Epilepsy (generalised)

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ABSTRACT

INTRODUCTION: About 3% of people will be diagnosed with epilepsy during their lifetime, but about 70% of people with epilepsy eventually go into remission. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of monotherapy in newly diagnosed generalised epilepsy (tonic clonic type)? What are the effects of additional treatments in people with drug-resistant generalised epilepsy? What are the effects of surgery in people with drug-resistant generalised epilepsy? We searched: Medline, Embase, The Cochrane Library, and other important databases up to August 2011 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 8 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: monotherapy using carbamazepine, gabapentin, lamotrigine, levetiracetam, phenobarbital, phenytoin, sodium valproate, or topiramate; addition of second-line drugs (lamotrigine or levetiracetam) for drug-resistant epilepsy; and hemispherectomy for drug-resistant epilepsy.

QUESTIONS

What are the effects of monotherapy in generalised epilepsy (tonic clonic type)? . . . 3

What are the effects of additional treatments in people with drug-resistant generalised epilepsy? . . . 10

What are the effects of surgery in people with drug-resistant epilepsy? . . . 12

INTERVENTIONS

GENERALISED EPILEPSY: MONOTHERAPY

Likely to be beneficial

Sodium valproate for generalised epilepsy* . . . 3

Carbamazepine for generalised epilepsy* . . . 4

Phenobarbital for generalised epilepsy* . . . 5

Phenytoin for generalised epilepsy* . . . 6

Lamotrigine for generalised epilepsy* . . . 7

Topiramate for generalised epilepsy* . . . 8

Levetiracetam for generalised epilepsy* . . . 9

Gabapentin for generalised epilepsy* . . . 9

TREATING DRUG-RESISTANT GENERALISED EPILEPSY

Beneficial

Addition of second-line antiepileptics (in drug-resistant generalised epilepsy) . . . 10

SURGERY IN PEOPLE WITH DRUG-RESISTANT EPILEPSY

Unknown effectiveness

Hemispherectomy for drug-resistant epilepsy 12

Covered elsewhere in Clinical Evidence

Pharmacological and surgical treatments of partial epilepsy; drug withdrawal and relapse in undefined epilepsy type; behavioural and psychological treatments of undefined epilepsy type; and pharmacological treatment of a single seizure that may progress to epilepsy, see review on Epilepsy (partial). Treatment of typical absence seizures in children, see review on Absence seizures in children.

To be covered in future updates

Oxcarbazepine (monotherapy)

Multiple subpial transections

Corpus callosotomy

Footnote

*Categorisation based on consensus.

Key points

- During their lifetime, about 3% of people will be diagnosed with epilepsy, but about 70% of people with epilepsy eventually go into remission.
- Carbamazepine, gabapentin, lamotrigine, levetiracetam, phenobarbital, phenytoin, sodium valproate, and topiramate are widely considered effective in controlling seizures in newly diagnosed generalised (tonic clonic) epilepsy, but we found no RCTs comparing them with placebo, and a placebo-controlled trial would now be considered unethical.

  Systematic reviews found no reliable evidence on which to base a choice among antiepileptic drugs; we don't know if any one antiepileptic drug is more likely to reduce seizures compared with the others.
- Adding second-line drugs to usual treatment reduces seizure frequency in people with drug-resistant generalised epilepsy.
- We don't know whether hemispherectomy improves seizure control in people with drug-resistant epilepsy.

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DEFINITION

Epilepsy is a group of disorders rather than a single disease. Seizures can be classified by type as generalised (categorised as generalised tonic clonic, absence, myoclonic, tonic, and atonic seizures) or partial or focal (categorised as simple partial, complex partial, and secondary generalised tonic clonic seizures). [1] A person is considered to have epilepsy if they have had two or more unprovoked seizures. This review deals with pharmacological and surgical treatments of generalised epilepsy only. For information on drug withdrawal and relapse in undefined epilepsy type (generalised or partial), behavioural and psychological treatments of undefined epilepsy type, and pharmacological treatment of a single seizure that may progress to epilepsy, or pharmacological or surgical treatments of partial epilepsy, see review on Epilepsy (partial). Status epilepticus is not covered in this review.

INCIDENCE/ PREVALENCE

Epilepsy (generalised or partial) is common, with an estimated average prevalence of 5.5/1000 people in Europe, [2] 6.8/1000 people in the US, [3] and 7.5/1000 people in Australia. Prevalence rates in developing countries vary widely, with studies carried out in sub-Saharan Africa reporting rates of 5.2 to 74.4/1000 people, [4] studies in Asia reporting overall prevalence rates of 1.5 to 14.0/1000 people, [5] and Latin America reporting rates of 17 to 22/1000 people. [6] The worldwide incidence of epilepsy (defined as 2 or more unprovoked seizures occurring at least 24 hours apart) is 50.4/100,000 people per year. The incidence is approximately 45.0/100,000 per year for high-income countries and 81.7/100,000 per year for low- and middle-income countries. [7] The worldwide incidence of single unprovoked seizures is 23 to 61/100,000 person-years. [8] About 3% of people will be diagnosed with epilepsy at some time in their lives. [9]

AETIOLOGY/ RISK FACTORS

Epilepsy is a symptom rather than a disease, and it may be caused by various disorders involving the brain. The causes/risk factors include birth/neonatal injuries, congenital or metabolic disorders, head injuries, tumours, infections of the brain or meninges, genetic defects, degenerative disease of the brain, cerebrovascular disease, or demyelinating disease. Epilepsy can be classified by cause. [1] **Idiopathic generalised** epilepsies (such as juvenile myoclonic epilepsy or childhood absence epilepsy) are largely genetic. **Symptomatic generalised** epilepsies (such as West syndrome and Lennox–Gastaut) are associated with diffuse cerebral dysfunction and may be caused by anoxic brain injury or metabolic defect. **Cryptogenic epilepsies** are those that cannot be classified as idiopathic or symptomatic.

