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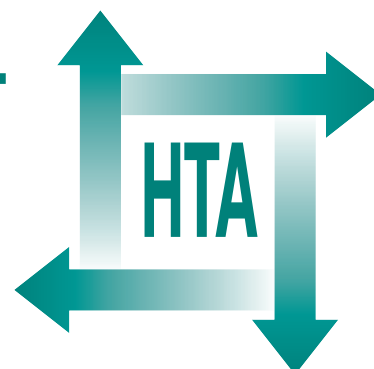
## **Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation**

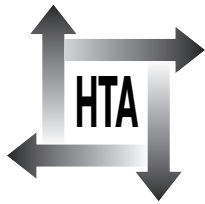
J Wilby, A Kainth, N Hawkins, D Epstein,  
H McIntosh, C McDaid, A Mason, S Golder,  
S O'Meara, M Sculpher, M Drummond and  
C Forbes



April 2005

**Health Technology Assessment  
NHS R&D HTA Programme**





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# Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation

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**Declared competing interests of authors:** Neil Hawkins has undertaken consultancy for GlaxoSmithKline in therapeutic areas unrelated to the treatment of epilepsy. Mark Sculpher has undertaken consultancy or reviewed research findings for Aventis and GlaxoSmithKline, but on products unrelated to epilepsy. Michael Drummond has served on an Advisory Board for Aventis Pharma Ltd, but not related to epilepsy. He has also undertaken consultancy from Pfizer and GlaxoSmithKline, but in fields unrelated to epilepsy.

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## Abstract

### Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation

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**Objectives:** To examine the clinical effectiveness, tolerability and cost-effectiveness of gabapentin (GBP), lamotrigine (LTG), levetiracetam (LEV), oxcarbazepine (OXC), tiagabine (TGB), topiramate (TPM) and vigabatrin (VGB) for epilepsy in adults.

**Data sources:** Electronic databases. Internet resources. Pharmaceutical company submissions.

**Review methods:** Selected studies were screened and quality assessed. Separate analyses assessed clinical effectiveness, serious, rare and long-term adverse events and cost-effectiveness. An integrated economic analysis incorporating information on costs and effects of newer and older antiepileptic drugs (AEDs) was performed to give direct comparisons of long-term costs and benefits.

**Results:** A total of 212 studies were included in the review. All included systematic reviews were Cochrane reviews and of good quality. The quality of randomised controlled trials (RCTs) was variable. Assessment was hampered by poor reporting of methods of randomisation, allocation concealment and blinding. Few of the non-randomised studies were of good quality. The main weakness of the economic evaluations was inappropriate use of the cost-minimisation design. The included systematic reviews reported that newer AEDs were effective as adjunctive therapy compared to placebo. For newer versus older drugs, data were available for all three monotherapy AEDs, although data for OXC and TPM were limited. There was limited, poor-quality evidence of a significant improvement in cognitive function with LTG and OXC compared with older AEDs. However, there were no consistent statistically significant differences in other clinical outcomes, including proportion of seizure-free patients. No studies assessed effectiveness of AEDs in

people with intellectual disabilities or in pregnant women. There was very little evidence to assess the effectiveness of AEDs in the elderly; no significant differences were found between LTG and carbamazepine monotherapy. Sixty-seven RCTs compared adjunctive therapy with placebo, older AEDs or other newer AEDs. For newer AEDs versus placebo, a trend was observed in favour of newer drugs, and there was evidence of statistically significant differences in proportion of responders favouring newer drugs. However, it was not possible to assess long-term effectiveness. Most trials were conducted in patients with partial seizures. For newer AEDs versus older drugs, there was no evidence to assess the effectiveness of LEV, LTG or OXC, and evidence for other newer drugs was limited to single studies. Trials only included patients with partial seizures and follow-up was relatively short. There was no evidence to assess effectiveness of adjunctive LEV, OXC or TPM versus other newer drugs, and there were no time to event or cognitive data. No studies assessed the effectiveness of adjunctive AEDs in the elderly or pregnant women. There was some evidence from one study (GBP versus LTG) that both drugs have some beneficial effect on behaviour in people with learning disabilities. Eighty RCTs reported the incidence of adverse events. There was no consistent or convincing evidence to draw any conclusions concerning relative safety and tolerability of newer AEDs compared with each other, older AEDs or placebo. The integrated economic analysis for monotherapy for newly diagnosed patients with partial seizures showed that older AEDs were more likely to be cost-effective, although there was considerable uncertainty in these results. The integrated analysis suggested that newer

AEDs used as adjunctive therapy for refractory patients with partial seizures were more effective and more costly than continuing with existing treatment alone. Combination therapy, involving new AEDs, may be cost-effective at a threshold willingness to pay per quality-adjusted life year (QALY) greater than £20,000, depending on patients' previous treatment history. There was, again, considerable uncertainty in these results. There were few data available to determine effectiveness of treatments for patients with generalised seizures. LTG and VPA showed similar health benefits when used as monotherapy. VPA was less costly and was likely to be cost-effective. The analysis indicated that TPM might be cost-effective when used as an adjunctive therapy, with an estimated incremental cost-effectiveness ratio of £34,500 compared with continuing current treatment alone.

**Conclusions:** There was little good-quality evidence from clinical trials to support the use of newer monotherapy or adjunctive therapy AEDs over older drugs, or to support the use of one newer AED in preference to another. In general, data relating to clinical effectiveness, safety and tolerability failed to demonstrate consistent and statistically significant differences between the drugs. The exception was comparisons between newer adjunctive AEDs and placebo, where significant differences favoured newer AEDs. However, trials often had relatively short-term treatment durations and often failed to limit recruitment to either partial or generalised onset

seizures, thus limiting the applicability of the data. Newer AEDs, used as monotherapy, may be cost-effective for the treatment of patients who have experienced adverse events with older AEDs, who have failed to respond to the older drugs, or where such drugs are contraindicated. The integrated economic analysis also suggested that newer AEDs used as adjunctive therapy may be cost-effective compared with the continuing current treatment alone given a QALY of about £20,000. There is a need for more direct comparisons of the different AEDs within clinical trials, considering different treatment sequences within both monotherapy and adjunctive therapy. Length of follow-up also needs to be considered. Trials are needed that recruit patients with either partial or generalised seizures; that investigate effectiveness and cost-effectiveness in patients with generalised onset seizures and that investigate effectiveness in specific populations of epilepsy patients, as well as studies evaluating cognitive outcomes to use more stringent testing protocols and to adopt a more consistent approach in assessing outcomes. Further research is also required to assess the quality of life within trials of epilepsy therapy using preference-based measures of outcomes that generate cost-effectiveness data. Future RCTs should use CONSORT guidelines; and observational data to provide information on the use of AEDs in actual practice, including details of treatment sequences and doses.



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## Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

### Glossary

**Absence seizure<sup>a</sup>** Previously called ‘petit mal’, this is a generalised seizure involving a brief interruption of consciousness. The person may look blank and their eyelids may flutter.

**Adverse effect<sup>b</sup>** Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with the treatment.

**Adverse event<sup>b</sup>** A response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of the disease, or for the modification of physiological function.

**Amblyopia<sup>c</sup>** Dimness of vision, without detectable organic lesion of the eye.

**Amnesia<sup>c</sup>** Pathological impairment of memory.

**Anorexia<sup>c</sup>** Lack or loss of appetite for food.

**Aphasia<sup>c</sup>** Defect or loss of the power of expression by speech, writing or signs or of comprehending spoken or written language, due to injury or disease of the brain centres.

**Asthenia<sup>c</sup>** Lack or loss of strength and energy, weakness.

**Ataxia<sup>c</sup>** Failure of muscular coordination; irregularity of muscular action.

**Atonic seizure<sup>a</sup>** Generalised seizure involving a sudden loss of muscle tone so that the person falls to the ground. Recovery is rapid but there may be injuries due to the fall.

**Co-morbidity** In a study looking at treatment for one disease or condition, some of the individuals with that disease will also have

other diseases or conditions that could be affecting their outcomes. Any other such condition is called a ‘co-morbidity’.

**Complex partial seizure<sup>a</sup>** Partial seizure in which the person’s awareness is impaired. The person may show confused behaviour and ‘automatisms’ such as lip-smacking, chewing, undressing, picking up objects and wandering aimlessly. The seizure usually lasts a few minutes and the person has no memory of what has happened. This type of seizure often originates in the temporal lobe of the brain, in which case the person may be said to have temporal lobe epilepsy. However, complex partial seizures may also originate in other lobes (areas) of the brain.

**Confidence interval (CI)** Quantifies the uncertainty in measurement. Usually reported as 95% CI, that is, the range of values within which one is 95% sure that the true value for the whole population lies.

**Cost-benefit analysis (CBA)** A form of economic evaluation where both costs and benefits are expressed in the same units, usually monetary units, that is, all of the health benefits (e.g. disability days avoided, life-years gained, medical complications avoided) are translated into monetary units. This type of analysis is not widely used in the economic evaluation of drugs or technologies, as it is often difficult to determine the cost of health benefits.

**Cost-consequences analysis (CCA)** A form of cost-effectiveness analysis where costs and effectiveness (consequences) are presented separately and the decision-maker is left to make their own view about the relative importance of these factors.

*continued*

## Glossary continued

### **Cost-effectiveness acceptability curve (CEAC)**

A graphical representation of the probability of an intervention being cost-effective over a range of monetary values for society's willingness to pay for an additional unit of health gain.

### **Cost-effectiveness analysis (CEA)**

A form of economic evaluation where costs are expressed in monetary units and effectiveness is expressed in some unit of effectiveness. Units of effectiveness are usually the same as those clinical outcomes used to measure effectiveness in clinical trials or practice. When comparing two interventions, the difference in cost and effectiveness between the two interventions is expressed as an incremental cost-effectiveness ratio (ICER), with the difference in cost in the numerator and the difference in effectiveness in the denominator. A particular form of cost-effectiveness is sometimes referred to as cost-utility analysis, where the measure of effectiveness is typically measured in terms of quality-adjusted life-years (QALYs).

### **Cost-minimisation analysis (CMA)**

A special form of cost-effectiveness analysis and the simplest form of economic evaluation. Costs are expressed in monetary units and the patient outcome is assumed to be the same in both/all of the intervention groups evaluated. Hence, the object of this type of analysis is to identify the least expensive alternative.

### **Cost-utility analysis (CUA)**

A special form of cost-effectiveness analysis in which the units of effectiveness are QALYs. Cost-utility analyses are important in the evaluation of cancer therapies, as such therapies are often associated with potentially serious or intolerable adverse events.

**Crossover trial** A trial in which each of the study groups will receive each of the treatments, but in a randomised order: that is, they will start off in one arm of the trial, but will deliberately 'cross over' to the other arm(s) in turn.

**Diplopia<sup>c</sup>** The perception of two images of a single object.

**Dyspepsia<sup>c</sup>** Impairment of the power or function of digestion; usually applied to epigastric discomfort after meals.

**Emotional lability<sup>c</sup>** Emotional instability.

**Equivalence margin** The meaningful difference to be ruled out when two drugs are compared for equivalence (i.e. how much difference is allowed between treatments for them to be considered equivalent). This should be specified and justified *a priori* because selection of a meaningful difference may be influenced by the trial results.

**Focal seizures** See Partial seizures.

**Expected value of perfect information** A measure of the cost of uncertainty associated with a given decision problem in terms of health forgone and resource costs. Perfect information through further research would remove this uncertainty and hence the cost of uncertainty is synonymous with the value of perfect information. Often graphically represented over a range of monetary values for society's threshold willingness to pay for an additional unit of health gain. This measure offers an insight into whether the necessary (but not sufficient) conditions are met for additional research to be cost-effective.

**Generalised seizures<sup>a</sup>** Generalised seizures are those in which the abnormal electrical activity begins in both hemispheres (sides) of the brain at the same time.

**Hazard ratio** The hazard (the instantaneous risk of patient experiencing a particular event at a specified time point) associated with one category of patients divided by the hazard for another set of patients. The hazard ratio can be estimated at an instant or averaged over an interval.

**Heterogeneous** Of differing origins or different types.

**International League Against Epilepsy (ILAE)<sup>d</sup>** The ILAE is a global professional non-profit international organisation and a non-governmental organisation in official relations with the WHO. The ILAE's objectives are: to advance and disseminate knowledge about epilepsy (and have developed guidelines for the classification of epilepsy and the design of investigative trials); to promote research, education and training; and to improve

*continued*

## Glossary continued

services and care for patients, especially by prevention, diagnosis and treatment.

### **Incremental cost-effectiveness ratio (ICER)**

An expression of the additional cost of health gain associated with an intervention relative to an appropriate comparator. Expressed as the difference in mean costs (relative to the comparator) divided by the difference in mean effects. Sometimes expressed with confidence intervals.

**Logistic regression** See Regression analysis

**Meta-analysis** The statistical pooling of the results of a collection or related individual studies, to increase statistical power and synthesise their findings.

**Multivariate analysis** Measuring the impact of more than one variable at a time while analysing a set of data, for example, looking at the impact of age, gender and occupation on a particular outcome.

**Myoclonic seizure<sup>a</sup>** Generalised seizure involving brief jerks of part of or the whole body. Recovery is rapid.

**Number needed to treat** A number which gives you an estimate of how many people need to receive a treatment before one person would experience the beneficial outcome.

**Nystagmus<sup>c</sup>** Involuntary rapid movement (horizontal, vertical, rotatory, or mixed) of the eyeball.

**Open-label trial** A non-blind/non-masked trial: one where both the clinician and patient know what drug a participant is taking, and at what dose.

**Paresthesia<sup>c</sup>** Morbid or perverted sensation; an abnormal sensation, such as burning, prickling, formication.

**Partial seizures<sup>a</sup>** Seizure in which the abnormal electrical activity begins in one part of the brain. Which part of the brain is involved will determine what actually happens during the seizure.

**Pharyngitis<sup>c</sup>** Sore throat; inflammation of the pharynx.

**Postictal** The period following a seizure during which a patient may have drowsiness or be confused.

**Power** Statistical power of a study: a study needs to have a specific level of 'power' in order to be able to detect reliably a difference that a treatment might cause. To be powerful enough, the study needs to have enough participants, who experience enough of the outcomes in question, to be able to come up with statistically significant results.

**Pruritus<sup>c</sup>** Itching.

**Q-statistic** A statistical test performed when pooling studies to assess the degree of homogeneity between a group of studies. If  $Q > s - 1$  (where  $s$  is the number of studies to be combined) and the accompanying  $p$ -value is less than a predefined cut-off value (e.g. 0.05), then there is significant heterogeneity between studies. However, this test has low statistical power, especially where only small numbers of studies are to be combined and often a more stringent cut-off value is used for judging statistical significance (i.e.  $p$ -value of  $\leq 0.10$  is considered significant).

**Quality-adjusted life-year (QALY)** An index of health gain where survival duration is weighted or adjusted by the patient's quality of life during the survival period. QALYs have the advantage of incorporating changes in both quantity (mortality) and quality (morbidity) of life.

**Quality of life (QoL)** A concept incorporating all the factors that might impact on an individual's life, including factors such as the absence of disease or infirmity and other factors which might affect their physical, mental and social well-being.

**Refractory disease** Disease that has failed to respond to appropriate treatment.

**Regression analysis** A statistical modelling technique. Regression analysis is used to estimate or predict the relative influence of more than one variable on something, for example, the effect of age, gender and educational level on the prevalence of a disease. There are different types of these models, including 'linear' and 'logistic' regression.

*continued*

## Glossary continued

**Relative risk (RR)<sup>e</sup>** The ratio of risk in the intervention group to the risk in the control group. The risk is the ratio of people with an event in a group to the total in the group. A relative risk (or risk ratio) of 1 indicates no difference between comparison groups. For undesirable outcomes a relative risk that is <1 indicates that the intervention was effective in reducing the risk of that outcome.

**Rhinitis<sup>c</sup>** Inflammation of the nasal mucous membrane.

**Risk ratio** See Relative risk.

**Secondarily generalised seizure<sup>a</sup>** Seizures where the abnormal electrical activity starts in one part of the brain and then spreads to involve the whole brain. The seizure begins with a partial seizure – this is the warning, and sometimes this phase is extremely brief – and then becomes a generalised seizure, most commonly tonic clonic.

**Simple partial seizure<sup>a</sup>** A partial seizure in which the person remains fully conscious but experiences unusual sensations such as strange tastes or smells, feelings of fear or *déjà vu* or involuntary twitching of limbs. A simple partial seizure is often called an aura or warning, because it may precede another type of seizure.

**Somnolence<sup>c</sup>** Drowsiness or sleepiness, particularly in excess.

**Status epilepticus<sup>a</sup>** When a seizure continues for a prolonged period (longer than 30 minutes), or when seizures occur one after the other with no recovery between. Status epilepticus is an emergency and requires immediate medical attention.

**Tonic seizure<sup>a</sup>** Generalised seizure in which the person's body becomes stiff and they may fall backwards. The seizure usually lasts less than a minute and recovery is rapid.

**Tonic-clonic seizure<sup>a</sup>** Also called convulsion or 'grand mal', this is a generalised seizure. The person becomes stiff and may fall. This is followed by rhythmical jerking of the limbs, usually lasting a few minutes. The person may bite their tongue and may be incontinent. They may feel confused or sleepy afterwards, and take a while to recover fully.

**Utility** A measure of the strength of an individual's preference for a given health state or outcome. Utilities assign numerical values on a scale from 0 (death) to 1 (optimal or 'perfect' health), and provide a single number that summarises health-related quality of life. Hence utility has been described as a global measure of health-related quality of life. Sometimes 'utility' is only used to refer to preferences (on the 0–1 scale) that are elicited using methods which introduce risky scenarios to the respondent (standard gamble), with the term 'values' used to refer to other type of preferences.

**Values** An alternative measure of the strength of an individual's preference for a given health state or outcome. In contrast to utilities, values reflect preferences elicited in a riskless context.

**Vertigo<sup>c</sup>** A sensation of rotation or movement of one's self or of one's surroundings in any plane; sometimes used erroneously to mean any form of dizziness.

### Visual field defect/visual field constriction

The visual field is the area which can be seen by an individual when looking straight ahead without moving the eyes. Damage to the rod cells of the peripheral retinae narrows the field causing peripheral loss, also called visual field constriction. This can lead to tunnel vision, night blindness and difficulty with changing lighting conditions.

**Washout period** (See Crossover trial). A stage in a crossover trial after the first treatment is withdrawn, but before the second treatment is started. The washout period allows time for any active effects of the first treatment to wear off before the next phase begins.

<sup>a</sup> Definition adapted from the National Society for Epilepsy: <http://www.epilepsynse.org.uk/pages/info/glossary/index.cfm>

<sup>b</sup> World Health Organization.<sup>2</sup>

<sup>c</sup> Definition adapted from note *a*.

<sup>d</sup> Definition adapted from the ILAE website: <http://www.ilae-epilepsy.org/>

<sup>e</sup> Definition provided by the Cochrane Collaboration Glossary.

**List of abbreviations**

ABNC	Aldenkamp–Baker Neurotoxicity Scale	CPS	complex partial seizure
ADR	adverse reaction	CRD	Centre for Reviews and Dissemination
AE	adverse event	CSAG	Clinical Standards Advisory Group
AED	antiepileptic drug	CSM	Committee on Safety of Medicines
AEP	Adverse Events Profile	CT	computed tomography
ANCOVA	analysis of covariance	CUA	cost–utility analysis
ANOVA	analysis of variance	CZP	clonazepam
AZM	acetazolamide	DARE	Database of Abstracts of Reviews of Effects
BD	birth defect	df	degrees of freedom
BDI	Beck Depression Inventory	DZP	diazepam
BMI	body mass index	EAI	epilepsy activity index
BMJ	<i>British Medical Journal</i>	ECG	electrocardiography
BNF	British National Formulary	EEG	electroencephalogram
BPD	bipolar disorder	EOG	electrooculogram
BVRT	Benton Visual Retention Test	ERG	electroretinogram
CBA	cost–benefit analysis	FIQ	Full-scale Intelligence Quotient
CBZ	carbamazepine	FNR	flunarizine
CCA	cost–consequences analysis	GABA	$\gamma$ -Aminobutyric acid
CCTR	Cochrane Controlled Trials Register	GBP	gabapentin
CDRS	Cornell Dysthymia Rating Self-report Scale	GPRD	General Practice Research Database
CDSR	Cochrane Database of Systematic Reviews	GTC	generalised tonic–clonic
CEA	cost-effectiveness analysis	HEED	Health Economic Evaluations Database
CEAC	cost-effectiveness acceptability curve	HR	hazard ratio
CHE	Centre for Health Economics	HRQoL	health-related quality of life
CI	confidence interval	HSTAT	Health Service Technology Assessment Text
CLB	clobazam	ICER	incremental cost-effectiveness ratio
CMA	cost-minimisation analysis	ICH	International Conference on Harmonisation
CNS	central nervous system	ICS	International Classification of Seizures
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms		
COWA	Controlled Oral Word Association		
CPI	Conference Papers Index		

*continued*

**List of abbreviations continued**

ILAE	International League Against Epilepsy	PRM	primidone
IQ	intelligence quotient	PSSRU	Personal Social Services Research Unit
ISTP	Index to Scientific and Technical Proceedings	QALY	Quality-adjusted life-year
ITT	intention-to-treat	QOL	quality of life
LEV	levetiracetam	QOLIE	Quality of Life in Epilepsy Inventory
LSI	Life Satisfaction Index	RCT	randomised controlled trial
LSM	least-squares mean	RR	relative risk
LSSS	Liverpool Seizure Severity Scale	SchHARR	School of Health and Related Research
LTG	lamotrigine	SCI	Science Citation Index
MANCOVA	multivariate analysis of covariance	SD	standard deviation
MANOVA	multivariate analysis of variance	SE	standard error
MRI	magnetic resonance imaging	SEALS	Side Effects and Life Satisfaction Inventory
MSFRR	medium seizure frequency reduction rate	SEM	standard error of the mean
NCCHTA	National Coordinating Centre for Health Technology Assessment	SG	standard gamble
NGPSE	National General Practice Study of Epilepsy	SGTC	secondarily generalised tonic-clonic
NHS EED	NHS Economic Evaluation Database	SIGN	Scottish Intercollegiate Guidelines Network
NICE	National Institute for Clinical Excellence	SJS	Stevens-Johnson syndrome
NNT	number needed to treat	SMR	standardised mortality rate
NRR	National Research Register	SPC	summary of product characteristics
OR	odds ratio	SPMS	simple partial motor seizure
OXC	oxcarbazepine	SPS	simple partial seizure
PACT	prescription analysis and cost	SUDEP	sudden unexpected death in epilepsy
PB	phenobarbital	TEN	toxic epidermal necrosis
PCA	principal component analysis	TGB	tiagabine
PEM	prescription event monitoring	TPM	topiramate
PGTC	primary generalised tonic-clonic	TRIP	Turning Research Into Practice
PHT	phenytoin	VAS	visual analogue scale
PMS	postmarketing surveillance	VEP	visual evoked potential
POMS	Profile of Moods State		
POS	partial onset seizure		

*continued*

**List of abbreviations *continued***

VF	visual field	WBC	white blood cell
VFC	visual field constriction	WMHTAC	West Midlands Health Technology Assessment Collaboration
VFD	visual field defect	WMS	Wechsler Memory Scale
VGB	vigabatrin	WPSI	Washington Psychosocial Seizure Inventory
VPA	valproate	ZNS	zonisamide
WAIS-R	Wechsler Adult Intelligence Scale – Revised		

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.







## Executive summary

### Background

Epilepsy is a complex neurological condition responsible for considerable morbidity and mortality. It affects over 400,000 individuals within the UK and is responsible for over 1000 deaths per year. Initial treatment approaches focus on drug therapy, either monotherapy or adjunctive therapy. In the event of drug treatment failure, surgery might be considered but is limited to a very specific group of patients. Drug therapy is, therefore, the mainstay of treatment. Because many individuals can require many years of, if not lifelong, treatment with antiepileptic drugs (AEDs), the clinical effectiveness, tolerability and cost-effectiveness of drug therapy are a major considerations. A number of drug therapies are licensed for the treatment of epilepsy in adults, although many are limited to specific types of epilepsy and therapy regimens. However, at present, there does not appear to be a uniform approach to the selection or sequence of AED therapy.

### Aims of the review

To examine the clinical effectiveness, tolerability and cost-effectiveness of gabapentin (GBP), lamotrigine (LTG), levetiracetam (LEV), oxcarbazepine (OXC), tiagabine (TGB), topiramate (TPM) and vigabatrin (VGB) for epilepsy in adults.

### Methods

#### Search strategy

Over 36 electronic databases and Internet resources were searched from inception to May/September 2002. In addition, bibliographies of retrieved articles were searched and pharmaceutical company submissions examined for further studies.

#### Inclusion/exclusion criteria

Studies of newer AED therapies for the treatment of adults with newly diagnosed or refractory epilepsy were included. Relevant comparators included older AEDs, other newer AEDs and

placebo. Only randomised controlled trials (RCTs) and systematic reviews were included in the review of clinical effectiveness, and in addition non-randomised experimental studies and observational studies were included in the review of serious, rare and long-term adverse events. The assessment of cost-effectiveness included only cost-minimisation, cost-effectiveness and cost-utility analyses. Two reviewers independently screened all titles and abstracts and made final decisions on the inclusion/exclusion of studies based on full copies of articles. Any disagreements were resolved through discussion.

#### Data extraction and quality assessment

Data were extracted by one reviewer and checked by another. Two reviewers, using specified criteria, independently assessed the quality of all included studies. Any disagreements were resolved through discussion.

#### Analysis strategy

Separate analyses were performed to assess clinical effectiveness, serious, rare and long-term adverse events and cost-effectiveness. An integrated economic analysis incorporating information on both the costs and effects of newer and older AEDs was performed to allow direct comparisons of long-term costs and benefits.

### Results

#### Included studies

A total of 8095 titles and abstracts were screened for relevance and full copies of 1098 studies were ordered and assessed for inclusion/exclusion. A total of 212 studies were included in the review: 13 systematic reviews, 101 effectiveness publications covering 88 RCTs, 88 non-randomised experimental studies and observational publications covering 77 studies, and 21 economic evaluations.

#### Quality of clinical effectiveness studies

All included systematic reviews were Cochrane reviews and of good quality. The quality of RCTs was variable. Assessment was hampered by poor reporting of methods of randomisation, allocation concealment and blinding. Few of the non-randomised studies were of good quality.

### Quality of economic evaluations

The main weakness of the published economic evaluations was inappropriate use of the cost-minimisation design. Other issues included basing conclusions on a small number of trials and using inappropriate assumptions to extrapolate beyond the length of time of the study. Only two of the 10 company submissions incorporated most of the main features that were felt necessary to model the treatment of epilepsy, and even these lacked a systematic approach to obtaining and synthesising effectiveness data.

### Assessment of clinical effectiveness

The included systematic reviews reported that newer AEDs were effective as adjunctive therapy compared to placebo.

### Monotherapy

Twenty-one RCTs (12 LTG, eight OXC and one TPM) compared monotherapy with placebo (two studies), older AEDs (17 studies) or other newer AEDs (two studies). For new AEDs versus placebo, data were only available from two trials of OXC. Considering certain limitations of the trials, the statistically significant differences in proportion of seizure-free participants and time to event outcomes in favour of OXC monotherapy versus placebo should be interpreted with caution. There were no data for LTG or TPM.

For newer drugs versus older drugs, data were available for all three monotherapy AEDs, although data for OXC and TPM were limited. There was limited, poor-quality evidence of a significant improvement in cognitive function with LTG and OXC compared with older AEDs. However, no consistent statistically significant differences were found in other clinical outcomes, including proportion of seizure-free patients. Evidence for the effectiveness of newer AEDs versus other newer AEDs was limited to one study of LTG versus GBP. The relevance of this study to clinical practice is unclear, given that GBP is not licensed for monotherapy and the study included patients with either partial or generalised seizures.

No studies assessed effectiveness of AEDs in people with intellectual disabilities or in pregnant women. There was very little evidence to assess the effectiveness of AEDs in the elderly; no significant differences were found between LTG and carbamazepine monotherapy.

### Adjunctive therapy

Sixty-seven RCTs (10 GBP, 21 LTG, three LEV, two OXC, seven TGB, 14 TPM and 15 VGB)

compared adjunctive therapy with placebo (56 studies), older AEDs (seven studies) or other newer AEDs (four studies). Three of the four studies of newer AEDs compared to other newer AEDs investigated two newer AEDs each, and the other study investigated three newer AEDs. For newer AEDs versus placebo, a trend was observed in favour of newer drugs, and there was evidence of statistically significant differences in proportion of responders in favour of newer drugs. However, as the length of follow-up was limited in many trials, it was not possible to assess long-term effectiveness. Most trials were conducted in patients with partial seizures.

For newer AEDs versus older drugs, there was no evidence to assess the effectiveness of LEV, LTG or OXC, and evidence for other newer drugs was limited to single studies. Trials only included patients with partial seizures and follow-up was relatively short. Data were available for proportion of seizure-free patients, proportion of responders and limited quality of life and cognitive outcomes. The available evidence showed mainly non-significant differences, and should be regarded with caution because of weaknesses in the design and quality of the studies.

There was no evidence to assess effectiveness of adjunctive LEV, OXC or TPM versus other newer drugs, and there were no time to event or cognitive data. Available evidence was limited to single studies, with the exception of two studies that compared GBP with VGB and two studies that compared GBP with LTG. In general, studies enrolled patients with partial seizures and follow-up was limited. One study showed a statistically significant difference in proportion of responders in favour of VGB over GBP. Another study of patients with intellectual disabilities found statistically significant differences in quality of life in favour of GBP over LTG. These findings should be interpreted with caution because of flaws in the quality of the studies.

No studies assessed the effectiveness of adjunctive AEDs in the elderly or pregnant women. A number of studies included people with intellectual disabilities, but only three provided data exclusively from this population. There was some evidence from one study (GBP versus LTG) that both drugs have some beneficial effect on behaviour in people with learning disabilities.

### Adverse events

Eighty RCTs reported the incidence of adverse events. There was no consistent or convincing

evidence from these studies to draw any clear conclusions concerning relative safety and tolerability of newer AEDs compared with each other, older AEDs or placebo. Observational data provided some evidence of possible serious, rare and long-term adverse events beyond those reported in RCTs. However, the evidence reviewed does not provide proof of association between drug and event.

### Assessment of cost-effectiveness

Regarding monotherapy for newly diagnosed patients with partial seizures, the integrated economic analysis showed similar health benefits for the various AEDs and that newer AEDs were more expensive than older therapies. Consequently, the older AEDs were more likely to be cost-effective. There was considerable uncertainty in these results.

The integrated analysis suggested that newer AEDs used as adjunctive therapy for refractory patients with partial seizures were more effective and more costly than continuing with existing treatment alone. Combination therapy, involving new AEDs, may be cost-effective at a threshold willingness to pay per quality-adjusted life year (QALY) greater than £20,000. The exact value of this threshold depends on patients' previous treatment history. There was, again, considerable uncertainty in these results.

There were few data available to determine effectiveness of treatments for patients with generalised seizures. LTG and VPA showed similar health benefits when used as monotherapy. VPA was less costly and was likely to be cost-effective. The analysis indicated that TPM might be cost-effective when used as an adjunctive therapy, with an estimated incremental cost-effectiveness ratio of £34,500 compared with continuing current treatment alone.

### Conclusions

There was little good-quality evidence from clinical trials to support the use of newer monotherapy or adjunctive therapy AEDs over older drugs, or to support the use of one newer AED in preference to another. In general, data relating to clinical effectiveness, safety and tolerability failed to demonstrate consistent and statistically significant differences between the drugs. The exception was comparisons between newer adjunctive AEDs and placebo, where significant differences favoured newer AEDs.

However, trials often had relatively short-term treatment durations and often failed to limit recruitment to either partial or generalised onset seizures, thus limiting the applicability of the data.

Text removed due to reference to commercial-in-confidence data.

In addition, newer AEDs, used as monotherapy, may be cost-effective for the treatment of patients who have experienced adverse events with older AEDs, who have failed to respond to the older drugs, or where such drugs are contraindicated. The integrated economic analysis also suggested that newer AEDs used as adjunctive therapy may be cost-effective compared with the continuing current treatment alone given a threshold willingness to pay per QALY of about £20,000.

### Recommendations for research

There is a need for the following:

- more direct comparisons of newer versus newer and newer, versus older AEDs within clinical trials, considering different treatment sequences within both monotherapy and adjunctive therapy;
- good-quality trials with appropriate designs, ideally adopting the International League Against Epilepsy guidelines on the design of trials, particularly with regard to length of follow-up;
- trials specifically to recruit patients with either partial or generalised seizures;
- more good-quality trials to investigate effectiveness and cost-effectiveness in patients with generalised onset seizures;
- more good-quality trials to investigate effectiveness in specific populations of epilepsy patients;
- studies evaluating cognitive outcomes to use more stringent testing protocols and to adopt a more consistent approach in assessing outcomes;
- further research to assess quality of life within trials of epilepsy therapy, adopting any measure shown to have validity in the assessment of epilepsy patients, but also using preference-based measures of outcomes that generate appropriate utilities for cost-effectiveness analysis; future RCTs to be adequately reported according to CONSORT guidelines; and
- observational data to provide information on the use of AEDs in actual practice, including details of treatment sequences and doses.



# Chapter I

## Objectives and background

### Aim of the review

The aim of this review was to examine the clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults. For the purposes of this review newer antiepileptic drugs (AEDs) included gabapentin (GBP) (Neurontin<sup>®</sup>, Parke-Davis), lamotrigine (LTG) (Lamictal<sup>®</sup>, GlaxoSmithKline), levetiracetam (LEV) (Keppra<sup>®</sup>, UCB Pharma), oxcarbazepine (OXC) (Trileptal<sup>®</sup>, Novartis Pharmaceuticals), tiagabine (TGB) [Gabatril<sup>®</sup>, Cephalon (UK)], topiramate (TPM) (Topomax<sup>®</sup>, Janssen-Cilag) and vigabatrin (VGB) (Sabril<sup>®</sup>, Hoechst Marion Roussel). A concurrent review was performed by the West Midlands Health Technology Assessment Collaboration (WMHTAC), Birmingham, to examine the clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in children.

### Background

#### Description of underlying health problem

Epilepsy is a neurological disorder characterised by recurring seizures and is generally defined by two or more unprovoked seizures. The seizures are presumed to be the consequence of an abnormal and excessive discharge of a set of neurons in the brain. The condition comprises different seizure types and syndromes.<sup>3,4</sup> This has created complexities in establishing the incidence and prevalence<sup>5</sup> and prognosis of epilepsy.<sup>6</sup> A recent analysis of the prevalence of treated epilepsy based on a sample of 211 general practices [1.4 million individuals from the UK General Practice Research Database (GPRD)], estimated that the total number of patients being treated for epilepsy in England and Wales in 1998 was almost 400,000.<sup>3</sup> It is estimated that the risk of premature death among individuals with epilepsy is 2–3 times higher than in the general population.<sup>8</sup> Approximately 1000 people die in the UK each year from causes directly related to epilepsy. Around half of these are due to sudden unexpected death in epilepsy (SUDEP), for which an important risk factor is seizure frequency.<sup>9</sup> However, establishing the exact number and nature of epilepsy-related deaths from national data is difficult.<sup>9</sup>

In 1998, prevalences of 7.7 per 1000 men (age-standardised prevalence 7.4) and 7.6 per 1000 women (age-standardised prevalence 7.2) were reported. Prevalence increased over the age-span in both sexes, although was higher in men over 55 years old than in women of the same age group. Prevalence was <2 per 1000 in the under 5-years-old group increasing to over 4 per 1000 in 5–15 year olds. This increased to 15.1 per 1000 in men and to 11.0 per 1000 in women aged ≥ 85 years. This confirms earlier findings that incidence and prevalence is highest in the elderly population.<sup>10,11</sup> Overall, the UK GPRD figures are higher than those in other studies but fall within the broadly agreed estimate of 5–10 per 1000.<sup>5,12</sup> Variability in the reported incidence and prevalence of epilepsy has been attributed to differences in case ascertainment, the age groups studied and the location of studies.<sup>1</sup>

A relationship has been found between epilepsy prevalence and social deprivation, although the mechanism is still unclear.<sup>7,13</sup> The National Statistics Office report found a difference of 25% in prevalence in areas categorised as most deprived compared with least deprived.<sup>7</sup> In the least deprived category, the prevalence was 6.3 per 1000 in females and 6.0 per 1000 in males rising to 7.9 per 1000 in females and 8.0 per 1000 in males in the most deprived. This confirms findings from studies conducted in the USA, although there have been no previous similar studies in the UK.<sup>12</sup>

Epilepsy does not have one underlying cause. Attributable causes in adults include hippocampal sclerosis, cortical dysgenesis, vascular insults, head injuries and drug or alcohol abuse.<sup>12</sup>

Seizures are generally categorised into two main types: partial and generalised onset (*Table 1*). Partial onset seizures arise from a focal or local cortical lesion and may or may not lead to a loss of consciousness. Partial seizures may then spread to the whole brain causing a generalised seizure (secondary generalisation). Generalised onset seizures involve both sides of the brain and range from brief absence attacks to major convulsions.<sup>3</sup> The categorisation of seizure type can be difficult and this may be a factor in the variable estimates

**TABLE I** Classification of epileptic seizures<sup>3,12</sup>

I. Partial seizures	A. Simple (consciousness not impaired)	A1. With motor manifestations A2. With sensory manifestations A3. With autonomic manifestations A4. With psychic manifestations
	B. Complex	B1. With simple partial features (as above, A1–A4) at onset followed by impairment of consciousness B2. With impairment of consciousness at onset (both B1 and B2 may be followed by automatism)
	C. Secondarily generalised	C1. Simple partial seizure evolving to generalised seizure C2. Complex partial seizure evolving to generalised seizure C3. Simple partial seizure evolving to complex partial seizure evolving to generalised seizure
II. Generalised seizures	A. Absence seizures (may be typical or atypical) B. Myoclonic seizures C. Clonic seizures D. Tonic seizures E. Tonic–clonic seizures F. Atonic seizures	
III. Unclassified seizures		

of the frequency of the different seizure types.<sup>5</sup> Partial seizures are the most common seizure type experienced. In the National General Practice Study of Epilepsy, 52% of patients had partial seizures (with or without secondary generalisation), 39% had generalised seizures and 9% of seizures were unclassifiable.<sup>10</sup> Even higher frequencies of partial seizures (72%) have been reported in other studies.<sup>14</sup>

Onset of epilepsy can occur at any age, but is most common during childhood or older age. Not all patients with seizures develop the chronic condition; some children have seizures that do not progress into adulthood and some adults may experience remission. A prospective study found that, after 9 years, 71% of newly diagnosed patients had experienced a 5-year remission. When patients with acute symptomatic seizures and those who had experienced only one seizure were excluded, 60% achieved a 5-year remission.<sup>6</sup> However, despite receiving medical therapy, up to one third of patients experience persistent seizures or refractory epilepsy.<sup>15,16</sup>

When considering the impact of epilepsy on the life of an individual, the social and psychological consequences can be as important as the seizures experienced. The Clinical Standards Advisory Group (CSAG) has highlighted how epilepsy may impact on many aspects of individuals' lives such as employment prospects, personal development,

mental health and personal relationships.<sup>12</sup> The relationship between the physical, psychological and socio-economic aspects of epilepsy is likely to be a complex one. Physical dimensions such as seizure frequency and seizure severity and the side-effects of AEDs are likely to have different significance for different patient groups.<sup>17</sup> For example, it is suggested that seizure severity may have a greater impact on psychosocial well-being than seizure frequency in individuals experiencing refractory epilepsy.<sup>17</sup>

### Current service provision

There is a professional consensus that neurologists should take the lead role in the treatment of adult epilepsy.<sup>12</sup> Other healthcare professionals also play an important role. GPs are involved in the monitoring, auditing and surveillance of epilepsy. Other specialists involved in management include general physicians, geriatricians and psychiatrists involved in the care of people with learning disabilities who have epilepsy.<sup>12</sup> The aim of treatment is to reduce seizure frequency and preferably to enable individuals to be seizure free. In a broader sense, good treatment will also improve psychosocial outcomes.<sup>12</sup> AEDs are the primary route through which seizure reduction is achieved. No drug treatment and neurosurgery are other options. Older AEDs include carbamazepine (CBZ), benzodiazepines, acetazolamide (AZM), ethosuximide, phenobarbital (PB) and other barbiturates,

**TABLE 2** Mode of action and recommended dose of newer AEDs in adults<sup>20,21</sup>

Drug	Mode of action	Recommended dose
GBP	Structurally related to the neurotransmitter GABA. The exact mode of action remains unclear, but appears to differ from mechanisms used by other drugs	0.9–1.2 g/day Maximum dose 2.4 g/day
LTG	Use-dependent blocker of voltage-gated sodium channels and inhibitor of glutamate release	Monotherapy 100–200 mg/day (up to 500 mg/day) Adjunctive therapy with VPA 100–200 mg/day Adjunctive therapy without VPA 200–400 mg/day (up to 700 mg/day)
LEV	Pyrrolidone derivative. Mechanism of action is unknown but appears to be unrelated to existing mechanisms used by other drugs	3 g/day
OXC	Thought to block voltage-sensitive sodium channels. In addition increases potassium conductance and modulation of high-voltage activated calcium channels, which may also have a role in controlling seizures	0.6–2.4 g/day
TGB	Inhibits the uptake of the neurotransmitter GABA, which results in an increase in GABA-mediated inhibition within the brain	With enzyme-inducing drugs 30–45 mg/day Without enzyme-inducing drugs 15–30 mg/day
TPM	Sulphamate-substituted monosaccharide. Mode of action probably involves the following: blockade of voltage-sensitive sodium channels; enhancement of GABA activity; antagonism of certain subtypes of glutamate receptor; and inhibition of some isoenzymes of carbonic anhydrase	200–400 mg/day Maximum 800 mg/day
VGB	Selective irreversible inhibitor of GABA transaminase (enzyme responsible for the breakdown of the neurotransmitter GABA). Increases levels of GABA-mediated inhibition within the brain	2–3 g/day Maximum 3 g/day

GABA,  $\gamma$ -aminobutyric acid.

phenytoin (PHT) and valproate (VPA). Each has a different profile of action, set of indications and potential side-effects.<sup>18</sup>

The choice of drug depends upon the seizure type experienced by a particular patient and likely tolerability of potential side-effects.<sup>18</sup> Drugs are administered as monotherapy or as adjunctive therapy if monotherapy is not effective. The CSAG survey found that 70% of those with mild epilepsy (in a community and hospital sample), 46% of those with severe epilepsy in the community sample and 32% of those in the hospital sample were on monotherapy.<sup>12</sup> In a general practice sample, 65% were receiving monotherapy.<sup>19</sup> Three of the most commonly used older AEDs are CBZ, VPA and PHT.<sup>12,19</sup> There is evidence of a slight decrease in the use of older AEDs between 1994 and 1998.<sup>7</sup> In males, the decrease was from 99.8 to 98.1% and in females from 99.4 to 96.8%. Those over 65 years old were most likely to be prescribed older AEDs. There

was little variation in prescribing patterns across NHS Regional Office areas.<sup>7</sup>

### Description of interventions

Since 1989, several newer AEDs have been licensed which are promoted as being as effective as the older drugs but with fewer side-effects.<sup>7</sup> For the purposes of this review the newer AEDs under investigation are GBP, LTG, LEV, OXC, TGB, TPM and VGB (see 'Aim of the review', p. 1).

### Mode of action

The newer AEDs are most commonly used either as second-line monotherapy or as adjunctive therapy to conventional drugs. The drugs have a range of modes of action as outlined in *Table 2*.

Both older and newer drugs in some cases interact with each other and with other drugs, which is an important consideration in adjunctive therapy. For this reason, adjunctive therapy should preferably be used only when monotherapy with several



**TABLE 3** Summary of interactions between AEDs<sup>20,21</sup>

Drug	Interactions
CBZ	Often decreases plasma concentration of clobazam, clonazepam, LTG, an active metabolite of OXC and of PHT (but may also raise PHT concentration), TGB, TPM and VPA
GBP	No reported interactions
LTG	Sometimes increases plasma concentration of an active metabolite of CBZ (but evidence is conflicting)
LEV	No reported interactions
OXC	Sometimes decreases plasma concentration of CBZ (but may raise concentration of active metabolite of CBZ). Sometimes increases plasma concentration of PHT. Often increases plasma concentration of PB
PHT	Often decreases plasma concentration of clonazepam, CBZ, LTG, an active metabolite of OXC, and of TGB, TPM, and VPA. Often increases plasma concentration of PB. Sometimes lowers plasma concentration of ethosuximide and PRM (by increasing conversion to PB)
TGB	No reported interactions
TPM	Sometimes increases plasma concentration of PHT
VGB	Often reduces plasma concentration of PHT. Sometimes decreases plasma concentration of PB, and PRM
VPA	Sometimes lowers plasma concentration of active metabolite of OXC. Often increases plasma concentration of active metabolite of CBZ and of LTG, PRM, PB and PHT (but may also lower). Sometimes increases plasma concentration of ethosuximide and PRM (and tendency for significant increase in PB level)

CZP, clonazepam; PRM, primidone.

alternative drugs has proved ineffective. These interactions are often complex and may enhance the toxicity of the drugs without resulting in a corresponding increase in antiepileptic effect. The most common interactions are usually caused by hepatic enzyme induction or hepatic enzyme inhibition. These interactions are highly variable and unpredictable. Plasma monitoring is therefore often recommended when using adjunctive therapy. *Table 3* summarises important interactions between AEDs.

