Standard antiepileptic drugs (phenobarbital, phenytoin, carbamazepine, valproic acid) for management of convulsive epilepsy in adults and children

Q 7: For adults and children with convulsive epilepsy, which standard antiepileptic drugs (phenobarbital, phenytoin, carbamazepine, valproic acid) when compared to placebo/a comparator produce benefits/harm in the specified outcomes?

Background

Epilepsy should be treated because it decreases morbidity and premature mortality. The mainstay of treatment for epilepsy is antiepileptic drugs (AEDs) taken daily to prevent the recurrence of seizures. Worldwide, phenobarbital, phenytoin, carbamazepine, and valproic acid are commonly used antiepileptic drugs. Carbamazepine and phenytoin are considered first line treatments in many countries. In Europe, carbamazepine is used in preference to phenytoin, whereas phenytoin is more commonly used in the USA. To date, it is unclear if differences exist in efficacy between these two drugs, and the difference in the European and USA approach may relate to local practices. In generalized onset seizures, it is generally believed that valproate monotherapy is more effective than phenytoin monotherapy, while phenytoin monotherapy is more effective than valproate monotherapy in partial onset seizures. To date, however, there is no hard evidence from individual randomized controlled trials to support this belief. In USA and much of Europe, phenobarbital is no longer considered a first line drug due to worries over its short and long term tolerability. In children, there is concern about behavioural disturbance caused by phenobarbital. In resource poor settings, phenobarbital in view of its low cost is an important option.

Population/Intervention(s)/Comparison/Outcome(s) (PICO)

Population:	adults and children with convulsive epilepsy
Interventions:	phenobarbital
	phenytoin
	carbamazepine
	valproic acid
Comparison:	placebo

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one intervention versus other

Outcomes: seizure recurrence

mortality

adverse events

quality of life

PICO table

Serial no.	Intervention/Comparison	Outcomes	Systematic reviews
I	phenobarbital, phenytoin, carbamazepine, valproic acid vs. Placebo	Seizure recurrence Mortality Adverse events Quality of life	No review available
2	Phenobarbital vs. carbamazepine	Seizure recurrence Adverse events	Cochrane Review: Smith et al, 2003, last assessed as up-to-date 30.09.06
3	Phenobarbital vs. phenytoin	Seizure recurrence Adverse events	Cochrane Review: Taylor et al, 2003, last assessed as up-to-date 21.12.06
4	Phenytoin vs. carbamazepine	Seizure recurrence Adverse events	Cochrane Review: Smith et al, 2002, last assessed as up-to-date 26.07.07
5	Phenytoin vs. valproic acid	Seizure recurrence Adverse events	Cochrane Review: Smith et al, 2001, last assessed as up-to-date 26.07.07

6	Carbamazepine vs. valproic acid	Seizure recurrence Adverse events	Cochrane Review: Marson et al, 2000, last assessed as up-to-date 26.07.07
7	phenobarbital vs. valproate	Seizure recurrence Adverse events	No review available

Narrative description of the studies that went into the analysis

We found no systematic reviews of studies that compared AEDs monotherapy with placebo as these have ethical issues.

Smith et al, 2003 included randomized or quasi-randomized, blinded or unblinded controlled trials in children or adults with partial onset seizures or generalized onset tonic-clonic seizures. Studies compared phenobarbital with carbamazepine. The analysis included 684 participants from four trials, representing 59% of the participants recruited into the nine trials that met the review inclusion criteria.

Taylor et al, 2003 included randomized controlled trials in children or adults with partial onset seizures or generalized onset tonic-clonic seizures. Studies compared phenobarbitone monotherapy with phenytoin monotherapy. The analysis included four of ten studies meeting the inclusion criteria, amounting to 599 individuals, or approximately 65% of the potential data.

Smith et al, 2002 included randomized controlled trials in children or adults with partial onset seizures or generalized onset tonic-clonic seizures. Studies compared carbamazepine monotherapy with phenytoin monotherapy. The analysis included 551 participants from three trials, representing 61% of the participants recruited into the nine trials that met our inclusion criteria.

Smith et al, 2001 included randomized controlled trials in children or adults with partial onset seizures or generalized onset tonic-clonic seizures. Studies compared phenytoin monotherapy with valproate monotherapy. The analysis included 669 individuals from five trials, representing 60% of the participants recruited into the eleven trials that met the review inclusion criteria.