PROGNOSIS

About 60% of untreated people have no further seizures during the 2 years after their first seizure. [10] Prognosis is good for most people with epilepsy. About 70% go into remission, defined as being seizure free for 5 years on or off treatment. This leaves 20% to 30% who develop chronic epilepsy, which is often treated with multiple antiepileptic drugs. [11]

AIMS OF INTERVENTION

To reduce the risk of subsequent seizures and to improve the prognosis of the seizure disorder; to improve quality of life; to minimise adverse effects of treatment.

OUTCOMES

For treatment of newly diagnosed epilepsy: Time to remission, time to first seizure after treatment, retention on allocated treatment or time to withdrawal of allocated treatment. **For treatment of drug-resistant epilepsy:** Percentage reduction in seizure frequency, proportion of responders (response defined as at least 50% reduction in seizure frequency). **For all:** quality of life, adverse effects.

METHODS

Clinical Evidence search and appraisal August 2011. The following databases were used to identify studies for this systematic review: Medline 1966 to August 2011, Embase 1980 to August 2011, and The Cochrane Database of Systematic Reviews 2011, Issue 3 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least double-blinded for drug trials, and containing >20 individuals of whom >80% were followed up. At least 3 months' follow-up was required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We aimed to include studies in people with generalised epilepsy or where a subgroup analysis was carried out in people with generalised epilepsy. However, where studies included a mixture of partial and generalised epilepsy, we included studies in which at least 60% of people had generalised epilepsy. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical

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data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 14). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of monotherapy in generalised epilepsy (tonic clonic type)?

OPTION SODIUM VALPROATE FOR GENERALISED EPILEPSY

Seizure frequency

Compared with carbamazepine We don't know whether sodium valproate is more effective at achieving 12-month remission or increasing time to first seizure in people with generalised epilepsy (low-quality evidence).

Compared with phenytoin Sodium valproate and phenytoin seem equally effective at achieving 12-month remission and at increasing time to first seizure in people with generalised epilepsy (moderate-quality evidence).

Note

We found no direct information from RCTs about whether sodium valproate used as monotherapy in people with generalised epilepsy is better than no active treatment. However, there is consensus that sodium valproate reduces seizure rates.

For GRADE evaluation of interventions for epilepsy, see table, p 14 .

Benefits:

Sodium valproate versus placebo:
We found no systematic review or RCTs.

Sodium valproate versus carbamazepine:
See benefits of carbamazepine, p 4 .

Sodium valproate versus phenytoin:
See benefits of phenytoin, p 6 .

Sodium valproate versus other antiepileptic drugs:
We found no systematic review or RCTs.

Harms:

For general information on adverse outcomes in pregnancy and effects of antiepileptic drugs on bone mineral density, see review on Epilepsy (partial). Antiepileptic drugs have also been associated with an increased risk of suicidal behaviour and ideation. [12]

Sodium valproate versus placebo:
We found no RCTs.

Sodium valproate versus carbamazepine:
See harms of carbamazepine, p 4 .

Sodium valproate versus phenytoin:
See harms of phenytoin, p 6 .

Sodium valproate versus other antiepileptic drugs:
We found no RCTs.

Comment:

Placebo-controlled trials of sodium valproate would now be considered unethical.

We found one large RCT (716 people, 63% idiopathic generalised epilepsy, 27% unclassified epilepsy) of a pragmatic design that compared sodium valproate, lamotrigine, and topiramate in people with generalised epilepsy. [13] The RCT was open label — to allow clinicians to determine the rate of titration and dosing regimen they thought best for each person — and as such does not meet current *Clinical Evidence* inclusion criteria. However, because of a paucity of data comparing the newer antiepileptics with each other, and the large size of the trial, we have reported the data here. We will also revisit our inclusion criteria at future updates of this review to consider inclusion of these large pragmatic studies.The first date of randomisation in the RCT was 12 January 1999,

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and the last date was 31 August 2004; the number recruited each year was not reported. The last date of follow-up was reported as 13 January 2006. The authors report that the study failed to recruit the required numbers, but the differences between the drugs was larger than expected, and there were sufficient events during follow-up to compensate for this deficiency. The RCT found no significant differences in time to treatment failure (defined as unacceptable adverse effects after randomisation and inadequate seizure control) between sodium valproate and lamotrigine (HR >1 indicates that failure occurs more rapidly with lamotrigine; HR 1.25, 95% CI 0.94 to 1.68). However, sodium valproate was associated with a lower risk of treatment failure compared with topiramate (HR >1 indicates that failure occurs more rapidly with topiramate; HR 1.57, 95% CI 1.19 to 2.08). The RCT found that sodium valproate significantly increased the proportion of people who achieved 12-month remission compared with lamotrigine (HR >1 indicates that 12-month remission occurs more rapidly with lamotrigine; HR 0.76, 95% CI 0.62 to 0.94) but there was no significant difference compared with topiramate (HR >1 indicates that failure occurs more rapidly with topiramate; HR 0.93, 95% CI 0.76 to 1.15). The RCT was insufficiently powered to provide relative efficacy for individual seizure types or sub-syndromes within the idiopathic epilepsies. [13]

OPTION CARBAMAZEPINE FOR GENERALISED EPILEPSY

Seizure frequency
Compared with sodium valproate We don't know whether carbamazepine is more effective at achieving 12-month remission or increasing time to first seizure in people with generalised epilepsy (low-quality evidence).