#### Current indications

Most of the newer drugs are licensed for adjunctive therapy only (GBP, LEV, TGB, TPM and VGB). LTG and OXC are licensed for monotherapy or adjunctive therapy (see *Table 4*). Both LTG and TPM are licensed for the widest range of seizure types; partial onset seizures (POs), primary onset and secondarily generalised tonic-clonic (SGTCs) seizures and seizures associated with Lennox–Gestaut syndrome (see *Table 4*). All of the other newer drugs are licensed for the treatment of partial seizures with or without secondary generalisation (see *Table 4*). All the drugs are indicated for second-line treatment, but only LTG and OXC are licensed for first-line therapy in newly diagnosed epilepsy. All the drugs can be used as second-line treatment where older AEDs have been unsuccessful in controlling epilepsy. Owing to its associated toxicities VGB is

often considered as a drug of last resort for the treatment of refractory partial and secondary generalised seizures that have not responded to other AEDs.

#### Warnings or cautions

*Table 5* details the current warnings or cautions and side-effects for the newer drugs.<sup>21</sup> The adverse effects of AEDs as a drug group are dose-related, mild, transient central nervous system effects.<sup>22</sup> For adverse effects that occur with all the drugs, frequency and severity vary across drugs. For example, sedation is more common with barbiturates and benzodiazepines.<sup>22</sup> Other adverse effects are related to specific properties shared by only certain drugs. For example, reduced efficacy of oral contraceptives can occur with inducers of enzymes that metabolise these steroids.<sup>22</sup>

In particular, caution is recommended when treating specific populations of patients. When treating elderly patients, caution is required with GBP (may require reduced dose), LTG, OXC and VGB (closely monitor neurological function). Antiepileptic treatment during pregnancy and breastfeeding is also problematic. During pregnancy, total plasma concentrations of antiepileptics (particularly PHT) may fall, especially in the later stages of pregnancy, but free plasma concentrations may remain the same (or even rise). AEDs also pose a risk to the unborn

**TABLE 4** Licensed indications for the newer AEDs<sup>21</sup>

Drug name	Licensed indication						
	Monotherapy	Adjunctive therapy	Newly diagnosed	Partial onset	Generalised onset	Adult	Child
GBP	No	Yes	No	Yes	No	Yes	Yes >6 y only
LTG	Yes	Yes	Yes	Yes	Yes	Yes	Yes <12 y mono not recommended
LEV	No	Yes	No	Yes	No	Yes	No
OXC	Yes	Yes	Yes	Yes	No	Yes	Yes >6 y only
TGB	No	Yes	No	Yes	No	Yes	Yes >12 y only
TPM	No	Yes	No	Yes	Yes	Yes	Yes >2 y only
VGB	No <sup>a</sup>	Yes	No	Yes	No	Yes	Yes

<sup>a</sup> VGB is licensed for use as monotherapy in West's syndrome.

**TABLE 5** Summary of warnings, cautions and side-effects of newer AEDs

Drug	Warnings or cautions <sup>21</sup>	Side-effects <sup>21</sup>
GBP	Avoid sudden withdrawal (taper off over at least 1 week); history of psychotic illness, elderly (may need to reduce dose), renal impairment, diabetes mellitus, false-positive readings with some urinary protein tests; pregnancy and breastfeeding	Somnolence, dizziness, ataxia, fatigue; also nystagmus, tremor, diplopia, amblyopia; pharyngitis, dysarthria, weight gain, dyspepsia, amnesia, nervousness, coughing, asthenia, paraesthesia, arthralgia, purpura, leucopenia; rhinitis, myalgia, headache, rarely pancreatitis, altered liver function tests and Stevens–Johnson syndrome; nausea and vomiting reported
LTG	Closely monitor (including hepatic, renal and clotting parameters) and consider withdrawal if rash, fever, influenza-like symptoms, drowsiness or worsening of seizure control develops; avoid abrupt withdrawal (taper off over 2 weeks or longer) unless serious skin reaction occurs; hepatic and renal impairment; elderly; pregnancy and breastfeeding. The Committee on Safety of Medicines (CSM) has advised prescribers to be alert for symptoms and signs suggestive of bone marrow failure such as anaemia, bruising or infection. Aplastic anaemia, bone marrow depression and pancytopenia have been associated rarely with LTG	Commonly rashes, fever, malaise, influenza-like symptoms, drowsiness and rarely hepatic dysfunction, lymphadenopathy, leucopenia and thrombocytopenia reported in conjunction with rash; angioedema and photosensitivity; diplopia, blurred vision, conjunctivitis, dizziness, drowsiness, insomnia, headache, ataxia, tiredness, gastrointestinal disturbances (including vomiting), irritability, aggression, tremor, agitation, confusion; headache, nausea, dizziness, diplopia and ataxia in patients also taking CBZ usually resolve when dose of either drug is reduced. Serious skin reactions have occurred and have been associated with concomitant use of VPA, initial LTG dose higher than recommended and more rapid dose escalation than recommended
LEV	Hepatic impairment; renal impairment; pregnancy and breastfeeding; avoid sudden withdrawal	Drowsiness, asthenia, dizziness; less commonly, anorexia, diarrhoea, dyspepsia, nausea, amnesia, ataxia, depression, emotional lability, aggression, insomnia, nervousness, tremor, vertigo, headache, diplopia, rash; also respiratory tract infection

*continued*

**TABLE 5** Summary of warnings, cautions and side-effects of newer AEDs (cont'd)

Drug	Warnings or cautions <sup>21</sup>	Side-effects <sup>21</sup>
OXC	Hypersensitivity to CBZ; avoid abrupt withdrawal; hepatic and renal impairment; pregnancy and breastfeeding; elderly, hyponatraemia (monitor plasma sodium concentration in patients at risk), heart failure (monitor body weight), cardiac conduction disorders	Nausea, vomiting, constipation, diarrhoea, abdominal pain, dizziness, headache, drowsiness, agitation, amnesia, asthenia, ataxia, confusion, impaired concentration, depression, tremor, hyponatraemia, acne, alopecia, rash, vertigo, nystagmus, visual disorders including diplopia; less commonly urticaria, leucopenia; rarely arrhythmias, Stevens–Johnson syndrome, systemic lupus erythematous, hepatitis, thrombocytopenia, angioedema, hypersensitivity reactions
TGB	Hepatic impairment; avoid abrupt withdrawal; may impair performance of skilled tasks (e.g. driving)	Diarrhoea, dizziness, tiredness, nervousness, tremor, concentration difficulties, emotional lability, speech impairment; rarely confusion, depression, drowsiness, psychosis; leucopenia reported
TPM	Avoid abrupt withdrawal; ensure adequate hydration (especially if predisposition to nephrolithiasis); pregnancy; hepatic impairment; renal impairment. Has been associated with acute myopia with secondary angle closure glaucoma, typically within 1 month of starting treatment. Choroidal effusions resulting in anterior displacement of the iris and lens have also been reported. If raised intra-ocular pressure occurs, the advice of the Committee on Safety of Medicines is to seek specialist ophthalmological advice, reduce intra-ocular pressure and stop TPM as soon as is feasible	Abdominal pain, nausea, anorexia, weight loss; impaired concentration and memory, confusion, impaired speech, emotional lability with mood disorders and depression, altered behaviour, ataxia, abnormal gait, paraesthesia, dizziness, drowsiness, fatigue, asthenia, visual disturbances, diplopia, nystagmus, acute myopia with angle closure glaucoma, taste disorder, hypersalivation, also psychotic symptoms, aggression, cognitive problems, leucopenia
VGB	Renal impairment; elderly (closely monitor neurological function); avoid sudden withdrawal (taper over 2–4 weeks); history of psychosis, depression or behavioural problems; pregnancy and breastfeeding; absence seizures may be exacerbated. Is associated with visual field defects with onset varying from 1 month to several years after starting. In most cases, visual field defects have persisted despite discontinuation. Visual testing is advised before treatment and at 6-month intervals. Patients should be warned to report any new visual problems that develop and those with symptoms should be referred for an urgent ophthalmological opinion	Drowsiness (rarely causes marked sedation, stupor and confusion with non-specific slow wave EEG), fatigue, visual field defects, dizziness, nervousness, irritability, behavioural effects such as excitation and agitation especially in children; depression, abnormal thinking, headache, nystagmus, ataxia, tremor, paraesthesia, impaired concentration; less commonly confusion, aggression, psychosis, mania, memory disturbance, visual disturbance (e.g. diplopia); also weight gain, oedema, gastrointestinal disturbances, alopecia, rash; less commonly urticaria, occasional increase in seizure frequency (especially if myoclonic), decrease in liver enzymes, slight increase in haemoglobin; photophobia and retinal disorders (e.g. peripheral retinal atrophy); optic neuritis, optic atrophy also reported

foetus, although this risk is reduced if treatment is limited to monotherapy. The associated teratogenicity results in an increased risk of neural tube and other defects, particularly when using CBZ, OXC, PHT and VPA. It is recommended that any woman taking AEDs who may become pregnant should be fully informed of the possible consequences. If women wish to become pregnant they should be referred for specialist advice and if they become pregnant whilst undergoing treatment with AEDs, they should be counselled and offered antenatal screening ( $\alpha$ -fetoprotein

measurement and a second trimester ultrasound scan) in order to assess the risk to the foetus.

### Costs

Over recent years, there has been an increase in prescriptions for newer AEDs in the treatment of epilepsy.<sup>7</sup> Between 1994 and 1998 there was an increase from 6.8 to 11.9% of men being prescribed the newer drugs and from 7.5 to 13.7% of women. The prescribing of newer AEDs was highest in the 5–15-year-old group for both sexes and lowest in men aged 75–84 years and women

aged  $\geq 85$  years. The threefold increase in the cost of prescribing AEDs in the community has been largely attributed to the increased prescribing of newer AEDs, which are more expensive.<sup>7</sup> Of the four drugs that accounted for the highest percentage of these costs, GBP and LTG accounted for 44% of the total cost and 9% of the

total prescription volume, whereas CBZ and VPA accounted for 35% of the total cost and 56% of the total volume.<sup>7</sup> These data are based on prescribing analyses and cost (PACT) data, which also include prescriptions for conditions other than epilepsy, e.g. GBP is primarily licensed for the treatment of neuropathic pain.



# Chapter 2

## Methods

### Assessment of clinical effectiveness

#### Search strategy

The sources below were searched for studies relating to the clinical effectiveness of the newer AEDs, GBP, LTG, LEV, OXC, TGB, TPM and VGB. This first set of literature searches were designed to retrieve systematic reviews and randomised controlled trials (RCTs) only. However, some databases cannot be reliably restricted by study type and in these cases the search was not limited by study design, and the results of the searches were screened by hand. A range of free text terms and subject headings were used as appropriate. Further details of the search strategies are reported in Appendix 2.

#### CRD internal administration databases (searched 20 March 2002)

- Database of Abstracts of Reviews of Effects (DARE)
- Health Technology Assessment Database (HTA)

#### Internet resources and databases (searched 2 April 2002)

- Controlled Clinical Trials  
<http://controlled-trials.com>
- Health Evidence Bulletins Wales  
<http://www.uwcm.ac.uk/uwcm/1b/pep>
- Health Services Technology Assessment Text (HSTAT)  
<http://text.nlm.nih.gov/>
- Index to Scientific and Technical Proceedings (ISTP)  
<http://wos.mimas.ac.uk/>
- National Coordinating Centre for Health Technology Assessment (NCCHTA)  
<http://www.hta.nhsweb.nhs.uk>
- National Guideline Clearinghouse  
<http://www.ahcpr.gov/clinic/assess.htm>
- National Institute for Clinical Excellence (NICE) (published appraisals)  
<http://www.nice.org.uk/nice-web/>
- Science Citation Index (SCI) (1981 onwards)  
<http://wos.mimas.ac.uk/>
- Scottish Intercollegiate Guidelines Network (SIGN) Guidelines  
<http://www.sign.ac.uk/>
- Turning Research Into Practice (TRIP) Index  
<http://www.ceres.uwcm.ac.uk/framset.cfm?section=trip>

#### CD-ROM resources

- Cochrane Controlled Trials Register (CCTR) (2002: Issue 1) (searched: 2 April 2002)
- Cochrane Database of Systematic Reviews (CDSR) (2002: Issue 1) (searched: 2 April 2002)
- EMBASE (1980–February 2002) (searched: 27 March 2002)
- MEDLINE (1966–March 2002) (searched: 26 March 2002)
- National Research Register (NRR) (2002: Issue 1) (searched: 2 April 2002)
- PREMEDLINE (up to 22 March 2002) (searched: 26 March 2002)
- PsycINFO (1967–week 3, July 2002) (searched: 3 September 2002)

#### Online resources (searched 8 April 2002)

- Conference Papers Index (CPI) (1973 onwards)

#### Paper resources

- *Clinical evidence: a compendium of the best available evidence for effective health care*. Issue 6, 2001. London: BMJ Publishing Group.

No date or language restrictions were placed on any of the literature searches. Owing to financial and logistical constraints, non-English publications were not included in the review. However, not limiting the literature searches by language enabled an estimate of the size of the non-English literature to be obtained. In addition, search strategies were not limited by age although the review only included data relating to adults. This was due to the fact that many records do not mention the appropriate patient group within the title, abstract or indexing.

The bibliographies of all included studies were reviewed in order to identify any further relevant studies. A list of studies found from bibliographies and industry submissions, but not meeting the inclusion criteria for this review, are listed in Appendix 3.

#### Inclusion and exclusion criteria

Two reviewers independently screened all titles and abstracts in order to determine relevance. Full paper manuscripts of potentially relevant titles and abstracts were obtained where possible and the eligibility of the study for inclusion in the

review was assessed by two authors independently, according to the four criteria outlined below. Any discrepancies were resolved by consensus and, if necessary, a third reviewer was consulted. Studies that did not fulfil all of the criteria were excluded. Owing to time and financial constraints, only studies reported in English were included in the analysis section of this review. Eligible studies in other languages were identified but only brief details tabulated.

### Study design

The following study designs were included in the review:

- Single-blinded, double-blinded or unblinded RCTs using a parallel or crossover design, designed to assess the equivalence, non-inferiority or superiority of comparators
- Systematic reviews meeting the criteria for inclusion in DARE (<http://nhscrd.york.ac.uk/darehp.htm>)

### Participants

Studies recruiting adults (i.e. individuals aged 18 years or over) with either newly diagnosed or refractory epilepsy were included. Seizure types included POS (with or without secondary generalisation) and generalised onset seizures. Trials enrolling only patients with single seizures, status epilepticus, seizures following neurosurgery or head injury and trigeminal neuralgia were excluded. Studies that enrolled participants with excluded indications were evaluated to determine whether (1) the study results reported data for the excluded indications groups of participants separately or (2) the number of excluded indications participants was small. In either case the relevant data were included in this review.

Studies with mixed age groups were identified during the inclusion/exclusion process. The data reported in these studies were discussed and divided accordingly in coordination with the Birmingham review team responsible for reviewing the evidence for the treatment of children. The discussion determined whether (1) the study results reported data for the different age groups of participants separately or (2) the numbers of younger or older participants were small. Data were only extracted if relevant to the age group under consideration.

### Interventions

Newer AEDs (GBP, LTG, LEV, OXC, TGE, TPM and VGB) used either as monotherapy and/or adjunctive therapy were included. Comparators included older AEDs, newer AEDs or placebo.

Trials in which epilepsy surgery was the comparator were excluded. Older AEDs included AZM, benzodiazepines, CBZ, ethosuximide, PB and other barbiturates, PHT and VPA.

### Outcomes

A wide range of outcomes were extracted from the studies, including:

- Time to withdrawal after randomisation.
- Time to first, second or other seizure after randomisation (time to first seizure after randomisation allowed the determination of the proportion of patients at different time points who remained seizure free).
- Time to achieving remission (e.g. at 6 months, 1 year or 2 years).
- Change in seizure severity.
- Change in seizure frequency.
- Proportion of responders (response defined as a  $\geq 50\%$  reduction in seizure frequency).
- Change in seizure-free interval.
- Change in seizure duration.
- Change in seizure pattern.
- Change in functional capacity.
- Patient-related quality of life (QoL).
- Cognitive function.
- Withdrawal from therapy due to one or more adverse events (AEs)
- Incidence, prevalence and severity of adverse events at different time points.

However, the analysis focused on the following outcomes

- proportion of seizure-free participants
- proportion of participants experiencing at least a 50% reduction in seizure frequency (i.e. responders)
- time to exit/withdrawal
- time to first seizure
- all QoL outcomes
- all outcomes relating to cognitive function
- safety (incidence of adverse events, mortality rate) and tolerability (incidence of withdrawals).

Appendix 4 lists the definitions for QoL outcomes included in the review and Appendix 5 those for cognitive outcomes.

### Data extraction strategy

Data relating to study design, participants, interventions and outcomes were extracted in a standardised manner into an Access database by one reviewer and independently checked for accuracy by a second reviewer. Details of the types of data extracted are listed in Appendix 6.

Attempts were made where possible to contact authors for missing data. Data from studies with multiple publications were extracted and reported as a single study. Where studies reported cognitive/QoL data and seizure frequency outcomes in separate publications, both publications were considered.

## Quality assessment strategy

### Systematic reviews

To be included in the review of effectiveness, as previously mentioned, all systematic reviews were required to meet the criteria necessary for inclusion in DARE. Refer to Appendix 7 for the list of criteria used to assess the quality of systematic reviews. These criteria assess the quality of the review and so any reviews meeting the inclusion criteria were judged to be of reasonable quality. Assessment of the criteria was performed by one reviewer and independently checked by a second reviewer. Disagreements were resolved through consensus and, if necessary, a third reviewer was consulted.

### Randomised controlled trials

The quality of the individual RCTs was assessed using criteria adapted from those used in the publication *Undertaking systematic reviews of research on effectiveness: CRD's guidance for carrying out or commissioning reviews*.<sup>23</sup> In addition, quality issues specifically pertaining to crossover<sup>24,25</sup> and equivalence trials<sup>26,27</sup> were applied where appropriate. Refer to Appendix 8 for the list of criteria used to assess the quality of the individual RCTs.

In each case, the quality of the trials was assessed by one reviewer and independently checked by a second reviewer. Disagreements were resolved through consensus and, if necessary, a third reviewer was consulted.

### Handling company submissions

Data submitted by drug manufacturers by the deadline of 6 September 2002 were included. Submissions were checked for unpublished studies and any additional relevant information in relation to already published studies. Unpublished studies were assessed according to the inclusion/exclusion criteria above. Data extraction and quality assessment were carried out as for published studies. No submissions were received from the manufacturers of GBP or VGB.

### Data analysis

#### Systematic reviews

Data identified from systematic reviews are summarised in table form and briefly discussed in

relation to the requirements and findings of this current review.

### Randomised controlled trials

Data from the RCTs were presented in tables and discussed in a narrative. Effect sizes [relative risks (RRs) or hazard ratios (HRs) with 95% confidence intervals (CIs)] were reported where appropriate. RRs and HRs were considered to be statistically significant if the range of the 95% CIs did not include 1. Data were only pooled statistically (fixed-effects model) if studies were considered to be clinically and statistically ( $Q$ -statistic) homogeneous. Owing to the low power of the  $Q$ -statistic where numbers of studies are small (i.e.  $<20$ ), a  $p$ -value of 0.10 was used as a threshold for statistical significance. Studies were only pooled using the fixed-effects model if the  $Q$ -statistic was less than the number of degrees of freedom (df) and the associated  $p$ -value  $>0.10$ .

## Assessment of serious, rare and long-term adverse events studies

### Search strategy

Literature searches were carried out to identify serious, rare and long-term adverse events not likely to have been found by the clinical effectiveness RCT search strategies. The searches aimed to find studies of adverse effects of the seven drugs irrespective of the condition treated. Therefore, no epilepsy terms were added. It is well reported in the literature that conducting electronic database searching for adverse events is problematic.<sup>28-30</sup> The procedure for tracing papers of adverse events is not as well established as in other areas of research such as RCTs and systematic reviews. A broad experimental search strategy was therefore adopted using textwords and thesaurus terms for each drug limited to the appropriate subheadings and known serious or rare adverse effects as both textwords and thesaurus terms. Adverse effects deemed serious fell into one or more of the following categories: death, life threatening, hospitalisation, disability (including vision), congenital abnormality, cancer and overdose.

Databases were searched from the date of inception to the most recent date available.

### Internet resources and databases (all searched 9 September 2002)

- ABPI electronic Medicines Compendium (eMC) (Version 2)  
<http://emc.vhn.net/>



- Controlled Clinical Trials  
<http://controlled-trials.com>
- Developmental and Reproductive Toxicology (DART/ETIC)  
<http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?DARTETIC>
- Drug Checker – Interactions Search  
<http://www.drugs.com/data/channel/md/drkoop.cfm?int=1://>
- Drug facts and comparisons  
<http://www.drugfacts.com>
- Emedicine  
<http://www.emedicine.com/>
- General Practice Notebook  
<http://www.gpnotebook.co.uk>
- Health Evidence Bulletins of Wales  
<http://hebw.uwcm.ac.uk/>
- HSTAT  
<http://text.nlm.nih.gov/>
- ISTP (1990 onwards)  
<http://wos.mimas.ac.uk/>
- The Merck Manual  
<http://www.merck.com>
- NCHTA  
<http://www.hta.nhsweb.nhs.uk>
- National Guideline Clearinghouse  
<http://www.ahcpr.gov/clinic/assess.htm>
- NICE (published appraisals)  
<http://www.nice.org.uk/nice-web/>
- SCI (1981 – onwards)  
<http://wos.mimas.ac.uk/>
- SIGN Guidelines  
<http://www.sign.ac.uk/>
- TOXLINE – Toxicology Bibliographic Information (1965 – present)  
<http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?TOXLINE>
- TRIP Index  
<http://www.ceres.uwcm.ac.uk/framset.cfm?section=trip>

#### **CD-ROM resources (searched 10 September 2002)**

- EMBASE (1980 – week 36, 2002)
- MEDLINE (1996 – week 4, August 2002)

#### **Paper resources (searched: 4 September 2002)**

- *ABPI medicines compendium*. Epsom: Datapharm Communications; 2002.
- *AHFS First professional edition version 2.71*. Bethesda, MD: American Society of Health-System Pharmacists; 2002.
- *British National Formulary (BNF)*. London: British Medical Association/Royal Pharmaceutical Society of Great Britain. Issue 43 March 2002.

- Dukes MNG, Aronson JK, editors. *Meylers's side effects of drugs: an encyclopedia of adverse reaction and interactions*. 14th ed. Oxford: Elsevier; 2000.
- Sweetman SC, editor. *Martindale: the complete drug reference*. 33rd ed. London: Pharmaceutical Press; 2002.

Further details of the full search strategy are reported in Appendix 2.

#### **Inclusion and exclusion criteria**

In this review, non-randomised experimental studies and observational studies were included to enhance retrieval of information about serious, rare and long-term AEs. Reporting of safety data in RCTs is largely inadequate<sup>31–34</sup> and most systematic reviews of RCTs only include safety data as reported in the primary studies. Furthermore, RCTs are often too small and of insufficient duration to detect rare and delayed AEs. Consequently, evaluation of the safety of therapeutic interventions needs to go beyond RCTs.

Two reviewers independently screened all titles and abstracts against predefined inclusion criteria. Differences were resolved by discussion and full papers were obtained for all studies potentially eligible for inclusion. Two reviewers then independently applied the inclusion criteria to all full papers and differences were again resolved by discussion.

Three categories of studies were included:

- Studies that investigated the effects of newer AEDs, including safety and/or tolerability. Study designs eligible for inclusion were uncontrolled trials, open-label extension phases of controlled trials, cohort studies (controlled or uncontrolled) and case-control studies. These studies, RCTs of newer AEDs in diseases other than epilepsy, and RCTs of dose or titration comparisons in epilepsy, were included only if more than 300 participants were exposed to the newer AED or if follow-up exceeded 6 months. These limits were based on the duration and size of effectiveness RCTs to identify longer and larger studies. Combination therapies and dose comparisons were included within the aforementioned parameters. Case series, case reports, cross-sectional studies, audits and surveys were excluded.
- Studies that investigated a specific adverse effect [such as visual field defects (VFDs)]. Study designs eligible for inclusion were as described above but without the restriction on study size or duration.

- Reports of prescription event monitoring (PEM) studies and prospective postmarketing surveillance (PMS) studies. Spontaneous case reports of suspected adverse drug reactions such as those collated by the Medicines Control Agency and other bodies were not included.

### Data extraction strategy

One reviewer extracted data using a standardised data extraction form (see Appendix 9). Adverse effects data were extracted in detail only for serious, rare and long-term effects and for withdrawal or discontinuation of treatment due to adverse effects. Published sources were used for guidance on the nature of serious and rare AEs associated with the newer AEDs.<sup>22,35,36</sup> Serious included death, life threatening, hospitalisation, disability, congenital abnormality, cancer and overdose. Both serious and rare included any effect defined as such in the study reports. Long-term was defined as longer than 6 months.

PEM and prospective PMS studies were data extracted directly into summary tables by one reviewer.

### Quality assessment strategy

Data on methodological quality were extracted by one reviewer using standardised data extraction forms. Cohort and case-control studies were assessed using criteria derived from Centre for Reviews and Dissemination (CRD) Report 4 (see Appendix 10).<sup>23</sup> RCTs, non-randomised and uncontrolled studies were assessed against the criteria used in the review of effectiveness (see Appendix 8). As there is no tool to assess the internal validity of open-label extension phase or follow-up studies, three appraisal questions taken from the tools used to assess other study designs were applied. These were chosen as useful indicators of selection bias (one aspect of internal validity), and how appropriate the dose of AED and the length of follow-up were (aspects of external validity). PMS and PEM studies were not quality assessed owing to the lack of an appropriate tool; the methods used in those studies are summarised in the included studies tables.

### Handling company submissions

Data submitted by drug manufacturers by the deadline of 6th September 2002 were searched for relevant studies according to the aforementioned inclusion criteria. No submissions were received from the manufacturers of GBP or VGB.

### Data analysis

Tables describing the included studies and a narrative synthesis were presented for each drug.

## Assessment of cost-effectiveness

### Search strategy

Those databases restricted by study design in the clinical effectiveness searches were searched again using a search strategy designed to retrieve cost-effectiveness studies or economic models. Two specialist databases were also searched, the NHS Economic Evaluation Database (NHS EED) and the Health Economic Evaluations Database (HEED). No economic filter was necessary for these databases.

### CRD internal administration databases (searched 20 March 2002)

- NHS EED

### CD-ROM resources

- EMBASE (1980–February 2002) (searched: 27 March 2002)
- HEED (March 2002) (searched: 28 March 2002)
- MEDLINE (1966–March 2002) (searched: 27 March 2002)
- PREMEDLINE (up to 22 March 2002) (searched: 27 March 2002)

Further details of the search strategies used are reported in Appendix 2.

### Inclusion and exclusion criteria

Three reviewers independently screened all of the titles and abstracts of the retrieved references according to following inclusion criteria. Any disagreements were resolved by consensus.

### Study design

Only full economic evaluations were included. Types of designs included:

- Cost-effectiveness analyses (CEAs) including cost-minimisation analyses (CMAs) and cost-consequences analyses
- Cost-benefit analyses (CBAs)
- Cost-utility analyses (CUAs)

### Participants

Studies recruiting adults (i.e. individuals aged  $\geq 18$  years) with either newly diagnosed or refractory epilepsy were included. Seizure types included both POS (with or without secondary generalisation) and generalised onset. Trials

enrolling only patients with single seizures, status epilepticus, seizures following neurosurgery or head injury and trigeminal neuralgia were excluded. Studies that enrolled participants with both included and excluded indications were evaluated to determine whether (1) data for included and excluded participants were reported separately or (2) the number of participants with excluded indications was small. Any relevant data were included.

### **Interventions**

Newer AEDs (GBP, LTG, LEV, OXC, TGB, TPM and VGB) used either as monotherapy and/or adjunctive therapy were included. Comparators included older AEDs, newer AEDs or placebo. Trials where epilepsy surgery was the comparator were excluded. Older AEDs included AZM, benzodiazepines, CBZ, ethosuximide, PB and other barbiturates, PHT and VPA.

### **Outcomes**

In order to be included in the review of cost-effectiveness, evaluations had to report both costs and clinical effectiveness.

### **Data extraction strategy**

Data from each individual study were extracted into an Access database by one reviewer and checked by a second reviewer. Details of the categories of data extracted are presented in Appendix 11.

### **Quality assessment strategy**

The quality of each published economic evaluation was assessed independently by two reviewers using the criteria listed in Appendix 12. Appendix 13 lists the economic model with any associated quality issues. In both cases, disagreements were resolved through discussion with a third reviewer if necessary.

### **Handling company submissions**

Data submitted by drug manufacturers by the deadline of 6 September 2002 were included. Submissions were checked for unpublished economic evaluations and models. Such evaluations were subjected to similar processes (carried out by reviewers DE and NH) of study selection, data extraction and data analysis as reported for published evaluations.

### **Data analysis**

Summary tables of the data within the included economic evaluations are presented along with a critical appraisal of the design and findings of each of the evaluations. In addition, an overview and comparison of the models reported within the company submissions is presented, in order to assess the suitability of the evaluations for use in an integrated economic evaluation of all the newer AEDs.

Both the clinical and cost-effectiveness sections of the report employ meta-analysis techniques to summarise the trial evidence in order to aid decision-making. The clinical effectiveness analysis employed traditional meta-analytic techniques. The pooling of data in the clinical effectiveness section was only performed where the data were found to be statistically homogeneous. The CEA required a measure of the absolute response rate for each treatment under consideration. A systematic analysis using mixed treatment comparisons was undertaken in order to estimate these measures. The heterogeneity between studies was to some extent incorporated in the measures of uncertainty surrounding the mean response rates.

### **Integrated economic evaluation**

In order to determine the cost-effectiveness of the newer AEDs, all of the relevant available treatments must be directly compared. As described in the section 'Analysis' (p. 22), none of the published evaluations or industry submissions represented a direct comparison of all of the newer and older AEDs specified in the scope for this review. Therefore, a decision analytic model was developed which incorporated all of the available information on the cost-effectiveness of the various newer and older AEDs that allowed direct comparisons to be made. The details of the structure of this analytic model, the information used to parameterise it and the results of the analysis are described in the section 'Integrated analysis of cost-effectiveness' (p. 105). In summary, a CUA was performed: using quality-adjusted life-years (QALYs) calculated using utility weights estimated from EQ-5D responses and UK public valuations, so that the cost-effectiveness of the newer AEDs could be compared with the cost-effectiveness of treatments for other conditions.

# Chapter 3

## Results

### Quantity of research available

#### Clinical effectiveness studies

##### **Included studies**

*Figure 1* summarises the inclusion/exclusion process. A total of 4211 titles and abstracts were screened for relevance. Of these, 887 full paper copies of studies were ordered. After further examination, an additional 616 papers were excluded. From the remaining 271 papers and additional studies in the manufacturers' submissions, 142 studies were finally included in the review: 13 systematic reviews, 108 effectiveness studies (see Appendix 14) and 21 economic papers. The remaining 121 papers were identified as duplicate publications and abstracts. For studies with multiple publications only the main publication for each study has been assessed. Related publications are listed (see Appendix 15) and were checked for any additional information missing from the main publication. Where studies had separate publications for seizure outcomes and QoL/cognitive outcomes, both publications were included.

Seven clinical effectiveness RCTs and one economic evaluation that met the inclusion criteria were not published in English. Owing to time constraints these were not included in the main assessment of effectiveness (see Appendix 16).

The manufacturers' submissions revealed an additional six relevant clinical effectiveness RCTs and 10 economic evaluations. These were also included in the review, bringing the total number of studies to 142 (13 systematic reviews, 108 effectiveness RCTs and 21 economic evaluations).

##### **Excluded studies**

In total, 3324 references did not appear to be relevant and were excluded at the first stage of screening (title and abstract screening). After further examination, 616 of the papers were excluded for the following reasons: literature reviews/background (175); systematic reviews/meta-analyses not meeting criteria (132); not RCT (118); not relevant intervention (9); not relevant population (18); not relevant outcomes (4); dose comparison studies (19); unavailable publications [104; consisting of NRR records of registered trials

in progress (92) and unable to obtain the paper (12)]; methodology papers (6); follow-up studies (19); unsure (4); ongoing studies (4); and non-English studies (4). For the 12 papers not obtainable, these were from six journal issues, and comprised conference abstracts (9), foreign language papers (1) and background papers (2). Non-English language studies are summarised in Appendix 16 and ongoing studies are summarised in Appendix 17.

#### Serious, rare and long-term adverse events studies

##### **Included studies**

Literature searches retrieved a total of 3884 titles and abstracts, which were screened for relevance. A total of 227 full paper copies of potentially relevant studies were ordered. Further examination of these papers revealed 86 publications that met the inclusion criteria. These publications related to 75 studies. Two additional studies were identified from the manufacturers' submissions, bringing the total number of studies included in the review to 77.

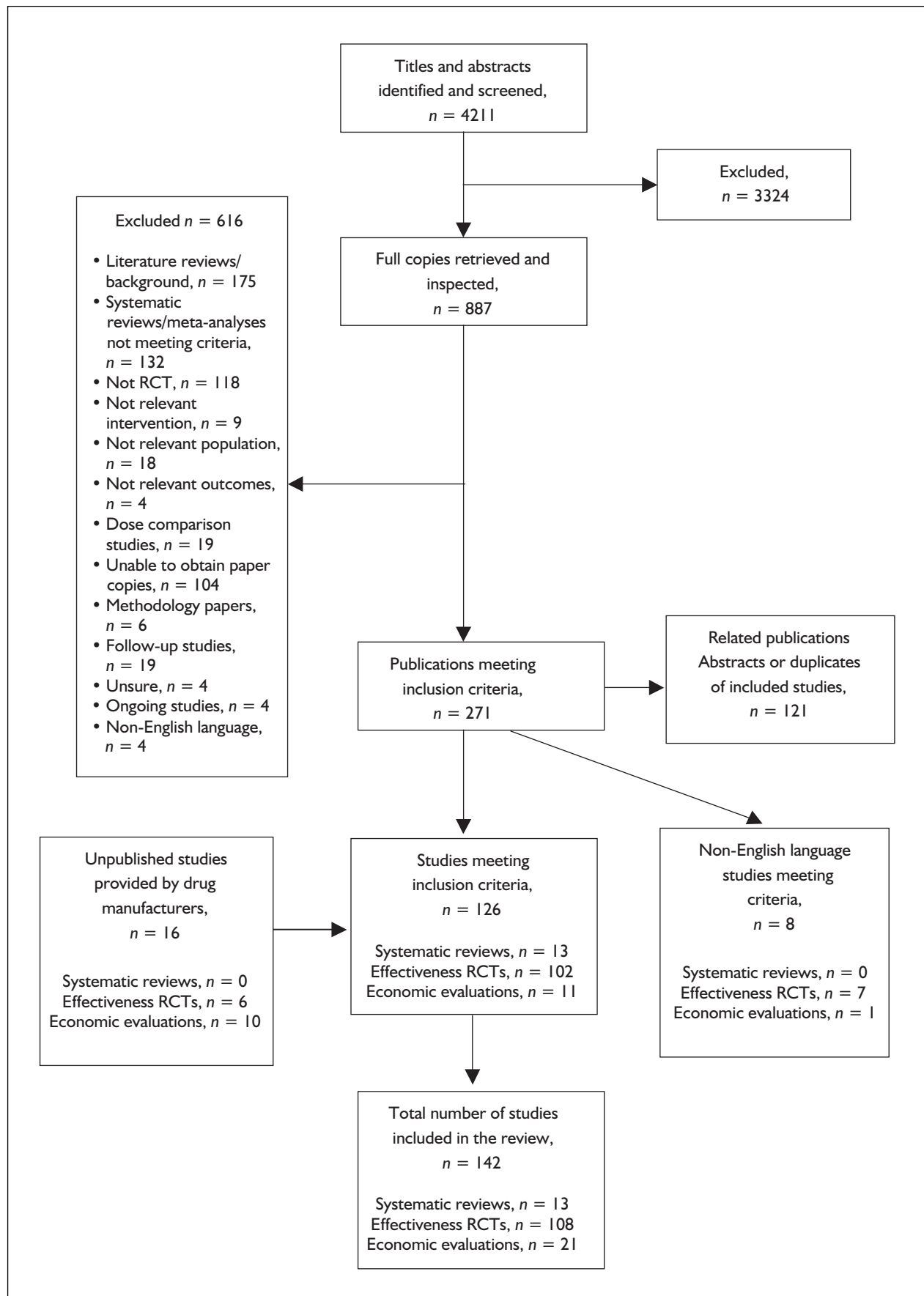
##### **Excluded studies**

During the screening of title and abstracts, 3657 papers were excluded as not being relevant. After further examination of the 227 full papers that were ordered a further 110 studies (141 publications) were excluded for the following reasons: non-English publication (60), incorrect study design (13), insufficient number of participants (3), length of follow-up too short (7), insufficient number of participants and length of follow-up too short (11), no relevant data (4), duplicate publications (2), ongoing study (1), study included in main review of clinical effectiveness (1), pooled data (not systematic review) (2) and review (not systematic) (6).

#### Cost-effectiveness studies

##### **Included studies**

All 4211 titles and abstracts were screened for relevance as in *Figure 1*. Of these, 55 were selected as being potentially relevant. Seven references referred to the ongoing UK SANAD trial and authors were contacted regarding the availability of interim results. Full paper copies of the remaining 48 titles/abstracts were ordered.



**FIGURE I** Summary of study identification, retrieval and inclusion/exclusion

After further examination, a total of 12 papers were found to fulfil the inclusion criteria for economic evaluations. Of these 12 papers, two were found to address the same study. In total, 11 economic evaluations of AEDs were included in the review.

In addition to these published evaluations, submissions from five of the drug manufacturers (no submissions were received from the manufacturers of GBP or VGB) revealed an additional 10 previously unpublished economic evaluations, bringing the total number of economic evaluations included in the assessment of cost-effectiveness to 21.

### **Excluded studies**

Of the 4211 references retrieved through the literature searches, 4156 were excluded at the first stage of screening (title and abstract screening) as they did not appear to be relevant. After further examination of the 48 full paper copies that were ordered, a further 36 references were excluded for the following reasons: background papers (24), no economics data (4), letters or comments on the economic evaluations (4), duplicates (2), economic evaluation of surgery (1) and non-English publication (1).

## **Quality of included studies**

### **Clinical effectiveness studies**

#### **Systematic reviews**

The quality of the systematic reviews was assessed using criteria developed by CRD for DARE (see Appendix 7). Only reviews considered as being of adequate quality according to these criteria were included in the review and hence all of the reviews were of reasonable quality. In addition, all of the included reviews were produced by the Cochrane Collaboration and so were subject to the organisation's own quality standards.

#### **Randomised controlled trials**

The quality of the effectiveness studies was assessed as outlined in the methods section using the criteria listed in Appendix 8. Details of the quality of individual studies are reported in Appendix 18 according to drug and study design (parallel and crossover studies). In addition, a summary table is provided in Appendix 19 listing the main quality issues of concern for each study and the assessment of quality according to the three quality issues that have been shown to affect study outcomes: use of an appropriate method of randomisation; use of an appropriate method of

allocation concealment; and effective blinding of outcome assessors, clinicians and participants.<sup>37</sup>

The quality assessment shows that there were a number of problems associated with the studies. Certain problems only related to individual studies, but there were a number of issues that were common across studies. It was difficult to assess the true quality of many studies owing to poor reporting. For example, the summary table (see Appendix 19) shows that many details relating to randomisation, allocation concealment and blinding were not reported. In certain circumstances, only abstract reports were available and so again details relating to the quality of the studies concerned were often lacking. However, important issues of study quality such as those reported above are discussed in the results section of the report in order to put the findings of the studies in context and highlight any potentially biased results.

In the following section, each of the quality criteria is discussed individually and the overall quality of the studies is summarised briefly according to the criterion.

### **1. Were the eligibility criteria for the study specified?**

Reporting the eligibility criteria for a study is important in determining how applicable the findings of the study are to the general population of individuals with epilepsy. In this review, it was important in determining whether studies should be included in terms of the ages of the participants (only studies of adults were included in this review) and in assessing the effectiveness of the drugs in specific groups of individuals (i.e. the elderly, those with intellectual disabilities and pregnant women).

The majority of studies (95) were judged to have provided adequate details of their eligibility criteria. However, details were lacking in 16 studies and four failed to provide details.<sup>38-40</sup> Two of these studies were only published in abstract form.<sup>40,41</sup>

### **2. Was an *a priori* power calculation for adequate sample population size performed?**

An *a priori* power calculation is important in determining whether a study has sufficient numbers of participants to detect significant differences in the outcome measures under assessment. In the case of equivalence studies this is particularly important as a greater number of participants are required to demonstrate

equivalence and hence any *a priori* power calculation should be adequate to test the null hypothesis.

Details of *a priori* power calculations were presented in less than half of the studies (50). In the remaining studies (63) details were not presented and in two cases it was unclear whether the power calculations were performed before or after the study was completed.<sup>39,42</sup>

### **3. Was the number of participants who were randomised stated?**

This criterion is important when assessing the size of the study and for assessing what happened to participants through the process of the trial in order to assess the potential for 'attrition bias' or 'exclusion bias'.

The majority of the studies reported the number of participants randomised. Only six studies failed to do so.<sup>40,43-47</sup> Five of these studies were reported in abstract form only.<sup>40,44-47</sup>

### **4. Was the method used to assign participants to the treatment groups really random?**

Adequate randomisation is important in preventing bias in study findings. For the purposes of this review, computer-generated random numbers and random number tables were accepted as adequate. In contrast, approaches considered inadequate included the use of alternation, case record numbers and birth dates or days of the week. These are classed as 'quasi' methods of randomisation.

Poor reporting was the main problem in assessing this criterion. In 74 studies there was insufficient information to assess whether the process of randomisation was adequate. However, where details were reported (41), the methods were found to be adequate in all cases.

### **5. Was the allocation of treatment concealed?**

This criterion relates to the concealment of the treatment allocation process so as to prevent tampering or interference. Research has shown that lack of adequate allocation concealment is associated with bias and this criterion has been found to be more important than the method of randomisation in preventing bias.<sup>37</sup> For this review, methods considered to provide adequate concealment of the treatment allocation included centralised or pharmacy-controlled assignment or where the following were used: serially numbered containers, serially numbered opaque envelopes and on-site computer-based systems where

assignment is unreadable until after allocation. Other robust methods considered adequate to prevent foreknowledge of the allocation sequence to clinicians were also considered as fulfilling this criterion. Any predictable or decipherable sequence was considered inadequate.

In the majority of studies (78), it was unclear whether the method used in the study was adequate, as the method used was not reported. However, 37 studies used methods that were considered adequate.

### **6. Were the outcome assessors blinded to the treatment allocation?**

Outcome assessors may have an opinion about the efficacy of the treatment under investigation. This may influence the reporting of the outcome data if the treatment allocation is not blinded, thereby distorting study findings. In addition, if outcome assessors are aware of which treatment patients are receiving, this may influence their interpretation of marginal findings or cause them to provide differential encouragement during assessments. Blinding of outcome assessors ensures that they are ignorant of the allocated intervention. This protects against performance and detection bias, and can also contribute to adequate concealment of allocation.

The majority of studies (80) did not report whether outcome assessors were blinded to treatment allocation. Twenty studies reported outcome assessors to be blinded and 10 reported that they were unblinded. In four studies assessors were blinded to some but not all of the outcomes assessed.<sup>48-51</sup>

### **7. Were those individuals who administered the intervention blinded to the treatment allocation?**

Individuals administering the intervention may have an opinion about the efficacy of the treatment under investigation. Again blinding prevents any such individuals from unduly influencing the trial outcomes. Blinding of individuals administering the intervention ensures that they are ignorant of the allocated intervention. This protects against performance and detection bias, and can also contribute to adequate concealment of allocation.

The majority of studies (68) did not report if those administering the interventions were blinded to treatment allocation. Where reported, administrators were blinded in 31 studies and unblinded in 16 studies.

**8. Were the participants who received the intervention blinded to the treatment allocation?**

Participants' opinions about a particular treatment may also influence the outcome of a trial if treatment allocation is unblinded.