Marson et al, 2000 included randomized controlled trials comparing carbamazepine and valproate monotherapy for epilepsy in children or adults. Studies compared carbamazepine and valproate monotherapy. The analysis included 1265 participants from five trials, representing 85% of the participants recruited into the eight trials that met the inclusion criteria.

References of studies that went into the analysis

Marson AG et al (2000). Carbamazepine versus valproate monotherapy for epilepsy. *Cochrane Database of Systematic Reviews*, (3):CD001030.

Smith TC, Marson AG, Williamson PR (2001). Phenytoin versus valproate monotherapy for partial onset seizures and generalized onset tonic-clonic seizures. *Cochrane Database of Systematic Reviews*, (4):CD001769.

Smith TC, Marson AG, Williamson PR (2003). Carbamazepine versus phenobarbitone monotherapy for epilepsy. *Cochrane Database of Systematic Reviews*, (1):CD001904.

Smith TC et al (2002). Carbamazepine versus phenytoin monotherapy for epilepsy. *Cochrane Database of Systematic Reviews*, (2):CD001911.

Taylor S et al (2003). Phenobarbitone versus phenytoin monotherapy for partial onset seizures and generalized onset tonic-clonic seizures. *Cochrane Database of Systematic Reviews*, (2):CD002217.

GRADE tables

Table 1

Author(s): Dua T, Barbui C
Date: 2009-08-19
Question: Should phenobarbital vs. carbamazepine be used for epilepsy (adults and children)?
Settings:
Bibliography: Smith TC, Marson AG, Williamson PR (2003). Carbamazepine versus phenobarbitone monotherapy for epilepsy. *Cochrane Database of Systematic Reviews*, (1):CD001904.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	phenobarbital	carbamazepine	Relative (95% CI)	Absolute		
remission (time to)												

7[1]	randomized trials	very serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	117/318 (36.8%)	163/362 (45%)	HR 0.87 (0.65 to 1.17)[4]	44 fewer per 1000 (from 128 fewer to 53 more)	VERY LOW	CRITICAL
seizure (time to first-seizure)												
7[5]	randomized trials	very serious[2]	very serious[6]	no serious indirectness	no serious imprecision	none	150/318 (47.2%)	213/362 (58.8%)	HR 0.85 (0.68 to 1.05)[7]	59 fewer per 1000 (from 135 fewer to 18 more)	VERY LOW	CRITICAL
treatment acceptability (dropouts)												
7[8]	randomized trials	serious[9]	serious[10]	no serious indirectness	no serious imprecision	none	116/314 (36.9%)	99/360 (27.5%)	HR 1.63 (1.23 to 2.15)	133 more per 1000 (from 52 more to 224 more)	LOW	IMPORTANT
Mortality												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
quality of life (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] From Analysis 1.2 of Smith et al, 2003 Cochrane Review.

[2] All studies are described as randomized, but 4 out of 7 are unblinded and 4 out of 7 have a high dropout rate (exceeding 30%).

[3] Some confidence intervals do not overlap (I-squared = 58%).

[4] The analysis by diagnostic subgroup revealed an odds ratio of 0.61 (95% CI 0.36 to 1.03) for generalized seizures and an odds ratio of 1.03 (0.72 to 1.49) for partial onset seizures.

[5] From Analysis 1.3 of Smith et al, 2003 Cochrane Review.

[6] I-squared = 88%. Inconsistency of estimates is particularly evident between studies conducted in individuals with generalized seizures (OR 1.50, 95% CI 0.95 to 2.35, in favour of carbamazepine) and studies conducted in individuals with partial onset seizures (OR 0.71, 95% CI 0.55 to 0.91, in favour of phenobarbital).

[7] The analysis by diagnostic subgroup revealed an odds ratio of 1.50 (95% CI 0.95 to 2.35) in favour of carbamazepine over phenobarbital for generalized seizures, and an odds ratio of 0.71 (0.55 to 0.91) in favour of phenobarbital over carbamazepine for partial onset seizures.

[8] From Analysis 1.1 of Smith et al, 2003 Cochrane Review.

