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Appendices

Go to main text

The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review

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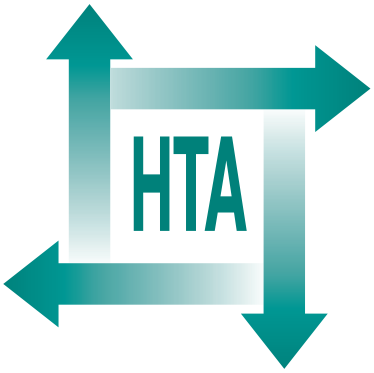

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Appendix 1

Details of intervention drugs

Details given in *Table 53* are taken in each case from the appropriate Summary of Products Characteristics.

TABLE 53 *Details of newer drugs for treatment of epilepsy*

Drug and launch date	Indications for treatment in the UK	Dosage	Documented side-effects and drug interactions	Cost (MIMS, January 2003)
Gabapentin (Neurontin®) Launched: May 1993 and licensed in children aged ≥6 years in November 1999	*Adults and children >12 years:* Add-on therapy for partial seizures with or without secondary generalisation not satisfactorily controlled with other AED(s) *Children 6–12 years:* Add-on therapy for partial seizures with or without secondary generalisation in patients not satisfactorily controlled with other AED(s), or who cannot tolerate other AED(s). A neurological specialist should initiate and supervise treatment	*Adults and children >12 years:* Titration according to manufacturer's guidance to maximum of 2400 mg/day, taken in three divided doses *Children 6–12 years:* Titration according to manufacturer's guidance to recommended dose of between 25 and 35 mg/kg/day	Adults: most common somnolence, dizziness, ataxia, fatigue. Also nystagmus, tremor, diplopia, amblyopia, dysarthria, amnesia, asthenia, paraesthesia, arthralgia, purpura, leucopenia, dyspepsia, anxiety, weight gain. Rare reports of pancreatitis, elevated LFTs, erythema multiforme, SJS Children (aged 3–12 years): most common emotional lability, nervousness, thinking abnormally. Also somnolence, fatigue, weight gain, hostility, dizziness, hyperkinesia, nausea/vomiting Patients taking gabapentin can experience mood and behavioural disturbances. Caution is recommended in patients with a history of psychotic illness Antacids can reduce the bioavailability of gabapentin. No interactions have been demonstrated between gabapentin and phenytoin, valproate, carbamazepine or phenobarbital Monitoring of gabapentin plasma concentrations is not required	Capsules: 100 mg £22.86 ×100 300 mg £53.00 ×100 400 mg £61.33 ×100 Tablets: 600 mg £106.00 ×100 800 mg £122.66 ×100

continued

TABLE 53 *Details of newer drugs for treatment of epilepsy (cont'd)*

Drug and launch date	Indications for treatment in the UK	Dosage	Documented side-effects and drug interactions	Cost (MIMS, January 2003)
Lamotrigine (Lamictal®) Launched: 1991	*Adults and children >12 years:* Monotherapy or add-on therapy of simple partial, complex partial, secondarily generalised and primary generalised tonic–clonic seizures	*Monotherapy:* Titration according to manufacturer's guidance until optimal response achieved. The usual maintenance dose is 100–200 mg/day. Up to 500 mg has been used *Add-on therapy:* Dose dependent on concomitant medication, with higher initial and maintenance doses used for patients also taking enzyme-inducing AEDs (e.g. phenytoin, carbamazepine). The usual maintenance dose is 100–200 mg/day in non-users of enzyme-inducing AEDs and 200–400 mg/day in users of enzyme-inducing AEDs	Include diplopia, blurred vision, conjunctivitis, dizziness, drowsiness, headache, tiredness, gastrointestinal disturbance, irritability/aggression, tremor, agitation, confusion, hallucinations Adverse skin reactions, generally within the first 8 weeks of lamotrigine treatment; most cases mild and self-limiting. Serious reactions, including SJS, toxic epidermal necrolysis and a hypersensitivity syndrome have been reported. The approximate incidence of rashes reported as SJS in adults and children >12 years old is 1 in 1000. The risk in children under 12 years old is greater than this. The overall risk of rash appears to be associated with high initial doses of lamotrigine, and concomitant use of valproate Haematological abnormalities (neutropenia, leucopenia, anaemia, thrombocytopenia, pancytopenia, aplastic anaemia granulocytosis), movements disorders and elevated LFTs have been reported Enzyme-inducing AEDs enhance the metabolism of lamotrigine, which may increase dosage requirements. Valproate reduces the metabolism of lamotrigine, increasing its half-life. There is no evidence that lamotrigine affects the pharmacokinetics of other AEDs	Tablets: 25 mg £21.95 ×56 50 mg £37.31 ×56 100 mg £64.37 ×56 200 mg £109.42 ×56 Dispersible/chewable tablets: 2 mg £9.37 ×30 5 mg £8.75 ×28 25 mg £21.95 ×56 100 mg £64.37 ×56
	Children 2–12 years: Add-on therapy for simple partial, complex partial, secondarily generalised and primary generalised tonic–clonic seizures Treatment of seizures associated with the Lennox–Gastaut syndrome	Dose dependent on concomitant medication, with higher initial and maintenance doses used for patients also taking enzyme-inducing AEDs (e.g. phenytoin, carbamazepine). The usual maintenance dose is 1–5 mg/kg/day in non-users of enzyme-inducing AEDs and 5–15 mg/kg/day in users of enzyme-inducing AEDs		

continued

TABLE 53 *Details of newer drugs for treatment of epilepsy (cont'd)*

Drug and launch date	Indications for treatment in the UK	Dosage	Documented side-effects and drug interactions	Cost (MIMS, January 2003)
Levetiracetam (Keppra®) Launched: November 2000	*Adults and adolescents >16 years:* Add-on therapy for partial-onset seizures with or without secondary generalisation	Titration according to manufacturer's guidance to 3 g/day (taken in two divided doses)	Adults: most common somnolence, asthenia, dizziness. Others include: headache, amnesia, ataxia, convulsion, tremor, depression, emotional lability, hostility, insomnia, nervousness, abnormal behaviour, aggression, anger, anxiety, confusion, hallucination, irritability, psychotic disorder No interactions have been demonstrated between levetiracetam and carbamazepine, gabapentin, lamotrigine, phenobarbital, phenytoin, primidone, valproate, digoxin or warfarin Plasma level monitoring of levetiracetam is not required	Tablets: 250 mg £29.70 ×60 500 mg £49.50 ×60 1000 mg £94.50 ×60
Oxcarbazepine (Trileptal®) Launched: March 2000	*Adults and children aged ≥6 years:* Monotherapy or add-on therapy for partial seizures with or without secondary generalised tonic–clonic seizures	Titration according to manufacturer's guidance. Therapeutic effects seen at doses of between 600 and 2400 mg/day	Common include fatigue, asthenia, dizziness, headache, somnolence, ataxia, emotional lability, nystagmus, tremor, impaired concentration, nausea, vomiting, constipation, diarrhoea, acne, alopecia, rash, diplopia, vision disorders, vertigo, hyponatraemia. Uncommon or rare effects include angioedema, leucopenia, increases in transaminases and/or alkaline phosphatase, hepatitis, SJS, systemic lupus erythematosus Approximately 25–30% of patients who have exhibited hypersensitivity reactions to carbamazepine may experience hypersensitivity reactions with oxcarbazepine Interactions: oxcarbazepine both inhibits and induces the activity of some of the cytochrome P450 enzymes in the liver, resulting in increases or decreases in the plasma levels of some AEDs and other drugs (e.g. it accelerates the metabolism of hormonal contraceptives) Plasma monitoring is not required to optimise oxcarbazepine therapy	Tablets: 150 mg £10.00 ×50 300 mg £20.00 ×50 600 mg £40.00 ×50

continued

TABLE 53 *Details of newer drugs for treatment of epilepsy (cont'd)*

Drug and launch date	Indications for treatment in the UK	Dosage	Documented side-effects and drug interactions	Cost (MIMS, January 2003)
Tiagabine (Gabitril®) Launched: September 1998	*Adults and children over 12 years:* Add-on therapy for partial seizures with or without secondary generalisation where control is not achieved by optimal doses of at least one other AED	Titration according to manufacturer's guidance to usual maintenance dose of 15–30 mg/day. Patients taking enzyme-inducing AEDs may require higher maintenance doses of 30–45 mg/day	Include dizziness, tiredness, nervousness, tremor, diarrhoea, concentration difficulties, depressed mood, emotional lability, slowness in speech. In patients with a history of serious behavioural problems, there is a risk of symptom recurrence during treatment with tiagabine Others (rare): spontaneous bruising, hallucination, delusion, visual field defects. If visual symptoms develop, referral to an ophthalmologist is recommended Enzyme-inducing AEDs enhance the metabolism of tiagabine. Tiagabine does not interact with phenytoin, carbamazepine, phenobarbital, warfarin, digoxin, theophylline, hormonal contraceptives. Tiagabine reduces the plasma concentration of valproate (not considered clinically significant)	Tablets: 5 mg £45.37 ×100 10 mg £90.74 ×100 15 mg £136.11 ×100
Topiramate (Topamax®) Launched: 1995	*Adults and children over 2 years:* Add-on therapy (where control is inadequate using conventional first-line AEDs) for partial seizures with or without secondarily generalisation; seizures associated with Lennox–Gastaut syndrome; and primary generalised tonic–clonic seizures	*Adults and children >16 years:* Titration to usual maintenance dose of 200–400 mg. *Children aged 2–16 years:* Titration to usual maintenance dose of 5–9 mg/kg/day	Adults: abdominal pain, ataxia, anorexia, asthenia, confusion, difficulty with concentration/attention and memory, diplopia and other CNS effects. Others include abnormal gait, aggressive reaction, apathy, cognitive problems Children: somnolence, anorexia, fatigue, insomnia, nervousness, personality disorder, and other CNS effects. Others include emotional lability, agitation, apathy, cognitive problems, psychomotor slowing, confusion, hallucination, depression and leucopenia Rare: nephrolithiasis, acute myopia with secondary angle-closure glaucoma Interactions with other AEDs: addition of topiramate to phenytoin may increase phenytoin plasma concentrations. Phenytoin and carbamazepine decrease plasma concentrations of topiramate. Topiramate increases the clearance of oestrogen in oral contraceptives so a high strength preparation should be used Plasma monitoring of topiramate is not required to optimise therapy	Tablets: 25 mg £22.02 ×60 50 mg £36.17 ×60 100 mg £64.80 ×60 200 mg £125.83 ×60 Sprinkle capsules: 15 mg £16.88 ×60 25 mg £25.32 ×60 50 mg £41.60 ×60

continued

TABLE 53 *Details of newer drugs for treatment of epilepsy (cont'd)*

Drug and launch date	Indications for treatment in the UK	Dosage	Documented side-effects and drug interactions	Cost (MIMS, January 2003)
Vigabatrin (Sabril®) Launched: 1989	Treatment in combination with other AEDs for patients with resistant partial epilepsy with or without secondary generalisation, where all other appropriate drug combinations have proved inadequate or have not been tolerated Monotherapy in the treatment of infantile spasms (West's syndrome) Vigabatrin should only be initiated by a specialist in epileptology, neurology or paediatric neurology, and follow-up should be arranged under supervision of one of these specialists	Adults: Titration according to manufacturer's guidance. Maximal efficacy seen in the 2–3 g/day range. *Children:* Starting dose is 40 mg/kg/day. Maintenance doses recommended in relation to body weight are: 10–15 kg: vigabatrin 0.5–1 g/day 15–30 kg: vigabatrin 1–1.5 g/day 30–50 kg: vigabatrin 1.5–3 g/day >50 kg: vigabatrin 2–3 g/day When used as monotherapy for infantile spasms (West's syndrome) the recommended starting dose is 50 mg/kg/day, which may be titrated over 1 week if necessary. Doses of up to 150 mg/kg/day have been used	Adults: CNS effects such as somnolence, fatigue, drowsiness and impaired concentration predominate Children: excitation or agitation is frequent Others include headache, weight gain, tremor, oedema, nausea, abdominal pain, blurred vision, diplopia, nystagmus. Rare: encephalopathic symptoms, angioedema, urticaria, optic neuritis, optic atrophy Visual field defects: reported in ~1 in 3 patients receiving vigabatrin. The degree of visual field restriction may be severe. Most cases have been asymptomatic – this effect can only be reliably detected by systematic perimetry, which is usually possibly only in patients with a developmental age of >9 years. In children aged ≥3 years, a specifically developed method based on field-specific visual evoked potentials is available from the manufacturer to test the presence of peripheral vision. This method has currently not been validated in the detection of vigabatrin attributed visual field defects Electroretinography may be useful but should be used only in children <3 years of age Available data suggest that visual field defects are irreversible even after discontinuation of vigabatrin, hence it should only be used after careful assessment of the balance of benefits and risk compared with alternatives. Use in patient with any pre-existing clinically significant visual field defect is not recommended Interactions: used with phenytoin, decreases in phenytoin plasma concentrations have been observed. No clinically significant interactions have been demonstrated with carbamazepine, phenobarbital or valproate Plasma monitoring: there is no correlation between plasma concentration and efficacy	Tablets: 500 mg £44.85 ×100 Powder sachets: 500 mg £24.33 ×50

CNS, central nervous system; LFT, liver function test; SJS, Stevens Johnson Syndrome.

Appendix 2

Treatment choices

Off-licence and off-label prescribing are far more common in paediatric than in adult practice. This is a consequence of the limitations of existing drug labelling whereby many drugs are not licensed for use in children or for children of certain ages. The indications for which drugs are licensed may also be narrower for children than for adults. Hence in order to access adequate therapeutic choices, paediatricians prescribe drugs off-label (drug not licensed for a child of that age, or for that indication, or in that formulation or at that dose) and more rarely off-licence (no UK licence exists). Off-label and off-licence prescribing are acceptable, within the limits of generally accepted good practice. An indication of what is considered good prescribing practice in paediatrics is given in the Royal College of Paediatrics and Child Health publication *Medicines for Children*, one aim of which is to "present current practice based on the authority of experts". Although ideally prescribing should be based upon high-quality research evidence, such evidence is often not available to support paediatric prescribing.

Medicines for Children provides some general guidance on good practice in prescribing AEDs. Monotherapy is preferred: "drugs should be used alone and in sequence", but treatment with two drugs can result in "significantly improved seizure control in 5–10% of children". The use of three AEDs is not generally acceptable. It also states that routine blood monitoring of AED levels is not justified, and haematological and biochemical monitoring should only be undertaken if clinically indicated.

The Royal College of Paediatrics and Child Health's formulary suggests the treatment choices shown in *Table 54* for the various seizure types and epilepsy syndromes and the licensed indications for the AEDs on the UK market are given in *Table 55*.

TABLE 54 *Treatment choices for children for various seizure types and epilepsy syndromes*[a]

Seizure type/epilepsy syndrome	First choice	Alternatives
Generalised	Sodium valproate	Gabapentin
Tonic–clonic (tonic and/or clonic)	Sodium valproate, carbamazepine	Lamotrigine, phenobarbitone, phenytoin, topiramate
Atonic (astatic)	Sodium valproate	Clobazam, lamotrigine, phenytoin, topiramate
Myoclonic	Sodium valproate	Clonazepam, lamotrigine
Absence	Sodium valproate	Clonazepam, ethosuximide, lamotrigine
Partial	Carbamazepine	Gabapentin, lamotrigine
Simplex/complex	Carbamazepine	Sodium valproate, topiramate, vigabatrin
Infantile spasms (West's syndrome)	Vigabatrin	Nitrazepam, prednisolone, hydrocortisone or ACTH, sodium valproate
Lennox–Gastaut	Sodium valproate	Carbamazepine, clobazam, lamotrigine, topiramate
Landau–Kleffner	Prednisolone	Clobazam, lamotrigine, sodium valproate, vigabatrin

[a] Recommended by the Royal College of Paediatrics and Child Health (*Medicines for Children*, London: Royal College of Paediatrics and Child Health; 1999).

TABLE 55 *Licensed indications for AEDs. Data taken from:* Medicines for Children. *London: Royal College of Paediatrics and Child Health; 1999*

Drug	Indication	Age group	Conditions attached	Posology	Dosage titration
Carbamazepine (Tegretol)	• Partial seizures • Generalised tonic–clonic			Usually 10–20 mg/kg/day in several divided doses	
		10–15 years		600–1000 mg in divided doses	• 100–200 mg initially • Increment slowly
		5–10 years		400–600 mg daily in divided doses	• 100–200 mg initially • Increment slowly
		1–5 years		200–400 mg daily in divided doses	• 100 mg initially • Increment slowly
Ethosuximide (Emeside)	• Absence seizures (petit mal) even when complicated with grand mal (generalised tonic–clonic seizures) • Myoclonic seizures	Children over 6 years		500–2000 mg daily	• 500 mg daily for 4–7 days • Increment of 250 mg daily every 5–7 days up to maximum of 2000 mg • Control usually in range 1000–1500 mg daily
Ethosuximide (Zarontin)	• Absence seizures (petit mal) • Absence seizures (petit mal) complicated with grand mal (generalised tonic–clonic seizures) and other forms of epilepsy. However, other AED needed in this case	Children over 6 years		500–2000 mg daily	• 500 mg daily for 4–7 days • Increment of 250 mg daily every 4–7 days up to maximum of 2000 mg
		Infants and children under 6 years		250 mg daily–20 mg/kg/day	• 250 mg daily • Small increments usually to 20 mg/kg/day
Gabapentin (Neurontin)	Add-on therapy for • Partial seizures • Partial seizures with secondary generalisation	Over 12 years	Patients who have not achieved satisfactory control with or who are intolerant to standard anticonvulsants used alone or in combination	900–1200 mg daily	• 300 mg on day 1 • 300 mg twice daily on day 2 • 300 mg three times daily on day 3 • Increment of 300 mg daily until optimum response up to a maximum of 2400 mg daily
		6–12 years	As for children over 12 years but only if risk–benefit is considered favourable. Drug should be initiated and supervised by a neurological specialist	25–35 mg/kg/day given in three divided doses	• 10 mg/kg/day on day 1 • 20 mg/kg/day on day 2 • 25–35 mg/kg/day on day 3 • Maintenance dose 900 mg/day for children weighing 26–36 kg • 1200 mg/day for children weighing 37–50kg

continued

TABLE 55 *Licensed indications for AEDs. Reproduced from* Medicines for Children. *London: Royal College of Paediatrics and Child Health; 1999 (cont'd)*

Drug	Indication	Age group	Conditions attached	Posology	Dosage titration
		Children under 6 years	Not recommended		
Lamotrigine (Lamictal)	Monotherapy of • Partial seizures • Partial seizures with secondary generalised tonic–clonic seizures • Primary generalised tonic–clonic seizures	Over 12 years	Not recommended as monotherapy for those aged under 12 years	Usually 100–200 mg/day as a once-daily dose or two divided doses	• 25 mg once daily for 2 weeks • 50 mg daily for 2 weeks • Increment of 50–100 mg every 1–2 weeks until optimum response up to 500 mg/day
	Add-on therapy of • Partial seizures • Partial seizures with secondary generalised tonic–clonic seizures • Primary generalised tonic–clonic seizures	Over 12 years		For patients on sodium valproate with or without other AED. Usually 100–200 mg daily as a single or two divided doses	• 25 mg once daily on alternate days for 2 weeks or 12.5 mg once daily every day • Increment of 25–50 mg every 1–2 weeks until optimum
		Over 12 years		For patients on enzyme-inducing AED with or without other AED except valproate. Usually 200–400 mg/day in two divided doses	• 50 mg once daily for 2 weeks • 50 mg twice daily for 2 weeks • Increment of up to 100 mg daily every 2–3 weeks until optimum up to a maximum of 700 mg/day
		2–12 years	Do not give if calculated dose is < 1 mg/day (see last column)	For patients on valproate with or without AED. Usual maintenance 1–5 mg/kg/day	• 0.15 mg/kg once daily for 2 weeks • 0.3 mg/day for weeks 3 and 4 • Increment of 0.3 mg/kg every 1–2 weeks until optimum to maximum of 5 mg/kg daily as one or two divided doses
		2–12 years		For patients on enzyme-inducing AED with or without other AED except valproate. Usual maintenance 5–15 mg/kg/day	• 0.6 mg/kg/day in two divided doses for 2 weeks • 1.2 mg/kg/day for 2 weeks • Maximum increment of 1.2 mg/kg every 1–2 weeks
Oxcarbazepine (Trileptal)	Monotherapy and adjunctive therapy of • Partial seizures • Partial seizures with secondary generalised tonic–clonic seizures	Recommended for use in children aged ≥ 6 years		8–10 mg/kg/day in two divided doses to maximum of 46 mg/kg/day	• 8–10 mg/kg/day in two divided doses • Increment of maximum of 10 mg/kg/day at weekly intervals to a maximum daily dose of 46 mg/kg/day

continued

TABLE 55 *Licensed indications for AEDs. Reproduced from* Medicines for Children. *London: Royal College of Paediatrics and Child Health; 1999 (cont'd)*

Drug	Indication	Age group	Conditions attached	Posology	Dosage titration
Phenytoin (Epanutin)	• Partial seizures • Tonic–clonic seizures • Combination	Infants and children		5 mg/kg/day in two divided doses to maximum of 300 mg daily	• 5 mg/kg/day • Increment to maximum of 300 mg daily
Primidone	• Partial (focal) seizures • Generalised (grand mal) myoclonic jerks	Children over 9 years		750–1500 mg usually in two divided doses	• 125 mg once daily in the evening • Increment by 125 mg daily every 3 days until 500 mg daily • Increment by 250 mg daily to maximum of 1.5 g total daily dose
		Children 6–9 years		750–1000 mg in two divided doses	• 125 mg once daily in the evening • Increment by 125 mg daily every 3 days until 500 mg daily • Increment by 125 mg to maximum of 1 g total daily dose
		Children 2–5 years		500–750 mg in two divided doses	• 125 mg once daily in the evening • Increment by 125 mg daily every 3 days until 500 mg daily • Increment by 125 mg to maximum of 750 mg total daily dose
		Children up to 2 years		250–500 mg in two divided doses	• 125 mg once daily in the evening • Increment by 125 mg daily every 3 days until 500 mg daily
Tiagabine	Add-on therapy of • Partial seizures • Partial seizures with secondary generalised seizures	Children over 12 years only	For patients not controlled by optimal doses of at least one other AED	10–45 mg/day	• First dose with breakfast and second dose with evening meal • 5 mg twice daily for week 1 • 5 mg morning and 10mg evening for week 2 • 10 mg morning and evening for week 3 • 15 mg morning and evening for week 4 • For patients taking enzyme-inducing AED usual maintenance is 30–45 mg/day with daily doses above 30 mg given in three divided doses • For patients not on enzyme-inducing AED, maintenance dose expected to be in the region of 30 mg/kg

continued

TABLE 55 *Licensed indications for AEDs. Reproduced from* Medicines for Children. *London: Royal College of Paediatrics and Child Health; 1999 (cont'd)*

Drug	Indication	Age group	Conditions attached	Posology	Dosage titration
		2–12 years		For patients on enzyme-inducing AED with or without other AED except valproate	• 0.6 mg/kg given as two divided doses for 2 weeks • 1.2 mg/kg for 2 weeks given as two divided doses • Increments of 1.2 mg/kg every 1–2 weeks until optimum to maximum of 15 mg/kg as two divided doses
		Under 2 years	Not recommended		
Topiramate	Add-on therapy of • Partial seizures • Partial seizures with secondary generalised seizures • Primary generalised tonic–clonic seizures • Seizures associated with Lennox–Gastaut syndrome	Over 16 years		200 mg/day minimum 200–400 mg/day in two divided doses	• 25 mg daily for 1 week • Increment of 25–50 mg at 1–2 weekly intervals in two divided doses until optimum to 800 mg/day
		2–16 years		5–9 mg/kg/day in two divided doses	• 25 mg nightly for the first week • Increment of 1–3 mg/kg/day in two divided doses at 1–2 weekly intervals (exceptionally up to 30 mg/kg/day)
Valproate (Convulex)	• Partial seizures • Generalised seizures	Children (undefined)		15–30 mg/kg/day in 2–4 divided doses	• 15 mg/kg/day • Increment of 5–10 mg/kg/day up to 30 mg/kg/day (slow increase) • Increase or decrease dose if concomitant AED used (no details given)
Valproate (Epilim Chrono)	• Partial seizures • Generalised seizures • Other epilepsy	Children over 20 kg		20–30 mg/kg/day	• 400 mg/day • Spaced increment usually to 20–30 mg/kg/day and maximum of 35 mg/kg/day
		Children under 20 kg			Formulation not recommended
Valproate (Epilim EC)	• Partial seizures • Generalised seizures • Other epilepsy	Children over 20 kg		400 mg/day to 35 mg/kg body weight	• 400 mg/day • Spaced increment usually to 20–30 mg/kg/day and maximum of 35 mg/kg/day

continued

TABLE 55 *Licensed indications for AEDs. Reproduced from* Medicines for Children. *London: Royal College of Paediatrics and Child Health; 1999 (cont'd)*

Drug	Indication	Age group	Conditions attached	Posology	Dosage titration
		Children under 20 kg		20 mg/kg/day	• 20 mg/kg/day • Increment in severe cases but plasma level monitoring is required • Above 40 mg/kg/day clinical and haematological parameters required
Valproate (Epilim Syrup)	As with Epilim EC				
Vigabatrin	• Partial seizures • Partial seizures with secondary generalisations	Children (age not defined)	Add-on when other appropriate combinations are inadequate or intolerable Monotherapy for infantile spasms (West's syndrome) • To be initiated by a specialist in epileptology, neurology or paediatric neurology • Follow-up by a specialist • Gradual withdrawal if ineffective	• Bodyweight 10–15 kg: 0.5–1 g/day • Bodyweight 15–30 kg: 1–1.5 g/day • Bodyweight 30–50 kg: 1.5–3 g/day • Bodyweight >50 kg: 2–3 g/day • Upper dose not to be exceeded	• 40 mg/kg/day initially
		Infants (age not defined)	Monotherapy for infantile spasms (West's syndrome) • To be initiated by a specialist in epileptology, neurology or paediatric neurology • Follow-up by a specialist • Gradual withdrawal if ineffective	50–150 mg/kg/day	• 50 mg/kg/day • Increment over a period of 1 week up to 150 mg/kg/day

Appendix 3

Influential factors for adverse effects of AEDs in children

Factors (*Table 56*) contributing to children having different adverse effect profiles to adults include the following:

1. During the neonatal and infantile periods, maturation of the gastrointestinal system is still highly active, leading to substantial changes in gastrointestinal pH, gastric emptying, enzymic activity and intestinal flora.[235–237] From a theoretical perspective, it is to be expected that the pharmacokinetic profile of drugs would be highly variable and different from that of adults in this developmental period. This may explain the reported erratic absorption of phenytoin and phenobarbitone in the neonates.[238] Unfortunately, given the increasing difficulty in undertaking clinical studies in infancy, there have been few recent studies on the subject.
2. Changes in body fat ratio will also alter the distribution of the various AEDs due to changes in volume of distribution. Lipophilic drugs would be expected to have a lower volume of distribution in neonates than in adults and older children owing to the higher total body water to total body fat ratio in the younger subjects. However as infants also have lower albumin levels than older subjects, other factors such as extent of protein binding will alter the apparent volume of distribution, making predictions difficult. For example, phenytoin and valproic acid are highly protein bound. Therefore, clinical experience and close monitoring are necessary, particularly with the newer AEDs.
3. Changes in renal function.
4. Changes in hepatic metabolic activity.

Renal function reaches that of adults by 2–3 years of age but is only about one-quarter at birth and 50–75% at 6 months of age. The extents of renal elimination of AEDs are shown in *Figure 11*.

The differences in metabolic and pharmacokinetic profiles of the newer AEDs are often promoted as justification for preferring the newer agents over the older AEDs since efficacy may be similar. Although some of the newer agents have a lower propensity for drug–drug interactions, have linear pharmacokinetics and are less reliant on a single clearance pathway, the extent to which these translate into clear clinical benefits is debatable (see Appendix 5 for interactions with oral contraceptives). For example, gabapentin is essentially completely eliminated renally and is therefore not susceptible to hepatic enzyme induction or inhibition interactions. This is often perceived to be an advantage. However, it has also been suggested[239] that drugs which are less reliant on a single route of clearance (hepatic or renal) may be preferable to those that are eliminated by one route only (e.g. oxcarbazepine versus carbamazepine). This argument is only valid in the presence of one organ dysfunction, most notably renal impairment. Despite the debate, less reliance on hepatic elimination is generally an advantage, particularly when inducible metabolic enzymes are involved.

TABLE 56 *Putative factors for altered pharmacokinetics of AEDs in infancy and childhood*

Factor	Neonates/infants	Children
Renal elimination	Lower[a]	Same[a]
Metabolic activity		
Cytochrome P monooxygenase	Lower	Higher[a]
Uridine diphosphate glucuronyltransferase	Lower	Same
Albumin levels and protein binding	Lower	Same

[a] Activity or concentration levels relative to adults.

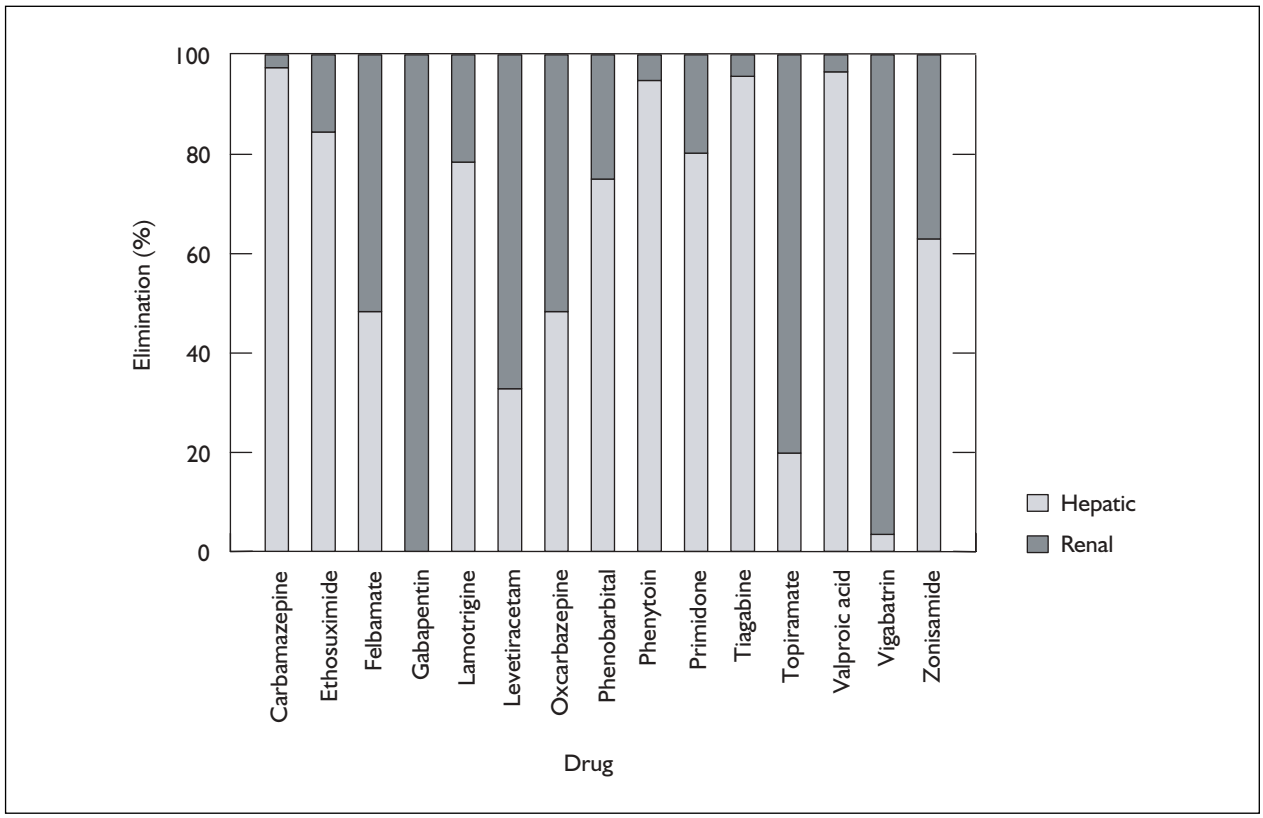

FIGURE 11 *Relative percentage renal and hepatic elimination of AEDs*

The complexity of the likely drug–drug interactions between AEDs is shown in the interaction matrix in *Table 57*. This indicates that it may often be more profitable to consider the drug interaction profile rather than any single drug–drug interaction.

TABLE 57 *Matrix showing interactions between AEDs*[a]

	Drug 1											
Drug 2	**Carbamazepine**	**Gabapentin**	**Lamotrigine**	**Levetiracetam**	**Oxcarbazepine**	**Phenobarbitone**	**Phenytoin**	**Primidone**	**Tiagabine**	**Topiramate**	**Valproic acid**	**Vigabatrin**
Carbamazepine		O	P0, S↑, E(1)	ϕ(2)(1)	⊟(M), (2)	⊟(2)	⊟(2) ?	⊟(2)	NCS(2), E(1)	NCS(2), ⊟(1)	⊟(2)?, A(2)	NCS(2)
Gabapentin	O		P0(2)	ϕ(2)(1)		O	O	O			A(2)	
Lamotrigine	P0, S↑, E(2)	P0(1)		ϕ(2)(1), P0(1)	P0(1)	E(2), P0(1)	E(2)P0(1), ↓(2)	E(2), P0(1)	P0(1)	P0(1)	A(2), P0(1)	P0(1)
Levetiracetam	ϕ(2)(1)	ϕ(2)(1)	ϕ(2)(1), P0(2)			ϕ(2)(1)	ϕ(2)(1)	ϕ(2)(1)			ϕ(2)(1), A(2)	
Oxcarbazepine	⊟(M), (1)		P0(2)			⊞(1), ◫(M)	⊞(1), ⊟(M)				ϕ(1), ⊟(M), A(2)	
Phenobarbitone	⊟(1)	O	E(1), P0(2)	ϕ(2)(1)	⊞(2), ⊟(M)		?		NCS(2), E(1)	NCS(2)	A(2)	NCS(2)
Phenytoin	⊟(1) ?	O	E(1) P0(2), ↓(1)	ϕ(2)(1)	⊞(2), ⊟(M)	?		A(2)	NCS(2), E(1)	NCS(2)[b], ⊟(1)	?, A(2)	⊟(1)(2), ?
Primidone	⊟(1)	O	E(1), P0(2)	ϕ(2)(1)			A(1)		E(1)	NCS(2)	A(2)	
Tiagabine	NCS(1), E(2)		P0(2)			NCS(1), E(2)	NCS(1), E(2)	E(2)			A(2)	NCS(1)
Topiramate	NCS(1), ⊟(2)		P0(2)			NCS(1)	NCS(1)[b], ⊟(2)	NCS(1)			NCS(2) (1)	
Valproic acid	⊟(1)?, A(1)	O	P0(2), A(1)	ϕ(2)(1), A(1)	ϕ(2), ⊟(M), A(1)	A(1)	?, A(1)	A(1)	A(1)	NCS(2) (1)		A(1)
Vigabatrin	NCS(1)		P0(2)			NCS(1)	⊟(1)(2), ?		NCS(2)		A(2)	

[a] ϕ, No effect on the drug shown in parentheses; O, no interaction found to date; ⊞, increases the plasma concentration of the antiepileptic shown in parentheses; ⊟, decreases the plasma concentration of the antiepileptic shown in parentheses; A, pharmacodynamic effect of the drug is altered, so clinical observation is recommended; Cl↑, increases the clearance of the drug shown in parentheses; Cl↓, decreases the clearance of the drug shown in parentheses; E, increases the metabolism of drug shown; M, the monohydroxy derivative of oxcarbazepine, the pharmacologically active metabolite; NCS, any interaction likely to be not clinically significant; P, protein binding sites; P0, no effect on protein binding site; Pc, competes for protein binding site; S↑, side-effect of drug enhanced; ?, significance and direction of reported interaction unclear, more work needed; ↑, effect enhanced; ↓, effect inhibited.

[b] Some patients may show increased plasma concentrations of phenytoin; monitoring of phenytoin levels advised.

Appendix 4

Long-term adverse effects

While short-term adverse events of moderate frequency are generally adequately captured by short-term clinical trials, the rarer and/or longer term adverse effects are not. Adverse effects, which may be cumulative and which have been suggested for some AEDs, are considered below with particular reference to paediatric patients.

Effect on body weight, mineral bone density and growth

All three of these potential long-term adverse effects of AED are of particular importance in the pharmacotherapy of children. Valproate[240] and gabapentin[241] appear the most prone to induce weight gain, which can be marked and progressive. Carbamazepine may also be associated with some weight gain, while lamotrigine and phenytoin appear to have no effect.[242] Topiramate, on the other hand, may reduce food intake and cause weight loss.[243] Marked weight gain may lead to obesity and marked weight loss to impaired growth. Adolescent girls in particular may consider such events sufficiently detrimental to become non-compliant with therapy.

Long-term use of phenytoin, phenobarbital and primidone have been associated with decreased bone density. A suggested mechanism is that via potent induction of hepatic metabolic enzymes they increase the breakdown of vitamin D and hence interfere with bone mineralisation. From this it has been assumed that AEDs which do not induce the cytochrome P450 system would be free from this adverse effect. A recent study has shown that this inference is flawed.[244] In that study comparing valproate monotherapy with phenytoin monotherapy and control subjects matched for age and sex, bone mineral density decreased by 13% in the valproate group and 13% in the phenytoin group compared with the control group. In a substantial number of patients the demineralisation was marked enough for the subjects to be classified as having osteoporosis. Elevation of serum calcium level and suppression of formation of 1,25-dihydroxy-vitamin D through a negative feedback loop has been suggested. However, more recent work points to a direct effect of the AED on bone cells.[245] Unlike phenytoin, valproate has no significant hepatic enzyme inducer activity. Some case reports suggest these effects may result in an increased likelihood of bone fracture but confirmation through controlled studies is clearly needed.[236,246]

Whether AED effects on body weight and bone mineral density alter growth in children has not been explored in detail. However, one observational study[247] of 103 children over 6–71 months suggests that lamotrigine does not interfere with growth, an observation consistent with its lack of effect on weight. Longer term comparative studies are necessary to confirm this. Similar studies on topiramate and felbamate, AEDs most frequently associated with weight loss, are required.

Cognitive effects

A substantial literature has accumulated on this topic largely characterised by inconclusive or contradictory observations contingent upon methodological difficulties and pitfalls associated with this line of enquiry.[248] Although certain AEDs appear to be involved more than others as a cause of cognitive impairment, it is probable that no single drug causes impairment in every patient and that no drug can be assumed never to impair. Subgroups of patients at higher risk cannot be defined.

Phenobarbitone, primidone and topiramate are generally perceived as having more detrimental cognitive effects than the other AEDs in common use.[239] Carbamazepine, phenytoin, sodium valproate (valproic acid) and zonisamide fall in an intermediate group in this respect whereas gabapentin, lamotrigine, tiagabine, levetiracetam, vigabatrin and oxcarbazepine are regarded as having little or no effect (*Table 58*). However, the evidence base is of low quality and controlled studies have generally been short-term (for up to 12 weeks) so that longer term effects have not been reliably probed. Despite case reports of impairment of memory and concentration, placebo-controlled studies using batteries of cognitive tests and tests of mood and adjustment

TABLE 58 *Potential for adverse cognitive effects of commonly used anti-epileptic drugs*

Marked	Some	Little or none
Phenobarbitone	Carbamazepine	Gabapentin
Primidone	Phenytoin	Lamotrigine
Topiramate	Valproic acid	Levetiracetam
	Zonisamide	Oxcarbazepine
		Tiagabine
		Vigabatrin

have failed to show any adverse effects for vigabatrin and tiagabine;[161,249] whether the newer AEDs are associated with adverse cognitive effects in the longer term remains to be answered through controlled studies.