Participants were blinded to treatment allocation in the majority of studies, although in 15 studies they were not. Three studies did not provide sufficient detail to determine whether participants were blind.<sup>40,52,53</sup> However, two of these studies were reported in abstract form only and hence lack detail.<sup>40,52</sup>

**9. Was the success of the blinding procedure assessed?**

Where blinding procedures were reported, it is important that the success of such procedures is assessed to determine if individuals remained blinded throughout the study or if at any point blinding was broken.

This criterion was not applicable in 12 studies where outcome assessors, those administering the intervention and participants were unblinded. Where applicable, the majority of the studies (100) did not report whether the success of the blinding procedure was assessed and only three studies reported assessing the success of blinding.<sup>54-56</sup>

**10. Were details of the baseline comparability of the treatment groups presented?**

It is important that details of the baseline comparability of treatment groups are presented in order to determine if the groups were similar at the start of the study. Treatment groups should be similar in terms of baseline characteristics such as age and gender, and also characteristics that are specific to the prognosis and outcome. Ideally, treatment groups should be similar for all the factors that determine the clinical outcomes, except whether they received the experimental treatment.

Sixty-seven studies presented details of baseline comparability of treatment groups and 34 studies did not present any such details. Fourteen studies presented some but not all specified baseline comparability details.

**11. Were adjustments made for differences in the baseline characteristics of the treatment groups?**

If treatment groups differ in terms of baseline characteristics, statistical analyses that permit adjustment of the study result for baseline differences should be used to ensure that any observed effects in outcome are unaffected. Ideally, both adjusted and unadjusted analyses

should be used, if baseline differences exist, and estimates should be compared and implications for any observed differences discussed. Where there were no differences in baseline characteristics, this criterion was not applicable.

Adjustments for differences in baseline characteristics were not applicable for the majority of studies (66). Where applicable, seven studies made adjustments and 42 provided insufficient detail to determine if adjustments were made.

**12. Were appropriate doses of the intervention drugs used?**

Doses of control drug should be appropriate for clinical practice. For the purpose of this review, appropriate dose ranges were as reported by the BNF.<sup>21</sup> Any doses below the lowest recommended limit or exceeding the upper recommended limit were considered inappropriate.

The majority of studies (94) used appropriate doses of the intervention drug. In 14 studies, some doses were appropriate, but others were not. In three studies all doses were outwith the recommended range.<sup>41,45,57</sup> Four studies failed to report the dose of the intervention drug.<sup>58-61</sup> Three of these were only published in abstract form.<sup>59-61</sup>

**13. Were appropriate doses of the control drugs used?**

Doses of control drug should be appropriate for clinical practice. For the purpose of this review, appropriate dose ranges were as reported by the BNF.<sup>21</sup> Any doses below the lowest recommended limit or exceeding the upper recommended limit were considered inappropriate. This criterion was considered not applicable for placebo.

This criterion was not applicable in 71 studies. Where applicable, all but 10 studies used appropriate doses. In five studies, some doses were appropriate but others were not. In one study the dose was higher than the recommended range.<sup>45</sup> Four studies, two of which were reported in abstract form only,<sup>59,61</sup> failed to report the dose of control drug.<sup>58,59,61,62</sup>

**14. Were any co-interventions identified that could influence the outcomes for the treatment groups?**

Co-interventions may influence outcome effects and so weaken or distort findings. This is particularly important if two treatment groups differ in this regard. The presence of co-interventions is most problematic when studies are not double-blind, or when very effective non-study



treatments are allowed at the physician's discretion.<sup>63</sup> For the purpose of this review newer AEDs, other than those under investigation, were considered to be co-interventions that could influence the outcomes.

Only 10 of the studies reported co-interventions that may have influenced the outcomes. The remaining studies did not report any such co-interventions.

### **15. Was patient adherence to the assigned treatment assessed?**

It is important to assess patient adherence to treatment, as deviations from the treatment protocol could influence outcome effects. For the purpose of this review, one appropriate method for assessing patient compliance was the measurement of plasma AED levels. Residual pill counts were also considered appropriate, although this method would be open to abuse unless medication was administered under supervision. Participant response to questioning was considered inadequate.

Over half of the studies (63) failed to report whether compliance was assessed. The remaining studies (52) used adequate methods of assessment.

### **16. Were all patients who were originally considered for the study accounted for at its conclusion?**

Some participants may leave before the conclusion of a trial. Such participants may systematically differ from those participants who complete the study. For example, some patients may not attend assessments if they are too ill to travel, or others may feel well and therefore not attend. All participants who entered the study should be accounted for at its conclusion. There is cause for concern if a large proportion of randomised patients are lost to follow-up. This is particularly pertinent if more patients are lost from one treatment group than the other.<sup>64</sup>

The majority of studies (93) accounted for all patients and six did not.<sup>43,65-69</sup> Twelve studies, including eight abstracts,<sup>40,41,44-47,59,60</sup> provided insufficient information. In four studies, one of which was an abstract,<sup>61</sup> all patients were accounted for in some, but not all, outcome assessments.<sup>57,61,70,71</sup>

### **17. Was a valid intention-to-treat analysis included?**

In an intention-to-treat (ITT) analysis, all participants are analysed according to their initial treatment assignment, regardless of any treatment

change, withdrawal or non-compliance. This preserves the values of randomisation and protects against attrition bias.

Thirty-two studies performed a valid ITT analysis. Approximately half of the studies (55) failed to report a valid ITT analysis and in 18 studies it was unclear whether a true ITT analysis was used. Seven studies used a valid ITT population for some but not all outcomes and in three studies, one of which was an abstract<sup>47</sup> and another of which was provided on a 'commercial-in-confidence' basis,<sup>72</sup> it was unclear from the information provided whether the analysis was based on ITT or per protocol data.<sup>47,72,73</sup>

### **18. Were at least 80% of the participants originally included in the randomisation process included in the follow-up assessments? (i.e. were less than 20% of the follow-up data classified as missing data?)**

The larger the amount of missing data within a study, the greater is the potential for bias. Patients with missing data may have different prognoses or experience different adverse events compared with other participants. Alternatively, their condition may have improved and so they have failed to return for further assessment.<sup>63</sup>

In the majority of studies (83) this criterion was met. In 18 studies, over 20% of data were classified as missing. In three studies, the criterion was partially met<sup>39,74,75</sup> and the remaining 11 studies reported insufficient information.

### **19. Were appropriate methods used to account for missing follow-up data in the intention-to-treat analysis? (i.e. sensitivity analyses to examine the effect of missing data and different methods of accounting for missing data)**

Where an ITT analysis is used, appropriate methods should be used to account for missing or incomplete data. Appropriate methods include last observation carried forward (the last observed value is used where data are incomplete) and ITT repeated measures models using maximum likelihood or generalising estimating equations. This criterion was not applicable to studies that failed to report an ITT analysis (55).

The majority of the studies (55) failed to report methods used to account for missing data and only four studies reported the use of appropriate methods.<sup>76-80</sup>

The next four criteria relate only to crossover studies ( $n = 30$ ).

### 1. Did all participants have established epilepsy with a constant and predictable seizure frequency and type?

Crossover studies are only appropriate in participants with stable disease which returns to a baseline state once treatment is complete, allowing subsequent treatments to be assessed under equivalent conditions.<sup>81</sup> Therefore, this type of study is only appropriate when patients have established epilepsy with a constant and predictable seizure type and frequency.

Nearly all (25) of the crossover studies (30) met this criterion. Four studies, two of which were abstracts,<sup>40,82</sup> provided insufficient information.<sup>40,49,50,82</sup> Only one study failed to meet this criterion.<sup>53</sup>

### 2. Was the crossover design appropriate (for the patient groups included in the study)?

As crossover studies are only suitable for patients with established epilepsy, in most cases patients will already be on a standard AED therapy that can be continued during the trial. Crossover studies are therefore most appropriate for assessing adjunctive therapy in patients with refractory epilepsy, but not for trials of monotherapy in newly diagnosed patients.<sup>81</sup>

Crossover designs were appropriate in all but two of the studies.<sup>53,69</sup>

### 3. Was an appropriate washout allowed between the different treatments? (i.e. the investigators should justify their choice of washout period. They may monitor blood levels of the treatment drugs or perform statistical analysis to look for treatment period interactions)

In crossover trials, the administration of treatment in the initial period may have an effect that carries over into the second period. The possibility of such a carryover effect can be reduced with an appropriate washout period between treatments. This period should be sufficient to allow the intervention drug to be eliminated from the body.

Most studies (18) used appropriate washout periods. In seven studies, there was no justification for the lack of a washout period.<sup>49,50,80,83–86</sup> Five studies, two of which were abstracts,<sup>40,82</sup> failed to provide the information necessary to judge whether this criterion was met.<sup>39,40,69,82,87</sup>

### 4. Was an appropriate analysis using paired data performed?

In crossover studies, each patient receives all of

the interventions. Within-patient variation is usually smaller than that between different patients, and in such cases there is considered to be a correlation between responses to the different treatments. Crossover trials should be analysed using a method specific to paired data, such as the McNemar test or a paired *t*-test. The analysis may also examine the possibility of order, period, or period-by-treatment interaction effects.<sup>25</sup>

The majority of the crossover studies (19) performed an appropriate analysis using paired data. Three studies, two of which were abstracts,<sup>40,82</sup> did not report sufficient detail to determine if an appropriate analysis was used.<sup>40,82,83</sup> Seven studies failed to perform an appropriate analysis,<sup>49,53,69,88–91</sup> and in one study some analyses were appropriate but others were not.<sup>84</sup>

The next six criteria relate only to equivalence studies ( $n = 2$ ).

### 1. Was the equivalence margin specified before the study?

Study findings may influence the selection of a meaningful difference between two drugs. The equivalence margin (the choice of a meaningful difference to be ruled out) should be specified and justified *a priori*.<sup>27</sup>

For the two equivalence and two non-inferiority trials, two specified an equivalence margin before the study,<sup>92,93</sup> and the other two did not report sufficient detail in order to assess this criterion.<sup>69,94</sup>

### 2. Was the active control treatment previously found to be effective?

It is a fundamental requirement that the control regimen (including the dosing schedule) is clearly effective. Ideally, this should be reported in a systematic review of placebo-controlled trials, with benefits that exceed a minimal clinically important effect and minimum inertial heterogeneity. Although two drugs may be shown to be equivalent, it is not possible to determine if both are effective or ineffective in the absence of such detail.<sup>27</sup>

The active control treatment was previously found to be effective in three of the equivalence/non-inferiority trials.<sup>69,92,93</sup> The other trial did not report sufficient detail in order to assess this criterion.<sup>94</sup>

### 3. Were the study participants and outcome variables similar to those in the original trials establishing the efficacy of the active control?

Patients in equivalence trials and their risk of adverse outcomes should be as similar as possible to the patients and outcomes in the placebo-controlled trials in which efficacy of the active control was established. This similarity ensures that the active control will have its usual effect.<sup>27</sup>

One trial met this criterion,<sup>93</sup> and the other three did not report sufficient detail to assess this criterion.<sup>69,92,94</sup>

### 4. Was it appropriate to test a null hypothesis?

Equivalence trials are designed to rule out meaningful differences between two treatments; they test the null hypothesis that there is a difference (unlike superiority trials which are designed to disprove a null hypothesis that there is no difference between two treatments using a two-sided approach).<sup>27</sup> A drug may be thought to be non-inferior to an active control only if the upper limit of the 95% CI for the difference in efficacy is less than a prespecified equivalence margin.

In two trials it was appropriate to test a null hypothesis,<sup>92,93</sup> and the other two trials did not provide sufficient information to determine if this was appropriate.<sup>69,94</sup>

### 5. Were treatments applied in an optimal fashion?

Issues regarding the design or execution of the intervention and follow-up that can lead to the false-negative conclusion that the two treatments are the same when they are not should be avoided. Such issues include non-equipotent doses, low compliance, incomplete follow-up, other effective therapies to the patient (co-interventions) that may distort the results and lack of blinding.<sup>27</sup>

This criterion was only partially met by all four trials, as treatments were applied in an optimal fashion with regard to certain aspects but not others.

### 6. Was the analysis appropriate for an equivalence trial?

In equivalence trials, ITT analysis may lead to the false-positive conclusion that treatments are equivalent when they are not. In such trials a per protocol analysis should be used. However, this can also have limitations, such as if withdrawal rates between the two treatment groups differ, for example if there are substantially more AEs in one

treatment group, the bias may go in either direction. Characteristics for those excluded from the 'per protocol' analysis must therefore be carefully examined for any such biases.<sup>27</sup>

The analysis was appropriate in two studies,<sup>92,93</sup> and inappropriate in one study.<sup>69</sup> In the remaining study it was unclear from the information provided whether the analysis was appropriate.<sup>94</sup>

### Serious, rare and long-term adverse events studies

Refer to Appendix 20 for the results of the quality assessment of serious, rare and long-term AE studies.

### Cost-effectiveness studies

Refer to Appendix 21 for the results of the quality assessment of cost-effectiveness studies.

## Analysis

### Assessment of clinical effectiveness

#### Systematic reviews

Thirteen systematic reviews were identified as meeting the inclusion criteria; all were produced by the Cochrane Collaboration or based on their reviews. Nine of the reviews were published as full systematic reviews. Protocols were only available for the remaining four reviews (i.e. no outcome data were available). Overall, the reviews considered all of the drugs included in this review. However, the effectiveness of the drugs was only considered in relation to adjunctive therapy versus placebo. One review considered comparisons of the drugs against each other but this was based on indirect comparisons as no trial data were available. Participants of all ages were considered in the systematic reviews, in contrast to this review, which only considers data relating to adults. Brief details of the reviews and their stage of development are presented in *Table 6*. Further details of the reviews are presented in *Tables 7* and *8* and Appendix 22.

Results from two published reviews and five Cochrane Collaboration systematic reviews<sup>96–98,105,108</sup> are shown in *Table 7*. These reviews evaluated adjunctive therapy for the outcome of 50% responders with odds ratios (ORs) and 95% CIs in comparisons of newer drugs versus placebo.

A brief summary of the overall findings of the eight reviews is presented in *Table 8*.

**TABLE 6** A brief summary of systematic reviews and protocols meeting the inclusion criteria

Author, year	Study details
Adab, 2002 <sup>95</sup>	Protocol. Review due Issue 2, 2003. Common AEDs and their use in pregnancy
Castillo, 2002 <sup>96</sup>	Review. RCTs of OXC vs placebo (adjunctive therapy only) in patients (adults and children). Looks at effectiveness and AEs. Includes one study involving only children
Chaisewikul, 2002 <sup>97</sup>	Review. RCTs of LEV vs placebo (adjunctive therapy only) in patients (adults and children). Looks at effectiveness and AEs
Jette, 2002 <sup>98</sup>	Review. RCTs of TPM vs placebo (adjunctive therapy only) in patients (adults and children). Looks at effectiveness and AEs. Includes one study involving only children
Kälviäinen, 2002 <sup>99</sup>	Review withdrawn. Review is delayed owing to problems in obtaining data. RCTs of VGB vs CBZ (monotherapy only) in patients (adults and children). Looks at effectiveness and AEs
Marson, 1997 <sup>100</sup>	Review. RCTs of GBP, LTG, TGB, TPM, VGB or zonisamide vs placebo (adjunctive therapy only) in patients (adults and children). Looks at effectiveness and AEs. Includes one study involving only children. Also reported in Chadwick 1996, <sup>101</sup> Chadwick 1997, <sup>102</sup> Marson 1996 <sup>103</sup>
Marson, 2001 <sup>104</sup>	Review. RCTs of LEV, OXC (remacemide and zonisamide) vs placebo (adjunctive therapy only) in patients (adults and children). Looks at effectiveness and AEs. Includes one study involving only children
Marson, 2002 <sup>105</sup>	Review. RCTs of GBP vs placebo (adjunctive therapy only) in patients (adults and children). Looks at effectiveness and AEs. Includes one study involving only children
Muller, 2002 <sup>106</sup>	Protocol. RCTs of OXC vs PHT (monotherapy only) in patients (adults and children). Looks at effectiveness and AEs.
Pereira, 2002 <sup>107</sup>	Review. RCTs of TGB vs placebo (adjunctive therapy only) in patients (adults and children). Looks at effectiveness and AEs.
Ramaratnam, 2002 <sup>108</sup>	Review. RCTs of LTG vs placebo (adjunctive therapy only) in patients (adults and children). Looks at effectiveness and AEs. Includes one study involving only children
Rashid, 2002 <sup>109</sup>	Protocol. RCTs of TGB vs placebo (adjunctive therapy only) in patients (adults and children). Looks at effectiveness and AEs. (This study was withdrawn after this work was completed.)
White, 2002 <sup>110</sup>	Protocol withdrawn. RCTs of LTG vs CBZ (monotherapy only) in patients (adults and children). Looks at effectiveness and AEs. The completion of this individual patient data review has been delayed owing to difficulties in acquiring individual patient data for one of the four included trials.

Overall, the systematic reviews were of good quality, but did not encompass all of the drugs, treatment comparisons and outcome measures required for this review. The reviews looked at adjunctive GBP, LTG, LEV, OXC, TGB, TPM and VGB versus placebo, and considered time to exit/withdrawal, proportion of 50% responders and the incidence of specified adverse events as outcomes measures. Logistic regression analyses to study the effect of drug dose were performed where possible and did show evidence of a dose response relationship for GBP and LEV. Some of the reviews were in the process of being updated and may therefore not have included all of the studies identified in this review.

In conclusion, the reviews reported that the newer AEDs (GBP, LTG, LEV, OXC, TGB, TPM and VGB) were effective as adjunctive treatments

in comparison with placebo based on the outcome measures considered. The authors concluded that the findings of the reviews could not be extrapolated to long-term use or to monotherapy. The findings of this review will be discussed in the context of these previous reviews, where relevant in the discussion section (see Chapter 4).

#### **Randomised controlled trials**

The following section is divided into licensed and unlicensed drug indications. All of the drugs are licensed for adjunctive therapy in patients with refractory partial seizures. However, only LTG, LEV and OXC are licensed for use in newly diagnosed patients and only LTG and TPM are licensed for treating generalised seizures. In addition, OXC, LTG and TPM are the only newer AEDs currently licensed for monotherapy. Overall,

**TABLE 7** Proportion of 50% responders for newer AEDs versus placebo in adjunctive therapy (systematic review data)

Drug	Proportion of 50% responders: OR (95% CI)		
	Chadwick 1996 <sup>101</sup>	Marson, 1997 <sup>100</sup>	Cochrane Collaboration Reviews <sup>96–98,105,108</sup>
GBP	2.31 (95% CI: 1.54 to 3.45)	2.29 (95% CI: 1.53 to 3.43)	1.93 (95% CI: 1.37 to 2.71)
LEV			3.81 (95% CI: 2.78 to 5.22)
LTG	2.24 (95% CI: 1.42 to 3.53)	2.32 (95% CI: 1.47 to 3.68)	2.71 (95% CI: 1.87 to 3.91)
OXC			3.35 (95% CI: 2.32 to 4.83)
TGB	3.01 (95% CI: 1.99 to 4.55)	3.03 (95% CI: 2.01 to 4.58)	
TPM	4.27 (95% CI: 2.84 to 6.43)	4.07 (95% CI: 2.87 to 5.78)	4.21 (95% CI: 2.79 to 5.20)
VGB	3.68 (95% CI: 2.45 to 5.51)	3.67 (95% CI: 2.44 to 5.51)	

**TABLE 8** Summary of the findings of included systematic reviews

Author, Year	Summary of findings
Castillo, 2002 <sup>96</sup>	OXC has efficacy as an adjunctive treatment in patients with drug-resistant partial epilepsy, in both adults and children. However, the trials reviewed were of relatively short duration, and provide no evidence about the long-term effects of OXC. Results cannot be extrapolated to monotherapy or to patients with other types of epilepsy
Chaisewikul, 2002 <sup>97</sup>	LEV reduces seizure frequency when used as an adjunctive treatment for patients with a drug-resistant localisation-related (partial) epilepsy, and seems well tolerated. Minimum effective and maximum tolerated doses have not been identified. The trials reviewed were of 16–24 weeks duration and results cannot be used to confirm longer term effects. Our results cannot be extrapolated to monotherapy or to patients with other seizure types or epilepsy syndromes. Great care should also be taken with any attempt to apply these results to children
Jette, 2002 <sup>98</sup>	TPM has efficacy as an adjunctive treatment for drug-resistant partial epilepsy. However, the trials reviewed were of relatively short duration and provide no evidence for long-term efficacy of TPM. Results cannot be extrapolated to monotherapy or treating other epilepsy types
Marson, 2001 <sup>104</sup>	The data suggest a useful effect for LEV, OXC and zonisamide. LEV has the more favourable 'responder-withdrawal ratio' followed by zonisamide and OXC
Marson, 1997 <sup>100</sup> Chadwick, 1996 <sup>101</sup> Chadwick, 1997 <sup>102</sup> Marson, 1996 <sup>103</sup>	The review shows clear evidence that each of these drugs (GBP, LTG, TGB, TPM, VGB or zonisamide) is better than placebo at preventing seizures. When the results are compared across drugs, the CIs overlap, and there is therefore no conclusive evidence of differences in efficacy and tolerability. However, owing to the lack of actual study data these comparisons across drugs are based on indirect comparisons and are therefore subject to potentially severe bias
Marson, 2002 <sup>105</sup>	GBP has efficacy as an adjunctive treatment in patients with drug-resistant epilepsy. However, the trials reviewed were of relatively short duration, and provided no evidence for the long-term efficacy of GBP. Results cannot be extrapolated to monotherapy or patients with other epilepsy types
Pereira, 2002 <sup>107</sup>	TGB reduces seizure frequency but is associated with some side-effects when used as an adjunctive treatment for people with drug-resistant localisation-related seizures
Ramaratnam, 2002 <sup>108</sup>	LTG adjunctive therapy is effective in reducing the seizure frequency in patients with drug-resistant partial epilepsy. Further trials are needed to assess the long-term effects of LTG and to compare it with other adjunctive drugs

LTG is the only one of the newer group of AEDs (included in this review) which is licensed for mono-adjunctive therapy, partial and generalised seizures and refractory and newly diagnosed patients. In this review, a few trials included patients with partial and patients with generalised seizures. The proportion of patients with each

seizure type was often not reported and the outcome data were not reported separately for the two groups. This makes interpretation of these trials problematic. Owing to difficulties in differentiating between partial and generalised seizure types clinically, especially in older trials, studies with mixed populations are included in the

licensed section of the review even where the drug is licensed only for partial seizures. However, data have been reported separately from those studies that recruited only partial or only generalised epilepsy patients. The relevance of the findings from 'mixed seizure type' studies to patients with either partial or generalised seizure types remains unclear.

Within the unlicensed section, only very brief details of the studies are presented in tables. The main focus of the review is on the licensed use of the drugs. This section is presented as a narrative and divided up in terms of monotherapy and adjunctive therapy, subdivided in each case into newer drug versus placebo, newer drug versus older drug and newer drug versus newer drug comparisons (newer drugs being the seven drugs under investigation).

Estimates of effect from individual trials are based on ITT data, that is, all those participants included in the randomisation process are considered in the final analysis based on the treatment groups to which they were originally assigned. In some cases these data were not reported in the studies or, where ITT data were presented, a true ITT population was not reported. In this review, missing data have been assumed to be a negative outcome. Ideally, a sensitivity analysis should have been performed to consider both the worst (i.e. assuming missing data as negative outcomes) and best (i.e. assuming missing data as positive outcomes) scenarios, but this was not possible owing to time constraints. The ITT analysis used in this review therefore presents a conservative estimate of the effects.

Individual estimates of effect are presented as Forest plots (unpooled) where possible. No consideration has been given to the effect of dose, although ideally the effects of different doses should be explored using a logistic regression analysis. This was not possible within the time frame of this review.

Effect sizes for the proportion of seizure-free participants, proportion of 50% responders and the number of participants experiencing AEs have been expressed as RRs with 95% CIs. In the case of time to event outcomes such as time to first seizure and time to exit/withdrawal, the data require special consideration and statistical analysis in the form of survival curves or HRs. All of these statistical methods take into account the fact that the outcome of interest may never be observed over the period of follow-up (i.e.

observations may be censored) and that throughout the follow-up period individuals will be lost to the analysis. For the purposes of this review, HRs with 95% CI intervals are used to represent effect sizes and any comparisons tested using a log-rank test (with accompanying *p*-values) where appropriate. Although HRs are the preferred way of reporting effect sizes for time to event outcomes, these data were not always reported. Where possible, HRs were calculated if sufficient alternative data were available. Where this was not possible, the data are reported as in the trial. In some cases where data were presented as HRs, the accompanying CIs were not reported as 95% CIs. In order to make an equivalent comparison between studies, these were converted into 95% CIs using the following equations:

$$\ln(95\% \text{ lower CI}) = \ln(\text{HR}) - \{1.96 [\ln(\text{HR}) - \ln(\text{lower } 90\% \text{ CI})]/1.645\}$$

$$\ln(95\% \text{ upper CI}) = \ln(\text{HR}) + \{1.96 [\ln(\text{HR}) - \ln(\text{lower } 90\% \text{ CI})]/1.645\}$$

where HR = hazard ratio, ln = natural logarithm and 1.645 is the *Z* value for 90%. The ln 95% CIs were then converted back to 95% CIs.

Data from the studies were presented separately for each study. In addition, where it was considered clinically and statistically reasonable to do so, the data were pooled. Where data were pooled, a *Q*-statistic was used to test for the presence of statistical heterogeneity and study data were combined using a fixed-effects model.

In the absence of current methodology for the assessment of cognitive and QoL outcomes, data have been summarised in tables and discussed in a narrative.

Data relating to safety (number of AEs and number of deaths) and tolerability (number of withdrawals) of the drugs were summarised in tables. Owing to the vast number of different AEs reported, it was not feasible within the confines of this review to report data for every event. Consequently, analysis was limited to the five most commonly reported AEs associated with each of the seven AEDs. The data were subdivided according to the specific event and the drug under investigation. In addition, RRs (95% CI) were calculated for each individual study within the subsections and these data were summarised in the text. Owing to problems with the reporting of data relating to safety and tolerability (i.e. missing data due to not every AE being considered in every

study and some studies only reporting data where the incidence of AEs reached a certain threshold value) and the presence of statistical heterogeneity ( $Q$ -statistic and  $p$ -value), combining data from the different studies was problematic and they were not combined.

Throughout the review, the quality of the studies was considered when interpreting the findings. Specific problems with individual studies were highlighted and the overall quality of all of the studies was considered.

Studies are subgrouped where feasible according to epilepsy syndrome or type of seizure where these data are available. Different types of epilepsy syndrome/seizure type (e.g. POSs or generalised onset seizures) are considered separately and, where possible subgroup analyses of the following were performed: women of childbearing age, adults with learning disabilities and the elderly. In addition, throughout this chapter the findings of the studies are reported in association with any potential quality issues that may possibly impact on robustness of the data.

A number of studies included in the review used crossover, equivalence and non-inferiority designs rather than the more common parallel superiority designs. Where crossover designs were used, only first-phase data have been included in Forest plots and pooled RRs. Where Cochrane systematic reviews reported first-phase data, these were extracted and included in the analysis. By using only first-phase data, readers should be aware that the data lose statistical power to detect a difference between treatments. Ideally, studies should have performed a paired analysis suitable for crossover studies, but this was often not performed. Where this has been used, the paired data have also been presented in the text accompanying the Forest plots.

Where equivalence or non-inferiority designs have been used, the International League Against Epilepsy (ILAE) recommends that per protocol data be used. However, these data were not always reported and, in order to present equivalent data in the Forest plots, ITT data from equivalence studies have been used. Readers should be aware that ITT data are more likely to show false equivalence. If per protocol data were available these have been reported in the text accompanying the Forest plots.

A number of trials used a conditional response design, which is likely to affect the clinical

relevance and applicability of the data. Such trials required that participants achieve a specified reduction in seizure frequency whilst undergoing AED treatment in the pretrial phase, in order to be included in the main assessment phase of the trial. Similarly, a small number of trials included participants who were undergoing evaluation for surgical treatment. Surgery is a treatment option for some patients but it is appropriate for only a very specific group of patients. Both of these trial designs were highlighted where appropriate and considered separately in the analyses.

Data extraction tables from the included RCTs of clinical effectiveness are presented in Appendix 23. These are organised by drug (alphabetically) and then grouped first by licensed or non-licensed use and then by crossover or parallel study design.

To assist the reader, boxed summary statements have been placed at the end of each results section and subsection.

### **Licensed indications**

#### **Monotherapy**

Only LTG, OXC and TPM are licensed for use as monotherapy and only data relating to these drugs are discussed in the following section. If applicable, the use of other drugs (GBP, LEV, TGB, and VGB) as monotherapy is discussed and briefly summarised in the unlicensed section of this report.

Overall, 21 studies investigated the effects of monotherapy: LTG (12), OXC (8) and TPM (1). Two compared newer AEDs with placebo<sup>78,111</sup> and one compared one newer AED with another AED.<sup>93</sup> The remaining studies all compared newer AEDs with older AEDs. All were parallel studies, two used a non-inferiority design<sup>93,94</sup> and the remainder were superiority trials. Treatment periods ranged between 1.5 and 56 weeks (mean = 33 weeks). A number of studies were continued for extended periods, but such 'follow-up' periods usually adopted an open-label, non-randomised design, which was not eligible for inclusion in the main part of the review, although it was considered in the review of rare, serious and long-term AEs.

Five studies included patients with refractory epilepsy<sup>78,112–115</sup> and two studies included patients with refractory and patients with newly diagnosed epilepsy.<sup>72,116</sup> The remaining studies only included patients with newly diagnosed epilepsy. Three studies included only patients with POSs<sup>78,111,112</sup> and one study included only patients with

**TABLE 9** Number of monotherapy studies assessing each comparison and outcome

Comparison	No. of studies reporting outcome measures						
	N	Seizure free	50% responders	Time to 1st seizure	Time to exit	Cognitive	QoL
New vs placebo	2 (OXC)	2 (OXC)	0	1 (OXC)	1 (OXC)	0	0
New vs old	12 (LTG)	10 (LTG)	3 (LTG)	4 (LTG)	5 (LTG)	1 (LTG)	6 (LTG)
	6 (OXC) 1 (TPM)	4 (OXC)	2 (OXC) 1 (TPM)	1 (TPM)	2 (OXC) 1 (TPM)	1 (OXC)	1 (OXC)
New vs new	1 (LTG)	1 (LTG)	0	1 (LTG)	1 (LTG)	0	0

N, total number of studies.

**TABLE 10** Summary of studies (monotherapy, newer drugs vs placebo) assessing the proportion of seizure-free participants

Drug	Study characteristics <sup>a</sup>				
	Refractory/ newly diagnosed	Seizure type	Dose Follow-up N	Comments	Study details
LTG				No studies	
OXC	Refractory	Partial	2400 mg/day 10 days N = 102	Specifically includes patients under evaluation for surgery	Schachter, 1999 <sup>78</sup>
	Newly diagnosed	Partial	1200 mg/day 90 days N = 67		Sachdeo, 1998 <sup>111</sup>
TPM				No studies	

N, total number of randomised participants.  
<sup>a</sup> Both were parallel, superiority trials unless stated otherwise.

generalised onset seizures.<sup>62</sup> The remaining 17 studies recruited mixed populations of patients, some of whom had partial seizures and others who had generalised seizures. The proportion of participants with each seizure type was often not reported and similarly outcome data were not reported separately for each of the different seizure types. The relevance of these data to individual seizure types was unclear. Similarly, there was no information on the use of monotherapy in pregnant women and individuals with intellectual disabilities and only one study examined the effects of monotherapy in elderly patients.<sup>117</sup> This makes it difficult to make statements about the use of monotherapy in these groups of patients. In terms of the size of the monotherapy trials, the number of participants ranged from 37 to 877 (mean = 288). *Table 9* summarises the number of studies assessing monotherapy AEDs and the outcomes reported.

## I. Newer drugs versus placebo

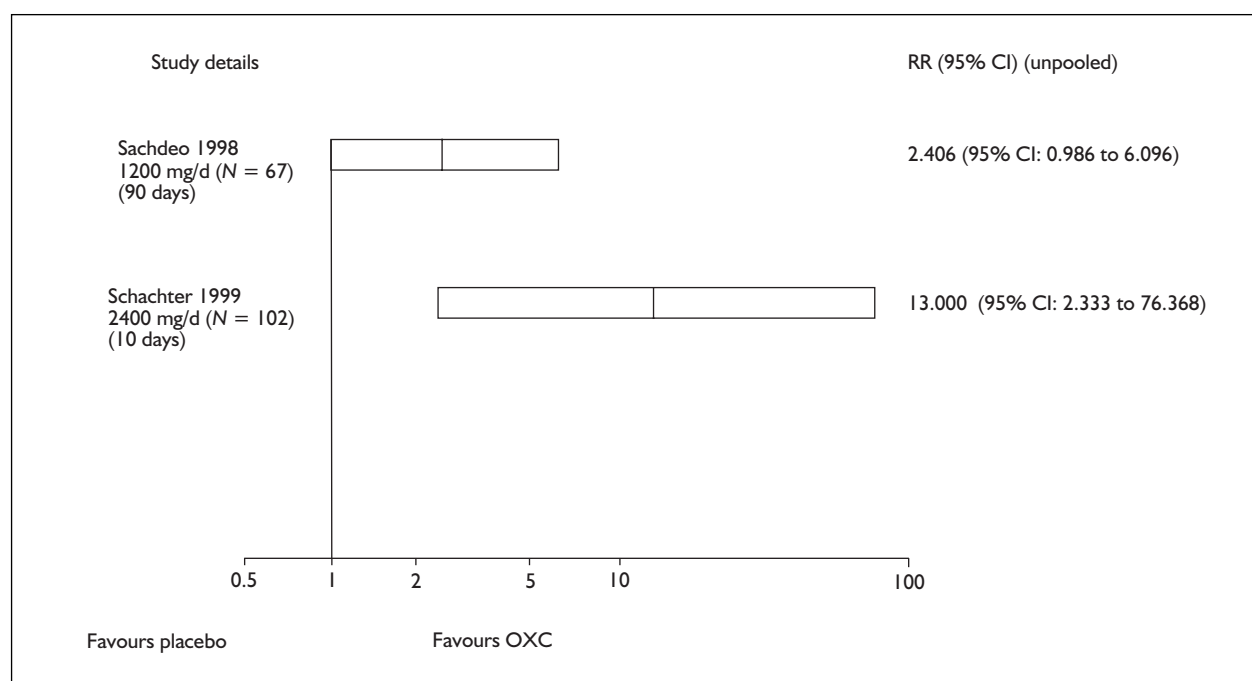
### a. Seizure frequency

#### i. Seizure freedom

Both studies of newer drugs versus placebo (monotherapy) reported the proportion of seizure-free participants. A summary of the main characteristics of these studies is presented in *Table 10*.

No studies examined the use of LTG or TPM, and evidence for OXC was limited to only two relatively small trials (169 participants in total). Both trials considered participants with partial seizures; however, one trial looked at newly diagnosed participants whereas the other examined refractory patients. The two trials also used different doses of drug (1200 and 2400 mg/day) and neither trial examined effects over a long period of time. In particular, the trial of refractory partial patients only considered





**FIGURE 2** Proportion of seizure-free participants (unpooled RRs, 95% CI) for monotherapy trials of OXC vs placebo (ITT data)

treatment over a 10-day period and was carried out in a specific group of patients who were undergoing evaluation for possible surgery. Therefore, the findings of this trial have limited applicability to the general population of patients with partial seizures. In view of the clinical heterogeneity between the studies it was not appropriate to combine the individual RRs (see *Figure 2*).

The unpooled RRs show that monotherapy OXC is favoured over placebo, but only the data from the larger trial proved to be statistically significant. In addition, these findings must be viewed in the context of their short duration and relatively small population sizes. Taking these factors into consideration along with the relatively limited applicability of the larger study of potential candidates for surgery, there is very little evidence on which to base an assessment of the effectiveness of monotherapy OXC, LTG or TPM versus placebo.

#### ii. 50% reduction in seizure frequency

No studies of newer drugs versus placebo (monotherapy) reported the proportion of participants who experienced at least a 50% decrease in seizure frequency.

#### b. Time to first seizure

One of the two studies of newer drugs versus placebo (monotherapy) reported time to first

seizure. A summary of the main characteristics of this study is presented in *Table 11*.

The study examined the use of OXC in 67 newly diagnosed patients with partial seizures over a relatively short 90-day period. The study reported the median time to first seizure for each of the treatment arms (OXC, 11.67 days; placebo, 3.23 days;  $p = 0.0457$ ), but failed to report an HR. The reported data appear to favour OXC over placebo, but this finding must be considered in the context of the relatively small population size and treatment period.

#### c. Time to withdrawal/exit

One of the two studies of newer drugs versus placebo (monotherapy) reported the time to withdrawal/exit. A summary of the main characteristics of this study is presented in *Table 12*.

The study examined the use of 2400 mg/day OXC in 102 patients with refractory partial seizures over a 10-day period, during which the patients were evaluated as potential candidates for surgery. Such patients represent a very specific group for whom drug treatment has proved particularly ineffective and problematic. The aetiology of their seizures is also very specific and hence findings from such a group of patients are unlikely to be applicable to the general population of patients with epilepsy. The log-rank test significantly favoured OXC over

**TABLE 11** Summary of studies (monotherapy, newer drugs vs placebo) assessing time to first seizure

Drug	Study characteristics <sup>a</sup>				Study details
	Refractory/ newly diagnosed	Seizure type	Dose/ Follow-up N	Comments	
LTG				No studies	
OXC	Newly diagnosed	Partial	1200 mg/day 90 days N = 67		Sachdeo, 1998 <sup>111</sup>
TPM				No studies	

N, total number of participants randomised.  
<sup>a</sup> Parallel, superiority trial.

**TABLE 12** Summary of studies (monotherapy, newer drugs vs placebo) assessing time to withdrawal/exit

Drug	Study characteristics <sup>a</sup>				Study details
	Refractory/ newly diagnosed	Seizure type	Dose Follow-up N	Comments	
LTG				No studies	
OXC	Refractory	Partial	2400 mg/day 10 days N = 102	Specifically includes potential candidates for surgery	Schachter, 1999 <sup>78</sup>
TPM				No studies	

N, total number of participants randomised.  
<sup>a</sup> Parallel, superiority trial.

placebo ( $p = 0.0001$ ) and similarly the Cox's proportional hazards regression model also showed significance in favour of OXC ( $p = 0.0001$ ). However, this apparent evidence in favour of OXC should be considered with caution in the light of the limited data, the short treatment period and the lack of generalisability of the results.

#### d. Quality of life

No studies of newer drugs versus placebo (monotherapy) reported QoL outcomes.

#### e. Cognitive function

No studies of newer drugs versus placebo (monotherapy) reported cognitive function outcomes.

#### Summary statement for monotherapy newer AEDs versus placebo

Data were only available for proportion of seizure-free participants and the time to event outcomes (first seizure and exit/withdrawal). There were no data for LTG or TPM monotherapy versus placebo, and only two trials compared OXC with placebo. Both OXC trials included only two patients with partial seizures (refractory in one case and newly diagnosed patients in the other).

In conclusion, there is no evidence on which to base an assessment of LTG and TPM. The evidence to support OXC in favour of placebo was also very limited. The data come from small trials conducted over short treatment durations and one trial relates specifically to patients undergoing evaluation for surgery, limiting its applicability. Considering all of these factors, the statistically significant differences observed in the proportion of seizure-free participants and the time to event outcomes in favour of OXC versus placebo should be regarded with caution.

## 2. Newer drugs versus older drugs

### a. Seizure frequency

#### i. Seizure freedom

Fifteen out of 19 studies of newer drugs versus older drugs (monotherapy) reported the proportion of seizure-free participants. A summary of the main characteristics of these studies is presented in *Table 13*.

Overall, 10 parallel superiority trials compared LTG with an older drug. The drug dose varied, but in each case was within the recommended range. The majority of the trials (seven trials) were carried out in newly diagnosed patients with either partial or generalised seizures. Other trials specifically looked at newly diagnosed patients with generalised seizures (one trial) or refractory patients with either partial or generalised seizures

(two trials). It was unclear in the remaining trial whether patients were refractory or newly diagnosed. The main comparators were CBZ (six trials) and VPA (three trials). The remaining trials used PHT (one trial) or conventional therapy (two trials), which involved physicians choosing the comparator that patients received. Overall, the studies recruited between 115 and 877 participants (mean = 347) and followed up the effects of therapy for between 18 and 48 weeks (mean = 30 weeks).

Overall the trials were of reasonable quality. Two were open-label trials, one of which may possibly have been underpowered according to the *a priori* sample size calculations.<sup>118</sup> The other showed a baseline difference in seizure rate between the study groups, which does not appear to have been

**TABLE 13** Summary of studies (monotherapy, newer drugs vs older) assessing proportion of seizure-free participants

Drug	Study characteristics <sup>a</sup>				
	Refractory/ newly diagnosed	Seizure type	Dose Follow-up N	Comments	Study details
LTG	Newly diagnosed	Combination of partial/generalised	Median 200 mg/day 20 weeks N = 712	LTG vs VPA or CBZ (doses NS). The physician was allowed to choose after randomisation which of two conventional therapies (CBZ or VPA) was used	GlaxoSmithKline, 2000 <sup>118</sup>
	Newly diagnosed	Combination of partial/generalised	Median 200 mg/day 18 weeks N = 385	LTG vs CBZ (Median 600 mg/day)	Nieto Barrera, 2001 <sup>119</sup>
	Newly diagnosed	Combination of partial/generalised	100 mg/day or 200 mg/day 26 weeks N = 343	Two doses of LTG compared with CBZ (600 mg/day)	Reunanen, 1996 <sup>120</sup>
	Newly diagnosed	Combination of partial/generalised	150 mg/day 48 weeks N = 260	LTG vs CBZ (600 mg/day)	Brodie, 1995 <sup>121</sup>
	Newly diagnosed	Combination of partial/generalised	75–500 mg/day 24 weeks N = 150	Specifically looks at elderly patients, LTG vs CBZ (200–2000 mg/day)	Brodie, 1999 <sup>117</sup>
	Newly diagnosed	Combination of partial/generalised	Max. 400 mg/day 48 weeks N = 181	LTG vs PHT (max. 600 mg/day)	Steiner, 1999 <sup>75</sup>
	Newly diagnosed	Generalised	100–500 mg/day 24 weeks N = 313	LTG vs VPA (dose NS)	GlaxoSmithKline, 2001 <sup>62</sup>

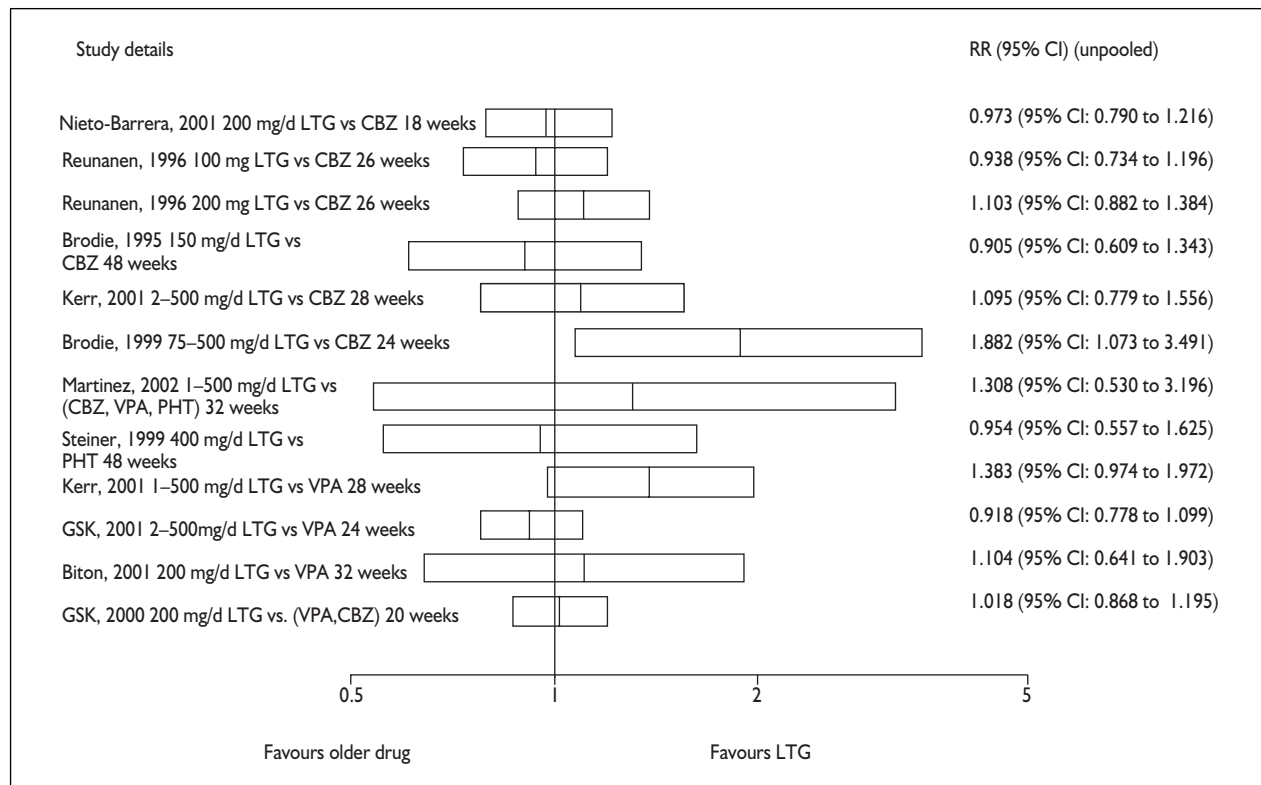
*continued*

**TABLE 13** Summary of studies (monotherapy, newer drugs vs older) assessing proportion of seizure-free participants (cont'd)

Drug	Study characteristics <sup>a</sup>				
	Refractory/ newly diagnosed	Seizure type	Dose Follow-up N	Comments	Study details
	Refractory	Combination of partial/generalised	100–500 mg/day 32 weeks N = 115	LTG vs conventional therapy (CBZ, PHT or VPA; doses NS). Physicians were allowed to choose which of the conventional therapies their patients received	Martinez, 2002 <sup>114</sup>
	Refractory	Combination of partial/generalised	200–500 mg/day 28 weeks N = 877	LTG vs CBZ (dose NS) and LTG vs VPA (dose NS). Participants were assigned to either the LTG vs CBZ or the LTG vs VPA branch of the study according to their physician's choice	Kerr, 2001 <sup>122</sup>
	Combination of newly diagnosed/ refractory	Combination of partial/generalised	200 mg/day 32 weeks N = 133	LTG vs VPA (20 mg/kg/day)	Biton, 2001 <sup>116</sup>
OXC	Newly diagnosed	Combination of partial/generalised	Median 900 mg/day 48 weeks N = 249	OXC vs VPA (600–2700 mg/day)	Christe, 1997 <sup>123</sup>
	Newly diagnosed	Combination of partial/generalised	Dose NS 12 months N = 37	OXC vs PHT (dose NS)	Aikia, 1992 <sup>58</sup>
	Newly diagnosed	Combination of partial/generalised	600–2100 mg/day 48 weeks N = 287	OXC vs PHT (100–650 mg/day)	Bill, 1997 <sup>124</sup>
	Newly diagnosed	Combination of partial/generalised	300–1800 mg/day 48 weeks N = 194	OXC vs CBZ (300–1400 mg/day)	Dam, 1989 <sup>125</sup>
TPM	Newly diagnosed	Combination of partial/generalised	100 and 200 mg/day 6 months N = 621	Non-inferiority trial. Two doses of TPM compared with VPA (1250 mg/day) and CBZ (600 mg/day). Physicians were allowed to choose whether they wanted participants to be entered into the TPM vs CBZ or the TPM vs VPA branch of the trial. Study includes children (≥ 6 years) – data not presented separately	Privitera, 2002 <sup>94</sup>

N, total number of randomised participants; NS, not stated.