Compared with phenobarbital We don't know whether carbamazepine is more effective at achieving 12-month remission or increasing time to first seizure in people with generalised epilepsy (low-quality evidence).

Compared with lamotrigine We don't know whether carbamazepine controlled release is more effective at increasing time to withdrawal (combined measure of efficacy and tolerability) in older people with epilepsy (very low-quality evidence).

Note
We found no direct information from RCTs about whether carbamazepine used as monotherapy in people with generalised epilepsy is better than no active treatment. However, there is consensus that carbamazepine reduces seizure rates.

For GRADE evaluation of interventions for epilepsy, see table, p 14 .

Benefits:

Carbamazepine versus placebo:
We found no systematic review or RCTs.

Carbamazepine versus sodium valproate:
We found one systematic review comparing carbamazepine versus sodium valproate (search date 2007, 5 RCTs, 4 of the RCTs included 395 people with generalised epilepsy, aged 3−79 years, at least 47% men, follow-up <5 years). [14] RCTs included in the review recruited people if they had generalised-onset tonic clonic seizures with or without other generalised seizure types (e.g., absence or myoclonus). A meta-analysis of the generalised epilepsy subgroup found no significant difference between sodium valproate and carbamazepine for 12-month remission or time to first seizure (HR >1 for an event more likely with sodium valproate; 12-month remission: HR 0.96, 95% CI 0.75 to 1.24; first seizure: HR 0.86, 95% CI 0.68 to 1.09; see comment below).

Carbamazepine versus phenobarbital:
We found one systematic review (search date 2006, 4 RCTs, 680 people aged 2−68 years, 157 with generalised epilepsy, at least 52% men) comparing carbamazepine versus phenobarbital. [15] Meta-analysis of the subgroup of people with generalised epilepsy found no significant difference between groups in time to first seizure or in 12-month remission (first seizure: HR 1.50, 95% CI 0.95 to 2.35; 12-month remission: HR 0.61, 95% CI 0.36 to 1.03).

Carbamazepine versus phenytoin:
We found one systematic review (search date 2009, 10 RCTs, 903 people aged 4−82 years with partial onset epilepsy or generalised-onset tonic clonic seizures, at least 47% men). [16] The review carried out a meta-analysis using individual patient data; however, it did not present a separate analysis in people with generalised-onset epilepsy and the majority of people (78%) had partial-onset epilepsy, so we have not reported this further here (for further details, see review on Epilepsy [partial]).

Carbamazepine versus lamotrigine:
See benefits of lamotrigine, p 7 .

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Carbamazepine versus other antiepileptic drugs:
We found no systematic review or RCTs.

Harms:

For general information on adverse outcomes in pregnancy and effects of antiepileptic drugs on bone mineral density, see review on Epilepsy (partial). Antiepileptic drugs have also been associated with an increased risk of suicidal behaviour and ideation. [12]

Carbamazepine versus placebo:
We found no RCTs.

Carbamazepine versus sodium valproate:
The review found no significant difference between sodium valproate and carbamazepine for treatment withdrawal (HR >1 for an event more likely with sodium valproate; HR 0.89, 95% CI 0.62 to 1.29). [14]

Carbamazepine versus phenobarbital:
The review found no significant differences in treatment withdrawal between carbamazepine and phenobarbital (HR 1.78, 95% CI 0.87 to 3.62). [15]

Carbamazepine versus phenytoin:
The review did not present a separate analysis in people with generalised-onset epilepsy. [16]

Carbamazepine versus lamotrigine:
See harms of lamotrigine, p 7 .

Carbamazepine versus other antiepileptic drugs:
We found no RCTs.

Comment:

Placebo-controlled trials of carbamazepine would now be considered unethical.

Carbamazepine versus sodium valproate:
Although the systematic review found no significant difference between sodium valproate and carbamazepine, the confidence interval is wide and this result does not establish equivalence of sodium valproate and carbamazepine. [14] Also, the age distribution of people classified as having generalised epilepsy suggests errors in the classification of epilepsy type. Failure of the RCTs to document generalised seizures other than tonic clonic seizures is an important limitation. The review did not present results separately for adults and children. [14]

Carbamazepine versus phenobarbital:
The review did not present results separately for adults and children. [15]

OPTION PHENOBARBITAL FOR GENERALISED EPILEPSY

Seizure frequency
Compared with carbamazepine We don't know whether phenobarbital is more effective at achieving 12-month remission or increasing time to first seizure in people with generalised epilepsy (low-quality evidence).

Note
We found no direct information from RCTs about whether phenobarbital used as monotherapy in people with generalised epilepsy is better than no active treatment. However, there is consensus that phenobarbital reduces seizure rates.

For GRADE evaluation of interventions for epilepsy, see table, p 14 .

Benefits:

Phenobarbital versus placebo:
We found no systematic review or RCTs.