Fatal adverse drug reactions

Reported fatal adverse drug reactions to AEDs are rare, and are unlikely to occur with a short-term clinical trial. Anticonvulsants, however, were associated with 65 out of 390 suspected fatal adverse drug reactions reported via the UK Committee on Safety of Medicines Yellow Card Scheme between 1964 and 2000.[250] Anticonvulsants were the class of drugs most often associated with fatalities. Although there is probably under-reporting, association of a drug does not necessarily indicate a causal link. Equally adverse drug reactions are under-reported, so fatalities related to anticonvulsants may have been underestimated. It is notable that almost one-third of the fatalities, 20 deaths, were associated with newer drugs, despite the shorter duration of use. Valproate was associated with 31 deaths, including 21 with liver failure. Some of these were in young children in whom caution in prescribing valproate is advised, hence lower rates of hepatoxicity might be expected in future. As the authors suggest, prospective studies of both older and newer AEDs are required.

Antiepileptic drugs and polycystic ovarian syndrome

The polycystic ovarian syndrome is characterised by enlarged ovaries with multiple follicular cysts. Patients with the syndrome present with chronic anovulatory cycles and symptoms of hyperandrogenesis, notably hirsutism, acne and menstrual irregularities. Associated endocrine and metabolic effects include elevation of the ratio of levels of luteinising hormone to follicle stimulating hormone, insulin resistance, abnormal lipid profiles and obesity. Valproate therapy has been reported to increase the rate of occurrence of the polycystic ovarian syndrome,[251] which is already substantially higher than in the non-epileptic population.[252] Other antiepileptic drugs do not seem to be associated with any substantial risk of the syndrome. In fact it has been reported that switching from valproate to lamotrigine therapy led to reversal of features of the syndrome.[253]

Appendix 5

Drug interactions with the contraceptive pill

One potential adverse effect of AEDs is upon the metabolism of contraceptive steroids leading to potential loss of contraceptive cover with oral contraceptives and implants. A prospective Northern England population-based study of a cohort of 400 women with epilepsy taking AEDs attributed failure of oral contraception as the cause of unplanned pregnancy found at a rate of >50% among 300 women responding to interview.[254]

Many of the AEDs are potent inducers of liver enzymes also involved in the metabolism and clearance of oral contraceptive steroids. For example, it has been shown that phenytoin and carbamazepine can reduce the area under the blood level curve of ethinylestradiol and levonorgestrel by as much as half.[255,256] The cytochrome monooxygenase isoenzymes, in particular the CYP3A family, are usually involved.[257] As the levels of the steroids drop, contraceptive cover is impaired.

It has been often assumed that for AEDs with less important hepatic metabolism and enzyme induction, the risk of interaction with contraception is lowered. However, the apparently clear hepatic mechanism of interaction between some AEDs and oral or implanted steroid contraceptive failure does not necessarily infer lack of interaction from AEDs that do not induce liver enzymes. For oxcarbazepine (structurally similar to carbamazepine[258]), the hepatic route of elimination is proportionately less than for carbamazepine (*Figure 11*) and it has apparently little effect on the cytochrome enzymes, including CYP3A and does not undergo metabolic autoinduction. This altered metabolic profile relative to carbamazepine leads to more stable pharmacokinetics and less susceptibility of its own metabolism to other enzyme inducers such as erythromycin[259] and verapamil,[260] but this is not translated into a lack of interaction with the contraceptive steroids. Indeed, recent studies suggest that oxcarbazepine reduces the plasma concentrations of both the oestrogen and progestogen component of oral contraceptive steroids sufficiently to lead to contraceptive failure.[261] The mechanism of this interaction remains to be confirmed.

Liver metabolism accounts for only about 20% of topiramate's clearance, which is predominantly renal (*Figure 11*). However, it has been shown to interfere with the metabolism of oral contraceptive steroids sufficiently to suggest a risk of contraceptive failure. Serum levels of the steroids may drop by one-fifth to one-third.[262] Again the mechanism of interaction is unclear as enzyme induction appears to be an insufficient explanation.[263]

Current summaries of product characteristics suggest that of the newer AEDs, oxcarbazepine and topiramate may reduce the efficacy of the contraceptive pill.

Some of the newer AEDs are less prone to this interaction with contraceptive agents. Indeed, there is positive evidence to suggest that gabapentin, lamotrigine, sodium valproate and tiagabine are free from it and therefore may have an advantage, at least in this respect, over AEDs that are not.

Evidence in support of absence or presence of an interaction is presented in *Table 59*.

Strategies, suggested in the literature, for dealing with this potential problem are (a) a switch to an AED which does not interfere with the contraceptive agent being used and (b) use of oral contraceptive agents with a higher estradiol content (to 50 μg or even higher if breakthrough bleeding still occurs). The optimal option would need to take account of the family history of the subject and whether the patient is stabilised on the AED or contraceptive agent at the time when co-administration is considered.

TABLE 59 *Interaction of AEDs and oral contraceptives with potential loss of contraceptive cover*

Likelihood	Antiepileptic	References (first author and year)
Evidence suggesting likely to	Carbamazepine	Crawford (1990)[256]
	Phenobarbitone	
	Phenytoin	Odlind (1986),[264] Haukkamaa (1986);[265] Orme (1990)[255]
	Primidone	
	Oxcarbazepine	Fattore (1999)[261]
	Topiramate	Doose (1994);[262] Rosenfeld (1997)[263]
Evidence uncertain	Ethosuximide	
	Felbamate	
Positive evidence against any interaction	Gabapentin	Eldon (1993, 1998)[266,267]
	Lamotrigine	Holdich (1991)[268]
	Sodium valproate	Crawford (1985)[269]
	Tiagabine	Mengel (1994)[270]
	Vigabatrin	Bartoli (1997)[271]

Appendix 6

Teratogenicity

Epileptic women are more likely to give birth to children with congenital malformations. For example, in a North of England prospective study of epileptic women taking AEDs, malformations were reported significantly more common at 5% (95% CI 3.1 to 7.6%) than among the local population (odds ratio 2.15).[254] Moreover it is generally accepted that the use of AEDs may increase this risk.[272] Despite this increased risk, the incidence of congenital abnormalities is still low, although well-controlled studies of sufficient power to give precise risk data have not been undertaken for both ethical and pragmatic reasons. It is not surprising that there is no clear information on which of the newer AEDs, if any, is safer for use during pregnancy.

Current evidence about the teratogenicity of the older and newer AEDs is largely derived from preclinical animal studies and experience of clinical use and observational studies. Valproate is associated with a twofold increased risk of spina bifida (*Table 60*). AEDs that render folate deficiency either through inhibition of dihydrofolate reductase or through an induced increase in utilisation of the vitamin are often assumed to be teratogenic. Phenytoin, primidone, carbamazepine and phenobarbitone are the more potent metabolic enzyme inducers and folate supplementation is thought to reduce the risk of abnormalities from the use of these, but the evidence is not conclusive. Folate supplementation may lead to a reduction in the levels of some of the AEDs, most notably phenytoin, with potential loss of seizure control.[273]

Studies on the teratogenic potential of the newer AEDs are sparse and generally involve small numbers of subjects. In one study three of 46 newborns exposed *in utero* to lamotrigine developed serious congenital abnormalities[274] and in a second report two of 37 mothers exposed to the drug delivered babies with abnormalities. One case report describes minor multiple abnormalities in the newborn of a mother receiving topiramate monotherapy.[275] Growth deficiency and hirsutism were noted. Because oxcarbazepine, unlike carbamazepine, does not interfere with folate metabolism and is not metabolised to the 10, 11-epoxide, it is sometimes assumed that it is less likely to be teratogenic. This inference is unsafe and serious malformations have been reported although a follow-up of 947 patients suggests that the risk is small.[276]

Vigabatrin is unique among the AEDs in being associated with a high incidence of visual field defects in long-term users. The adverse effect can be disabling and as many as one-third of those on the drug may be affected. Although the effect of *in utero* exposure is unclear, the results of studies on albino rabbits suggest that retino-toxicity may be a problem. One case report describes multiple congenital abnormalities, including anophthalmia, following exposure to vigabatrin, carbamazepine and dexamethasone during pregnancy.[277]

Table 60 summarises relevant information about the risk of teratogenicity and foetotoxicity of current AEDs.

The British Epilepsy Association has produced information for women about epilepsy and pregnancy.[286]

TABLE 60 *Teratogenicity of AEDs*

Drug	Preclinical and animal data	Observational studies, including case reports	Effect on folate metabolism and activity
Gabapentin	Foetotoxic in rodents. Delayed ossification.[278] SPC suggests otherwise		
Lamotrigine	Animal studies do not suggest any teratogenic effects (SPC)	Several reports suggest some risk of abnormalities to foetuses exposed to the drug.[274,279,280]	Weak inhibitor of dihydrofolate reductase.[281]
Oxcarbazepine	Animal studies suggest a lower potential for teratogenicity. However, embryo mortality, delayed growth and malformations reported	Serious birth defects, including cleft palate, possible (SPC)	Does not interfere with folate metabolism.[282]
Phenytoin		Reports of increased incidence of congenital malformations including cleft lip/palate and heart malformations. Foetal growth retardation and mental deficiency reported (SPC)	Enzyme induction leads to increased folate requirement and deficiency
Primidone		Possible increase incidence of congenital malformations (SPC)	Enzyme induction leads to increased folate requirement and deficiency
Tiagabine	No evidence of teratogenicity in animals (SPC). However, there is some evidence of peri- and postnatal toxicity (SPC)	Of 27 women exposed to tiagabine during pregnancy, nine gave birth to live babies with only one anomaly (hip dislocation), most likely not linked to the drug. Four had spontaneous miscarriages.[283]	
Topiramate	Teratogenic in mice, rats and rabbits. Right-sided digit abnormalities in rats and rib and vertebral malformations in rabbits.[284]	Case report of multiple minor abnormalities.[275] Hypospadias (abnormal siting of urethra) in male infants reported (SPC)	
Valproic acid		Increased incidence of congenital malformations reported (SPC). Reported associated with 2-fold increased risk of spina bifida.[285]	
Vigabatrin	No teratogenicity seen in rats or rabbits but incidence of cleft palate increased in rabbits (SPC). Retinotoxicity is a possibility	Increased incidence of abnormalities reported (SPC)	No significant effect on folate metabolism

SPC, summary of product characteristics.

Appendix 7

Search strategies

Effectiveness search strategies

Source Cochrane Library (CCTR) 2002, Issue 1

(((LABILENO or LAMICTAL) or LAMOTRIGINE) or LTG)
(LAMICITIN or DICHLOROPHENYLTRIAZINEDIYLDIAMINE)
EPILEP*
EPILEPSY*:ME
SEIZURE*
SEIZURES*:ME
CONVULSION*
(#1 or #2)
((((#3 or #4) or #5) or #6) or #7)
(#8 and #9)
(((GABAPENTIN or GBP) or NEURONTIN) or NEUROTONIN)
(#9 and #11)
((LEVETIRACETAM or ETIRACETAM) or KEPPRA)
(#9 and #13)
((OXCARBAZEPINE or TRILEPTAL) or OXOCARBAZEPINE)
(#9 and #15)
((TIAGABINE or GABITRIL) or TIABEX)
(#9 and #17)
(((TOPIRAMATE or EPITOMAX) or TOPAMAX) or TOPIMAX)
(#9 and #19)
((VIGABATRIN or SABRIL) or SABRILEX)
(#9 and #21)
(BW 430C)
BW-430C
(((((((#10 or #12) or #14) or #16) or #18) or #20) or #22)

Source MEDLINE (Ovid) 1966–October 2001

1 randomized controlled trial.pt. (33379)
2 controlled clinical trial.pt. (6309)
3 randomized controlled trials/ (8400)
4 random allocation/ (5181)
5 double blind method/ (12409)
6 single blind method/ (2078)
7 or/1-6 (54307)
8 (animal not human).sh. (263556)
9 7 not 8 (50867)
10 clinical trial.pt. (67258)
11 exp clinical trials/ (21222)
12 (clin$ adj25 trial$).ti,ab. (21031)
13 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (11868)
14 placebos/ (2187)
15 placebo$.ti,ab. (14464)
16 random$.ti,ab. (58660)
17 research design/ (6838)
18 or/10-17 (130936)
19 18 not 8 (122599)
20 19 not 9 (73326)
21 9 or 20 (124193)
22 lamotrigine.mp. (503)
23 (labileno or lamictal or ltg).mp. [mp=title, abstract, registry number word, mesh subject heading] (113)
24 bw 430c.tw. (0)
25 bw 430 c.tw. (0)
26 bw 430c78.tw. (0)
27 84057-84-1.rn. (369)
28 or/22-27 (512)
29 exp epilepsy/ (9541)
30 epilep$.ti,ab. (7616)
31 seizure$.ti,ab. (7702)
32 convuls$.ti,ab. (1592)
33 or/29-32 (13421)
34 33 and 28 and 21 (100)
35 gabapentin.mp. (514)
36 goe 3450.tw. (1)
37 go 3450.tw. (0)
38 ci 945.tw. (7)
39 1 aminomethyl cyclohexaneacetic acid.tw. (6)
40 (neurontin or neurotonin or gbp).tw. (146)
41 "60142-96-3".rn. (392)
42 or/35-41 (585)
43 42 and 21 and 33 (67)
44 etiracetam.mp. (38)
45 1 1 carbamoylpropyl 2 pyrrolidinone.tw. (0)
46 alpha ethyl 2 oxo 1 pyrrolidineacetamide.tw. (0)
47 (etiracetam or keppra or levetiracetam).tw. (50)
48 lo 59.tw. (0)
49 ucb 6474.tw. (0)
50 ucb I059.tw. (0)
51 "ucb I 059".tw. (0)
52 102767-28-2.rn. (0)
53 or/44-52 (54)
54 53 and 21 and 33 (24)
55 (lamicitin or dichlorophenyltriazinediyldiamine).tw. (0)
56 28 or 55 (512)

57	56 and 33 and 21 (100)
58	oxcarbazepine.mp. (101)
59	gp 47680.tw. (0)
60	(oxocarbazepine or trileptal).tw. (3)
61	28721-07-5.rn. (56)
62	or/58-61 (102)
63	62 and 21 and 33 (29)
64	tiagabine.mp. (164)
65	(gabitril or tiabex).tw. (7)
66	"nnc 05 0328".tw. (0)
67	nnc 328.tw. (1)
68	"no 05 0328".tw. (0)
69	"no 05 0329".tw. (0)
70	no 328.tw. (1160)
71	no 329.tw. (1060)
72	115103-54-3.rn. (107)
73	or/64-72 (2358)
74	73 and 33 and 21 (54)
75	topiramate.mp. (259)
76	(epitomax or topamax or topimax).tw. (7)
77	mcn 4853.tw. (0)
78	rwj 17021.tw. (0)
79	rwj 17021-000.tw. (0)
80	97240-79-4.rn. (197)
81	or/75-80 (259)
82	81 and 21 and 33 (73)
83	vigabatrin.mp. (321)
84	(sabril or sabrilex).tw. (6)
85	3 amino 5 carboxyhexene.tw. (0)
86	4 amino 4 ethenylbutyric acid.tw. (0)
87	4 amino 4 vinylbutanoic acid.tw. (0)
88	4 amino 5 hexenoic acid.tw. (0)
89	4 aminohex 5 enoic acid.tw. (0)
90	4 vinyl 4 aminobutyric acid.tw. (0)
91	4 vinylaminobutyric acid.tw. (0)
92	4 vinylgaba.tw. (0)
93	gamma vinyl 4 aminobutyric acid.tw. (0)
94	gamma vinyl gaba.tw. (34)
95	gamma vinylgaba.tw. (1)
96	gamma vinyl gamma aminobutyric acid.tw. (5)
97	mdl 71754.tw. (1)
98	n vinyl 4 aminobutyric acid.tw. (0)
99	n vinyl gaba.tw. (0)
100	n vinyl gamma aminobutyric acid.tw. (0)
101	rmi 71754.tw. (1)
102	rmi 71890.tw. (0)
103	60643-86-9.rn. (238)
104	or/83-103 (323)
105	104 and 33 and 21 (65)
106	57 or 43 or 54 or 63 or 74 or 82 or 105 (281)

Source MEDLINE and PreMEDLINE (Silverplatter) 1999–March 2002

No.	Records	Request
1	3481	PT = "RANDOMIZED-CONTROLLED-TRIAL"
2	537	PT = "CONTROLLED-CLINICAL-TRIAL"
3	1295	"Randomized-Controlled-Trials"/ all subheadings
4	1335	"double-blind-method"/ all subheadings
5	247	"single-blind-method"/ all subheadings
6	6580	PT = "CLINICAL-TRIAL"
7	3007	explode "Clinical-Trials"/ all subheadings
8	2354	(clin* near trial*) in ti,ab
9	1862	(singl* or doubl* or tripl* or trebl*) near (blind* or mask*)
10	183	"Placebos"/ all subheadings
11	1689	placebo* in ti,ab
12	7106	random* in ti,ab
13	651	"Research-Design"/ all subheadings
14	623	"Random-Allocation"
15	7425	(control* near (trial* or stud*)) in ti,ab,mesh
16	375	crossover in ti,ab,mesh
17	8297	explode "Evaluation-Studies"/ all subheadings
18	14053	tg=comparative-study
19	33676	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18
20	3355	editorial in pt
21	2387	comment in pt
22	7626	letter in pt
23	42015	TG = "ANIMAL"
24	113442	TG = "HUMAN"
25	27770	#23 not (#23 and #24)
26	28283	#19 not (#20 or #21 or #22 or #25)
27	0	labileno
28	0	lamictal
29	45	lamotrigine
30	0	lamicitin
31	0	dichlorophenyltrazinediyldiamine
32	10	ltg
33	0	bw 430c
34	0	bw 430 c
35	0	bw 430c78
36	57	gabapentin
37	2	neurontin
38	0	neurotonin
39	10	gbp
40	0	goe 3450
41	0	go 3450
42	0	ci 945
43	1	1 aminomethyl cyclohexaneacetic acid
44	13	etiracetam
45	1	keppra

46	33	lev
47	0	levetiracetum
48	0	1 1 carbamoylpropyl 2 pyrrolidinone
49	0	alpha ethyl 2 oxo 1 pyrrolidineacetamide
50	0	lo 59
51	0	ucb 6474
52	0	ucb I059
53	0	ucb I 059
54	15	oxcarbazepine
55	0	gp 47680
56	2	trileptal
57	0	oxocarbazepine
58	20	tiagabine
59	0	gabitril
60	0	nnc 05 0328
61	0	nnc 328
62	0	no 05 0328
63	0	no 05 0329
64	0	no 328
65	0	no 329
66	0	tiabex
67	42	topiramate
68	0	epitomax
69	0	mcn 4853
70	0	rwj 17021
71	0	rwj 17021-000
72	0	topamax
73	0	topimax
74	46	vigabatrin
75	0	3 amino 5 carboxyhexene
76	0	4 amino 4 thenylbutyric acid
77	0	4 amino 5 hexenoic acid
78	0	4 aminohex 5 anoic acid
79	0	4 vinylaminobutyric acid
80	0	4 vinylgaba
81	0	gamma vinyl 4 aminobutyric acid
82	4	gamma vinyl gaba
83	0	gamma vinylgaba
84	0	gamma vinyl gamma aminobutyric acid
85	0	mdl 71754
86	0	n vinyl 4 aminobutyric acid
87	0	n vinyl gaba
88	0	n vinyl gamma aminobutyric acid
89	0	rmi 71754
90	0	rmi 71890
91	0	sabril
92	0	sabrilex
93	3	gvg
94	26	"84057-84-1" in cas
95	38	"60142-96-3" in cas
96	11	"28721-07-5;" in CAS
97	11	"115103-54-3" in cas
98	30	"97240-79-4" in cas
99	33	"60643-86-9" in CAS
100	26	84057-84-1 in cas
101	38	60142-96-3 in cas
102	13	33996-58-6 in cas
103	11	115103-54-3 in cas
104	11	28721-07-5 in cas
105	30	97240-79-4 in cas
106	38	60142-96-3 in cas
107	4	oxc
108	33	"Vigabatrin"/ all subheadings
109	3157	#27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #7 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62
110	154	#63 or #64 or #65 or #66 or #67 or #68 or #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89 or #90 or #91 or #92 or #93 or #94 or #95 or #96 or #97 or #98
111	148	#99 or #100 or #101 or #102 or #103 or #104 or #105 or #106 or #107 or #108
112	3215	#109 or #110 or #111
113	2607	#26 and #112
114	1042	explode "Epilepsy"/ all subheadings
115	790	epilep* in ti ab
116	814	seizure* in ti ab
117	153	convuls* in ti ab
118	1438	#114 or #115 or #116 or #117
*119	62	#113 and #118

Source EMBASE (Ovid) 1980–February 2002

1 randomized controlled trial/ (62250)
2 exp clinical trial/ (231444)
3 exp controlled study/ (1326226)
4 double blind procedure/ (42691)
5 randomization/ (3918)
6 placebo/ (56460)
7 single blind procedure/ (3541)
8 (control adj (trial$ or stud$ or evaluation$ or experiment$)).mp. [mp=title, abstract, subject headings, drug trade name, original title, device manufacturer, drug manufacturer name] (25280)
9 ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp. (62468)

10 (placebo$ or matched communities or matched schools or matched populations).mp. (94204)
11 (comparison group$ or control group$).mp. (90140)
12 (clinical trial$ or random$).mp. (396527)
13 (quasiexperimental or quasi experimental or pseudo experimental).mp. (757)
14 matched pairs.mp. (1278)
15 or/1-14 (1618664)
16 (lamicitin or dichlorophenyltriazinediyldiamine).mp. (0)
17 bw 430c.tw. (8)
18 bw 430 c.tw. (5)
19 bw 430c78.tw. (2)
20 (labileno or lamictal or lamotrigine or ltg).mp. (2927)
21 84057-84-1.rn. (2836)
22 or/16-21 (2927)
23 epilep$.mp. (43625)
24 seizure$.mp. (44049)
25 convulsion$.mp. (13276)
26 exp "seizure epilepsy and convulsion"/ (72221)
27 or/23-26 (83514)
28 15 and 22 and 27 (747)
29 (gabapentin or neurontin or neurotonin or gbp).mp. (2974)
30 goe 3450.tw. (3)
31 ci 945.tw. (12)
32 1 aminomethyl cyclohexaneacetic acid.tw. (16)
33 60142-96-3.rn. (2729)
34 go 3450.tw. (3)
35 or/29-34 (2980)
36 35 and 15 and 27 (501)
37 (etiracetam or keppra or levetiracetam).mp. (259)
38 1 1 carbamoylpropyl 2 pyrrolidineacetamide.mp. (0)
39 alpha ethyl 2 oxo 1 pyrrolidineacetamide.mp. (1)
40 lo59.mp. (5)
41 ucb 6474.mp. (3)
42 ucb I059.mp. (0)
43 "ucb I 059".mp. (0)
44 102767-28-2.rn. (259)
45 or/37-44 (259)
46 45 and 15 and 27 (108)
47 (oxcarbazepine or oxocarbazepine or trileptal).mp. (808)
48 gp 47680.tw. (12)
49 28721-07-5.rn. (796)
50 or/47-49 (808)
51 50 and 15 and 27 (252)
52 (tiagabine or gabitril or tiabex).mp. (782)
53 "nnc 05 0328".mp. (4)
54 nnc 328.mp. (2)
55 "no 05 0328".mp. (4)
56 "no 05 0329".mp. (1)
57 no 328.mp. (4290)
58 no 329.mp. (3935)
59 115103-54-3.rn. (768)
60 or/52-59 (8928)
61 60 and 15 and 27 (307)
62 (topiramate or epitomax or topamax or topimax or topiramate).mp. (1134)
63 mcn 4853.mp. (5)
64 rwj 17021.mp. (3)
65 rwj 17021-000.mp. (2)
66 97240-79-4.rn. (1124)
67 or/62-66 (1134)
68 67 and 15 and 27 (358)
69 (vigabatrin or sabril or sabrilex).mp. (2619)
70 3 amino 5 carboxyhexene.mp. (0)
71 4 amino 4 ethenylbutyric acid.mp. (0)
72 4 amino 4 vinylbutanoic acid.mp. (0)
73 4 amino 5 hexenoic acid.mp. (5)
74 4 aminohex 5 enoic acid.mp. (6)
75 4 vinyl 4 aminobutyric acid.mp. (1)
76 4 vinylaminobutyric acid.mp. (0)
77 4 vinylgaba.mp. (0)
78 gamma vinyl 4 aminobutyric acid.mp. (1)
79 gamma vinyl gaba.mp. (345)
80 gamma vinylgaba.mp. (12)
81 gamma vinyl gamma aminobutyric acid.mp. (23)
82 mdl 71754.mp. (9)
83 n vinyl 4 aminobutyric acid.mp. (0)
84 n vinyl gaba.mp. (0)
85 n vinyl gamma aminobutyric acid.mp. (0)
86 rmi 71754.mp. (10)
87 rmi 71890.mp. (0)
88 60643-86-9.rn. (2597)
89 or/69-88 (2647)
90 89 and 15 and 27 (758)
91 28 or 36 or 46 or 51 or 61 or 68 or 90 (1723)

Source Science Citation Index (Web of Science) 1981–February 2002

The search strategy was limited to the drug terms and epilepsy:

labileno or lamictal or lamotrigine or lamicitin or dichlorophenyltrazinediyldiamine or ltg or gabapentin or neurontin or neurotonin or gbp or goe or aminomethyl cyclohexaneacetic acid or levetiracetam or etiracetam or keppra or lev or lvt or carbamoylpropyl or pyrrolidineacetamide or ucb or oxcarbazepine or trileptal or oxocarbazepine or oxc or tiagabine or gabitril or nnc or tiabex or tgb or topiramate or tpm or epitomax or mcn or rwj or topamax or topimax or vigabatrin or carboxyhexene or ethenybutyric acid or vinylbutyric acid or vinylbutanoic acid or aminobutyric acid or vinylaminobutyric acid or

hexenoic acid or enoic acid or vinylgaba or gamma vinyl or gamma vinylgaba or vinyl gaba or mdl or rmi or sabril or sabrilex or gvg
and
epilep* or seizure* or convulsion*
National Research Register 2002, Issue 1
See Cochrane Library (CCTR) strategy.

Search strategies for the decision-analytic model

Existing models

Source MEDLINE (Ovid) 1966–March 2002

1 exp epilepsy/ (59840)
2 epilep$.ti,ab. (42684)
3 seizure$.ti,ab. (39297)
4 convuls$.ti,ab. (14151)
5 or/1-4 (86797)
6 markov$.mp. (2677)
7 monte carlo method/ (4890)
8 exp models statistical/ (58231)
9 exp decision support techniques/ (24727)
10 or/6-9 (85935)
11 5 and 10 (507)
12 limit 11 to human (452)
13 5 and 6 (15)
14 limit 13 to human (12)
15 9 and model$.ti,ab. (5589)
16 model$.ti,ab. (503151)
17 9 and 16 (5589)
18 modle$.mp. (9)
19 model$.mp. (689115)
20 6 or 7 or 19 (691092)
21 5 and 20 (5963)
22 limit 21 to human (2309)
23 limit 22 to yr=2000-2002 (488)
24 decision analysis.ti,ab. (1645)
25 5 and 24 (10)
26 from 25 keep 1-10 (10)

Economic evaluation

Source MEDLINE (Ovid) 1966–March 2002

1 lamotrigine.mp. (1109)
2 (labileno or lamictal or ltg).mp. [mp=title, abstract, cas registry/ec number word, mesh subject heading] (329)
3 bw 430c.tw. (0)
4 bw 430 c.tw. (0)
5 bw 430c78.tw. (0)
6 84057-84-1.rn. (844)
7 or/1-6 (1195)
8 exp epilepsy/ (59957)
9 epilep$.ti,ab. (42769)
10 seizure$.ti,ab. (39371)
11 convuls$.ti,ab. (14160)
12 or/8-11 (86940)
13 gabapentin.mp. (976)
14 goe 3450.tw. (1)
15 go 3450.tw. (2)
16 ci 945.tw. (10)
17 1 aminomethyl cyclohexaneacetic acid.tw. (16)
18 (neurontin or neurotonin or gbp).tw. (402)
19 "60142-96-3".rn. (756)
20 or/13-19 (1221)
21 etiracetam.mp. (82)
22 1 1 carbamoylpropyl 2 pyrrolidinone.tw. (0)
23 alpha ethyl 2 oxo 1 pyrrolidineacetamide.tw. (1)
24 (etiracetam or keppra or levetiracetam).tw. (98)
25 lo 59.tw. (0)
26 ucb 6474.tw. (0)
27 ucb I059.tw. (0)
28 "ucb I 059".tw. (0)
29 102767-28-2.rn. (0)
30 or/21-29 (110)
31 (lamicitin or dichlorophenyltriazinediyldiamine).tw. (0)
32 7 or 31 (1195)
33 oxcarbazepine.mp. (305)
34 gp 47680.tw. (2)
35 (oxocarbazepine or trileptal).tw. (10)
36 28721-07-5.rn. (204)
37 or/33-36 (306)
38 tiagabine.mp. (329)
39 (gabitril or tiabex).tw. (8)
40 "nnc 05 0328".tw. (2)
41 nnc 328.tw. (1)
42 "no 05 0328".tw. (3)
43 "no 05 0329".tw. (1)
44 no 328.tw. (4967)
45 no 329.tw. (4604)
46 115103-54-3.rn. (222)
47 or/38-46 (9823)
48 topiramate.mp. (427)
49 (epitomax or topamax or topimax).tw. (8)
50 mcn 4853.tw. (2)
51 rwj 17021.tw. (1)
52 rwj 17021-000.tw. (1)
53 97240-79-4.rn. (325)
54 or/48-53 (427)
55 vigabatrin.mp. (1145)
56 (sabril or sabrilex).tw. (17)
57 3 amino 5 carboxyhexene.tw. (0)
58 4 amino 4 ethenylbutyric acid.tw. (0)
59 4 amino 4 vinylbutanoic acid.tw. (0)
60 4 amino 5 hexenoic acid.tw. (2)
61 4 aminohex 5 enoic acid.tw. (3)
62 4 vinyl 4 aminobutyric acid.tw. (1)
63 4 vinylaminobutyric acid.tw. (0)
64 4 vinylgaba.tw. (0)
65 gamma vinyl 4 aminobutyric acid.tw. (1)

66 gamma vinyl gaba.tw. (324)
67 gamma vinylgaba.tw. (9)
68 gamma vinyl gamma aminobutyric acid.tw. (26)
69 mdl 71754.tw. (2)
70 n vinyl 4 aminobutyric acid.tw. (0)
71 n vinyl gaba.tw. (0)
72 n vinyl gamma aminobutyric acid.tw. (0)
73 rmi 71754.tw. (3)
74 rmi 71890.tw. (0)
75 60643-86-9.rn. (945)
76 or/55-75 (1220)
77 economics/ (8873)
78 exp "costs and cost analysis"/ (95129)
79 cost of illness/ (4160)
80 exp health care costs/ (13479)
81 economic value of life/ (3929)
82 exp economics medical/ (8842)
83 exp economics hospital/ (10301)
84 economics pharmaceutical/ (1013)
85 exp "fees and charges"/ (18628)
86 (cost or costs or costed or costly or costing).tw. (111619)
87 (economic$ or pharmacoeconomic$ or pricing).tw. (46851)
88 or/77-87 (221866)
89 32 or 20 or 30 or 37 or 47 or 54 or 76 (13279)
90 12 and 88 and 89 (47)

Source EMBASE (Ovid) 1980–March 2002

1 (lamicitin or dichlorophenyltriazinediyldiamine).mp. (0)
2 bw 430c.tw. (8)
3 bw 430 c.tw. (5)
4 bw 430c78.tw. (2)
5 (labileno or lamictal or lamotrigine or ltg).mp. (2970)
6 84057-84-1.rn. (2878)
7 or/1-6 (2970)
8 epilep$.mp. (43885)
9 seizure$.mp. (44271)
10 convulsion$.mp. (13316)
11 exp "seizure epilepsy and convulsion"/ (72635)
12 or/8-11 (83963)
13 (gabapentin or neurontin or neurotonin or gbp).mp. (3045)
14 goe 3450.tw. (3)
15 ci 945.tw. (12)
16 1 aminomethyl cyclohexaneacetic acid.tw. (16)
17 60142-96-3.rn. (2795)
18 go 3450.tw. (3)
19 or/13-18 (3051)
20 (etiracetam or keppra or levetiracetam).mp. (270)
21 1 1 carbamoylpropyl 2 pyrrolidineacetamide.mp. (0)
22 alpha ethyl 2 oxo 1 pyrrolidineacetamide.mp. (1)
23 lo59.mp. (5)
24 ucb 6474.mp. (3)
25 ucb I059.mp. (0)
26 "ucb I 059".mp. (0)
27 102767-28-2.rn. (270)
28 or/20-27 (270)
29 (oxcarbazepine or oxocarbazepine or trileptal).mp. (828)
30 gp 47680.tw. (12)
31 28721-07-5.rn. (816)
32 or/29-31 (828)
33 (tiagabine or gabitril or tiabex).mp. (792)
34 "nnc 05 0328".mp. (4)
35 nnc 328.mp. (2)
36 "no 05 0328".mp. (4)
37 "no 05 0329".mp. (1)
38 no 328.mp. (4315)
39 no 329.mp. (3958)
40 115103-54-3.rn. (778)
41 or/33-40 (8986)
42 (topiramate or epitomax or topamax or topimax or topiramate).mp. (1168)
43 mcn 4853.mp. (5)
44 rwj 17021.mp. (3)
45 rwj 17021-000.mp. (2)
46 97240-79-4.rn. (1158)
47 or/42-46 (1168)
48 (vigabatrin or sabril or sabrilex).mp. (2635)
49 3 amino 5 carboxyhexene.mp. (0)
50 4 amino 4 ethenylbutyric acid.mp. (0)
51 4 amino 4 vinylbutanoic acid.mp. (0)
52 4 amino 5 hexenoic acid.mp. (5)
53 4 aminohex 5 enoic acid.mp. (7)
54 4 vinyl 4 aminobutyric acid.mp. (1)
55 4 vinylaminobutyric acid.mp. (0)
56 4 vinylgaba.mp. (0)
57 gamma vinyl 4 aminobutyric acid.mp. (1)
58 gamma vinyl gaba.mp. (346)
59 gamma vinylgaba.mp. (13)
60 gamma vinyl gamma aminobutyric acid.mp. (23)
61 mdl 71754.mp. (9)
62 n vinyl 4 aminobutyric acid.mp. (0)
63 n vinyl gaba.mp. (0)
64 n vinyl gamma aminobutyric acid.mp. (0)
65 rmi 71754.mp. (10)
66 rmi 71890.mp. (0)
67 60643-86-9.rn. (2613)
68 or/48-67 (2663)
69 7 or 19 or 28 or 32 or 41 or 47 or 68 (15487)
70 cost benefit analysis/ (13518)
71 cost effectiveness analysis/ (24959)
72 cost minimization analysis/ (409)
73 cost utility analysis/ (615)
74 economic evaluation/ (1050)

75 (cost or costs or costed or costly or costing).tw. (92118)
76 (economic$ or pharmacoeconomic$ or price$ or pricing).tw. (42697)
77 (technology adj assessment$).tw. (855)
78 or/70-77 (135768)
79 78 and 12 and 69 (99)

Source Health Economic Evaluation Database (HEED) May 2002

labileno or lamictal or lamotrigine or lamicitin or dichlorophenyltrazinediyldiamine or ltg or gabapentin or neurontin or neurotonin or gbp or goe or aminomethyl cyclohexaneacetic acid or levetiracetam or etiracetam or keppra or lev or lvt or carbamoylpropyl or pyrrolidineacetamide or ucb or oxcarbazepine or trileptal or oxocarbazepine or oxc or tiagabine or gabitril or nnc or tiabex or tgb or topiramate or tpm or epitomax or mcn or rwj or topamax or topimax or vigabatrin or carboxyhexene or ethenybutyric acid or vinylbutyric acid or vinylbutanoic acid or aminobutyric acid or vinylaminobutyric acid or hexenoic acid or enoic acid or vinylgaba or gamma vinyl or gamma vinylgaba or vinyl gaba or mdl or rmi or sabril or sabrilex or gvg

Source NHS Database of Reviews of Effectiveness (DARE), HTA Database, NHS Economic Evaluation Database (NHS EED), NHS CRD internal administration databases

See Cochrane Library (CCTR) effectiveness search strategy.

Quality of life

Source MEDLINE (Ovid) 1966–March 2002

1 epilepsy/ (31939)
2 quality of life/ (30464)
3 life style/ (15874)
4 health status/ (18422)
5 health status indicators/ (6272)
6 or/2-5 (65755)
7 1 and 6 (374)
8 limit 7 to (human and english language) (322)

Appendix 8

Studies with mixed age populations

Seventy-three publications were retrieved in which it was possible to determine that the study population was mostly ≥18 years old but contained some patient(s) <18 years of age. In most of these studies the number of these patients was not reported but it was clear that in all of them the majority of patients were ≥18 years old. They are listed in *Table 61* according to diagnosis, study drug and publication date. Further details with regard to study population, intervention and trial design are provided in Appendix 9.