<sup>a</sup> All were parallel, superiority trials unless stated otherwise.



**FIGURE 3** Proportion of seizure-free participants (unpooled RRs, 95% CI) for monotherapy LTG vs older drugs (ITT data)

considered in the findings.<sup>119</sup> One trial used a lower than recommended dose of comparator (CBZ 600 mg/day), which potentially favoured LTG.<sup>120</sup> Finally, three trials allowed physicians to choose which comparator participants received either before<sup>122</sup> or after<sup>114,118</sup> they were randomised.

RRs (95% CI) were calculated for each individual study based on ITT data (see *Figure 3*).

Owing to the presence of clinical (different participants, drug doses, follow-up periods and comparators) and statistical (*Q*-statistic) heterogeneity, it was inappropriate to pool the data. Examining the unpooled data, only one study showed a statistically significant difference that favoured LTG over the older comparator drug (CBZ).<sup>117</sup> This study was specifically conducted in elderly patients ( $\geq 65$  years) with newly diagnosed partial/generalised seizures, which may limit its applicability to the general population of patients with epilepsy. Overall, based on the available evidence, LTG does not appear to be more or less effective than older drugs in terms of the proportion of seizure-free participants.

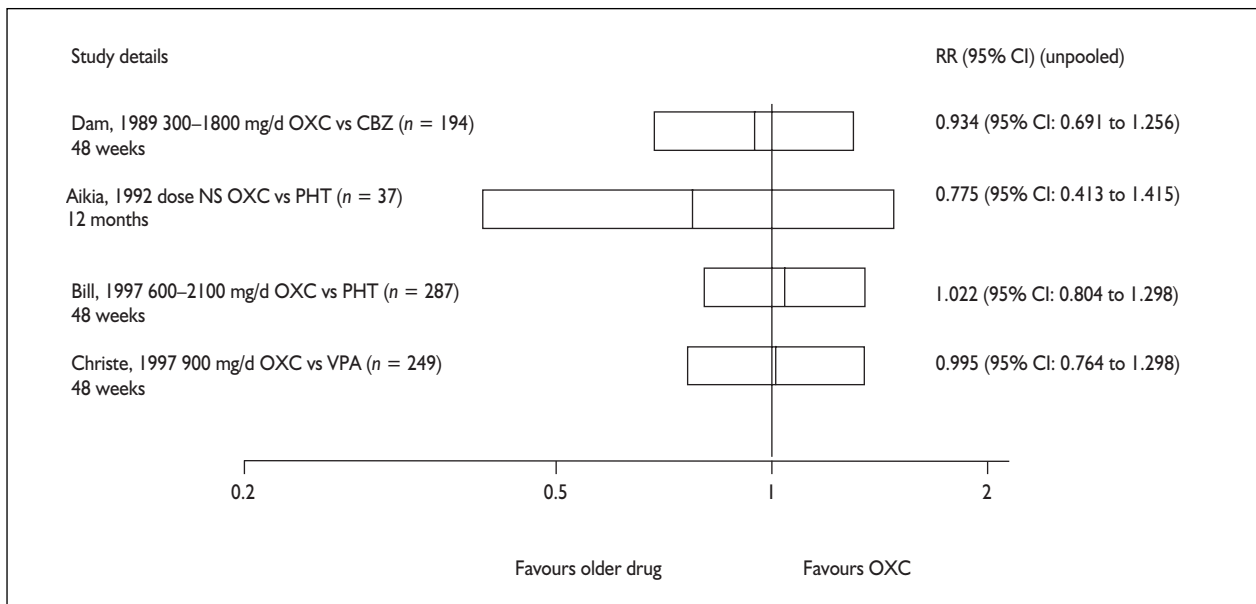
Four parallel superiority studies investigated the effectiveness of monotherapy OXC versus an older

drug.<sup>58,123–125</sup> All examined refractory patients with either partial or generalised seizures for periods of around 1 year (range 48–52 weeks, mean 49 weeks). OXC is licensed only for the treatment of partial seizures and so the relevance of the findings from these mixed groups of patients is unclear.

The population size varied from 37 to 287 participants (mean = 192). Two of the trials compared OXC with PHT,<sup>58,124</sup> one with CBZ<sup>125</sup> and the fourth with VPA.<sup>123</sup> All used doses of OXC and comparator within the recommended ranges.

Overall, the quality of the studies was reasonable. The main aim of one of the trials comparing OXC with PHT was to investigate cognitive outcomes and the study included only a small number of participants (37).<sup>58</sup>

Owing to clinical (different participant characteristics, drugs, drug doses and length of follow-up) and statistical (*Q*-statistic) heterogeneity, in the majority of cases it was not appropriate to pool data. The unpooled data are shown in *Figure 4*. None of the studies showed statistically significant differences between OXC and older drugs.



**FIGURE 4** Proportion of seizure-free participants (RRs, 95% CI) for monotherapy trials of OXC vs older drugs (ITT data)

**TABLE 14** Proportion of seizure-free participants (pooled RRs, 95% CI) for studies of monotherapy OXC vs PHT (ITT data)

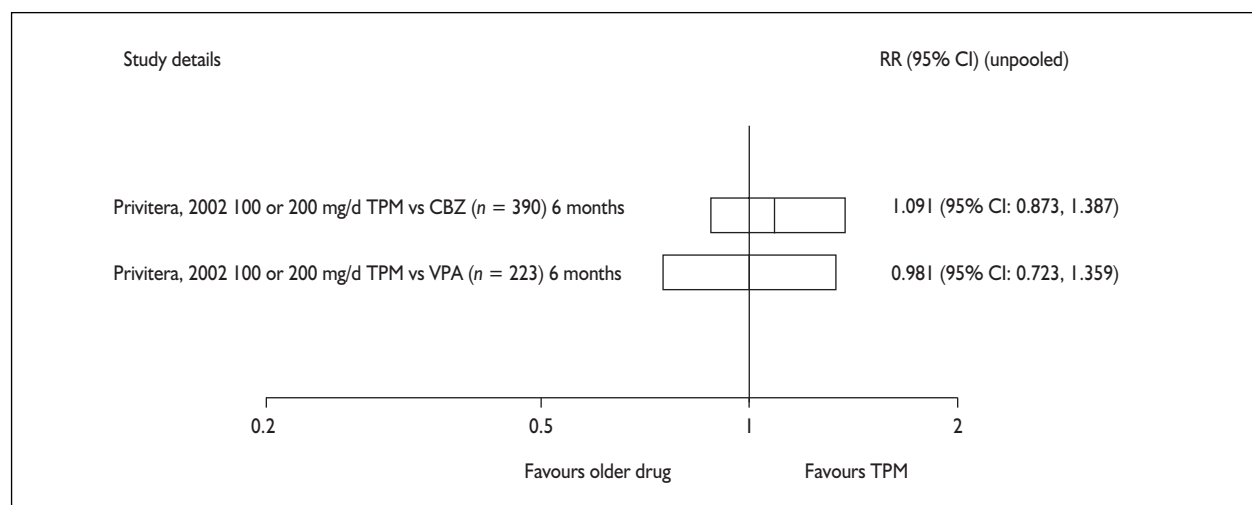
Characteristics	Studies	RR (95% CI)
n = 37	Aikia, 1992 <sup>58</sup>	0.775 (95% CI: 0.413 to 1.415)
n = 287	Bill, 1997 <sup>124</sup>	1.022 (95% CI: 0.804 to 1.298)
<b>OXC vs PHT in newly diagnosed patients with partial/generalised seizures, 48–52 weeks follow-up</b>	<b>Pooled (n = 2)</b>	<b>Pooled RR = 0.987 (95% CI: 0.791 to 1.232)</b>
		<b>Heterogeneity, Q = 0.702 (df = 1), p = 0.402</b>

Data were pooled from the two trials comparing OXC and PHT (see *Table 14*).<sup>58,124</sup> The resultant pooled RR (fixed effects) was not significant. Overall, based on the available evidence, monotherapy OXC does not appear to be more or less effective than older drugs. Of particular concern is that the studies included both patients with partial and patients with generalised seizure types, but OXC is licensed only for partial seizures. Therefore, the applicability of the findings to the licensed monotherapy treatment of patients with partial seizures is also unclear.

Data relating to the comparison of monotherapy TPM with older drugs were limited to one unpublished non-inferiority study comparing TPM with CBZ or VPA, which was submitted by the manufacturer.<sup>94</sup> This study involved 621 newly diagnosed participants with either partial or generalised seizures and followed the effects of therapy over a period of 6 months. However, the study suffered from a number of potential

problems with regards to its overall design and quality, which may influence the robustness of the data.

First, both children and adults were included in the study and the outcome data were not presented separately for children and adults. As this review is concerned only with the treatment of adults, the data from this study may not be generally applicable. Second, physicians were allowed to choose which branch of the trial they wished participants to enter (i.e. TPM versus VPA or TPM versus CBZ). Within each of the specified branches participants were initially randomised to one of two doses of TPM (100 or 200 mg/day) or the comparator drug. However, the study was only powered with the aim of combining the two TPM dose groups within each branch should the 200 mg/day group not appear to be more effective. This suggests that the study was probably not sufficiently powered to detect a difference between the two doses. The study also pooled the



**FIGURE 5** Proportion of seizure-free participants (RRs, 95% CI) for monotherapy trials of TPM vs older drugs (ITT data)

TPM treatment groups across the branches and compared the combined TPM group with the older drugs, thereby breaking the randomisation within the two branches. The authors state the groups were homogeneous based on a chi-squared analysis, but the findings of the study should be interpreted with caution in view of the design used. Finally, the dose of comparator (600 mg/day CBZ) was below the usual recommended dose (800–1200 mg/day), which may bias the findings in favour of TPM.

In order to provide an equivalent comparison between studies, unpooled RRs based on ITT data are shown in *Figure 5* for both comparisons of TPM with older drugs (TPM versus VPA and TPM versus CBZ). Both were not statistically significant and should be interpreted with great caution for the reasons stated previously. However, as this trial uses a non-inferiority design, the ILAE recommends that per protocol data be used. In this case, the per protocol data were not reported in the trial report and so this analysis could not be performed. Using ITT data suggests false equivalence. In summary, based on the available evidence, monotherapy TPM does not appear to be more or less effective than older drugs.

#### ii. 50% reduction in seizure frequency

Five out of the 19 studies of newer drugs versus older drugs (monotherapy) reported the proportion of participants who experienced at least a 50% decrease in seizure frequency. A summary of the main characteristics of these studies is presented in *Table 15*.

Three studies compared LTG with an older drug.<sup>114,116,122</sup> Two studies<sup>116,122</sup> used VPA as a

comparator, of which one<sup>122</sup> also compared LTG with CBZ. The third study compared LTG with ‘conventional therapy’, which included VPA, CBZ or PHT.<sup>114</sup> All of the studies used doses of LTG within the recommended ranges. The studies included mixed populations of patients with partial or generalised seizures. Two of the studies focused on refractory disease<sup>114,122</sup> but it was unclear whether the third study<sup>116</sup> involved newly diagnosed or refractory patients. All of the trials followed participants for a similar period (range 28–32 weeks, mean 31 weeks). Two trials<sup>114,116</sup> included 115–133 participants whereas the third trial was larger (877 participants).<sup>122</sup>

Overall, the trials were of reasonable quality, although two involved physicians choosing which older drug therapy participants received.<sup>114,122</sup> This may have influenced the findings of the studies.

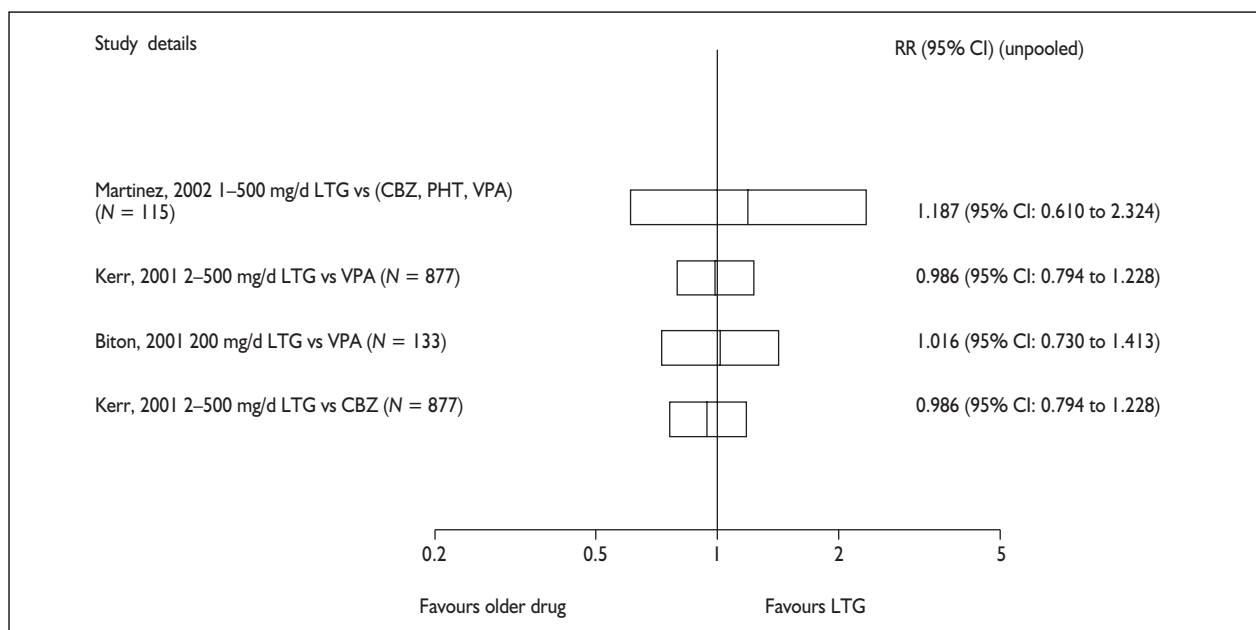
RRs (95% CI) were calculated for each individual study based on ITT data (see *Figure 6*). None of the studies showed statistically significant differences between LTG and older drugs. Pooled RRs (95% CI) were not calculated owing to the presence of clinical (different participant characteristics, drug comparisons, drug doses and length of follow-up) and statistical ( $Q$ -statistic) heterogeneity between the three studies. Overall, the available evidence shows no consistent statistically significant differences between LTG and older drugs. In addition, it is difficult to assess the applicability of findings from the trials of mixed seizure types to the individual seizure types.

Two studies compared monotherapy OXC with older comparator drugs. Both used CBZ as a

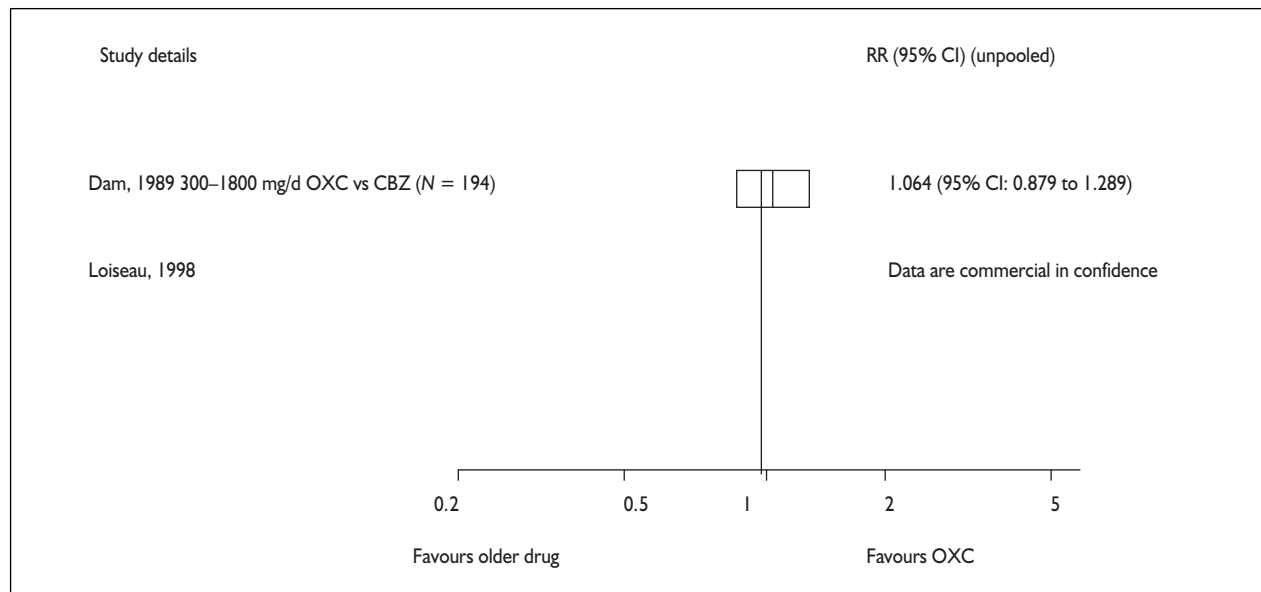
**TABLE 15** Summary of studies (monotherapy, newer drugs vs older drugs) assessing proportion of participants experiencing at least a 50% decrease in seizure frequency

Drug	Study characteristics <sup>a</sup>				
	Refractory/ newly diagnosed	Seizure type	Dose Follow-up N	Comments	Study details
LTG	Refractory	Combination of partial/generalised	100–500 mg/day 32 weeks N = 115	LTG vs conventional therapy (CBZ, PHT or VPA; doses NS). Physicians were allowed to choose which of the conventional therapies their patients received	Martinez, 2002 <sup>114</sup>
	Refractory	Combination of partial/generalised	200–500 mg/day 28 weeks N = 877	LTG vs CBZ (dose NS) LTG vs VPA (dose NS). Participants were assigned to either the LTG vs CBZ or the LTG vs VPA branch of the study according to their physician's choice	Kerr, 2001 <sup>122</sup>
	Combination of newly diagnosed/ refractory	Combination of partial/generalised	200 mg/day 32 weeks N = 133	LTG vs VPA (20 mg/kg/day)	Biton, 2001 <sup>116</sup>
OXC	Newly diagnosed	Combination of partial/generalised	300–1800 mg/day 48 weeks N = 194	OXC vs CBZ (300–1400 mg/day)	Dam, 1989 <sup>125</sup>
			<b>[Information relating to this study is designated commercial-in-confidence and has been removed]</b>		
TPM	No studies				

N, total number of participants randomised; NS, not stated.  
<sup>a</sup> All were parallel, superiority trials unless stated otherwise.

**FIGURE 6** Proportion of 50% responders (unpooled RRs, 95% CI) for monotherapy trials of LTG vs older drugs (ITT data)





**FIGURE 7** Proportion of 50% responders (unpooled RRs, 95% CI) for monotherapy trials of OXC vs older drugs (ITT data)

comparator in patients with either partial or generalised seizures. One study focused on 194 newly diagnosed patients and followed treatment over a period of 48 weeks.<sup>125</sup> Information relating to the other study is designated commercial-in-confidence<sup>72</sup> (text relating to this study has been removed).

It was not possible to combine the data from the two trials owing to clinical (participant characteristics) and statistical ( $Q$ -statistic) heterogeneity between the studies. The published trial was of reasonable quality and the unpooled RR failed to show any statistically significant differences between OXC and CBZ in terms of the proportion of 50% responders (see *Figure 7*).<sup>125</sup>

Overall, based on the available evidence, there were no statistically significant differences between OXC and older drugs.<sup>125</sup> Of particular concern is that the study included both patients with partial and patients with generalised seizure types, but OXC is licensed only for the treatment of partial seizures. Therefore, the applicability of findings to the licensed monotherapy treatment of patients with partial seizures is unclear.

No studies that compared monotherapy TPM with older drugs were identified.

#### *b. Time to first seizure*

Five out of 19 studies of newer versus older drugs (monotherapy) reported the time to first seizure. A summary of the main characteristics of these studies is presented in *Table 16*.

No studies compared monotherapy OXC with older drugs with regard to the time to first seizure.

Three studies examined the effectiveness of monotherapy LTG versus CBZ<sup>117,120,121</sup> and a fourth study compared monotherapy LTG with PHT.<sup>75</sup> All of the studies used a parallel superiority design and recruited newly diagnosed patients with either partial or generalised seizure types. One of the studies specifically examined the effects of monotherapy LTG in elderly patients aged  $\geq 65$  years.<sup>117</sup> In general, the studies were of reasonable size recruiting between 150 and 260 participants (mean = 205) and followed the course of treatment for between 24 and 48 weeks (mean = 37 weeks).

Overall, the quality of the studies was reasonable. However, two of studies used doses of comparator (600 mg/day CBZ) below the usual recommended range (800–1200 mg/day), which may bias the findings in favour of LTG.<sup>120,121</sup>

*Table 17* reports the findings of the four monotherapy LTG studies. Where HRs (95% CI) were reported, data have been included in the table. Study data were not combined owing to clinical (different study designs, length of follow-up, drug doses, comparators) and statistical heterogeneity.

None of the studies reported statistically significant differences between monotherapy LTG and older drugs. Two studies reported individual HRs for the different seizure types (partial and

**TABLE 16** Summary of studies (monotherapy, newer drugs vs older drugs) assessing time to first seizure

Drug	Study characteristics <sup>a</sup>				
	Refractory/ newly diagnosed	Seizure type	Dose Follow-up N	Comments	Study details
LTG	Newly diagnosed	Combination of partial/generalised	75–500 mg/day 24 weeks N = 150	Specifically looks at elderly patients, LTG vs CBZ (200–2000 mg/day)	Brodie, 1999 <sup>117</sup>
	Newly diagnosed	Combination of partial/generalised	Max. 400 mg/day 48 weeks N = 181	LTG vs PHT (max. 600 mg/day)	Steiner, 1999 <sup>75</sup>
	Newly diagnosed	Combination of partial/generalised	150 mg/day 48 weeks N = 260	LTG vs CBZ (600 mg/day)	Brodie, 1995 <sup>121</sup>
	Newly diagnosed	Combination of partial/generalised	100 or 200 mg/day 26 weeks N = 228	Two doses of LTG vs CBZ (600 mg/day)	Reunanen, 1996 <sup>120</sup>
OXC	No studies				
TPM	Newly diagnosed	Combination of partial/generalised	100 or 200 mg/day 6 months N = 621	Non-inferiority trial. Two doses of TPM compared with CBZ (600 mg/day). Physicians were allowed to choose whether they wanted participants to be entered into the TPM vs CBZ or the TPM vs VPA branch of the trial	Privitera, 2002 <sup>94</sup>

N, total number of randomised participants.  
<sup>a</sup> All were parallel, superiority trials unless stated otherwise.

**TABLE 17** Individual HR (95% CI) (time to first seizure) for newer vs older drugs (monotherapy)

Drug	Study	Comparators	HR (95% CI)
LTG	Brodie, 1999 <sup>117</sup>	LTG vs CBZ	No difference between the treatments
	Steiner, 1999 <sup>75</sup>	LTG vs PHT	All seizure types: HR 1.4 (95% CI: 0.8 to 2.3) Partial seizures: HR 1.0 (95% CI: 0.5 to 2.2) Primary generalised seizures: HR 1.5 (95% CI: 0.7 to 3.2). Secondarily generalised seizures: none occurred in the LTG group so no HR could be calculated. Difference between LTG and PHT was not significant
	Brodie, 1995 <sup>121</sup>	LTG vs CBZ	HR 0.8 (95% CI: 0.6 to 1.2). There was no significant difference between the two groups in time to first seizure either for the whole study population or for the subgroup with partial seizures with or without secondary generalisation or the subgroup with primary tonic-clonic seizures
	Reunanen, 1996 <sup>120</sup>	Two doses of LTG vs CBZ	LTG 100 mg/day vs CBZ: HR = 0.8 (95% CI: 0.5 to 1.4) LTG 200 mg/day vs CBZ: HR = 0.9 (95% CI: 0.5 to 1.6)
TPM	Privitera, 2002 <sup>94</sup>	TPM vs CBZ	Only combined HR given for 100/200 mg/day TPM vs CBZ/VPA: 1.081 (95% CI: 0.847 to 1.380)
	Privitera, 2002 <sup>94</sup>	TPM vs VPA	

generalised), but again both failed to find statistically significant differences between monotherapy LTG and older comparators.<sup>75,121</sup>

Only one study investigated the effectiveness of monotherapy TPM over a 6-month treatment period.<sup>94</sup> The study used a non-inferiority design and recruited 621 newly diagnosed patients (both partial and generalised seizure types). Two doses of TPM (100 and 200 mg/day) were compared with 600 mg/day CBZ and 1250 mg/day VPA. There were a number of issues relating to the quality of this study, which may have affected the robustness of the final data. These have been discussed previously with regard to the reporting of the proportion of seizure-free participants, and similarly great caution is required when interpreting the findings of this study with regard to time to first seizure.

*Table 17* shows that there were no statistically significant differences between TPM (100/200 mg/day) and older drugs (CBZ and PHT combined).

Overall, the evidence relating to time to first seizure suggested there were no significant differences between newer and older drugs in newly diagnosed patients. However, data for OXC and TPM were limited and consequently it is difficult to make overall conclusions about the effectiveness of newer versus older drugs.

### c. Time to withdrawal/exit

Eight out of 19 studies of newer versus older drugs (monotherapy) reported the time to withdrawal/exit. A summary of the main characteristics of these studies is presented in *Table 18*.

Five studies compared the effectiveness of monotherapy LTG versus older drugs. Two made comparisons with CBZ,<sup>120,121</sup> one with PHT,<sup>75</sup> one with VPA<sup>112</sup> and one with conventional treatment.<sup>114</sup> Three studies recruited newly diagnosed patients with either partial or generalised seizures<sup>75,120,121</sup> and the remaining two studies recruited refractory patients with either partial<sup>112</sup> or mixed seizures (partial or generalised).<sup>114</sup> The numbers of participants recruited varied from 115 to 260 (mean = 188) and treatment durations from 12 to 48 weeks (mean = 33 weeks).

Overall, the studies were of reasonable quality. However, two studies used doses of comparator (CBZ 600 mg/day), which were lower than the recommended range, thereby possibly favouring

LTG.<sup>120,121</sup> One study suffered from a high dropout rate, resulting in a large amount of missing data that could influence the study findings.<sup>112</sup> In addition, one other study allowed physicians to choose which of the comparator drugs patients received once they had been randomised to conventional treatment, which could bias the study findings.<sup>114</sup>

Three of the studies reported HRs (see *Table 19*). There were no statistically significant differences in time to exit/withdrawal in the study comparing LTG with phenytoin.<sup>75</sup> Similarly, one study comparing LTG with CBZ failed to find a statistically significant difference between the two drugs, although the 200 mg/day LTG dose did show a non-significant difference in favour of LTG.<sup>120</sup> The remaining study that compared monotherapy LTG with CBZ reported a statistically significant difference in time to exit/withdrawal in favour of LTG (HR 1.57, 95% CI: 1.07 to 2.31).<sup>121</sup> However, as has already been discussed both studies used low doses of CBZ which could influence the outcome in favour of LTG.

The two remaining studies of LTG monotherapy only reported mean/median times to exit/withdrawal and there was insufficient data to calculate an HR (see *Table 19*). These studies reported a difference in favour of LTG, which in the case of partial seizures in refractory patients appeared to be statistically significant, although the study only followed patients over a 12-week period.<sup>112</sup> The significance of these findings is unclear in view of the potential quality issues previously mentioned and the inability to calculate and compare appropriate data (i.e. HRs). Data were not combined owing to clinical (different populations, length of follow-up, drug doses, comparators) and statistical heterogeneity. Overall, the evidence comparing monotherapy LTG with older drugs is limited.

Two parallel superiority studies compared the effectiveness of monotherapy OXC versus older drugs.<sup>123,124</sup> Both recruited large numbers (249<sup>123</sup> and 287<sup>124</sup>) of newly diagnosed patients with either partial or generalised seizures and used treatment periods of 48 weeks. One study compared OXC with VPA<sup>123</sup> and the other with PHT.<sup>124</sup> Both studies were of reasonable quality, but failed to report HRs.

Data from the two studies were not combined owing to clinical (different comparators) and statistical (*Q*-statistic) heterogeneity. The unpooled

**TABLE 18** Summary of studies (monotherapy, newer drugs vs older drugs) assessing time to withdrawal/exit

Drug	Study characteristics <sup>a</sup>				
	Refractory/ newly diagnosed	Seizure type	Dose Follow-up N	Comments	Study details
LTG	Newly diagnosed	Combination of partial/generalised	Max. 400 mg/day 48 weeks N = 181	LTG vs PHT (max. 600 mg/day)	Steiner, 1999 <sup>75</sup>
	Newly diagnosed	Combination of partial/generalised	150 mg/day 48 weeks N = 260	LTG vs CBZ (600 mg/day)	Brodie, 1995 <sup>121</sup>
	Newly diagnosed	Combination of partial/generalised	100 mg/day or 200 mg/day 26 weeks N = 228	LTG (100 mg/day or 200 mg/day) vs CBZ (600 mg/day)	Reunanen, 1996 <sup>120</sup>
	Refractory	Partial	400–500 mg/day 12 weeks N = 156	LTG vs VPA (100 mg/day)	Gilliam, 1998 <sup>112</sup>
	Refractory	Combination of partial/generalised	NS 32 weeks N = 115	LTG vs conventional therapy (CBZ, PHT or VPA; doses NS). Physicians were allowed to choose which of the conventional therapies their patients received	Martinez, 2002 <sup>114</sup>
OXC	Newly diagnosed	Combination of partial/generalised	Mean = 900 g/day 48 weeks N = 249	OXC vs VPA (600–2700 mg/day)	Christe, 1997 <sup>123</sup>
	Newly diagnosed	Combination of partial/generalised	Mean = 1028 g/day 48 weeks N = 287	OXC vs PHT (100–650 mg/day)	Bill, 1997 <sup>124</sup>
TPM	Newly diagnosed	Combination of partial/generalised	100 mg/day or 200 mg/day 6 months N = 621	Non-inferiority trial. Two doses of TPM (100 or 200 mg/day) were combined and compared with CBZ (600 mg/day) or VPA (1250 mg/day). Physicians were allowed to choose whether they wanted participants to be entered into the TPM vs CBZ or the TPM vs VPA branches of the trial	Privitera, 2002 <sup>94</sup>

N, total number of randomised participants; NS, not stated.  
<sup>a</sup> All were parallel, superiority trials unless stated otherwise.

**TABLE 19** Time to exit/withdrawal (unpooled data) for monotherapy trials of newer vs older AEDs

Drug	Study	Comparators	HR (95% CI) (or other reported data)
LTG	Steiner, 1999 <sup>75</sup>	LTG vs PHT	Unadjusted HR = 0.885, (95% CI: 0.555 to 1.410) Adjusted (for baseline seizure counts) HR = 0.935 (95% CI: 0.583 to 1.499)
	Brodie, 1995 <sup>121</sup>	LTG vs CBZ	HR 1.57 (95% CI: 1.07 to 2.31)
	Reunanen, 1996 <sup>120</sup>	LTG vs CBZ	LTG 100 mg vs CBZ: HR = 0.9 (95% CI: 0.6 to 1.3) LTG 200 mg vs CBZ: HR = 1.3 (95% CI: 0.8 to 1.9)
	Gilliam, 1998 <sup>112</sup>	LTG vs VPA	LTG: Median = 168 days ( $p \leq 0.001$ ) VPA: Median = 57 days
	Martinez, 2002 <sup>114</sup>	LTG vs conventional therapy (CBZ/PHT/VPA)	LTG ( $n = 57$ ): mean time = 175 days (SD 83.1) Conventional therapy (PHT, VPA or CBZ) ( $n = 58$ ): mean time = 156 days (SD 80.7)
OXC	Christe, 1997 <sup>123</sup>	OXC vs VPA	The log-rank test showed no difference between treatment groups ( $p = 0.33$ ) (data not reported)
	Bill, 1997 <sup>124</sup>	OXC vs PHT	The log-rank test showed a statistically significant difference between treatment groups ( $p = 0.02$ ) in favour of OXC (data not reported)
TPM	Privitera, 2002 <sup>94</sup>	TPM vs CBZ	Only combined HR given for 100/200 mg/day TPM vs CBZ/VPA: 1.223 (95% CI: 0.917 to 1.631)
	Privitera, 2002 <sup>94</sup>	TPM vs VPA	

SD, standard deviation.

data (see *Table 19*) showed a statistically significant difference between treatment groups ( $p = 0.02$ ) in favour of OXC compared with PHT.<sup>124</sup> No statistically significant differences were evident between monotherapy OXC and VPA,<sup>123</sup> although this study did use a lower mean dose of OXC than that of Bill and colleagues.<sup>124</sup>

Only one study compared monotherapy TPM versus older drugs.<sup>94</sup> This study has been discussed previously with regard to the proportion of seizure-free patients and the time to first seizure. The HR reported in *Table 19*, suggests that although a difference in favour of TPM versus the older drugs (CBZ and VPA) was evident, it was not statistically significant. However, as reported previously, this study suffers from a number of potential problems that may bias the findings and so the data regarding time to exit/withdrawal should also be regarded with great caution. This leaves no good-quality evidence on which to base an assessment of monotherapy TPM versus older drugs.

#### d. Quality of life

Nine out of 19 studies of monotherapy treatment compared QoL outcomes between newer drugs and older drugs. These studies are briefly described in *Table 20*.

Seven studies used monotherapy LTG. One compared LTG with CBZ,<sup>77</sup> one with PHT,<sup>75</sup> two with VPA<sup>122,126</sup> and two with conventional therapy.<sup>114,118</sup> Three studies used monotherapy OXC. One compared OXC with CBZ,<sup>125</sup> one with PHT<sup>124</sup> and one with VPA.<sup>123</sup> There were no studies of monotherapy TPM.

All of the studies used a parallel superiority design, but a variety of measures were used to assess quality of life (see *Table 21*). In total, 10 different types of QoL measures were used, all of which were used in the LTG studies and two in the OXC studies, with subjective global evaluations by both the patient and the physician/investigator being common to both drugs. The most common measure used was subjective global evaluation by the physician/investigator.

Details of the individual study data are reported in Appendix 23 and details of the individual QoL measures in Appendix 4. *Table 22* summarises the overall findings of the QoL assessments. Three of the six LTG trials were in newly diagnosed patients with either partial or generalised seizure types.<sup>75,77,118</sup> Two trials included patients with either refractory partial or generalised seizures.<sup>114,122</sup> One trial included both refractory

**TABLE 20** Total number of studies assessing QoL outcomes (monotherapy, newer vs older drugs)

Drug	Total no. of studies assessing QoL outcomes			Study details
	Crossover	Parallel	All studies	
LTG	0	6	6	Gillham, 2000; <sup>77</sup> GlaxoSmithKline, 2000; <sup>118</sup> Kerr, 2001; <sup>122</sup> Martinez, 2002; <sup>114</sup> Sackellares, 2000; <sup>126</sup> Steiner, 1999 <sup>75</sup>
OXC	0	3	3	Bill, 1997; <sup>124</sup> Christe, 1997; <sup>123</sup> Dam, 1989 <sup>125</sup>
TPM	0	0	0	

**TABLE 21** Types of QoL assessments used (monotherapy, newer vs older drugs)

QoL measure	No. of studies using QoL measure			
	LTG	OXC	TPM	Total
SEALS	3	0	0	3
QOLIE-89	1	0	0	1
QOLIE-31	2	0	0	2
Subjective global evaluations (patient)	1	2	0	3
Subjective global evaluations (physician/investigator)	1	3	0	4
Patient acceptability	1	0	0	1
BDI	1	0	0	1
POMS	1	0	0	1
CDRS	1	0	0	1
Liverpool AEP	1	0	0	1
Total no. of different measures used	10	2	0	–

BDI, Beck Depression Inventory; CDRS, Cornell Dysthymia Rating Self-report Scale; Liverpool AEP, Adverse Events Profile; POMS, Profile of Moods States; QOLIE-31, Quality of Life in Epilepsy Inventory-31; QOLIE-89, Quality of Life in Epilepsy Inventory-89; SEALS, Side Effect and Life Satisfaction Inventory.

**TABLE 22** Summary of overall findings of QoL assessments (monotherapy, newer vs older drugs)

Drug	Summary of findings of QoL assessments
LTG	Four <sup>75,77,114,122</sup> of the six <sup>75,77,114,118,122,126</sup> studies examining LTG found statistically significant differences in favour of LTG on at least one measure of QoL. However, the quality of these studies was generally poor. Based on the available evidence, it is unclear whether LTG monotherapy is more or less effective than older drugs in terms of QoL.
OXB	Only one <sup>124</sup> of the three <sup>123–125</sup> studies examining OXC found statistically significant differences in favour of OXC, using subjective measures of QoL. Based on these findings, there is no strong evidence for OXC monotherapy affecting QoL in comparison with older drugs.

and newly diagnosed patients who experienced either partial or generalised seizure types.<sup>126</sup> The studies recruited between 122 and 877 participants (mean = 422) and followed-up the effects of therapy for between 20 and 48 weeks (mean = 34 weeks). Overall, the quality of the trials was poor. Four trials may have lacked power to detect differences between the AEDs.<sup>114,118,122,126</sup> Three trials allowed physicians

to choose which comparator participants received either before<sup>122</sup> or after<sup>114,118</sup> they were randomised and were also open-label trials. One trial provided no details of patients baseline characteristics.<sup>122</sup> In one trial over 50% of patients in each of the two treatment groups discontinued by the end of the study and the dose of the comparator drug was sometimes not within the recommended range.<sup>75</sup> All of these issues could

affect study findings and must be considered when interpreting the data.

All three studies using SEALS<sup>75,77,122</sup> and both studies using QOLIE-31<sup>114,122</sup> found statistically significant differences in QoL in favour of LTG in comparison with older AEDs. However, in some cases these differences were only found at one time point and not in subsequent assessments.<sup>77</sup> One study using one or more of the other eight types of QoL measures reported statistically significant differences in at least one of these measures in favour of LTG.<sup>126</sup> Considering these findings in context of the quality issues discussed above, there was no strong evidence either in favour of or against LTG monotherapy compared with older drugs in terms of quality of life.

All three OXC trials included newly diagnosed patients with either partial or generalised seizures. However, OXC is not licensed for the treatment of generalised seizures. Follow-up was 48 weeks<sup>125</sup> or 56 weeks,<sup>123,124</sup> and studies recruited between 235 and 287 participants (mean = 257). Overall, the trials were of reasonable quality. However, two studies used doses of OXC and comparator drugs that were not within the recommended range.<sup>124,125</sup> One of these studies may have lacked

power to detect differences between AEDs and no sample size calculations were reported.<sup>125</sup> In addition, over 20% of the follow-up data were classified as missing. These issues may influence the study findings and should be taken into consideration when interpreting the data.

Only one study found statistically significant differences in favour of OXC in comparison with an older drug. This used subjective QoL measures (patient and physician global evaluations).<sup>124</sup> Based on these findings, there is no strong evidence of OXC monotherapy affecting QoL compared with older drugs.

#### e. Cognitive function

Two out of 19 studies of newer versus older AEDs assessed some aspect of cognitive functioning (see *Table 23*). One study compared monotherapy LTG with CBZ<sup>47</sup> and the other compared monotherapy OXC with CBZ.<sup>58</sup> Both were parallel studies of newly diagnosed patients with partial or generalised seizures, which used similar durations of treatment (48 weeks<sup>47</sup> and 52 weeks<sup>58</sup>).

Nine different cognitive assessment measures were used (see *Table 24*).

**TABLE 23** Total number of studies assessing cognitive function

Drug	Total no. of studies assessing cognitive function			Study details
	Crossover	Parallel	All studies	
LTG	0	1	1	Brodie, 1999 <sup>47</sup>
OXC	0	1	1	Aikia, 1992 <sup>58</sup>
TPM	0	0	0	

**TABLE 24** Assessments used to measure cognitive function

Cognitive measure	No. of studies using cognitive measure			
	LTG	OXC	TPM	Total
Stroop test	1	1	0	2
Logical reasoning test	1	0	0	1
Verbal learning	1	0	0	1
Recognition test	1	0	0	1
Semantic processing test	1	0	0	1
List learning	0	1	0	1
Trailmaking test A	0	1	0	1
Trailmaking test B	1	1	0	2
Modified finger tapping test	0	1	0	1
Total no. of different measures used	6	5	0	–

**TABLE 25** Summary of overall findings of cognitive assessments

Drug	Summary of findings of cognitive assessments
LTG	The authors concluded that a long-term differential effect on cognitive functioning was found in favour of LTG <sup>47</sup>
OXC	The one study in this category found that there were no significant differences in the effects of OXC compared to PHT with cognitive functioning <sup>58</sup>

Details of the individual study data are reported in Appendix 23 and details of the cognitive measures in Appendix 5. *Table 25* summarises the overall findings of the cognitive assessments.

Six cognitive tests reported a significant difference in favour of LTG on at least one visit.<sup>47</sup> Data included four follow-up visits and nine different outcome measures. However, it was unclear whether the two treatment groups had similar baseline levels of cognitive function. In addition, the number of participants was lower than the total number included in the main effectiveness part of the trial.<sup>127</sup> The larger sample presented a weaker positive effect in favour of LTG. The study did not specify whether the cognitive assessor was blind to treatment allocation, what time of day tests were performed or whether participants who were postictal had their assessment rescheduled. Given the potentially poor quality of the study, the findings should be interpreted with caution.

The OXC study did not report an *a priori* estimate of sample size.<sup>58</sup> Given the small sample size (37 participants), the study may be underpowered. It was not possible to carry out a full assessment of the quality of the trial owing to poor reporting of randomisation, concealment and blinding. ITT data were not reported.

The study did not state whether participants who were postictal had their assessment rescheduled. It also did not specify whether repeated testing was carried out at the same time of day or whether tests were administered in a set order.

