
39	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw.	47902
40	(data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw.	42150
41	(handsearch* or hand search*).ti,ab,kf,kw.	12618
42	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw.	41907
43	(meta analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf,kw.	309706
44	(meta regression* or metaregression*).ti,ab,kf,kw.	14981
45	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	622998
46	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.	376740
47	(cochrane or (health adj2 technology assessment) or evidence report).jw.	29268
48	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw.	23436
49	(outcomes research or relative effectiveness).ti,ab,kf,kw.	15425
50	((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf,kw.	6733
51	(multi* adj3 treatment adj3 comparison*).ti,ab,kf,kw.	391
52	umbrella review*.ti,ab,kf,kw.	962
53	(multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.	26
54	(multiparamet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.	18
55	(multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.	21
56	or/33-55	30651908
57	34 or 56	30651908
58	3 and 12 and 22 and 57	4481
59	(Conference Abstract or Conference Paper or Conference Review or Editorial or Erratum or comment or Letter or note).pt.	8204229

60	58 not 59	3503
61	limit 60 to english language	3277
62	limit 61 to yr="1990 -Current"	3189

EBM Reviews - Cochrane Central Register of Controlled Trials – January 2022 Search run April 1 2022

#	Searches	Results
1	exp Status Epilepticus/	121
2	(status epilepticus or absence status or petit mal status or chronic progressive epilepsia partialis continua or epilepsia partialis continua or kojevnikov* epileps* or kojewnikow* syndrome?).tw.	545
3	1 or 2	562
4	Phenytoin/	567
5	(antisacer or difenin or dihydan or dilantin or diphenylhydantoin? or epamin or epanutin or fenitoin or hydantol or phenytoin).tw.	1360
6	Levetiracetam/	232
7	(etiracetam or keppra or levetiracetam or "alpha ethyl 2 oxo 1 pyrrolidineacetamide").tw.	997
8	Valproic Acid/	927
9	(valproate or convulsofin or depakene or depakine or depakote or dipropyl acetate or divalproex or ergenyl or magnesium valproate or propylisopropylacetic acid or valproic acid or vupral).tw.	2618
10	exp phenobarbital/ or primidone/	484
11	(gardenal or hysteps or luminal or phenemal or phenobarbital or phenobarbitone or phenylbarbital or phenylethylbarbituric acid or apo primidone or desoxyphenobarbital or liskantin or misodine or mizodin or mylepsinum or mysoline or primaclone or primidon holsten or primidone or resimatil or sertan).tw.	3214
12	or/4-11	7581
13	Status Epilepticus/mo	0
14	treatment outcome/	143183
15	Recurrence/	12449
16	Death/	222
17	exp mortality/	13958
18	"Drug-Related Side Effects and Adverse Reactions"/	1660
19	adverse effects.fs.	0
20	(adverse effect? or adverse event? or safe or safety or effective* or death? or mortalit* or outcome?).tw.	985382
21	(seizure? adj5 (cessation? or recurren* or reduce? or reducing or reduction)).tw.	1947
22	or/13-21	1032121
23	randomized controlled trial.pt.	545949
24	controlled clinical trial.pt.	92954
25	randomi#ed.ab.	754976
26	placebo.ab.	312595

27	clinical trials as topic.sh.	33316
28	randomly.ab.	287579
29	trial.ti.	372980
30	or/23-29	1345845
31	exp animals/ not humans.sh.	12
32	30 not 31 [Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision); Ovid format]	1345837
33	(systematic review or meta-analysis).pt.	657
34	meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/	502
35	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kw.	16179
36	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kw.	679
37	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kw.	8217
38	(data synthes* or data extraction* or data abstraction*).ti,ab,kw.	2692
39	(handsearch* or hand search*).ti,ab,hw.	1532
40	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kw.	5108
41	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kw.	1877
42	(meta regression* or metaregression*).ti,ab,kw.	588
43	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.	31450
44	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.	15568
45	(cochrane or (health adj2 technology assessment) or evidence report).jw.	1157
46	(comparative adj3 (efficacy or effectiveness)).ti,ab,kw.	39827
47	(outcomes research or relative effectiveness).ti,ab,kw.	4758
48	((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kw.	842
49	(multi* adj3 treatment adj3 comparison*).ti,ab,kw.	171
50	(mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kw.	33
51	umbrella review*.ti,ab,kw.	13
52	(multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kw.	1
53	(multiparamet* adj2 evidence adj2 synthesis).ti,ab,kw.	1
54	(multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kw.	1
55	or/33-54 [CADTH Search Filter for Systematic Reviews/Meta-Analysis/Health Technology Assessment – OVID Medline, Embase, PsycINFO]	89882
56	32 or 55	1360304
57	3 and 12 and 22 and 56	139
58	limit 57 to (yr="1990 -Current" and english language)	108