TABLE 61 *Mixed age publications listed by diagnosis, drug and year of publication*

Drug	Year	Reference	No.
Newly diagnosed partial seizures			
Tiagabine	1999	Aikia, 1999[137]	1
Refractory partial seizures			
Gabapentin	2000	Lindberger *et al.*, 2000[138]	2
Lamotrigine	1989	Binnie *et al.*, 1989[139]	3
Levetiracetam	2000	Cramer *et al.*, 2000[140]	4
Oxcarbazepine	2000	Barcs *et al.*, 2000[141]	5
Tiagabine	2001	Cramer *et al.*, 2001[287]	6
Newly diagnosed partial seizures with or without secondary generalisation			
Tiagabine	1997	Brodie *et al.*, 1997[142]	7
Vigabatrin	1993	Tanganelli and Saltarelli, 1993[143]	8
Vigabatrin	1997	Canger *et al.*, 1997[144]	9
Vigabatrin	1999	Chadwick *et al.*, 1999[145]	10
Refractory partial seizures with or without secondary generalisation			
Gabapentin	1990	Andrews *et al.*, 1990[146]	11
Gabapentin	1991	Sivenius *et al.*, 1991[147]	12
Gabapentin	1993	McLean *et al.*, 1993[148]	13
Gabapentin	1994	Anhut *et al.*, 1994[149]	14
Gabapentin	1997	Leach *et al.*, 1997[150]	15
Gabapentin	1999	Lopes-Lima *et al.*, 1999[288]	16
Lamotrigine	1993	Schapel *et al.*, 1993[151]	17
Lamotrigine	1993	Smith *et al.*, 1993[152]	18
Lamotrigine	1994	Severi *et al.*, 1994[153]	19
Levetiracetam	2000	Cereghino *et al.*, 2000[154]	20
Levetiracetam	2000	Cramer *et al.*, 2000[155]	21
Levetiracetam	2000	Shorvon *et al.*, 2000[156]	22
Levetiracetam	2002	Boon *et al.*, 2002[289]	23
Oxcarbazepine	1999	Schachter *et al.*, 1999[157]	24
Topiramate	1999	Korean Topiramate Study Group, 1999[158]	25
Vigabatrin	1993	Dodrill *et al.*, 1993[290]	26
Vigabatrin	1994	Grunewald *et al.*, 1994[159]	27
Vigabatrin	1999	Brodie and Mumford, 1999[160]	28
Refractory complex partial seizures			
Tiagabine	1997	Dodrill *et al.*, 1997[161]	29
Tiagabine	1998	Uthman *et al.*, 1998[291]	30
Tiagabine	2000	Dodrill *et al.*, 2000[162]	31
Vigabatrin	1996	Beran *et al.*, 1996[163]	32

continued

TABLE 61 *Mixed age publications listed by diagnosis, drug and year of publication (cont'd)*

Drug	Year	reference	No.
Refractory complex partial seizures with or without secondary generalisation			
Gabapentin	1995	Ben Menachem *et al.*, 1995[164]	33
Levetiracetam	2000	Ben Menachem and Falter, 2000[165]	34
Tiagabine	1997	Sachdeo *et al.*, 1997[166]	35
Vigabatrin	1984	Rimmer and Richeus, 1984[167]	36
Vigabatrin	1985	Gram *et al.*, 1985[168]	37
Vigabatrin	1995	Cramer *et al.*, 1995[169]	38
Vigabatrin	1996	Provinciali *et al.*, 1996[170]	39
Refractory primary generalised seizures			
Gabapentin	1996	Chadwick *et al.*, 1996[171]	40
Lamotrigine	1998	Beran *et al.*, 1998[172]	41
Topiramate	1999	Biton *et al.*, 1999[173]	42
Newly diagnosed primary generalised seizures or partial seizures			
Gabapentin	1998	Chadwick *et al.*, 1998[174]	43
Lamotrigine	1995	Brodie *et al.*, 1995[175]	44
Lamotrigine	1996	Dam, 1996[176]	45
Lamotrigine	1996	Reunanen *et al.*, 1996[292]	46
Lamotrigine	1999	Steiner *et al.*, 1999[177]	47
Lamotrigine	2000	Gillham *et al.*, 2000[293]	48
Lamotrigine	2000	Kalogjera *et al.*, 2000[178]	49
Lamotrigine	2001	Biton *et al.*, 2001[242]	50
Lamotrigine	2001	Edwards *et al.*, 2001[294]	51
Oxcarbazepine	1989	Dam *et al.*, 1989[179]	52
Oxcarbazepine	1992	Aikia *et al.*, 1992[295]	53
Oxcarbazepine	1997	Bill *et al.*, 1997[180]	54
Oxcarbazepine	1997	Christe *et al.*, 1997[181]	55
Topiramate	2001	Wheless *et al.*, 2001[182]	56
Vigabatrin	1995	Kalviainen *et al.*, 1995[183]	57
Refractory primary generalised seizures or partial seizures			
Lamotrigine	1987	Binnie *et al.*, 1987[184]	58
Levetiracetam	2000	Betts *et al.*, 2000[185]	59
Oxcarbazepine	1987	Houtkooper *et al.*, 1987[186]	60
Topiramate	1999	Coles *et al.*, 1999[296]	61
Vigabatrin	1986	Loiseau *et al.*, 1986[187]	62
Vigabatrin	1986	Tartara *et al.*, 1986[188]	63
Vigabatrin	1987	Rimmer *et al.*, 1987[189]	64
Vigabatrin	1987	Tassinari *et al.*, 1987[190]	65
Vigabatrin	1988	Reynolds *et al.*, 1988[192]	66
Vigabatrin	1991	Reynolds *et al.*, 1991[191]	67
Vigabatrin	1993	Gillham *et al.*, 1993[193]	68
Vigabatrin	1993	McKee *et al.*, 1993[297]	69
Epilepsy diagnosed (no further details)			
Lamotrigine	1999	Carmant *et al.*, 1999[194]	70
Lamotrigine	1999	Kerr *et al.*, 1999[298]	71
Lamotrigine	1999	Montouris *et al.*, 1999[195]	72
Lamotrigine	2000	Fakhoury *et al.*, 2000[196]	73

Appendix 9

RCT publications of mixed age studies

Tables 62–134 give further details of RCT publications in which the study populations were predominantly adult but included some patients under 18 years of age. Numbers in square brackets refer to the identification numbers in the last column of *Table 61*.

Study population newly diagnosed with partial seizures

TABLE 62 *[1] Aika, 1999*[137]

Drug(s)	Tiagabine		
Target maintenance dose (mode)	10–20 mg/day (?mode)		
Seizure or syndrome	Newly diagnosed partial epilepsy		
Type of trial design	Parallel		
Add-on or monotherapy	Monotherapy		
Control(s)	Carbamazepine		
Eligible age	15–75 years		
		Carbamazepine	**Tiagabine**
Number randomised		34	33
Age (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
Diagnosed seizure types, *n* (%)	Not reported	Not reported	Not reported
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported		

Study population diagnosed with refractory partial seizures

TABLE 63 *[2] Lindberger* et al.*, 2000*[138]

Drug(s)	Gabapentin		
Target maintenance dose (mode)	1800 mg/day gabapentin (oral); 1000 mg/day vigabatrin (oral)		
Seizure or syndrome	Partial seizures		
Type of trial design	Parallel		
Add-on or monotherapy	Add-on		
Control(s)	Vigabatrin		
Eligible age	12–75 years		
		Vigabatrin	**Gabapentin**
Number randomised		52	50
Age (weeks, months, years) (mean, SD; median, range)		Median 33.0 years, range 14–56 years	Median 34.5 years, range 13–68 years
Diagnosed seizure types, *n* (%)	Not reported		
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported		

TABLE 64 *[3] Binnie* et al.*, 1989*[139]

Drug(s)	Lamotrigine		
Target maintenance dose (mode)	75–200 mg/day		
Seizure or syndrome	Refractory partial seizures with or without other seizure types		
Type of trial design	Cross over		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age			
		Placebo	**Lamotrigine**
Number randomised		15	15
Age (weeks, months, years) (mean, SD; median, range)		Not reported separately by arm. Mean 37.1, SD 10.3; range 16–51 years	Not reported separately by arm. Mean 37.1, SD 10.3; range 16–51 years
Diagnosed seizure types, *n* (%)	Not reported	Not reported	Not reported
Diagnosed syndrome(s), *n* (%)		Not reported separately by study arm	Not reported separately by study arm
	Idiopathic/unknown	22	22
	Symptomatic	8	8
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported	Not reported	Not reported

TABLE 65 *[4] Cramer* et al.*, 2000*[140]

Drug(s)	Levetiracetam		
Target maintenance dose (mode)	1000 or 3000 mg/day in two doses/day (oral)		
Seizure or syndrome	Inadequately controlled partial seizures		
Type of trial design	Parallel		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age	16–70 years		
		Placebo	**Levetiracetam**
Number randomised		Not reported	Not reported
Age (weeks, months, years) (mean, SD; median, range)		Not reported separately by arm. Mean 38.7, SD 10.9 years	Not reported separately by arm. Mean 38.7, SD 10.9 years
Diagnosed seizure types, *n* (%)		Not reported separately by study arm	Not reported separately by study arm
	Simple and complex partial	(63)	(63)
	Simple and complex partial with secondary generalisation	(32)	(32)
	Partial secondarily generalised	(1.6)	(1.6)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported		

TABLE 66 *[5] Barcs* et al.*, 2000*[141]

Drug(s)	Oxcarbazepine		
Target maintenance dose (mode)	600, 1200 or 2400 mg/day (oral)		
Seizure or syndrome	Uncontrolled partial epilepsy		
Type of trial design	Parallel		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age	15–65 years		
		Placebo	**Oxcarbarzepine: 600; 1200; 2400 mg/day**
Number randomised		173	169; 178; 174
Age (weeks, months, years) (mean, SD; median, range)		Mean 34.3 years; range 15–65 years	Mean 34.6; 33.8; 35.2 years; range 15–65; 16–64; 15–66 years
Diagnosed seizure types, *n* (%)	Secondarily generalised	51 (29)	49 (29); 68 (38); 60 (34)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	All seizures Secondarily generalised seizures	Median 8.6/month Median 3.5/month	Median 9.6; 9.8; 10/month Median 3.5; 2.0; 2.4/month

TABLE 67 *[6] Cramer* et al.*, 2001*[287]

Drug(s)	Tiagabine		
Target maintenance dose (mode)	Not reported		
Seizure or syndrome	Poorly controlled partial epilepsy		
Type of trial design	Parallel		
Add-on or monotherapy	Add-on		
Control(s)	Alternative standard AED (phenytoin or carbamazepine)		
Eligible age	15–65 years		
		Standard AED	**Tiagabine + carbamazepine; Tiagabine + phenytoin**
Number randomised		101	105; 67
Age (weeks, months, years) (mean, SD; median, range)		Mean 33 years	Mean 37; mean 41 years
Diagnosed seizure types, *n* (%)	Not reported		
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Complex partial seizures	Mean 22, SD 66/month	Mean 13, SD 28/month (carbamazepine) Mean 29, SD 82/month (phenytoin)

Study population newly diagnosed with partial seizures with or without secondary generalisation

TABLE 68 *[7] Brodie* et al., *1997,*[142] *abstract*

Drug(s)	Tiagabine		
Target maintenance dose (mode)	5–10 mg/day, in two doses/day		
Seizure or syndrome	Newly diagnosed partial seizures with or without secondary generalisation		
Type of trial design	Parallel		
Add-on or monotherapy	Monotherapy		
Control(s)	Carbamazepine		
Eligible age	12–85 years		
		Carbamazepine	**Tiagabine**
Number randomised		Not reported	Not reported
Age (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
Diagnosed seizure types, *n* (%)	Not reported	Not reported	Not reported
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported		

TABLE 69 *[8] Tanganelli* et al., *1993*[143]

Drug(s)	Vigabatrin		
Target maintenance dose (mode)	3 g/day (?mode)		
Seizure or syndrome	Newly diagnosed partial seizures with or without secondary generalisation		
Type of trial design	Cross-over		
Add-on or monotherapy	Monotherapy		
Control(s)	Carbamazepine		
Eligible age			
		Carbamazepine	**Vigabatrin**
Number randomised		5	6
Age (weeks, months, years) (mean, SD; median, range)		22, 25, 26, 29, 47 years	17, 20, 31, 36, 43, 58 years
Diagnosed seizure types, *n* (%)	Complex partial Secondarily generalised	5 (100) 2 (40)	6 (100) 0 (0)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported here		

TABLE 70 *[9] Canger and Saltarelli, 1997*[144]

Drug(s)	Vigabatrin		
Target maintenance dose (mode)	2 g/day		
Seizure or syndrome	Newly diagnosed simple or complex partial seizures with or without secondary generalisation		
Type of trial design	Parallel		
Add-on or monotherapy	Monotherapy		
Control(s)	Carbamazepine		
Eligible age			
		Carbamazepine	**Vigabatrin**
Number randomised		8	8
Age (weeks, months, years) (mean, SD; median, range)		1 patient <18 years old	0 patients <18 years old
Diagnosed seizure types, *n* (%)	Not reported for all randomised patients		
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported		

TABLE 71 *[10] Chadwick, 1999*[145]

Drug(s)	Vigabatrin		
Target maintenance dose (mode)	2 g/day, in two doses/day (oral)		
Seizure or syndrome	Newly diagnosed partial seizures with or without secondary generalisation		
Type of trial design	Parallel		
Add-on or monotherapy	Monotherapy		
Control(s)	Carbamazepine		
Eligible age	12–65 years		
		Carbamazepine	**Vigabatrin**
Number randomised		226	220
Age (weeks, months, years) (mean, SD; median, range)		Mean 36, SD 16; range 13–72 years	Mean 35, SD 15; range 12–75 years
Diagnosed seizure types, *n* (%)	Any seizures	226 (100)	220 (100)
	Simple partial	63 (28)	74 (34)
	Complex partial	91 (40)	92 (42)
	Secondarily generalised	150 (66)	139 (63)
	Not known	8 (4)	8 (4)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	NA		

Study population diagnosed with refractory partial seizures with or without secondary generalisation

TABLE 72 *[11] Andrews* et al.*, 1990*[146] *[UK Gabapentin Group]*

Drug(s)	Gabapentin
Target maintenance dose (mode)	1200 mg/day, in three doses/day (oral)
Seizure or syndrome	Refractory partial seizures with or without secondary generalisation
Type of trial design	Parallel
Add-on or monotherapy	Add-on
Control(s)	Placebo
Eligible age	

		Placebo	**Gabapentin**
Number randomised		66	61
Age (weeks, months, years) (mean, SD; median, range)		Mean 31; range 14–73 years	Mean 30; range 15–62 years
Diagnosed seizure types, *n* (%)	Not reported	Not reported	Not reported
Diagnosed syndrome(s), *n* (%)	Not reported	Not reported	Not reported
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	All seizures	Median 13, range 1–216/month	Median 13, range 3–368/month
	Secondary tonic–clonic	Median 4, range 0.3–32/month	Median 5, range 0.3–47/month

TABLE 73 *[12] Sivenius* et al.*, 1991*[147]

Drug(s)	Gabapentin
Target maintenance dose (mode)	900 or 1200 mg/day (?mode)
Seizure or syndrome	Refractory simple or complex partial with or without secondarily generalised seizures
Type of trial design	Parallel
Add-on or monotherapy	Add-on
Control(s)	Placebo
Eligible age	

		Placebo	**Gabapentin: 900; 1200 mg**
Number randomised		18	16; 9
Age (weeks, months, years) (mean, SD; median, range)		Not reported separately by arm. Mean 39; range16–59 years	Not reported separately by arm. Mean 39; range 16–59 years
Diagnosed seizure types, *n* (%)	Simple partial	0 (0)	0 (0); 2 (22)
	Simple+complex partial	0 (0)	1 (6); 0 (0)
	Complex partial	10 (56)	6 (37); 3 (33)
	Complex partial + secondarily generalised	7 (39)	9 (56); 4 (44)
	Secondarily generalised	1 (6)	0 (0); 0 (0)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	All seizures	Median 36/3 months	Median: 26, 23/3 months

TABLE 74 *[13] McLean* et al.*, 1993*[148] *[US Gabapentin Study Group]*

Drug(s)	Gabapentin		
Target maintenance dose (mode)	600, 900 or 1800 mg/day, in three doses/day (oral)		
Seizure or syndrome	Refractory partial seizures with or without secondary generalisation		
Type of trial design	Parallel		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age	At least 16 years old		
		Placebo	**Gabapentin: 600; 1200; 1800 mg**
Number randomised		98	53, 101, 54
Age (weeks, months, years) (mean, SD; median, range)		Mean 34; range 17–66 years	Mean 34; 34; 35; range 16–67; 19–65; 18–70 years
Diagnosed seizure types, *n* (%)		Not reported separately by study arm	Not reported separately by study arm
	Simple partial	154 (50)	154 (50)
	Complex partial	284 (98)	284 (98)
	Secondarily generalised partial	193 (63)	193 (63)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	All partial	Mean 31.1; median 10.7, range 2.3–455/months	Mean 21.7; 51.7; 31.5; median 10.0; 11.0; 2.7, range 2.0–272; 2.3–1093; 3.7–208/months

TABLE 75 *[14] Anhut* et al.*, 1994*[149]

Drug(s)	Gabapentin		
Target maintenance dose (mode)	900 or 1200 mg/day, in three doses/day (oral)		
Seizure or syndrome	Refractory simple, complex and secondarily generalised partial seizures		
Type of trial design	Parallel		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age			
		Placebo	**Gabapentin: 900; 1200 mg**
Number randomised		109	111, 52
Age (weeks, months, years) (mean, SD; median, range)		Not reported separately by arm. Mean 32; range 12–67 years	Not reported separately by arm. Mean 32; range 12–67 years
Diagnosed seizure types, *n* (%)	Simple partial	40 (36.7)	42 (37.8); 23 (44.2)
	Complex partial	98 (89.9)	99 (89.2); 48 (92.3)
	Secondarily generalised	58 (53.2)	61 (55.0); 31 (59.6)
	Other	19 (17.4)	28 (25.2); 3 (5.8)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	All partial	Median 9.3/month	Median: 10.3; 9.8/month
	Simple partial	Median 3.8/month	Median: 8.3; 5.0/month
	Complex partial	Median 7.8/month	Median: 7.0; 6.3/month
	Secondarily generalised	Median 1.0/month	Median: 2.0; 1.3/month

TABLE 76 *[15] Leach* et al.*, 1997*[150]

Drug(s)	Gabapentin		
Target maintenance dose (mode)	400, 600 and 800 mg/day, in three doses/day (?mode)		
Seizure or syndrome	Refractory partial seizures with or without secondary generalisation		
Type of trial design	Cross-over		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age			
		Placebo	**Gabapentin**
Number randomised		13	14
Age (weeks, months, years) (mean, SD; median, range)		Not reported separately by arm. Range 16–67, 1 patient <18 years	Not reported separately by arm. Range 16–67, 1 patient <18 years
Diagnosed seizure types, *n* (%)		Not reported separately by study arm	Not reported separately by study arm
	Simple partial	9	9
	Complex partial	17	17
	Secondarily generalised tonic–clonic	17	17
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)		Not reported separately by study arm	Not reported separately by study arm
	Seizures /wk	Median 7, range 3–212	Median 7, range 3–212

TABLE 77 *[16] Lopes-Lima* et al.*, 1999*[288] *abstract*

Drug(s)	Gabapentin		
Target maintenance dose (mode)	1800–2400 mg/day (mode?)		
Seizure or syndrome	Uncontrolled partial epilepsy with or without secondary generalisation		
Type of trial design	Parallel		
Add-on or monotherapy	Monotherapy		
Control(s)	Valproate		
Eligible age			
		Valproate	**Gabapentin**
Number randomised		Not reported	Not reported
Age (weeks, months, years) (mean, SD; median, range)		Not reported separately by arm. Mean 37.8 years	Not reported separately by arm. Mean 37.8 years
Diagnosed seizure types, *n* (%)	Not reported	Not reported	Not reported
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported		

TABLE 78 *[17] Schapel* et al.*, 1993*[151]

Drug(s)	Lamotrigine
Target maintenance dose (mode)	150 or 300 mg/day, in two doses/day (oral)
Seizure or syndrome	Refractory partial seizures with or without secondary generalisation
Type of trial design	Cross-over
Add-on or monotherapy	Add-on
Control(s)	Placebo
Eligible age	

		Placebo	**Lamotrigine**
Number randomised		21	20
Age (weeks, months, years) (mean, SD; median, range)		Not reported separately by arm. Mean 31; median 28, range 17–63 years	Not reported separately by arm. Mean 31; median 28, range 17–63 years
Diagnosed seizure types, *n* (%)	Not reported		
Diagnosed syndrome(s), *n* (%)	Idiopathic/unknown Symptomatic	11 (50) 10 (50)	8 (40) 12 (60)
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	All seizures	Mean 10.4, SD 10.0; range 0.5–46/3 months	Mean 10.5, SD 9.5; range 0–37/3 months

TABLE 79 *[18] Smith* et al.*, 1993*[152]

Drug(s)	Lamotrigine
Target maintenance dose (mode)	200 or 400 mg/day (?mode)
Seizure or syndrome	Refractory partial seizures with or without secondary generalisation
Type of trial design	Cross-over
Add-on or monotherapy	Add-on
Control(s)	Placebo
Eligible age	12–70 years

		Placebo	**Lamotrigine**
Number randomised		Not reported separately	Not reported separately
Age (weeks, months, years) (mean, SD; median, range)		Not reported separately by arm. Mean 33.7; range 15–67 years	Not reported separately by arm. Mean 33.7; range 15–67 years
Diagnosed seizure types, *n* (%)		Not reported separately by arm	Not reported separately by arm
	Simple partial only	9 (11)	9
	Simple and complex partial	6 (7.4)	6
	Complex partial only	30 (37)	30
	Secondarily generalised tonic–clonic	36 (44)	36
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)		Not reported separately by arm	Not reported separately by arm
	Simple partial	Mean 25.9; range 2–70/month	Mean 25.9; range 2–70/month
	Complex partial Secondarily generalised	Mean 25.2; range 1–760/month	Mean 25.2; range 1–760/month
	Tonic–clonic	Mean 5.3; range 1–27/month	Mean 5.3; range 1–27/month

TABLE 80 *[19] Severi* et al.*, 1994*[153]

Drug(s)	Lamotrigine		
Target maintenance dose (mode)	100 or 200 mg/day (?mode)		
Seizure or syndrome	Partial seizures with and without secondary generalisation		
Type of trial design	Parallel		
Add-on or monotherapy	Monotherapy		
Control(s)	Carbamazeoine		
Eligible age			
		Carbamazepine	**Lamotrigine: 100; 200 mg**
Number randomised		9	9; 9
Age (weeks, months, years) (mean, SD; median, range)		Not reported separately by arm. Mean 39.7; range 17–58 years	Not reported separately by arm. Mean 39.7; range 17–58 years
Diagnosed seizure types, *n* (%)		Not reported separately by study arm	Not reported separately by study arm
	Simple and or complex partial seizures	8 (30)	8 (30)
	Simple and or complex partial with generalisation	19 (70)	19 (70)
Diagnosed syndrome(s), *n* (%)		Not reported separately by study arm	
	Cryptogenic partial epilepsy	15 (56)	
	Symptomatic partial epilepsy	12 (44)	
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported here		

TABLE 81 *[20] Cereghino* et al.*, 2000*[154]

Drug(s)	Levetiracetam		
Target maintenance dose (mode)	500 or 1500 mg/day, in two doses/day (oral)		
Seizure or syndrome	Refractory partial seizures with or without secondary generalisation		
Type of trial design	Parallel		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age	16–70 years		
		Placebo	**Levetiracetam: 500; 1500 mg**
Number randomised		95	98; 101
Age (weeks, months, years) (mean, SD; median, range)		Mean 38, SD 11 years	Mean 38, SD 11; mean 38, SD 11 years
Diagnosed seizure types, *n* (%)	Not reported		
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Partial seizures	Median 1.77/week	Median 2.53; 2.08/week

TABLE 82 *[21] Cramer* et al.*, 2000*[155]

Drug(s)	Levetiracetam		
Target maintenance dose (mode)	1 or 3 g/day, in two doses/day (?mode)		
Seizure or syndrome	Refractory simple or partial seizures with or without secondary generalisation		
Type of trial design	Parallel		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age	16–70 years		
		Placebo	**Levetiracetam: 1; 3 g**
Number randomised		81	80, 85
Age (weeks, months, years) (mean, SD; median, range)		Mean 38.5, SD 11.3 years	Mean 39.1, SD 11.3; Mean 38.5, SD 10.2 years
Diagnosed seizure types, *n* (%)	Simple or complex partial	(64.2)	(65.0); (69.4)
	Simple or complex partial with secondary generalisation	(35.8)	(31.3); (29.4)
	Simple partial with secondary generalisation	(0)	(3.7); (1.2)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Partial	Mean 5.66, SD 18.79/week	Mean 7.55, SD 13.99; Mean 5.15, SD 15.58/week

TABLE 83 *[22] Shorvon* et al.*, 2000*[156] *[same patient group as Boon* et al.*, 2002*[289]*]*

Drug(s)	Levetiracetam		
Target maintenance dose (mode)	1000 or 2000 mg/day, in two doses/day (oral)		
Seizure or syndrome	Uncontrolled simple or complex partial seizures with or without secondary generalisation		
Type of trial design	Parallel		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age	16–65 years		
		Placebo	**Levetiracetam: 1000; 2000 mg**
Number randomised		112	106; 106
Age (weeks, months, years) (mean, SD; median, range)		Mean 37, SD 12; range 16–69 years	Mean 36, SD 10; mean 37, SD 12; range 16–68; 14–65 years
Diagnosed seizure types, *n* (%)	Simple partial	40 (36)	31 (29); 30 (28)
	Complex partial	93 (83)	84 (79); 93 (88)
	Secondarily generalised	26 (23)	28 (26); 29 (27)
	Other	8 (7)	4 (4); 10 (9)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	All seizures	Median 2.5/week	Median 2.82; 2.58/week

TABLE 84 *[23] Boon* et al.*, 2002[289] [same patient group as Shorvon* et al.*, 2000[156]]*

Drug(s)	Levetiracetam		
Target maintenance dose (mode)	1000 or 2000 mg/day, in two doses/day (oral)		
Seizure or syndrome	Uncontrolled simple or complex partial seizures with or without secondary generalisation		
Type of trial design	Cross-over		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age			
		Placebo vs 1 g; Placebo vs 2 g	**Levetiracem 1 g vs Placebo 1 g vs 2 g Levetiracem 2 g vs Placebo 2 g vs 1 g**
Number randomised		58; 54	53; 53 54; 52.
Age (weeks, months, years) (mean, SD; median, range)		Mean 37, SD 11; mean 37, SD 13; range 18–64; 16–69 years	Mean 37, SD 9; mean 36, SD 11; range 17–68; 16–56 years Mean 37, SD 11; mean 37, SD 12; range 18–64; 14–65 years
Diagnosed seizure types, *n* (%)	Simple partial	21 (36); 19 (35)	12 (23); 19 (36) 10 (19); 20 (38)
	Complex partial	49 (84); 44 (81)	42 (79); 42 (79) 48 (89); 45 (87)
	Secondarily generalised	15 (26); 11 (20)	11 (21); 17 (32) 14 (26); 15 (29)
	Unclassifiable	7 (12); 1 (2)	2 (4); 2 (4) 4 (7); 6 (12)
Diagnosed syndrome(s), *n* (%)	Cryptogenic/idiopathic	30 (52); 32 (63)	29 (55); 30 (57) 30 (56); 30 (58)
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	All seizures	Median 2.01; 2.65/week	Median 3.03; 2.55/week Median 2.10; 4.34/week

TABLE 85 *[24] Schachter* et al.*, 1999[157]*

Drug(s)	Oxcarbazepine		
Target maintenance dose (mode)	2400 mg/day, in two doses/day (oral)		
Seizure or syndrome	Refractory partial seizures with or without secondary generalisation		
Type of trial design	Parallel		
Add-on or monotherapy	Monotherapy		
Control(s)	Placebo		
Eligible age	11–65 years		
		Placebo	**Oxcarbazepine**
Number randomised		51	51
Age (weeks, months, years) (mean, SD; median, range)		Mean 34 years	Mean 33 years
Diagnosed seizure types, *n* (%)	Not reported		
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	All partial seizures	Mean 4.4/48 h prior to randomisation	Mean 4.9/48 h prior to randomisation

Table 86 *[25] Korean Topiramate Study Group, 1999*[158]

Drug(s)	Topiramate		
Target maintenance dose (mode)	600 mg/day (oral)		
Seizure or syndrome	Refractory partial seizures with or without secondary generalisation		
Type of trial design	Parallel		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age	16–65 years		
		Placebo	**Topiramate**
Number randomised		86	91
Age (weeks, months, years) (mean, SD; median, range)		Mean 29.77, SD 8.71 years	Mean 29.58, SD 7.80 years
Diagnosed seizure types, *n* (%)	Simple partial motor Complex partial Secondarily generalised tonic–clonic	5 (5.8) 72 (83.7) 39 (34.9)	11 (12.1) 70 (76.9) 31 (34.1)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	All seizures	Mean 11.5, SD 2.4; Median 5.6/month	Mean 9.4, SD 14.8; Median 5.6/month

TABLE 87 *[26] Dodrill* et al.*, 1993*[290] *[same trial as French* et al.*, 1993*[299]*]*

Drug(s)	Vigabatrin		
Target maintenance dose (mode)	3 g/day		
Seizure or syndrome	Refractory complex partial seizures or partial seizures with secondary generalisation		
Type of trial design	Parallel		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age			
		Placebo	**Vigabatrin**
Number randomised		85	83
Age (wks, months, yrs) (mean, SD; median, range)		Mean 34.39, SD 8.66 years; range not reported	Mean 34.25, SD 8.24 years; range not reported
Diagnosed seizure types, *n* (%)	Not reported for all randomised patients		
Diagnosed syndrome(s), *n* (%)	Not reported for all randomised patients		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported for all randomised patients		

TABLE 88 *[27] Grunewald* et al.*, 1994*[159]

Drug(s)	Vigabatrin		
Target maintenance dose (mode)	3 g/day, in two doses/day (?mode)		
Seizure or syndrome	Refractory simple and complex seizures with and without secondary generalisation		
Type of trial design	Parallel		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age			
		Placebo	**Vigabatrin**
Number randomised		23	22
Age (weeks, months, years) (mean, SD; median, range)		Median 27, range 16–55 years	Median 29, range 17–59 years
Diagnosed seizure types, *n* (%) separately		Not reported separately by study arm	Not reported by study arm
	Simple partial	35	35
	Complex partial	44	44
	Secondarily generalised	14	14
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Simple partial	Median 2/8, range 0–55 weeks	Median 4/8, range 0–91 weeks
	Complex partial	Median 8/8, range 0–124 weeks	Median 15/8, range 0–38 weeks
	Secondarily generalised	Median 0/8, range 0–13 weeks	Median 0/8, range 0–17 weeks

TABLE 89 *[28] Brodie and Mumford, 1999*[160]

Drug(s)	Vigabatrin		
Target maintenance dose (mode)	2–4 g/day (oral)		
Seizure or syndrome	Refractory simple or partial seizures with or without secondary generalisation		
Type of trial design	Parallel		
Add-on or monotherapy	Add-on		
Control(s)	Valproate		
Eligible age	12–75 years		
		Valproate	**Vigabatrin**
Number randomised		107	108
Age (weeks, months, years) (mean, SD; median, range)		Median 36, range 16–66 years	Median 37, range 12–78 years
Diagnosed seizure types, *n* (%)	All seizures	107 (100)	108 (100)
	Simple partial	35 (33)	33 (31)
	Complex partial	71 (66)	74 (69)
	Secondarily generalised	19 (18)	17 (16)
	Not known	0 (0)	2 (2)
Diagnosed syndrome(s), *n* (%)			
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	All seizures	Mean 6.9; median 5/month	Mean 6.8; median 5/month

Study population diagnosed with refractory complex partial seizures

TABLE 90 *[29] Dodrill* et al.*, 1997[161] [some details from Uthman* et al.*, 1998[291]]*

Drug(s)	Tiagabine		
Target maintenance dose (mode)	16, 32, 56 mg/day (?mode)		
Seizure or syndrome	Intractable complex partial epilepsy		
Type of trial design	Parallel		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age	12–77 years		
		Placebo	**Tiagabine: 13; 32; 56 mg**
Number randomised		91	61; 88; 57
Age (weeks, months, years) (mean, SD; median, range)		Not reported separately All: mean 34; range 12–77 years	Not reported separately All: mean 34; range 12–77 years
Diagnosed seizure types, *n* (%)	Not reported	Not reported	Not reported
Diagnosed syndrome(s) *n* (%)			
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	All seizures Secondarily generalised seizures	Median 8.6/month Median 7.4, range 2.8–109/month	Median 9.7; 13.7; 9.1/month Median 7.4; 8.5; 9.6, range 2.6–170; 2.2–401; 2.1–209/month

Table 91 *[30] Uthman* et al.*, 1998[291]*

Drug(s)	Tiagabine		
Target maintenance dose (mode)	16, 32, 56 mg/day, in four doses/day (?mode)		
Seizure or syndrome	Intractable complex partial epilepsy		
Type of trial design	Parallel		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age	12–77 years		
		Placebo	**Tiagabine: 13; 32; 56 mg**
Number randomised		91	61; 88; 57
Age (weeks, months, years) (mean, SD; median, range)		Not reported separately by arm. Mean 34; range 12–77 years	Not reported separately by arm. Mean 34; range 12–77 years
Diagnosed seizure types, *n* (%)		Not reported separately by study arm	Not reported separately by study arm
	Simple partial Secondarily generalised tonic–clonic	166 (57) 106 (36)	166 (57) 106 (36)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Simple partial seizures Complex partial seizures	Median 8.6/month Median 7.4, range 2.8–109/month	Median 9.7; 13.7; 9.1/month Median 7.4; 8.5; 9.6, range 2.6–170; 2.2–401; 2.1–209/month

TABLE 92 *[31] Dodrill* et al.*, 2000*[162]

Drug(s)	Tiagabine		
Target maintenance dose (mode)	Not reported (see ref. Biton *et al.*[335])		
Seizure or syndrome	Complex partial seizures		
Type of trial design	Parallel		
Add-on or monotherapy	Add-on		
Control(s)	Phenytoin or carbamazepine		
Eligible age	Receiving carbamazepine or phenytoin; 13 patients <16 years old excluded		
		Carbamazepine + phenytoin; phenytoin + carbamazepine	**Carbamazepine + tiagabine; phenytoin + tiagabine**
Number randomised		71; 66	82; 58
Age (weeks, months, years) (mean, SD; median, range)		Mean 33.3, SD 13.1; mean 40.42, SD 12.2 years	Mean 37.1, SD 13.1; mean 39.4, SD 13.5 years
Diagnosed seizure types, *n* (%)	All partial Complex partial Generalised tonic–clonic	70 (99); 66 (100) 70 (99); 66 (100) 23 (32); 20 (30)	81 (99); 57 (98) 81 (99); 58 (100) 24 (29); 22 (40)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Total partial seizures Complex partial seizures Generalised tonic–clonic seizures	Median 7; 6/month Median 10; 8/month Median 2; 2/month	Median 6; 7/month Median 7; 9/month Median 2; 1/month

TABLE 93 *[32] Beran* et al.*, 1996*[163]

Drug(s)	Vigabatrin		
Target maintenance dose (mode)	2 or 3 g/day (oral)		
Seizure or syndrome	Uncontrolled complex partial seizures		
Type of trial design	Cross-over		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age	16–65 years		
		Placebo	**Vigabatrin: 2; 3 g**
Number randomised		Unclear	Unclear
Age (weeks, months, years) (mean, SD; median, range)		Not reported separately by arm. Range 17–64 years	Not reported separately by arm. Range 17–64 years
Diagnosed seizure types, *n* (%)	Not reported		
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported		

Study population diagnosed with refractory complex partial seizures with or without secondary generalisation

TABLE 94 *[33] Ben Menachem* et al.*, 1995*[164]

Drug(s)	Gabapentin		
Target maintenance dose (mode)	900 or 1200 mg/day (?mode)		
Seizure or syndrome	Refractory complex partial seizures with or without secondary generalisation		
Type of trial design	Parallel		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age			
		Placebo	**Gabapentin: 900; 1200 mg**
Number randomised		12	16; 8
Age (weeks, months, years) (mean, SD; median, range)		Not reported separately by arm. Mean 37; range 16–66 years	Not reported separately by arm. Mean 37; range 16–66 years
Diagnosed seizure types, *n* (%)	Not reported		
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Reported by histogram only	~20/month	~37; 50/month

Table 95 *[34] Ben Menachem and Falter, 2000*[165]

Drug(s)	Levetiracetam		
Target maintenance dose (mode)	3 g/day, in two doses/day (oral)		
Seizure or syndrome	Refractory complex partial seizures with or without secondary generalisation		
Type of trial design	Parallel		
Add-on or monotherapy	Add-on (with secondary monotherapy for responders)		
Control(s)	Placebo		
Eligible age	16–70 years		
		Placebo	**Levetiracetam**
Number randomised		105	181
Age (weeks, months, years) (mean, SD; median, range)		Mean 36, SD 12 years	Mean 37, SD 12 years
Diagnosed seizure types, *n* (%)	Not reported		
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Partial	Median 1.75/week	Median 1.69/week

TABLE 96 *[35] Sachdeo* et al.*, 1997*[166]

Drug(s)	Tiagabine		
Target maintenance dose (mode)	32 mg/day, in two from 4 doses/day (oral)		
Seizure or syndrome	Refractory complex partial seizures with or without secondary generalisation		
Type of trial design	Parallel		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age	12–75 years		
		Placebo	**Tiagabine: 2; 4×/day**
Number randomised		107	106; 105
Age (weeks, months, years) (mean, SD; median, range)		Mean 35.3; range 13–71 years	Mean 33.4; 32.6; range 12–67; 12–66 years
Diagnosed seizure types, *n* (%)	Not reported		
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Complex partial seizures	Median 8.0/month	Median: 8.4; 7.9/month

TABLE 97 *[36] Rimmer and Richeus, 1984*[167]

Drug(s)	Vigabatrin		
Target maintenance dose (mode)	3 g/day (?mode)		
Seizure or syndrome	Refractory complex partial seizures with or without secondary generalisation		
Type of trial design	Cross-over		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age			
		Placebo	**Vigabatrin**
Number randomised		Not reported	Not reported
Age (weeks, months, years) (mean, SD; median, range)		Not reported separately by arm. Mean 33; range 16–61 years	Not reported separately by arm. Mean 33; range 16–61 years
Diagnosed seizure types, *n* (%)	Not reported		
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported for all randomised patients		

TABLE 98 *[37] Gram* et al.*, 1985*[168]

Drug(s)	Vigabatrin		
Target maintenance dose (mode)	3 g/day, in two doses/day (oral)		
Seizure or syndrome	Refractory complex partial seizures with or without generalisation		
Type of trial design	Cross-over		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age			
		Placebo	**Vigabatrin**
Number randomised		Not reported	Not reported
Age (weeks, months, years) (mean, SD; median, range)		Not reported by arm. Range 17–63 years	Not reported by arm. Range 17–63 years
Diagnosed seizure types, *n* (%)	Not reported	Not reported	Not reported
Diagnosed syndrome(s), *n* (%)	Not reported	Not reported	Not reported
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported	Not reported	Not reported

TABLE 99 *[38] Cramer* et al.*, 1995*[169]

Drug(s)	Vigabatrin		
Target maintenance dose (mode)	4 g/day, in two doses/day (oral)		
Seizure or syndrome	Refractory complex partial seizures with or without secondary generalisation		
Type of trial design	Parallel		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age	16–50 years		
		Placebo	**Vigabatrin**
Number randomised		Not reported	Not reported
Age (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
Diagnosed seizure types, *n* (%)	Not reported		
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported		

TABLE 100 *[39] Provinciali et al, 1996*[170]

Drug(s)	Vigabatrin		
Target maintenance dose (mode)	2–3 g/day (?mode)		
Seizure or syndrome	Refractory complex partial seizures with or without secondary generalisation		
Type of trial design	Parallel		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age	17–66 years		
		Placebo	**Vigabatrin**
Number randomised		20	20
Age (weeks, months, years) (mean, SD; median, range)		Median 38.2, range 20–66 years	Median 34.8, range 17–66 years
Diagnosed seizure types, *n* (%)	Complex partial Secondarily generalised	13 (65) 7 (35)	11 (55) 9 (45)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	All seizures	4/week and 16/month medians or means unclear	5/week and 15/month medians or means unclear

Study population diagnosed with refractory primary generalised seizures

TABLE 101 *[40] Chadwick et al, 1996*[171]

Drug(s)	Gabapentin		
Target maintenance dose (mode)	1200 mg/day (?mode)		
Seizure or syndrome	Refractory generalised seizures		
Type of trial design	Parallel		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age	≥ 12 years		
		Placebo	**Gabapentin**
Number randomised		71	58
Age (weeks, months, years) (mean, SD; median, range)		Mean 29; range 13–61 years	Mean 30; range 16–62 years
Diagnosed seizure types, *n* (%)	Not reported		
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Generalised tonic–clonic	Mean 7.3; median 3.3, range 0–103.3/month	Mean 7.4; median 3.9, range 0–54.3/month

TABLE 102 *[41] Beran* et al.*, 1998*[172]

Drug(s)	Lamotrigine		
Target maintenance dose (mode)	75 or 150 mg/day (oral)		
Seizure or syndrome	Treatment-resistant idiopathic generalised epilepsy		
Type of trial design	Cross-over		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age	15–50 years		
		Placebo	**Lamotrigine**
Number randomised		Total 26; not reported separately by arm	Total 26; not reported separately by arm
Age (weeks, months, years) (mean, SD; median, range)		Not reported separately by arm. Mean 29; range 15–50 years	Not reported separately by arm. Mean 29; range 15–50 years
Diagnosed seizure types, *n* (%)		Not reported separately by study arm	Not reported separately by study arm
	Absence only	8 (31)	8 (31)
	Absence and tonic–clonic	12 (42)	12 (42)
	Tonic–clonic only	2 (8)	2 (8)
	Myoclonic only	1 (4)	1 (4)
	Myoclonic and tonic–clonic	1 (4)	1 (4)
	Absence, myoclonic and tonic–clonic	2 (8)	2 (8)
Diagnosed syndrome(s), *n* (%)		Not reported separately by study arm	Not reported separately by study arm
	Idiopathic generalised	26 (100)	26 (100)
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported	Not reported	Not reported