Overall, the studies do not present strong good-quality evidence of either a positive or negative effect of newer drugs compared with older drugs. Both studies included participants with partial or generalised onset seizures, although OXC is not licensed for generalised onset seizures. Data were not reported separately for the different seizure types, consequently the relevance of the findings to clinical practice is unclear.

#### Summary statement for monotherapy newer versus older AEDs

The most commonly reported outcome measure in studies comparing newer monotherapy AEDs with older AEDs was the proportion of seizure-free patients. Data were available for all three monotherapy AEDs, although data relating to OXC were limited. Similarly, only one poor-quality study reported for monotherapy TPM.

In most cases the studies recruited a mixture of newly diagnosed patients with partial or generalised seizures, so the applicability of the findings to individual seizure types was unclear. All of the trials were of a reasonable size but none considered treatment periods of greater than 1 year duration. Older drugs comparators included CBZ, VPA and PHT.

There was limited poor-quality evidence to suggest a significant difference in cognitive function for LTG and OXC compared with older AEDs. However, no consistent statistically significant differences were found in the other outcomes.

### 3. Newer drugs versus newer drugs

#### a. Seizure frequency

##### i. Seizure freedom

The one study that compared a newer AED with another newer AED (monotherapy) reported the proportion of seizure-free participants. A summary of the main characteristics of this study is presented in *Table 26*.

This non-inferiority study included 309 newly diagnosed participants with either partial or generalised seizures and compared monotherapy LTG with monotherapy GBP.<sup>93</sup> This was a reasonable quality study but only followed treatment over a 30-week period. In addition,



**TABLE 26** Summary of studies (monotherapy, newer drugs vs newer drugs) assessing proportion of seizure-free participants

Drug	Study characteristics <sup>a</sup>				
	Refractory/ newly diagnosed	Seizure type	Dose Follow-up N	Comments	Study details
LTG	Newly diagnosed	Combination of partial/generalised	100–300 mg/day 30 weeks N = 309	Non-inferiority trial LTG vs GBP 1800–3600 mg/day	Brodie, 2002 <sup>93</sup>
OXC			No studies		
TPM			No studies		

N, total number of participants randomised.  
<sup>a</sup> Parallel, superiority trial.

**TABLE 27** Summary of studies (monotherapy, newer drugs vs newer drugs) assessing time to first seizure

Drug	Study characteristics <sup>a</sup>				
	Refractory/ newly diagnosed	Seizure type	Dose Follow-up N	Comments	Study details
LTG	Newly diagnosed	Combination	100–300 mg/day 30 weeks N = 309	Non-inferiority trial, LTG vs GBP 1800–3600 mg/day	Brodie, 2002 <sup>93</sup>
OXC			No studies		
TPM			No studies		

N, total number of participants randomised.  
<sup>a</sup> Parallel, superiority trial.

**FIGURE 8** Proportion of seizure-free participants (RR, 95% CI) for the monotherapy trial of LTG vs GBP (per protocol data)

**[Data have been designated commercial-in-confidence and have been removed]**

the dose of GBP was above that currently recommended, but as yet GBP is only licensed for adjunctive and not monotherapy use, hence this comparison is not relevant to clinical practice.

One study considered this outcome and is presented in *Table 27*.

Details of this study have been reported previously with regard to the proportion of seizure-free participants. Based on ITT data there was no

difference between monotherapy LTG and GBP (HR = 1.061, 95% CI: 0.758 to 1.485). However, ITT data may suggest false equivalence. As mentioned previously, the relevance of this study to clinical practice is unclear and similarly it was difficult to assess the effectiveness of newer AEDs versus other newer AEDs given the lack of data.

ii. 50% reduction in seizure frequency  
**[Data have been designated commercial-in-confidence and have been removed]**

b. Time to first seizure  
**[Data have been designated commercial-in-confidence and have been removed]**

**TABLE 28** Summary of studies (monotherapy, newer drugs vs newer drugs) assessing time to withdrawal/exit

Drug	Study characteristics <sup>a</sup>				
	Refractory/ newly diagnosed	Seizure type	Dose Follow-up N	Comments	Study details
LTG	Newly diagnosed	Combination partial/generalised seizures	100–300 mg/day 30 weeks N = 309	Non-inferiority trial, LTG vs GBP 1800–3600 mg/day	Brodie, 2002 <sup>93</sup>
OXC			No studies		
TPM			No studies		

N, total number of participants randomised.  
<sup>a</sup> Parallel, superiority trial.

**c. Time to withdrawal/exit**

The one study that compared a newer AED with another newer AED (monotherapy) reported the time to withdrawal/exit. A summary of the main characteristics of this study is presented in *Table 28*.

This study has been considered with regards to previously described outcomes comparing newer monotherapies versus each other.

**[Data have been designated commercial-in-confidence and have been removed]**

This study had an upper 90% CI, which was less than the predetermined upper equivalence level (1.85). However, when the data were recalculated to report 95% CIs, this was not the case. Although this HR was based on evaluable patient data as recommended by ILAE guidelines for equivalence/non-inferiority trials, the relevance to practice is unclear given the fact that GBP is not licensed for monotherapy use.

**[Data have been designated commercial-in-confidence and have been removed]**

Given the lack of available data comparing newer drugs with each other, it was difficult to assess the effectiveness of newer AEDs compared with other newer AEDs.

**d. Quality of life**

The one study that compared a newer AED with another newer AED (monotherapy) did not report QoL outcomes.

**e. Cognitive function**

The one study that compared a newer AED with

another newer AED (monotherapy) did not report cognitive function outcomes.

**Summary statement for monotherapy newer versus newer AEDs**

**[Data have been designated commercial-in-confidence and have been removed]**

There was insufficient evidence to assess the effectiveness of one newer AED compared with another.

**4. The use of monotherapy in special populations (elderly, intellectually disabled and pregnant women)**

There were no studies of monotherapy that examined effectiveness in participants with intellectual disabilities. Similarly, there were no studies that included pregnant women; in fact, women of childbearing age were required to use adequate methods of contraception in order to be included in trials. One study did, however, examine the effectiveness of monotherapy in elderly patients.<sup>117</sup> This parallel superiority trial compared LTG monotherapy with CBZ monotherapy in newly diagnosed patients with partial and/or generalised seizures over a period of 24 weeks. All of the participants (150) were aged  $\geq 65$  years. The study reported no statistically significant differences between the treatment groups with respect to time to first seizure and the proportion of seizure-free participants (RR = 0.905, 95% CI: 0.609 to 1.343). Although this was a reasonable quality study with no obvious problems in terms of its design, it followed treatment over only a relatively short period and the BNF advises caution when treating elderly

patients with LTG. In view of the lack of data, it was difficult to make any assessments regarding the effectiveness of monotherapy LTG, or monotherapy in general, in elderly patients.

#### Summary statement for monotherapy studies

The most commonly reported outcome measure was the proportion of seizure-free participants, followed by the time to event outcomes (first seizure and exit/withdrawal). The majority of data related to newly diagnosed participants and mixed populations of patients with partial or generalised seizures. Few studies reported data regarding the proportion of 50% responders, cognitive and QoL outcomes. In general, trials considered only the short-term effects of therapy and there was little good-quality evidence for the effectiveness of monotherapy AEDs (LTG, OXC and TPM), especially with regard to TPM and OXC.

There was insufficient evidence to assess the relative effectiveness of one newer drug as monotherapy versus another. Compared with older AEDs (CBZ, VPA and PHT), newer AEDs failed to show any statistically significant differences in outcomes, with the exception of cognitive function, where limited poor-quality evidence suggested a difference in favour of LTG and OXC compared with older AEDs. Similarly, there was little evidence to assess the effectiveness of the newer AEDs compared with placebo. Limited evidence to suggest a difference in the proportion of seizure-free participants and the time to event outcomes in favour of OXC compared with placebo should be regarded with caution.

No studies assessed the effectiveness of monotherapy AEDs in people with intellectual disabilities or pregnant women. There was very little evidence to assess the effectiveness of monotherapy AEDs in the elderly. No significant differences were found between monotherapy LTG and monotherapy CBZ in this population.

*Adjunctive therapy* All seven newer AEDs are licensed for use as adjunctive therapy in POSs. However, only LTG and TPM are licensed for use in generalised onset seizures.

Overall, 68 studies investigated the effects of adjunctive therapy: GBP (10 studies), LTG (21 studies), LEV (four studies), OXC (two studies),

TGB (seven studies), TPM (14 studies) and VGB (15 studies). Seven compared newer AEDs with old<sup>44,66,69,84,128-130</sup> and four compared one newer AED with another AED.<sup>61,131-133</sup> The remaining studies all compared newer AEDs with placebo. Forty-six studies used a parallel design and 26 were crossover studies. There was one equivalence trial.<sup>69</sup> Treatment periods ranged between 1 week and 78 weeks (mean = 22 weeks). A number of studies were continued for extended periods, but such 'follow-up' periods usually adopted an open-label, non-randomised design, which was not eligible for inclusion in the main part of the review, although was considered in the review of rare, serious and long-term AEs.

All of the studies included only patients with refractory epilepsy. Three studies included only patients with generalised onset seizures,<sup>76,79,134</sup> and 13 studies included patients with partial or generalised seizures.<sup>51,82-86,88,131,135-139</sup> The proportion of participants with each seizure type was often not reported in studies of mixed seizure types and similarly outcome data were not reported separately for each of the different seizure type. The relevance of these data to individual seizure types was unclear. The remaining studies recruited only patients with POSs. There was no information on the use of monotherapy in pregnant women and elderly patients. This makes it difficult to make statements about the use of adjunctive therapy in these groups of patients. However, eight studies included patients with intellectual disabilities.<sup>49,66,84,85,131,137,140,141</sup> In terms of the size of the adjunctive trials, the number of participants ranged from 10 to 629 (mean = 133).

*Table 29* summarises the number of studies assessing adjunctive AEDs and the outcomes reported.

#### 1. Newer drugs versus placebo

##### a. Seizure frequency

##### i. Seizure freedom

Twenty-six out of 56 studies of newer drugs versus placebo (adjunctive therapy) reported the proportion of seizure-free participants. A summary of the main characteristics of these studies is presented in *Table 30*.

One crossover trial compared adjunctive GBP (2400 mg/day) with placebo in patients with refractory partial seizures.<sup>90</sup> The study was of reasonable quality but included only 27 participants and used a relatively short treatment period of 12 weeks. First-phase data were not reported, but the authors reported that two out of 21 participants remained seizure free during GBP

**TABLE 29** Number of adjunctive studies assessing each comparison and outcome

Comparison	N	No. of studies reporting outcome measures					
		Seizure-free	50% responders	Time to 1st seizure	Time to exit	Cognitive	QoL
New vs placebo	5 (GBP)	1 (GBP)	5 (GBP)	0	0	1 (GBP)	3 (GBP)
	17 (LTG)	5 (LTG)	14 (LTG)			2 (LTG)	9 (LTG)
	4 (LEV)	4 (LEV)	4 (LEV)			3 (TGB)	1 (LEV)
	1 (OXC)	1 (OXC)	1 (OXC)			6 (VGB)	2 (TGB)
	5 (TGB)	2 (TGB)	5 (TGB)				9 (TPM)
	12 (TPM)	10 (TPM)	11 (TPM)				8 (VGB)
	12 (VGB)	5 (VGB)	11 (VGB)				
New vs old	2 (GBP)	1 (GBP)	1 (GBP)	0	0	1 (TGB)	1 (GBP)
	1 (LTG)	1 (VGB)	1 (TGB)			1 (TPM)	1 (TGB)
	1 (OXC)		1 (VGB)				2 (TPM)
	1 (TGB)						
	2 (TPM)						
	1 (VGB)						
New vs new <sup>a</sup>	3 (GBP)	3 (GBP)	3 (GBP)	0	0	0	2 (GBP)
	3 (LTG)	3 (LTG)	3 (LTG)				2 (LTG)
	1 (TGB)	1 (TGB)	1 (TGB)				1 (TGB)
	2 (VGB)	2 (VGB)	2 (VGB)				1 (VGB)

N, total number of studies.  
<sup>a</sup> N in newer AEDs vs other newer AEDs refers to the number of studies reporting comparisons including the drugs and therefore does not represent the total number of studies.

**TABLE 30** Summary of studies (adjunctive therapy, newer drugs vs placebo) assessing proportion of seizure-free participants

Drug	Study characteristics <sup>a</sup>				
	Refractory/newly diagnosed	Seizure type	Dose Follow-up N	Comments	Study details
GBP	Refractory	Partial	2400 mg/day 12 weeks N = 27	Crossover study	Leach, 1997 <sup>90</sup>
LTG	Refractory	Partial	100–250 mg/day 7 days N = 10	Crossover study	Binnie, 1987 <sup>50</sup>
	Refractory	Partial	Max. 500 mg/day 28 weeks N = 334		Schachter, 1995 <sup>56</sup>
	Refractory	Combination of partial/generalised	100 or 200 mg/day 16 weeks N = 68	Specifically looks at patients with intellectual disabilities	Veendrick-Meekes, 2000 <sup>137</sup>
	Refractory	Combination of partial/generalised	500 or 300 mg/day 24 weeks N = 216	Two doses of LTG compared with placebo	Matsuo, 1993 <sup>142</sup>
LEV	Refractory	Partial	1000 or 3000 mg/day 38 weeks N = 294	Two doses of LEV compared with placebo	Cereghino, 2000 <sup>143</sup>

*continued*

**TABLE 30** Summary of studies (adjunctive therapy, newer drugs vs placebo) assessing proportion of seizure-free participants (cont'd)

Drug	Study characteristics <sup>a</sup>				
	Refractory/ newly diagnosed	Seizure type	Dose Follow-up N	Comments	Study details
	Refractory	Partial	3000 mg/day 16 weeks N = 286	One dose of LEV compared with placebo	Ben-Menachem, 2000 <sup>144</sup>
	Refractory	Partial	1000 or 2000 mg/day 16 weeks N = 324	Two doses of LEV compared with placebo. Reports first-phase data for crossover study; Boon, 2002 <sup>80</sup>	Shorvon, 2000 <sup>145</sup>
	Refractory	Combination of partial/generalised	2000 or 4000 mg/day 24 weeks N = 119	Two doses of LEV compared with placebo	Betts, 2000 <sup>139</sup>
OXC	Refractory	Partial	600, 1200 or 2400 mg/day 28 weeks N = 694	Three doses of OXC compared with placebo	Barcs, 2000 <sup>70</sup>
TGB	Refractory	Partial	12–52 mg/day 7 weeks N = 46	Crossover study. Entry into the trial was dependent on the fulfilment of certain response criteria	Richens, 1995 <sup>146</sup>
	Refractory	Partial	16–64 mg/day 6 weeks N = 44	Crossover study. Entry into the trial was dependent on the fulfilment of certain response criteria	Crawford, 2001 <sup>147</sup>
TPM	Refractory	Partial	600 mg/day 12 weeks N = 60		Tassinari, 1996 <sup>42</sup>
	Refractory	Partial	400 mg/day 11 weeks N = 47		Sharief, 1996 <sup>148</sup>
	Refractory	Partial	600 mg/day 18 weeks N = 177		Korean Topiramate, Study Group, 1999 <sup>149</sup>
	Refractory	Partial	200, 400 or 600 mg/day 16 weeks N = 181	Three doses of TPM compared with placebo	Faught, 1996 <sup>67</sup>
	Refractory	Partial	1000 mg/day 19 weeks N = 209		Rosenfeld, 1996 <sup>41</sup>
	Refractory	Partial	200 mg/day 12 weeks N = 263		Guberman, 2002 <sup>150</sup>

continued

**TABLE 30** Summary of studies (adjunctive therapy, newer drugs vs placebo) assessing proportion of seizure-free participants (cont'd)

Drug	Study characteristics <sup>a</sup>				Study details
	Refractory/ newly diagnosed	Seizure type	Dose Follow-up N	Comments	
	Refractory	Partial	800 mg/day 13 weeks N = 56		Ben-Menachem, 1996 <sup>151</sup>
	Refractory	Partial	600, 800 or 1000 mg/day 18 weeks N = 190	Three doses of TPM compared with placebo	Privitera, 1996 <sup>68</sup>
	Refractory	Generalised onset	175 or 225 or 400 mg/day 20 weeks N = 80		Barrett, 1997 <sup>76</sup>
	Refractory	Generalised onset	175–400 mg/day 20 weeks N = 80		Biton, 1999 <sup>79</sup>
VGB	Refractory	Partial	2–3 g/day 4 months N = 40		Provinciali, 1996 <sup>152</sup>
	Refractory	Partial	Max. 4 g/day 4 weeks N = 111		Bruni, 2000 <sup>153</sup>
	Refractory	Partial	1, 3 or 6 g/day 12 weeks N = 174	Three doses of VGB compared with placebo	Dean, 1999 <sup>154</sup>
	Refractory	Partial	3 g/day 12 weeks N = 182		French, 1996 <sup>155</sup>

N, total number of participants randomised; NS, not stated.  
<sup>a</sup> All were parallel, superiority trials unless stated otherwise.

treatment compared with none out of 21 participants during the placebo period.

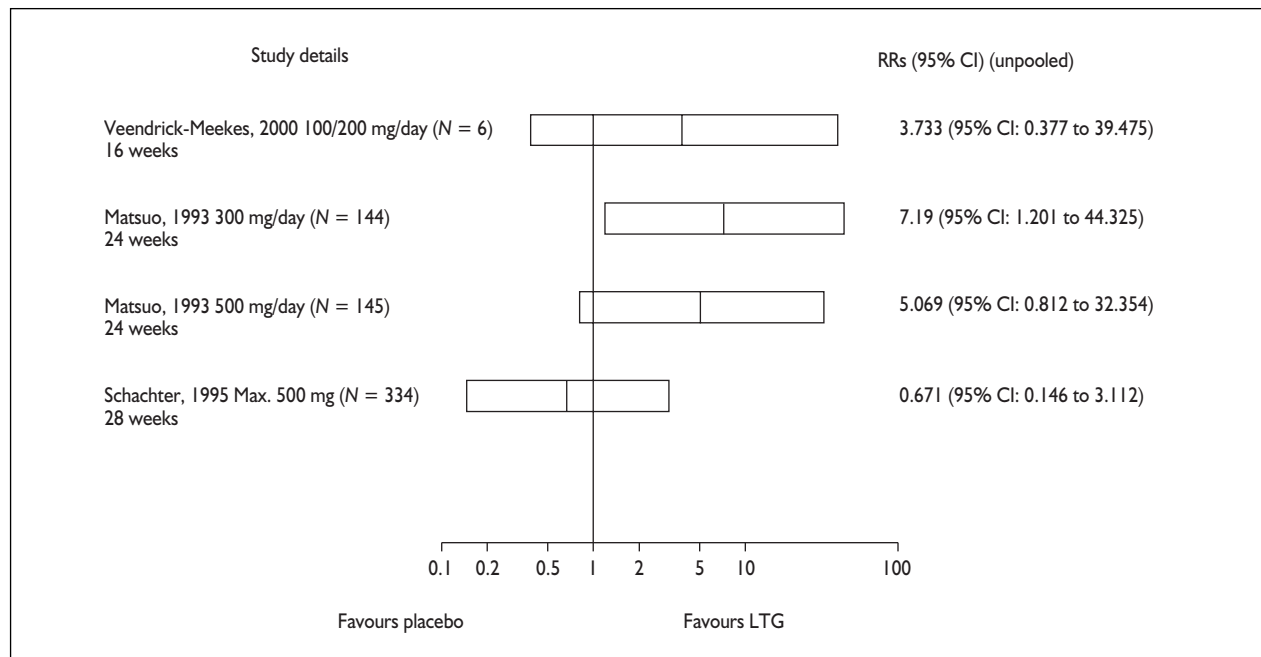
Four superiority trials, one of which used a crossover design,<sup>50</sup> compared adjunctive LTG versus placebo in patients with refractory epilepsy. In two trials, patients had either partial or generalised seizures<sup>137,142</sup> and in the other two all patients had partial seizures.<sup>50,56</sup> The trials followed up between 10 and 334 patients (mean = 130) for periods of 1–28 weeks (mean = 15 weeks). Drug doses varied between trials, but in each case were within the recommended range. One trial used two separate doses of LTG.<sup>142</sup>

The trials were of reasonable quality. The crossover study used a very short treatment period of only 7 days and it was difficult to assess baseline

comparability between treatment groups.<sup>50</sup> One trial included only patients with intellectual disabilities, and therefore findings may have limited applicability.<sup>137</sup> These issues could affect the findings of the studies and should be considered when interpreting the data.

Owing to the presence of clinical (different participants, drug doses and follow-up periods) and statistical (*Q*-statistic) heterogeneity, it was inappropriate to pool data. The unpooled RRs are presented in *Figure 9*.

The crossover study failed to report first-phase data (not included in *Figure 9*) and did not carry out an appropriate analysis for crossover data. However, the study reported no difference between LTG and placebo in the number of patients remaining seizure free.



**FIGURE 9** Proportion of seizure-free participants (unpooled RRs, 95% CIs) for adjunctive trials of LTG vs placebo (ITT data)

Only one study in *Figure 9* showed a statistically significant difference, which favoured LTG 300 mg/day over placebo.<sup>142</sup> Overall, however, the evidence suggests a trend in favour of LTG compared with placebo.

Four superiority trials, one of which was a crossover trial,<sup>145</sup> compared adjunctive LEV with placebo in patients with refractory epilepsy. Three studies included only patients with refractory partial seizures.<sup>143–145</sup> The remaining study included both patients with refractory partial and refractory generalised seizures.<sup>139</sup> The trials included between 119 and 324 patients (mean = 256) and followed patients for periods of 16–38 weeks (mean = 23.5 weeks). Drug doses varied between trials. Three trials compared two separate doses of LEV with placebo and one compared only one dose of LEV with placebo.<sup>144</sup>

The trials were of reasonable quality. One study used a dose of LEV (4000 mg/day) which is outwith the recommended range.<sup>139</sup> The crossover trial did not use a washout period between treatments.<sup>145</sup>

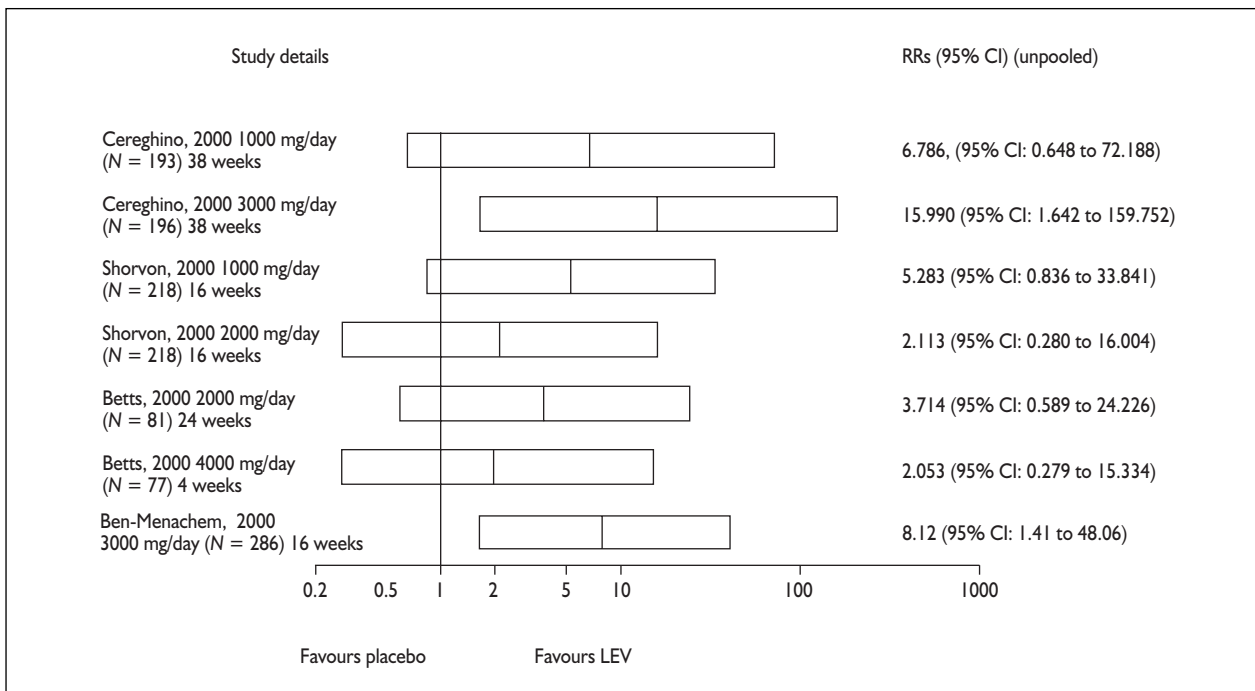
In view of the clinical (different participants, drug doses and follow-up periods) and statistical (*Q*-statistic) heterogeneity between studies, it was inappropriate to pool data. *Figure 10* shows the unpooled RRs.

First-phase data from the crossover study<sup>80</sup> were reported in a separate publication<sup>145</sup> and are included in *Figure 10*. Final crossover data showed that 10 out of 183 participants in the 1000 mg/day LEV group, compared with 10 out of 175 in the 2000 mg/day LEV group and two out of 172 in the placebo group, remained seizure free.

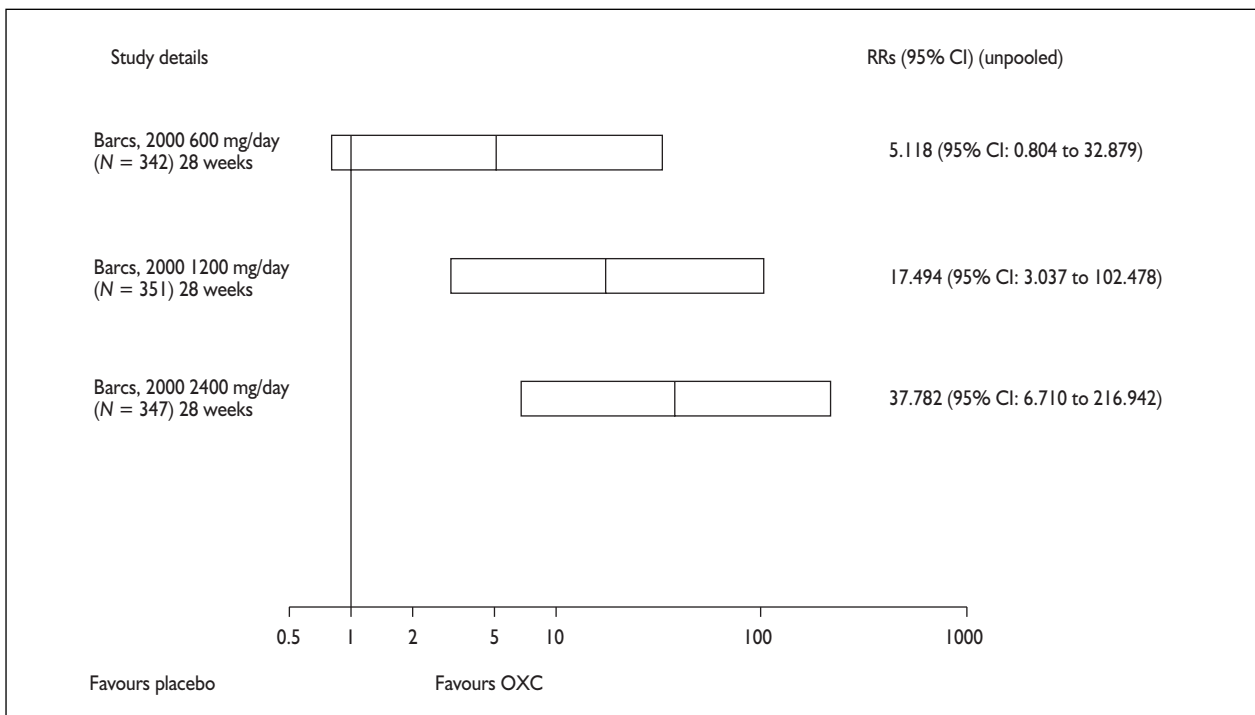
In *Figure 10*, only two trials showed a statistically significant difference, favouring LEV 3000 mg/day over placebo.<sup>143,144</sup> Overall, there was a trend in favour of LEV compared with placebo.

Only one parallel superiority trial of 694 refractory patients with partial seizures compared adjunctive OXC with placebo.<sup>70</sup> The trial compared three separate doses of OXC (600, 1200 and 2400 mg/day). All doses were within the recommended range. The trial was of reasonable quality, but followed treatment for only a relatively short period (28 weeks). The RRs for each of the OXC doses are shown in *Figure 11*. All of the doses favoured OXC over placebo but the differences were significant for only two of the doses (1200 and 2400 mg/day). Overall, there was very limited evidence on which to base an assessment of the effectiveness of adjunctive OXC compared with placebo.

Two crossover studies compared TGB with placebo in patients with refractory partial seizures.<sup>146,147</sup>



**FIGURE 10** Proportion of seizure-free participants (unpooled RRs, 95% CIs) for adjunctive trials of LEV vs placebo (ITT data)

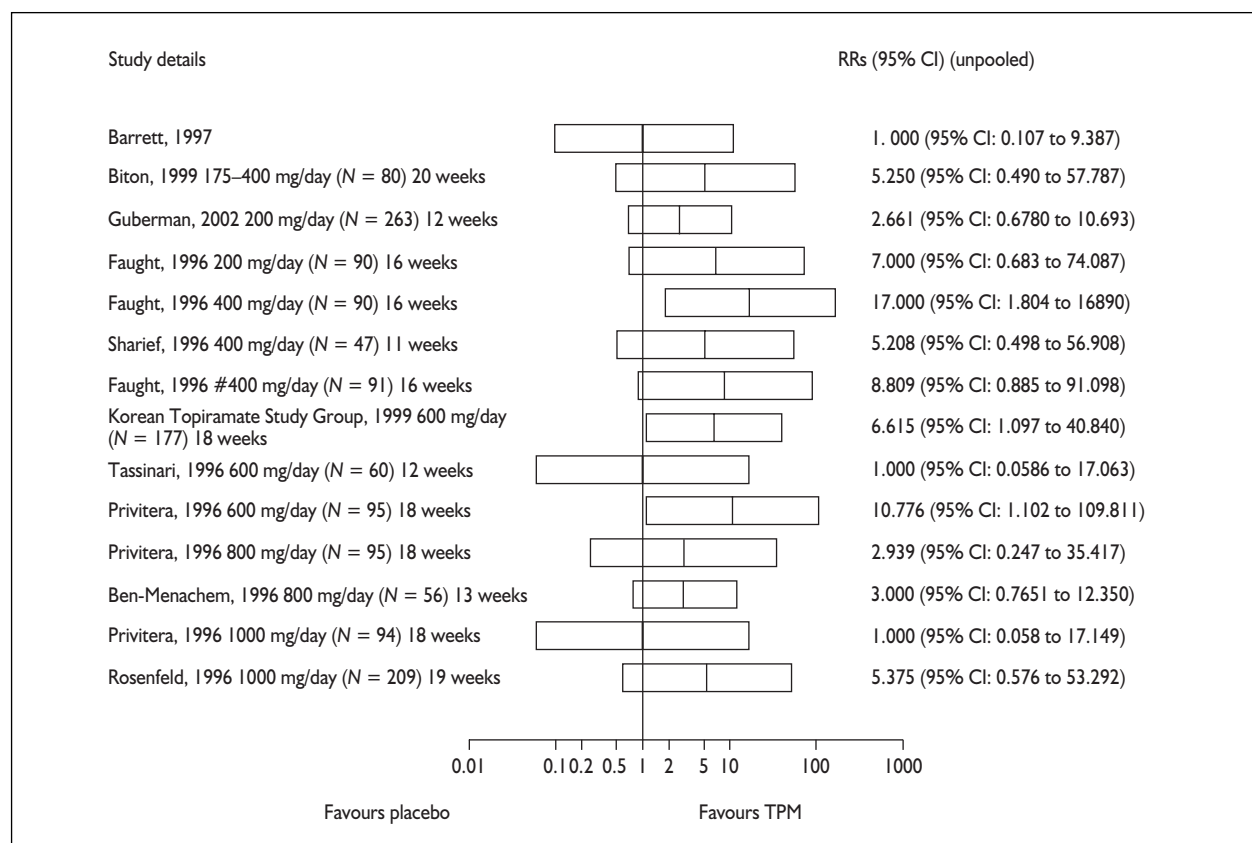


**FIGURE 11** Proportion of seizure-free participants (RRs, 95% CIs) for the adjunctive trial of OXC vs placebo (ITT data)

Both included only small numbers of participants (46<sup>146</sup> and 44<sup>147</sup>) and used only short treatment periods of 6<sup>147</sup> and 7 weeks.<sup>146</sup> Neither study presented first-phase data. However, one trial reported that one out of 42 participants with complex partial seizures, two out of 13 with simple

partial seizures and 10 out of 27 with SGTC seizures remained seizure free whilst receiving TGB (these data include participants who were also seizure free during the placebo period).<sup>146</sup> The other trial reported that three out of 36 participants with partial seizures remained seizure free while using





**FIGURE 12** Proportion of seizure-free participants (unpooled RRs, 95% CIs) for adjunctive trials of TPM vs placebo (ITT data)

TGB compared with one out of 36 participants using placebo.<sup>147</sup> Both studies were of limited applicability as only participants achieving specific reductions in seizure frequency whilst receiving TGB treatment were allowed to enter the trial (i.e. both were response conditional trials). Overall, there are limited data on which to base an assessment of the effectiveness of TGB compared with placebo.

Ten superiority parallel trials compared adjunctive TPM with placebo in refractory patients. Two trials included patients with generalised onset seizures<sup>76,79</sup> and the remainder included patients with only partial seizures. Studies included between 47 and 263 participants (mean = 134) and used treatment period of between 11 and 20 weeks (mean = 16 weeks). The studies used various doses of TPM, but all were within the recommended range. Two trials compared three separate doses of TPM, each of the three having a different maintenance dose.<sup>67,68</sup>

Overall, the studies were of reasonable quality, although newer AEDs were allowed as concomitant medications in two trials, which may confound the findings.<sup>79,150</sup>

Owing to the presence of clinical (different participants, drug doses and follow-up periods) and statistical ( $Q$ -statistic) heterogeneity, it was inappropriate to pool the data in most cases. Unpooled RRs are presented in *Figure 12*.

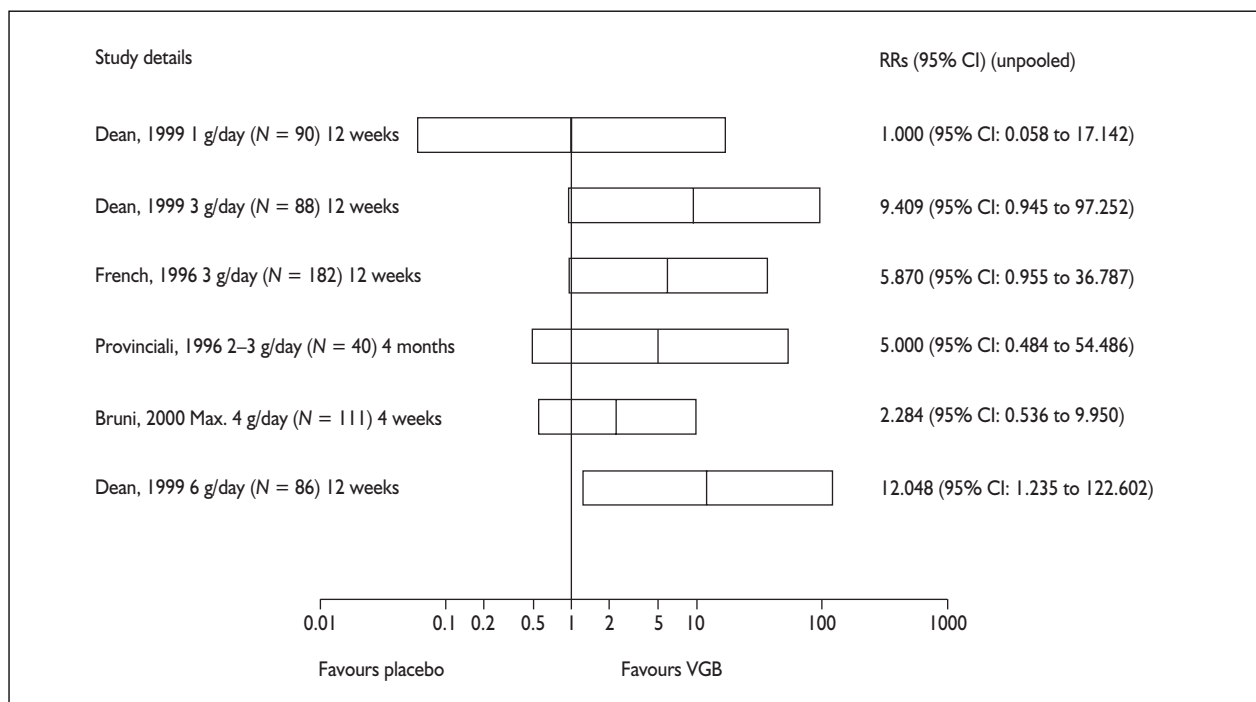
*Figure 12* shows that all but three of the comparisons with placebo favoured TPM, although only three studies showed statistically significant differences (TPM 400<sup>67</sup> and 600 mg/day<sup>68,149</sup>).

Data from the two 20-week trials involving 80 patients with generalised seizures were pooled (see *Table 31*).<sup>76,79</sup> The pooled RR (fixed effects) favoured TPM over placebo but was not statistically significant. Data were also pooled from the two trials of 400 mg/day TPM in patients with partial seizures (see *Table 31*).<sup>67,148</sup> The pooled RR (fixed effects) showed a statistically significant difference in favour of TPM. Similarly, the pooled RR (fixed effects) from three trials that used 600 mg/day TPM in patients with partial seizures also showed a statistically significant difference in favour of TPM (see *Table 31*).<sup>42,67,149</sup>

Overall, the evidence shows that adjunctive TPM is more effective than placebo.

**TABLE 31** Proportion of seizure-free participants (pooled RRs, 95% CIs) for adjunctive trials of TPM vs placebo (ITT data)

Characteristics	Studies	Pooled RR (95% CI) (fixed effects)
N = 80	Barrett, 1997 <sup>76</sup>	1.000 (95% CI: 0.107 to 9.387)
N = 80	Biton, 1999 <sup>79</sup>	5.250 (95% CI: 0.490 to 57.787)
<b>Refractory, generalised seizures, 175–400 mg/day, 20 weeks follow-up</b>	<b>Pooled (n = 2)</b>	<b>2.393 (95% CI: 0.364 to 15.724)</b> <b>Heterogeneity: Q = 0.653 (df = 1), p = 0.419</b>
N = 90	Faught, 1996 <sup>67</sup>	17.000 (95% CI: 1.804 to 168.953)
N = 47	Sharief, 1996 <sup>148</sup>	5.208 (95% CI: 0.498 to 56.908)
<b>Refractory, partial seizures, 400 mg/day</b>	<b>Pooled (n = 2)</b>	<b>11.165 (95% CI: 1.469 to 84.849)</b> <b>Heterogeneity: Q = 0.336 (df = 1), p = 0.562</b>
N = 91	Faught, 1996 <sup>67</sup>	8.809 (95% CI: 0.885 to 91.098)
N = 177	Korean Topiramate Study Group, 1999 <sup>149</sup>	6.615 (95% CI: 1.097 to 40.840)
N = 60	Tassinari, 1996 <sup>42</sup>	1.000 (95% CI: 0.059 to 17.063)
<b>Refractory, partial seizures, 600 mg/day</b>	<b>Pooled (n = 3)</b>	<b>6.774 (95% CI: 1.821 to 25.192)</b> <b>Heterogeneity: Q = 1.063 (df = 3), p = 0.786</b>

**FIGURE 13** Proportion of seizure-free participants (unpooled RRs, 95% CIs) for adjunctive trials of VGB vs placebo (ITT data)

Four trials compared adjunctive VGB with placebo in patients with refractory partial seizures.<sup>152–155</sup> The studies included between 40 and 182 patients (mean = 127) and followed treatment for between 4 weeks and 4 months (mean = 11 weeks). The trials were of reasonable quality. However, one trial of 40 patients was possibly underpowered and was designed to evaluate cognitive and QoL outcomes.<sup>152</sup> One trial compared three different doses of VGB with placebo but one dose exceeded the recommended limit.<sup>154</sup> One trial contained

patients who deviated from the prespecified inclusion criteria.<sup>153</sup>

In view of the clinical (different drug doses and follow-up periods) and statistical (*Q*-statistic) heterogeneity between studies, it was not appropriate to combine the individual RRs. *Figure 13* shows the unpooled RRs.

The unpooled data shown in *Figure 13* shows a trend in favour of VGB, although only one study

showed statistically significant difference in favour of VGB (6 g/day) compared with placebo.<sup>154</sup> This dose exceeded the recommended dose range.

ii. 50% reduction in seizure frequency

Fifty out of 56 studies of newer drugs versus placebo (adjunctive therapy) reported the proportion of participants who experienced at least a 50% decrease in seizure frequency. A summary of the main characteristics of these studies is presented in *Table 32*.