[9] All studies are described as randomized, but 4 out of 7 are unblinded.

[10] Some confidence intervals do not overlap (I-squared = 40%).

Table 2

Standard antiepileptic drugs (phenobarbital, phenytoin, carbamazepine, valproic acid) for management of convulsive epilepsy in adults and children

Author(s): Dua T, Barbui C
Date: 2009-08-19
Question: Should phenobarbital vs. phenytoin be used for epilepsy (adults and children)?
Settings:
Bibliography: Taylor S et al (2003). Phenobarbitone versus phenytoin monotherapy for partial onset seizures and generalized onset tonic-clonic seizures. *Cochrane Database of Systematic Reviews*, (2):CD002217.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	phenobarbital	phenytoin	Relative (95% CI)	Absolute		
remission (time to)												
4[1]	randomized trials	very serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	99/249 (39.8%)	158/306 (51.6%)	HR 0.84 (0.68 to 1.05)	60 fewer per 1000 (from 127 fewer to 17 more)	VERY LOW	CRITICAL
seizure (time to first-seizure)												
4[4]	randomized trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	137/266 (51.5%)	214/326 (65.6%)	HR 0.84 (0.68 to 1.05)	64 fewer per 1000 (from 140 fewer to 18 more)	LOW	CRITICAL
treatment acceptability (dropouts)												
3[6]	randomized trials	serious[7]	very serious[8]	no serious indirectness	no serious imprecision	none	109/220 (49.5%)	102/279 (36.6%)	HR 1.62 (1.22 to 2.14)	156 more per 1000 (from 60 more to 257 more)	VERY LOW	IMPORTANT
Mortality												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
quality of life (Better indicated by lower values)												

0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] From analysis 1.2 of Taylor et al, 2003 Cochrane Review.
[2] Two out of four studies were unblinded, and two out of four studies have dropout rates exceeding 30%.
[3] No explanation was provided.
[4] From Analysis 1.3 of Taylor et al, 2003 Cochrane Review.
[5] Two out of 4 studies are unblinded, and one study has a dropout rate exceeding 30%.
[6] From Analysis 1.1 of Taylor et al, 2003 Cochrane Review.
[7] Two out of three studies are unblended.
[8] Heterogeneity exceeds 75% (I-squared = 79%).

Table 3

Author(s): Dua T, Barbui C
Date: 2009-08-19
Question: Should carbamazepine vs. phenytoin be used for epilepsy (adults and children)?
Settings:
Bibliography: Smith TC et al (2002). Carbamazepine versus phenytoin monotherapy for epilepsy. *Cochrane Database of Systematic Reviews*, (2):CD001911.

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	carbamazepine	phenytoin	Relative (95% CI)	Absolute		
remission (time to)												
3[1]	randomized trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	155/282 (55%)	134/269 (49.8%)	HR 1.00 (0.78 to 1.29)	0 fewer per 1000 (from 82 fewer to 91 more)	LOW	CRITICAL
seizure (time to first-seizure)												
3[3]	randomized trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	185/282 (65.6%)	177/269 (65.8%)	HR 0.91 (0.74 to 1.12)	35 fewer per 1000 (from 110 fewer to 41 more)	LOW	CRITICAL

treatment acceptability (dropouts)											
4[4]	randomized trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	108/301 (35.9%)	103/290 (35.5%)	HR 0.97 (0.74 to 1.28)	9 fewer per 1000 (from 78 fewer to 75 more)	LOW	IMPORTANT
Mortality											
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
quality of life (Better indicated by lower values)											
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] From Analysis 1.2 of Smith et al, 2002 Cochrane Review.

[2] Two out of three studies are unblinded, and two out of three studies have a dropout rate exceeding 30%.

[3] From Analysis 1.4 of Smith et al, 2002 Cochrane Review.

[4] From Analysis 1.1 of Smith et al, 2002 Cochrane Review.

[5] Two studies are unblinded and one is single-blinded.

Table 4

Author(s): Dua T, Barbui C

Date: 2009-08-19

Question: Should phenytoin vs. valprioc acid be used for epilepsy (adults and children)?