TABLE 103 *[42] Biton* et al.*, 1999*[173]

Drug(s)		Topiramate	
Target maintenance dose (mode)		5.2–9.3 mg/kg/day (depending on body mass), in two doses/day (oral)	
Seizure or syndrome		Refractory primary generalised tonic–clonic seizures with or without other generalised seizure types	
Type of trial design		Parallel	
Add-on or monotherapy		Add-on	
Control(s)		Placebo	
Eligible age		At least 4 years	
		Placebo	**Topiramate**
Number randomised		41	39
Age (weeks, months, years) (mean, SD; median, range)		Mean 25.6, SD 13.4; range 3.0–50 years; *n* = 13 aged ≤ 16 years	Mean 26.8, SD 12.8; range 5.0–59 years; n = 8 aged ≤ 16 years
Diagnosed seizure types, *n* (%)	Tonic–clonic	40 (98)	39 (100)
	Tonic–clonic only	13 (32)	13 (33)
	Absence	16 (39)	16 (41)
	Tonic	10 (24)	9 (23)
	Myoclonic	8 (20)	8 (21)
	Drop attack	5 (12)	2 (5)
	Atypical absence	4 (10)	2 (5)
	Clonic	1 (2)	1 (3)
	Other	1 (2)	1 (3)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	All seizures	Median 17.5, range 2–79, 109/month	Median 15.3, range 1–1134/month
	Primary generalised tonic–clonic	Median 4.5, range 1–300/month	Median 5.0, range 1–298/month

Study population mixed: some patients with newly diagnosed partial seizures and others with newly diagnosed primary generalised seizures

TABLE 104 *[43] Chadwick* et al.*, 1998*[174]

Drug(s)	Gabapentin		
Target maintenance dose (mode)	300, 900 or 1800 mg/day (oral)		
Seizure or syndrome	Newly diagnosed partial seizures with or without secondary generalisation or generalised tonic–clonic seizures		
Type of trial design	Parallel		
Add-on or monotherapy	Monotherapy		
Control(s)	Carbamazepine		
Eligible age			
		Carbamazepine	**Gabapentin: 300; 900; 1800 mg**
Number randomised		74	72; 72; 74
Age (weeks, months, years) (mean, SD; median, range)		Mean 34, SD 16.4; range 13–72 years	Mean 37, SD 17.3; 34, SD 16.0; 37, SD 16.9; range 12–83; 15–73; 12–86 years
Diagnosed seizure types, *n* (%)	Simple partial	32 (43)	17 (24); 21 (29); 27 (36)
	Complex partial	32 (43)	28 (39); 32 (44); 34 (46)
	Secondarily generalised tonic–clonic	37 (50)	32 (44); 38 (53); 41 (5)
	Generalised tonic–clonic	17 (23)	22 (31); 14 (19); 11 (15)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	NA		

TABLE 105 *[44] Brodie* et al.*, 1995*[175]

Drug(s)	Lamotrigine		
Target maintenance dose (mode)	150 mg/day, in two doses/day (oral)		
Seizure or syndrome	Partial with and without secondary generalisation, primary and secondary tonic–clonic seizures		
Type of trial design	Parallel		
Add-on or monotherapy	Monotherapy		
Control(s)	Carbamazepine		
Eligible age	≥ 13 years		
		Carbamazepine	**Lamotrigine**
Number randomised		129	131
Age (weeks, months, years) (mean, SD; median, range)		Median 27; range 13–81 years	Median 28; range 14–70 years
Diagnosed seizure types, *n* (%)	Partial with and without secondary generalisation	73 (57)	73 (56)
	Primary generalised tonic–clonic seizures	62 (48)	60 (46)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported		

TABLE 106 *[45] Dam, 1996*[176]

Drug(s)	Lamotrigine
Target maintenance dose (mode)	100 or 200 mg/day (?mode)
Seizure or syndrome	Newly diagnosed primary generalised seizures (presumed) or partial seizures with or without secondary generalisation
Type of trial design	Parallel
Add-on or monotherapy	Monotherapy (presumed)
Control(s)	Carbamazepine
Eligible age	12–72 years

		Carbamazepine	**Lamotrigine: 100; 200 mg**
Number randomised		117	115; 111
Age (weeks, months, years) (mean, SD; median, range)		Not reported separately by arm. Range 12–72 years	Not reported separately by arm. Range 12–72 years
Diagnosed seizure types, *n* (%)	Not reported		
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported		

TABLE 107 *[46] Reunanen* et al.*, 1996*[292]

Drug(s)	Lamotrigine
Target maintenance dose (mode)	100 or 200 mg/day, single dose/day (oral)
Seizure or syndrome	Newly diagnosed or recurrent untreated partial and/or generalised tonic–clonic seizures
Type of trial design	Parallel
Add-on or monotherapy	Monotherapy
Control(s)	Carbamazepine
Eligible age	>12 years

		Carbamazepine	**Lamotrigine: 100; 200 mg**
Number randomised		117	115;111
Age (weeks, months, years) (mean, SD; median, range)		Mean 32; range 13–71 years	Mean 33; 30; range 13–72; 12–66 years
Diagnosed seizure types, *n* (%)	Not reported		
Diagnosed syndrome(s), *n* (%)	'Symptomatic'	(25)	(25); (22)
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	All seizures	Mean 14.5; median 3.0/6 months	Mean 9.3; 11.9; median 3.0; 3.0/6 months

TABLE 108 *[47] Steiner* et al.*, 1999*[177]

Drug(s)	Lamotrigine
Target maintenance dose (mode)	Not specified
Seizure or syndrome	Newly diagnosed untreated epilepsy
Type of trial design	Parallel
Add-on or monotherapy	Monotherapy
Control(s)	Phenytoin
Eligible age	14–75 years

		Phenytoin	**Lamotrigine**
Number randomised		95	86
Age (weeks, months, years) (mean, SD; median, range)		Median 27, range 13–74 years	Median 28, range 13–70 years
Diagnosed seizure types, *n* (%)	Partial only	26 (27)	24 (28)
	Partial with secondary generalisation	20 (21)	20 (23)
	Primary generalised tonic–clonic	49 (52)	42 (49)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	All seizures	Median 4, range 1–200/6 months	Median 3, range 2–600/6 months

TABLE 109 *[48] Gillham* et al.*, 2000*[293] *[details as Brodie* et al.*, 1995*[175]*]*

Drug(s)	Lamotrigine
Target maintenance dose (mode)	150 mg/day, in two doses/day (oral)
Seizure or syndrome	Newly diagnosed epilepsy
Type of trial design	Parallel
Add-on or monotherapy	Monotherapy
Control(s)	Carbamazepine
Eligible age	≥ 13 years

		Carbamazepine	**Lamotrigine**
Number randomised		129	131
Age (weeks, months, years) (mean, SD; median, range)		Median 27, range 13–81 years	Median 28, range 14–70 years
Diagnosed seizure types, *n* (%)	Not reported	Not reported	Not reported
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported		

TABLE 110 *[49] Kalogjera* et al.*, 2000,*[178] *abstract*

Drug(s)	Lamotrigine		
Target maintenance dose (mode)	200–500 mg/day (mode?)		
Seizure or syndrome	New onset partial or generalised seizures		
Type of trial design	Parallel		
Add-on or monotherapy	Unclear		
Control(s)	Valproate		
Eligible age	≥ 12 years		
		Valproate	**Lamotrigine**
Number randomised		68	65
Age (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
Diagnosed seizure types, *n* (%)	Not reported	Not reported	Not reported
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported		

TABLE 111 *[50] Biton* et al.*, 2001*[242]

Drug(s)	Lamotrigine		
Target maintenance dose (mode)	200 mg/day (oral)		
Seizure or syndrome	Epilepsy with any seizure type		
Type of trial design	Parallel		
Add-on or monotherapy	Monotherapy		
Control(s)	Valproate		
Eligible age	At least 12 years		
		Valproate	**Lamotrigine**
Number randomised		68	65
Age (weeks, months, years) (mean, SD; median, range)		Mean 30.1, SD 14; range 12–76 years; 19% <18 years	Mean 34.5, SD 16; range 12–68 years; 18% <18 years
Diagnosed seizure types, *n* (%)	Complex partial	23 (34)	17 (26)
	Partial with secondary generalisation	18 (26)	18 (28)
	Generalised tonic–clonic	55 (81)	50 (77)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported		

TABLE 112 *[51] Edwards* et al.*, 2001[294] [details as Biton* et al.*, 2001[242]]*

Drug(s)	Lamotrigine		
Target maintenance dose (mode)	200 mg/day (oral)		
Seizure or syndrome	Epilepsy with any seizure type		
Type of trial design	Parallel		
Add-on or monotherapy	Monotherapy		
Control(s)	Valproate		
Eligible age	At least 12 years		
		Valproate	**Lamotrigine**
Number randomised		68	65
Age (weeks, months, years) (mean, SD; median, range)		Mean 30.1, SD 14; range 12–76 years; 19% <18 years	Mean 34.5, SD 16; range 12–68 years; 18% <18 years
Diagnosed seizure types, *n* (%)	Complex partial	(34)	(26)
	Partial with secondary generalisation	(26)	(28)
	Generalised tonic–clonic	(81)	(77)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported		

TABLE 113 *[52] Dam* et al.*, 1989[179]*

Drug(s)	Oxcarbazepine		
Target maintenance dose (mode)	"best therapeutic dose with satisfactory tolerability" [at least 300 mg/day] (?mode)		
Seizure or syndrome	Primary generalised seizures or partial seizures with or without secondary generalisation		
Type of trial design	Parallel		
Add-on or monotherapy	Monotherapy		
Control(s)	Carbamazepine		
Eligible age	15–65 years old		
		Carbamazepine	**Oxcarbazepine**
Number randomised		100	94
Age (weeks, months, years) (mean, SD; median, range)		Median 33, range 15–63 years	Median 32.5, range 14–63 years
Diagnosed seizure types, *n* (%)	Not reported	Not reported	Not reported
Diagnosed syndrome(s), *n* (%)	Not reported	Not reported	Not reported
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Unclear		

TABLE 114 *[53 Aikia* et al.*, 1992*[295]

Drug(s)	Oxcarbazepine		
Target maintenance dose (mode)	To achieve 30–120 μmol/l oxcarbazepine metabolite in plasma		
Seizure or syndrome	Newly diagnosed generalised seizures or partial seizures with or without secondary generalisation		
Type of trial design	Parallel		
Add-on or monotherapy	Monotherapy		
Control(s)	Phenytoin		
Eligible age			
		Phenytoin	**Oxcarbazepine**
Number randomised		18	19
Age (weeks, months, years) (mean, SD; median, range)		Mean 32.7, SD 12.5 years; not reported for all randomised patients	Mean 33.6, SD 14.0 years; not reported for all randomised patients
Diagnosed seizure types, *n* (%)	Not reported for all randomised patients		
Diagnosed syndrome(s), *n* (%)	Not reported for all randomised patients		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported for all randomised patients		

TABLE 115 *[54] Bill* et al.*, 1997*[180]

Drug(s)	Oxcarbazepine		
Target maintenance dose (mode)	450–2400 mg/day, in three doses/day (oral)		
Seizure or syndrome	Newly diagnosed untreated seizures with partial or generalised onset		
Type of trial design	Parallel		
Add-on or monotherapy	Monotherapy		
Control(s)	Phenytoin		
Eligible age	16–65 years		
		Phenytoin	**Oxcarbazepine**
Number randomised		144	143
Age (weeks, months, years) (mean, SD; median, range)		Mean 26.6; range 15–91 years	Mean 27.1; range 16–63 years
Diagnosed seizure types, *n* (%)	Partial ± generalisation	98 (68)	84 (59)
	Generalised without partial onset	46 (32)	58 (41)
	No main type	0 (0)	1 (1)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	All seizures	Mean 0.84; median 0.23/week	Mean 0.98; median 0.20/week

TABLE 116 *[55] Christe* et al.*, 1997*[181]

Drug(s)	Oxcarbazepine		
Target maintenance dose (mode)	900–2400 mg/day, in three doses/day (oral)		
Seizure or syndrome	Newly diagnosed seizures with partial or generalised onset		
Type of trial design	Parallel		
Add-on or monotherapy	Add-on		
Control(s)	Valproate		
Eligible age	15–65 years		
		Valproate	**Oxcarbazepine**
Number randomised		121	128
Age (weeks, months, years) (mean, SD; median, range)		Mean 32.5; range 15–64 years	Mean 32.4; range 15–65 years
Diagnosed seizure types, *n* (%)	Partial ± generalisation Generalised without partial onset	78 (65) 43 (36)	76 (59) 52 (41)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	All seizures	Mean 0.58; median 0.13/week	Mean 1.09; median 0.25/week

TABLE 117 *[56] Wheless* et al.*, 2001,*[182] *abstract*

Drug(s)	Topiramate		
Target maintenance dose (mode)	100 or 200 mg/day (mode?)		
Seizure or syndrome	Newly diagnosed epilepsy (any seizure type or syndrome)		
Type of trial design	Parallel		
Add-on or monotherapy	Monotherapy		
Control(s)	Valproate, carbamazepine		
Eligible age	≥ 6 years		
		Valproate/carbamazepine	**Topiramate**
Number randomised		Total 626 (?); not reported separately by arm	Not reported
Age (weeks, months, years) (mean, SD; median, range)		Not reported separately by arm. 119 patients 6–16 years old	Not reported separately by arm. 119 patients 6–16 years old
Diagnosed seizure types, *n* (%)	Not reported	Not reported	Not reported
Diagnosed syndrome(s), *n* (%)	Not reported	Not reported	Not reported
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported	Not reported	Not reported

TABLE 118 *[57] Kalviainen* et al.*, 1995*[183]

Drug(s)	Vigabatrin		
Target maintenance dose (mode)	50 mg/kg/day (?mode)		
Seizure or syndrome	Newly diagnosed tonic–clonic generalised seizures or partial seizures with or without generalisation		
Type of trial design	Parallel		
Add-on or monotherapy	Monotherapy		
Control(s)	Carbamazepine		
Eligible age	15–64 years		
		Carbamazepine	**Vigabatrin**
Number randomised		50	50
Age (weeks, months, years) (mean, SD; median, range)		Mean 37, SD 16 years	Mean 33, SD 16 years
Diagnosed seizure types, *n* (%)	Complex partial only	4 (8)	4 (8)
	Partial and secondarily generalised	11 (22)	10 (20)
	Secondarily generalised only	27 (54)	25 (50)
	Primary generalised	1 (2)	4 (8)
	Unclassified generalised	7 (14)	7 (14)
Diagnosed syndrome(s), *n* (%)	Cryptogenic	40 (80)	35 (70)
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	NA		

Study population mixed: some patients diagnosed with refractory partial seizures, others with refractory primary generalised seizures

TABLE 119 *[58] Binnie* et al.*, 1987*[184]

Drug(s)	Lamotrigine		
Target maintenance dose (mode)	50–400 mg/day, in two doses/day (to give peak of ~0.003 mg/ml in plasma)		
Seizure or syndrome	Refractory simple or complex partial, or atonic, or absence, or tonic–clonic, or myoclonic		
Type of trial design	Cross-over		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age			
		Placebo	**Lamotrigine**
Number randomised		5	5
Age (weeks, months, years) (mean, SD; median, range)		24, 29, 29, 29, 46 years	16, 25, 27, 37, 43 years
Diagnosed seizure types, *n* (%)	Simple partial	1 (20)	0 (0)
	Complex partial	2 (40)	1 (20)
	Tonic–clonic	0 (0)	1 (20)
	Complex partial and tonic–clonic	1 (20)	2 (40)
	Simple and complex partial and myoclonic	1 (20)	0 (0)
	Atonic and myoclonic and absence	0 (0)	1 (20)
Diagnosed syndrome(s), *n* (%)	Not reported	Not reported	Not reported
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported	Not reported	Not reported

TABLE 120 *[59] Betts* et al.*, 2000*[185]

Drug(s)	Levetiracetam		
Target maintenance dose (mode)	2 or 4 g/day, in two doses /day (oral)		
Seizure or syndrome	Refractory generalised tonic–clonic seizures or partial seizures with or without secondary generalisation		
Type of trial design	Parallel		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age	16–70 years		
		Placebo	**Levetiracetam: 2; 4 g**
Number randomised		39	42; 38
Age (weeks, months, years) (mean, SD; median, range)		Mean 35, SD 12 years	Mean 39, SD 13; mean 40, SD 12 years
Diagnosed seizure types, *n* (%)	Not reported		
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported		

TABLE 121 *[60] Houtkooper* et al.*, 1987*[186]

Drug(s)	Oxcarbazepine		
Target maintenance dose (mode)	Tolerable dose (oral)		
Seizure or syndrome	Refractory partial or generalised or mixed seizure types		
Type of trial design	Cross–over		
Add-on or monotherapy	Add on		
Control(s)	Carbamazepine		
Eligible age			
		Carbamazepine	**Oxcarbazepine**
Number randomised		Not reported	Not reported
Age (weeks, months, years) (mean, SD; median, range)		Not reported separately by arm. Median 29, range 15–50 years	Not reported separately by arm. Median 29, range 15–50 years
Diagnosed seizure types, *n* (%)		Not reported separately by study arm	Not reported separately by study arm
	Generalised	9 (19)	9 (19)
	Partial	10 (21)	10 (21)
	Both generalised and partial	29 (60)	29 (60)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported for all randomised patients		

TABLE 122 *[61] Coles* et al.*, 1999,*[296] *abstract*

Drug(s)	Topiramate		
Target maintenance dose (mode)	Not reported		
Seizure or syndrome	Refractory primary generalised or partial onset tonic-clonic		
Type of trial design	Parallel		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age			
		Placebo	**Topiramate**
Number randomised		Total 128; not reported separately by arm	Total 128; not reported separately by arm
Age (weeks, months, years) (mean, SD; median, range)		Not reported separately by arm. Median 39 years	Not reported separately by arm. Median 39 years
Diagnosed seizure types, *n* (%)		Not reported separately by study arm	Not reported separately by study arm
	Simple partial	29 (23)	29 (23)
	Complex partial	79 (62)	79 (62)
	Secondarily generalised partial	41 (32)	41 (32)
	Primary generalised tonic–clonic	12 (9)	12 (9)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported		

TABLE 123 *[62] Loiseau* et al.*, 1986*[187]

Drug(s)	Vigabatrin		
Target maintenance dose (mode)	3 g/day, in two doses/day (oral)		
Seizure or syndrome	Refractory complex partial or generalised seizures		
Type of trial design	Cross-over		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age			
		Placebo	**Vigabatrin**
Number randomised		Not reported	Not reported
Age (weeks, months, years) (mean, SD; median, range)		Not reported separately by arm. Mean 28.9, SD 14.9; median 24, range 10–58 years	Not reported separately by arm. Mean 28.9, SD 14.9; median 24, range 10–58 years
Diagnosed seizure types, *n* (%)		Not reported separately by study arm	Not reported separately by study arm
	Complex	10 (43)	10 (43)
	Complex with secondary generalisation	9 (39)	9 (39)
	Tonic–clonic, myoclonic, absence	1 (4)	1 (4)
	Myoclonic absence	1 (4)	1 (4)
	Tonic–clonic absence	1 (4)	1 (4)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported for all randomised patients		

TABLE 124 *[63] Tartara* et al.*, 1986*[188]

Drug(s)	Vigabatrin		
Target maintenance dose (mode)	2 or 3 g/day, in two doses/day (oral)		
Seizure or syndrome	Refractory absence or atonic or partial with or without secondary generalisation		
Type of trial design	Cross-over		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age	16–65 years		
		Placebo	**Vigabatrin**
Number randomised		Not reported	Not reported
Age (weeks, months, years) (mean, SD; median, range)		Not reported separately by arm. Mean 30.5, SD 9.7; median 30, range 17–50 years	Not reported separately by arm. Mean 30.5, SD 9.7; median 30, range 17–50 years
Diagnosed seizure types, *n* (%)		Not reported separately by study arm	Not reported separately by study arm
	Complex partial	15 (65)	15 (65)
	Complex partial with secondary generalisation	2 (9)	2 (9)
	Simple partial with secondary generalisation	3 (13)	3 (13)
	Absence	2 (9)	2 (9)
	Atonic	1 (4)	1 (4)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported for all randomised patients		

TABLE 125 *[64] Rimmer* et al.*, 1987*[189]

Drug(s)	Vigabatrin		
Target maintenance dose (mode)	Acute single dose of 3 g (oral)		
Seizure or syndrome	Light-triggered primary generalised tonic–clonic or complex partial with secondary generalisation		
Type of trial design	Cross-over		
Add-on or monotherapy	Mixed		
Control(s)	Acute single dose of valproate of 1 g (oral)		
Eligible age			
		Valproate	**Vigabatrin**
Number randomised		Total 6; not reported separately by arm	Total 6; not reported separately by arm
Age (weeks, months, years) (mean, SD; median, range)		Not reported separately by arm. Mean 18; range 10–25 years	Not reported separately by arm. Mean 18; range 10–25 years
Diagnosed seizure types, *n* (%)		Not reported separately by study arm	Not reported separately by study arm
	Complex secondarily generalised	2 (33)	2 (33)
	Primary generalised tonic–clonic	4 (66)	4 (66)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported		

TABLE 126 *[65] Tassinari* et al.*, 1987*[190]

Drug(s)	Vigabatrin		
Target maintenance dose (mode)	2–3 g/day, in two doses/day (oral)		
Seizure or syndrome	Refractory primary generalised seizures or complex partial seizures with or without secondary generalisation		
Type of trial design	Parallel		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age	10–58 years		
		Placebo	**Vigabatrin**
Number randomised		15	16
Age (weeks, months, years) (mean, SD; median, range)		Not reported separately by arm. Mean 28.9, SD 11.5; range 10–58 years	Not reported separately by arm. Mean 28.9, SD 11.5; range 10–58 years
Diagnosed seizure types, *n* (%)		Not reported separately by study arm	Not reported separately by study arm
	Complex partial with or without secondarily generalised	15 (100)	15 (100)
	Complex with atonic	8 (53)	8 (53)
	Partial (various types)	7 (47)	7 (47)
	Progressive myoclonic	1 (7)	1 (7)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	All seizures	Not reported separately by study arm; reported for 30 of 31 randomised patients. Mean 12.2, SD 17.8; range 1–89/week	Not reported separately by study arm; reported for 30 of 31 randomised patients. Mean 12.2, SD 17.8; range 1–89/week

TABLE 127 *[66] Reynolds* et al.*, 1988,*[192] *abstract*

Drug(s)	Vigabatrin		
Target maintenance dose (mode)	3 g/day (?mode)		
Seizure or syndrome	Refractory generalised tonic–clonic seizures or partial seizures with or without generalisation		
Type of trial design	Parallel ("responders" only randomised)		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age	16–61 years		
		Placebo	**Vigabatrin**
Number randomised		Total 19; not reported separately by arm	Total 19; not reported separately by arm
Age (weeks, months, years) (mean, SD; median, range)		Not reported for randomised patients	Not reported for randomised patients
Diagnosed seizure types, *n* (%)	Not reported	Not reported	Not reported
Diagnosed syndrome(s), *n* (%)	Not reported	Not reported	Not reported
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported	Not reported	Not reported

TABLE 128 *[67] Reynolds* et al.*, 1991*[191]

Drug(s)	Vigabatrin
Target maintenance dose (mode)	3 g/day, in two doses/day (oral)
Seizure or syndrome	Refractory generalised seizures or partial seizures with or without secondary generalisation
Type of trial design	Parallel (after randomisation of "responders")
Add-on or monotherapy	Add-on
Control(s)	Placebo
Eligible age	16–65 years

		Placebo	**Vigabatrin**
Number randomised		10	10
Age (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
Diagnosed seizure types, *n* (%)	Not reported	Not reported	Not reported
Diagnosed syndrome(s), *n* (%)	Not reported	Not reported	Not reported
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported	Not reported	Not reported

TABLE 129 *[68] Gillham* et al.*, 1993*[193] *[same trial as McKee* et al.*, 1993*[297]*]*

Drug(s)	Vigabatrin
Target maintenance dose (mode)	3 g/day, in two doses/day (?mode)
Seizure or syndrome	Refractory generalised tonic–clonic or complex partial seizures with or without secondary generalisation
Type of trial design	Cross-over
Add-on or monotherapy	Add-on
Control(s)	Placebo
Eligible age	17–53 years

		Placebo	**Vigabatrin**
Number randomised		Total 24; not reported separately by arm	Total 24; not reported separately by arm
Age (weeks, months, years) (mean, SD; median, range)		Not reported separately by arm. Mean 32.5, SD 9.9 years	Not reported separately by arm. Mean 32.5, SD 9.9 years
Diagnosed seizure types, *n* (%)		Not reported separately by study arm	Not reported separately by study arm
	Complex partial	8 (33)	8 (33)
	Complex partial and generalised tonic–clonic	14 (58)	14 (58)
	Generalised tonic-clonic	2 (8)	2 (8)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported		

TABLE 130 *[69] McKee* et al., *1993*[297] *[same trial as Gillham* et al., *1993*[193]*]*

Drug(s)	Vigabatrin		
Target maintenance dose (mode)	3 g/day, in two doses/day (?mode)		
Seizure or syndrome	Refractory generalised tonic–clonic or complex partial seizures with or without secondary generalisation		
Type of trial design	Cross-over		
Add-on or monotherapy	Add-on		
Control(s)	Placebo		
Eligible age	17–53 years		
		Placebo	**Vigabatrin**
Number randomised		Total 24; not reported separately by arm	Total 24; not reported separately by arm
Age (weeks, months, years) (mean, SD; median, range)		Not reported separately by arm. Mean 32.5, SD 9.9 years	Not reported separately by arm. Mean 32.5, SD 9.9 years
Diagnosed seizure types, *n* (%)		Not reported separately by study arm	Not reported separately by study arm
	Complex partial	8 (33)	8 (33)
	Complex partial and generalised tonic–clonic	14 (58)	14 (58)
	Generalised tonic–clonic	2 (8)	2 (8)
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported		

Study population diagnosed with epilepsy or refractory epilepsy but with no further refinement

TABLE 131 *[70] Carmant* et al., *1999,*[194] *abstract; interim results only*

Drug(s)	Lamotrigine		
Target maintenance dose (mode)	Details industrial submission SCAB 3001 protocol		
Seizure or syndrome	Details industrial submission SCAB 3001 protocol		
Type of trial design	Details industrial submission SCAB 3001 protocol		
Add-on or monotherapy	Monotherapy		
Control(s)	Valproate		
Eligible age	≥ 2 years		
		Valproate	**Lamotrigine**
Number randomised		Not reported	Not reported
Age (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
Diagnosed seizure types, *n* (%)	Not reported	Not reported	Not reported
Diagnosed syndrome(s), *n* (%)	Not reported	Not reported	Not reported
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported	Not reported	Not reported

TABLE 132 *[71] Kerr* et al.*, 1999,[298] abstract; interim results only*

Drug(s)	Lamotrigine
Target maintenance dose (mode)	Details industrial submission SCAB 3001 protocol
Seizure or syndrome	Details industrial submission SCAB 3001 protocol
Type of trial design	Details industrial submission SCAB 3001 protocol
Add-on or monotherapy	Monotherapy
Control(s)	Valproate
Eligible age	≥ 2 years

		Valproate	**Lamotrigine**
Number randomised		Not reported	Not reported
Age (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
Diagnosed seizure types, *n* (%)	Not reported	Not reported	Not reported
Diagnosed syndrome(s), *n* (%)	Not reported	Not reported	Not reported
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported	Not reported	Not reported

TABLE 133 *[72] Montouris* et al.*, 1999,[195] abstract; interim results only*

Drug(s)	Lamotrigine
Target maintenance dose (mode)	200–500 mg/day (?mode)
Seizure or syndrome	Not reported
Type of trial design	Parallel
Add-on or monotherapy	Monotherapy
Control(s)	Valproate
Eligible age	At least 12 years

		Valproate	**Lamotrigine**
Number randomised		13	16
Age (weeks, months, years) (mean, SD; median, range)		Median 25 years	Median 26 years
Diagnosed seizure types, *n* (%)	Not reported	Not reported	Not reported
Diagnosed syndrome(s), *n* (%)	Not reported	Not reported	Not reported
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported	Not reported	Not reported

TABLE 134 *[73] Fakhoury* et al.*, 2000,[196] abstract*

Drug(s)	Lamotrigine
Target maintenance dose (mode)	Not reported
Seizure or syndrome	Uncontrolled epilepsy
Type of trial design	Parallel
Add-on or monotherapy	Add on and monotherapy
Control(s)	Carbamazepine
Eligible age	≥ 16 years

		Carbamazepine	**Lamotrigine**
Number randomised		Not reported	Not reported
Age (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
Diagnosed seizure types, *n* (%)	Not reported	Not reported	Not reported
Diagnosed syndrome(s), *n* (%)	Not reported		
Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported		

Appendix 10

List of excluded studies

TABLE 135 *List of excluded studies with reasons for exclusion*

No.	ID	Reference	Reason for exclusion
1	3181	Anon, 2000[301]	Letter
2	319	Abdulrazzak, 2000[302]	Not randomised
3	200	Aberg, 1999[303]	Not randomised
4	372	Aldenkamp, 1998[304]	Abstract. No information on age of patients
5	337	Aldenkamp, 1999[305]	Abstract. No information on age of patients
6	3	Aldenkamp, 2000[306]	Patients ⩾18 years
7	3990	Aldenkamp, 2002[307]	Healthy volunteers
8	2488	Anhut, 1995[308]	Abstract. No information on age of patients
9	344	Anderson, 1999[309]	Not randomised
10	2026	Angeleri, 1992[310]	Not randomised
11	1804	Anhut, 1995[311]	Open-label extension study
12	2755	Appleton, 2001[312]	Open-label extension study
13	1557	Arteaga, 1996[313]	Open-label extension study
14	2062	Arteaga, 1992[314]	Not randomised
15	3713	Arteaga, 1993[315]	Intervention not relevant
16	15	Arzimanoglou, 2001[316]	Not randomised
17	3903	Banin, 2000[317]	Not randomised
18	424	Bartoli, 1997[271]	Healthy volunteers
19	1910	Bartolini, 1993[318]	Not randomised
20	3033	Belmonte, 1999[319]	Not randomised
21	497	Ben Menachem, 1996[320]	Patients ⩾18 years
22	427	Ben Menachem, 1997[321]	Age range patients ⩾18 years
23	423	Ben Menachem, 1997[322]	Abstract. No information on age of patients
24	723	Beran, 2001[323]	Not randomised
25	2491	Bergey, 1995[324]	Abstract. No information on age of patients. Data superseded
26	1457	Bergey, 1997[325]	Patients ⩾18 years
27	1774	Bernardina, 1995[326]	Not randomised
28	1534	Besag, 1997[327]	Open-label extension study
29	384	Betts, 1998[328]	Abstract. No information on age of patients
30	377	Beydoun, 1998[329]	Patients ⩾18 years
31	1170	Beydoun, 1999[330]	Abstract. No information on age of patients
32	402	Beydoun, 1998[331]	Abstract. No data on age
33	3431	Bielicka-Cymerman, 1999[332]	Patients ⩾18 years
34	29	Birbeck, 2000[333]	Patients ⩾18 years
35	476	Biton, 1997[334]	Abstract. No information on age of patients
36	373	Biton, 1998[335]	Abstract. No information on age of patients
37	3421	Biton, 1999[336]	Abstract of review
38	333	Biton, 2000[337]	Abstract. Data superseded
39	1183	Biton, 1999[338]	Correction for Biton *et al*. 1999
40	332	Biton, 2000[339]	Abstract. Data superseded
41	494	Boas, 1996[340]	Patients ⩾18 years
42	1251	Boati, 1998[341]	Patients ⩾18 years
43	564	Brodie, 1993[342]	Abstract. No information on age of patients
44	413	Brodie, 1998[343]	Open-label extension study
45	1187	Brodie, 1999[344]	Patients ⩾18 years
46	1814	Brodie, 1995[345]	Correction for Brodie *et al*.1995[175]
47	474	Brodie, 1997[346]	Open-label extension study
48	617	Browne, 1989[347]	Patients ⩾18 years
49	3623	Browne, 1983[348]	Not randomised

continued

TABLE 135 *List of excluded studies with reasons for exclusion (cont'd)*

No.	ID	Reference	Reason for exclusion
50	3616	Browne, 1986[349]	Open-label extension study
51	2158	Browne, 1987[350]	Patients ⩾18 years
52	2115	Browne, 1991[351]	Open-label extension study
53	2856	Brozmanova, 1995[352]	Open-label extension study
54	3907	Bruni, 2000[353]	Patients ⩾18 years
55	2309	Bruni, 1998[354]	Patients ⩾18 years
56	37	Bruni, 1999[355]	Not randomised
57	4030	Buchanan, 1996[356]	Not randomised
58	3213	Buchholt, 1995[357]	Abstract. Case series
59	1429	Canger, 1996[358]	Not randomised
60	3109	Carrazana, 2001[359]	Abstract. Case study
61	438	Chadwick, 1997[360]	Abstract. No information on age of patients
62	3141	Chiron, 2000[361]	Intervention not relevant
63	3415	Clark, 1999[362]	Not randomised
64	631	Cocito, 1989[363]	Not randomised
65	2261	Cocito, 1993[364]	Not randomised
66	2577	Collins, 2000[365]	Case series
67	2857	Coppola, 1995[366]	Not randomised
68	44	Coppola, 2001[367]	Not randomised
69	4359	Coppola, 2002[368]	Not randomised
70	46	Cramer, 1999[369]	Letter on generalities
71	50	Crawford, 2001[370]	Patients ⩾18 years
72	644	Crawford , 1987[371]	Patients ⩾18 years
73	3690	Curatolo, 1994[372]	Not randomised
74	453	Czapinski, 1997[373]	Patients ⩾18 years
75	527	Dalla, 1995[374]	Not randomised
76	428	Davies, 1997[375]	Review
77	1792	De Romanis, 1995[376]	Patients ⩾18 years
78	218	Dean, 1999[377]	Patients ⩾18 years
79	526	Dodrill, 1995[249]	Patients ⩾18 years
80	2499	Dodrill, 1995[378]	Abstract. No information on age of patients
81	374	Dodrill, 1998[379]	Abstract. No information on age of patients
82	59	Dodrill, 1999[380]	Not RCT; invalid comparitor group
83	410	Dollar, 1998[381]	Open-label extension study
84	2099	Drory, 1991[382]	Review
85	3250	Dulac, 2001[383]	Abstract. Non-randomised pharmacokinetic study
86	4045	Dulac, 1996[384]	Review
87	2630	Duric, 1999[385]	Abstract. Randomisation compromised
88	318	Edwards, 2000[386]	Abstract. Data superseded
89	2853	Eriksson, 1995[387]	Abstract. Data superseded
90	906	Eriksson, 2001[388]	Not randomised
91	2879	Farrell, 1995[389]	Not randomised
92	348	Fattore, 1999[261]	Healthy women
93	1621	Faught, 1996[390]	Patients ⩾18 years
94	436	Faught, 1997[391]	Review
95	2631	Fichtner, 1999[392]	Open-label extension study
96	2637	Franzoni, 1999[393]	Not randomised
97	3710	French, 1993[299]	Abstract. No information on age of patients
98	1634	French, 1996[394]	Patients ⩾18 years
99	2148	Froscher, 1988[395]	Intervention not relevant
100	2563	Frye, 2000[396]	Not epilepsy
101	3796	Galas-Zgorzalewicz, 1999[397]	Not randomised
102	2506	Garofalo, 1995[398]	Abstract. No information on age of patients
103	2510	Garofalo, 1995[399]	Not randomised
103	1421	Gherpelli, 1997[400]	Not randomised
104	454	Glauser, 1997[401]	Open-label extension study
105	1082	Glauser, 2000[402]	Open-label extension study

continued

TABLE 135 *List of excluded studies with reasons for exclusion (cont'd)*

No.	ID	Reference	Reason for exclusion
106	421	Glauser, 1997[403]	Abstract. Data superseded
107	412	Glauser, 1998[404]	Open-label extension study
108	3498	Glauser, 1998[405]	Open-label extension study
109	3636	Gobbi, 1995[406]	Not randomised
110	658	Gram, 1983[407]	Not randomised
111	3786	Gross-Tsur, 1999[408]	Not randomised
112	3899	Gross-Tsur, 2000[409]	Case series
113	3161	Guberman, 2000[410]	Not randomised
114	562	Hamilton, 1993[411]	Healthy volunteers
115	545	Handforth, 1994[412]	Patients ⩾18 years
116	2056	Hanefeld, 1992[413]	Not randomised
117	3287	Hanny, 1999[414]	Not randomised
118	1126	Harding 1998[415]	Healthy volunteers
119	2505	Hayes, 1995[416]	Abstract. No information on age of patients
120	2511	Hayes, 1995[417]	Not randomised
121	2500	Hayes, 1995[418]	Abstract. No information on age of patients
122	417	Hogan, 1998[419]	Abstract. No information on age of patients
123	93	Hogan, 2000[420]	No information on age of patients
124	3425	Hosain, 1999[421]	Not randomised
125	3240	Houtkooper, 1984[422]	Abstract. No information on age of patients
126	3638	Ignatowicz, 1995[423]	Not randomised
127	2842	Isojarvi, 1995[424]	Not randomised
128	2874	Isojarvi, 1995[425]	Not randomised
129	620	Jawad, 1989[426]	Not randomised
130	368	Kalviainen, 1998[427]	Patients ⩾18 years
131	416	Kalviainen, 1998[428]	Abstract. No information on age of patients
132	504	Kalviainen, 1996[429]	Patients ⩾18 years
133	825	Kluger, 2001[430]	Not randomised
134	2682	Kohrman, 1998[431]	Not randomised
135	3641	Koul, 1995[432]	Not randomised
136	379	Kraemer, 1998[433]	Abstract. No information on age of patients
137	430	Lee, 1997[434]	Abstract. No information on age of patients
138	1876	Leiderman, 1994[435]	Review
139	2632	Leoni, 1999[436]	Not randomised
140	122	Levisohn, 2000[437]	Review
141	336	Lindberger, 1999[438]	Abstract. No information on age of patients
142	3596	Livingston, 1989[439]	Not randomised
143	608	Loiseau, 1990[440]	Patients ⩾18 years
144	632	Luna, 1989[441]	Not randomised
145	2378	Mandelbaum, 2001[442]	Not randomised
146	4094	Marescauz, 1996[443]	Review
147	282	Martin, 2001[444]	Patients range ⩾18 years
148	2665	Martin, 1999[445]	Healthy volunteers
149	312	Martinez, 2000[446]	Abstract. No information on age of patients
150	3642	Martinez Bermejo, 1995[447]	Not randomised
151	3525	Martinezlage, 1995[448]	Abstract. No information on age of patients
152	2636	Martinovic, 1999[449]	Not randomised
153	503	Matsuo, 1996[450]	Patients ⩾18 years
154	577	Matsuo, 1993[451]	Patients ⩾18 years
155	403	Mattson, 1998[452]	Open-label extension study
156	1899	McKee, 1994[453]	Not randomised
157	341	Meador, 1999[454]	Healthy volunteers
158	3116	Meador, 2001[455]	Healthy volunteers
159	132	Mecarelli, 2001[456]	Healthy volunteers
160	625	Mervaala, 1989[457]	Not randomised
161	550	Messenheimer, 1994[458]	Patients ⩾18 years
162	397	Messenheimer, 1998[459]	Open-label extension study
163	1428	Michelucci, 1996[460]	Patients ⩾18 years

continued

TABLE 135 *List of excluded studies with reasons for exclusion (cont'd)*

No.	ID	Reference	Reason for exclusion
164	3527	Michelucci, 1995[461]	Patients ⩾18 years
165	395	Michelucci, 1998[462]	Abstract. Patients ⩾18 years
166	2031	Michelucci, 1992[463]	Not randomised
167	1928	Michelucci, 1994[464]	Open-label extension study
168	3032	Micheu, 1999[465]	Not randomised
169	2515	Mikati, 1995[466]	Not randomised
170	2991	Mims, 1997[467]	Not randomised
171	135	Montouris, 2000[468]	Open-label extension study
172	3389	Morita, 2000[469]	Abstract. Case–control study
173	258	Mortimore, 1998[470]	Not randomised. Patients ⩾18 years
174	141	Muscas, 2000[471]	Not randomised
175	2855	Muszkat, 1995[472]	Not randomised
176	387	Noachtar, 1998[473]	Healthy volunteers
177	1791	O'Donoghue, 1995[474]	Letter about Brodie *et al*. 1995
178	1925	Oommen, 1994[475]	Open-label extension study
179	575	Penry, 1993[476]	Abstract. No information on age of patients
180	1430	Pledger, 1996[477]	Review
181	515	Privitera, 1996[478]	Patients ⩾18 years
182	604	Ramsay, 1991[479]	Patients ⩾18 years
183	356	Ramsey, 1999[480]	Abstract. Data superseded 2002
184	484	Regesta, 1997[481]	Abstract. No information on age of patients
185	486	Regesta, 1997[482]	Patients ⩾18 years
186	483	Regesta, 1997[483]	Abstract. No information on age of patients
187	657	Reinikainen, 1984[484]	Patients ⩾18 years
188	641	Reinikainen, 1987[485]	Patients ⩾18 years
189	520	Richens, 1995[486]	Patients ⩾18 years
190	932	Richens, 2000[487]	Not a relevant intervention. Patients ⩾18 years
191	4133	Richens, 1996[488]	'Adults' but no other information on age of patients
192	169	Ritter, 2000[489]	Open-label extension study
193	394	Ritter, 1998[490]	Abstract. Long-term extension of RCT
194	508	Rosenfeld W, 1996[491]	Abstract. No information on age of patients
195	3432	Rosenfeld, 1999[492]	Not randomised
196	1265	Rowbotham, 1998[493]	Not epilepsy. Patients ⩾18 years
197	3347	Sachdeo, 1995[494]	Abstract. No information on age of patients
198	457	Sachdeo, 1997[495]	Open-label extension study
199	2125	Sander, 1990[496]	Patients ⩾18 years
200	2854	Sanmarti, 1995[497]	Not randomised
201	3342	Schachter, 1995[498]	Abstract. No information on age of patients
202	530	Schachter, 1995[499]	Patients ⩾18 years
203	534	Schachter, 1995[500]	Review
203	458	Schacter, 1997[501]	Abstract. No information on age of patients
204	599	Schapel, 1991[502]	Abstract. Data superseded
205	1937	Schlumberger, 1994[503]	Not randomised
206	560	Schmidt, 1993[504]	Abstract. No information on age of patients
207	2054	Schmitz-Moormann, 1992[505]	Not randomised
208	3381	Schwabe, 2000[506]	Not randomised
209	495	Sharief, 1996[507]	Patients ⩾18 years
210	3022	Siemes, 1999[508]	Not randomised
211	639	Sillanpaa, 1988[509]	Not randomised
212	376	Sinclair, 1998[510]	Healthy adults
213	3643	Siskova, 1995[511]	Not randomised
214	3621	Sivenius, 1985[512]	Not randomised
215	3618	Sivenius, 1986[513]	Abstract. No information on age of patients
216	3607	Sivenius, 1988[514]	Open-label extension study
217	580	Smith, 1993[515]	Not randomised
218	4151	Steiner, 1996[516]	Not epilepsy

continued

TABLE 135 *List of excluded studies with reasons for exclusion (cont'd)*

219	469	Steinhoff, 1997[517]	Healthy adults
220	558	Stolarek, 1994[518]	No information on age of patients
221	3646	Tanganelli, 1995[519]	Abstract. No information on age of patients
222	516	Tanganelli, 1996[520]	Patients ⩾18 years
223	2064	Tartara, 1992[521]	Patients ⩾18 years
224	3526	Tassinari, 1995[522]	Abstract. No information on age of patients
225	496	Tassinari, 1996[523]	Patients ⩾18 years
226	2276	The Italian Study Group on Vigabatrin, 1992[524]	Not randomised
227	511	Thomas, 1996[525]	Healthy volunteers
228	2490	Trudeau, 1995[526]	Abstract. No information on age of patients
229	3341	Uldall, 1995[527]	Not randomised
230	188	Uldall, 2000[528]	Not randomised
231	3357	Uthman, 1993[529]	Abstract. No information on age of patients
232	193	Wheless, 2000[530]	Review
233	2867	Wieser, 1995[531]	Open-label extension study
234	1779	Wieser, 1995[532]	Patients ⩾18 years
235	199	Yen, 2000[533]	Patients ⩾18 years
236	573	Yuen, 1993[534]	Abstract. No information on age of patients
237	3654	Zahner, 1995[535]	Abstract. No information on age of patients
238	2951	Zakrzewska, 1997[536]	Not epilepsy