Five superiority trials, one of which was a crossover trial,<sup>90</sup> compared adjunctive GBP with placebo in patients with refractory epilepsy.<sup>73,90,138,156,157</sup> Four trials included only patients with partial seizures and the remaining trial<sup>138</sup> included both patients with partial and patients with generalised seizures. The studies included between 27 and 306 patients (mean = 155) and used treatment period of up to 14 weeks. Various doses of GBP were used, but all were within the recommended range. Two trials compared two doses of GBP

**TABLE 32** Summary of studies (adjunctive therapy, newer drugs vs placebo) assessing proportion of participants experiencing at least a 50% decrease in seizure frequency

Drug	Study characteristics <sup>a</sup>				
	Refractory/ newly diagnosed	Seizure type	Dose Follow-up N	Comments	Study details
GBP	Refractory	Partial	2400 mg/day 12 weeks N = 27	Crossover study	Leach, 1997 <sup>90</sup>
	Refractory	Partial	900 and 1200 mg/day 12 weeks N = 272	Two doses of GBP compared with placebo	Anhut, 1994 <sup>156</sup>
	Refractory	Partial	1200 mg/day 14 weeks N = 127		UK Gabapentin Study Group No. 5, 1990 <sup>73</sup>
	Refractory	Partial	900 and 1200 mg/day 3 months N = 43	Two doses of GBP compared with placebo	Sivenius, 1991 <sup>157</sup>
	Refractory	Combination of partial/generalised	600 or 1200 or 1800 mg/day 12 weeks N = 306	Three doses of GBP compared with placebo	US Gabapentin Study Group No. 5, 1993 <sup>138</sup>
LTG	Refractory	Combination of partial/generalised	Max. 400 mg/day 14 weeks N = 98	Crossover study	Messenheimer, 1994 <sup>158</sup>
	Refractory	Combination of partial/generalised	75–400 mg/day 11 months N = 56	Crossover study	Boas, 1996 <sup>136</sup>
	Refractory	Combination of partial/generalised	75, 100 or 200 mg/day 12 weeks N = 34	Crossover study	Binnie, 1989 <sup>159</sup>
	Refractory	Combination of partial/generalised	100–300 mg/day 12 weeks N = 24	Crossover study	Jawad, 1989 <sup>160</sup>
	Refractory	Combination of partial/generalised	150 or 300 mg/day 7 weeks N = 23	Crossover study	Loiseau, 1990 <sup>89</sup>

*continued*

**TABLE 32** Summary of studies (adjunctive therapy, newer drugs vs placebo) assessing proportion of participants experiencing at least a 50% decrease in seizure frequency (cont'd)

Drug	Study characteristics <sup>a</sup>				
	Refractory/ newly diagnosed	Seizure type	Dose Follow-up N	Comments	Study details
	Refractory	Combination of partial/generalised	Max. 400 mg/day 20 weeks N = 43	Crossover study	Yaqub, 1995 <sup>82</sup>
	Refractory	Partial	150 or 300 mg/day 12 weeks N = 41	Crossover study	Schapel, 1993 <sup>161</sup>
	Refractory	Partial	Max. 300 mg/day 28 weeks N = 23	Crossover study	Schmidt, 1993 <sup>91</sup>
	Refractory	Partial	200 or 400 mg/day 18 weeks N = 81	Crossover study	Smith, 1993 <sup>55</sup>
	Refractory	Partial	150 or 300 mg/day 12 weeks N = 29	Crossover study	Cordova, 1995 <sup>40</sup>
	Refractory	Partial	50–200 mg/day 36 weeks N = 22	Crossover study	Stolarek 1994 <sup>162</sup>
	Refractory	Generalised	75 or 150 mg/day 24 weeks N = 26	Crossover study	Beran, 1998 <sup>134</sup>
	Refractory	Combination of partial/generalised	100 or 200 mg/day 16 weeks N = 68	Specifically looks at patients with intellectual disabilities	Veendrick-Meekes, 2000 <sup>137</sup>
	Refractory	Combination of partial/generalised	500 or 300 mg/day 24 weeks N = 216	Two doses of LTG compared with placebo	Matsuo, 1993 <sup>142</sup>
LEV	Refractory	Partial	1000 or 3000 mg/day 38 weeks N = 294	Two doses of LEV compared with placebo	Cereghino, 2000 <sup>143</sup>
	Refractory	Partial	3000 mg/day 16 weeks N = 286	One dose of LEV compared with placebo	Ben-Menachem, 2000 <sup>144</sup>
	Refractory	Partial	1000 or 2000 mg/day 16 weeks N = 324	Two doses of LEV compared with placebo. Presents first-phase data for crossover study, Boon 2002 <sup>80</sup>	Shorvon, 2000 <sup>145</sup>
	Refractory	Combination of partial/generalised	2000 or 4000 mg/day 24 weeks N = 119	Two doses of LEV compared with placebo	Betts, 2000 <sup>139</sup>
OXC	Refractory	Partial	600, 1200 or 2400 mg/day 28 weeks N = 694	Three doses of OXC compared with placebo	Barcs, 2000 <sup>70</sup>

continued

**TABLE 32** Summary of studies (adjunctive therapy, newer drugs vs placebo) assessing proportion of participants experiencing at least a 50% decrease in seizure frequency (cont'd)

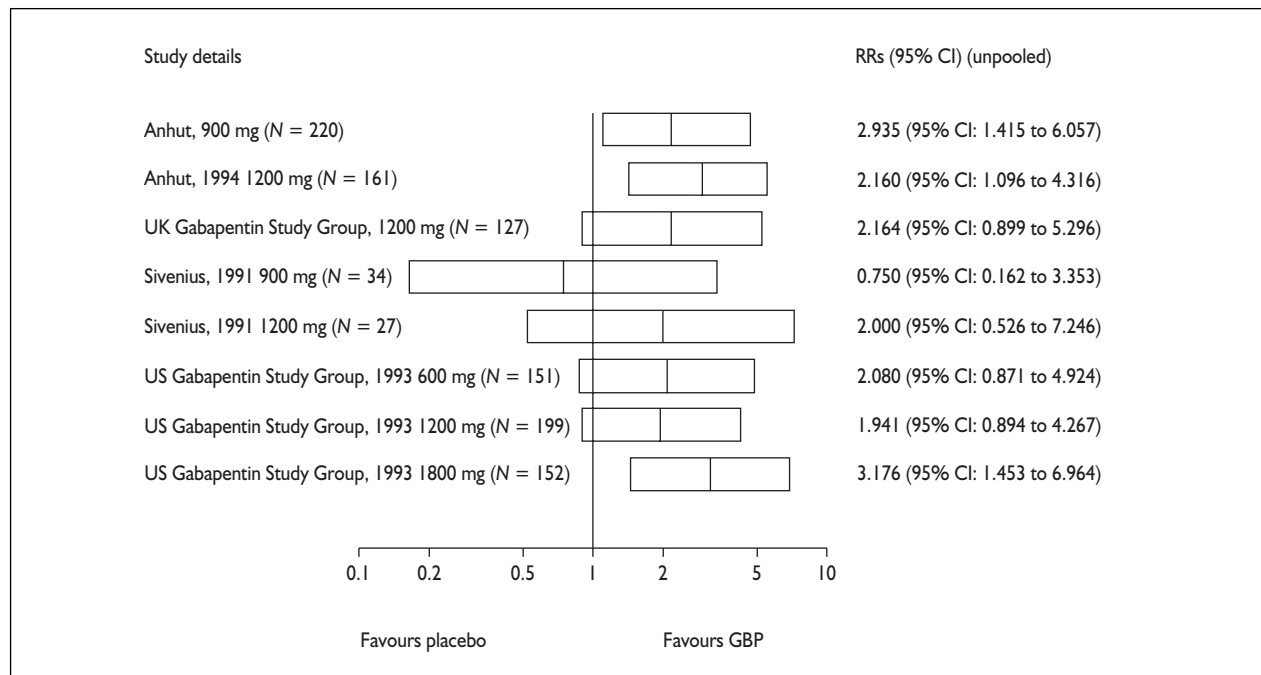
Drug	Study characteristics <sup>a</sup>				
	Refractory/ newly diagnosed	Seizure type	Dose Follow-up N	Comments	Study details
TGB	Refractory	Partial	12–52 mg/day 7 weeks N = 46	Crossover study. Entry into the trial was dependent on the fulfilment of certain response criteria	Richens, 1995 <sup>146</sup>
	Refractory	Partial	Titrated 6 weeks N = 44	Crossover study. Entry into the trial was dependent on the fulfilment of certain response criteria	Crawford, 2001 <sup>147</sup>
	Refractory	Partial	32 mg/day 16 weeks N = 318	Specifically looks at patients with intellectual disabilities. Two dose regimens of TGB compared with placebo	Sachdeo, 1997 <sup>140</sup>
	Refractory	Partial	16, 32 or 56 mg/day 12 weeks N = 297	Three doses of TGB compared with placebo	Uthman, 1998 <sup>163</sup>
	Refractory	Partial	30 mg/day 22 weeks N = 154		Kälviäinen, 1998 <sup>164</sup>
TPM	Refractory	Generalised	175, 225 or 400 mg/day based on body weight 20 weeks N = 80		Barrett, 1997 <sup>76</sup>
	Refractory	Generalised	175–400 mg/day 20 weeks N = 80		Biton, 1999 <sup>79</sup>
	Refractory	Partial	200 mg/day 12 weeks N = 263		Guberman, 2002 <sup>150</sup>
	Refractory	Partial	1000 mg/day 19 weeks N = 209		Rosenfeld, 1996 <sup>41</sup>
	Refractory	Partial	200, 400 or 600 mg/day 16 weeks N = 181	Three doses of TPM compared with placebo	Faught, 1996 <sup>67</sup>
	Refractory	Partial	600 mg/day 18 weeks N = 177		Korean Topiramate Study Group, 1999 <sup>149</sup>
	Refractory	Partial	600 mg/day 12 weeks N = 60		Tassinari, 1996 <sup>42</sup>
	Refractory	Partial	400 mg/day 11 weeks N = 47		Sharief, 1996 <sup>148</sup>

continued

**TABLE 32** Summary of studies (adjunctive therapy, newer drugs vs placebo) assessing proportion of participants experiencing at least a 50% decrease in seizure frequency (cont'd)

Drug	Study characteristics <sup>a</sup>				
	Refractory/ newly diagnosed	Seizure type	Dose Follow-up N	Comments	Study details
VGB	Refractory	Partial	800 mg/day 13 weeks N = 56		Ben-Menachem, 1996 <sup>151</sup>
	Refractory	Partial	300 mg/day 14 weeks N = 46		Yen, 2000 <sup>165</sup>
	Refractory	Partial	600, 800 or 1000 mg/day 18 weeks N = 190	Three doses of TPM compared with placebo	Privitera, 1996 <sup>68</sup>
	Refractory	Combination of partial/generalised	2 or 3 g/day 3 months N = 31	Specifically looks at patients with intellectual disabilities. Crossover study	Tassinari, 1987 <sup>85</sup>
	Refractory	Combination of partial/generalised	3 g/day 10 weeks N = 23	Crossover study	Loiseau, 1986 <sup>83</sup>
	Refractory	Combination of partial/generalised	2–3 g/day 7 weeks N = 23	Crossover study	Tartara, 1986 <sup>86</sup>
	Refractory	Combination of partial/generalised	2–3 g/day 12 weeks N = 24	Crossover study	McKee, 1993 <sup>54</sup>
	Refractory	Partial	3 g/day 9 weeks N = 24	Includes patients with intellectual disabilities. Crossover study	Rimmer, 1984 <sup>49</sup>
	Refractory	Partial	2 or 3 g/day 8 weeks N = 80	Crossover study. Two doses of VGB compared with placebo	Beran, 1996 <sup>87</sup>
	Refractory	Partial	3 g/day 12 weeks N = 182		French, 1996 <sup>155</sup>
	Refractory	Partial	1, 3 or 6 g/day 12 weeks N = 174	Three doses of VGB compared with placebo	Dean, 1999 <sup>154</sup>
	Refractory	Partial	Max. 4 g/day 4 weeks N = 111		Bruni, 2000 <sup>153</sup>
	Refractory	Partial	3 g/day 18 weeks N = 45		Grunewald, 1994 <sup>38</sup>

N, total number of participants randomised; NS, not stated.  
<sup>a</sup> All were parallel, superiority trials unless stated otherwise.



**FIGURE 14** Proportion of 50% responders (unpooled RRs, 95% CIs) for adjunctive trials of GBP vs placebo (ITT data)

(900 and 1200 mg/day) with placebo,<sup>156,157</sup> and one trial compared three doses (600, 1200 and 1800 mg/day).<sup>138</sup>

One study of 43 participants failed to report a power calculation for sample size and was likely to have been insufficiently powered.<sup>157</sup> Another trial only included patients that were deemed likely to complete the trial.<sup>138</sup> This trial included patients with both partial and generalised seizures, although GBP is only licensed for the treatment of partial seizures. One trial found statistically significant differences between GBP and placebo groups in some baseline characteristics, including the duration of epilepsy.<sup>156</sup>

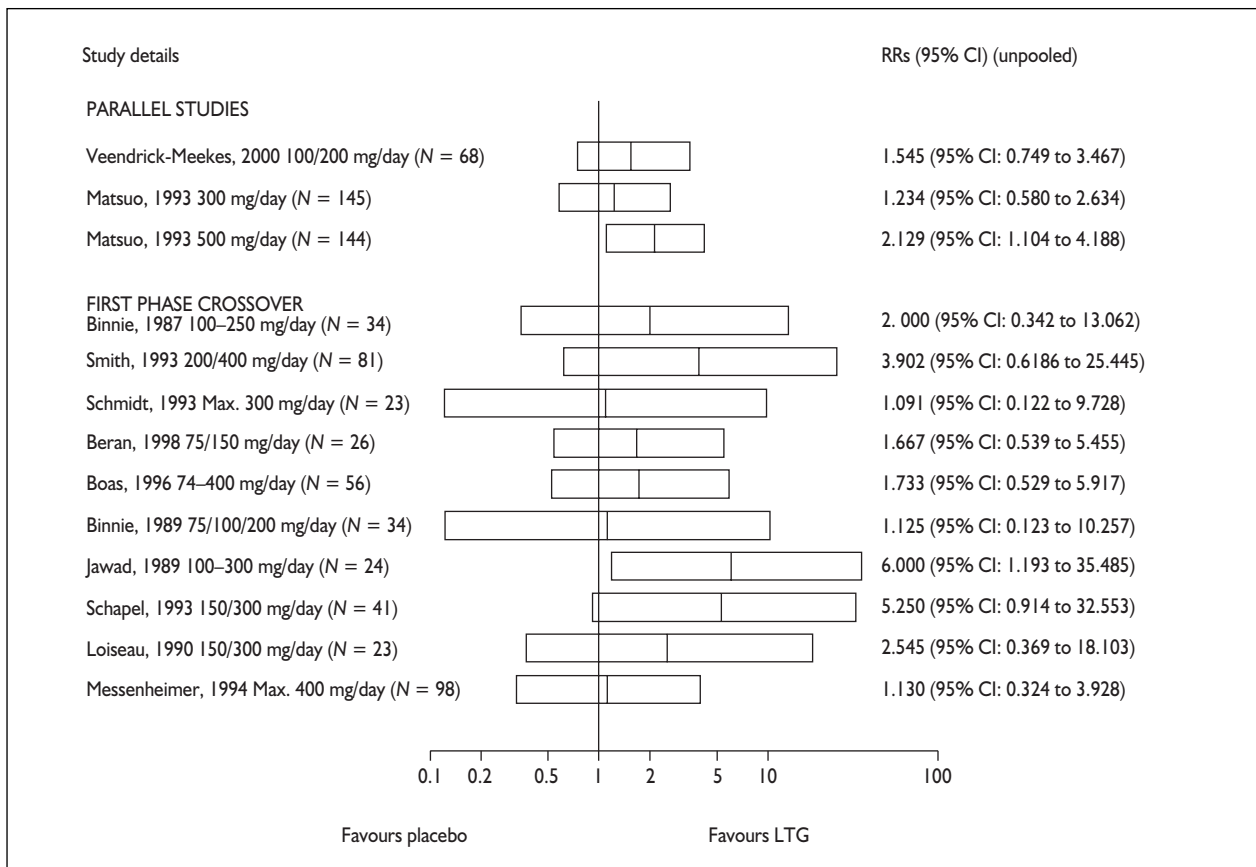
Owing to the presence of clinical (different participants, drug doses and follow-up periods) and statistical (*Q*-statistic) heterogeneity, it was inappropriate to pool data. *Figure 14* shows the unpooled RRs for the four parallel trials. The crossover study failed to report first phase data, but reported that nine out of 21 participants responded to treatment with adjunctive GBP.<sup>90</sup>

The unpooled data show a trend in favour of GBP compared with placebo, but only two studies showed statistically significant differences in favour of GBP (900 and 1200 mg/day GBP in one study<sup>156</sup> and 1800 mg/day GBP<sup>138</sup> in the other). Overall, the evidence favours adjunctive GBP

compared with placebo in the treatment of refractory partial seizures.

Twelve crossover trials<sup>40,55,82,89,91,134,136,158–162</sup> and two parallel trials<sup>137,142</sup> compared adjunctive LTG with placebo in patients with refractory epilepsy. One trial included only patients with partial seizures<sup>162</sup> and another only patients with generalised seizures.<sup>134</sup> The remainder of the trials included patients with either partial or generalised seizures. The studies included between 22 and 216 participants (mean = 56) and used treatment periods of between 7 and 44 weeks (mean = 20 weeks). Various doses of LTG were used, but all were within the recommended range. One parallel trial compared two doses of LTG with placebo.<sup>142</sup>

In two trials, an appropriate paired analysis for crossover trials did not appear to have been conducted.<sup>89,161</sup> In addition, one of these trials had skewed data owing to the inclusion of a participant with a very large number of seizures.<sup>89</sup> In another trial, assessment of blinding success suggested that it may not have been effective, and over 20% of follow-up data was classified as missing.<sup>55</sup> One trial was only reported as an abstract.<sup>82</sup> In a further trial, eligibility criteria were altered during the study and one patient received monotherapy LTG.<sup>136</sup> One of the two parallel trials included only participants with intellectual disabilities.<sup>137</sup>



**FIGURE 15** Proportion of 50% responders (unpooled RRs, 95% CIs) for adjunctive trials of LTG vs placebo (ITT data)

Owing to the presence of clinical (different participants, drug doses and follow-up periods) and statistical ( $Q$ -statistic) heterogeneity, it was not possible to pool all of the data. *Figure 15* shows the unpooled RRs for the first phase of nine crossover studies and the two parallel studies. Two crossover studies did not report first-phase data<sup>40,82</sup> and the third did not report first-phase data for the placebo group.<sup>162</sup> One of these studies reported that 52.7% (19/36) of participants receiving LTG responded to treatment,<sup>82</sup> another reported that 37.5% of participants receiving LTG responded to treatment<sup>40</sup> and the final study reported that four out of 22 participants responded to treatment with LTG.<sup>162</sup>

The unpooled data showed a trend in favour of LTG compared with placebo, but only two trials showed significant differences in favour of LTG (500<sup>142</sup> and 100–300 mg/day<sup>160</sup>).

First-phase data from six of the crossover studies were pooled (see *Table 33*).<sup>89,136,158–161</sup> The pooled RR (fixed-effects model) showed a statistically significant difference (RR = 2.251, 95% CI: 1.146 to 4.424) in favour of LTG compared with

placebo. Overall, the evidence favours adjunctive LTG compared with placebo.

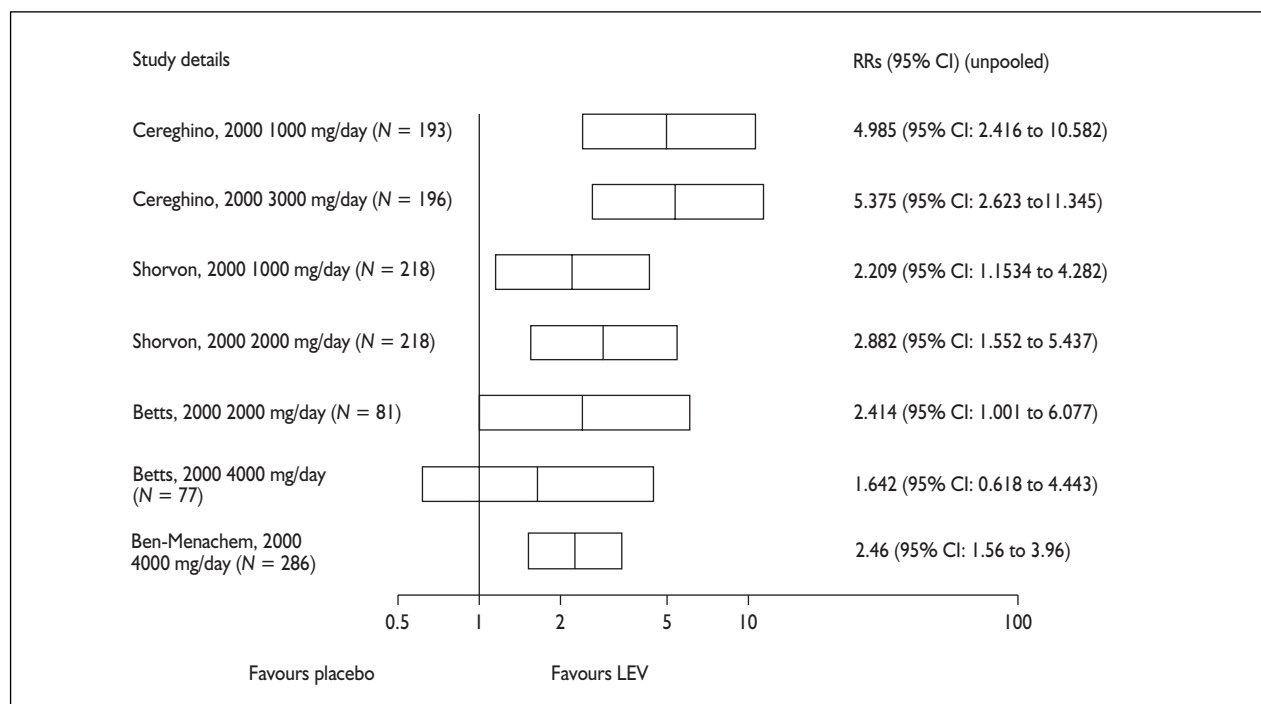
Four superiority trials,<sup>139,143–145</sup> including one crossover study,<sup>145</sup> compared adjunctive LEV with placebo in patients with refractory seizures. Three studies included only patients with partial seizures<sup>143–145</sup> and one included patients with partial or generalised seizures.<sup>139</sup> The trials included between 119 and 324 patients (mean = 256) and followed patients for periods of 16–38 weeks (mean = 23.5 weeks). Drug doses varied between trials. Three trials compared two separate doses of LEV with placebo and one compared only one dose of LEV with placebo.<sup>144</sup>

In view of the clinical (different participants, drug doses and follow-up periods) and statistical ( $Q$ -statistic) heterogeneity, data were not pooled. Unpooled RRs are shown in *Figure 16*<sup>139,143,145</sup> including first-phase data from the crossover studies<sup>145</sup> This trial reported final crossover data showing that 48 out of 183 (26.2%) participants responded while receiving LEV compared with 21 out of 172 (12.2%) while receiving placebo ( $p = 0.004$ ).



**TABLE 33** Proportion of 50% responders (pooled RRs, 95% CIs) for adjunctive studies of LTG vs placebo (ITT data)

Characteristics	Studies	Pooled RR (95% CI) (fixed effects)
N = 56	Boas, 1996 <sup>136</sup>	1.733 (95% CI: 0.529 to 5.917)
N = 34	Binnie, 1989 <sup>159</sup>	1.125 (95% CI: 0.123 to 10.257)
N = 24	Jawad, 1989 <sup>160</sup>	6.000 (95% CI: 1.193 to 35.485)
N = 41	Schapel, 1993 <sup>161</sup>	5.250 (95% CI: 0.914 to 32.553)
N = 23	Loiseau, 1990 <sup>89</sup>	2.545 (95% CI: 0.369 to 18.103)
N = 98	Messenheimer, 1994 <sup>158</sup>	1.130 (95% CI: 0.324 to 3.928)
<b>1st-phase crossover studies, refractory, partial/generalised seizures, all doses 75–400 mg/day</b>	<b>Pooled (n = 6)</b>	<b>2.251 (95% CI: 1.146 to 4.424)</b> <b>Heterogeneity: Q = 3.072 (df = 5) p = 0.689</b>

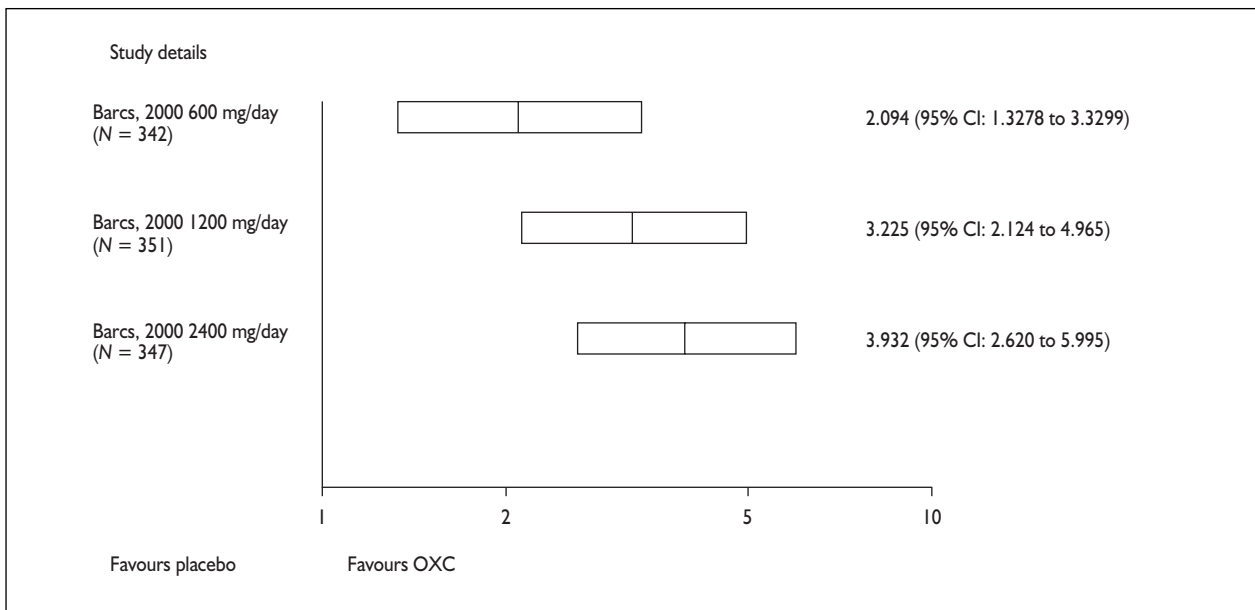
**FIGURE 16** Proportion of 50% responders (unpooled RRs, 95% CIs) for adjunctive trials of LEV vs placebo (ITT data)

The unpooled data show that all four studies showed statistically significant differences in favour of licensed doses of LEV compared with placebo (1000,<sup>143,145</sup> 2000 mg/day<sup>139,145</sup> and 3000 mg/day<sup>143,144</sup> doses of LEV). Overall, the evidence favours LEV as compared with placebo in the treatment of refractory partial seizures.

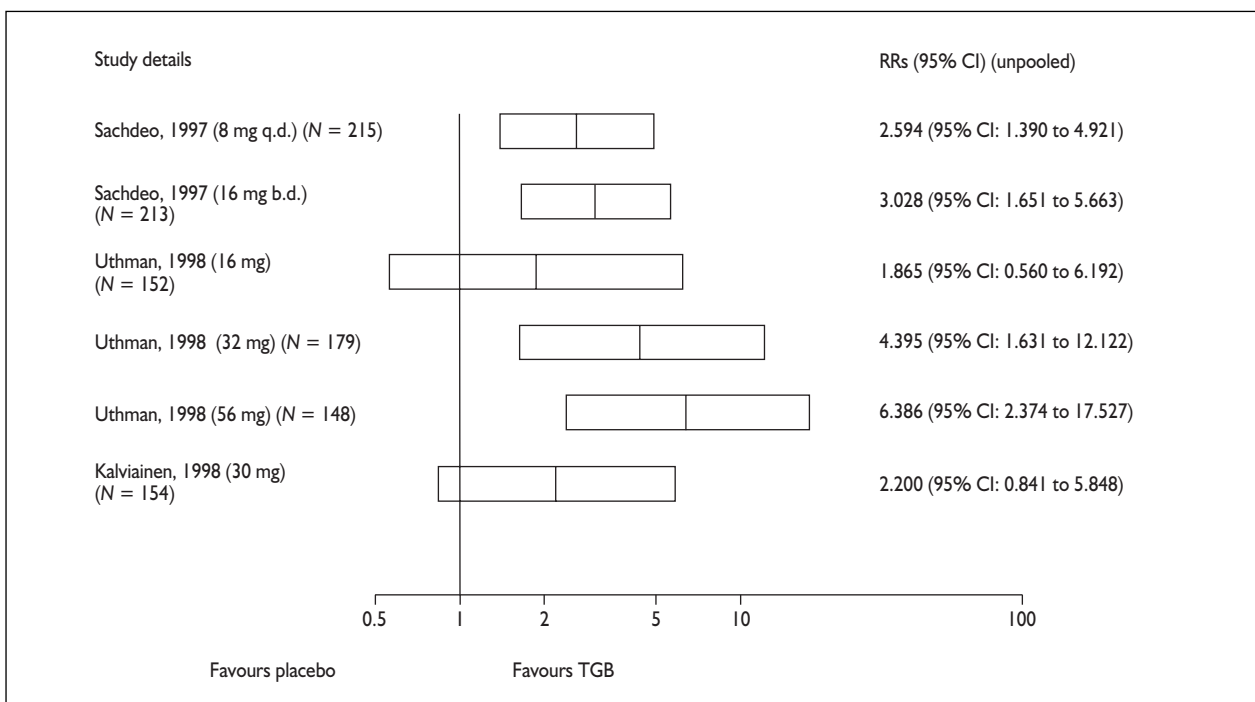
Evidence for OXC was limited to one trial of three doses of OXC (600, 1200 and 2400 mg/day) compared with placebo in 694 patients with refractory partial seizures.<sup>70</sup> The limitations of this study have been previously discussed in the proportion of seizure-free participants. *Figure 17* shows that RRs for each of the three OXC doses compared with placebo.

A statistically significant difference in favour of OXC was reported for each of the three doses of OXC (600, 1200 and 2400 mg/day). Although the evidence was limited to one trial with 694 participants, it appears that adjunctive OXC is favoured in comparison with placebo in patients with refractory partial seizures.

Three parallel trials<sup>140,163,164</sup> and two crossover trials<sup>146,147</sup> compared adjunctive TGB with placebo in patients with refractory partial seizures. The studies included between 44 and 318 participants (mean = 172) and used treatment period of between 6 and 22 weeks (mean = 13 weeks). Various doses of TGB were used, but all were within the recommended range. One trial



**FIGURE 17** Proportion of 50% responders (RRs, 95% CIs) for the adjunctive trial of OXC vs placebo (ITT data)



**FIGURE 18** Proportion of 50% responders (unpooled RRs, 95% CIs) for adjunctive trials of TGB vs placebo (ITT data)

compared three doses of TGB with placebo<sup>163</sup> and another trial compared two different dose regimens (but same daily dose) of TGB with placebo.<sup>140</sup>

In one of these trials, over 20% of participants withdrew after the pretrial phase.<sup>146</sup> One trial allowed the use of VGB as a concurrent AED,<sup>164</sup>

and another trial included only patients with intellectual disabilities.<sup>140</sup>

The unpooled RRs for the three parallel studies are shown in *Figure 18*.<sup>140,163,164</sup> Neither of the two crossover studies reported first-phase data and so are not shown in *Figure 18*.<sup>146,147</sup> One reported that 11 out of 42 participants with complex partial

**TABLE 34** Proportion of 50% responders (pooled RR, 95% CI) for adjunctive trials of TGB vs placebo (ITT data)

Characteristics	Studies	Pooled RR (95% CI) (fixed effects)
N = 213	Sachdeo, 1997 <sup>140</sup> 16 mg b.d.	3.028 (95% CI: 1.651 to 5.663)
N = 179	Uthman, 1998 <sup>163</sup>	4.395 (95% CI: 1.631 to 12.122)
N = 154	Kälviäinen, 1998 <sup>164</sup>	2.200 (95% CI: 0.841 to 5.848)
<b>Refractory, partial seizures, 30–32 mg/day</b>	<b>Pooled (n = 3)</b>	<b>3.090 (95% CI: 1.925 to 4.961)</b> <b>Heterogeneity Q = 0.873 (df = 2),</b> <b>p = 0.646</b>

seizures, seven out of 13 with simple partial seizures and 17 out of 27 with secondary generalised tonic-clonic (GTC) seizures responded to TGB treatment.<sup>146</sup> The other reported that 12 out of 36 participants responded during TGB therapy.<sup>147</sup> However, entry into both crossover trials was dependent on the fulfilment of response criteria where participants were required to achieve a certain reduction in seizure frequency.<sup>146,147</sup> This limits the applicability of their findings.

The unpooled data from the three parallel trials show a trend in favour of TGB compared with placebo, with statistically significant differences in two of the studies.<sup>140,163</sup> Data for doses of 30 and 32 mg/day TGB were pooled from the three parallel trials (see Table 34). The pooled RR (fixed-effects model) showed a statistically significant difference in favour of TGB (RR = 3.090, 95% CI: 1.925 to 4.961). Overall, the evidence shows a statistically significant difference in favour of adjunctive TGB (30/32 mg/day) compared with placebo in patients with partial seizures.

Eleven superiority parallel trials compared adjunctive TPM with placebo in patients with refractory epilepsy. Nine trials included only patients with partial seizures<sup>41,42,67,68,148–151,165</sup> and two included only patients with generalised seizures.<sup>76,79</sup> Trials included between 46 and 263 participants (mean = 126) and followed treatment over periods of between 11 and 20 weeks (mean = 16 weeks). Different doses of TPM were used but all were within the recommended range. Two trials compared three different doses of TPM with placebo.<sup>67,68</sup> The limitations of the studies have been discussed previously for the proportion of seizure-free participants.

Owing to the presence of clinical (different participants, drug doses and follow-up periods) and statistical (*Q*-statistic) heterogeneity, the pooling of data was limited. Figure 19 shows the unpooled RRs.

All but one of the studies<sup>76</sup> and one TPM dose (200 mg/day) of another trial<sup>67</sup> showed statistically significant differences in favour of TPM compared with placebo.

Data were pooled from two trials following up 80 patients with generalised seizures for 20 weeks (see Table 35). The pooled RR (fixed-effects model) showed a statistically significant difference in favour of TPM (RR = 2.324, 95% CI: 1.378 to 3.918). Data were pooled from the two studies of 400 mg/day TPM in patients with partial seizures (see Table 35).<sup>67,148</sup> The pooled RR (fixed-effects model) also showed a statistically significant difference in favour of TPM (RR = 2.929, 95% CI: 1.558 to 5.509). Finally, data were pooled from the three of 600 mg/day TPM in patients with partial seizures (see Table 35).<sup>42,67,149</sup> The pooled RR (fixed-effects model) was again statistically significant in favour of TPM compared with placebo (RR = 3.505, 95% CI: 2.304 to 5.332). Based on these findings, it appears that TPM (400 and 600 mg/day) adjunctive therapy is more effective than placebo. This applies to both the treatment of partial and generalised seizures.

Six crossover studies<sup>49,54,83,85–87</sup> and four parallel studies<sup>38,153–155</sup> compared adjunctive VGB with placebo in patients with refractory seizures. In all but four of the trials, which involved patients with both generalised and partial seizures,<sup>54,83,85,86</sup> all patients had partial seizures. The trials recruited between 23 and 182 (mean = 72) patients and followed them up for periods of 4–18 weeks (mean = 10 weeks). One trial used two separate arms and one used three separate arms of VGB, each with a different maintenance dose.

Owing to the presence of clinical (different participants, drug doses and follow-up periods) and statistical (*Q*-statistic) heterogeneity, it was inappropriate to pool data. Figure 20 shows the unpooled RRs derived from the four parallel group RCTs. The six crossover trials did not report first-phase data and were not included in

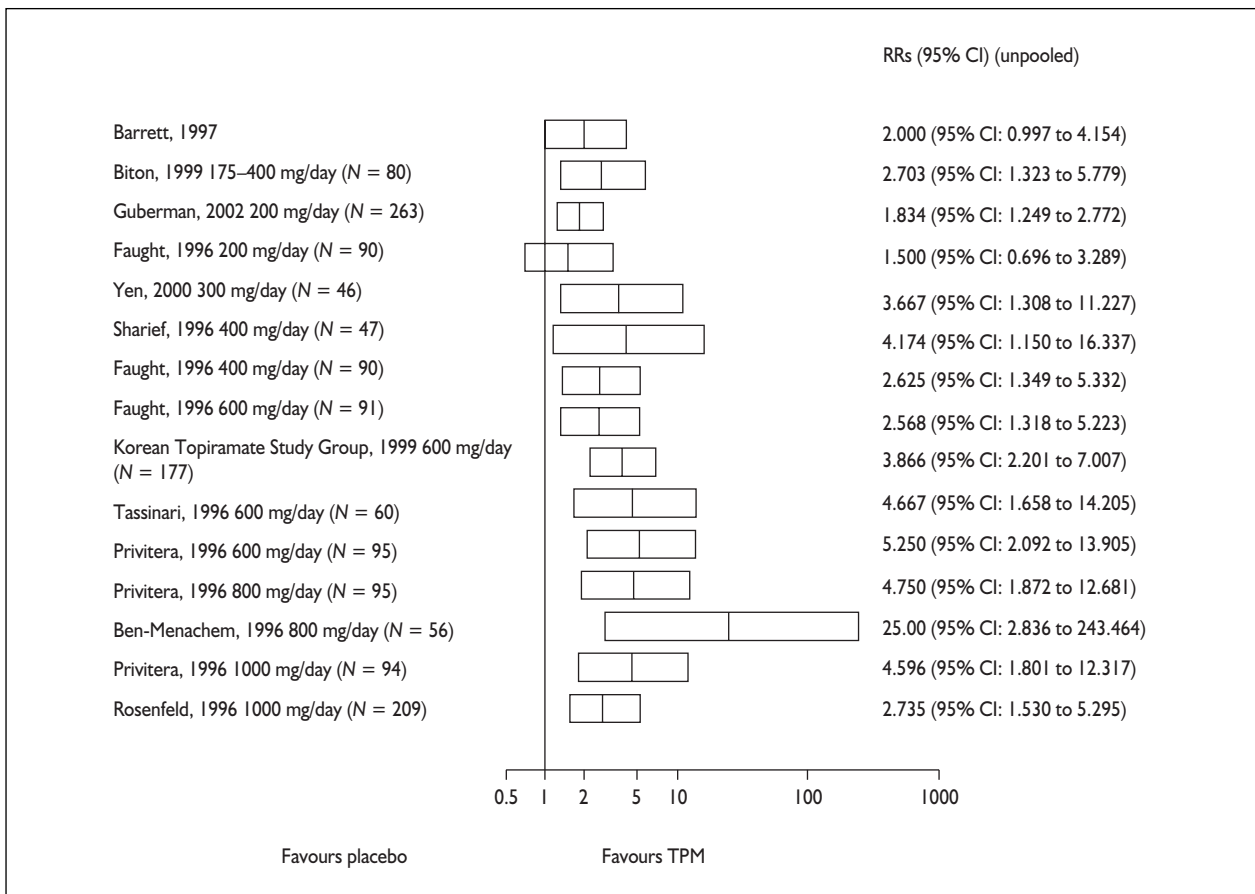


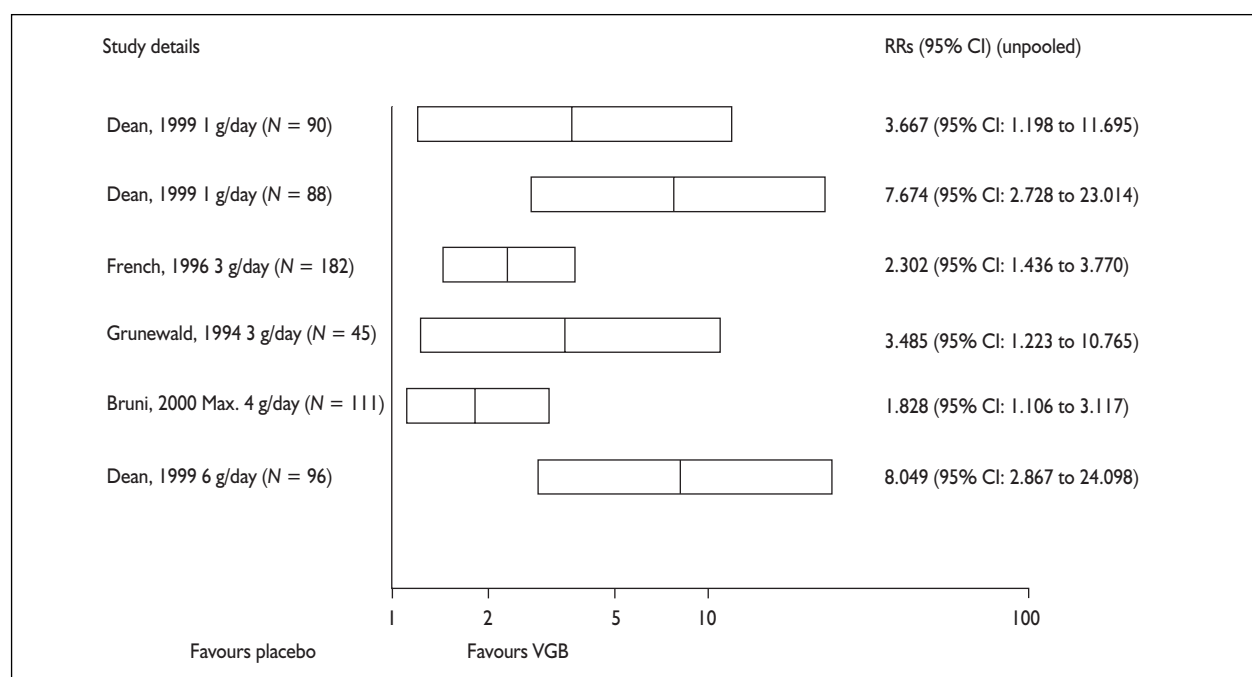
FIGURE 19 Proportion of 50% responders (unpooled RRs, 95% CIs) for adjunctive trials of TPM vs placebo (ITT data)

TABLE 35 Proportion of 50% responders (pooled RRs, 95% CIs) for adjunctive studies of TPM vs placebo (ITT data)

Characteristics	Studies	Pooled RR (95% CI) (fixed effects)
N = 80	Barrett, 1997 <sup>76</sup>	2.000 (95% CI: 0.997 to 4.154)
N = 80	Biton, 1999 <sup>79</sup>	2.703 (95% CI: 1.323 to 5.779)
<b>Refractory, generalised seizures, 175–400 mg/day, 20 weeks follow-up</b>	<b>Pooled (n = 2)</b>	<b>2.324 (95% CI: 1.378 to 3.918)</b> <b>Heterogeneity: Q = 0.318 (df = 1), p = 0.573</b>
N = 47	Sharief, 1996 <sup>148</sup>	4.174 (95% CI: 1.150 to 16.337)
N = 90	Faught, 1996 <sup>67</sup>	2.625 (95% CI: 1.349 to 5.332)
<b>Refractory, partial seizures, 400 mg/day, follow-up</b>	<b>Pooled (n = 2)</b>	<b>2.929 (95% CI: 1.558 to 5.509)</b> <b>Heterogeneity: Q = 0.326 (df = 1), p = 0.5679</b>
N = 90	Faught, 1996 <sup>67</sup>	2.568 (95% CI: 1.318 to 5.223)
N = 177	Korean Topiramate Study Group, 1999 <sup>149</sup>	3.866 (95% CI: 2.201 to 7.007)
N = 60	Tassinari, 1996 <sup>42</sup>	4.667 (95% CI: 1.658 to 14.205)
<b>Refractory, partial seizures, 600 mg/day, follow-up 12–18 weeks</b>	<b>Pooled (n = 3)</b>	<b>3.505 (95% CI: 2.304 to 5.332)</b> <b>Heterogeneity: Q = 1.101 (df = 2), p = 0.577</b>

Figure 20. However, they reported the number of patients who achieved at least a 50% reduction in seizure frequency with VGB, which ranged from 33 to 67%.<sup>49,54,83,85–87</sup> In the trial that reported the largest benefit, it was unclear if an appropriate

paired analysis was performed or if patients had constant and predictable seizure frequencies.<sup>49</sup> That study and two others<sup>83,85</sup> did not report a washout period but the possible effects on the reported findings were not mentioned. Four of the



**FIGURE 20** Proportion of 50% responders (unpooled RRs, 95% CIs) for adjunctive trials of VGB vs placebo (ITT data)

crossover trials were conducted in patients with partial or generalised seizures but VGB is licensed only for the treatment of partial seizures. However, there was no clear pattern of difference in the percentage responders in these studies compared with the studies that included only partial seizures. One trial conducted in patients with intellectual disabilities showed the lowest response rate (33%),<sup>85</sup> but the trial that included some patients (10%) with intellectual disabilities showed the highest response rate.<sup>49</sup> The findings from the crossover trials were therefore clearly inconsistent.

The parallel trials all showed statistically significant differences in favour of VGB as measured by the proportion of responders (*Figure 20*). In two of the trials the maintenance dose used in one of the VGB arms exceeded the recommended limit.<sup>153,154</sup> In one trial, some randomised patients were found not to satisfy the prespecified inclusion criteria,<sup>153</sup> which may impact on the ITT data included in this review.

Overall, the evidence favoured adjunctive VGB over placebo.

#### **b. Time to first seizure**

None of the 55 studies of newer drugs versus placebo (adjunctive therapy) reported the time to first seizure.

#### **c. Time to withdrawal/exit**

None of the 55 studies of newer drugs versus

placebo (adjunctive therapy) reported the time to exit/withdrawal.

#### **d. Quality of life**

Thirty-one out of 55 studies of newer drugs versus placebo (adjunctive therapy) reported QoL outcomes (see *Table 36*).

Three studies used GBP,<sup>90,138,156</sup> nine LTC,<sup>55,56,89,91,136,137,142,158,161</sup> one levetiracetam,<sup>166</sup> two TGB,<sup>39,167</sup> nine TPM<sup>42,67,68,76,79,148,149,151,165</sup> and seven VGB.<sup>38,51,87,152–154,168,169</sup> Twenty-two studies were parallel superiority trials and 10 were crossover trials. No studies of adjunctive OXC reported QoL outcomes.

A variety of measures were used to assess QoL (see *Table 37*). In total 21 different types of QoL measures were used: GBP (three measures), LTC (10 measures), LEV (one measure), TGB (five measures), TPM (two measures) and VGB (12 measures). The majority of measures were used only once both between and within study drugs. The most commonly reported measures were subjective global evaluations by both the patient and the physician/investigator.