Settings:

Bibliography: Smith TC, Marson AG, Williamson PR (2001). Phenytoin versus valproate monotherapy for partial onset seizures and generalized onset tonic-clonic seizures. *Cochrane Database of Systematic Reviews*, (4):CD001769.

Quality assessment							**Summary of findings**					**Importance**
							No of patients		**Effect**		**Quality**	
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Phenytoin**	**valproic acid**	**Relative (95% CI)**	**Absolute**		

remission (time to)												
8[1]	randomized trials	very serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	156/258 (60.5%)	147/256 (57.4%)	HR 1.04 (0.78 to 1.38)[3]	14 more per 1000 (from 88 fewer to 118 more)	LOW	CRITICAL
seizure (time to first-seizure)												
9[4]	randomized trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	182/306 (59.5%)	189/333 (56.8%)	HR 0.92 (0.74 to 1.14)	30 fewer per 1000 (from 105 fewer to 48 more)	LOW	CRITICAL
treatment acceptability (dropouts)												
9[6]	randomized trials	very serious[7]	serious[8]	no serious indirectness	no serious imprecision	none	74/249 (29.7%)	71/278 (25.5%)	HR 1.10 (0.79 to 1.54)	22 more per 1000 (from 48 fewer to 110 more)	VERY LOW	IMPORTANT
Mortality												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
quality of life (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] From Analysis 1.2 of Smith et al, 2001 Cochrane Review.

[2] Six out of 8 studies are unblinded, and the remaining two are single-blind. Additionally, dropout rates exceed 30% in six out of 8 studies.

[3] The subgroup analysis by diagnostic group (partial onset seizures versus generalized onset seizures) did not reveal any significant difference.

[4] From Analysis 1.4 of Smith et al, 2001 Cochrane Review.

[5] Seven out of nine studies are unblinded, and the remaining two studies are single blind. Additionally, six out of nine studies have a dropout rate exceeding 30%.

[6] From Analysis 1.1 of Smith et al, 2001 Cochrane Review.

[7] All nine studies are unblended.

[8] Heterogeneity exceeds 50% (I-squared = 56%).

Table 5

Author(s): Dua T, Barbui C
Date: 2009-08-20
Question: Should carbamazepine vs. valproic acid be used for epilepsy (adults and children)?
Settings:
Bibliography: Marson AG et al (2000). Carbamazepine versus valproate monotherapy for epilepsy. *Cochrane Database of Systematic Reviews*, (3):CD001030.

Standard antiepileptic drugs (phenobarbital, phenytoin, carbamazepine, valproic acid) for management of convulsive epilepsy in adults and children

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	carbamazepine	valproic acid	Relative (95% CI)	Absolute		
remission (time to)												
9[1]	randomized trials	very serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	373/611 (61%)	394/614 (64.2%)	HR 0.87 (0.74 to 1.02)[4]	51 fewer per 1000 (from 110 fewer to 7 more)	VERY LOW	CRITICAL
seizure (time to first-seizure)												
9[5]	randomized trials	very serious[6]	very serious[7]	no serious indirectness	no serious imprecision	none	435/611 (71.2%)	429/614 (69.9%)	HR 1.09 (0.96 to 1.25)[8]	31 more per 1000 (from 15 fewer to 78 more)	VERY LOW	CRITICAL
treatment acceptability (dropouts)												
9[9]	randomized trials	serious[10]	serious[11]	no serious indirectness	no serious imprecision	none	196/593 (33.1%)	202/602 (33.6%)	HR 0.97 (0.79 to 1.18)	8 fewer per 1000 (from 60 fewer to 47 more)	LOW	IMPORTANT
Mortality												
0	no evidence available					none	0/0 (0%)	0/0 (0%)	Not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)		IMPORTANT
quality of life (Better indicated by lower values)												
0	no evidence available					none	0	0	-	MD 0 higher (0 to 0 higher)		IMPORTANT

[1] From Analysis 1.2 of Marson et al, 2000 Cochrane Review.

[2] Six out of nine studies are unblinded, and seven out of nine have dropout rates exceeding 30%.

[3] Although the I-squared did not reveal significant heterogeneity, inspection of the forest plot showed that confidence intervals do not overlap.

[4] The subgroup analysis by diagnostic group showed no difference between carbamazepine and valproic acid in generalized epilepsy, and an advantage for carbamazepine over valproic acid in partial onset seizures (OR 0.82, 95% CI 0.67 to 1.00).