Phenobarbital versus carbamazepine:
See benefits of carbamazepine, p 4 .

Phenobarbital versus other antiepileptic drugs:
We found no systematic review or RCTs.

Harms:

For general information on adverse outcomes in pregnancy and effects on bone mineral density of antiepileptic drugs, see review on Epilepsy (partial). Antiepileptic drugs have also been associated with an increased risk of suicidal behaviour and ideation. [12]

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Phenobarbital versus placebo:
We found no RCTs.

Phenobarbital versus carbamazepine:
See harms of carbamazepine, p 4 .

Phenobarbital versus other antiepileptic drugs:
We found no RCTs.

Comment: Placebo-controlled trials of phenobarbital would now be considered unethical.

OPTION PHENYTOIN FOR GENERALISED EPILEPSY

Seizure frequency
Compared with sodium valproate Phenytoin and sodium valproate seem equally effective at achieving 12-month remission and at increasing time to first seizure in people with generalised epilepsy (moderate-quality evidence).

Compared with oxcarbazepine We don't know whether phenytoin is more effective at achieving 6-month and 12-month remission or at increasing time to first seizure in people with generalised epilepsy (low-quality evidence).

Note
We found no direct information from RCTs about whether phenytoin used as monotherapy in people with generalised epilepsy is better than no active treatment. However, there is consensus that phenytoin reduces seizure rates.

For GRADE evaluation of interventions for epilepsy, see table, p 14 .

Benefits:

Phenytoin versus placebo:
We found no systematic review or RCTs.

Phenytoin versus sodium valproate:
We found one systematic review (search date 2007, 5 RCTs, 669 people with epilepsy, of whom 395 people aged 3–95 years had generalised epilepsy, at least 36% men) comparing phenytoin and sodium valproate. [17] RCTs included in the review recruited people if they had generalised-onset tonic clonic seizures with or without other generalised seizure types (e.g., absence or myoclonus). [17] A meta-analysis of the generalised epilepsy subgroup found no significant difference between sodium valproate and phenytoin in 12-month remission or in time to first seizure (HR >1 for an event more likely with phenytoin; 12-month remission: 4 RCTs, 270 people: HR 1.06, 95% CI 0.71 to 1.57; time to first seizure: HR >1 indicates a clinical advantage for valproate; 5 RCTs, 395 people: HR 1.03, 95% CI 0.77 to 1.39; see comment below).

Phenytoin versus carbamazepine:
See benefits of carbamazepine, p 4 .

Phenytoin versus oxcarbazepine:
We found one systematic review (search date 2008, 2 RCTs, 480 people, 147 with generalised epilepsy) comparing oxcarbazepine versus phenytoin. [18] It included a subgroup analysis in people with generalised epilepsy. The review found no significant difference between oxcarbazepine and phenytoin for time to first seizure in people with generalised epilepsy (HR >1 indicates a clinical advantage of oxcarbazepine; HR 0.90, 95% CI 0.54 to 1.51) or in achieving 6-month or 12-month remission (HR >1 indicates a clinical advantage for phenytoin; time to 6-month remission: HR 1.03, 95% CI 0.48 to 2.20; time to 12-month remission: HR 1.08, 95% CI 0.50 to 2.34). [18]

Phenytoin versus other antiepileptic drugs:
We found no systematic review or RCTs.

Harms:

For general information on adverse outcomes in pregnancy and effects of antiepileptic drugs on bone mineral density, see review on Epilepsy (partial). Antiepileptic drugs have also been associated with an increased risk of suicidal behaviour and ideation. [12]

Phenytoin versus placebo:
We found no RCTs.

Phenytoin versus sodium valproate:
The review found no significant difference between sodium valproate and phenytoin in time to treatment withdrawal in people with generalised epilepsy (HR >1 for an event more likely with phenytoin: HR 0.98, 95% CI 0.60 to 1.58). [17]

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Phenytoin versus carbamazepine:
See harms of carbamazepine, p 4 .

Phenytoin versus oxcarbazepine:
The review found no significant difference between oxcarbazepine and phenytoin for time to treatment withdrawal in people with generalised epilepsy (HR >1 indicates a clinical advantage for oxcarbazepine: HR 1.03, 95% CI 0.48 to 2.20). [18]

Phenytoin versus other antiepileptic drugs:
We found no RCTs.

Comment: Placebo-controlled trials of phenytoin would be considered unethical.

Phenytoin versus sodium valproate:
Although the systematic review found no difference between sodium valproate and phenytoin, the confidence interval is wide and this result does not establish equivalence of sodium valproate and phenytoin. [17] Also, the age distribution of people classified as having generalised epilepsy suggests errors in the classification of epilepsy type. Failure of the RCTs to document generalised seizures other than tonic clonic seizures is an important limitation. The review did not present results separately for adults and children. [17]

OPTION LAMOTRIGINE FOR GENERALISED EPILEPSY

Seizure frequency
Compared with carbamazepine We don't know whether lamotrigine is more effective than carbamazepine controlled release at increasing time to withdrawal (combined measure of efficacy and tolerability) in older people with epilepsy (very low-quality evidence).

Note
We found no direct information from RCTs about whether lamotrigine used as monotherapy in people with generalised epilepsy is better than no active treatment. However, there is consensus that lamotrigine reduces seizure rates.

For GRADE evaluation of interventions for epilepsy, see table, p 14 .

Benefits:

Lamotrigine versus placebo:
We found no systematic review or RCTs.