Details of the individual study data are reported in Appendix 23 and details of the individual QoL measures in Appendix 4. *Table 38* summarises the overall findings of the QoL assessments. Three trials of GBP, one of which was a crossover trial,<sup>90</sup> were carried out in patients with refractory partial

**TABLE 36** Total number of studies (adjunctive therapy, newer drugs vs placebo) assessing quality of life outcomes

Drug	Total no. of studies assessing QoL outcomes			Study details
	Crossover	Parallel	All studies	
GBP	1	2	3	US Gabapentin Study Group No. 5, 1993; <sup>138</sup> Leach, 1997; <sup>90</sup> Anhut, 1994 <sup>156</sup>
LTG	6	3	9	Schachter, 1995; <sup>56</sup> Matsuo, 1993; <sup>142</sup> Veendrick-Meekes, 2000; <sup>137</sup> Schmidt, 1993; <sup>91</sup> Boas, 1996; <sup>136</sup> Loiseau, 1990; <sup>89</sup> Schapel, 1993; <sup>161</sup> Smith, 1993; <sup>55</sup> Messenheimer, 1994 <sup>158</sup>
LEV	0	1	1	Cramer, 2000 <sup>166</sup>
OXC	0	0	0	No studies
TGB	1	1	2	Dodrill, 1997; <sup>167</sup> Sveinbjornsdottir, 1994 <sup>39</sup>
TPM	0	9	9	Barrett, 1997; <sup>76</sup> Biton, 1999; <sup>79</sup> Faight, 1996; <sup>67</sup> Korean Topiramate Study Group, 1999; <sup>149</sup> Tassinari, 1996; <sup>42</sup> Sharief, 1996; <sup>148</sup> Ben-Menachem, 1996; <sup>151</sup> Yen, 2000; <sup>165</sup> Privitera, 1996 <sup>68</sup>
VGB	2	5	7	Provinciali, 1996; <sup>152</sup> Bruni, 2000; <sup>153</sup> Dodrill, 1995; <sup>168</sup> Gillham, 1993; <sup>51</sup> Beran, 1996; <sup>87</sup> Grunewald, 1994; <sup>38</sup> Dodrill, 1993 <sup>169</sup>

**TABLE 37** Types of QoL assessments used (adjunctive therapy, newer AEDs vs placebo)

QoL measure	No. of studies using QoL measure							Total
	GBP	LTG	LEV	OXC	TGB	TPM	VGB	
Goodrich Inventory	0	0	0	0	0	0	1	1
POMS	0	0	0	0	1	0	3	4
SEALS	1	1	0	0	0	0	0	2
Subjective global evaluations (patient)	2	1	0	0	0	9	1	13
Subjective global evaluations (physician/investigator)	2	8	0	0	0	7	2	19
Subjective global evaluations (carer)	0	1	0	0	0	0	0	1
WPSI	0	0	0	0	1	0	3	4
Zung Depression Scale	0	0	0	0	0	0	1	1
QOLIE-3I	0	0	1	0	0	0	0	1
Mood Rating Scale	0	0	0	0	1	0	4	5
Mood Adjective Checklist	0	0	0	0	1	0	1	2
Staff/family assessment	0	0	0	0	1	0	0	1
General Health Questionnaire-28	0	0	0	0	0	0	1	1
Hospital Anxiety and Depression Scale	0	1	0	0	0	0	1	2
Behaviour Checklist	0	0	0	0	0	0	1	1
LSI	0	0	0	0	0	0	1	1
Nottingham Health Profile	0	1	0	0	0	0	0	1
Affect Balance Scale	0	1	0	0	0	0	0	1
Social Problems Questionnaire	0	1	0	0	0	0	0	1
Rosenberg Self-esteem Scale	0	1	0	0	0	0	0	1
Mastery Scale	0	1	0	0	0	0	0	1
Total no. of different measures used	3	10	1	0	5	2	12	–

LSI, Life Satisfaction Index; POMS, Profile of Moods State; WPSI, Washington Psychosocial Seizure Inventory; QOLIE, Quality of Life in Epilepsy Inventory; SEALS, Side Effects and Life Satisfaction Inventory.

**TABLE 38** Summary of overall findings of QoL assessments (adjunctive therapy, newer vs placebo)

Drug	Summary of findings of QoL assessments
GBP	Only one <sup>156</sup> of the three <sup>90,138,156</sup> studies examining GBP found statistically significant differences in favour of GBP using measures of QoL. Based on these findings, there was no strong evidence of differences in QoL in favour of adjunctive GBP in comparison with placebo
LTG	Six <sup>55,56,137,142,158,161</sup> of the nine <sup>55,56,89,91,136,137,142,158,161</sup> LTG studies found statistically significant differences in favour of LTG using some measure of QoL. Most of these differences were found using a subjective measure, which may have biased the findings, and studies were flawed with regard to other quality issues. Based on these findings, there was a trend in favour of adjunctive TPM compared with placebo, but this was based on potentially flawed data
LEV	The trial of LEV reported some statistically significant differences in favour of LEV compared with placebo in some subscales of QOLIE-31. <sup>166</sup> There was very little evidence on which to base an assessment of effectiveness of adjunctive LEV in comparison with placebo
TGB	Neither TGB study reported any statistically significant differences between treatment groups. Based on these findings, there was no evidence of differences in QoL between adjunctive TGB and placebo <sup>39,167</sup>
TPM	Five out of nine <sup>42,67,68,76,79,148,149,151,165</sup> TPM studies found statistically significant differences in favour of TPM using at least one form of global evaluation. However, all of these evaluations were based on subjective assessments and the studies were flawed with regard to a number of other quality issues. Based on these findings, there was a trend in favour of adjunctive TPM as compared with placebo, but this was based on potentially flawed data
VGB	Two <sup>87,152</sup> of the seven <sup>38,51,87,152,153,168,169</sup> VGB trials found statistically significant differences in favour of VGB and one found statistically significant differences in favour of placebo using at least one measure of QoL. All studies were flawed with regard to quality issues, and based on these findings there is no strong evidence either in favour of or against VGB adjunctive therapy compared to placebo in terms of QoL

seizures. The crossover trial treated 27 participants for 28 weeks and the parallel trials treated 272<sup>156</sup> and 306<sup>138</sup> participants, respectively, for 12 weeks. The trials were generally of reasonable quality. However, the crossover trial may possibly have been underpowered as no *a priori* power calculation was reported, the number of participants was low and over 20% of follow-up data were classified as missing. In addition, an appropriate analysis using paired data was not performed. Most participant baseline characteristics were presented only for combined treatment arms in one parallel study,<sup>156</sup> and in the other, one of the GBP doses used a target maintenance dose that was below recommendation range.<sup>138</sup> Only one study found statistically significant differences in favour of GBP in comparison with placebo, using subjective QoL measures (patient and physician global ratings).<sup>156</sup> Based on these findings, there is no strong evidence of any differences in QoL between adjunctive GBP and placebo.

The LEV trial treated 385 patients with refractory partial seizures for 38 weeks.<sup>166</sup> This trial was not powered to detect differences in QoL outcomes and participants were allowed to take other concurrent newer AEDs, which may confound the data. There was significant improvement with both LEV doses compared with placebo for seizure

worry and for 3000 mg/day LEV for overall QoL. In summary, there was very little good-quality evidence on which to base an assessment of adjunctive LEV compared with placebo and any significant findings should be treated with caution in view of the potential for bias.

Both TGB trials treated patients with refractory partial seizures for 20 weeks. The crossover trial recruited 22 patients<sup>39</sup> and the parallel trial recruited 322 patients.<sup>167</sup> The eligibility criteria for study entry were not specified in the crossover trial. In addition, the choice of washout period was not justified and the possibility of carryover effects was not investigated in the analysis of QoL. The parallel trial failed to present details of all relevant participant baseline characteristics, and the only details available were for the combined treatment groups. Neither study reported any statistically significant differences in QoL between adjunctive TGB and placebo.

Seven LTG trials included patients with refractory partial seizures,<sup>55,56,89,91,142,158,161</sup> and two included patients with either partial or generalised refractory seizures.<sup>136,137</sup> The crossover trials included between 23 and 108 patients (mean = 56) and used treatment periods of between 28 and 46 weeks (mean = 34 weeks). The parallel trials treated between 68 and 446 (mean = 243) patients

for between 16 and 28 weeks (mean = 23 weeks). Five trials did not present any details of *a priori* power calculations and may have possibly been underpowered.<sup>56,91,136,137,158</sup> One parallel trial did not present details of all relevant participant baseline characteristics, but where available details were only presented for combined treatment arms.<sup>137</sup> Two crossover trials reported that over 20% of follow-up data were missing<sup>55,136</sup> and two other crossover trials did not present an appropriate analysis using paired data.<sup>89,91</sup>

Five studies reported statistically significant differences in favour of LTG compared with placebo using some form of subjective global physician or investigator evaluation.<sup>56,137,142,158,161</sup> Another study reported statistically significant differences for happiness and mastery in favour of LTG.<sup>55</sup> Overall, adjunctive LTG was favoured in comparison with placebo, but the evidence was potentially flawed.

All trials of TPM included patients with refractory partial seizures, with the exception of two trials where patients had generalised seizures.<sup>76,79</sup> Trials included between 46 and 240 patients (median = 123) and followed treatment for between 11 and 20 weeks (median = 15 weeks). Six trials may have been underpowered; five failed to report *a priori* sample size calculations.<sup>67,68,148,151,165</sup> In one further trial it was unclear whether the sample size calculation was performed *a priori*.<sup>42</sup> Two of the trials failed to present details of all relevant baseline characteristics and the only details presented were for combined treatment arms.<sup>42,151</sup> In three trials, not all patients originally randomised to the study were accounted for at its conclusion,<sup>67,68,151</sup> and in two trials, patients were allowed to use newer AEDs other than TPM, which may confound the data.<sup>76,79</sup> In one of these trials, a large number of the participants did not fulfil the entry requirements for the trial.<sup>76</sup> One trial used doses of TPM that exceeded the recommended limit.<sup>68</sup>

Six studies found statistically significant differences in subjective patient global evaluations in favour of TPM compared with placebo.<sup>67,68,76,149,151,165</sup> and five of these studies also reported statistically significant differences in subjective physician global evaluations in favour of TPM.<sup>67,68,149,151,165</sup> Overall, adjunctive TPM was favoured in comparison with placebo, but the evidence was potentially flawed.

All of the VGB studies included patients with refractory partial seizures, with the exception of

one study that included patients with refractory generalised seizures.<sup>51</sup> However, VGB is not licensed for the treatment of generalised onset seizures. The studies included between 24 and 203 patients (mean = 112) and followed treatment for between 4 and 32 weeks (mean = 17 weeks). None of the studies reported *a priori* sample size calculation, and may potentially have been underpowered. In two trials, some doses of VGB exceeded the recommended limit,<sup>153,168</sup> and in three further studies, the number of participants completing the study was unclear.<sup>51,152,169</sup> In one of these, trials over 20% of follow-up data were classified as missing.<sup>51</sup> One study included patients who did not fulfil the entry criteria for the trial<sup>153</sup> and in another study not all relevant details of baseline comparability between the treatment groups were presented,<sup>169</sup> One trial used an open-label design thereby increasing the risk of bias.<sup>152</sup> In one of two crossover trials, the duration chosen for the washout period was not justified.<sup>87</sup> All of these issues could affect the findings of the studies and must be considered when interpreting the findings.

Two studies found statistically significant differences in favour of VGB; one used a measurement of global patient and investigator evaluations,<sup>87</sup> and the other study found differences in depression and LSI scores.<sup>152</sup> Another study reported statistically significant differences in favour of placebo using POMS, WPSI and the mood rating scale.<sup>153</sup> Overall, there was no good-quality evidence of consistent statistically significant differences in QoL between adjunctive VGB therapy and placebo.

#### e. Cognitive function

Twelve out of 55 studies of newer AEDs versus placebo assessed some aspect of cognitive function (see *Table 39*). The majority of studies used VGB.<sup>38,51,152,153,168,169</sup> One study used GBP,<sup>90</sup> two used LTG<sup>55,88</sup> and three used TGB.<sup>39,43,167</sup> No studies of LEV, OXC or TPM were found.

A total of 51 different cognitive assessment measures were used (see *Table 40*).

Details of the individual study data are reported in Appendix 23 and details of the individual cognitive measures in Appendix 5. *Table 41* summarises the overall findings of the cognitive assessments.

The GBP study included 27 participants in a crossover design and found no significant differences between adjunctive GBP and placebo.<sup>90</sup> The authors did not report an *a priori* sample size



**TABLE 39** Total number of studies assessing cognitive function

Drug	Total no. of studies assessing cognitive function			Study details
	Crossover	Parallel	All studies	
GBP	1	0	1	Leach, 1997 <sup>90</sup>
LTG	2	0	2	Banks, 1991; <sup>88</sup> Smith, 1993 <sup>55</sup>
LEV	0	0	0	No studies
OXC	0	0	0	No studies
TGB	1	2	3	Kälviäinen, 1996; <sup>43</sup> Dodrill, 1997; <sup>167</sup> Sveinbjornsdottir, 1994 <sup>39</sup>
TPM	0	0	0	No studies
VGB	1	5	6	Dodrill, 1995; <sup>168</sup> Provinciali, 1996; <sup>152</sup> Bruni, 2000; <sup>153</sup> Grunewald, 1994; <sup>38</sup> Dodrill, 1993; <sup>169</sup> Gillham, 1993 <sup>51</sup>

**TABLE 40** Assessments used to measure cognitive function

Cognitive measure	No. of studies using cognitive measure							Total
	GBP	LTG	LEV	OXC	TGB	TPM	VGB	
Wonderlic Personnel Test	0	0	0	0	1	0	3	4
Lafayette Grooved Pegboard Test	0	0	0	0	1	0	3	4
Stroop Test	1	2	0	0	3	0	4	10
Benton Visual Retention Test (BVRT)	0	0	0	0	1	0	3	4
Controlled Oral Word Association (COWA)	0	0	0	0	2	0	3	5
Symbol Digit Modalities	0	0	0	0	1	0	3	4
Rey Auditory-Verbal Learning Test/List Learning (from Adult Memory and Information Processing Battery)	0	0	0	0	3	0	4	7
Digit Cancellation Test	0	0	0	0	1	0	2	3
Italian Matrix Test	0	0	0	0	0	0	1	1
Bell's Test	0	0	0	0	0	0	1	1
H barrage Test	0	0	0	0	0	0	1	1
Toulouse Pieron	0	0	0	0	0	0	1	1
Trailmaking Test A	0	1	0	0	0	0	1	2
Trailmaking Test B	0	1	0	0	0	0	1	2
Digit Symbol Test	0	1	0	0	0	0	1	2
Reaction Times	0	0	0	0	0	0	1	1
Forward Digit Span	0	0	0	0	1	0	1	2
Corsi's Blocks	0	0	0	0	1	0	1	2
Buschke-Fuld Test	0	0	0	0	0	0	1	1
Digit Span Test	0	0	0	0	0	0	1	1
Verbal Recall	0	0	0	0	0	0	1	1
Design Learning	0	0	0	0	0	0	1	1
Information Processing Tasks A and B (from Adult Memory and Information Processing Battery)	0	0	0	0	0	0	1	1
Verbal Fluency	0	0	0	0	0	0	1	1
Bilateral/Bimanual Hand Movements	0	0	0	0	1	0	1	2
Tapping Rate	0	0	0	0	1	0	1	2
Decision Time	1	0	0	0	0	0	1	2
Movement Time	1	0	0	0	0	0	1	2
Threshold Detection Test	1	0	0	0	0	0	1	2
Forward Digit Span	1	0	0	0	0	0	1	2
Backward Digit Span	1	0	0	0	0	0	1	2
Forward Visual Span	1	0	0	0	0	0	0	1
Backward Visual Span	1	0	0	0	0	0	0	1

continued

**TABLE 40** Assessments used to measure cognitive function (cont'd)

Cognitive measure	No. of studies using cognitive measure							Total
	GBP	LTG	LEV	OXC	TGB	TPM	VGB	
Paired Associate Learning Test	1	0	0	0	0	0	1	2
National Adult Reading Test	0	1	0	0	0	0	0	1
Digit Span Test	0	1	0	0	0	0	0	1
Rey Complex Figure Test	0	1	0	0	0	0	0	1
Leeds Psychomotor Test	0	1	0	0	0	0	0	1
Number Cancellation Test (from the Adult Memory and Information Processing Battery)	0	1	0	0	1	0	0	2
Logical Prose Story A [from the Wechsler Memory Scale (WMS)]	0	0	0	0	1	0	0	1
Alternating S Task	0	0	0	0	1	0	0	1
Letter Cancellation Task	0	0	0	0	1	0	0	1
Modified Finger-tapping Test	0	0	0	0	1	0	0	1
Visual Reproduction (a subtest of the WMS)	0	0	0	0	1	0	0	1
Auditory and Visual Reaction Time	0	0	0	0	1	0	0	1
Binary Choice Reaction Time	0	0	0	0	1	0	0	1
Semantic Processing	0	0	0	0	1	0	0	1
Simple Reaction Time	0	0	0	0	1	0	0	1
Verbal Memory	0	0	0	0	1	0	0	1
Tracking Task	0	0	0	0	0	0	1	1
Rivermead Behavioural Memory Test	0	0	0	0	0	0	1	1
<b>Total no. of different measures used</b>	<b>9</b>	<b>9</b>	<b>0</b>	<b>0</b>	<b>23</b>	<b>0</b>	<b>34</b>	<b>–</b>

**TABLE 41** Summary of overall findings of cognitive assessments

Drug	Summary of findings of cognitive assessments
GBP	One study showed no effect of GBP compared with placebo <sup>90</sup>
LTG	One of two studies reported indications of reduced cerebral efficiency, but that it was unclear whether this was due to LTG alone or polypharmacy effects <sup>88</sup>
TGB	Overall there was no difference in cognitive function between TGB and placebo. One of three <sup>39,43,167</sup> studies found that one cognitive score (Form F of the Benton Visual Retention Test) out of 37 favoured placebo compared with adjunctive TGB <sup>167</sup>
VGB	Six studies provided some evidence of effect on some tests but overall this was inconsistent between trials. One study reported an improvement in three out of 12 cognitive tests (Bells; Trailmaking Test B and the Buschke–Fuld test). <sup>152</sup> One study reported a poorer performance in dominant hand-tapping frequency in the VGB group and in one design-learning task out of 16 other cognitive tests. <sup>38</sup> One study reported a poorer performance in the Stroop test with VGB. <sup>153</sup> The other three studies reported no significant difference between VGB and placebo. <sup>51,168,169</sup>

calculation or whether the outcome assessors were blinded. There were three follow-up assessments in each treatment phase, repeated testing was carried out at the same time of day and the authors did report testing for an order effect.<sup>90</sup>

One of the LTG studies ( $n = 12$ ) concluded that there were indications of reduced cerebral efficiency with LTG in patients with refractory partial seizures,<sup>88</sup> whereas the other study ( $n = 81$ ) showed no significant differences in neuropsychological test scores between LTG and placebo.<sup>55</sup> Only one of the studies specified that

tests were administered in a set order.<sup>88</sup> The other study reported that neuropsychological testing was not carried out if patients were postictal, but testing did not appear to have been rescheduled, and therefore those participants may have been lost from the study.<sup>55</sup>

One of the three TGB studies found a deterioration in cognitive function with TGB in one out of 37 analyses. Although that was the only study that reported an *a priori* power calculation for sample size ( $n = 297$ ), the one statistically significant finding could have occurred by chance

given the large number of analyses performed.<sup>167</sup> The other two studies found no difference between TGB and placebo, but as they recruited small numbers of participants they may have been underpowered to detect a difference in cognitive function.<sup>39,43</sup> Only one study reported that the individuals who carried out neuropsychological assessments were blind to treatment allocation.<sup>43</sup> Only one study reported more than one (three) follow-up assessments in each treatment phase.<sup>39</sup>

VGB was used in one crossover<sup>51</sup> and five parallel group studies.<sup>38,152,153,168,169</sup> The crossover study ( $n = 24$ , two patients had generalised onset seizures) concluded that VGB did not cause cognitive impairment. The individuals who carried out the neuropsychological assessments were blind to treatment allocation, there were three follow-up assessments in each treatment phase and repeated testing was conducted at the same time of day.<sup>51</sup>

One parallel group study ( $n = 40$ ) found an improvement with VGB in three cognitive tests.<sup>152</sup> In two of the tests the adjunctive VGB group scores were significantly poorer than the control group at baseline. The individuals who carried out the neuropsychological assessments were blind to the treatment allocation but the patients were not blinded. The study had two follow-up assessments, tests were administered in a set order and testing was not carried out if patients were postictal. Another study ( $n = 45$ ) showed a small but statistically significant reduction in motor speed and a modest impairment of performance on a visual memory task with VGB.<sup>38</sup> That study was the only one to report a truly random assignment method. Repeated testing was carried out at the same time of day; however, the authors do not appear to have taken into account the possible impact of mood on neuropsychological performance, and did not report the order in which the cognitive tests were performed. One other study ( $n = 111$ ) reported a poorer performance on the Stroop test with VGB.<sup>153</sup> The other two parallel group trials ( $n = 174$  and  $182$ ) reported no significant differences between VGB and placebo.<sup>168,169</sup> Two of the trials reported administering the tests in a set order<sup>168,169</sup> and the other that tests were preformed according to standardised procedures of administration (not specified).<sup>153</sup> Only one study reported an ITT analysis.<sup>153</sup> None of the VGB studies reported whether they had used a method that was adequate to conceal treatment allocation.

Overall, many of the cognitive function tests were common to only a few studies, and although the

Stroop test was used in 10 studies not all of them used the same scoring system; therefore, it was difficult to make comparisons between studies. The evidence for the newer drugs being superior to placebo in terms of their impact on cognitive functioning was neither strong nor consistent. Also, the findings need to be considered in the context of study quality. A complete quality assessment of all the studies was not possible because of poor reporting.

#### Summary statement for newer AEDs versus placebo

A number of studies assessed the clinical effectiveness of newer AEDs versus placebo. The majority of studies were in patients with refractory partial seizures and there was little evidence concerning the use of adjunctive therapy in patients with generalised seizures. The most commonly reported outcome was the proportion of 50% responders, although a large number of the studies also reported the proportion of seizure-free participants and cognitive/QoL data. No studies reported time to event outcomes (time to exit/withdrawal and time to first seizure).

Overall, the evidence for clinical effectiveness suggested a trend in favour of newer adjunctive AEDs compared with placebo. This trend was not always statistically significant, with the exception of the proportion of 50% responders. Differences in QoL outcomes suggested a similar trend in favour of adjunctive LTG and TPM. However, many trials only considered therapy over a period of 12–16 weeks or less, so it was not possible to assess long-term effectiveness. Studies of cognitive function reported limited and inconsistent effects.

## 2. Newer drugs versus older drugs

### a. Seizure frequency

#### i. Seizure freedom

Two out of 10 studies of newer drugs versus older drugs (adjunctive therapy) reported the proportion of seizure-free participants. A summary of the main characteristics of these studies is presented in *Table 42*.

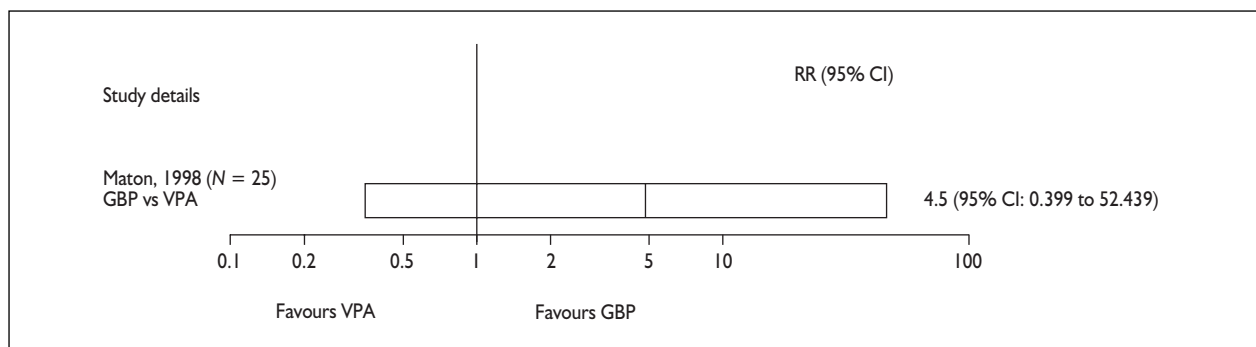
No studies compared LTG, LEV, OXC, TGB or TPM with older drugs.

One parallel superiority trial compared adjunctive GBP with VPA in 25 patients with refractory partial seizures.<sup>128</sup> Treatment was followed up over

**TABLE 42** Summary of studies (adjunctive therapy, newer drugs vs older drugs) assessing proportion of seizure-free participants

Drug	Study characteristics <sup>a</sup>				
	Refractory/ newly diagnosed	Seizure type	Dose Follow-up N	Comments	Study details
GBP	Refractory	Partial	Individually titrated 12 weeks N = 25	GBP vs VPA (individually titrated)	Maton, 1998 <sup>128</sup>
LTG	No studies				
LEV	No studies				
OXC	No studies				
TGB	No studies				
TPM	No studies				
VGB	Refractory	Partial	4 g/day max. 12 weeks N = 215	To enter the double-blind phase of the trial, participants had to achieve at least a 50% decrease in seizure frequency without adverse events, during the pretrial period. Specifically looks at patients with intellectual disabilities. VGB vs VPA	Brodie, 1999 <sup>66</sup>

N, total number of participants randomised; NS, not stated.  
<sup>a</sup> Both were parallel, superiority trials.

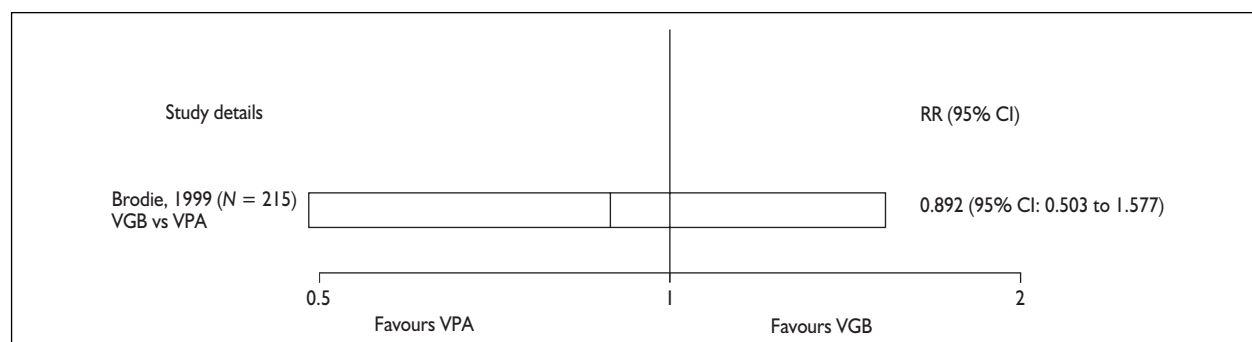
**FIGURE 21** Proportion of seizure-free participants (RR, 95% CI) for the adjunctive trial of GBP vs VPA (ITT data)

a 12-week period. However, the study was terminated prematurely owing to poor recruitment and concurrent medications may have confounded treatment effects. The RR (95% CI) reported in *Figure 21* favoured GBP over placebo, but was not statistically significant.

Only one parallel superiority trial in 215 patients with refractory partial seizures compared VGB with VPA over a 12-week period.<sup>66</sup> The trial specifically recruited individuals with intellectual

disabilities, who were required to achieve at least a 50% decrease in seizure frequency without any adverse events while receiving VGB during the pretrial period. This limits the applicability of the study findings. The RR (95% CI) reported in *Figure 22* favours VPA over VGB, but this difference is not statistically significant.

Overall, there was very little evidence on which to base an assessment of the effectiveness of newer AEDs as adjunctive therapy versus older AEDs.



**FIGURE 22** Proportion of seizure-free participants (RR, 95% CI) for adjunctive trial of VGB vs VPA (ITT data)

**TABLE 43** Summary of studies (adjunctive therapy, newer drugs vs older drugs) assessing proportion of participants experiencing at least a 50% decrease in seizure frequency

Drug	Study characteristics <sup>a</sup>				
	Refractory/ newly diagnosed	Seizure type	Dose Follow-up N	Comments	Study details
GBP	Refractory	Partial	Individually titrated 12 weeks N = 25	GBP vs VPA	Maton, 1998 <sup>128</sup>
LTG			No studies		
LEV			No studies		
OXC			No studies		
TGB	Refractory	Partial	80 mg/day 16 weeks N = 349	TGB vs CBZ TGB vs PHT	Sommerville, 1998 <sup>129</sup>
TPM			No studies		
VGB	Refractory	Partial	4 g/day max. 12 weeks N = 215	To enter the double-blind phase of the trial, participants had to achieve at least a 50% decrease in seizure frequency without adverse events, during the pretrial period. Specifically looks at patients with intellectual disabilities. VGB vs VPA	Brodie, 1999 <sup>66</sup>

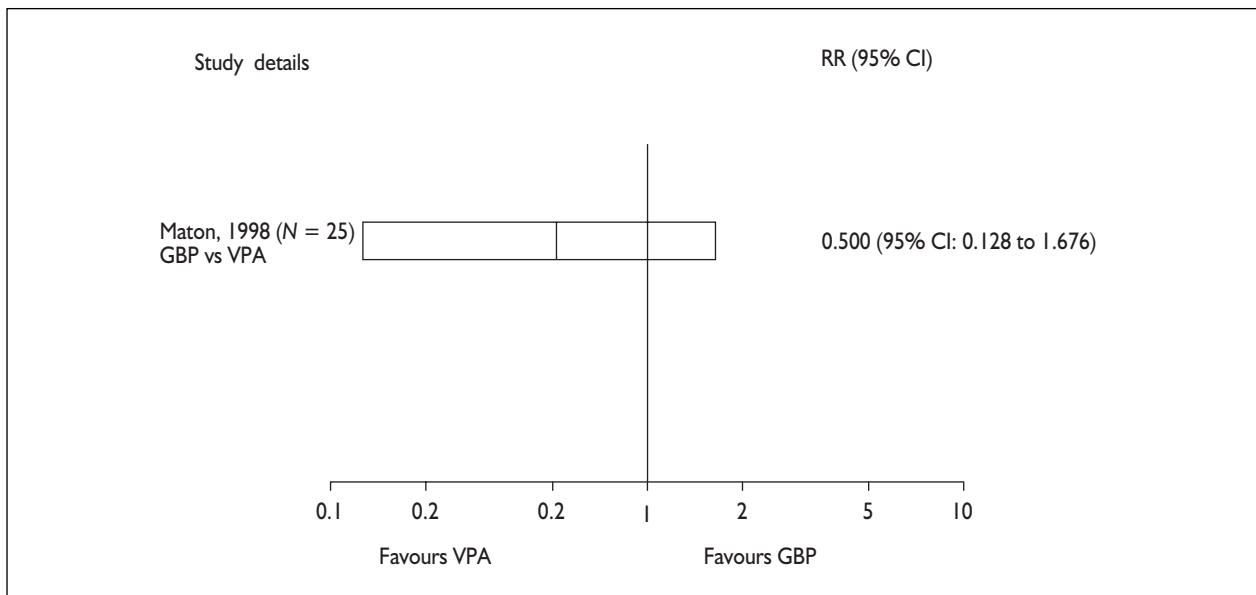
N, total number of participants randomised; NS, not stated.  
<sup>a</sup> All were parallel, superiority trials unless stated otherwise.

ii. 50% reduction in seizure frequency

Three out of 10 studies of newer drugs versus older drugs (adjunctive therapy) reported the proportion of participants who experienced at least a 50% decrease in seizure frequency. A summary of the main characteristics of these studies is presented in *Table 43*.

No studies compared LTG, LEV, OXC or TPM with older drugs with regard to proportion of responders.

One parallel superiority trial of 25 patients with refractory partial seizures compared adjunctive GBP with VPA over a 12-week period.<sup>128</sup> The



**FIGURE 23** Proportion of 50% responders (RR, 95% CI) for the adjunctive trial of GBP vs VPA (ITT data)

study had certain limitations, which have already been discussed with regard to the proportion of seizure-free participants. The RR (95% CI) shown in *Figure 23* favours VPA over GBP, but this difference was not statistically significant.

One parallel superiority trial of 349 patients with refractory partial seizures compared TGB with older AEDs (CBZ and PHT) over a 16-week period.<sup>129</sup> This was a reasonable quality trial. The unpooled RRs for each comparison are shown in *Figure 24*. No difference was shown between TGB and CBZ. However, the RR significantly favoured PHT in comparison with TGB.

**FIGURE 24** Proportion of 50% responders (RRs, 95% CIs) for the adjunctive trial of TGB vs older AEDs (ITT data)

**[Data have been designated commercial-in-confidence and have been removed]**

Only one parallel superiority trial of 215 patients with refractory partial seizures compared VGB with VPA during a 12-week period.<sup>66</sup> This study suffered from certain limitations, which have been discussed with regard to the proportion of seizure-free participants. The RR shown in *Figure 25* favours VGB, but the difference is not statistically significant.

Overall, there was very little evidence on which to base an assessment of the effectiveness of newer adjunctive AEDs versus older AEDs.

#### b. Time to first seizure

None of the 10 studies of newer drugs versus

older drugs (adjunctive therapy) reported the time to first seizure.

#### c. Time to withdrawal/exit

None of the 10 studies of newer drugs versus older drugs (adjunctive therapy) reported the time to exit/withdrawal.

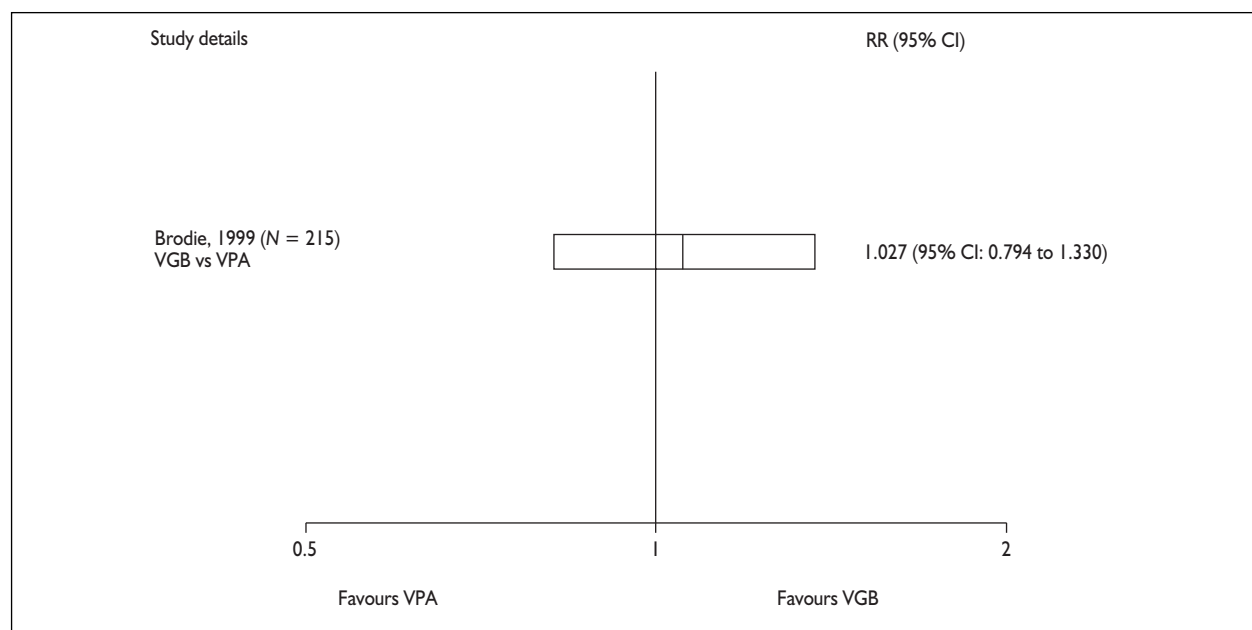
#### d. Quality of life

Four out of 10 of the studies of newer drugs versus older drugs (adjunctive therapy) reported QoL outcomes (see *Table 44*).

No studies of adjunctive LTG, LEV, OXC or VGB reported QoL outcomes. One study used GBP, one TGB and two TPM. All studies were parallel superiority trials. Various measures were used to assess QoL (see *Table 45*). In total seven different types of measures were used; GBP (one measure) TGB (four measures) and TPM (three measures). Within each drug, measures were each used in only one study. However, the POMS was used to assess the effects of both TGB and TPM.

Details of the individual study data are reported in Appendix 23 and details of the individual QoL measures in Appendix 4. *Table 46* summarises the overall findings of the QoL assessments.

One trial of 32 patients with refractory partial seizures compared GBP with VPA for 14–18 weeks.<sup>128</sup> The trial recruited less than one-quarter of the number of participants required, and was therefore terminated prematurely. Participants were not blind to their treatment



**FIGURE 25** Proportion of 50% responders (RR, 95% CI) for the adjunctive trial of VGB vs VPA (ITT data)

**TABLE 44** Total number of studies assessing QoL outcomes (adjunctive therapy, newer vs older drugs)

Drug	Total no. of studies assessing QoL function			Study details
	Crossover	Parallel	All studies	
GBP	0	1	1	Maton, 1998 <sup>128</sup>
LTG				No studies
LEV				No studies
OXC				No studies
TGB	0	1	1	Cramer, 2001 <sup>65</sup>
TPM	0	2	2	Meador, 2001; <sup>44</sup> Aldenkamp, 2000 <sup>130</sup>
VGB				No studies

**TABLE 45** Types of QoL assessments used (adjunctive therapy, newer vs older drugs)

QoL measure	No. of studies using QoL measure							Total
	GBP	LTG	LEV	OXC	TGB	TPM	VGB	
Mood problems	0	0	0	0	0	1	0	1
POMS	0	0	0	0	1	1	0	2
ABNC	0	0	0	0	0	1	0	1
WPSI	0	0	0	0	1	0	0	1
Mood Rating Scale	0	0	0	0	1	0	0	1
QOLIE-89	0	0	0	0	1	0	0	1
QoL measure not stated	1	0	0	0	0	0	0	1
<b>Total no. of different measures used</b>	1	0	0	0	4	3	0	–

ABNC, Aldenkamp–Baker Neurotoxicity Scale.

**TABLE 46** Summary of overall findings of QoL assessments (adjunctive therapy, newer vs older drugs)

Drug	Summary of findings of QoL assessments
GBP	The trial comparing GBP with VPA was of poor quality and did not report data. <sup>128</sup> Therefore, there was no evidence on which to base an assessment of the effectiveness of GBP adjunctive therapy compared with older drugs in terms of QoL
TGB	One poor-quality trial did not show any statistically significant differences between TGB and CBZ. <sup>65</sup> Therefore, there was very little evidence on which to base an assessment of the effectiveness of adjunctive therapy with TGB versus older AEDs
TPM	Neither of the TPM studies reported any statistically significant differences between TPM and VPA. <sup>44,130</sup> One study was only available as an abstract and it was not possible to assess fully the quality of the study. <sup>44</sup> Based on these findings, there was no evidence on which to base an assessment of adjunctive therapy with TPM versus older AEDs

**TABLE 47** Total number of studies assessing cognitive function

Drug	Total no. of studies assessing cognitive function			Study details
	Crossover	Parallel	All studies	
GBP	0	0	0	
LTG	0	0	0	
LEV	0	0	0	
OXC	0	0	0	
TGB	0	1	1	Dodrill, 2000 <sup>57</sup>
TPM	0	2	2	Meador, 2001; <sup>44</sup> Aldencamp, 2000 <sup>130</sup>
VGB	0	0	0	

allocation and some received concurrent treatment with other newer AEDs, which may confound the study findings. Although collected, QoL data were not assessed.

One trial of 349 patients with refractory partial seizures compared TGB with CBZ over a period of 24 weeks.<sup>65</sup> Not all participants were accounted for at the end of the study, and over 20% of the outcome data were classified as missing. In some cases patients received doses of TGB that exceeded maximum recommended doses. These issues could affect the study findings. The study did not report any statistically significant differences between TGB as adjunctive therapy and older drugs in terms of QoL.

Two trials of patients ( $n = 59$ ,<sup>130</sup>  $n = 76$ <sup>44</sup>) with refractory partial seizures compared TPM with VPA over a period of 24 weeks. One trial was of reasonable quality.<sup>130</sup> The other trial was only reported as an abstract and so quality could not be fully assessed. Neither of the studies reported any statistically significant differences in QoL between TPM and older AEDs.

#### e. Cognitive function

Three out of 10 studies of newer versus older AEDs assessed some aspect of cognitive function (see *Table 47*). Two studies compared TPM with VPA adjunctive to CBZ. One study compared TGB with PHT adjunctive to CBZ, and TGB with CBZ adjunctive to PHT.

A total of 13 different cognitive assessment measures were used (see *Table 48*).

Details of the individual study data are reported in Appendix 23 and details of the cognitive measures in Appendix 5. *Table 49* summarises the overall findings of the cognitive assessments.

One study ( $n = 177$ ) compared TGB with PHT and CBZ over a 16-week period in patients with refractory partial seizures.<sup>57</sup> Neither allocation concealment nor the blinding of the outcome assessor was reported. Eight different measures were used to assess cognitive function at baseline and at two follow-up visits. The study showed a significant improvement in two tests (Digit Cancellation Test, COWA) with TGB compared



**TABLE 48** Assessments used to measure cognitive function

Cognitive measure	No. of studies using cognitive measure							Total
	GBP	LTG	LEV	OXC	TGB	TPM	VGB	
Wonderlic Personnel Test	0	0	0	0	1	0	0	1
Lafayette Grooved Pegboard Test	0	0	0	0	1	0	0	1
Stroop Test	0	0	0	0	1	0	0	1
VSRT	0	0	0	0	1	0	0	1
COWA	0	0	0	0	1	1	0	2
Symbol Digit Modalities	0	0	0	0	1	1	0	2
Rey Auditory–Verbal Learning Test	0	0	0	0	1	1	0	2
Digit Cancellation Test	0	0	0	0	1	0	0	1
Finger-tapping Test	0	0	0	0	0	1	0	1
Simple Reaction Time	0	0	0	0	0	1	0	1
Binary Choice Reaction Test	0	0	0	0	0	1	0	1
Computerised Visual Searching Task	0	0	0	0	0	1	0	1
Recognition of Words and Figures	0	0	0	0	0	1	0	1
<b>Total no. of different measures used</b>	0	0	0	0	8	8	0	–

**TABLE 49** Summary of overall findings of cognitive assessments

Drug	Summary of findings of cognitive assessments
TGB	One study that compared TGB with CBZ and PHT concluded that there was no convincing evidence for differences between the drugs. <sup>57</sup> There was a significant difference in favour of TGB over CBZ in two tests, and a trend towards improvement with TGB compared with PHT in one test
TPM	One study reported a small but statistically significant difference in favour of VPA over TPM in two tests, but insufficient information was available to assess the study fully. <sup>44</sup> The other study showed a significant difference in favour of VPA in one test but concluded overall that the differences found between TPM and VPA were small. <sup>130</sup>

with CBZ adjunctive to PHT. There was a trend towards improvement in one test (Digit Cancellation Test) with TGB compared with PHT adjunctive to CBZ. It was not stated whether tests were carried out in a set order, if repeated testing was carried out at the same time of day or whether postictal participants were assessed.

One TPM study ( $n = 76$ ) used 23 neuropsychometric tests and seven mood tests.<sup>44</sup> Results were reported in summary and not per test. It was unclear exactly how many statistical analyses were performed as some of the tests may have generated more than one score. The study was only available as an abstract and therefore it was not possible to assess its quality adequately. There were two follow-up assessments over 20 weeks. At the end of the study two tests (Symbol Digit Modalities, COWA) showed significant negative baseline-to-titration changes with TPM compared with VPA. It was not stated whether tests were carried out in a set order, if repeated testing was carried out at the same time

of day or whether postictal participants were assessed.

The other TPM study ( $n = 59$ ) reported an *a priori* sample size calculation, adequate concealment of allocation and blinding of the outcome assessors.<sup>130</sup> Assessments were not performed on postictal patients or if a patient had recently taken an antihistamine or consumed an unusual quantity of caffeine, and repeated testing was carried out at the same time of day. However, 20 change scores were tested without correction for multiple testing and the analyses were not based on ITT. One outcome measure of memory (Rey Test Immediate Recall) showed a statistically significant change in mean score from baseline to end-point in favour of VPA.

Overall, there was no strong or consistent evidence that adjunctive TPM or TGB affect cognitive function any more or less than the older drugs used as comparators. All of the studies considered only short-term effects.

**Summary statement for newer versus older AEDs**

There was no evidence to assess the effectiveness of adjunctive LEV, LTG or OXC versus older drugs. Evidence for GBP, TGB, TPM and VGB was limited to single studies that compared the newer drugs with CBZ, PHT or VPA. Trials only included patients with refractory partial seizures and treatment periods were relatively short (3 months). Data were only available for the proportion of seizure-free patients, proportion of 50% responders, and limited QoL and cognitive outcomes.

Overall, there was very limited evidence on which to base an assessment of the clinical effectiveness of adjunctive treatment with newer AEDs versus older AEDs. Available evidence shows mainly non-significant differences between newer and older drugs, and should be regarded with great caution in view of problems with the design and quality of the studies.

**3. Newer drugs versus newer drugs****a. Seizure frequency****i. Seizure freedom**

All four studies of newer drugs versus newer drugs (adjunctive therapy) assessed the proportion of seizure-free participants. A summary of the main characteristics of the studies is presented in *Table 50*.

No studies compared LEV, OXC or TPM with other newer AEDs with respect to the proportion of seizure-free participants.

Three parallel superiority trials of between 83 and 404 (mean = 196) patients with refractory seizures compared adjunctive treatment with GBP with other newer AEDs.<sup>61,131,132</sup> Two studies used treatment periods of 24 weeks<sup>131,132</sup> and the third followed treatment over a period of 18 months.<sup>61</sup> Two trials included patients with partial seizures<sup>61,132</sup> and the third included patients with partial or generalised seizures.<sup>131</sup> Two trials compared GBP with LTG<sup>61,131</sup> and two compared GBP with VGB.<sup>61,132</sup>

Two of the studies used an open-label design.<sup>61,131</sup> One study was only reported as an abstract and it was not possible to assess fully the quality of the study.<sup>61</sup> One study included patients with intellectual disabilities and hence findings may have limited applicability.<sup>131</sup> The remaining study

was discontinued prematurely and failed to recruit the required number of participants.<sup>132</sup> This study also found baseline differences between treatment groups in the duration of epilepsy and in some cases doses of GBP and VGB exceeded the recommended limit.