[5] From Analysis 1.3 of Marson et al, 2000 Cochrane Review.

[6] Six out of nine studies are unblinded, and all nine studies have dropout rates exceeding 30%.

[7] Estimates and confidence intervals are very dissimilar (I-squared = 83%).

[8] The subgroup analysis by diagnostic group showed no significant difference between carbamazepine and valproic acid in generalized epilepsy, and an advantage for carbamazepine over valproic acid in partial onset seizures (OR 1.22, 95% CI 1.04 to 1.44).
[9] From Analysis 1.1 of Marson et al, 2000 Cochrane Review.
[10] Six out of nine studies are unblended.
[11] Some confidence intervals do not overlap 8I-squared = 62%).

Additional evidence that was not graded

According to NICE guidelines (Stokes et al, 2004), clinically significant side-effects in adults include the following:

Carbamazepine: allergic skin reactions, including urticaria, which may be severe. Accommodation disorders, for example blurred vision, diplopia, ataxia and nausea. Particularly at the start of treatment, or if the initial dose is too high, certain types of adverse reaction occur very commonly or commonly.

Phenobarbital: drowsiness, lethargy and mental depression.

Phenytoin: hypersensitivity reactions including skin rash. Common undesirable effects include drowsiness, ataxia and slurred speech and these are usually dose related. Coarsening of facial features, gingival hyperplasia and hirsutism may occur rarely. Some haemopoetic complications have been reported including some anaemia's (these usually respond to folic acid). Motor twitchings, dyskinesias (rare), tremor (rare), and mental confusion have all been observed.

Sodium valproate: sedation and tremor have been reported occasionally. Transient hair loss, which may sometimes be dose related, has often been reported. Regrowth normally begins within 6 months. Increase in weight may also occur. Severe liver damage has been very rarely reported. Encephalopathy and pancreatitis may occur rarely. Also, hyperammonaemia without change in liver function tests may occur frequently and is usually transient. Blood dyscrasias, may occur frequently and the blood picture return to normal when the drug is discontinued. Sodium valproate has been associated with amenorrhoea and irregular periods. Sodium valproate is associated with a higher risk of fetal malformations if taken in pregnancy.

According to NICE guidelines (Stokes et al, 2004), clinically significant side-effects in children and adolescents include the following:

Carbamazepine: allergic skin reactions, including urticaria, which may be severe. Accommodation disorders, for example blurred vision, diplopia, ataxia and nausea. Particularly at the start of treatment, or if the initial dose is too high, certain types of adverse reaction occur very commonly or commonly.

Phenobarbital: drowsiness, lethargy and mental depression. In addition, allergic skin reactions and hyperkinesia.

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Phenytoin: hypersensitivity reactions including skin rash. Common undesirable effects include drowsiness, ataxia and slurred speech and these are usually dose related. Coarsening of facial features, gingival hyperplasia and hirsutism may occur rarely. Some haemopoetic complications have been reported including some anaemia's (these usually respond to folic acid). Motor twitchings, dyskinesias (rare), tremor (rare), and mental confusion have all been observed.

Sodium valproate: sedation and tremor have been reported occasionally. Transient hair loss, which may sometimes be dose related, has often been reported. Regrowth normally begins within 6 months. Increase in weight may also occur. Gastric disorders frequently occur at the start of treatment. Occasionally, hyperactivity, aggression and behavioural deterioration have been reported. Severe liver damage has been very rarely reported. Those most at risk are aged under 3 years but this is most probably related to undiagnosed metabolic disease, so special consideration should be given to children in this age group, where the diagnosis is unclear and where children are on polytherapy. Increases in the levels of liver enzymes are common, particularly at the beginning of therapy; they are also transient. Encephalopathy and pancreatitis may occur rarely. Also, hyperammonaemia without change in liver function tests may occur frequently and is usually transient. Also blood dyscrasias may occur frequently and the blood picture return to normal when the drug is discontinued. Sodium valproate has been associated with amenorrhoea and irregular periods. Sodium valproate is associated with a higher risk of fetal malformations if taken in pregnancy.