Appendix 11

Unobtainable publications

TABLE 136 *List of unobtainable publications*

No.	Reference
1	Aikia, 1989[537]
2	Loiseau, 1989[538]
3	Sivenius, 1989[539]
4	Hsiang-Yu, 1999[540]
5	Kharlamov, 1999[541]
6	Kivity, 1999[542]
7	Mirza, 1999[543]
8	Mojs, 1999[544]
9	Rintahaka, 1999[545]
10	Slapal, 1999[546]
11	Sokic, 1999[547]
12	Uran, 1999[548]
13	Uran, 1999[549]
14	Uysal, 1999[550]
15	Biraben, 2000[551]
16	Brodie, 2000[552]
17	Carpay, 2000[553]
18	Gil, 2000[554]
19	Kazibutowska, 2000[555]
20	Kwan, 2000[556]
21	Mecarelli, 2000[102]
22	Meador, 2000[557]
23	Neto, 2000[558]
24	Privitera, 2000[559]
25	Veendrick-Meekes, 2000[560]
26	Abou, 2001[561]
27	Cramer, 2001[562]
28	Kerr, 2001[563]
29	O'Neill, 2001[101]
30	Remy, 1986[103]
31	Michelucci, 1988[564]
32	Angeleri, 1990[565]
33	Dulac, 1991[566]
34	Kalviainen, 1991[567]
35	Espe-Lillo, 1995[568]
36	Belopitova, 2000[104]

Appendix 12

Health state questionnaire

HEALTH STATE AES

The patient experiences unacceptable side-effects of drug therapy (that cannot be controlled by a change of dose) such that a change of therapy is initiated

Below is the health state description section of the EuroQol instrument that has been slightly modified to relate to a child population.

Drawing on your clinical experience and by placing a tick in one box in each group below, please indicate which statement best describes the *average child* in State AES. The child has focal epilepsy, is between the ages of 7 and 12 years, has no motor impairments, and either does or does not have moderate learning difficulties.

	Child of age 7–12 years with focal epilepsy and no motor impairments	
	Without learning difficulties	With moderate learning difficulties
Mobility		
He/she has no problems walking about	☐	☐
He/she has some problems walking about	☐	☐
He/she is confined to bed	☐	☐
Self-care*		
He/she has no problems with self-care	☐	☐
He/she has some problems with washing or dressing him/herself	☐	☐
He/she is unable to wash or dress him/herself	☐	☐
Usual activities (e.g. going to school, hobbies, sports, playing)*		
He/she has no problems with usual activities	☐	☐
He/she has some problems with usual activities	☐	☐
He/she is unable to do his/her usual activities	☐	☐
Pain/discomfort		
He/she has no pain or discomfort	☐	☐
He/she has moderate pain or discomfort	☐	☐
He/she has extreme pain or discomfort	☐	☐

Anxiety/depression

He/she is not anxious or depressed	☐	☐
He/she is moderately anxious or depressed	☐	☐
He/she is extremely anxious or depressed	☐	☐

* 'No problems' would suggest a healthy child with no impairment and no learning difficulties.

Appendix 13

Trial data

Trial details	Trial ID	Nieto-Barrera, 2001
	Drug(s)	Lamotrigine
	Target maintenance dose (mode)	Lamotrigine 2–15 mg/kg/day (oral); carbamazepine 5–40 mg/kg/day (oral)
	Seizure or syndrome	Newly diagnosed partial epilepsy
	Type of trial design	Parallel
	Add-on or monotherapy?	Monotherapy
	Control(s)	Carbamazepine
	Study start and end dates	Not stated
	Centres and location	Multicentre; Europe, Egypt, Mexico
Trial design	Baseline	None
	Titration (including details of schedule and frequency of doses)	Lamotrigine: 6 weeks Dose escalated every 2 weeks from 0.5 mg/kg/day to target of 2–15 mg/kg/day (2–12 years old) or from 25 mg/day to target of 200–700 mg/day (13–64 years old) One dose per day Carbamazepine: Titration period not stated. Titration schedule not stated; "slow increase until best response was obtained, according to data sheet recommendations". Doses of 5–40 mg/kg/day (2–12 years old) or 100–1500 mg/day (13–64 years old)
	Maintenance	18 weeks
	Withdrawal	None
	Timing and additional eligibility for randomisation/continuation on study	NA (no baseline phase)
	Comments on design	Titration schedule much more clearly defined for lamotrigine; patients on lamotrigine arm 'withdrawn' if dose reduction required during escalation phase or while on lowest maintenance dose, but no similar criteria given for carbamazepine
Quality assessment	Was assignment of treatment described as random?	Yes
	Was method of randomisation described?	No (except stratified by age and country)
	Was the method really random?	Can't tell
	Was allocation of treatment concealed?	Can't tell
	Who was blinded to treatment?	Open-label study
	Was method of blinding adequately described?	NA
	Were eligibility criteria described?	Yes
	Were groups comparable at study entry?	Yes (data not reported for children separately)
	Were groups treated identically apart from the intervention?	Can't tell
	Was ITT used?	No

continued

	Were withdrawals stated?	Yes (but see comment)		
	Were reasons for withdrawals stated?	Information incomplete		
	Was a power calculation done?	No		
	Comments	Mixed age trial, ages 2–83 years. Patients aged 13–64 years regarded as a single group but results for age group 2–12 years reported separately; these results will be used for this review. Numbers withdrawing not stated for all reasons; Kaplan–Meier curve for all-cause withdrawal provides estimate of percentage withdrawing		
Eligibility criteria	Inclusion criteria	1. Newly diagnosed or currently untreated partial epilepsy 2. Seizures easily recognised by patient or carer and classifiable by the International Classification of Seizures 1981 3. At least 2 partial seizures in the 6 months previous to study with at least one partial seizure or secondarily generalised tonic–clonic seizure in the 3 months preceding study 4. Evidence of focal radiological or EEG abnormalities		
	Exclusion criteria	None reported		
Baseline characteristics			Carbamazepine	Lamotrigine
	Number randomised		75	153
	Number analysed		64	134
	Age (weeks, months, years) (mean, SD; median, range)		Median 19, range 2–83 years	Median 20, range 2–77 years
	Male:female		53:47	53:47
	Weight (kg, lb) (mean, SD; median, range)		Mean 54 kg	Mean 54 kg
	Duration of epilepsy (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
	Age at diagnosis (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
	Newly diagnosed, *n* (%)		Not reported	Not reported
	Previously diagnosed, *n* (%)		Not reported	Not reported
	Refractory, *n* (%); definition of refractory		–	–
	Diagnosed seizure types, *n* (%)	Simple partial Complex partial Secondarily generalised Generalised	88 (21) 185 (44) 228 (55) 6 (1)	32 (16) 78 (39) 126 (63) 1 (<1)
	Diagnosed syndrome(s), *n* (%)	–	–	–
	Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	All seizures	Mean 10.07; median 0.67, range 0.2–1500 month	Mean 6.84; median 0.50, range 0.2–600 month
	No. of concomitant AEDs, *n* (%)	None	(100)	(100)
	Concomitant AEDs, *n* (%)	–	–	–
	Previous AEDs, *n* (%)	–	Not stated	Not stated
	Comments		Baseline characteristics reported for whole group only Eligibility included currently untreated epilepsy; not clear if any patients previously treated	

continued

Monitoring and outcomes	Was monitoring of plasma levels done (including study drug)?	No		
	Were arrangements to blind plasma monitoring results mentioned?	NA		
	Who recorded seizure frequency?	Patient or carer		
	How often was seizure frequency measured?	Daily (seizure diaries)		
	Frequency of clinic visits	0, 4, 12, 24 weeks (and on withdrawal if before 24 weeks)		
	Primary outcome(s) including time-points if repeated	1. Proportion seizure-free in the last 16 weeks of treatment and who had not withdrawn before week 22 2. Proportion seizure-free in the last 16 weeks of treatment and who had not withdrawn before week 18		
	Secondary outcome(s) excluding adverse events	Time to withdrawal from study (measure of global effectiveness combining efficacy and tolerability)		
	'*Ad hoc*' outcomes (if emphasised and not in methods)	Proportion withdrawn for adverse events		
	Comments	Primary outcomes include only patients who did not withdraw before weeks 22 and 18; this destroys the principle of ITT and compromises randomisation		
Results (ITT only; unadjusted where available)			Carbamazepine	Lamotrigine
	Median follow-up		24 months	24 months
	Maintenance dose achieved		Mean 16.9; median 16.0, range 5.2–36.5	Mean 3.4; median 2.7, range 0.05–10.5 mg/day
	Withdrawals including reasons where specified, *n* (%)	Total withdrawals (all causes)	11 (15)	21 (13)
		Withdrawal for adverse events	5 (7)	8 (5)
			Results (difference or by arm)	CI for difference; *p*-value
	Primary outcome(s)	1. Seizure-free in last 16 weeks and follow-up to week 22	48/64 (75%) carbamazepine 89/134 (66%) lamotrigine	–22 to 5%; $p = 0.205$
		2. Seizure-free in last 16 weeks and follow-up to week 18	48/75 (64%) carbamazepine 89/158 (56%) lamotrigine	–21 to 6%; p = ns
			ITT analysis not possible with these outcomes	
	Secondary outcomes	Global effectiveness (time to withdrawal from study)	Proportions withdrawing: 11 (15%) carbamazepine 21 (13%) lamotrigine	
			Kaplan–Meier curves not given for 2–12 years age group	
	'*Ad hoc*' outcomes	Proportion withdrawn for adverse events	5/75 (7%) carbamazepine 8/158 (5%) lamotrigine	$p = 0.761$

continued

	Comments (including whether unadjusted results reported)	Primary outcomes limit analysis to patients who complete study to week 18 or 22; does not allow ITT analysis Doses achieved in weeks 7–24 given in mg/day rather than mg/kg/day for age range 2–12 years

Trial details	Trial ID	Zamponi, 1999
	Drug(s)	Vigabatrin
	Target maintenance dose (mode)	Vigabatrin 50–60 mg/kg/day; carbamazepine 1520 mg/kg/day (oral) [typographical error?]
	Seizure or syndrome	Newly diagnosed partial epilepsy
	Type of trial design	Parallel
	Add-on or monotherapy?	Monotherapy
	Control(s)	Carbamazepine
	Study start and end dates	Not reported
	Centres and location	1 centre in Italy
Trial design	Baseline	None
	Titration (including details of schedule and frequency of doses)	4 weeks Carbamazepine: starting dose 5 mg/kg/day increased at 3–4-day intervals (dose increments not stated) Vigabatrin: starting dose 10–15 mg/kg/day increased at 3–4 day intervals (dose increments not stated) 2 doses/day
	Maintenance	100 weeks (assumed from "2 year follow-up", assumed to refer to total trial period)
	Withdrawal	None
	Timing and additional eligibility for randomisation/continuation on study	NA (no baseline period)
	Comments on design	Very poor quality of reporting; not clear that trial was randomised
Quality assessment	Was assignment of treatment described as random?	Yes
	Was method of randomisation described?	No
	Was the method really random?	Can't tell
	Was allocation of treatment concealed?	Can't tell
	Who was blinded to treatment?	Open study
	Was method of blinding adequately described?	NA
	Were eligibility criteria described?	No
	Were groups comparable at study entry?	Can't tell; large imbalance in numbers randomised for a small single-centre study, large age difference, patient characteristics poorly reported
	Were groups treated identically apart from the intervention?	Can't tell
	Was ITT used?	Can't tell
	Were withdrawals stated?	Yes
	Were reasons for withdrawals stated?	Yes (but see comment)

continued

	Was a power calculation done?	No		
	Comments	Very poor quality of reporting Reasons for withdrawal were stated but cannot be certain that these were complete data		
Eligibility criteria	Inclusion criteria	Children with newly diagnosed partial epilepsy		
	Exclusion criteria	Not reported		
Baseline characteristics			Carbamazepine	Vigabatrin
	Number randomised		32	38
	Number analysed		Not stated	Not stated
	Age (weeks, months, years) (mean, SD; median, range)		Mean 9 years 5 months; range 3–13 years 2 months	Mean 7 years 4 months range 6 months–10 years 3 months
	Male:female		17:15	21:17
	Weight (kg, lb) (mean, SD; median, range)		Not reported	Not reported
	Duration of epilepsy (weeks, months, years) (mean, SD; median, range)		<1 month 27 (84.3%); 2 years 2 (6.2%); no data 3 (9.6%)	<1 month 35 (92.1%); 18 months 1 (2.6%); 5 years 2 (5.2%)
	Age at diagnosis (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
	Newly diagnosed, *n* (%)		32 (100%)	38 (100%) (8 patients had received a different drug started less than 1 month before)
	Previously diagnosed, *n* (%)		None	None
	Refractory, *n* (%); definition of refractory		NA	NA
	Diagnosed seizure types, *n* (%)	Complex partial Secondarily generalised Unilateral Partial with spasms Partial elementary	15 (46.8) 14 (43.7) 0 (–) 0 (–) 3 (9.3)	17 (44.7) 18 (47.3) 1 (2.6) 2 (5.2) 0 (–)
	Diagnosed syndrome(s), *n* (%)	Partial idiopathic Cryptogenic Symptomatic	9 (28.1) 16 (50) 7 (21.8)	12 (31.5) 16 (42.1) 10 (26.3)
	Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Number of seizures prior to starting treatment: <10 10–50 >50	 28 (87.5) 4 (12.5) 0 (–)	 30 (78.9) 5 (13.1) 3 (7.8)
	No. of concomitant AEDs, *n* (%)	NA	NA	NA
	Concomitant AEDs, *n* (%)	NA	NA	NA
	Previous AEDs, *n* (%)	Carbamazepine Clobazam	None, or not Reported 1 (2.6)	6 (15.7)

continued

		Valproate		1 (2.6) (4 discontinued owing to rash on carbamazepine; 4 discontinued owing to lack of efficacy)
	Comments		8/38 patients on vigabatrin had started an alternative treatment within 1 month previously; no similar treatment switches described for the carbamazepine group. Raises question as to whether trial was prospectively randomised and when treatment actually started	
Monitoring and outcomes	Was monitoring of plasma levels done (including study drug)?	No		
	Were arrangements to blind plasma monitoring results mentioned?	NA (open study)		
	Who recorded seizure frequency?	Not reported		
	How often was seizure frequency measured?	Not reported		
	Frequency of clinic visits	Months 1, 3, 6, 12, 18, 24		
	Primary outcome(s) including time points if repeated	Not clear if any outcomes prespecified		
	Secondary outcome(s) excluding AEs	Not clear if any outcomes prespecified		
	'*Ad hoc*' outcomes (if emphasised and not in methods)	Number of relapses (not defined)		
	Comments	–		
Results (ITT only; unadjusted where available)			Carbamazepine	Vigabatrin
	Median follow-up		2 years (assumed)	2 years (assumed)
	Maintenance dose achieved		1520 mg/kg/day [typographical error?]	50–60 mg/kg/day
	Withdrawals including reasons where specified, *n* (%)	Total withdrawals Lack of efficacy Adverse events	8 2 6	6 5 1
			Results (difference, or by arm)	CI for difference; *p*-value
	Primary outcome(s)	None stated	NA	NA
	Secondary outcomes	None stated	NA	NA
	'*Ad hoc*' outcomes	Number of relapses (not defined; assumed to be recurrence of seizures)	7/32 (21.9%) carbamazepine 9/38 (23.7%) vigabatrin	No comparative analysis reported
	Comments (including whether unadjusted results reported)		Very poor reporting	

continued

Adverse events			Carbamazepine	Vigabatrin
	Criteria for reporting	None stated		
	Events, *n* (%)	Irritability/excitability	0	6 (15.7)
		Weight gain	3 (9.3)	10 (26.3)
		Excessive sedation	6 (18.7)	0 (–)
		Rash	6 (18.7)	0 (–)
	Comments		Authors note that an increased risk of asymptomatic visual filed constriction may be associated with vigabatrin and that "in affected patients" the treatment was discontinued	
Conclusions	Authors' conclusions	Vigabatrin and carbamazepine are of similar efficacy in children with newly diagnosed partial epilepsy		
	Our conclusions	This trial is extremely poorly reported; it is not clear whether it was prospectively randomised, there are no inclusion or exclusion criteria given, unclear methodology, no definition of the outcome measure, etc. The maintenance dose of carbamazepine is reported as per kg but appears more likely to be an absolute dose. An abstract reporting preliminary results of this study was published in 1995.[573] At that time 57 patients were enrolled, 30 randomised to vigabatrin and 27 to carbamazepine. Outcome seemed to be 'recurrences', again no definition		

Trial details	Trial ID	Duchowny, 1999
	Drug(s)	Lamotrigine
	Target maintenance dose (mode)	1–15 mg/kg/day, maximum 750 mg/day (oral; chewable/dispersible caplets or tablets)
	Seizure or syndrome	Partial seizures
	Type of trial design	Parallel
	Add-on or monotherapy?	Add-on
	Control(s)	Placebo
	Study start and end dates Centres and location	Not reported 40 centres in USA, France
Trial design	Baseline	8 weeks
	Titration (including details of schedule and frequency of doses)	6 weeks Titrated in four stages to target daily maintenance dose of 1–15 mg/kg/day depending on whether patients taking enzyme-inducing (EI) AEDs and/or valproate; maximum absolute doses from 150 mg (valproate and no EIAED) to 750 mg (EIAED and no valproate) Number of doses per day not stated
	Maintenance	12 weeks
	Withdrawal	None (post- RCT tapering of drug over 1–6 weeks, depending on maintenance dose used during RCT study)
	Timing and additional eligibility for randomisation/continuation on study	Postbaseline; actual criteria for randomisation not stated but at screening patients were expected to have at least 4 seizures during each consecutive 4-week period of the baseline phase
	Comments on design	Follow-up visit 1 week after tapering complete. Thus the approach will lead to some variability in total follow-up for different patients. Tapering followed by open-label study; patients entered this during tapering phase and so were either maintained on constant dose of lamotrigine or had lamotrigine introduced during this phase. Results after 18 weeks on study are therefore difficult to interpret

continued

Quality assessment	Was assignment of treatment described as random?	Yes
	Was method of randomisation described?	Yes
	Was the method really random?	Yes
	Was allocation of treatment concealed?	Yes
	Who was blinded to treatment?	Described as 'double-blind'
	Was method of blinding adequately described?	'Lamotrigine and matching placebo'
	Were eligibility criteria described?	Yes
	Were groups comparable at study entry?	Baseline seizure rates for simple and complex partial seizures appear substantially higher in placebo group
	Were groups treated identically apart from the intervention?	Presumably, if blinding adequate; dose titration refers explicitly to lamotigine only, not clear how/if placebo doses titrated in same way
	Was ITT used?	Yes
	Were withdrawals stated?	Yes
	Were reasons for withdrawals stated?	Yes
	Was a power calculation done?	Yes
	Comments	–
Eligibility criteria	Inclusion criteria	1. Confirmed diagnosis of epilepsy limited to partial seizures (simple partial, complex partial or partial becoming generalised) 2. Incompletely controlled by existing therapy (judged likely to experience at least 4 seizures in two consecutive 4-week periods during baseline) 3. Age 2–16 years (USA) or 2–12 years (France) 4. Weight at least 10 kg (unless AED therapy was limited to EI AEDs) 5. Receiving up to 2 AEDs, excluding felbamate or gabapentin 6. Ability to maintain complete and accurate records of seizures throughout the study 7. Postpubescent girls required to use an appropriate method of contraception
	Exclusion criteria	1. Previous exposure to lamotrigine 2. Using corticosteroid therapy for asthma 3. Primary generalised, pseudo-, drug-induced or metabolic seizures 4. Intracerebral, structural lesions or history of status epilepticus within the previous 12 weeks 5. Demonstrated medical non-compliance, drug abuse (prescribed, illicit, legal), psychiatric disorders or progressive neurological disorders 6. Clinically significant chronic cardiac, renal or hepatic condition 7. Vagal stimulation or ketogenic diet or likelihood of surgical treatment for epilepsy during the study 8. Pregnancy 9. Use of other investigational or psychoactive drugs, except for methylphenidate, dextroamphetamine or clonidine to treat attention-deficit hyperactivity disorder

Baseline characteristics	Placebo	Lamotrigine
Number randomised	101	98
Number analysed	101	98
Age (weeks, months, years) (mean, SD; median, range)	30 (29.7%) <6 years; <6 years; 62 (61.3%) 6–12 years; 9 (8.9%) >12 years	27 (27.5%) <6 years; 58 (59.1%) 6–12 years; 13 (13.2%) >12 years

continued

	Male:female		56:45	47:51
	Weight (kg, lb) (mean, SD; median, range)		Mean 32.5, SD 19.1 kg	Mean 36.1, SD 19.4 kg
	Duration of epilepsy (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
	Age at diagnosis (weeks, months, years) (mean, SD; median, range)		Median age at first seizure 1.0 years, range <1–11 years)	Median age at first seizure 1.3 years range <1–14 years
	Newly diagnosed, *n* (%)		None (assumed from eligibility)	None (assumed from eligibility)
	Previously diagnosed, *n* (%)		101 (100%)	98 (100%)
	Refractory, *n* (%); definition of refractory		101 (100%); incompletely controlled on existing therapy	98 (100%); incompletely controlled on existing therapy
	Diagnosed seizure types, *n* (%)		Not reported All patients had to have epilepsy with partial seizures only	Not reported All patients had to have epilepsy with partial seizures only
		Secondarily generalised	'Approximately half'	'Approximately half'
	Diagnosed syndrome(s), *n* (%)		–	–
	Baseline seizure frequency (per day, week, month) (mean, SD; median, range)		Data presented graphically only Median/week	Data presented graphically only Median/week
		All partial seizures Secondarily generalised Partial (not secondarily generalised)	~7.5 ~1.8 ~5.7 (by subtraction)	~10 ~1.6 ~8.4 (by subtraction)
	No. of concomitant AEDs, *n* (%)		All patients receiving 1 or 2 concomitant AEDs; ~50% were receiving 1 vs 2	All patients receiving 1 or 2 concomitant AEDs; ~50% were receiving 1 vs 2
	Concomitant AEDs, *n* (%)		Not reported	Not reported
	Previous AEDs, *n* (%)		Not reported	Not reported
	Comments		Some possible differences in baseline seizure rates	
Monitoring and outcomes	Was monitoring of plasma levels done (including study drug)?	No (but see comments)		
	Were arrangements to blind plasma monitoring results mentioned?	NA (but see comments)		
	Who recorded seizure frequency?	Not stated; daily diaries presumably completed by parent/guardian or patient		
	How often was seizure frequency measured?	Daily (diaries)		
	Frequency of clinic visits	2-weekly (weeks 1–6), 4-weekly (weeks 7–18)		
	Primary outcome(s) including time–points if repeated	% change in frequency of all partial seizures between baseline and entire double-blind period and maintenance phase of double-blind period; calculated from average weekly seizure frequency		
	Secondary outcome(s) excluding AEs	1. % change in frequency of secondarily generalised seizures 2. Proportion of patients with ≤ 25%, 26–49% and ≥ 50% reduction in all partial seizures 3. Number of days when each patient was seizure free		

continued

	'*Ad hoc*' outcomes (if emphasised and not in methods)	Compliance		
	Comments	One investigator measured plasma lamotrigine levels in 3 patients and entered concentrations in charts, violating the blinding; these patients were allowed to complete the study. The study site was closed after all study medication properly discontinued		
Results (ITT only; unadjusted where available)			Placebo	Lamotrigine
	Median follow-up		18 weeks 84/98 completed 18 weeks	18 weeks 83/101 completed 18 weeks
	Maintenance dose achieved	EIAED	Not reported	EIAEDs + no VPA (n = 53), mean 11.6 SD 3.6, median 12.9 mg/kg/day; No EIAEDs + VPA (n = 22), mean 2.7 SD 0.4, median 2.7 mg/kg/day; EIAEDs + VPA (n = 18), mean 3.9 SD 0.9, median 4.2 mg/kg/day
	Withdrawals including reasons where specified, n (%)	Total withdrawals Inadequate response Adverse events Withdrew consent Protocol violations	18 (17.8) 8 (7.9) 6 (5.9) 2 (1.9) 2 (1.9)	14 (14.2) 6 (6.1) 5 (5.1) 1 (1.0) 2 (2.0)
			Results (difference, or by arm)	CI for difference; p-value
	Primary outcome(s)	[Median] % change in frequency of all partial seizures during: entire 18-week follow-up	Placebo –6.7% Lamotrigine –36.1%	p = 0.008
		12-week maintenance period	Placebo –12.8% Lamotrigine –44%	p = 0.012
	Secondary outcomes	1. % change in frequency of secondarily generalised seizures	Not based on whole population	p < 0.05
		2. Proportion of patients with ≤ 25%, 26–49% and ≥ 50% reduction in all partial seizures	Results available graphically only	p < 0.05
		3. Number of days when each patient was seizure free (all partial seizures)	Placebo +3.2% Lamotrigine +28.0% (median change)	p = 0.003
	'*Ad hoc*' outcomes			
	Comments (including whether unadjusted results reported)	% change in seizure frequency adjusted for centre effects Percentage changes reported are median (weekly) % changes		

continued

Adverse events			Placebo	Lamotrigine
	Criteria for reporting	Events in >10% of patients in either group		
	Events, *n* (%)	Vomiting	19 (18.8)	22 (22.4)
		Somnolence	18 (17.8)	24 (24.4)
		Infection	22 (21.7)	21 (21.4)
		Dizziness	5 (4.9)	21 (21.4)
		Rash	18 (17.8)	16 (16.3)
		Headache	15 (14.8)	18 (18.3)
		Rhinitis	17 (16.8)	14 (14.2)
		Accidental injury	15 (14.8)	14 (14.2)
		Diarrhoea	13 (12.8)	13 (13.2)
		Fever	12 (11.8)	14 (14.2)
		Abdominal pain	7 (6.9)	13 (13.2)
		Tremor	2 (1.9)	12 (12.2)
		Nausea	2 (1.9)	11 (11.2)
		Otitis media	11 (10.8)	9 (9.1)
		Pharyngitis	10 (9.9)	11 (11.2)
		Ataxia	2 (1.9)	10 (10.2)
		Asthenia	6 (5.9)	11 (11.2)
		Proportion of patients reporting at least one AE	96 (95.0)	92 (93.8)
	Comments		$p \leq 0.05$ for dizziness, tremor, nausea, ataxia Rash includes erythema multiforme, maculopapular rash, urticaria, Stevens–Johnson syndrome and vesiculobullous rash	
Conclusions	Authors' conclusions	Lamotrigine is effective as adjunctive treatment for partial seizures. It is well tolerated although 2 patients were hospitalised owing to rash. Results are applicable to clinical practice because dose adjustments were based on concurrent AED therapy, individual tolerability, etc.		
	Our conclusions	Not clear how apparent differences in baseline seizure frequency may have affected results; ideally need analysis of covariance to explore this Although it is noted that the blinding was broken in 3 patients, it is not clear what happened to these patients or what influence this might have had on the results		

Trial details	Trial ID	Appleton, 1999
	Drug(s)	Gabapentin
	Target maintenance dose (mode)	600–1800 mg/day depending on weight (?mode)
	Seizure or syndrome	Partial seizures
	Type of trial design	Parallel
	Add-on or monotherapy?	Add-on
	Control(s)	Placebo
	Study start and end dates	1993–96
	Centres and location	54 centres in Europe, South Africa, USA
Trial design	Baseline	6 weeks
	Titration (including details of schedule and frequency of doses)	3 days Titrated to 23.2–35.3 mg/kg/day (total daily dose) 3 doses/day
	Maintenance	81 days
	Withdrawal	None
	Timing and additional eligibility for randomisation/continuation on study	Postbaseline; patients experiencing at least 1 seizure every 2 weeks and 4 seizures in total during baseline
	Comments on design	Dose titration refers explicitly to gabapentin only; not clear how/if placebo doses titrated in same way
Quality assessment	Was assignment of treatment described as random?	Yes
	Was method of randomisation described?	No
	Was the method really random?	Can't tell
	Was allocation of treatment concealed?	Can't tell
	Who was blinded to treatment?	Described as 'double-blind'
	Was method of blinding adequately described?	No description
	Were eligibility criteria described?	Yes
	Were groups comparable at study entry?	Yes
	Were groups treated identically apart from the intervention?	Can't tell (no description of blinding, and dose titration refers to gabapentin group only)
	Was ITT used?	Claimed, but not used. "ITT population defined as all randomised patients who received study medication"
	Were withdrawals stated?	Yes
	Were reasons for withdrawals stated?	Yes
	Was a power calculation done?	No
	Comments	–
Eligibility criteria	Inclusion criteria	1. Medically uncontrolled seizures; classified as simple partial, complex partial or partial becoming generalised 2. ≤ Age 12 years 3. Weight 17–72 kg at screening 4. Receiving 1–3 other AEDS (to remain unchanged throughout study)
	Exclusion criteria	1. Absence seizures, or seizures related to drugs, alcohol or acute medical illness 2. Structural CNS lesions or encephalopathies, diagnosed as progressive within 2 years prior to screening 3. Benign epilepsy syndromes

continued

Baseline characteristics			Placebo	Gabapentin
	Number randomised		Not stated	Not stated
	Number analysed		128	119
	Age (weeks, months, years) (mean, SD; median, range)		Mean 8.4, SD 2.7; median 9.0, range 3–12 years	Mean 8.5, SD 2.4; Median 9.0, range 3-12 years
	Male:female		75:53	59:60
	Weight (kg, lb) (mean, SD; median, range)		Not reported	Not reported
	Duration of epilepsy (weeks, months, years) (mean, SD; median, range)		Mean 5.4, SD 3.1; Median 5.3, range <1–11.9 years	Mean 5.7, SD 3.0 Median 5.9, range <1–11.3 years
	Age at diagnosis (weeks, months, years) (mean, SD; median, range)		Mean 3.0, SD 2.5; Median 2.5, range <1–10.7 years	Mean 2.7, SD 2.6; median 5.9, range <1–9.5 years
	Newly diagnosed, *n* (%)		0 (but duration short for some patients)	0 (but duration short for some patients)
	Previously diagnosed, *n* (%)		128 (100%) (but see comment above)	119 (100%) (but see comment above)
	Refractory, *n* (%); definition of refractory		Not stated; none given	Not stated; none given
	Diagnosed seizure types, *n* (%)	Simple partial	58 (45.3)	54 (45.4)
		Complex partial	112 (87.5)	99 (83.2)
		Secondarily generalised	70 (54.7)	73 (61.3)
		Myoclonic	12 (9.4)	16 (13.4)
		Tonic–clonic	13 (10.2)	15 (12.6)
		Tonic	11 (8.6)	8 (6.7)
		Atonic	9 (7.0)	8 (6.7)
		Atypical absence	7 (5.5)	7 (5.9)
		Clonic	2 (1.6)	2 (1.7)
		Absence	2 (1.6)	0 (–)
		Unclassified	4 (3.1)	5 (4.2)
	Diagnosed syndrome(s), *n* (%)	NA	NA	NA
	Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Partial seizures	Mean 63.3, SD 103.8; median 28.0, range 1.3–698/28 days	Mean 74.5, SD 268.3; median 24.1, range 2.7–2893/28 days
	No. of concomitant AEDs, *n* (%)	1	44 (34.4)	31 (26.1)
		2	57 (44.5)	58 (48.7)
		3	27 (21.1)	30 (25.2)
	Concomitant AEDs, *n* (%)	Not reported	–	–
	Previous AEDs, *n* (%)	Not reported	–	–
	Comments	–		
Monitoring and outcomes	Was monitoring of plasma levels done (including study drug)?	Yes (including study drug). "Gabapentin plasma levels and AED serum levels."		
	Were arrangements to blind plasma monitoring results mentioned?	No		
	Who recorded seizure frequency?	Parents/guardians		
	How often was seizure frequency measured?	Daily (diaries)		
	Frequency of clinic visits	4-weekly (weeks –6, 0, 4, 8, 12)		
	Primary outcome(s) including time points if repeated	Response ratio		

continued

	Secondary outcome(s) excluding AEs	1. Responder rate, defined as ≥ 50% reduction 2. % change in frequency of all partial seizures 3. % change in frequency for different types of partial seizure 4. Response ratio for different types of partial seizure 5. Investigator 'global assessment' 6. Parent/guardian 'global assessment'		
	'*Ad hoc*' outcomes (if emphasised and not in methods)			
	Comments	No reference given for 'response ratio', defined in text as (trt – baseline)/(trt + baseline); analysed using ANOVA but not clear that this is appropriate (assumes normally distributed data, which this won't be; data were transformed for non-normality on *ad hoc* basis).		
Results (ITT only; unadjusted where available)			Placebo	Gabapentin
	Median follow-up		12 weeks (assumed from low drop-out)	12 weeks (assumed from low drop-out)
	Maintenance dose achieved		Not reported	Not reported
	Withdrawals including reasons where specified, *n* (%)	Total withdrawals Lack of efficacy Adverse events Change in AED Other	28 (21.9) 19 (14.8) 3 (2.3) 2 (1.6) 4 (3.1)	21 (17.6) 11 (9.2) 6 (5.0) 0 (–) 4 (3.4)
		Median time to onset of AE resulting in withdrawal	24 days	13 days
		Median duration	6 days	7 days
			Results (difference, or by arm)	CI for difference; *p*-value
	Primary outcome(s)	Response ratio	Placebo –0.079 Gabapentin –0.146	$p = 0.1246$ (NB: data non-normal; analysis of transformed data gave $p = 0.0299$, but see comment below)
	Secondary outcomes	1. ≥ 50% reduction	Placebo 18%, gabapentin 21%	p = ns
		2. % change in frequency, all partial	Not reported for 'ITT'	Not reported for 'ITT'
		3. % change in frequency by type of partial seizure	Not reported for 'ITT'	Not reported for 'ITT'
		4. Response ratio by type of partial seizure	Not reported for 'ITT'	Not reported for 'ITT'
		5. Physician 'global assessment': seizure frequency well-being	 (Results not reproduced here) (Results not reproduced here)	 p = ns p = ns

continued

		6. Parent/guardian 'global assessment':		
		seizure frequency	(Results not reproduced here)	$p = 0.046$ (favouring gabapentin)
		well-being	(Results not reproduced here)	p = ns
	'*Ad hoc*' outcomes			
	Comments (including whether unadjusted results reported)	All results adjusted for centre Number randomised not reported; definition of ITT here implies that not all randomised patients included in analysis Most outcomes not reported for ITT population; note that ITT population used here does not meet technical definition of ITT (see comments on quality assessment) Response ratio also reported for 'ITT' population using rank-transformed data due to 'evidence of non-normality'; non-normality would be expected with this statistic and ANOVA is not an ideal means of analysis. Result for 'modified ITT' population reported without transformation and with no comment on normality		
Adverse events			Placebo	Gabapentin
	Criteria for reporting	Events in ≥ 2% of patients in either group		
	Events, *n* (%)	Viral infection	4 (3.1)	13 (10.9)
		Fever	4 (3.1)	12 (10.1)
		Nausea and/or vomiting	9 (7.0)	10 (8.4)
		Somnolence	6 (4.7)	10 (8.4)
		Pharyngitis	11 (8.6)	10 (8.4)
		Hostility	3 (2.3)	9 (7.6)
		Upper respiratory tract infection	8 (6.3)	7 (5.9)
		Headache	8 (6.3)	6 (5.0)
		Rhinitis	6 (4.7)	6 (5.0)
		Emotional lability	2 (1.6)	5 (4.2)
		Weight increase	1 (0.8)	4 (3.4)
		Fatigue	2 (1.6)	4 (3.4)
		Bronchitis	1 (0.8)	4 (3.4)
		Diarrhoea	4 (3.1)	3 (2.5)
		Convulsions	4 (3.1)	3 (2.5)
		Dizziness	2 (1.6)	3 (2.5)
		Hyperkinesia	1 (0.8)	3 (2.5)
		Respiratory infection	1 (0.8)	3 (2.5)
		Anorexia	3 (2.3)	2 (1.7)
		Coughing	4 (3.1)	2 (1.7)
		Otitis media	4 (3.1)	1 (0.8)
		Considered related to study drug (% events)	20%	34%
		Severe AEs	3 patients (3 events)	14 patients (23 events)
	Comments		–	

continued

Conclusions	Authors' conclusions	Gabapentin administered as add-on therapy is effective in this highly refractory population, reducing the incidence of partial onset seizures without provoking or worsening the severity of generalised seizures or status epilepticus Doses comparable (by weight) to adult doses, but probably slightly low. Some evidence of increased efficacy in adult population at higher doses Well tolerated in this population. Lower incidence of CNS side-effects than in previous trials with adult patients Lack of interaction with other AEDs is an advantage
	Our conclusions	Methodological weaknesses in design/conduct of trial difficult to quantify owing to lack of information on procedures for randomisation and blinding. Lack of this information, along with monitoring of gabapentin plasma levels with no description of how clinicians were blinded to these results, gives some cause for concern Analytical methods very weak and subject to considerable bias in the use of an apparently non-ITT population (described as ITT but with a definition that does not meet the usual definition of ITT). Results for the 'ITT' population underemphasised compared with results for the 'modified ITT' population. No clearly unbiased results are presented, but the least biased set of results (for the 'ITT' population) give no clear evidence for increased efficacy compared to placebo A more complete analysis would be required before any firm conclusions could be drawn