Lamotrigine versus carbamazepine:
We found one RCT (186 older people, aged at least 65 years, 55% male, at least 2 partial-onset or primary generalised tonic clonic seizures in the previous 6 months) comparing lamotrigine at a flexible dosing range 25 mg to 400 mg daily versus carbamazepine controlled release (CR) at a flexible dosing range of 100 mg to 800 mg over 40 weeks in people with newly diagnosed epilepsy. [19] The RCT did not report results on subgroup analyses according to seizure type or epilepsy type and did not specify how many people had generalised epilepsy. The RCT found no significant difference in time to withdrawal (combined measure of efficacy and tolerability) between lamotrigine and carbamazepine CR (184 people, absolute results shown graphically; HR [lamotrigine *v* carbamazepine] 0.77, 95% CI 0.45 to 1.31; P = 0.33; intention-to-treat analysis). [19]

Lamotrigine versus other antiepileptic drugs:
We found one large RCT comparing the effectiveness of sodium valproate, lamotrigine, and topiramate in the treatment of people with generalised epilepsy. [13] The RCT was open label and as such does not meet our inclusion criteria (see comment).

Harms:
For general information on adverse outcomes in pregnancy and effects of antiepileptic drugs on bone mineral density, see review on Epilepsy (partial). Antiepileptic drugs have also been associated with an increased risk of suicidal behaviour and ideation. [12]

Lamotrigine versus placebo:
We found no RCTs.

Lamotrigine versus carbamazepine:
The RCT found similar rates of treatment-emergent adverse effects in both groups (82/93 [88%] with lamotrigine *v* 79/92 [86%] with carbamazepine CR; statistical analysis not reported). It reported that central nervous system effects were the most common treatment-emergent adverse effect for both lamotrigine and carbamazepine (44/93 [47%] with lamotrigine *v* 45/92 [49%] with carbamazepine CR). The RCT found no significant difference between groups in withdrawals due to adverse effects (13/93 [14%] with lamotrigine *v* 23/92 [25%] with carbamazepine CR; P = 0.078). [19]

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Lamotrigine versus other antiepileptic drugs:
We found no RCTs.

Comment: Placebo-controlled trials of lamotrigine would now be considered unethical. There is a widespread consensus that lamotrigine has a broad-spectrum efficacy in both partial and generalised epilepsies in adults. However, we found no evidence from systematic reviews or RCTs to confirm the efficacy of lamotrigine in people with generalised epilepsy (tonic clonic type). We found one systematic review (search date 2009) comparing ethosuximide, sodium valproate, lamotrigine, or placebo in children or adolescents with absence seizures. The review identified one open-label RCT comparing lamotrigine versus sodium valproate as monotherapy, which did not meet *Clinical Evidence* inclusion criteria. [20] A subsequent RCT comparing ethosuximide, sodium valproate, or lamotrigine in children with newly diagnosed childhood absence epilepsy found that lamotrigine was significantly less effective than ethosuximide or sodium valproate at reducing treatment failure. See review on Absence seizures in children. [21]

We found one large RCT (716 people, 63% idiopathic generalised epilepsy, 27% unclassified epilepsy) of a pragmatic design comparing sodium valproate, lamotrigine, and topiramate in the treatment of people with generalised epilepsy. [13] The RCT was open label and as such does not meet our inclusion criteria; however, because of a paucity of data comparing newer antiepileptic drugs with each other, and the large size of the trial, we have reported the data here. For more details on study design and comparisons with sodium valproate, see comment on sodium valproate, p 3 . The RCT found no significant differences in time to treatment failure with lamotrigine compared with topiramate (HR >1 indicates that failure occurs more rapidly with topiramate; HR 1.25, 95% CI 0.96 to 1.64) and time to achieve 12-month remission between lamotrigine and topiramate (HR >1 indicates that 12-month remission occurs more rapidly with topiramate; HR 1.23, 95% CI 0.99 to 1.51).

Drug safety alert:
A drug safety alert has been issued on the risk of aseptic meningitis associated with lamotrigine. (www.fda.gov).

OPTION TOPIRAMATE FOR GENERALISED EPILEPSY

Note
We found no direct information from blinded RCTs about whether topiramate used as monotherapy in people with generalised epilepsy is better than no active treatment. However, there is consensus that topiramate reduces seizure rates.

For GRADE evaluation of interventions for epilepsy, see table, p 14 .

Benefits:

Topiramate versus placebo:
We found no systematic review or RCTs.

Topiramate versus other antiepileptic drugs:
We found one large RCT comparing the effectiveness of sodium valproate, lamotrigine, and topiramate in the treatment of people with generalised epilepsy. [13] The RCT was open label and as such does not meet our inclusion criteria (see comment).

Harms: For general information on adverse outcomes in pregnancy and effects of antiepileptic drugs on bone mineral density, see review on Epilepsy (partial). Antiepileptic drugs have also been associated with an increased risk of suicidal behaviour and ideation. [12]

Topiramate versus placebo:
We found no RCTs.

Topiramate versus other antiepileptic drugs:
We found no RCTs meeting *Clinical Evidence* inclusion criteria (see comment).

Comment: Placebo-controlled trials would now be considered unethical.