Reference List

Marson AG et al (2000). Carbamazepine versus valproate monotherapy for epilepsy. *Cochrane Database of Systematic Reviews*, (3):CD001030.

Smith TC, Marson AG, Williamson PR (2001). Phenytoin versus valproate monotherapy for partial onset seizures and generalized onset tonic-clonic seizures. *Cochrane Database of Systematic Reviews*, (4):CD001769.

Smith TC, Marson AG, Williamson PR (2003). Carbamazepine versus phenobarbitone monotherapy for epilepsy. *Cochrane Database of Systematic Reviews*, (1):CD001904.

Smith TC et al (2002). Carbamazepine versus phenytoin monotherapy for epilepsy. *Cochrane Database of Systematic Reviews*, (2):CD001911.

Stokes T et al (2004). NICE Clinical Guidelines and Evidence Review for the Epilepsies: diagnosis and management in adults and children in primary and secondary care. London: Royal College of General Practitioners.

Taylor S et al (2003). Phenobarbitone versus phenytoin monotherapy for partial onset seizures and generalized onset tonic-clonic seizures. *Cochrane Database of Systematic Reviews*, (2):CD002217.

From evidence to recommendations

Factor	Explanation
Narrative summary of the evidence base	Carbamazepine, phenobarbital, phenytoin, and sodium valproate are widely considered effective in controlling seizures, no systematic review of RCTs comparing them with placebo was found. It is considered unethical to conduct RCTs comparing standard AEDs with placebo in established epilepsy since it is believed that epilepsy should be treated as treatment decreases morbidity and premature mortality. Systematic reviews of head-to-head comparisons found evidence suggesting there is unlikely to be a clinically important difference among AEDs. Carbamazepine may have an advantage over valproic acid in partial onset seizures (time to first seizure: OR 1.22, 95% CI 1.04 to 1.44). In terms of treatment tolerability, there is evidence favouring carbamazepine and phenytoin over phenobarbital. Phenytoin despite being used as a first line drug, it has a problematic pharmacokinetic profile. All AEDs are associated with adverse effects. Phenobarbital is considered to be associated with a higher risk of short and long term tolerability problems. Sodium valproate is associated with a higher risk of fetal malformations if taken in pregnancy.
Summary of the quality of evidence	For critical outcomes, the quality of evidence was LOW or VERY LOW.
Balance of benefits versus harms	The balance of benefits versus harms is in favour of treatment of children and adults with convulsive epilepsy.

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Values and preferences including any variability and human rights issues	Epilepsy should be treated as treatment decreases morbidity and premature mortality and improves the quality of life of people with epilepsy.
Costs and resource use and any other relevant feasibility issues	Carbamazepine, Phenobarbital, phenytoin, and sodium valproate are included in the WHO list of essential medicines. Phenobarbital is commonly used as a first line drug in developing countries since it is much cheaper than other AEDs. Phenobarbital, being a controlled substance, there are strict regulations in many countries which affects its accessibility.
Final recommendation(s) Monotherapy with any of the standard antiepileptic drugs (carbamazepine, phenobarbital, phenytoin, and valproic acid) should be offered to children and adults with convulsive epilepsy. Given the acquisition costs, phenobarbital should be offered as a first option if availability can be assured. If available, carbamazepine should be offered to children and adults with partial onset seizures. Strength of recommendation: STRONG	
Any additional remarks Regulatory issues are a barrier to phenobarbital access in some settings and needs to be addressed	

Limitations

Although some head-to-head randomized trials comparing different antiepileptic drugs (carbamazepine, phenobarbital, phenytoin, and sodium valproate) have been carried out, the evidence is inconclusive and so it is very difficult to ascertain whether some antiepileptic drugs are more effective than others.

Standard antiepileptic drugs (phenobarbital, phenytoin, carbamazepine, valproic acid) for management of convulsive epilepsy in adults and children

Update of the literature search – June 2012

In June 2012 the literature search for this scoping question was updated. The following systematic review was found to be relevant without changing the recommendation:

Tudur Smith C, Marson AG, Clough HE, Williamson PR. Carbamazepine versus phenytoin monotherapy for epilepsy. Cochrane Database of Systematic Reviews 2002, Issue 2. Art. No.: CD001911. DOI: 10.1002/14651858.CD001911.