Trial details	Trial ID	Shapiro, 2000
	Drug(s)	Gabapentin
	Target maintenance dose (mode)	40 mg/kg/day (oral syrup)
	Seizure or syndrome	Partial seizures
	Type of trial design	Parallel
	Add-on or monotherapy?	Add-on
	Control(s)	Placebo
	Study start and end dates	Not reported
	Centres and location	Not reported
Trial design	Baseline	2 days
	Titration (including details of schedule and frequency of doses)	No titration 40 mg/kg/day 2 doses/day
	Maintenance	3 days
	Withdrawal	None
	Timing and additional eligibility for randomisation/continuation on study	
	Comments on design	Monitoring of seizure rate by continuous video-EEG recording over 72 h
Quality assessment	Was assignment of treatment described as random?	Yes
	Was method of randomisation described?	No
	Was the method really random?	Can't tell
	Was allocation of treatment concealed?	Can't tell

continued

	Who was blinded to treatment?	Described as 'double-blind'; EEG assessor blinded		
	Was method of blinding adequately described?	No description		
	Were eligibility criteria described?	Yes		
	Were groups comparable at study entry?	Yes		
	Were groups treated identically apart from the intervention?	Can't tell		
	Was ITT used?	Can't tell		
	Were withdrawals stated?	Not reported		
	Were reasons for withdrawals stated?	NA		
	Was a power calculation done?	Not reported		
	Comments	Abstract with few details		
Eligibility criteria	Inclusion criteria	1. Aged 1–36 months 2. Seizures not controlled by at least 1 AED 3. Partial seizures diagnosed by one of: matching clinical semiology with imaging/EEG evidence; EEG capture of a focal seizure		
	Exclusion criteria	None stated		
Baseline characteristics			Placebo	Gabapentin
	Number randomised		38	38
	Number analysed		Not reported	Not reported
	Age (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
	Male:female		Not reported	Not reported
	Weight (kg, lb) (mean, SD; median, range)		Not reported	Not reported
	Duration of epilepsy (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
	Age at diagnosis (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
	Newly diagnosed, *n* (%)		None (assumed)	None (assumed)
	Previously diagnosed, *n* (%)		38 (100%) (assumed from eligibility)	38 (100%) (assumed from eligibility)
	Refractory, *n* (%); definition of refractory	Not reported	Not reported	
	Diagnosed seizure types, *n* (%)	Not reported		
	Diagnosed syndrome(s), *n* (%)	Not reported		
	Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported		
	No. of concomitant AEDs, *n* (%)	Not reported		
	Concomitant AEDs, *n* (%)	Not reported		
	Previous AEDs, *n* (%)	Not reported		
	Comments			
Monitoring and outcomes	Was monitoring of plasma levels done (including study drug)?	No		
	Were arrangements to blind plasma monitoring results mentioned?	NA		

continued

	Who recorded seizure frequency?	A central EEG reader blinded to assignment.		
	How often was seizure frequency measured?	Continuously during baseline and maintenance phases		
	Frequency of clinic visits	Not reported		
	Primary outcome(s) including time points if repeated	1. Response ratio (measure of proportional change in rate of partial seizures between baseline and follow-up) 2. Responder rate; proportion whose seizure rate decreased by at least 50% relative to baseline		
	Secondary outcome(s) excluding AEs			
	'*Ad hoc*' outcomes (if emphasised and not in methods)			
	Comments			
Results (ITT only; unadjusted where available)			Placebo	Gabapentin
	Median follow-up		3 days (assumed)	3 days (assumed)
	Maintenance dose achieved		Not reported	Not reported
	Withdrawals including reasons where specified		Not reported	Not reported
			Results (difference, or by arm)	CI for difference; *p*-value
	Primary outcome(s)	1. Response ratio	Placebo –0.048 Gabapentin +0.018	p = ns
		2. Responder rate	Placebo not reported Gabapentin not reported	p = ns
	Secondary outcomes			
	'*Ad hoc*' outcomes			
	Comments (including whether unadjusted results reported)		–	
Adverse events			Placebo	Gabapentin
	Criteria for reporting	Most frequent		
	Events	Somnolence	Not reported	Not reported
		Nausea	Not reported	Not reported
		Vomiting	Not reported	Not reported
	Comments		–	
Conclusions	Authors' conclusions	Gabapentin was safe and well tolerated and reduced the rate of partial seizures		
	Our conclusions	Very limited information available from abstract. Trial was of very short duration, with small sample size		

Trial details	Trial ID	Glauser, 2000
	Drug(s)	Oxcarbazepine
	Target maintenance dose (mode)	30–46 mg/kg/day (oral, tablets)
	Seizure or syndrome	Partial seizures
	Type of trial design	Parallel
	Add-on or monotherapy?	Add-on
	Control(s)	Placebo
	Study start and end dates	Not reported [May 1995 to September 97 (industrial submission)]
	Centres and location	47 centres in Argentina, Chile, Uruguay, Australia, New Zealand, Canada, Israel, USA
Trial design	Baseline	8 weeks
	Titration (including details of schedule and frequency of doses)	2 weeks Titrated in four stages to target daily dose of 30–46 mg/kg/day [900 mg (body weight 20–29 kg), 1200 mg (29.1–39 kg) or 1800 mg (≥ 39.1 kg)] 2 doses/day
	Maintenance	14 weeks
	Withdrawal	None
	Timing and additional eligibility for randomisation/continuation on study	Postbaseline; patients experiencing at least 1 seizure every 4 weeks and at least 8 seizures in total during 8-week baseline period
	Comments on design	Dose titration refers explicitly to oxcarbazepine only; not clear how/if placebo doses titrated in same way
Quality assessment	Was assignment of treatment described as random?	Yes
	Was method of randomisation described?	Yes
	Was the method really random?	Yes
	Was allocation of treatment concealed?	Yes
	Who was blinded to treatment?	Described as 'double-blind'
	Was method of blinding adequately described?	Yes
	Were eligibility criteria described?	Yes
	Were groups comparable at study entry?	Yes
	Were groups treated identically apart from the intervention?	Can't tell (dose titration refers to oxcarbazepine group only)
	Was ITT used?	Not clear (see comment)
	Were withdrawals stated?	Yes
	Were reasons for withdrawals stated?	Yes
	Was a power calculation done?	Yes
	Comments	No follow-up available on 3 patients who discontinued treatment prematurely, but not clear if these data were 'missing' or never sought (31 patients discontinued in total)
Eligibility criteria	Inclusion criteria	1. Medically uncontrolled seizures; classified as simple partial, complex partial or partial becoming generalised (EEG features consistent with localisation-related epilepsy) 2. Age 3–17 years 3. Serum sodium concentration at least 130 mmol/l 4. Receiving 1–2 other AEDs 5. Absence of a progressive lesion

continued

	Exclusion criteria	1. Generalised status epilepticus during 6 months prior to trial 2. Seizures of metabolic, neoplastic, or active infectious origin 3. Non-compliance with medical treatment 4. Any medical condition likely to impact on outcome of trial 5. Attempted suicide 6. Substance abuse 7. Clinically significant laboratory abnormalities including AST (aspartate transaminase), ALT (alanine transaminase), WBC (white blood cells) 8. Hypersensitivity to carbamazepine; previous use of oxcarbazepine; felbamate within 90 days of baseline; felodipine, verapamil, monoamine oxidase inhibitors within 30 days of baseline 9. Participation in other investigational drug trial within 60 days of screening visit 10. Pregnant or nursing females or those trying to conceive		
Baseline characteristics			Placebo	Oxcarbazepine
	Number randomised		129	138
	Number analysed		128	136
	Age (weeks, months, years) (mean, SD; median, range)		Mean 11 years; range 3–17 years	Mean 11 years; range 3–17 years
	Male:female		71:58	70:68
	Weight (kg, lb) (mean, SD; median, range)		Mean 44 kg; range 16–89 kg	Mean 44 kg; range 16–130 kg
	Duration of epilepsy (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
	Age at diagnosis (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
	Newly diagnosed, *n* (%)		0	0
	Previously diagnosed, *n* (%)		129 (100)	138 (100)
	Refractory, *n* (%); definition of refractory		Not stated; none given	Not stated; none given
	Diagnosed seizure types, *n* (%)	Simple partial Complex partial Secondarily generalised	44 (34.1) 93 (72.1) 57 (44.1)	41 (29.7) 108 (78.2) 50 (36.2)
	Diagnosed syndrome(s), *n* (%)	NA	NA	NA
	Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Partial seizures	Median 13, range 2–554 per 28 days	Median 12, range 3–1470 per 28 days
		Secondarily generalised seizures	Median 0, range 0–86 per 28 days	Median 0, range 0–176 per 28 days
	No. of concomitant AEDs, *n* (%)		Not reported	Not reported
	Concomitant AEDs, *n* (%)	Carbamazepine Valproate Lamotrigine Phenytoin	55 (42.6) 31 (24.0) 29 (22.5) 22 (17.1)	77 (55.8) 23 (16.7) 22 (15.9) 21 (15.2)
	Previous AEDs, *n* (%)	Not reported	Not reported	Not reported
	Comments		Typographic error in Table 2 of paper; 27 oxcarbazepine patients reported with concomitant carbamazepine, but 77 consistent with % reported and text	

continued

Monitoring and outcomes	Was monitoring of plasma levels done (including study drug)?	Yes. "Concomitant AEDs" and of MHD (active oxcarbazepine metabolite) during maintenance phase.		
	Were arrangements to blind plasma monitoring results mentioned?	No		
	Who recorded seizure frequency?	Parents/guardians		
	How often was seizure frequency measured?	Not reported (diaries)		
	Frequency of clinic visits	Weeks –8, 0, 2, 4, 6, 8, 12, 16		
	Primary outcome(s) including time points if repeated	% change in frequency of all partial seizures per 28 days		
	Secondary outcome(s) excluding AEs	1. Responder rate, defined as ≥ 50% reduction in all partial seizure frequency per 28 days 2. % change in frequency of secondarily generalised seizures per 28 days		
	'*Ad hoc*' outcomes (if emphasised and not in methods)	1. % change in frequency of simple partial and complex partial seizures per 28 days 2. Seizure-free patients		
	Comments	% change in frequency of different seizure types reported together below		
Results (ITT only; unadjusted where available)			Placebo	Oxcarbazepine
	Median follow-up		16 weeks (assumed)	16 weeks (assumed)
	Maintenance dose achieved		Not reported	Median 31.4, range 6.4–51.4 mg/kg/day
	Withdrawals including reasons where specified, *n* (%)	Total withdrawals Lack of efficacy Adverse events Non-compliance Withdrew consent Lost to follow-up	10 (7.8) 4 (3.1) 4 (3.1) 0 (–) 1 (0.8) 1 (0.8)	21 (15.2) 0 (–) 14 (10.1) 4 (2.9) 2 (4.3) 0 (–)
			Results (difference, or by arm)	CI for difference; *p*-value
	Primary outcome(s)	% change in frequency of all partial seizures per 28 days during double-blind treatment	Placebo –9% Oxcarbazepine –35% (median % change)	$p = 0.0001$
	Secondary outcomes	1. ≥ 50% reduction in all partial seizure frequency	Placebo 22% Oxcarbazepine 41%	$p = 0.0005$
		2. % change in frequency of:		
		Simple partial	45% oxcarbazepine vs 16% placebo	Not reported
		Complex partial	42% vs 10%	Not reported
		Secondarily generalised	78% vs 33%	$p = 0.0012$
	'*Ad hoc*' outcomes	Seizure-free patients	Placebo $n = 1/128$ oxcarbazepine $n = 5/136$	Not reported

continued

	Comments (including whether unadjusted results reported)	All changes in seizure frequency reported as median reductions 50% responder rates reported for 135 (not ITT population of 136) oxcarbazepine patients (no explanation for missing patient) Changes reported for each seizure type apply only to patients with that type of seizure at baseline Sample size slightly less than target given in power calculation (267 vs 274) Analysis of responder rate adjusted for centre, sex, age and weight		
Adverse events			Placebo	Oxcarbazepine
	Criteria for reporting	Events in >10% of patients in either group		
	Events, *n* (%)	Viral infection	21 (16.2)	19 (13.7)
		Fever	20 (15.5)	21 (15.2)
		Nausea and/or vomiting	26 (20.1)	80 (57.9)
		Somnolence	18 (13.9)	48 (34.7)
		Pharyngitis	15 (11.6)	12 (8.6)
		Upper respiratory tract infection	15 (11.6)	10 (7.2)
		Headache	23 (17.8)	44 (31.8)
		Rhinitis	11 (8.5)	16 (11.5)
		Fatigue	11 (8.5)	18 (13.0)
		Dizziness	10 (7.7)	40 (28.9)
		Anorexia	13 (10.0)	9 (6.5)
		Ataxia	6 (4.6)	19 (13.7)
		Abnormal gait	4 (3.1)	14 (10.1)
		Nystagmus	2 (1.5)	14 (10.1)
		Diplopia	1 (0.7)	23 (16.6)
		Abnormal vision	2 (1.5)	19 (13.7)
		Abdominal pain	13 (10.0)	12 (8.6)
		Proportion of patients reporting ≥ 1 adverse event	106 (82)	126 (91)
	Comments		Rash reported in 5% placebo, 4% oxcarbazepine group	
Conclusions	Authors' conclusions	Oxcarbazepine-treated patients experienced statistically significant improvements over placebo in the primary end-point and in the number of patients with ≥ 50% reduction in seizure frequency Oxcarbazepine is safe, effective and well tolerated in children with partial seizures		
	Our conclusions	Fairly high-quality study, with reasonable conclusions		

Trial details	Trial ID	Litzinger, 1998		
	Drug(s)	Tiagabine		
	Target maintenance dose (mode)	0.7 mg/kg/day (assumed/day)		
	Seizure or syndrome	Refractory partial seizures		
	Type of trial design	Parallel		
	Add-on or monotherapy?	Add-on		
	Control(s)	Placebo		
	Study start and end dates	Not reported		
	Centres and location	Not reported		
Trial design	Baseline	8 weeks		
	Titration (including details of schedule and frequency of doses)	Not reported		
	Maintenance	12 weeks		
	Withdrawal	Not reported		
	Timing and additional eligibility for randomisation/continuation on study			
	Comments on design	Abstract with few details of design. Data not extractable, subgroup and postrandomised phase.		
Quality assessment	Was assignment of treatment described as random?	Abstract only, no details		
	Was method of randomisation described?	No		
	Was the method really random?	Can't tell		
	Was allocation of treatment concealed?	Can't tell		
	Who was blinded to treatment?	Abstract only, no details		
	Was method of blinding adequately described?	Abstract only, no details		
	Were eligibility criteria described?	Abstract only, no details		
	Were groups comparable at study entry?	Abstract only, no details		
	Were groups treated identically apart from the intervention?	Abstract only, no details		
	Was ITT used?	Abstract only, no details		
	Were withdrawals stated?	Abstract only, no details		
	Were reasons for withdrawals stated?	Abstract only, no details		
	Was a power calculation done?	Abstract only, no details		
	Comments	Abstract only, no details		
Eligibility criteria	Inclusion criteria	Abstract only, no details		
	Exclusion criteria	Abstract only, no details		
Baseline characteristics			Placebo	Tiagabine
	Number randomised		Abstract only, no details	Abstract only, no details
	Number analysed		Abstract only, no details	Abstract only, no details

continued

	Age (weeks, months, years) (mean, SD; median, range)	Abstract only, no details	Abstract only, no details
	Male:female	Abstract only, no details	Abstract only, no details
	Weight (kg, lb) (mean, SD; median, range)	Abstract only, no details	Abstract only, no details
	Duration of epilepsy (weeks, months, years) (mean, SD; median, range)	Abstract only, no details	Abstract only, no details
	Age at diagnosis (weeks, months, years) (mean, SD; median, range)	Abstract only, no details	Abstract only, no details
	Newly diagnosed, *n* (%)	Abstract only, no details	Abstract only, no details
	Previously diagnosed, *n* (%)	Abstract only, no details	Abstract only, no details
	Refractory, *n* (%); definition of refractory	Abstract only, no details	Abstract only, no details
	Diagnosed seizure types, n (%)	Abstract only, no details	Abstract only, no details
	Diagnosed syndrome(s), *n* (%)	Abstract only, no details	Abstract only, no details
	Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Abstract only, no details	Abstract only, no details
	No concomitant AEDs, *n* (%)	Abstract only, no details	Abstract only, no details
	Concomitant AEDs, *n* (%)	Abstract only, no details	Abstract only, no details
	Previous AEDs, *n* (%)	Abstract only, no details	Abstract only, no details
	Comments	Abstract only, no details	
Monitoring and outcomes	Was monitoring of plasma levels done (including study drug)?	Abstract only, no details	
	Were arrangements to blind plasma monitoring results mentioned?	Abstract only, no details	
	Who recorded seizure frequency?	Abstract only, no details	
	How often was seizure frequency measured?	Abstract only no details	
	Frequency of clinic visits	Abstract only no details	
	Primary outcome(s) including time points if repeated	Abstract only no details	
	Secondary outcome(s) excluding AEs	Abstract only no details	
	'*Ad hoc*' outcomes (if emphasised and not in methods)		
	Comments	Abstract only, no details	
Results (ITT only; unadjusted where available)		Placebo	Tiagabine
	Median follow-up	Abstract only, no details	Abstract only, no details

continued

	Maintenance dose achieved		Abstract only, no details	Abstract only, no details
	Withdrawals including reasons where specified		Abstract only, no details	Abstract only, no details
			Results (difference, or by arm)	CI for difference; *p*-value
	Primary outcome(s)	Abstract only, no details		
	Secondary outcomes	Abstract only, no details		
	'Ad hoc' outcomes	Abstract only, no details		
	Comments (including whether unadjusted results reported)	Abstract only, no details		
Adverse events			Placebo	Tiagabine
	Criteria for reporting	–		
	Events	Abstract only, no details		
	Comments		Abstract only, no details	
Conclusions	Authors' conclusions	–		
	Our conclusions	–		

Trial details	Trial ID	Elterman, 1999
	Drug(s)	Topiramate
	Target maintenance dose (mode)	125–400 mg/day (oral)
	Seizure or syndrome	Partial seizures
	Type of trial design	Parallel
	Add-on or monotherapy?	Add-on
	Control(s)	Placebo
	Study start and end dates	Not reported
	Centres and location	17 centres in USA, Costa Rica
Trial design	Baseline	8 weeks
	Titration (including details of schedule and frequency of doses)	8 weeks Titrated from 25 mg/day in four consecutive 2-week intervals to target of 125–400 mg/day, based on body weight 1 dose/day for first 2 weeks then 2 doses/day
	Maintenance	8 weeks
	Withdrawal	None
	Timing and additional eligibility for randomisation/continuation on study	Postbaseline; patients experiencing at least 6 partial seizures (at least 1 every 4-week interval) during baseline
	Comments on design	Dose titration refers explicitly to topiramate only; not clear how/if placebo doses titrated in same way

continued

Quality assessment	Was assignment of treatment described as random?	Yes
	Was method of randomisation described?	Yes
	Was the method really random?	Yes
	Was allocation of treatment concealed?	Yes
	Who was blinded to treatment?	Patients, investigators, study monitors and observers
	Was method of blinding adequately described?	No description
	Were eligibility criteria described?	Yes
	Were groups comparable at study entry?	Yes
	Were groups treated identically apart from the intervention?	Can't tell (no description of blinding, and dose titration refers to topiramate group only)
	Was ITT used?	Yes
	Were withdrawals stated?	Yes
	Were reasons for withdrawals stated?	Yes
	Was a power calculation done?	Yes
	Comments	
Eligibility criteria	Inclusion criteria	1. Medically uncontrolled partial seizures, with or without secondarily generalised seizures 2. Age between 1 and 16 years 3. Weight >16 kg 4. Receiving 1–2 other AEDs (at constant dose) 5. CT or MRI exclusion of potentially progressive neurological diseases 6. EEG/close cable television EEG confirmation of the diagnosis of partial epilepsy 7. Postmenarcheal females only if physically incapable of bearing children, or practising acceptable method of birth control
	Exclusion criteria	1. Lennox–Gastaut syndrome 2. Clinically significant ECG abnormalities 3. Generalised status epilepticus within the previous 3 months while complying with AEDs, or seizures occurring only in clustered pattern 4. Significant medical disease, nephrolithiasis, drug or alcohol abuse, recent significant psychiatric or mood disorder, use of drugs that increased the risk of renal stones (e.g. acetazolamide, high-dose vitamin C, antacids or calcium supplements in chronic doses) 5. Felbamate or centrally acting sympathomimetics excluded (by protocol amendment for safety reasons)

Baseline characteristics		Placebo	Topiramate
	Number randomised	45	41
	Number analysed	45	41
	Age (weeks, months, years) (Mean, SD; median, range)	Mean 9.0, SD 3.4; range 2–16 years	Mean 8.8, SD 3.6; range 2–16 years
	Male:female	25:20	23:18
	Weight (kg, lb) (mean, SD; median, range)	Mean 35.1, SD 16.3 kg	Mean 34.7, SD 15.8 kg
	Duration of epilepsy (weeks, months, years) (mean, SD; median, range)	Not reported	Not reported

continued

	Age at diagnosis (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
	Newly diagnosed, *n* (%)		0 (–)	0 (–)
	Previously diagnosed, *n* (%)		45 (100)	41 (100)
	Refractory, *n* (%); definition of refractory		45 (100)	41 (100)
	Diagnosed seizure types, *n* (%)	simple partial	12 (26.6)	11 (26.8)
		complex partial	37 (82.2)	31 (75.6)
		secondarily generalised	17 (37.7)	17 (41.4)
		other	3 (6.6)	3 (7.3)
	Diagnosed syndrome(s), *n* (%)	NA	NA	NA
	Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Partial seizures	Median 19, range 2–1133	Median 22, range 2–232
		Secondarily generalised seizures	Median 5, range 1–273/month	Median 6, range 1–89/month
	No. of concomitant AEDs, *n* (%)	1	24 (53.3)	15 (36.5)
		2	20 (44.4)	25 (60.9)
		3	1 (2.2)	1 (2.4)
	Concomitant AEDs, *n* (%)	Carbamazepine	26 (57.7)	25 (60.9)
		Valproate	10 (22.2)	10 (24.3)
		Phenytoin	9 (20)	6 (14.6)
		Gabapentin	4 (8.8)	10 (24.3)
		Lamotrigine	5 (11.1)	5 (12.1)
	Previous AEDs, *n* (%)	Not reported	Not reported	Not reported
	Comments		–	
Monitoring and outcomes	Was monitoring of plasma levels done (including study drug)?	Yes ("plasma AED including topiramate periodically during baseline and double-blind phases")		
	Were arrangements to blind plasma monitoring results mentioned?	No		
	Who recorded seizure frequency?	Parents/guardians		
	How often was seizure frequency measured?	Not reported (diaries used)		
	Frequency of clinic visits	Diary data collection days 1, 8, 15, 22, 50, 77		
	Primary outcome(s) including time points if repeated	% change in frequency of all partial seizures (average monthly rate)		
	Secondary outcome(s) excluding AEs	1. % change in frequency of secondarily generalised seizures (average monthly rate) 2. Proportion of patients with ≥ 50% reduction in all partial seizures 3. Proportion of patients with ≥ 75% reduction in all partial seizures 4. Proportion of patients with 100% reduction in all partial seizures 5. Parental global evaluation		
	'*Ad hoc*' outcomes (if emphasised and not in methods)	None		
	Comments	–		
Results (ITT only; unadjusted where available)			Placebo	Topiramate
	Median follow-up		16 weeks	16 weeks
	Maintenance dose achieved		Not reported	Median 5.9 mg/kg/day
	Withdrawals including reasons where specified, *n* (%)	Total withdrawals	2 (4.4)	0 (–)
		Adverse events	1 (2.2)	0 (–)
		Patient choice	1 (2.2)	0 (–)

continued

			Results (difference, or by arm)	CI for difference; *p*-value
	Primary outcome(s)	% change in frequency of all partial seizures (average monthly rate)	Placebo –10.5% Topiramate –33.1% (median % reduction)	$p = 0.034$
	Secondary outcomes	1. % change in frequency of secondarily generalised seizures (average monthly rate)	Placebo +10.6% Topiramate –31.6% (median % reduction)	Not reported
		2. Proportion of patients with ≥ 50% reduction in all partial seizures	Placebo 9 (20.0%) Topiramate 16 (39.0%)	p = ns
		3. Proportion of patients with ≥ 75% reduction in all partial seizures	Placebo 1 (2.2%) Topiramate 7 (17.0%)	$p = 0.019$
		4. Proportion of patients with 100% reduction in all partial seizures	Placebo 0 (–) Topiramate 2 (4.8%)	p = ns
		5. Parental global evaluation	(Results not reproduced here)	(Results not reproduced here)
	'*Ad hoc*' outcomes	None	NA	NA
	Comments (including whether unadjusted results reported)		Results adjusted for centre only	
Adverse events			Placebo	Topiramate
	Criteria for reporting	Events in ≥ 10% of patients in topiramate group		
	Events, *n* (%)	Upper respiratory tract infection	(36)	(41)
		Sinusitis	(27)	(17)
		Coughing	(11)	(15)
		Diarrhoea	(22)	(10)
		Somnolence	(13)	(12)
		Anorexia	(11)	(12)
		Emotional lability	(4)	(12)
		Difficulty concentrating/ attention	(2)	(12)
		Mood problems	(11)	(10)
		Aggressive reaction	(7)	(10)
		Nervousness	(7)	(10)
		Viral infection	(4)	(15)
		Otitis media	(11)	(10)
		Rash	(9)	(12)
		Purpura	(4)	(15)
		Fever	(24)	(29)
		Injury	(9)	(20)
		Fatigue	(7)	(15)
		Serious AEs	3 (6.6)	1 (2.4)

continued

	Comments	Parental evaluation of mental status also reported (verbal questioning of parents/guardians)
Conclusions	Authors' conclusions	Topiramate improves seizure control in patients with partial onset seizures with/without secondary generalisation. The doses of topiramate used in this study were lower than those used in others, therefore had higher doses been used a greater treatment effect might have been seen
	Our conclusions	Lack of information on how clinicians were blinded to plasma level monitoring results and on how placebo dose was titrated raises questions as to how blinding was maintained There are three abstracts associated with this paper: refs 574, 575 and 576. There are two small differences between the abstracts and the full paper: the abstracts say that age range was 2–17 years compared with the full paper 1–16 years; and 422 says that 3 patients withdrew whereas the others say only 2 withdrew

Trial details	Trial ID	Valentine, 1998
	Drug(s)	Vigabatrin
	Target maintenance dose (mode)	1.5–4 g/day (oral)
	Seizure or syndrome	Uncontrolled complex partial seizures with or without secondary generalisation
	Type of trial design	Parallel
	Add-on or monotherapy?	Add-on
	Control(s)	Placebo
	Study start and end dates	Not reported
	Centres and location	Multicentre (n = ?)
Trial design	Baseline	6 weeks
	Titration (including details of schedule and frequency of doses)	10 weeks
	Maintenance	7 weeks
	Withdrawal	None
	Timing and additional eligibility for randomisation/continuation on study	Not stated
	Comments on design	Underpowered, randomised only 75% of target of 120 patients
Quality assessment	Was assignment of treatment described as random?	Yes
	Was method of randomisation described?	No
	Was the method really random?	Can't tell
	Was allocation of treatment concealed?	Can't tell
	Who was blinded to treatment?	Not stated
	Was method of blinding adequately described?	No description
	Were eligibility criteria described?	No
	Were groups comparable at study entry?	Can't tell

continued

	Were groups treated identically apart from the intervention?	Can't tell		
	Was ITT used?	Claimed		
	Were withdrawals stated?	No		
	Were reasons for withdrawals stated?	No		
	Was a power calculation done?	Yes		
	Comments	Claimed of 127 patients entering baseline, 88 were randomised and used for ITT analysis		
Eligibility criteria	Inclusion criteria	Not stated		
	Exclusion criteria	Not stated		
Baseline characteristics			Placebo	Vigabatrin
	Number randomised		Total 88, not stated by arm	Total 88, not stated by arm
	Number analysed		88, not stated by arm	88, not stated by arm
	Age (weeks, months, years) (mean, SD; median, range)		Range 3–16 years, not stated by study arm	Range 3–16 years, not stated by study arm
	Male:female		Not stated	Not stated
	Weight (kg, lb) (mean, SD; median, range)		Not stated	Not stated
	Duration of epilepsy (weeks, months, years) (mean, SD; median, range)		Not stated	Not stated
	Age at diagnosis (weeks, months, years) (mean, SD; median, range)		Not stated	Not stated
	Newly diagnosed, *n* (%)		Not stated	Not stated
	Previously diagnosed, *n* (%)		Not stated	Not stated
	Refractory, *n* (%), definition of refractory		Not stated	Not stated
	Diagnosed seizure types, *n* (%)	Not reported		
	Diagnosed syndrome(s), *n* (%)	Not reported		
	Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported		
	No. of concomitant AEDs, *n* (%)	Not reported		
	Concomitant AEDs, *n* (%)	Not reported		
	Previous AEDs, *n* (%)	Not reported		
	Comments	–		
Monitoring and outcomes	Was monitoring of plasma levels done (including study drug)?	No		
	Were arrangements to blind plasma monitoring results mentioned?	NA		
	Who recorded seizure frequency?	Not stated		
	How often was seizure frequency measured?	Not stated		
	Frequency of clinic visits	Not stated		
	Primary outcome(s) including time points if repeated	≥ 50% reduction in seizure frequency		

continued

	Secondary outcome(s) excluding AEs		–	
	'*Ad hoc*' outcomes (if emphasised and not in methods)		–	
	Comments		–	
Results (ITT only; unadjusted where available)			Placebo	Vigabatrin
	Median follow-up		Not stated	not stated
	Maintenance dose achieved		Not stated	1.5–4 g/day
	Withdrawals including reasons where specified	Not reported		
			Results (difference, or by arm)	CI for difference; *p*-value
	Primary outcome(s)	≥ 50% reduction in seizure frequency	Placebo 26.7% Vigabatrin 55.8%	$p = 0.0089$
	Secondary outcomes			
	'*Ad hoc*' outcomes			
	Comments (including whether unadjusted results reported)		–	
Adverse events			Placebo	Vigabatrin
	Criteria for reporting	Treatment-related adverse events		
	Events, *n* (%)	All events Somnolence Headache Dizziness Increased seizure frequency	(66.7) Not reported Not reported Not reported Not reported	(65.9) Not reported Not reported Not reported Not reported
	Comments		–	
Conclusions	Authors' conclusions	Vigabatrin safe as add-on treatment for paediatric patients with uncontrolled complex partial seizures at a dose range of 0.5 to 4 g/day		
	Our conclusions	Insufficient reported detail to judge validity of authors' conclusion		

Trial details	Trial ID	Van Orman, 1998
	Drug(s)	Vigabatrin
	Target maintenance dose (mode)	20, 60, 100 mg/kg/day (?mode)
	Seizure or syndrome	Uncontrolled complex partial seizures with or without secondary generalisation
	Type of trial design	Parallel
	Add-on or monotherapy?	Add-on
	Control(s)	Placebo
	Study start and end dates	Not stated
	Centres and location	Multicentre ($n = ?$)
Trial design	Baseline	Not stated
	Titration (including details of schedule and frequency of doses)	6 weeks

continued

	Maintenance	8 weeks		
	Withdrawal	None		
	Timing and additional eligibility for randomisation/continuation on study	Not stated		
	Comments on design	Dose–response study		
Quality assessment	Was assignment of treatment described as random?	Yes		
	Was method of randomisation described?	Not stated		
	Was the method really random?	Can't tell		
	Was allocation of treatment concealed?	Can't tell		
	Who was blinded to treatment?	Not stated		
	Was method of blinding adequately described?	No description		
	Were eligibility criteria described?	No		
	Were groups comparable at study entry?	Can't tell		
	Were groups treated identically apart from the intervention?	Can't tell		
	Was ITT used?	Claimed		
	Were withdrawals stated?	No		
	Were reasons for withdrawals stated?	No		
	Was a power calculation done?	Yes		
	Comments	Underpowered, randomised only 63% of target of 200 patients		
Eligibility criteria	Inclusion criteria	Not stated		
	Exclusion criteria	Not stated		
Baseline characteristics			Placebo	Vigabatrin: 20; 60; 100 mg
	Number randomised		Total 126, not stated by arm	Total 126, not stated by arm
	Number analysed		126, not stated by arm	126, not stated by arm
	Age (weeks, months, years) (mean, SD; median, range)		Range 3–16 years, not stated by study arm	Range 3–16 years, not stated by study arm
	Male:female		Not stated	Not stated
	Weight (kg, lb) (mean, SD; median, range)		Not stated	Not stated
	Duration of epilepsy (weeks, months, years) (mean, SD; median, range)		Not stated	Not stated
	Age at diagnosis (weeks, months, years) (mean, SD; median, range)		Not stated	Not stated
	Newly diagnosed, *n* (%)		Not stated	Not stated
	Previously diagnosed, *n* (%)		Not stated	Not stated
	Refractory, *n* (%); definition of refractory		Not stated	Not stated
	Diagnosed seizure types, *n* (%)	Not stated		

continued

	Diagnosed syndrome(s), *n* (%)	Not stated		
	Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not stated		
	No concomitant AEDs, *n* (%)	Not stated		
	Concomitant AEDs, *n* (%)	Not stated		
	Previous AEDs, *n* (%)	Not stated		
	Comments		–	
Monitoring and outcomes	Was monitoring of plasma levels done (including study drug)?	No		
	Were arrangements to blind plasma monitoring results mentioned?	NA		
	Who recorded seizure frequency?	Not stated		
	How often was seizure frequency measured?	Not stated		
	Frequency of clinic visits	Not stated		
	Primary outcome(s) including time points if repeated	Reduction in patient mean monthly seizure frequency		
	Secondary outcome(s) excluding AEs			
	'*Ad hoc*' outcomes (if emphasised and not in methods)			
	Comments		–	
Results (ITT only; unadjusted where available)			Placebo	Vigatabin: 20; 60; 100 mg
	Median follow-up		Not stated	Not stated
	Maintenance dose achieved		Not stated	Not stated
	Withdrawals including reasons where specified	Not stated		
			Results (difference, or by arm)	CI for difference; *p*-value
	Primary outcome(s)	Reduction in patient mean monthly seizure frequency	Not stated	$p = 0.0142$ (100-mg group vs placebo) Greater reduction for active arm
	Secondary outcomes			
	'*Ad hoc*' outcomes			
	Comments (including whether unadjusted results reported)		–	
Adverse events			Placebo	Vigabatrin: 20; 60; 100 mg
	Criteria for reporting	Treatment-related adverse events		
	Events	All events Somnolence Dizziness Increased seizure frequency	(61.3) Not reported Not reported Not reported	(42.3); (65.5); (86.7) Not reported Not reported Not reported
	Comments			

continued

Conclusions	Authors' conclusions	Vigabatrin is safe and effective add-on treatment in paediatric patients with uncontrolled complex partial seizures
	Our conclusions	Insufficient reported detail to judge validity of authors' conclusion