We found one large RCT (716 people, 63% idiopathic generalised epilepsy, 27% unclassified epilepsy) of a pragmatic design that compared sodium valproate, lamotrigine, and topiramate in people with generalised epilepsy. [13] The RCT was open label and as such does not meet our inclusion criteria; however, because of a paucity of data comparing standard antiepileptics versus newer antiepileptics, and the large size of the trial, we have reported the data here. For more details on study design and comparisons with sodium valproate, see comment on sodium valproate, p 3 . The RCT found that topiramate was poorly tolerated compared with sodium valproate in people

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with generalised epilepsies or seizures that are difficult to classify. For more details about the comparison with lamotrigine see comment on lamotrigine, p 7 . However, this RCT was insufficiently powered to provide relative efficacy for individual seizure types or sub-syndromes within the idiopathic epilepsies.

OPTION LEVETIRACETAM FOR GENERALISED EPILEPSY

Note
We found no direct information from RCTs about whether levetiracetam used as monotherapy in people with generalised epilepsy is better than no active treatment. However, there is consensus that levetiracetam reduces seizure rates.

For GRADE evaluation of interventions for epilepsy, see table, p 14 .

Benefits:

Levetiracetam versus placebo:
We found no systematic review or RCTs.

Levetiracetam versus other antiepileptic drugs:
We found no systematic review or RCTs.

Harms:

For general information on adverse outcomes in pregnancy and effects of antiepileptic drugs on bone mineral density, see review on Epilepsy (partial). Antiepileptic drugs have also been associated with an increased risk of suicidal behaviour and ideation. [12]

Levetiracetam versus placebo:
We found no RCTs.

Levetiracetam versus other antiepileptic drugs:
We found no RCTs.

Comment:

We found no RCTs in people with generalised epilepsy (tonic clonic type). One placebo-controlled RCT comparing levetiracetam versus placebo in childhood and juvenile absence epilepsy found no treatment advantage with levetiracetam over placebo during 2 weeks of treatment. [22] However, the study was of small sample size and the treatment period was of short duration. We will address this comparison in full in future updates (see review on Absence seizures in children). Further research is needed to assess the role of levetiracetam monotherapy in generalised epilepsies.

OPTION GABAPENTIN FOR GENERALISED EPILEPSY

Note
We found no direct information from RCTs about whether gabapentin used as monotherapy in people with generalised epilepsy is better than no active treatment. However, there is consensus that gabapentin reduces seizure rates.

For GRADE evaluation of interventions for epilepsy, see table, p 14 .

Benefits:

Gabapentin versus placebo:
We found no systematic review or RCTs.

Gabapentin versus other antiepileptic drugs:
We found no systematic review or RCTs.

Harms:

For general information on adverse outcomes in pregnancy and effects on bone mineral density of antiepileptic drugs, see review on Epilepsy (partial). Antiepileptic drugs have also been associated with an increased risk of suicidal behaviour and ideation. [12]

Gabapentin versus placebo:
We found no RCTs.

Gabapentin versus other antiepileptic drugs:
We found no RCTs.

Comment:

Placebo-controlled trials would now be considered unethical.

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QUESTION **What are the effects of additional treatments in people with drug-resistant generalised epilepsy?**

OPTION **ADDITION OF SECOND-LINE ANTIEPILEPTIC DRUGS (GENERALISED EPILEPSY)**

Seizure frequency

Adding lamotrigine compared with adding placebo Adding lamotrigine seems more effective at decreasing the frequency of generalised tonic clonic seizures and at increasing the proportion of people with a 50% or greater reduction in generalised seizures (moderate-quality evidence).

Adding levetiracetam compared with adding placebo Adding levetiracetam seems more effective at reducing seizure frequency at 16 and 24 weeks (moderate-quality evidence).

For GRADE evaluation of interventions for epilepsy, see table, p 14 .

Benefits:

Adding lamotrigine versus adding placebo:

We found one systematic review [23] and one subsequent RCT [24] comparing addition of lamotrigine versus addition of placebo in people who had not responded to usual drug treatment.

The systematic review (search date 2010, 2 RCTs, 143 people, aged 2–55 years, 51% men) compared the addition of lamotrigine versus placebo in people with generalised tonic clonic seizures with or without other generalised seizure types (e.g., absence or myoclonic seizures). The review did not pool the data due to differences in study design between the two RCTs (one was a crossover RCT and the other a parallel RCT). [23] The first RCT (crossover design, 26 people with absence, myoclonic, or generalised tonic clonic seizures or a combination of these [excluding Lennox–Gastaut epilepsy], aged 15–50 years [mean age 29 years], 42% male) compared adding lamotrigine (75 mg or 150 mg once daily) versus adding placebo to usual drug treatment (up to 4 drugs allowed including valproate [26 people], carbamazepine [11 people], clonazepam [5 people], phenytoin [3 people], ethosuximide [2 people], primidone [2 people]). [25] The RCT reported results after crossover and separately by seizure type. It found that, in people with generalised tonic clonic or absence seizures, adding lamotrigine significantly increased the proportion of people with a 50% or greater reduction in seizure rate (percentage reduction in seizure rate calculated from the individual seizure rate in the adjunctive-lamotrigine treatment phase compared with the seizure rate in the adjunctive placebo phase) after 12 weeks' treatment (proportion of people with at least a 50% reduction in seizure rate: generalised seizures: 7/14 [50%], P = 0.03; absence seizures: 5/15 [33%], P <0.001). It found that, in people with myoclonic seizures, lamotrigine did not reduce seizure rate by at least 50% compared with placebo; however, statistical analysis was not possible for this group owing to the small number of people (proportion of people with at least a 50% reduction in seizure rate: myoclonic seizures: 0/2 [0%], statistical assessment not reported). [25] The second RCT (parallel design, 121 people with primary generalised tonic clonic seizures, aged 2–55 years [mean age about 26 years], 53% men) compared adding lamotrigine (maximum 200–400 mg/day) versus adding placebo to usual drug treatment (up to 2 drugs allowed). [26] The RCT included a dose-escalation phase (lamotrigine dose titrated to target dose over 7 weeks for people aged 12 years or more, or over 12 weeks for children aged 2–12 years versus placebo), followed by a maintenance phase (target lamotrigine dose versus placebo for 12 weeks). It found that adding lamotrigine significantly increased the proportion of people with a 50% or greater reduction in primary generalised tonic clonic seizures over both phases (19 or 24 weeks) and over the maintenance phase only (12 weeks) (proportion of people with a 50% or greater reduction in primary generalised tonic clonic seizures over both dose-escalation and maintenance phases: 64% with lamotrigine *v* 39% with placebo; P <0.05; over maintenance phase only: 72% with lamotrigine *v* 49% with placebo; P <0.05; absolute numbers not reported; intention-to-treat analysis). A high proportion of people (34/121 [28%]) in the RCT did not complete the study; however, the RCT included data on all randomised people who received at least one dose of study medication (117 people) in its intention-to-treat analysis. [26]

