ClinicalEvidence

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 July 2009 (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 eight 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? . . . 9

What are the effects of surgery in people with drug-resistant generalised epilepsy? . . . 11

INTERVENTIONS

GENERALISED EPILEPSY: MONOTHERAPY

Likely to be beneficial

Carbamazepine for generalised epilepsy* . . . 3

Gabapentin for generalised epilepsy* New . . . 9

Lamotrigine for generalised epilepsy* . . . 7

Levetiracetam for generalised epilepsy* New . . . 9

Phenobarbital for generalised epilepsy* . . . 4

Phenytoin for generalised epilepsy* . . . 5

Sodium valproate for generalised epilepsy* . . . 6

Topiramate for generalised epilepsy* . . . 8

TREATING DRUG-RESISTANT GENERALISED EPILEPSY

Beneficial

Addition of second-line antiepileptics (in drug-resistant generalised epilepsy) New . . . 9

SURGERY IN PEOPLE WITH DRUG-RESISTANT EPILEPSY

Unknown effectiveness

Hemispherectomy for drug-resistant generalised epilepsy New . . . 11

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.

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 United States [3] and 7.5/1000 people in Australia. Prevalence rates in developing countries vary widely, with studies carried 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 annual incidence rates of epilepsy are 24 to 56/100,000 people in Europe, [2] 44/100,000 in the United States, [7] 63 to 158/100,000 people in sub-Saharan Africa, [4] 113 to 190/100,000 people in Latin America, [6] and 28.1 to 60/100,000 people in Asia. [5] 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; in people in remission, to withdraw antiepileptic drugs without causing seizure recurrence; 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 July 2009. The following databases were used to identify studies for this systematic review: Medline 1966 to July 2009, Embase 1980 to July 2009, and The Cochrane Database of Systematic Reviews 2009, Issue 2 (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). 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 pre-determined 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 more than 20 individuals of whom more than 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 US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. To aid readability of the numerical 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 ratio (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 (into 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 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 to 79 years, at least 47% men, follow-up less than 5 years). [12] 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 greater than 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 to 68 years, 157 with generalised epilepsy, at least 52% men) comparing carbamazepine versus phenobarbital. [13] Meta-analysis of the subgroup of people with generalised epilepsy found no significant difference 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 no systematic review or RCTs.

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

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. [14]

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 greater than 1 for an event more likely with sodium valproate; HR 0.89, 95% CI 0.62 to 1.29). [12]

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). [13]

Carbamazepine versus phenytoin:
We found no RCTs.

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. [12] 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. [12]

Carbamazepine versus phenobarbital:
The review did not present results separately for adults and children. [13]

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 3 .

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 [14]

Phenobarbital versus placebo:
We found no RCTs.

Phenobarbital versus carbamazepine:
See harms of carbamazepine, p 3 .

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. [15] 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). [15] 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 greater than 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 greater than 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 3 .

Phenytoin versus oxcarbazepine:
We found one systematic review (search date 2008, 2 RCTs, 480 people, 147 with generalised epilepsy) comparing oxcarbazepine versus phenytoin. 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 greater than 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 greater than 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). [16]

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 [14]

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 greater than 1 for an event more likely with phenytoin: HR 0.98, 95% CI 0.60 to 1.58). [15]

Phenytoin versus carbamazepine:
See harms of carbamazepine, p 3 .

Phenytoin versus oxcarbazepine:
The review found no significant difference between oxcarbazepine and phenytoin for time to treatment withdrawal in people with generalised epilepsy (HR greater than 1 indicates a clinical advantage for oxcarbazepine: HR 1.03, 95% CI 0.48 to 2.20). [16]

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. [15] 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. [15]

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 3 .

Sodium valproate versus phenytoin:
See benefits of phenytoin, p 5 .

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. [14]

Sodium valproate versus placebo:
We found no RCTs.

Sodium valproate versus carbamazepine:
See harms of carbamazepine, p 3 .

Sodium valproate versus phenytoin:
See harms of phenytoin, p 5 .

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. [17] The RCT was open label — to allow clinicians to determine

the rate of titration and dosing regime they thought best for each person — and as such does not meet our 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. The first date of randomisation in the RCT was 12 January 1999, 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 greater than 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 greater than 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 achieved12-month remission compared with lamotrigine (HR greater than 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 greater than 1 indicates that failure occurs more rapidly with topiramate; HR 1.93, 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. [17]

OPTION LAMOTRIGINE FOR GENERALISED EPILEPSY

Seizure frequency

Compared with carbamazepine controlled release We don't know whether lamotrigine 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 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 controlled release:
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 to 400 mg daily with carbamazepine controlled release (CR) at a flexible dosing range of 100 to 800 mg over 40 weeks in people with newly diagnosed epilepsy. 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). [18]

Lamotrigine versus other antiepileptic drugs:
We found one systematic review (search date 2007, 5 RCTs) comparing ethosuximide, sodium valproate, lamotrigine, or placebo. The review identified one open-label RCT comparing lamotrigine versus sodium valproate as monotherapy, which did not meet *Clinical Evidence* inclusion criteria. [19] We found one other large RCT comparing the effectiveness of sodium valproate, lamotrigine, and topiramate in the treatment of people with generalised epilepsy. [17] 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 [14]

Lamotrigine versus placebo:
We found no RCTs.