Trial details	Trial ID	Guerreiro, 1997
	Drug(s)	Oxcarbazepine
	Target maintenance dose (mode)	450–2400 mg/day (oral)
	Seizure or syndrome	Newly diagnosed partial seizures with or without secondary generalisation, and generalised tonic–clonic seizures
	Type of trial design	Parallel
	Add-on or monotherapy?	Monotherapy
	Control(s)	Phenytoin
	Study start and end dates	1991–1995
	Centres and location	Multicentre; Brazil, Argentina
Trial design	Baseline	Retrospective baseline
	Titration (including details of schedule and frequency of doses)	8 weeks Oxcarbazepine: 150 mg/day gradually increasing according to clinical response to target of 450–2400 mg/day 3 doses/day Phenytoin: 50 mg/day gradually increasing according to clinical response to target of 150–800 mg/day 3 doses/day
	Maintenance	48 weeks
	Withdrawal	None (optional non-RCT continuation to open study)
	Timing and additional eligibility for randomisation/continuation on study	NA (retrospective baseline)
	Comments on design	No clear justification given for the use of phenytoin as comparator when it is not generally a first-choice treatment
Quality assessment	Was assignment of treatment described as random?	Yes
	Was method of randomisation described?	Yes
	Was the method really random?	Yes
	Was allocation of treatment concealed?	Can't tell
	Who was blinded to treatment?	Described as 'double-blind'
	Was method of blinding adequately described?	"Tablets with identical appearance"
	Were eligibility criteria described?	Yes
	Were groups comparable at study entry?	Yes
	Were groups treated identically apart from the intervention?	Can't tell
	Was ITT used?	Yes (for time to withdrawal outcome)
	Were withdrawals stated?	Yes
	Were reasons for withdrawals stated?	Yes
	Was a power calculation done?	Yes

continued

	Comments	Authors identify a primary outcome for each of efficacy, tolerability and clinical utility		
Eligibility criteria	Inclusion criteria	1. Newly diagnosed epilepsy with partial seizures, with or without secondary generalisation, or generalised tonic-clonic seizures 2. Minimum of 2 seizures separated by at least 48 h in previous 6 months 3. 5–18 years old 4. No previous AED except for emergency treatment for a maximum of 3 weeks		
	Exclusion criteria	1. Pregnant or risk of becoming pregnant 2. History of status epilepticus 3. Severe psychiatric disorder or severe mental retardation 4. Progressive neurological disorder 5. Alcoholism or drug abuse 6. Significant organic disease		
Baseline characteristics			Phenytoin	Oxcarbazepine
	Number randomised		96	97
	Number analysed		77	81
	Age (weeks, months, years) (mean, SD; median, range)		Mean 10.85; range 6–17 years	Mean 10.22; Range 5–17 years
	Male:female		50:46	46:51
	Weight (kg, lb) (mean, SD; median, range)		Mean 40.7; range 21–96 kg	Mean 36.4; range 16–72 kg
	Duration of epilepsy (weeks, months, years) (mean, SD; median, range)		Mean 37.7; range 0.8–728 weeks	Mean 30.2; range 0.8–272 weeks
	Age at diagnosis (weeks, months, years) (mean, SD; median, range)	Not stated	Not stated	
	Newly diagnosed, *n* (%)		96 (100) (although duration of epilepsy very long for some patients)	97 (100) (although duration of epilepsy very long for some patients)
	Previously diagnosed, *n* (%)		0 (–)	0 (–)
	Refractory, 234 (%); definition of refractory		None	None
	Diagnosed seizure types, *n* (%)	Partial seizures (any type)	78 (81.3)	73 (75.2)
		Generalised	17 (17.7)	22 (22.7)
		Unclassified	1 (1)	2 (2.1)
	Diagnosed syndrome(s), *n* (%)	Localisation-related, idiopathic	20	18
		Localisation-related, symptomatic	5	7
		Localisation-related, cryptogenic	50	46
		Generalised, idiopathic	11	11
		Generalised, cryptogenic or symptomatic	5	6
		Generalised, symptomatic	1	2

continued

		Others	4	6
		Unclassified	0	1
	Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	All seizure types	Mean 0.66; median 0.33/week	Mean 0.68; median 0.25/week
		2 seizures/week (*n*)	47	40
		3–10 seizures/week (*n*)	38	45
		11–99 seizures/week (*n*)	7	11
		≥ 100 seizures/week (*n*)	4	1
	No. of concomitant AEDs, *n* (%)	None	96 (100)	97 (100)
	Concomitant AEDs, *n* (%)	None	96 (100)	97 (100)
	Previous AEDs, *n* (%)	None	96 (100)	97 (100)
	Comments			
Monitoring and outcomes	Was monitoring of plasma levels done (including study drug)?	Yes		
	Were arrangements to blind plasma monitoring results mentioned?	Yes (results reported only as zero, low, within range, or high)		
	Who recorded seizure frequency?	Patient or carer		
	How often was seizure frequency measured?	Patient diaries (frequency not stated)		
	Frequency of clinic visits	Every 2 weeks during titration; every 8 weeks during maintenance		
	Primary outcome(s) including time points if repeated	Proportion of seizure-free patients (of those who reached maintenance period and had at least one seizure assessment during the maintenance period)		
	Secondary outcome(s) excluding AEs	1. Seizure frequency during maintenance 2. Overall evaluation of therapeutic effect (4-point ordinal scale) 3. Premature discontinuation due to unsatisfactory therapeutic effect 4. Premature discontinuation due to adverse events. 5. Overall evaluation of tolerability (4-point ordinal scale) 6. Clinical utility (time to premature discontinuation for any reason)		
	'*Ad hoc*' outcomes (if emphasised and not in methods)			
	Comments	Primary outcome measure precludes ITT analysis.		
Results (ITT only; unadjusted where available)			Phenytoin	Oxcarbazepine
	Median follow-up		56 weeks	56 weeks
	Maintenance dose achieved		Mean 5.8 mg/kg/day (at start of maintenance period)	Mean 18.8 mg/kg/day (at start of maintenance period)
	Withdrawals including reasons where specified, *n* (%)	Total withdrawals	34	24
		Loss to follow-up	9	8
		Adverse experiences	14	2
		Non-compliance	5	6
		Unsatisfactory therapeutic effect	3	4
		Protocol violation	2	3
		Concomitant illness	0	1
		Discontinuation at baseline	1	0

continued

			Results (difference, or by arm)	CI for difference; *p*-value
	Primary outcome(s)	Proportion of seizure-free patients (of those who reached maintenance period and had at least one seizure assessment during the maintenance period)	46/77 phenytoin 49/81 Oxcarbazepine	$p = 0.91$ (by logistic regression) Not based on ITT population
	Secondary outcomes	1. Seizure frequency during maintenance	Mean 0.04; Median 0 phenytoin Mean 0.07; median 0 oxcarbazephine	p = ns (not based on ITT population)
		2. Overall evaluation of therapeutic effect (4-point ordinal scale)	No data reported; not clear if ITT analysis	p = ns
		3. Premature discontinuation due to unsatisfactory therapeutic effect	3 phenytoin, 4 oxcarbazepine	p = ns
		4. Premature discontinuation due to adverse events	14 phenytoin, 2 oxcarbazepine	(Log-rank $p = 0.002$)
		5. Overall evaluation of tolerability (4-point ordinal scale)	Not reproduced here	$p = 0.001$ (physician assessment) $p = 0.038$ (patient assessment)
		6. Clinical utility (time to premature discontinuation for any reason)	34/96 phenytoin, 24/97 oxcarbazepine Odds ratio for discontinuation (phenytoin vs oxcarbazepine)	p = ns 1.99 1.0–3.9; $p = 0.046$ (not based on log-rank analysis)
	'*Ad hoc*' outcomes			
	Comments (including whether unadjusted results reported)	Not clear why logistic regression used to analyse treatment retention; survival analysis would be more appropriate. Note that odds ratio obtained in this way will be numerically greater than hazard ratio obtained by the appropriate analysis		
Adverse events			Phenytoin	Oxcarbazepine
	Criteria for reporting	Occurrence in >5% patients in either group		
	Events, *n* (%)	Somnolence	(29.8)	(25.0)
		Dizziness	(22.3)	(9.4)
		Headache	(14.9)	(13.5)
		Gum hyperplasia	(25.5)	(2.1)
		Apathy	(10.6)	(11.5)
		Ataxia	(13.8)	(0)
		Nervousness	(11.7)	(2.1)
		Nausea	(7.4)	(5.2)
		Abnormal thinking	(6.4)	(5.2)
		Rash	(5.3)	(4.2)
		Abdominal pain	(4.3)	(5.2)
		Hypertrichosis	(8.5)	(0)
		Vomiting	(5.3)	(0)

continued

		Increase in γ-glutamyl transpeptidase (5.3)	(0)
		At least one adverse event 84/94 (89.4)	79/96 (82.3)
	Comments	–	
Conclusions	Authors' conclusions	Oxcarbazepine is efficacious and safe for use in children and adolescents with partial seizures and generalised tonic–clonic seizures In addition oxcarbazepine has advantages over phenytoin in terms of tolerability and clinical utility (treatment retention)	
	Our conclusions	Oxcarbazepine appears equally effective as phenytoin at reducing seizures (partial and generalised tonic–clonoic); however, because ITT analysis was not performed and some patients were excluded from analysis, it is difficult to assess the reliability of this conclusion Authors state that the phenytoin dose was toward the low end of dose range used	

Trial details	Trial ID	Eriksson, 1998
	Drug(s)	Lamotrigine
	Target maintenance dose (mode)	Not reported
	Seizure or syndrome	Generalised seizures
	Type of trial design	Response-mediated withdrawal/cross-over
	Add-on or monotherapy?	Add-on
	Control(s)	Placebo
	Study start and end dates	Not reported
	Centres and location	1 centre, Scandinavia
Trial design	Baseline	8 weeks
	Titration (including details of schedule and frequency of doses)	up to 12 months (mean 5 months) Titrated from 1 mg/kg/day (or 0.5 mg/kg/day if taking valproate), with dose increased by the same amount every 2 weeks until clinical response or adverse effects seen. Dose optimised for each patient 2 doses/day
	Maintenance	2 × 12 weeks
	Withdrawal	3-week washout periods between titration and first 12-week maintenance phase and before second 12-week maintenance phase
	Timing and additional eligibility for randomisation/continuation on study	Only 'responders' entered the double-blind phase, i.e. patients experiencing ≥ 50% reduction in seizure frequency or in seizure severity (or both), or with definite improvements in behaviour or motor skills or both. Non-responders were defined as without positive effects of lamotrigine with plasma levels ≤ 10 μg/ml or children who had adverse events during the titration phase
	Comments on design	The way in which improvement in behavioural skills or motor improvements were assessed is not explained, which makes the definition of responder very subjective, although it seems from the definition of 'non-responder' that responder was defined by default Methods do not describe correct analysis for cross-over trial (although order and period effects are reported in results)
Quality assessment	Was assignment of treatment described as random?	Yes
	Was method of randomisation described?	No

continued

	Was the method really random?	Can't tell		
	Was allocation of treatment concealed?	Can't tell		
	Who was blinded to treatment?	Described as 'double-blind'		
	Was method of blinding adequately described?	No		
	Were eligibility criteria described?	Yes		
	Were groups comparable at study entry?	Can't tell		
	Were groups treated identically apart from the intervention?	Can't tell		
	Was ITT used?	Yes (2 patients withdrawn from lamotrigine arm at family request)		
	Were withdrawals stated?	Yes		
	Were reasons for withdrawals stated?	Yes		
	Was a power calculation done?	No		
	Comments	–		
Eligibility criteria	Inclusion criteria	1. Refractory or intractable generalised epilepsy 2. Children and adolescents >2 years of age 3. More than 2 seizures per month		
	Exclusion criteria	1. Liver, renal, or progressive neurological disease 2. Diagnosis of focal epilepsy		
Baseline characteristics			Placebo/lamotrigine	Lamotrigine/placebo
	Number randomised		8	9
	Number analysed		8	7
	Age (weeks, months, years) (mean, SD; median, range)		Mean 10.3; range 4.8–16.9 years	Mean 9.9; range 4.6–20.7 years
	Male:female		Not reported	Not reported
	Weight (kg, lb) (mean, SD; median, range)		Not reported	Not reported
	Duration of epilepsy (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
	Age at diagnosis (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
	Newly diagnosed, *n* (%)		0 (–)	0 (–)
	Previously diagnosed, *n* (%)		(100)	(100)
	Refractory, *n* (%); definition of refractory	Not seizure-free after treatment with at least 3 consecutive AEDs	(100)	(100)
	Diagnosed seizure types, *n* (%)	Tonic–clonic Tonic/atonic Myoclonic Atypical absences Other	5 (62.5) 7 (87.5) 8 (100) 7 (87.5) 2 (25)	5 (55.5) 8 (88.8) 8 (88.8) 8 (88.8) 8 (88.8) 2 lamotrigine patients included above not included in analysis; both experienced all 4 types of seizure

continued

	Diagnosed syndrome(s), *n* (%)	Lennox–Gastaut	5 (62.5)	8 (88.8) [2 withdrew]
		No data	3 (37.5)	1 (11.1)
	Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	All seizures	Mean 98.8; median 78.5, range 16–242/month	mean 113; median 92, range 13–315/month 2 Withdrawals: 167 and 150/month
	No. of concomitant AEDs, *n* (%)	1	1 (12.5)	0
		2	4 (50)	5 (55.5)
		3	3 (37.5)	4 (44.4)
	Concomitant AEDs, *n* (%)	Carbamazepine	4 (50)	4 (44.4) [1 withdrawal]
		Clonazepam	4 (50)	5 (55.5) [1 withdrawal]
		Ethosuximide	2 (25)	1 (11.1)
		Phenobarbital	0	2 (22.2)
		Valproate	5 (62.5)	6 (66.6)
		Vigabatrin	3 (37.5)	4 (44.4) [2 withdrawals]
	Previous AEDs, *n* (%)	Not reported	Not reported	Not reported
	Comments		Data for patients who entered randomised cross-over phase recorded here ($n = 17$); characteristics of the two patients who withdrew after randomisation noted above. Most characteristics calculated from tables of individual patient data given in paper	
Monitoring and outcomes	Was monitoring of plasma levels done (including study drug)?	Yes (including study drug)		
	Were arrangements to blind plasma monitoring results mentioned?	Results only known to a single coordinator (implies but does not state that this coordinator was not responsible for patient care or assessment)		
	Who recorded seizure frequency?	Parents/other caregivers		
	How often was seizure frequency measured?	Not stated (diaries)		
	Frequency of clinic visits	2-weekly (1 day visit to clinic, including 4-h observation of patient by nurse)		
	Primary outcome(s) including time points if repeated	% reduction in average monthly seizure frequency during randomised phase (both 12-week periods combined)		
	Secondary outcome(s) excluding AEs	1. Seizure severity 2. Functional status		
	'*Ad hoc*' outcomes (if emphasised and not in methods)	Analysis of results by seizure type and in patients with Lennox–Gastaut syndrome		
	Comments	–		
			Placebo/lamotrigine	Lamotrigine/placebo
Results (ITT only; unadjusted where available)	Median follow-up		27 or 30 weeks (not clear if first wash-out period before or after randomisation)	27 or 30 weeks (not clear if first wash-out period before or after randomisation)
	Maintenance dose achieved		Not reported	Not reported
	Withdrawals including reasons where specified, *n* (%)	Total	0	2
		Consent withdrawn	–	2

continued

			Results (difference, or by arm)	CI for difference; *p*-value
	Primary outcome(s)	% reduction in average monthly seizure frequency during double-blind phase	Results reported for each individual; 14/15 had lower seizure rate in lamotrigine period, 1/15 no change	$p < 0.0001$ Order effect: $p = 0.13$ Period × treatment: $p = 0.83$ Period effect: not mentioned
	Secondary outcomes	1. Seizure severity	Not reported	Not reported
		2. Functional status of patients	Not reported	Not reported
	'*Ad hoc*' outcomes	1. >50% reduction in seizure frequency on lamotrigine period compared with placebo period	9/15 patients	Not reported
		2. Analysis of results by seizure type and in patients with Lennox–Gastaut syndrome	Results not reproduced here	Not reported
	Comments (including whether unadjusted results reported)		Atypical absences and myoclonic events excluded from analyses owing to difficulty identifying these events in this patient population; not clear what effect this might have, or whether this decision was made prior to unblinding data 2 patients had atonic seizures when lamotrigine was added (not previously)	
Adverse events	Criteria for reporting	Not stated	Placebo phase	Lamotrigine phase
	Events, *n* (%)	Fatigue	10 (58.8)	
		More intense seizures	4 (23.5)	None
	Comments		Adverse event data listed here are those occurring during the randomised phase	
Conclusions	Authors' conclusions	Compared with placebo, lamotrigine produced a 'clear reduction' in seizure counts in responding children with refractory generalised epilepsies. Sample was representative of children with intractable generalised epilepsies (Lennox–Gastaut ~70% of these). Authors justify their more lax definition of responder as their definition encompasses clinically meaningful treatment effects in a population such as studied here. Differences (improvements) in behaviour and alertness were seen with lamotrigine (over placebo) irrespective of whether seizure frequency reduced		
	Our conclusions	The use of a cross-over design presents some difficulty in interpretation. In particular, it is not clear how, or if, drug was withdrawn during the 3-week 'washout' periods; this terminology would usually be used to refer to a 'drug-free' period, but in this trial it may have been used in order to titrate lamotrigine dose up or down prior to entering the maintenance phases Neither of the defined secondary end-points was reported		

Trial details	Trial ID	Motte, 1997
	Drug(s)	Lamotrigine
	Target maintenance dose (mode)	50–300 mg/day (tablets, oral)
	Seizure or syndrome	Lennox–Gastaut syndrome
	Type of trial design	Parallel
	Add-on or monotherapy?	Add-on
	Control(s)	Placebo
	Study start and end dates	1994–95
	Centres and location	43 centres in USA, Europe
Trial design	Baseline	4 weeks
	Titration (including details of schedule and frequency of doses)	6 weeks Initial and target doses dependent on body weight and concomitant valproate use (being lower if valproate taken)
		Number of doses/day not stated
	Maintenance	10 weeks
	Withdrawal	None
	Timing and additional eligibility for randomisation/continuation on study	Postbaseline; no additional eligibility criteria
	Comments on design	Dose titration refers explicitly to lamotrigine only; not clear how/if placebo doses titrated in same way
		For the first 2 weeks of the maintenance phase (weeks 7–8), patients took fixed doses of treatment achieved during the titration phase. During week 8 or 12 the dose of lamotrigine could be increased if seizures continued to the maximum stated daily dose (100–200 mg if taking valproate, 300–400 mg if not)
		During withdrawal phase, dose reduced to 50% for 2 weeks, then by further 50% to 25% for 2 weeks
Quality assessment	Was assignment of treatment described as random?	Yes
	Was method of randomisation described?	No
	Was the method really random?	Can't tell
	Was allocation of treatment concealed?	Can't tell
	Who was blinded to treatment?	Described as 'double-blind'
	Was method of blinding adequately described?	No description
	Were eligibility criteria described?	Yes
	Were groups comparable at study entry?	No; some imbalance in sex, and also a relatively large difference in the numbers randomised to the two groups (90 vs 79)
	Were groups treated identically apart from the intervention?	Can't tell (no description of blinding, and dose titration refers to gabapentin group only)
	Was ITT used?	Not clear (see comment)
	Were withdrawals stated?	Yes
	Were reasons for withdrawals stated?	Yes
	Was a power calculation done?	No
	Comments	Two patients are excluded for 'lack of completeness'; the report does not state to which arm(s) these patients were allocated

continued

Eligibility criteria	Inclusion criteria	1. More than one type of predominantly generalised seizure including tonic–clonic seizures and drop attacks for at least 1 year 2. Age <11 years at onset of epilepsy 3. Seizures at least every other day or with a similar average frequency 4. Intellectual impairment or a clinical impression of intellectual deterioration 5. Recent EEG demonstrating an abnormal background and a pattern of slow spike-and-wave complexes (<2.5 Hz)		
	Exclusion criteria	1. Progressive neurodegenerative disorder 2. Receiving >3 AEDs 3. Body weight <15 kg and taking valproate		
Baseline characteristics			Placebo	Lamotrigine
	Number randomised		90	79
	Number analysed		89	78
	Age (weeks, months, years) (mean, SD; median, range)		Mean 10.9, SD 5.9 years	Mean 9.6, SD 5.2 years
	Male:female		45:45	54:25
	Weight (kg, lb) (mean, SD; median, range)		Mean 34.3, SD 19.7 kg	Mean 32.5, SD 18.1 kg
	Duration of epilepsy (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
	Age at diagnosis (weeks, months, years) (mean, SD; median, range)		Not reported (had to be <11 years to be enrolled)	Not reported (had to be <11 years to be enrolled)
	Newly diagnosed, *n* (%)		0	0
	Previously diagnosed, *n* (%)		90 (100)	79 (100)
	Refractory, *n* (%); definition of refractory		Not stated; none given	Not stated; none given
	Diagnosed seizure types, *n* (%)	Infantile spasms (history of)	37 (41) had history of infantile spasms	31 (39) had history of infantile spasms
	Diagnosed syndrome(s), *n* (%)	Lennox–Gastaut syndrome	(100)	(100)
	Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Major seizures (drop attacks and tonic-clonic)	Median 13.5, range 1.5–592.8/week	Median 16.4, range 3.1–249.4/week
	No. of concomitant AEDs, *n* (%)		Not reported (all patients on 1–3 concomitant AEDs)	Not reported (all patients on 1–3 concomitant AEDs)
	Concomitant AEDs, *n* (%)	Carbamazepine Valproate Phenytoin Others	30 (33.3) 50 (55.5) 13 (14.4) 9 (10.0)	16 (20.2) 53 (67.0) 10 (12.6) 11 (13.9)
	Previous AEDs, *n* (%)		Not reported	Not reported
	Comments		Other AEDs taken included oxcarbazepine, clobazam, vigabatrin, clonazepam, phenobarbital, ethosuximide, nitrazepam, primidone	
Monitoring and outcomes	Was monitoring of plasma levels done (including study drug)?	Yes, including lamotrigine		
	Were arrangements to blind plasma monitoring results mentioned?	No		

continued

	Who recorded seizure frequency?	Parents/guardians		
	How often was seizure frequency measured?	Daily (diaries)		
	Frequency of clinic visits	weeks –4, 2, 4, 8, 12, 16, 20		
	Primary outcome(s) including time points if repeated	% change in frequency of major motor seizures (drop attacks and tonic–clonic seizures)		
	Secondary outcome(s) excluding AEs	1. Median change in frequency of drop attacks 2. Median change in frequency of tonic–clonic seizures 3. Median change in frequency of atypical absences 4. Responder rate, defined as ≥ 50% reduction in all major seizures		
	'*Ad hoc*' outcomes (if emphasised and not in methods)	–		
	Comments	Two patients were excluded from the analyses because of incomplete data		
Results (ITT only; unadjusted where available)			Placebo	Lamotrigine
	Median follow-up		16 weeks (assumed)	16 weeks (assumed)
	Maintenance dose achieved, *n* (%)		Not reported	Patients ≤ 25 kg + valproate 13.0 (4.9) Patients ≤ 25 kg no valproate 3.7 (0.9) Patients >25 kg + valproate 8.4 (3.3) Patients >25 kg no valproate 3.7 (1.5)
	Withdrawals including reasons where specified, *n* (%)	Total withdrawals Adverse events Worse seizure control Protocol violation Loss to follow-up Consent withdrawn	14 (15.5) 7 (7.7) 2 (2.2) 3 (3.3) 1 (1.1) 1 (1.1)	7 (8.8) 3 (3.7) 0 (–) 4 (5.0) 0 (–) 0 (–)
			Results (difference, or by arm)	CI for difference; *p*-value
	Primary outcome(s)	% change in frequency of major motor seizures (drop attacks and tonic-clonic seizures)	Placebo –9% Lamotrigine –32% (median reduction)	$p = 0.002$
	Secondary outcomes	1. % change in frequency of drop attacks	Placebo –9% Lamotrigine –34%	$p = 0.01$
		2. % change in frequency of tonic-clonic seizures	Placebo +10% Lamotrigine –36%	$p = 0.03$
		3. % change in frequency of atypical absences	Placebo –38% Lamotrigine –13%	$p = 0.96$
		4. Responder rate, defined as ≥ 50% reduction in major motor seizures	Placebo 16% Lamotrigine 33%	$p = 0.01$
	'*Ad hoc*' outcomes	–	–	–
	Comments (including whether unadjusted results reported)		Results adjusted for country effects	

continued

Adverse events			Placebo	Lamotrigine
	Criteria for reporting	Events in ⩾4% of patients in either group		
	Events, *n* (%)	Infection	7 (7.7)	10 (12.6)
		Fever	12 (13.3)	10 (12.6)
		Nausea and/or vomiting	6 (6.6)	7 (8.8)
		Somnolence	4 (4.4)	3 (3.7)
		Pharyngitis	9 (10.0)	11 (13.9)
		Cold/viral illness	0	4 (5.0)
		Headache	6 (6.6)	3 (3.7)
		Rhinitis	7 (7.7)	4 (5.0)
		Otitis media	4 (4.4)	1 (1.2)
		Bronchitis	6 (6.6)	7 (8.8)
		Constipation	2 (2.2)	4 (5.0)
		Rash	6 (6.6)	7 (8.8)
		Injury/accident	6 (6.6)	7 (8.8)
	Comments		Statistical difference between groups in cold/viral illness incidence ($p = 0.05$)	
Conclusions	Authors' conclusions	Add-on lamotrigine therapy reduces the frequency of seizures in children with Lennox–Gastaut syndrome (but not atypical absences) compared with placebo		
	Our conclusions	Methodological weaknesses in design/conduct of trial difficult to quantify owing to lack of information on procedures for randomisation and blinding and on whether ITT analysis used. Lack of this information, along with monitoring of AED plasma levels with no description of how clinicians were blinded to these results, gives some cause for concern		
		The trial is too small to claim evidence of any subgroup effects; the apparent benefit to placebo for atypical absence seizures could easily have arisen by chance		

Trial details	Trial ID	Sachdeo, 1999
	Drug(s)	Topiramate
	Target maintenance dose (mode)	6 mg/kg/day (oral assumed)
	Seizure or syndrome	Lennox–Gastaut
	Type of trial design	Parallel
	Add-on or monotherapy?	Add-on
	Control(s)	Placebo
	Study start and end dates	Not reported
	Centres and location	12 centres in USA
Trial design	Baseline	4 weeks
	Titration (including details of schedule and frequency of doses)	3 weeks Week 1, 1 mg/kg/day; week 2, 3 mg/kg/day; week 3, 6 mg/kg/day (target dose) 2 doses/day
	Maintenance	8 weeks
	Withdrawal	None
	Timing and additional eligibility for randomisation/continuation on study	Postbaseline; patients who 'qualified for entry' were randomised, but no specific criteria for this are mentioned
	Comments on design	Titration explicitly refers to both arms
Quality assessment	Was assignment of treatment described as random?	Yes
	Was method of randomisation described?	Yes
	Was the method really random?	Yes
	Was allocation of treatment concealed?	Yes
	Who was blinded to treatment?	Investigators, patients, study monitors and observers
	Was method of blinding adequately described?	'Blinded medication'; no further details
	Were eligibility criteria described?	Yes
	Were groups comparable at study entry?	Yes
	Were groups treated identically apart from the intervention?	Yes
	Was ITT used?	Yes
	Were withdrawals stated?	Yes
	Were reasons for withdrawals stated?	Yes
	Was a power calculation done?	Yes
	Comments	Trial includes patients up to the age of 30 years; results are not reported separately for children but this trial is included as a substantial proportion of patients are under 18 years old and Lennox–Gastaut is a syndrome which occurs only in childhood, and these data would therefore otherwise be excluded from both reviews being prepared for NICE
Eligibility criteria	Inclusion criteria	1. >1 and <30 years old, weighing at least 11.5 kg 2. Female patients practising birth control or premenarcheal 3. Drop attacks (tonic or atonic seizures) and either a history of or active atypical absence seizures 4. EEG showing slow spike-and-wave pattern 5. 60 seizures (including tonic–clonic, myoclonic, partial onset) in month prior to baseline while on 1 or 2 standard AEDs

continued

	Exclusion criteria		1. History of recent significant cardiovascular, respiratory, hepatic, renal, gastrointestinal or haematological illness, or malignancy or nephrolithiasis 2. Seizures due to progressive disease 3. Documented status epilepticus within 3 months of baseline 4. Drug/alcohol abuse, psychiatric or mood disorder requiring ECT or medication within 6 months of baseline 5. Treatment with experimental drug, acetazolamide or zonisamide within 60 days of baseline 6. Ketogenic diet or ACTH within 6 months of study 7. Use of benzodiazepines other than on an occasional basis (unless as concomitant AED) 8. History of poor compliance or inability to keep seizure calender 9. Clinically significant electrocardiogram abnormalities	
Baseline characteristics			Placebo	Topiramate
	Number randomised		50	48
	Number analysed		50	48
	Age (weeks, months, years) (mean, SD; median, range)		Mean 11.2, SD 7.7; range 2–42 years	Mean 11.2, SD 6.2; range 2–29 years
	Male:female		25:25	28:20
	Weight (kg, lb) (mean, SD; median, range)		Mean 31.6, SD 17.8; range 12–82.2 kg	Mean 36.7, SD 19; range 13.8–99.9 years
	Duration of epilepsy (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
	Age at diagnosis (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
	Newly diagnosed, *n* (%)		None (from eligibility)	None (from eligibility)
	Previously diagnosed, *n* (%)		50 (100) (from eligibility)	48 (100) (from eligibility)
	Refractory, *n* (%); definition of refractory		Not reported	Not reported
	Diagnosed seizure types, *n* (%)		All patients	
		Drop attacks (tonic and atonic)	95 (93)	
		Atonic	90 (88)	
		Atypical absence	70 (69)	
		Tonic	51 (50)	
		Myoclonic	46 (45)	
		Tonic–clonic	38 (37)	
		Complex partial	16 (16)	
		Absence	9 (9)	
		Secondarily generalised	4 (4)	
		Clonic	2 (2)	
		Unspecified types	6 (6)	
	Diagnosed syndrome(s), *n* (%)	Lennox–Gastaut	50 (100)	48 (100)
	Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Drop attacks (tonic and atonic)	Median 98, range 1–4324/month	Median 90, range 2–2459/month
		Drop attacks + tonic–clonic	Median 354, range 1–4324/month	Median 288, range 2–2459/month
		All seizure types	median 244, range 7–4324/month	Median 267, range 13–3795/month

continued

	No. of concomitant AEDs, *n* (%)	1 2 3	20 (40) 29 (58) 1 (2)	19 (40) 27 (56) 2 (<1)
	Concomitant AEDs, *n* (%)	Not reported but see comment	–	–
	Previous AEDs, *n* (%)	Not reported	–	–
	Comments		Protocol change after about 50% of patients recruited disallowed felbamate as a concomitant AED (owing to new safety information about felbamate becoming available); at this time 8 patients in the placebo arm and seven in the topiramate arm had been recruited who were taking felbamate which was subsequently withdrawn in 1 of the placebo and 2 of the topiramate patients	
Monitoring and outcomes	Was monitoring of plasma levels done (including study drug)?	Yes		
	Were arrangements to blind plasma monitoring results mentioned?	No		
	Who recorded seizure frequency?	Parent/guardian or patient		
	How often was seizure frequency measured?	Daily (diaries)		
	Frequency of clinic visits	Not clear		
	Primary outcome(s) including time points if repeated	1. % reduction vs baseline in average monthly seizure rate for all seizure types 2. Composite outcome based on % reduction in average monthly seizure rate for drop attacks (tonic + atonic), and parental global evaluation of improvement in seizure severity		
	Secondary outcome(s) excluding AEs	1. % reduction in average monthly seizure rate for major seizures (tonic, atonic and tonic-clonic) 2. % responders		
	'*Ad hoc*' outcomes (if emphasised and not in methods)	–		
	Comments	The second primary outcome is strange; it is not clear why these outcomes are combined. The results for each outcome are reported separately and via the combined approach		
Results (ITT only; unadjusted where available)			Placebo	Topiramate
	Median follow-up		11 weeks (assumed from low drop-out rate)	11 weeks (assumed from low drop-out rate)
	Maintenance dose achieved		92% achieved target dose	Median 5.8 mg/kg/day 71% achieved target dose (6 mg/kg/day)
	Withdrawals including reasons where specified, *n* (%)	Total withdrawals Patient choice	0 0	1 1
			Results (difference, or by arm)	CI for difference; *p*-value
	Primary outcome(s)	1. % reduction in average monthly seizure rate	Placebo median –8.8% Topiramate median –20.6%	p = ns

continued

		2. Composite: % reduction in average monthly drop attack rate and parental global evaluation (PGE)	Drop attacks: Placebo median +5.1% Topiramate median –14.8% PGE: Data not reproduced here Composite	 $p = 0.041$ $p = 0.037$ $p < 0.01$
	Secondary outcomes, seizure type(s)	1. % reduction average monthly seizure rate (tonic, atonic and tonic–clonic only) 2. % responders	Placebo median 5.2% Topiramate median 25.8%	$p = 0.015$
		Drop attacks: ≥50% reduction ≥75% reduction 100% reduction	 14% placebo vs 28% 6% vs 17% 0 vs 1 patient	 $p = 0.071$ Not reported Not reported
		Drop attacks or tonic–clonic: ≥50% reduction ≥75% reduction 100% reduction	 8% placebo vs 33% 4% vs 17% 0 vs 1 patient	 $p = 0.002$ Not reported Not reported
		All seizure types: ≥50% reduction ≥75% reduction 100% reduction	 'No difference' 0 vs 4 patients Not reported	 $p =$ ns Not reported Not reported
	'*Ad hoc*' outcomes	–	–	–
	Comments (including whether unadjusted results reported)		Results adjusted for investigator	
Adverse events			Placebo	Topiramate
	Criteria for reporting	>10% greater incidence in top arm (i.e. treatment-emergent events)		
	Events, *n* (%)	Somnolence	(22)	(42)
		Anorexia	(20)	(40)
		Nervousness	(10)	(21)
		Behavioural problems	(10)	(21)
		Fatigue	(4)	(19)
		Dizziness	(0)	(10)
		Weight loss	(0)	(10)
		Severe adverse events	(10)	(23)
	Comments		–	
Conclusions	Authors' conclusions	Study demonstrates that topiramate is effective as adjunct therapy for Lennox–Gastaut syndrome. Improvements in the frequency of drop attacks without limiting toxicity indicates that topiramate represents an important addition to the treatments available		
	Our conclusions	This is a good trial which is well-designed and fairly well reported. The results of this study are encouraging, but the follow-up period is very short and the dose of topiramate fairly low; withdrawal of drug and rechallenge during maintenance period were allowed, which would be likely to minimise the proportions withdrawing owing to adverse events during this short follow-up; no data are reported on drug withdrawal and rechallenge. Longer term data would be needed to establish the tolerability in clinical practice		

Trial details	Trial ID	Appleton, 1999
	Drug(s)	Vigabatrin
	Target maintenance dose (mode)	50–150 mg/kg/day (not stated)
	Seizure or syndrome	Infantile spasms
	Type of trial design	Parallel
	Add-on or monotherapy?	Monotherapy
	Control(s)	Placebo
	Study start and end dates	Not reported
	Centres and location	40 centres; Europe, Canada, France
Trial design	Baseline	2 or 3 days
	Titration (including details of schedule and frequency of doses)	5 days Titration in 3 steps; after 24 h if spasms not ceased, and again after 48 h according to the investigator's assessment of spasm frequency. Once established on a dose for >48 h the dose could only be changed in response to concerns about safety Number of doses per day not stated
	Maintenance	None
	Withdrawal	None
	Timing and additional eligibility for randomisation/continuation on study	None
	Comments on design	Baseline period was to determine baseline seizure frequency. Duration of 2 days for patients experiencing clusters of spasms, 3 days for patients with isolated spasms that did not cluster
Quality assessment	Was assignment of treatment described as random?	Yes
	Was method of randomisation described?	Yes
	Was the method really random?	Yes
	Was allocation of treatment concealed?	Yes
	Who was blinded to treatment?	Described as 'double-blind'
	Was method of blinding adequately described?	No
	Were eligibility criteria described?	Yes
	Were groups comparable at study entry?	Yes
	Were groups treated identically apart from the intervention?	Yes (if blinding adequate)
	Was ITT used?	Yes
	Were withdrawals stated?	Yes
	Were reasons for withdrawals stated?	Yes
	Was a power calculation done?	Yes
	Comments	–
Eligibility criteria	Inclusion criteria	1. Newly diagnosed (EEG proven) and previously untreated infantile spasms (classic or modified hypsarrhythmia) 2. Age 1–20 months 3. Infants whose parents/guardians able to give informed consent and who were considered capable of completing seizure diaries and attending clinic appointments

continued

	Exclusion criteria	1. Use of any medication (including prednisolone, hydrocortisone or ACTH) that could be considered to be an AED, within 2 months before entry into the study		
Baseline characteristics			Placebo	Vigabatrin
	Number randomised		20	20
	Number analysed		20	20
	Age (weeks, months, years) (mean, SD; median, range)		Mean 8; range 4–17 months	Mean 8; range 5–20 months
	Male:female		8:12	11:9
	Weight (kg, lb) (mean, SD; median, range)		Not reported	Not reported
	Duration of epilepsy (weeks, months, years) (mean, SD; median, range)		Mean 7; range 2–12 weeks	Mean 6; range 2–13 weeks
	Age at diagnosis (weeks, months, years) (mean, SD; median, range)		At onset of spasms, mean 6; range 1–15 months	At onset of spasms, mean 7; range 2–18 months
	Newly diagnosed, *n* (%)		20 (100)	20 (100)
	Previously diagnosed, *n* (%)		0	0
	Refractory, *n* (%); definition of refractory		0	0
	Diagnosed seizure types, *n* (%)	Not reported	Not reported	Not reported
	Diagnosed syndrome(s), *n* (%)	Infantile spasms (West's)	20 (100)	20 (100)
	Baseline seizure frequency (per day, week, month) (mean, SD; median, range)		Not reported	Not reported
	No. of concomitant AEDs, *n* (%)	NA	NA	NA
	Concomitant AEDs, *n* (%)	NA	NA	NA
	Previous AEDs, *n* (%)	NA	NA	NA
	Comments			
Monitoring and outcomes	Was monitoring of plasma levels done (including study drug)?	No		
	Were arrangements to blind plasma monitoring results mentioned?	NA		
	Who recorded seizure frequency?	Nursing staff and parents/guardians		
	How often was seizure frequency measured?	Daily and for 2 h of intensive monitoring each day		
	Frequency of clinic visits	Days –2, 0, 5 (1 and 3 also implied)		
	Primary outcome(s) including time points if repeated	1. % change in daily spasm frequency (24- and 2-h assessments) 2. Spasm-free patients on day 5		
	Secondary outcome(s) excluding AEs	1. Investigator 'global assessment' 2. Repeated EEG recordings		
	'*Ad hoc*' outcomes (if emphasised and not in methods)	1. Patients with 70% improvement on final day of follow-up (24- and 2-h assessments) 2. Patients with no change or worsening in spasm frequency on final day of follow-up (24-h assessment)		
	Comments	–		

continued

Results (ITT only; unadjusted where available)			Placebo	Vigabatrin
	Median follow-up		5 days	5 days
	Maintenance dose achieved		Mean 148 mg/kg	Mean 133 mg/kg
	Withdrawals including reasons where specified	None stated	0	0
			Results (difference, or by arm)	CI for difference; *p*-value
	Primary outcome(s)	1. % change in daily spasm frequency:	Placebo –25.9% Vigabatrin –77.9%	95% CI –56 to 65%
		24-h assessment	Placebo –54.6% Vigabatirn –71.9%	95% CI 55 to 89%; $p = 0.02$
		2. Seizure (spasm)-free patients, *n* (%)	Placebo 2 (10) Vigabatrin 7 (35)	95% CI 4 to 78% 95% CI 42 to 86%; $p = 0.342$
				$p = 0.063$
	Secondary outcomes	1. Investigator 'global assessment'	Placebo: 3 (15%) marked/moderate improvement; 4 (20%) patients deteriorated	$p < 0.0001$
			Vigabatrin: 16 (80%) marked/moderate improvement; 0 deteriorated	–
		2. Repeated EEG recordings	Hypsarrhythmia resolved in 1 of 2 seizure-free patients on placebo vs 5 of 7 on vigabatrin	
	'*Ad hoc*' outcomes	>70% improvement: 24-h assessment, *n* (%)	Placebo 3/20 (15) Vigabatrin 8/20 (40)	–
		2-h assessment, *n* (%)	Placebo 11/20 (55) Vigabatrin 13/17 (76)	–
		No change or worse (24-h assessment), *n* (%)	Placebo 9/20 (45) Vigabatrin 4/20 (20)	–
	Comments (including whether unadjusted results reported)		All means and CIs adjusted for geographical region and baseline spasm rate Three patients appear to be missing from lamotrigine group for the 2-h results	
Adverse events			Placebo	Vigabatrin
	Criteria for reporting	Not stated		
	Events, *n* (%)	Drowsiness	Not reported	8
		Behaviour change (irritability)	Not reported	1
		Number reporting ≥ 1 AE	6 (30)	12 (60)
	Comments		Adverse events in placebo group not described	

continued

Conclusions	Authors' conclusions	Study design has some limitations, with a short duration of follow-up, small sample size, questionable utility/validity of 2-h assessments (intensive monitoring) Results suggest that vigabatrin is effective; trial did not include patients with tuberous sclerosis, in whom vigabatrin might be most effective
	Our conclusions	Trial is of reasonable quality but, as the authors point out, the sample size is very small. Nevertheless, reasonably convincing evidence that vigabatrin is effective compared with no treatment