The subsequent RCT (153 people with primary generalised tonic clonic seizures with or without other generalised seizure types, 3 or more seizures during 8-week baseline period, aged at least 13 years, 51% male) compared adding extended-release lamotrigine (200−500 mg/day) versus adding placebo to usual drug treatment (up to 2 drugs allowed). [24] It found that adding extended-release lamotrigine significantly decreased frequency of primary generalised tonic clonic seizures compared with placebo (median percentage reduction in weekly seizure frequency from baseline: 75% with lamotrigine *v* 32% with placebo; P <0.0001). The addition of extended-release lamotrigine also significantly increased the proportion of people experiencing a 50% or greater reduction in seizure frequency (70% with lamotrigine *v* 32% with placebo; P <0.0001; absolute results presented graphically). [24]

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Adding levetiracetam versus adding placebo:
We found two RCTs comparing addition of levetiracetam versus addition of placebo in people who had not responded to usual drug treatment. [27] [28]

The first RCT (164 people, aged 4–65 years [mean age 29 years], 44% male, at least 3 generalised tonic clonic seizures/8-week baseline period) compared adding levetiracetam versus adding placebo to usual treatment (1 or 2 antiepileptic drugs including valproate [86 people], lamotrigine [45 people], carbamazepine [31 people], topiramate [19 people], phenytoin [17 people]). It found that adding levetiracetam (1000–3000 mg/day in adults, 20–60 mg/kg/day in children) significantly reduced seizure frequency from baseline compared with placebo at 24 weeks (mean percentage reduction in generalised tonic clonic seizures/week from baseline: 57% with levetiracetam *v* 28% with placebo; difference 28%, 95% CI 9% to 48%; P = 0.004). The RCT also found that levetiracetam increased the proportion of responders (defined as at least a 50% reduction in seizure frequency per week from baseline) compared with placebo at 24 weeks (generalised tonic clonic seizures: 72% with levetiracetam *v* 45% with placebo for generalised tonic clonic seizures; P <0.001; all seizures: 60% with levetiracetam *v* 30% with placebo; P <0.001; absolute results not reported). [27]

The second RCT (122 people, aged 12–65 years, 36% male, at least 8 days of myoclonic seizures/8-week baseline) compared adjunctive levetiracetam at 3000 mg daily versus placebo for 16 weeks. The RCT found that adding levetiracetam to usual care significantly increased the proportion of 50% responders compared with adding placebo to usual care (proportion of people with at least a 50% reduction from baseline in the number of myoclonic seizure days/week: 35/60 [58%] with levetiracetam *v* 14/60 [23%] with placebo; OR 4.77, 95% CI 2.12 to 10.77; P <0.001; at least a 50% reduction from baseline in all seizure days/week: 34/60 [57%] with levetiracetam *v* 13/60 [22%] with placebo; OR 5.90, 95% CI 2.48 to 14.04; P <0.001). The RCT also found that levetiracetam increased the proportion of people seizure free compared with placebo (8/60 [13%] with levetiracetam *v* 0/60 [0%] with placebo; P = 0.006). [28]

Harms:

For general information on adverse outcomes in pregnancy and effects of antiepileptic drugs on bone mineral density, see review on Epilepsy (partial). Antiepileptic drugs have also been associated with an increased risk of suicidal behaviour and ideation. [12]

Adding lamotrigine versus adding placebo:
The first crossover RCT identified by the review [23] found higher rates of rash with adding lamotrigine compared with adding placebo to usual care (7/26 [27%] with lamotrigine *v* 0/26 [0%] with placebo; significance assessment not reported). [25] Two of these people withdrew from the study owing to rash with lamotrigine. The second parallel RCT, identified by the review, [23] did not report rash in either treatment group. [26] It found higher rates of dizziness, nausea, and somnolence with adding lamotrigine compared with adding placebo to usual care (dizziness: 5% with lamotrigine *v* 2% with placebo; nausea: 5% with lamotrigine *v* 3% with placebo; somnolence: 5% with lamotrigine *v* 2% with placebo; absolute results and significance assessment not reported).