Lamotrigine versus carbamazepine controlled release:
The RCT found similar rates of treatment-emergent adverse effects in both groups (82/93 [88%] with lamotrigine *v* 79/92 [86%] with carbamazepine; 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 carba-

mazepine). The RCT found no significant difference in withdrawals due to adverse effects between groups (13/93 [14%] with lamotrigine *v* 23/92 [25%] with carbamazepine; P = 0.078). [18]

Lamotrigine versus other antiepileptic drugs:
We found no RCTs.
Drug safety alert:
A drug safety alert has been issued on the risk of aseptic meningitis associated with lamotrigine. (www.fda.gov)

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. Lamotrigine is also commonly used in childhood absence seizures despite of a lack of evidence for its efficacy.

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. [17] The RCT was open label and as such does not meet our inclusion criteria; however, because of a paucity of data comparing newer antiepileptics 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 6 . The RCT found no significant differences in time to treatment failure (HR greater than 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 greater than 1 indicates that 12-month remission occurs more rapidly with topiramate; HR 1.23, 95% CI 0.99 to 1.51).

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. [17] 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. [14]

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. [17] 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 6 . The RCT found that topiramate was poorly tolerated compared with sodium valproate in people with generalised epilepsies or seizures that are difficult to classify. For more details about the comparison with lamotrigine see comments on lamotrigine in the question covering treatment in generalised epilepsy. 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 New

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. [14]

Levetiracetam versus placebo:
We found no RCTs.

Levetiracetam versus other antiepileptic drugs:
We found no RCTs.

Comment:

Placebo-controlled trials would now be considered unethical.

OPTION GABAPENTIN FOR GENERALISED EPILEPSY New

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. [14]

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.

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

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

Seizure frequency
Adding lamotrigine compared with adding placebo Adding lamotrigine may be more effective at increasing the proportion of people with a 50% or greater reduction in generalised seizures or myoclonic seizures (low-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: We found three RCTs comparing the addition of active drugs versus placebo in people who had not responded to usual drug treatment. [20] [21] [22]

Lamotrigine versus placebo:
One crossover RCT (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 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]). 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 (% 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 less than 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). [20]

Levetiracetam versus placebo:
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 % 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 less than 0.001; all seizures: 60% with levetiracetam *v* 30% with placebo; P less than 0.001; absolute results not reported). [21]

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 less than 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 less than 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). [22]

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. [14]

Lamotrigine versus placebo:
The RCT 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). Two of these people withdrew from the study owing to rash with lamotrigine. [20]

Levetiracetam versus 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. [21]

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. [22]

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

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

OPTION HEMISPHERECTOMY FOR DRUG-RESISTANT GENERALISED EPILEPSY New

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%). [23]

GLOSSARY

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.

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

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.

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.

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

SUBSTANTIVE CHANGES

Levetiracetam New option added for which we found no RCTs satisfying *Clinical Evidence* inclusion criteria. Categorised as Likely to be beneficial, based on consensus.

Gabapentin New option added for which we no RCTs satisfying *Clinical Evidence* inclusion criteria. Categorised as Likely to be beneficial, based on consensus.

Addition of second-line antiepileptics (in drug-resistant generalised epilepsy) New option added for which we found three RCTs. [20] [21] [22] One RCT found that adding lamotrigine to usual drug treatment reduced seizures in people with generalised tonic clonic or absence seizures, compared with adding placebo to usual drug treatment. [20] Two RCTs found that adding levetiracetam to usual drug treatment reduced seizures in people with generalised epilepsy compared with adding placebo to usual drug treatment. [21] [22] Categorised as Beneficial.

Hemispherectomy New option added for which we found no systematic review or RCTs. Categorised as Unknown effectiveness.

Carbamazepine (generalised epilepsy) Two systematic reviews updated, search date updated, no new evidence included. [12] [13] Categorisation unchanged (Likely to be beneficial).

Lamotrigine One RCT added. [18] The RCT found no significant difference in time to withdrawal (combined measure of efficacy and tolerability) between carbamazepine controlled release and lamotrigine in older people with newly diagnosed epilepsy. Categorisation unchanged (Likely to be beneficial).

Phenytoin (generalised epilepsy) Two systematic reviews updated, search date updated, no new evidence included. [15] [16] Categorisation unchanged (Likely to be beneficial).

Sodium valproate (generalised epilepsy) Two systematic reviews updated, search date updated, no new evidence included. [12] [15] Categorisation unchanged (Likely to be beneficial).

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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) [12]	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) [13]	Seizure frequency	Carbamazepine *v* phenobarbital	4	−2	0	0	0	Low	Quality points deducted for sparse data and for subgroup analysis
5 (395) [15]	Seizure frequency	Phenytoin *v* sodium valproate	4	−1	0	0	0	Moderate	Quality point deducted for subgroup analysis
2 (147) [16]	Seizure frequency	Phenytoin *v* oxcarbazepine	4	−2	0	0	0	Low	Quality points deducted for sparse data and subgroup analysis
1 (186) [18]	Seizure frequency	Lamotrigine *v* carbamazepine controlled release	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?									
1 (26) [20]	Seizure frequency	Adding lamotrigine *v* adding placebo	4	−2	0	0	0	Low	Quality point deducted for sparse data and no pre-crossover results
2 (286) [21] [22]	Seizure frequency	Adding levetiracetam *v* adding placebo	4	−1	0	0	0	Moderate	Quality point deducted for incomplete reporting in one 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