Trial details	Trial ID	Vigevano, 1997
	Drug(s)	Vigabatrin
	Target maintenance dose (mode)	Lowest effective and tolerated dose, 110–150 mg/kg/day (?mode)
	Seizure or syndrome	Newly diagnosed infantile spasms
	Type of trial design	'Response-mediated' open cross-over study
	Add-on or monotherapy?	Monotherapy
	Control(s)	ACTH
	Study start and end dates	1992–95
	Centres and location	Italy
Trial design	Baseline	None
	Titration (including details of schedule and frequency of doses)	9 days vigabatrin in three 3-day stages: 1. 100 mg/kg/day for 3 days 2. If no response and if tolerant, then 125 mg/kg/day for 3 days 3. If no response and tolerant, then 150 mg/kg/day 2 doses/day ACTH No titration. Dose 10 IU 1 dose/day
	Maintenance	20 days, then continuation (responders) or cross-over (non-responders) for a further 20 days
	Withdrawal	None
	Timing and additional eligibility for randomisation/continuation on study	NA (newly diagnosed population)
	Comments on design	Overall, the trial compares strategies rather than treatments, i.e. the strategy of starting with vigabatrin and switching to ACTH if unsuccessful, vs starting with ACTH and switching to vigabatrin. The first 20-day period could be regarded as a simple parallel trial. [Results for the comparison of strategies are not in fact reported, i.e. comparing the two original randomised groups, and so in effect this is a simple parallel trial with 20-day follow-up]
Quality assessment	Was assignment of treatment described as random?	Yes
	Was method of randomisation described?	No
	Was the method really random?	Can't tell
	Was allocation of treatment concealed?	Can't tell
	Who was blinded to treatment?	Open-label study
	Was method of blinding adequately described?	NA
	Were eligibility criteria described?	Not in any detail

continued

	Were groups comparable at study entry?	Some imbalance in sex ratios; could be a chance effect and does not necessarily cast doubt on the randomisation		
	Were groups treated identically apart from the intervention?	Can't tell		
	Was ITT used?	Yes		
	Were withdrawals stated?	Yes		
	Were reasons for withdrawals stated?	Yes		
	Was a power calculation done?	No		
	Comments	–		
Eligibility criteria	Inclusion criteria	Newly diagnosed and previously untreated infantile spasms (diagnosed within 3 weeks of entry)		
	Exclusion criteria	Not reported		
Baseline characteristics			ACTH	Vigabatrin
	Number randomised		19	23
	Number analysed		19	23
	Age (weeks, months, years) (mean, SD; median, range)		Not reported (will be similar to age at diagnosis)	Not reported (will be similar to age at diagnosis)
	Male:female		7:12	14:9
	Weight (kg, lb) (mean, SD; median, range)		Not reported	Not reported
	Duration of epilepsy (weeks, months, years) (mean, SD; median, range)		<3 weeks (by eligibility criteria)	<3 weeks (by eligibility criteria)
	Age at diagnosis (weeks, months, years) (mean, SD; median, range)		Mean 5.3; range 2–9/months	Mean 5.8; range 2.5–9/months
	Newly diagnosed, *n* (%)		19 (100)	23 (100)
	Previously diagnosed, *n* (%)		–	–
	Refractory, *n* (%); definition of refractory		NA	NA
	Diagnosed seizure types, *n* (%)	Infantile spasms	19 (100)	23 (100)
	Diagnosed syndrome(s), *n* (%)	Symptomatic infantile spasms	11 (58)	16 (70)
		Hypoxic/ischaemic	5 (26)	6 (26)
		Cerebral malformation	3 (16)	4 (17)
		Tuberous sclerosis	1 (5)	3 (13)
		Neurofibromatosis	1 (5)	0 (–)
		Unknown cause	1 (5)	3 (13)
		Cryptogenic infantile spasms	8 (42)	7 (30)
	Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	–	Not reported	Not reported
	No. of concomitant AEDs, *n* (%)	–	None	None
	Concomitant AEDs, *n* (%)	–	NA	NA
	Previous AEDs, *n* (%)	–	NA	NA
	Comments		–	

continued

Monitoring and outcomes	Was monitoring of plasma levels done (including study drug)?	No		
	Were arrangements to blind plasma monitoring results mentioned?	NA		
	Who recorded seizure frequency?	Not reported		
	How often was seizure frequency measured?	Video-EEG recordings of sleep–wake cycle every 10 days Further details not reported		
	Frequency of clinic visits	Not reported		
	Primary outcome(s) including time points if repeated	None stated		
	Secondary outcome(s) excluding AEs	–		
	'*Ad hoc*' outcomes (if emphasised and not in methods)	Proportion spasm free after 20 days (phase 1)		
	Comments	No outcomes defined in the methods Outcomes reported for whole (40-day) trial period not analysed appropriately (i.e. by randomised treatment arm); results reproduced here relate only to the first phase, equivalent to a standard parallel groups trial		
Results (ITT only; unadjusted where available)			ACTH	Vigabatrin
	Median follow-up		40 days (assumed from low drop-out)	40 days (assumed from low drop-out)
	Maintenance dose achieved		10 IU/day	100–150 mg/kg/day
	Withdrawals including reasons where specified, *n* (%)	Withdrawals during phase 1 Irritability and agitation Irritability and raised blood pressure	1 0 1	1 1 0
			Results (difference, or by arm)	CI for difference; *p*-value
	Primary outcome(s)			
	Secondary outcomes			
	'*Ad hoc*' outcomes	Proportion spasm-free in phase 1, *n* (%)	14/19 (74) ACTH 11/23 (48) vigabatrin	$p = 0.12$
	Comments (including whether unadjusted results reported)		–	
Adverse events			ACTH	Vigabatrin
	Criteria for reporting	Not stated		
	Events, *n* (%)	All events Drowsiness Hypotonia Irritability Hypertension	7 (37) – – 7 (37) 7 (37)	3 (13) 2 (9) 2 (9) 1 (4) –
	Comments		–	

continued

Conclusions	Authors' conclusions	The study supports the belief that vigabatrin offers an effective therapy for management of infantile spasms and may be safer than ACTH, and that a therapeutic response is usually quick to appear. Vigabatrin may be particularly effective for patients with tuberous sclerosis and may effective for some patients resistant to ACTH. In view of well-recognised limitations for the use of ACTH, clinicians should consider using VGB as a first-line therapy for infantile spasms
	Our conclusions	The trial is too small to come to any firm conclusions regarding the comparative efficacy and safety of vigabatrin and ACTH; there is a strong trend favouring ACTH in terms of efficacy, whereas vigabatrin appears to be associated with fewer adverse events
		The trial is much too small to draw any conclusions about effectiveness in particular subgroups of patients
		Data on time to response are not reported in a way that allows comparison of time to achieve response. These data are reported completely separately for the two arms: 7/11 patients on vigabatrin responded in <3 days (range 1–14/day), whereas 11/14 patients on ACTH responded in <5 days (range 2–12/days)
		The analysis used for the whole period of the trial is inappropriate to the design and so there are no data reported enabling comparison of prescribing strategies (i.e. preferred drug order)

Trial details	Trial ID	Chiron, 1997
	Drug(s)	Vigabatrin
	Target maintenance dose (mode)	150 mg/kg/day (?mode)
	Seizure or syndrome	Infantile spasms due to tuberous sclerosis
	Type of trial design	'Response-mediated' open cross-over
	Add-on or monotherapy?	Monotherapy
	Control(s)	Hydrocortisone
	Study start and end dates	Not reported
	Centres and location	Multicentre, France
Trial design	Baseline	Not clear
	Titration (including details of schedule and frequency of doses)	No titration Vigabatrin 150 mg/kg/day Hydrocortisone 15 mg/day Dose frequency not reported
	Maintenance	1 month, then cross-over of non-responders and continuation of responders and cross-overs for a further month
	Withdrawal	None
	Timing and additional eligibility for randomisation/continuation on study	NA
	Comments on design	Patients described as newly diagnosed, but would be more accurate to say 'recently' diagnosed, as duration of epilepsy varied from 2 weeks to 10 months and prior AED treatment was not an exclusion criterion
Quality assessment	Was assignment of treatment described as random?	Yes
	Was method of randomisation described?	No
	Was the method really random?	Can't tell

continued

	Was allocation of treatment concealed?	Can't tell		
	Who was blinded to treatment?	Open-label study		
	Was method of blinding adequately described?	NA		
	Were eligibility criteria described?	Yes		
	Were groups comparable at study entry?	No; differences compatible with chance in such a small trial (see comment)		
	Were groups treated identically apart from the intervention?	Can't tell		
	Was ITT used?	Can't tell; possibly not (see comment)		
	Were withdrawals stated?	Yes		
	Were reasons for withdrawals stated?	Yes		
	Was a power calculation done?	No		
	Comments	Report refers to 22 'evaluable patients'; it is not clear that all randomised patients were included. The limited information on the method of randomisation and some imbalances in patient characteristics, especially with respect to duration of infantile spasms prior to the trial, give further cause for concern		
Eligibility criteria	Inclusion criteria	1. Tuberous sclerosis according to Gomez criteria 2. Epileptic spasms recorded by EEG or seen by an experienced physician 3. Diffuse interictal activity 4. Age 1 month to 2 years 5. Withdrawn from AEDs >1 week before commencement of study		
	Exclusion criteria	Previously treated with vigabatrin or ACTH or oral steroids		
Baseline characteristics			Hydrocortisone	Vigabatrin
	Number randomised		Not stated	Not stated
	Number analysed		11	11
	Age (weeks, months, years) (mean, SD; median, range)		Mean 7.9, SD 4.4; median 6, range 2–17 months	Mean 6.6, SD 1.7; median 7, range 4–9 months
	Male:female		5:6	5:6
	Weight (kg, lb) (mean, SD; median, range)			
	Duration of epilepsy (weeks, months, years) (mean, SD; median, range)		Mean 36.4, SD 31.9; range 15–300 days	Mean 24.4, SD 25.6; range 15–90 days
	Age at diagnosis (weeks, months, years) (mean, SD; median, range)		Mean 5.9, SD 3.2; range 1–14 months	Mean 5.8, SD 1.8; range 3–9 months
	Newly diagnosed, *n* (%)		Not reported	Not reported
	Previously diagnosed, *n* (%)		Not reported	Not reported
	Refractory, *n* (%); definition of refractory		Uncertain	Uncertain
	Diagnosed seizure types, *n* (%)	Infantile spasms Partial seizures	11 (100) 5 (45.4)	11 (100) 2 (18.2)
	Diagnosed syndrome(s), *n* (%)	Infantile spasms due to tuberous sclerosis	11 (100)	11 (100)

continued

	Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Infantile spasms (clusters)/day	Mean 3.64, SD 1.12; median 4.0, range 2–6/day	Mean 2.27, SD 1.01; median 2.0, range 1–4/day
		Partial	Not reported	Not reported
	No. of concomitant AEDs, *n* (%)	None	–	–
	Concomitant AEDs, *n* (%)	None	–	–
	Previous AEDs, *n* (%)	No details given	Not reported	Not reported
	Comments		–	
Monitoring and outcomes	Was monitoring of plasma levels done (including study drug)?	No		
	Were arrangements to blind plasma monitoring results mentioned?	NA		
	Who recorded seizure frequency?	Parents/guardians		
	How often was seizure frequency measured?	Daily (diaries)		
	Frequency of clinic visits	At randomisation, after 1 and 2 months		
	Primary outcome(s) including time points if repeated	Proportion spasm-free at 1 month		
	Secondary outcome(s) excluding AEs	Change in development quotient (monitored at entry and at 2 months)		
	'*Ad hoc*' outcomes (if emphasised and not in methods)	Time to response, defined as days on drug prior to becoming spasm free		
	Comments	The 'response-mediated' cross-over design does not allow a straightforward comparison of the drugs at 2 months; results reported here are for the first (1 month) period only, as for a simple parallel design		
Results (ITT only; unadjusted where available)			Hydrocortisone	Vigabatrin
	Median follow-up		2 months	2 months
	Maintenance dose achieved		15 mg/kg/day, except 2 patients	10/11 (and 7/7 after cross-over) 150 mg/kg/day; 1 patient 100 mg/kg/day
	Withdrawals including reasons where specified, *n* (%)	Total withdrawals	2 (18.2)	0
		Lack of efficacy	0	0
		Adverse events	2 (18.2)	0
		Change in AED	0	0
		Other	0	0
		Median time to onset of AE resulting in withdrawal	Not reported	
		Median duration	Not reported	
			Results (difference, or by arm)	CI for difference; *p*-value
	Primary outcome(s)	Proportion spasm-free at 1 month	5/11 hydrocortisone 11/11 vigabatrin	$p < 0.01$
	Secondary outcomes	1. Tolerability	9/11 hydrocortisone 5/11 vigabatrin	$p = 0.006$
		2. Development quotient	Not ITT, only 8 hydrocortisone and 9 vigabatrin patients evaluated	

continued

	'*Ad hoc*' outcomes	Time to response (days on drug prior to becoming spasm free)	Mean time to response: Vigabatrin: 4, range 0.5–14 days Hydrocortisone: 12.8, range 3–30 days	$p = 0.058$
	Comments (including whether unadjusted results reported)		Cross-over criteria were defined as 'non-responders at 1 month', with no further criteria given. Criteria do not seem to have been applied consistently, or there are some errors in the text. For example, two patients responded to hydrocortisone at day 30, both had side-effects, one was crossed over and one was not; one patient responded to hydrocortisone at day 19, listed as having no side-effects but was crossed over to vigabatrin The tabulated data imply that 7 patients crossed over from hydrocortisone to vigabatrin (including the two mentioned above who had responded to hydrocortisone), but the text implies that there were only 6 non-responders who should have crossed over (text states that 5/11 responded)	
Adverse events			Hydrocortisone	Vigabatrin
	Criteria for reporting	Events reported to or observed by investigator; data relate to both study periods		
	Events, *n* (%)	Adverse events (all)	17	8
		Drowsiness	–	3
		Hyper-excitability/-kinesia	5 (1 severe)	3 (1 severe)
		Sleep disorders	3 (1 severe)	–
		Weight	3	–
		Abdominal distension	2 (1 severe)	–
		Axial hypertonia	1	1 (severe)
		Hypotonia	–	1
		Hypertension	2	–
		Cushing syndrome	1	–
	Comments		5 patients experienced adverse events while receiving vigabatrin, 9 while receiving hydrocortisone	
Conclusions	Authors' conclusions	Vigabatrin is effective with good safety and should be used for first-line therapy for infantile spasms due to tuberous sclerosis Hydrocortisone induced recovery rate may be only marginally greater than spontaneous recovery rate and is associated with more adverse events than vigabatrin		
	Our conclusions	Although these results are very encouraging, this study is very small and the results should be interpreted with caution. Furthermore, there are some concerns about the methodological quality, particularly regarding the method of randomisation and a query as to whether all randomised patients were included in the analysis. Some anomalies in the reporting of the results also require some clarification		

Trial details	Trial ID	Frank, 1999
	Drug(s)	Lamotrigine
	Target maintenance dose (mode)	Maximum 1000 mg/day (oral, chewable, dispersible caplets)
	Seizure or syndrome	Typical absence seizures (newly diagnosed)
	Type of trial design	Withdrawal
	Add-on or monotherapy?	Monotherapy
	Control(s)	Placebo
	Study start and end dates	Not reported
	Centres and location	Multi-centre, USA
Trial design	Baseline	NA
	Titration (including details of schedule and frequency of doses)	Minimum 4 weeks; until seizure free or maximum dose reached
		Titration fixed for 4 weeks to 1 mg/kg/day, then increased in increments of 1 mg/kg/day according to clinical response
		2 doses/day
	Maintenance	0
	Withdrawal	4 weeks
	Timing and additional eligibility for randomisation/continuation on study	Patients achieving seizure freedom during titration phase were randomised to continue lamotrigine or switch to placebo
	Comments on design	
Quality assessment	Was assignment of treatment described as random?	Yes
	Was method of randomisation described?	No
	Was the method really random?	Can't tell
	Was allocation of treatment concealed?	Can't tell
	Who was blinded to treatment?	Described as 'double-blind'
	Was method of blinding adequately described?	No description, other than that study medication matched for size, shape, colour, taste
	Were eligibility criteria described?	Yes
	Were groups comparable at study entry?	Yes (some imbalance in age and weight, consistent with chance and the small sample size)
	Were groups treated identically apart from the intervention?	Yes (if blinding adequate)
	Was ITT used?	Yes
	Were withdrawals stated?	Yes
	Were reasons for withdrawals stated?	Yes
	Was a power calculation done?	Yes
	Comments	One patient withdrew consent at start of randomised phase
		Although randomised groups described as "reasonably balanced demographically", there were differences in mean age and weight (8.8, SD 3.1 years placebo vs 6.9, SD 2.3 years lamotrigine; weight 40.0, SD 16 kg placebo vs 30.2, SD 9.9 kg lamotrigine)
Eligibility criteria	Inclusion criteria	1. Newly diagnosed typical absence seizures 2. Age 2–16 years
	Exclusion criteria	1. Known or suspected structural lesion 2. History of poor compliance with medication or abuse of drugs 3. Progressive neurological illness 4. Psychiatric disorder requiring medication

continued

		5. Chronic cardiovascular, renal or hepatic disease 6. Use of investigational drug within previous 12 weeks 7. Any disease thought to interfere with absorption, distribution, metabolism or excretion of drugs in general		
Baseline characteristics			Placebo	Lamotrigine
	Number randomised		14	15
	Number analysed		14	14
	Age (weeks, months, years) (mean, SD; median, range)		Mean 8.8, SD 3.1 years	Mean 6.9, SD 2.3 years
	Male:female		5:9	5:9
	Weight (kg, lb) (mean, SD; median, range)		Mean 40.0, SD 16 kg	Mean 30.2, SD 9.9 kg
	Duration of epilepsy (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
	Age at diagnosis (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
	Newly diagnosed, *n* (%)		14 (100)	14 (100)
	Previously diagnosed, *n* (%)		0	0
	Refractory, *n* (%); definition of refractory		0	0
	Diagnosed seizure types, *n* (%)	Typical absence seizures	14 (100)	14 (100)
	Diagnosed syndrome(s), *n* (%)	NA	NA	NA
	Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	NA	Not reported	Not reported
	No. of concomitant AEDs, *n* (%)	NA	NA	NA
	Concomitant AEDs, *n* (%)	NA	NA	NA
	Previous AEDs, *n* (%)	NA	NA	NA
	Comments		One patient in lamotrigine group withdrew consent after randomisation	
Monitoring and outcomes	Was monitoring of plasma levels done (including study drug)?	Yes, including lamotrigine		
	Were arrangements to blind plasma monitoring results mentioned?	No		
	Who recorded seizure frequency?	Provocation testing		
	How often was seizure frequency measured?	24-h HV-EEG records obtained at baseline, end of dose titration, end of withdrawal phase		
	Frequency of clinic visits	Can't tell		
	Primary outcome(s) including time points if repeated	Proportion of patients who remained seizure free during withdrawal phase		
	Secondary outcome(s) excluding AEs	–		
	'*Ad hoc*' outcomes (if emphasised and not in methods)	–		
	Comments	Hyperventilation tests used to establish seizure freedom		

continued

Results (ITT only; unadjusted where available)			Placebo	Lamotrigine
	Median follow-up		Not stated	Not stated
	Maintenance dose achieved		Not reported	Median 5.0, range 2–15 mg/kg/day
	Withdrawals including reasons where specified, *n* (%)	Total withdrawals Withdrew consent	0 –	1 (6.6) 1 (6.6)
			Results (difference, or by arm)	CI for difference; *p*-value
	Primary outcome(s)	Proportion of patients who remained seizure-free during double-blind phase	21% placebo vs 64% lamotrigine	$p = 0.03$
	Secondary outcomes	–	–	–
	'*Ad hoc*' outcomes	–	–	–
	Comments (including whether unadjusted results reported)		Maintenance dose achieved – this is the median dose taken by patients who became seizure free during the open phase	
Adverse events			Placebo	Lamotrigine
	Criteria for reporting	Events reported by ≥ 5% of patients	Not reported	Frequency not reported
	Events	Nervous system complaints (e.g. asthenia, headache, dizziness, hyperkinsia) Rash Events related to infections, ailments common to childhood or flu syndromes		
	Comments		Events believed to be attributable to lamotrigine and reported by >1 patient also documented: abdominal pain, headache, nausea, anorexia, dizziness, hyperkinesia	
Conclusions	Authors' conclusions	Lamotrigine is effective treatment for children with newly diagnosed typical absence seizures		
	Our conclusions	The study is of reasonable quality, although lack of information on randomisation and blinding, along with monitoring of lamotrigine plasma levels with no description of how clinicians were blinded to these results, gives some cause for concern		

Trial details	Trial ID	Bourgeois, 1998		
	Drug(s)	Gabapentin		
	Target maintenance dose (mode)	30 mg/kg/day		
	Seizure or syndrome	BECTS		
	Type of trial design	Parallel		
	Add-on or monotherapy?	Monotherapy		
	Control(s)	Placebo		
	Study start and end dates	Not reported		
	Centres and location	Not clear		
Trial design	Baseline	Not reported		
	Titration (including details of schedule and frequency of doses)	Not reported		
	Maintenance	36 weeks		
	Withdrawal	None		
	Timing and additional eligibility for randomisation/continuation on study			
	Comments on design	Abstract with few details of design		
Quality assessment	Was assignment of treatment described as random?	Yes		
	Was method of randomisation described?	No		
	Was the method really random?	Can't tell		
	Was allocation of treatment concealed?	Can't tell		
	Who was blinded to treatment?	Described as double-blind		
	Was method of blinding adequately described?	No description		
	Were eligibility criteria described?	Yes		
	Were groups comparable at study entry?	Not reported		
	Were groups treated identically apart from the intervention?	Can't tell		
	Was ITT used?	Yes		
	Were withdrawals stated?	Yes		
	Were reasons for withdrawals stated?	Yes		
	Was a power calculation done?	Not reported		
	Comments	Abstract with few details of design		
Eligibility criteria	Inclusion criteria	1. 4–13 years old 2. At least 1 and not more than 10 partial or generalised seizures within 6 months of entry		
	Exclusion criteria	Not reported		
Baseline characteristics			placebo	gabapentin
	Number randomised		112	113
	Number analysed		112	113
	Age (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
	Male:female		Not reported	Not reported

continued

	Weight (kg, lb) (mean, SD; median, range)		Not reported	Not reported
	Duration of epilepsy (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
	Age at diagnosis (weeks, months, years) (mean, SD; median, range)		Not reported	Not reported
	Newly diagnosed, *n* (%)		Not reported	Not reported
	Previously diagnosed, *n* (%)		Not reported	Not reported
	Refractory, *n* (%), definition of refractory		None (assumed)	None (assumed)
	Diagnosed seizure types, *n* (%)	Not reported	–	–
	Diagnosed syndrome(s), *n* (%)	BECTS	112 (100)	113 (100)
	Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	Not reported	–	–
	No. of concomitant AEDs, *n* (%)	Not reported	–	–
	Concomitant AEDs, *n* (%)	Not reported	–	–
	Previous AEDs, *n* (%)	Not reported	–	–
	Comments	–		
Monitoring and outcomes	Was monitoring of plasma levels done (including study drug)?	No		
	Were arrangements to blind plasma monitoring results mentioned?	NA		
	Who recorded seizure frequency?	Not reported		
	How often was seizure frequency measured?	Not reported		
	Frequency of clinic visits	Not reported		
	Primary outcome(s) including time points if repeated	Time to treatment failure (defined as 1 secondary tonic–clonic seizure or 3 partial seizures, or status epilepticus, or seizure activity that had worsened)		
	Secondary outcome(s) excluding AEs	Not reported		
	'*Ad hoc*' outcomes (if emphasised and not in methods)	–		
	Comments	–		
Results (ITT only; unadjusted where available)			Placebo	Gabapentin
	Median follow-up		Not reported	Not reported
	Maintenance dose achieved		Not reported	Not reported
	Withdrawals including reasons where specified, *n* (%)	Adverse events	0 (0)	(–3.50)
			Results (difference, or by arm)	CI for difference; *p*-value
	Primary outcome(s)	Time to treatment failure	No hazard ratio; Kaplan–Meier survival plots not in abstract	$p = 0.06$ for difference by log-rank test

continued

	Secondary outcomes	Not reported	–	–
	'*Ad hoc*' outcomes	–	–	–
	Comments (including whether unadjusted results reported)	–		
Adverse events			Placebo	Gabapentin
	Criteria for reporting	Not reported		
	Events	–	–	–
	Comments		–	
Conclusions	Authors' conclusions	Gabapentin administered as monotherapy is effective in controlling seizures in children with BECTS		
	Our conclusions	Insufficient information to judge the efficacy of gabapentin. This benign syndrome is associated with good prognosis and is left untreated in many instances since side-effects associated with AEDs might be less desirable than the disadvantages of the condition		

Trial details	Trial ID	Chiron, 1996
	Drug(s)	Vigabatrin
	Target maintenance dose (mode)	No dose information (not stated)
	Seizure or syndrome	Any
	Type of trial design	Withdrawal
	Add-on or monotherapy?	Add-on
	Control(s)	Placebo
	Study start and end dates	Not stated (patients selected from cohort treated in vigabatrin trials 1987–90)
	Centres and location	1 centre; France
Trial design	Baseline	2 months (possibly retrospective)
	Titration (including details of schedule and frequency of doses)	NA (patients on vigabatrin for 3–39 months prior to entry)
	Maintenance	None
	Withdrawal	2 months
	Timing and additional eligibility for randomisation/continuation on study	None stated
	Comments on design	Not clear if the 2-month baseline phase was retrospective. Placebo patients were withdrawn from vigabatrin during the first 2 months; the remaining patients were withdrawn over the following 2 months (described as 'single-blind', implying that the patients were not informed that all active treatment would be withdrawn during this period). The data extracted here are from the first 2-month (double-blind) period Patients were 'dropped' and the randomisation code broken if seizure frequency increased by >50% or increased in severity compared with baseline
Quality assessment	Was assignment of treatment described as random?	Yes
	Was method of randomisation described?	No

continued

	Was the method really random?	Can't tell
	Was allocation of treatment concealed?	Can't tell
	Who was blinded to treatment?	Described as 'double-blind'
	Was method of blinding adequately described?	No
	Were eligibility criteria described?	Yes
	Were groups comparable at study entry?	Can't tell; 7/9 patients with infantile spasms were allocated 'continue vigabatrin' and the 'continue vigabatrin' group had a longer mean duration of vigabatrin treatment at entry (12.2 vs 8.6 months) but a shorter median (7 vs 9 months), with SD10.2 vs 4.1 months
	Were groups treated identically apart from the intervention?	Can't tell
	Was ITT used?	Yes (for primary outcome; see comment)
	Were withdrawals stated?	Yes
	Were reasons for withdrawals stated?	Yes
	Was a power calculation done?	No
	Comments	The policy of 'dropping' patients if they experienced a worsening of seizure frequency or severity makes ITT impossible for most end-points except for the primary end-point used here (proportion of patients completing phase)
Eligibility criteria	Inclusion criteria	Partial improvement in terms of seizure frequency or severity, or parental perception of benefit despite lack of response, after at least 3 months on vigabatrin as add-on therapy Note: patients selected from a total of 196 included in various vigabatrin trials at one hospital
	Exclusion criteria	1. Patients who had become and remained seizure free when treated with vigabatrin 2. Patients who had experienced an increase in seizure frequency or severity with no parental perception of benefit Note: 4/28 patients were included owing to some benefit in terms of severity or parental perception despite an increased seizure rate on vigabatrin; compared with before vigabatrin treatment started, 2 patients had experienced 120% increase (both allocated vigabatrin), the other two increased by 160% and 200%, respectively (both allocated placebo)

Baseline characteristics		Placebo	Vigabatrin
	Number randomised	13	15
	Number analysed	13	15
	Age (weeks, months, years) (mean, SD; median, range)	Mean 7.9; range 1.5–18.6 years	Mean 9.3; range 1.7–17.6 years
	Male:female	Not reported	Not reported
	Weight (kg, lb) (mean, SD; median, range)	Not reported	Not reported
	Duration of epilepsy (weeks, months, years) (mean, SD; median, range)	Not reported	Not reported
	Age at diagnosis (weeks, months, years) (mean, SD; median, range)	Not reported	Not reported
	Newly diagnosed, *n* (%)	0	0

continued

	Previously diagnosed, *n* (%)		13 (100)	15 (100)
	Refractory, *n* (%); definition of refractory		–	–
	Diagnosed seizure types, *n* (%)	Complex partial	5 (38.4)	6 (40)
		Simple partial	3 (23.0)	1 (6.6)
		Secondarily generalised	5 (38.4)	2 (13.3)
		Spasms	4 (30.7)	5 (33.3)
		Primary generalised (incl. tonic-clonic, absence, myoclonic, clonic, tonic)	4 (30.7)	5 (33.3)
	Diagnosed syndrome(s), *n* (%)	Partial	7 (53.8)	5 (33.3)
		Infantile spasms	2 (15.3)	7 (46.6)
		Lennox–Gastaut syndrome	1 (7.6)	1 (6.6)
		Symptomatic generalised	2 (15.3)	1 (6.6)
		Myoclonic	1 (7.6)	1 (6.6)
	Baseline seizure frequency (per day, week, month) (mean, SD; median, range)	All seizures	Mean 61.7, SD 59.4; median 46, range 4–200/month	Mean 50.6, SD 41.1; median 40, range 2.5–120/month
	No. of concomitant AEDs, *n* (%)	1	1 (7.6)	6 (40)
		2	11 (84.6)	9 (60)
		3	1 (7.6)	0
	Concomitant AEDs, *n* (%)	Carbamazepine	10 (76.9)	10 (66.6)
		Clobazam	2 (15.3)	5 (33.3)
		Clonazepam	2 (15.3)	2 (13.3) (see comment)
		Hydrocortisone	0	1 (6.6) (see comment)
		Phenytoin	5 (38.4)	4 (26.6)
		Progabide	3 (23.0)	1 (6.6)
		Valproate	4 (30.7)	1 (6.6)
	Previous AEDs, *n* (%)	–	–	–
	Comments		Patient characteristics were not tabulated; these data calculated from individual patient data provided in the paper	
			Duration of vigabatrin treatment prior to entry into this study ranged from 3 to 39 months	
			Some errors in abbreviations used for concomitant AEDs (HZ probably instead of HC and CZB probably instead of CBZ)	
Monitoring and outcomes	Was monitoring of plasma levels done (including study drug)?	No		
	Were arrangements to blind plasma monitoring results mentioned?	NA		
	Who recorded seizure frequency?	Not reported		
	How often was seizure frequency measured?	Not reported		
	Frequency of clinic visits	Not reported		
	Primary outcome(s) including time points if repeated	Number of patients remaining in the study at the end of the double-blind phase		
	Secondary outcome(s) excluding AEs	Seizure frequency		
	'*Ad hoc*' outcomes (if emphasised and not in methods)	–		
	Comments	–		

continued

Results (ITT only; unadjusted where available)			Placebo	Vigabatrin
	Median follow-up		2 months	2 months
	Maintenance dose achieved		Not reported	Not reported
	Withdrawals including reasons where specified	Not reported	Not reported	Not reported
			Results (difference, or by arm)	CI for difference; *p*-value
	Primary outcome(s)	Number of patients remaining in the study at the end of the double-blind phase, *n* (%)	Placebo 7 (46.1) Vigabatrin 12 (93.3)	$p < 0.01$
	Secondary outcomes	Seizure frequency	Placebo median 95 Vigabatrin median 46	$p < 0.05$
	'*Ad hoc*' outcomes	–	–	
	Comments (including whether unadjusted results reported)	Two patients in the vigabatrin group remained on study despite >50% increase in seizure frequency; one patient in placebo group was 'dropped' owing to an increase in seizure severity but not >50% increase in seizure frequency. Results analysed and reported both ways; result above is for those meeting the predefined criteria for this end-point		
Adverse events			Placebo	Vigabatrin
	Criteria for reporting	None stated		
	Events	Not reported	Not reported	Not reported
	Comments			
Conclusions	Authors' conclusions	Authors acknowledge methodological issues and propose that study design be considered and improved for future trials in childhood epilepsy		
	Our conclusions	There are a number of methodological problems with this trial. The design is quirky; an extremely heterogeneous population was recruited; the sample size is very small. The results are difficult to interpret		

Appendix 14

Results of economic analysis

TABLE 137 *Analysis of cost-effectiveness (results 2)*

	Costs and QALYs accrued from start of treatment					Costs and QALYs accrued from time of failure on CBZ				
	Lamotrigine (first-line monotherapy)					Lamotrigine (second-line monotherapy)				
Run	Costs (mean) (£)	QALYs (mean)	Incremental		ICER (£)/QALY	Costs (mean) (£)	QALYs (mean)	Incremental		ICER (£)/QALY
			Cost (£)	QALYs				Cost (£)	QALYs	
1	2,592	6.6194	272	–0.0158	–17,215	2,392	3.6042	290	–0.0557	–5,206
2	2,671	6.5307	344	–0.0629	–5,469	2,349	3.5897	274	0.0058	47,241
3	2,712	6.655	352	–0.0041	–85,854	2,456	3.627	367	–0.0082	–44,756
4	2,586	6.5691	276	–0.0251	–10,996	2,362	3.5875	283	–0.0463	–6,112
5	2,672	6.6449	346	0.0225	15,378	2,337	3.5983	268	–0.0266	–10,075
6	2,628	6.6301	285	0.0149	19,128	2,325	3.5839	227	–0.0311	–7,299
7	2,652	6.6255	364	0.0695	5,237	2,432	3.6465	314	0.0562	5,587
8	2,568	6.5718	276	–0.0573	–4,817	2,379	3.6222	275	–0.0203	–13,547
9	2,674	6.5677	334	–0.0773	–4,321	2,454	3.5571	401	–0.0373	–10,751
10	2,581	6.6727	225	–0.0537	–4,190	2,467	3.5187	379	–0.0756	–5,013
11	2,624	6.4645	327	–0.0626	–5,224	2,499	3.6487	385	0.0118	32,627
12	2,673	6.7164	345	0.0554	6,227	2,432	3.6198	329	0.0385	8,545
13	2,628	6.6037	283	–0.0396	–7,146	2,404	3.5215	313	–0.0525	–5,962
14	2,613	6.5742	268	–0.0195	–13,744	2,377	3.6261	314	–0.0089	–35,281
15	2,668	6.5778	387	–0.0108	–35,833	2,335	3.5939	275	–0.0495	–5,556
16	2,670	6.6187	355	0.005	71,000	2,373	3.5434	275	–0.0502	–5,478
17	2,677	6.7237	336	0.0961	3,496	2,417	3.5938	338	0.0005	676,000
18	2,581	6.6428	254	0.0252	10,079	2,441	3.6828	353	0.0598	5,903
19	2,610	6.6353	292	0.0092	31,739	2,458	3.5878	351	–0.04	–8,775
20	2,554	6.6604	257	0.0379	6,781	2,468	3.6044	366	0.0035	104,571

TABLE 138 *Analysis of cost-effectiveness (results 3)*

	Costs and QALYs accrued from time of failure on CBZ									
	Lamotrigine (first choice add-on therapy)					Gabapentin (first choice add-on therapy)				
Run	Costs (mean) (£)	QALYs (mean)	Incremental		ICER (£)/QALY	Costs (mean) (£)	QALYs (mean)	Incremental		ICER (£)/QALY
			Cost (£)	QALYs				Cost (£)	QALYs	
1	2,196	3.6175	94	–0.0424	–2,217	2,333	3.6047	231	–0.0552	–4,185
2	2,221	3.581	146	–0.0029	–50,345	2,248	3.5462	173	–0.0377	–4,589
3	2,276	3.5796	187	–0.0556	–3,363	2,302	3.5323	213	–0.1029	–2,070
4	2,254	3.6074	175	–0.0264	–6,629	2,330	3.6362	251	0.0024	104,583
5	2,205	3.5992	136	–0.0257	–5,292	2,288	3.5501	219	–0.0748	–2,928
6	2,231	3.5605	133	–0.0545	–2,440	2,307	3.5952	209	–0.0198	–10,556
7	2,210	3.5312	92	–0.0591	–1,557	2,318	3.6469	200	0.0566	3,534
8	2,185	3.5568	81	–0.0857	–945	2,259	3.5569	155	–0.0856	–1,811
9	2,246	3.5805	193	–0.0139	–13,885	2,302	3.6015	249	0.0071	35,070
10	2,217	3.6286	129	0.0343	3,761	2,306	3.5918	218	–0.0025	–87,200
11	2,211	3.6041	97	–0.0328	–2,957	2,349	3.5659	235	–0.071	–3,310
12	2,204	3.5966	101	0.0153	6,601	2,330	3.601	227	0.0197	11,523
13	2,215	3.5813	124	0.0073	16,986	2,303	3.6113	212	0.0373	5,684
14	2,235	3.5998	172	–0.0352	–4,886	2,339	3.5953	276	–0.0397	–6,952
15	2,243	3.622	183	–0.0214	–8,551	2,314	3.5773	254	–0.0661	–3,843
16	2,260	3.63	162	0.0364	4,451	2,292	3.5731	194	–0.0205	–9,463
17	2,249	3.5984	170	0.0051	33,333	2,292	3.639	213	0.0457	4,661
18	2,213	3.6108	125	–0.0122	–10,246	2,272	3.5927	184	–0.0303	–6,073
19	2,213	3.6124	106	–0.0154	–6,883	2,331	3.6108	224	–0.017	–13,176
20	2,226	3.5889	124	–0.0120	–10,333	2,286	3.5719	184	–0.029	–6,345

TABLE 139 *Analysis of cost-effectiveness (results 4)*

	Costs and QALYs accrued from time of failure on CBZ (base case analysis)									
	Topiramate (first choice add-on therapy)					Oxcarbazepine (first choice add-on therapy)				
Run	Costs (mean) (£)	QALYs (mean)	Incremental		ICER (£)/QALY	Costs (mean) (£)	QALYs (mean)	Incremental		ICER (£)/QALY
			Cost (£)	QALYs				Cost (£)	QALYs	
1	2,418	3.6232	316	–0.0367	–8,610	2,394	3.5902	292	–0.0697	–4,189
2	2,412	3.6462	337	0.0623	5,409	2,363	3.5675	288	–0.0164	–17,561
3	2,411	3.655	322	0.0198	16,263	2,454	3.6339	365	–0.0013	–280,769
4	2,455	3.5781	376	–0.0557	–6,750	2,394	3.5914	315	–0.0424	–7,429
5	2,362	3.6296	293	0.0047	62,340	2,356	3.5623	287	–0.0626	–4,585
6	2,366	3.5917	268	–0.0233	–11,502	2,449	3.6741	351	0.0591	5,939
7	2,450	3.6038	332	0.0135	24,593	2,416	3.5817	298	–0.0086	–34,651
8	2,373	3.6048	269	–0.0377	–7,135	2,478	3.6434	374	0.0009	415,556
9	2,383	3.6073	330	0.0129	25,581	2,444	3.6346	391	0.0402	9,726
10	2,431	3.6179	343	0.0236	14,534	2,461	3.6163	373	0.0220	16,955
11	2,450	3.602	336	–0.0349	–9,628	2,409	3.5765	295	–0.0604	–4,884
12	2,490	3.6019	387	0.0206	18,786	2,410	3.64	307	0.0587	5,230
13	2,410	3.5889	319	0.0149	21,409	2,378	3.6064	287	0.0324	8,858
14	2,356	3.5894	293	–0.0456	–6,425	2,447	3.6321	384	–0.0029	–132,414
15	2,423	3.6184	363	–0.0250	–14,520	2,349	3.5414	289	–0.1020	–2,833
16	2,370	3.6593	272	0.0657	4,140	2,433	3.5743	335	–0.0193	–17,358
17	2,449	3.6183	370	0.0250	14,800	2,416	3.6571	337	0.0638	5,282
18	2,510	3.5864	422	–0.0366	–11,530	2,472	3.6185	384	–0.0045	–85,333
19	2,491	3.617	384	–0.0108	–35,556	2,422	3.6539	315	0.0261	12,069
20	2,479	3.6348	377	0.0339	11,121	2,340	3.574	238	–0.0269	–8,848

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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