The subsequent RCT found no significant difference between extended-release lamotrigine and placebo groups in the number of people with an adverse effect. Headache was the most common adverse effect reported in both treatment groups. No serious rashes were reported in either treatment group. Adverse effects led to withdrawal from the study in one person in the lamotrigine extended-release group and two people in the placebo group. [24]

Adding levetiracetam versus adding placebo:
The first RCT found similar rates of any adverse effect or drug-related adverse effects between groups (any adverse effect: 57/79 [72%] with levetiracetam *v* 57/84 [68%] with placebo; drug-related adverse effects: 31/79 [39%] with levetiracetam *v* 25/84 [30%] with placebo; significance assessment not reported). The most frequently reported adverse effects with levetiracetam were nasopharyngitis, headache, fatigue, dizziness, and diarrhoea. [27]

The second RCT found similar rates of treatment-emergent adverse effects in both groups (45/60 [75%] with levetiracetam *v* 40/60 [67%] with placebo; significance assessment not reported). The most frequently reported adverse effects with levetiracetam were headache, somnolence, neck pains, and pharyngitis. [28]

Comment:

Few RCTs have compared second-line drugs directly versus each other. The RCTs did not report outcomes separately for adults and children.

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QUESTION What are the effects of surgery in people with drug-resistant epilepsy?

OPTION HEMISPHERECTOMY FOR DRUG-RESISTANT EPILEPSY

We found no direct information from RCTs about hemispherectomy in people with drug-resistant epilepsy.

For GRADE evaluation of interventions for epilepsy, see table, p 14 .

Benefits: We found no systematic review or RCTs on the effects of hemispherectomy in people with drug-resistant generalised epilepsy.

Harms: We found no RCTs.

Comment: One systematic review of two non-randomised studies (169 people with intractable hemispheric epilepsy) found that long-term seizure freedom after hemispherectomy was 61% (95% CI 54% to 68%). [29]

GLOSSARY

Atonic seizure Momentary loss of limb muscle tone causing sudden falling to the ground or drooping of the head.

Absence seizure Previously known as "petit mal". Brief episodes of unconsciousness with vacant staring, sometimes with fluttering of the eyelids, as if "daydreaming". People with absence seizure do not fall to the ground and generally have a rapid recovery. The condition is rare in adults.

Hemispherectomy is a surgical procedure in which a large part of a cerebral hemisphere (diseased) is removed. This procedure has recently been modified so that one side of the brain (that is, one cerebral hemisphere) is disconnected from the rest of the brain. This is called "functional hemispherectomy".

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Tonic clonic seizure Also known as a convulsion or "grand mal" attack. The person will become stiff (tonic) and collapse, and have generalised jerking (clonic) movements. Breathing might stop and the bladder might empty. Generalised jerking movements lasting typically for a few minutes are followed by relaxation and deep unconsciousness, before the person slowly comes round. People are often tired and confused, and may remember nothing. Tonic clonic seizures may follow simple partial or complex partial seizures (see above), where they are classified as secondary generalised tonic clonic seizures. Tonic clonic seizures occurring without warning and in the context of generalised epilepsy are classified as generalised tonic clonic seizures.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Addition of second-line antiepileptics New evidence added. [23] [24] Categorisation unchanged (Beneficial).

Carbamazepine for generalised epilepsy New evidence added, which did not present a separate analysis in people with generalised epilepsy. [16] Categorisation unchanged (Likely to be beneficial by consensus).

Phenytoin for generalised epilepsy New evidence added, which did not present a separate analysis in people with generalised epilepsy. [16] Categorisation unchanged (Likely to be beneficial by consensus).

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TABLE **GRADE evaluation of interventions for Epilepsy (generalised)**

Important outcomes	**Seizure frequency, quality of life, adverse effects**								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of monotherapy in newly diagnosed generalised epilepsy (tonic clonic type)?									
4 (395) [14]	Seizure frequency	Carbamazepine *v* sodium valproate	4	−1	0	−1	0	Low	Quality point deducted for subgroup analysis. Directness point deducted for uncertainty about epilepsy classification
4 (157) [15]	Seizure frequency	Carbamazepine *v* phenobarbital	4	−2	0	0	0	Low	Quality points deducted for sparse data and subgroup analysis
5 (395) [17]	Seizure frequency	Phenytoin *v* sodium valproate	4	−1	0	0	0	Moderate	Quality point deducted for subgroup analysis
2 (147) [18]	Seizure frequency	Phenytoin *v* oxcarbazepine	4	−2	0	0	0	Low	Quality points deducted for sparse data and subgroup analysis
1 (186) [19]	Seizure frequency	Lamotrigine *v* carbamazepine	4	−1	0	−2	0	Very low	Quality point deducted for sparse data. Directness points deducted for uncertainty about epilepsy type and population restricted to older people
What are the effects of additional treatments in people with drug-resistant generalised epilepsy?									
3 (296) [24] [25] [26]	Seizure frequency	Adding lamotrigine *v* adding placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (286) [27] [28]	Seizure frequency	Adding levetiracetam *v* adding placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting in 1 RCT

Type of evidence: 4 = RCT; 2 = Observational.
Consistency: similarity of results across studies.
Directness: generalisability of population or outcomes.
Effect size: based on relative risk or odds ratio.

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