Owing to the presence of clinical (different participants, drug doses and follow-up periods) and statistical (*Q*-statistic) heterogeneity, the pooling of data was limited. The unpooled RRs are shown in *Figure 26*.

One study comparing GBP with LTG showed no difference<sup>61</sup> (i.e. RR = 1) and the other favoured LTG.<sup>131</sup> Both of the studies comparing GBP with VGB favoured VGB, but the differences were not statistically significant. Data from these two studies were pooled using a fixed-effects model (see *Table 51*). The pooled RR (fixed-effects model) slightly favoured VGB over GBP, but again the difference was not significant.

Three parallel superiority trials examined the use of LTG in between 48 and 404 (mean = 178) refractory patients for periods of 20–78 weeks (mean = 41 weeks). One trial was carried out in patients who had either partial or generalised seizure types<sup>131</sup> and the other two trials were carried out in patients with partial seizures. Two trials compared LTG with GBP,<sup>61,131</sup> one with VGB<sup>61</sup> and one with TGB.<sup>133</sup> The studies were limited with respect to some quality issues, one of which was that all three studies were completely unblinded. Other limitations have been discussed previously in this section under the GBP studies. These limitations could affect the findings of the studies and should be considered when interpreting the data.

In view of clinical (different comparators, drug doses) and statistical (*Q*-statistic) heterogeneity between the studies, data were not pooled. The unpooled RRs are shown in *Figure 27*.

The study comparing LTG with TGB showed a slight difference in favour of LTG, but this was not statistically significant.<sup>133</sup> One of the two studies comparing LTG with GBP showed no difference<sup>61</sup> and the other favoured LTG, but this difference was not statistically significant.<sup>131</sup> The study comparing LTG with VGB showed a slight difference in favour of VGB, but this was not statistically significant.<sup>61</sup>

Overall, there was limited evidence on which to base an assessment of newer AEDs versus other

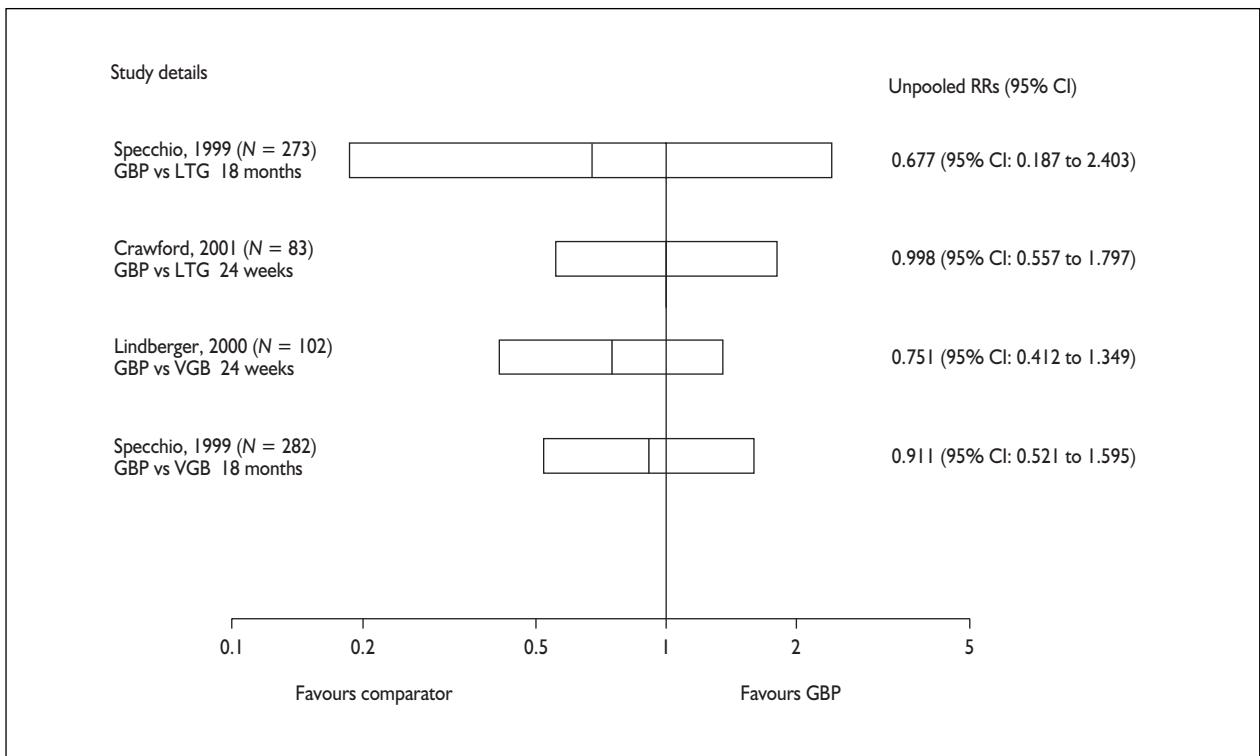
**TABLE 50** Summary of studies (adjunctive therapy, newer drugs vs newer drugs) assessing proportion of seizure-free participants

Drug	Study characteristics <sup>a</sup>				
	Refractory/ newly diagnosed	Seizure type	Dose Follow-up N	Comments	Study details
GBP	Refractory	Combination of partial/generalised	3600 mg/day 24 weeks N = 83	Specifically looks at patients with intellectual disabilities. GBP vs LTG (400 mg/day)	Crawford, 2001 <sup>131</sup>
	Refractory	Partial	1800–3600 mg/day 24 weeks N = 102	GBP vs VGB (1000–4000 mg/day)	Lindberger, 2000 <sup>132</sup>
	Refractory	Partial	Dose NS 18 months N = 404	GBP vs VGB (dose NS) GBP vs LTG (dose NS)	Specchio, 1999 <sup>61</sup>
LTG	Refractory	Partial	400 mg/day 20 weeks N = 48	LTG vs TGB (60 mg/day)	Chmielewska, 2001 <sup>133</sup>
	Refractory	Partial	Dose NS 18 months N = 404	LTG vs VGB (dose NS) LTG vs GBP (dose NS)	Specchio, 1999 <sup>61</sup>
	Refractory	Combination of partial/generalised	400 mg/day 24 weeks N = 83	LTG vs GBP (3600 mg/day). Specifically looks at patients with intellectual disabilities	Crawford, 2001 <sup>131</sup>
LEV			No studies		
OXC			No studies		
TGB	Refractory	Partial	60 mg/day 20 weeks N = 48	TGB vs LTG (400 mg/day)	Chmielewska, 2001 <sup>133</sup>
TPM			No studies		
VGB	Refractory	Partial	Dose NS 18 months N = 404	VGB vs GBP (dose NS) VGB vs LGT (doses NS)	Specchio, 1999 <sup>61</sup>
	Refractory	Partial	1000–4000 mg/day 24 weeks N = 102	VGB vs GBP (1800–3600 mg/day)	Lindberger, 2000 <sup>132</sup>

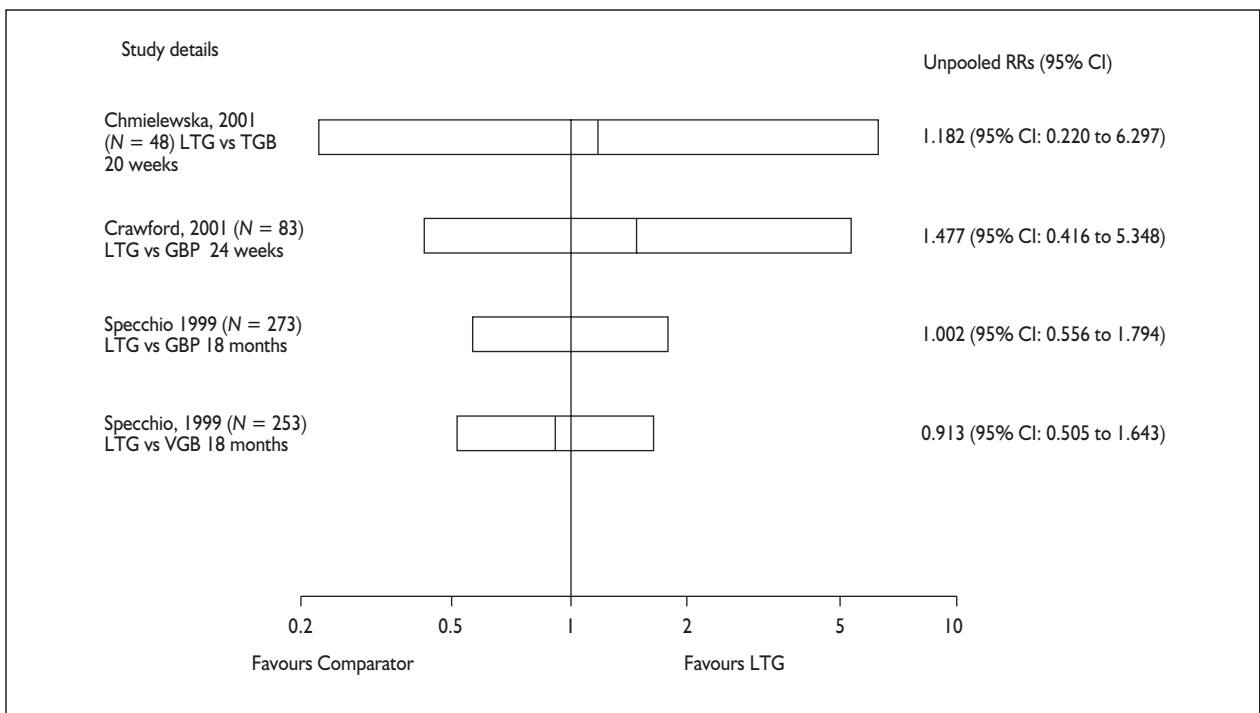
N, total number randomised; NS, not stated.  
<sup>a</sup> All were parallel, superiority trials.

**TABLE 51** Proportion of seizure-free participants (pooled RRs, 95% CIs) for adjunctive studies of GBP vs VGB (ITT data)

Characteristics	Studies	Pooled RR (95% CI) (fixed effects)
N=102	Lindberger, 2000 <sup>132</sup>	0.751 (95% CI: 0.412 to 1.349)
N=282	Specchio, 1999 <sup>61</sup>	0.911 (95% CI: 0.521 to 1.595)
<b>Refractory, partial, GBP vs VGB</b>	<b>Pooled (n = 2)</b>	<b>0.839 (95% CI: 0.555 to 1.267)</b> <b>Heterogeneity: Q = 0.212 (df = 1), p = 0.645</b>



**FIGURE 26** Proportion of seizure-free participants (unpoled RRs, 95% CIs) for adjunctive trials of GBP vs other newer AEDs (ITT data)



**FIGURE 27** Proportion of seizure-free participants (unpoled RRs, 95% CIs) for adjunctive trials of LTG vs other newer AEDs (ITT data)

**TABLE 52** Summary of studies (adjunctive therapy, newer drugs vs newer drugs) assessing proportion of participants experiencing at least a 50% decrease in seizure frequency

Drug	Study characteristics <sup>a</sup>				
	Refractory/ newly diagnosed	Seizure type	Dose Follow-up N	Comments	Study details
GBP	Refractory	Combination of partial/generalised	3600 mg/day 24 weeks N = 83	Specifically looks at patients with intellectual disabilities. GBP vs LTG (400 mg/day)	Crawford, 2001 <sup>131</sup>
	Refractory	Partial	1800–3600 mg/day 24 weeks N = 102	GBP vs VGB (1000–4000 mg/day)	Lindberger, 2000 <sup>132</sup>
	Refractory	Partial	Dose NS 18 months N = 282	GBP vs VGB (dose NS)	Specchio, 1999 <sup>61</sup>
LTG	Refractory	Partial	400 mg/day 20 weeks N = 48	LTG vs TGB (60 mg/day)	Chmielewska, 2001 <sup>133</sup>
	Refractory	Partial	Dose NS 18 months N = 404	LTG vs VGB (dose NS) LTG vs GBP (dose NS)	Specchio, 1999 <sup>61</sup>
	Refractory	Combination of partial/generalised	400 mg/day 24 weeks N = 83	Specifically looks at patients with intellectual disabilities. LTG vs GBP (3600 mg/day)	Crawford, 2001 <sup>131</sup>
LEV			No studies		
OXC			No studies		
TGB	Refractory	Partial	60 mg/day 20 weeks N = 48	TGB vs LTG (400 mg/day)	Chmielewska, 2001 <sup>133</sup>
TPM			No studies		
VGB	Refractory	Partial	Dose NS 18 months N = 404	VGB vs GBP (dose NS) VGB vs LTG (dose NS)	Specchio, 1999 <sup>61</sup>
	Refractory	Partial	1000–4000 mg/day 24 weeks N = 102	VGB vs GBP (180–3600 mg/day)	Lindberger, 2000 <sup>132</sup>

N, total number of randomised participants.  
<sup>a</sup> All were parallel, superiority trials.

newer AEDs. There were no data comparing LEV, OXC and TPM with other newer AEDs and data comparing GBP with LTG, GBP with VGB and LTG with TGB showed no consistent statistically significant differences in the proportion of seizure-free participants.

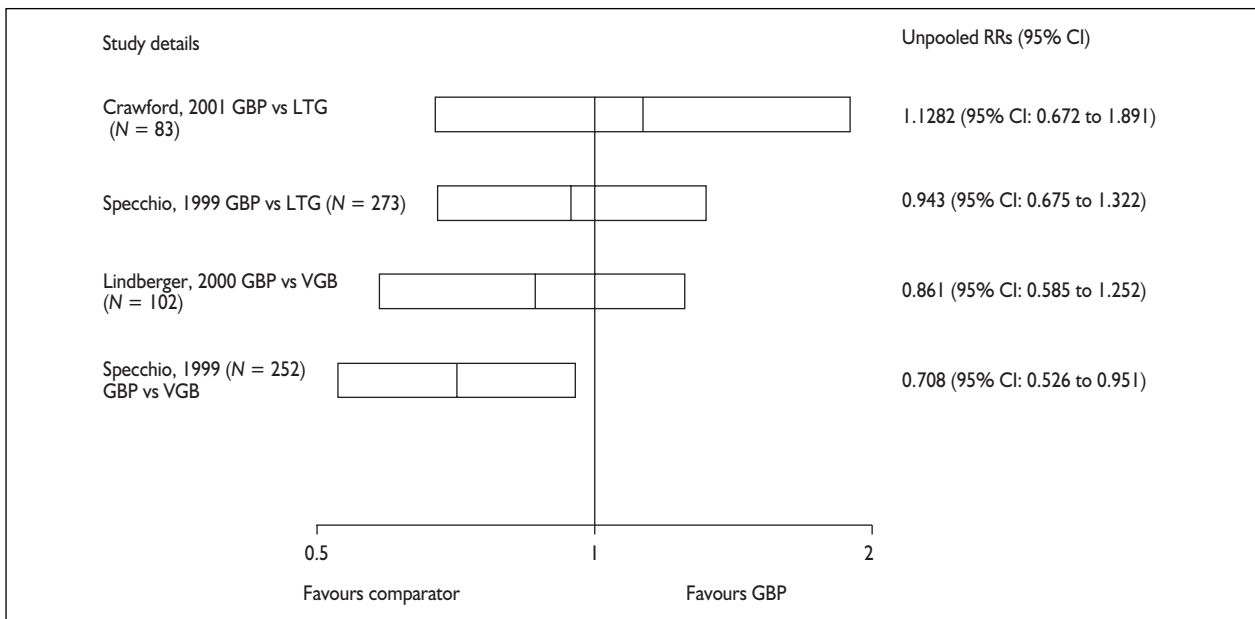
#### ii. 50% reduction in seizure frequency

All four of the studies of newer drugs versus newer drugs (adjunctive therapy) reported the proportion of participants who experienced at least a 50%

decrease in seizure frequency. A summary of the main characteristics of these studies is presented in *Table 52*.

No studies compared LEV, OXC or TPM with other newer drugs in terms of the proportion of responders.

Three parallel superiority trials examined the use of GBP.<sup>61,131,132</sup> The main characteristics of these studies and their limitations have been



**FIGURE 28** Proportion of 50% responders (unpooled RRs, 95% CIs) for adjunctive studies of GBP vs other newer AEDs (ITT data)

**TABLE 53** Proportion of 50% responders (pooled RR, 95% CI) for adjunctive trials of GBP vs VGB (ITT data)

Characteristics	Studies	Pooled RR (95% CI) (fixed effects)
N = 102	Lindberger, 2000 <sup>132</sup>	0.861 (95% CI: 0.585 to 1.252)
N = 282	Specchio, 1999 <sup>61</sup>	0.708 (95% CI: 0.526 to 0.951)
<b>Refractory, partial, GBP vs VGB</b>	<b>Pooled (n = 2)</b>	<b>0.755 (95% CI: 0.598 to 0.954)</b> <b>Heterogeneity: Q = 0.642 (df = 1), p = 0.423</b>

discussed with regard to the number of seizure-free participants.

Owing to the presence of clinical (different participants, drug doses and follow-up periods) and statistical (*Q*-statistic) heterogeneity, the pooling of data was limited. *Figure 28* shows the unpooled RRs.

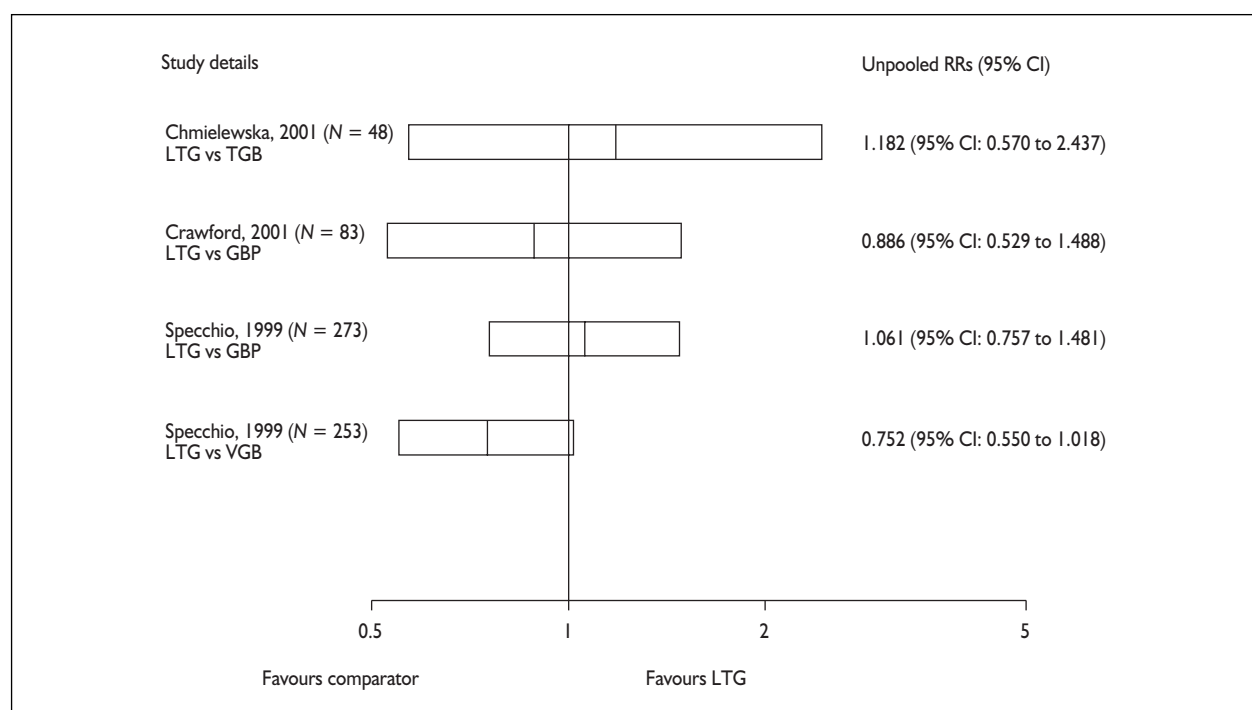
One of the studies comparing GBP with LTG favoured GBP<sup>131</sup> and the other study favoured LTG.<sup>61</sup> However, both differences were not statistically significant. Both of the studies comparing GBP with VGB<sup>61,132</sup> favoured VGB, but only one of the differences was statistically significant.<sup>61</sup> Data from these two studies were pooled (see *Table 53*). The pooled RR (fixed-effects model) also showed a statistically significant difference in favour of VGB in comparison with GBP.

Three parallel superiority trials compared adjunctive LTG with other newer AEDs.<sup>61,131,133</sup> The main characteristics of these trials and their limitations have already been discussed with regard

to the proportion of seizure-free participants. In view of clinical and statistical (*Q*-statistic) heterogeneity between the studies, data were not pooled. The unpooled RRs are shown in *Figure 29*.

The study comparing LTG with TGB showed a difference in favour of LTG, but this was not statistically significant.<sup>133</sup> One of the two studies comparing LTG with GBP favoured GBP<sup>131</sup> and the other favoured LTG,<sup>61</sup> but neither of these differences was statistically significant. The study comparing LTG with VGB showed a difference in favour of VGB, but was not statistically significant.<sup>61</sup>

Overall, there was limited evidence on which to base an assessment of newer AEDs versus other newer AEDs. There were no data comparing LEV, OXC and TPM with other newer AEDs and data comparing GBP with LTG, and LTG with TGB showed no consistent statistically significant differences in the proportion of seizure-free participants. However, a statistically significant difference in favour of VGB was found in trials comparing GBP with VGB.



**FIGURE 29** Proportion of 50% responders (unpooled RRs, 95% CIs) for adjunctive trials of LTG vs other newer AEDs (ITT data)

**TABLE 54** Total number of studies assessing QoL outcomes (adjunctive therapy, newer vs newer drugs)

Drug	Total no. of studies assessing QoL outcomes			Study details
	Crossover	Parallel	All studies	
GBP	0	2	2	Crawford, 2001; <sup>131</sup> Lindberger, 2000 <sup>132</sup>
LTG	0	2	2	Crawford, 2001; <sup>131</sup> Chmielewska, 2001 <sup>133</sup>
LEV				No studies
OXC				No studies
TGB	0	1	1	Chmielewska, 2001 <sup>133</sup>
TPM				No studies
VGB	0	1	1	Lindberger, 2000 <sup>132</sup>

**b. Time to first seizure**

None of the four studies of newer drugs versus newer drugs (adjunctive therapy) reported the time to first seizure.

**c. Time to withdrawal/exit**

None of the four studies of newer drugs versus newer drugs (adjunctive therapy) reported the time to exit/withdrawal.

**d. Quality of life**

Three of the four studies of newer drugs versus newer drugs (adjunctive therapy) reported QoL outcomes (see Table 54).

No studies reporting QoL outcomes compared LEV, OXC or TPM with other newer AEDs for adjunctive therapy. Two studies used GBP, one comparing GBP with LTG<sup>131</sup> and the other comparing GBP, VGB and LTG.<sup>132</sup> One study compared LTG with TGB<sup>133</sup>. All of the studies were parallel superiority trials. Two studies included patients with refractory partial seizures<sup>132,133</sup> and one refractory patients with either partial or generalised seizures. The studies recruited between 48 and 109 participants (mean = 86) and followed treatment for between 20 and 24 weeks.

**TABLE 55** Types of QoL assessments used (adjunctive therapy, newer vs newer drugs)

QoL measure	No. of studies using QoL measure							Total
	GBP	LTG	LEV	OXC	TGB	TPM	VGB	
Key Carer-rated Visual Analogue Scales	1	1	0	0	0	0	0	2
Crichton Royal Behavioural Rating Scale	1	1	0	0	0	0	0	2
Whelan and Speake Rating Scale	1	1	0	0	0	0	0	2
Subjective global evaluations (physician/investigator)	1	1	0	0	0	0	0	2
QOLIE-89	1	0	0	0	0	0	1	2
Subjective global evaluation (patient)	0	1	0	0	1	0	0	2
<b>Total no. of different measures used</b>	5	5	0	0	1	0	1	–

**TABLE 56** Summary of overall findings of QoL assessments (adjunctive therapy, newer vs newer drugs)

Drug	Summary of findings of QoL assessments
GBP	One study in patients with learning disability found statistically significant differences in favour of GBP over LTG. <sup>131</sup> The applicability of this finding to the general population of patients with epilepsy is unclear. One other study comparing GBP with VGB found no statistically significant differences between the two drugs. <sup>132</sup> There was very little consistent evidence of statistically significant differences between LTG and other newer drugs
LTG	One study, which included people with learning disabilities, found statistically significant differences in favour of GBP over LTG. <sup>131</sup> The applicability of this finding to the general population of patients with epilepsy is unclear. The other studies found no statistically significant differences between LTG and GBP and between LTG and TPM. There was very little consistent evidence of statistically significant differences between LTG and other newer drugs
TGB	One trial reported no statistically significant differences between TGB and LTG. <sup>133</sup> There was very little evidence on which to base an assessment of the effectiveness of adjunctive therapy with TGB compared with other newer drugs
VGB	One trial reported no statistically significant differences between VGB and GBP. <sup>132</sup> There was very little evidence on which to base an assessment of the effectiveness of adjunctive therapy with VGB compared with other newer drugs

Various measures were used to assess QoL (see Table 55). In total six different types of QoL measures were used; GBP (five measures), LTG (five measures), TGB (one measure) and VGB (one measure). Within trials of the same AED measures were only used in one trial.

Details of the individual study data are reported in Appendix 23 and details of individual QoL measures in Appendix 4. Table 56 summarises the overall findings of the QoL assessments.

Overall, the trials were of poor quality. Two studies recruited far fewer participants than suggested by *a priori* sample size calculations,<sup>131,132</sup> and one study was discontinued prematurely owing to poor recruitment.<sup>132</sup> Two studies were open-label,<sup>131,133</sup> and two studies used doses of newer drugs that

exceeded recommendations.<sup>131,132</sup> One trial only recruited patients with learning disabilities and so its findings may have limited applicability to the general population of patients with epilepsy.<sup>131</sup> This study reported significant differences in communication, cooperation and restlessness in favour of GBP compared with LTG. None of the other studies reported significant differences in cognitive function between the other AEDs.

There was no strong evidence of any consistent significant differences between LTG, GBP, TGB or VGB.

#### e. Cognitive function

None of the four studies of newer drugs versus newer drugs (adjunctive therapy) reported cognitive function outcomes.



### Summary statement for adjunctive newer versus newer AEDs

There is no evidence on which to base an assessment of the clinical effectiveness of adjunctive LEV, OXC or TPM versus other newer drugs. In addition, there are no data for any of the newer drugs regarding time to event outcomes (time to exit/withdrawal and time to first seizure) or cognitive outcomes. Evidence from comparisons of the other newer drugs with each other (GBP, LTG, TGB and VGB) is limited to single studies, with the exception of two studies that compared GBP with VGB and two studies that compared GBP with LTG. In general, the studies only examined refractory patients with partial seizures and only followed patients for a limited period (20–24 weeks). None of the studies showed a statistically significant difference between the newer drugs, with the exception of the comparisons of VGB with GBP, where one study showed a significant difference in the proportion of 50% responders in favour of VGB. One study of patients with intellectual disabilities found statistically significant differences in QoL in favour of GBP over LTG. These findings should be treated with caution in view of problems with the quality of the studies.

#### 4. The use of adjunctive therapy in special populations (elderly, intellectually disabled people and pregnant women)

There were no studies of adjunctive therapy that examined effectiveness in elderly participants. Similarly, there were no studies that included pregnant women; in fact, women of childbearing age were required to use adequate methods of contraception in order to be allowed to enter trials. However, a number of studies ( $n = 8$ ) examined the effectiveness of adjunctive therapy in participants with intellectual disabilities. Brief details of these trials are presented in *Table 57*.

Five studies compared a new AED with placebo; two studies compared new with old drugs; one study compared two new drugs.

Among the placebo-controlled trials, one study tested LTG in patients who all had an intellectual disability.<sup>137</sup> No details were reported about the randomisation process or sample size determination. No significant difference was shown in the proportion of responders or seizure free patients at 22 weeks or in a physician/patient global evaluation of improvement/efficacy/tolerability.

The difference in QoL measures was significant for physical adverse event scores but not significant for all other measures.

The placebo-controlled study of TGB included some patients described as mentally retarded but did not provide separate data for that subgroup.<sup>140</sup> A sample size calculation was reported and allocation was adequately concealed. Overall, a significant difference was shown in favour of TGB in the proportion of responders with complex partial seizures (TGB twice daily  $n = 106$ ,  $p < 0.001$  versus placebo; TGB four times daily  $n = 103$ ,  $p < 0.002$  versus placebo). The authors reported that tolerability was satisfactory for more than 80% of patients treated with TGB, but patients with intellectual disabilities were not mentioned specifically.

In three placebo-controlled studies of VGB, patients with mental disabilities comprised about one-third of the included patients, but none of the studies provided separate data for these patients. Selection of participants in one trial was based on a 50% reduction in seizure frequency in response to treatment in an earlier phase.<sup>141</sup> Change in seizure frequency (total seizures) from baseline among responders ( $n = 9$ ) was significantly in favour of VGB at 8 weeks ( $p = 0.002$ ). There was no mention of a power calculation and no details were reported about the randomisation process. The other two VGB studies were crossover trials. One reported results for two subgroups of patients; among patients with complex partial seizures only ( $n = 15$ ), the proportion of responders was significantly greater with VGB ( $p < 0.02$ ).<sup>85</sup> The other crossover study reported a significant reduction in the mean weekly complex partial seizure frequency with VGB, from baseline to 18 weeks follow-up ( $p < 0.001$ ), and to a lesser extent for tonic-clonic seizures ( $n = 11$ ,  $p < 0.05$ ).<sup>49</sup> Neither of the crossover studies reported allocation concealment or an adequate washout period; only the participants were blinded and only one trial appeared to have conducted an appropriate paired analysis.<sup>85</sup> All of the VGB studies used doses of 2–3 g/day for between 8 and 12 weeks.

In comparisons of new versus older drugs, a crossover study of OXC versus CBZ showed similar seizure frequencies with both drugs.<sup>84</sup> Different reports of this study were inconsistent in the assertion that all the patients had mental disabilities and the dose of OXC exceeded the recommended level. Although the administrators of treatment and the patients were blinded, other quality parameters were not well met. Randomisation was not clearly

**TABLE 57** Details of adjunctive studies examining effectiveness in individuals with intellectual disabilities

Drug	Study details	Study details
GBP	Parallel superiority trial of adjunctive GBP vs LTG in patients with refractory partial and/or generalised seizures. All participants ( $n = 109$ ) were reported as having intellectual disabilities as defined by DSM IV criteria	Crawford, 2001 <sup>131</sup>
LTG	Parallel superiority trial of adjunctive LTG vs placebo in patients with refractory partial and/or generalised seizures. All participants ( $n = 68$ ) had intellectual disability (DSM IV criteria) rated mild to profound	Veendrick-Meekes, 2000 <sup>137</sup>
LEV	No studies	
OXC	Crossover superiority trial of adjunctive OXC vs CBZ in patients with refractory partial and/or generalised seizures. All participants ( $n = 48$ ) had mental disabilities	Houtkooper, 1987 <sup>84</sup>
TGB	Parallel superiority trial of adjunctive TGB vs placebo in patients with refractory partial seizures. Approximately 80% of patients ( $n = 318$ ) had abnormal neurological histories. The most common reported conditions were chronic headaches, mental retardation, memory impairment and dizziness. No further information about the exact number of participants involved	Sachdeo, 1997 <sup>140</sup>
TPM	No studies	
VGB	Parallel superiority trial of adjunctive VGB vs placebo in patients with refractory partial seizures. 10/33 participants had neurological mental handicap, but results were not presented separately for this population Crossover superiority trial of adjunctive VGB vs placebo in patients with refractory partial and/or generalised seizures. 10/31 participants had mental disability, but results were not presented separately for this population Parallel superiority trial of adjunctive VGB vs VPA in patients with refractory partial seizures. Reported participants with mental disabilities were included but did not state how many. To enter the double-blind phase of the trial participants had to achieve at least a 50% decrease in seizure frequency without adverse events during the pretrial period Crossover superiority trial of adjunctive VGB vs placebo in patients with refractory partial seizures. 8/24 had mental disability	Reynolds, 1991 <sup>141</sup> Tassinari, 1987 <sup>85</sup> Brodie, 1999 <sup>66</sup> Rimmer, 1984 <sup>49</sup>

described, and neither a power calculation nor a washout period was reported. The results were not presented or analysed as matched paired data, and potential treatment or period effects and treatment–period interaction were not considered.

The other study compared VGB with VPA and CBZ.<sup>66</sup> An adequate sample size calculation was reported; however, it was not clear whether the 215 patients analysed as ITT were in fact the number randomised. The number of patients included who had mental disabilities was not explicitly stated and no separate analyses were conducted for that subgroup. Allocation concealment was not reported and only participants were blinded. Overall, the study showed no statistically significant differences in seizure reduction (change in seizure frequency, proportion of responders, proportion of seizure-free patients).

One study compared two new drugs, GBP with LTG, in 109 patients with intellectual disabilities

and partial or generalised seizures.<sup>131</sup> The authors' initial power calculation had to be adjusted owing to the lower numbers actually recruited. The proportion of seizure-free patients was 3/39 (7.7%) with GBP and 5/44 (11.4%) with LTG. No difference was shown in the proportion of responders or in the mean response ratio in the proportion of seizure-free participants. In an analysis of change in functional capacity, some parameters measured on one scale showed a statistically significant difference in favour of GBP (cooperation, communication and restlessness,  $p < 0.05$ ); three other scales showed no difference between the drugs. Within-group analysis of changes from baseline with GBP showed a significant improvement in several parameters measured on four scales, including seizure severity, sleeping pattern, attention, general health, cooperation, restlessness and level of challenging behaviour. Within-group analysis of changes from baseline with LTG showed a significant improvement in several parameters measured on

three out of four scales, seizure severity, level of challenging behaviour and general health; the Crichton Royal Behavioural Rating Scale showed no significant improvement. The authors concluded that both drugs provided effective treatment with positive benefits on behaviour in learning disabled patients. Potential quality flaws in the study include no description of allocation concealment, no blinding and no mention of ITT analysis. The maximum dose of gabapentin used exceeded the recommended limit.

#### Summary statement for adjunctive studies

The most commonly reported outcome measure was proportion of 50% responders, with a large number of studies also reporting the proportion of seizure-free patients and QoL outcomes. No studies reported time to event data (time to exit/withdrawal and time to first seizure). In general, trials only considered the short-term effects of therapy in patients with refractory partial seizures. There were very few data regarding the treatment of refractory generalised seizures.

Overall, there was very little good-quality evidence from trials of adjunctive AEDs on which to base an assessment of newer drugs versus older drugs and newer drugs versus other newer drugs. However, newer AEDs were significantly more effective than placebo with regard to the proportion of 50% responders.

No studies assessed the effectiveness of adjunctive AEDs in the elderly or pregnant women. A number of studies included people with intellectual disabilities, but only three provided data exclusively from this population. There was some evidence from one study (GBP versus LTG) that both drugs have some beneficial effect on behaviour in people with learning disabilities.

*Assessment of adverse events and tolerability from RCTs*  
Eighty-one RCTs recorded the incidence of AEs: 17 monotherapy studies and 64 adjunctive therapy studies. Sixteen monotherapy studies and 42 adjunctive therapy studies reported withdrawals due to limiting AEs. The extent and quality of AE data was variable and, in the majority of studies, secondary to the main aim of the study (which was to assess the clinical efficacy of the drug). Even where authors stated that the assessment of safety was a main aim of the study, this was often not reflected in the reporting of outcome data.

AE data were reported in various ways. Definitions and descriptions of AE differed, which made it difficult to assess the seriousness of an event, as they were rarely graded in any way. In a minority of studies the number of events rather than the number of participants who experienced each event was reported. In some instances it was unclear whether the events recorded were classified as drug related or whether all events were reported. Similarly, in many instances only events recorded in 5 or 10% of participants were reported. In some cases it was unclear whether predetermined thresholds were used.

Only LTG, OXC and TPM are licensed for use and considered in the assessment of monotherapy AEDs. *Table 58* shows the number of RCTs for each drug that reported data on the incidence of AEs (17 studies) and the number of withdrawals due to adverse events (16 studies).

*Table 59* shows the number of adjunctive therapy RCTs for each drug that reported data on the incidence of AEs (63 studies) and the number of withdrawals due to AEs (41 studies).

*Table 60* shows the number of trials of each drug that reported any withdrawals due to AEs, serious AEs and the five most common specific AEs reported for each drug.

**TABLE 58** Number of RCTs of monotherapy that reported the incidence of AEs and withdrawals

Drug	No. of studies reporting AEs	No. of studies reporting withdrawals due to AEs
GBP	0	0
LTG	12	12
LEV	0	0
OXC	5	4
TGB	0	0
TPM	0	0
VGB	0	0
Total	17	16

**TABLE 59** Number of RCTs of adjunctive therapy that reported the incidence of AEs and withdrawals due to AEs

Drug	No. of studies reporting AEs	No. of studies reporting withdrawals due to AEs
GBP	9	3
LTG	18	13
LEV	4	4
OXC	1	1
TGB	7	6
TPM	11	11
VGB	14	4
Total	64	42

**TABLE 60** Number of trials found for selected AEs and withdrawals

	GBP (n = 10)	LTG (n = 34)	LEV (n = 4)	OXC (n = 10)	TGB (n = 7)	TPM (n = 13)	VGB (n = 16)
Any AE (total)	7	14	4	5	7	3	6
Serious AEs	2	16	4	1	6	3	4
<b>Specific events</b>							
Asthenia	0	15	4	1	5	1	0
Ataxia	3	12	0	1	2	3	1
Dizziness	3	22	2	6	5	8	7
Drowsiness	1	3	0	1	0	0	10
Fatigue	3	3	0	3	1	8	7
Headache	2	23	3	5	6	10	8
Nausea	0	16	1	5	4	3	1
Nausea and/or vomiting	1	0	0	0	0	2	0
Vomiting	0	6	0	3	2	0	0
Paresthesia	0	1	0	1	1	4	0
Rash	0	11	0	1	0	1	0
Somnolence	4	21	4	5	5	10	0
Tremor (slight)	2	7	0	2	2	0	3
Weight decrease	0	1	0	0	0	5	0
Weight increase	0	3	0	0	0	0	5
<b>Withdrawals</b>							
Limiting AEs	3	25	3	5	6	11	4

Appendix 24 shows tables of unpooled RRs with 95% CIs derived from the number of comparisons for each drug within the included studies (some studies included more than one comparison). These are restricted to the five most common events reported for each drug, and also for withdrawals due to limiting AEs. The results presented are based on data reported in the trials, which in all cases except one<sup>87</sup> were based on ITT populations.

Considering any AE, five out of 12 comparisons showed a statistically significant lower incidence with placebo versus GBP. The remaining comparisons were not statistically significant. Two out of seven comparisons were significantly in favour of placebo over OXC. One of three comparisons was significantly in favour of placebo compared with TPM. Two of six comparisons were significantly in favour of placebo over VGB. In comparisons of LTG versus VPA, PHT or

conventional therapy four out of six showed a statistically significant result in favour of LTG. Results were inconsistent in comparisons between LTG and other newer AEDs (GBP, VGB); some trials favoured LTG whereas others favoured the comparator.

For serious AEs, as defined in the studies, one of seven comparisons was significantly in favour of LEV compared with placebo and the others showed no difference. One of six comparisons showed a significantly lower incidence of serious AEs with placebo than with VGB (6 g/day). Other comparisons showed no statistically significant differences.

In terms of the specific AEs listed in *Table 60*, two out of 17 comparisons showed a significantly lower incidence of asthenia (weakness) with LTG than VPA and PHT (one comparison each). All other comparisons showed no statistically significant

differences. For ataxia, between half and two-thirds of comparisons of GBP, LTG, OXC or TPM with placebo statistically showed significantly more events with the AED. One comparison showed significantly more events with GBP than with LTG. The remaining comparisons were not statistically significant. For dizziness, statistically significant differences in favour of placebo were shown in 50% or less of comparisons with GBP, LEV or OXC, in 30% or less of comparisons with TGB or TPM and in less than 20% of comparisons with LTG. No VGB comparisons showed a statistically significant difference. For slight tremor, two of three comparisons with VPA significantly favoured LTG, and the only comparison of LTG versus CBZ favoured CBZ. Between 20 and 40% of comparisons showed significantly more events with OXC, TGB or VGB than placebo.

For somnolence,  $\leq 50\%$  of comparisons between GBP, OXC or TPM and placebo showed a statistically significant difference, each in favour of placebo. Less than 50% of comparisons between LTG and placebo were significant, in favour of placebo. However, half of the 24 comparisons of LTG versus conventional treatment including CBZ, VPA and PHT showed a significant difference in favour of LTG. Few comparisons showed statistically significant differences in drowsiness between AEDs and placebo. One of two GBP comparisons significantly favoured placebo, as did three of 13 VGB comparisons. Analysis of fatigue showed one of six GBP comparisons and two out of 10 VGB comparisons to favour placebo significantly. In addition, two of five OXC comparisons and four of 12 TPM comparisons were also significantly in favour of placebo.

Among reports of nausea as an event in itself, among 18 comparisons of LTG three showed a significant difference in favour of placebo. One comparison significantly favoured LTG over VPA. Where the event reported was vomiting, two of seven LTG comparisons significantly favoured placebo, as did three of five OXC comparisons. One comparison was statistically significant in favour of TGB over CBZ. Where the event was reported as nausea and/or vomiting, the data showed no statistically significant differences for any of the newer AEDs.

Few studies reported change in weight. One of five comparisons of TPM versus placebo reported a decrease in weight in significantly more TPM patients. Two of six comparisons of VGB versus placebo reported increase in weight in significantly more VGB patients. Other findings for weight

increase include two of three comparisons that showed a statistically significant result in favour of LTG over VPA or GBP.

Headache was significantly more common with LTG in only three of 26 comparisons.

For paresthesia, half of the comparisons of TPM with placebo significantly favoured placebo. For rash, the findings from 12 comparisons involving LTG were inconsistent, some in favour of LTG and others favouring the comparator.

Withdrawals due to limiting AEs were not reported in most of the clinical effectiveness studies. GBP provided the highest number of comparisons (3/5), showing a significant difference in favour of placebo, followed by TPM (5/15). Less than 30% of comparisons of LTG, LEV, OXC and TGB showed significant differences, in each case in favour of placebo. Where different AEDs were compared, two of 28 LTG comparisons were statistically significant and favoured LTG over CBZ or VPA. One comparison significantly favoured VPA over LTG. One comparison significantly favoured OXC over PHT.

#### Summary of assessment of adverse events and tolerability from RCTs

There appears to be no consistent or convincing evidence from these RCTs to draw any clear conclusions concerning the relative safety and tolerability of newer AEDs compared with each other or with older AEDs, or even placebo. It was inappropriate to pool these data because retrieval of all relevant data was hampered by the quality of reporting.

#### Assessment of serious, rare and long-term adverse events

##### **Serious, rare and long-term adverse events**

The included studies are summarised in Appendix 25 (*Tables 99–109*). No studies of LEV met the inclusion criteria.

The data presented purposely focus on AEs that could be regarded as serious, rare or long-term. Where the investigators commented on the relationship between an AE and a specific AED, this has been noted. Otherwise, all events reported here must be interpreted as observations rather than evidence of a causal association with a particular drug or combination of drugs. It should also be noted that since these data were not derived from direct comparisons, they cannot be used to compare directly one drug with another.

Owing to time constraints, the search for studies did not include all relevant databases and inclusion was restricted to the English language. Consequently, it is unlikely that all relevant studies have been included. Covert duplicate publication and publication of cumulative data without reference to previous analyses were encountered. Obvious duplicate data were considered as one study. Where overlap was suspected, this has been noted in the tables and text.

None of the included studies were conducted exclusively in elderly populations, but the age range in the majority of studies did extend to patients in their 70s. Six primary studies (one LTG, one TPM, three VGB, one various AEDs) included patients with some description of mental disability. The only data explicitly concerning pregnant women comes from one PEM and one PMS study. Only seven of the included primary research studies listed pregnancy or the risk of pregnancy as exclusion criteria; the others did not mention this population at all.

#### **Quality of the included studies**

When the question of interest concerns AEs rather than efficacy, the conventional hierarchy of evidence is not necessarily the best guide. The strongest evidence cannot automatically be assumed to come from RCTs. Other study designs may be more appropriate to the question although they are open to various sources of bias. Threats to internal validity must be minimised in the design and conduct of a study to ensure that the findings are reliable. Quality assessment of the additional primary studies reviewed for serious, rare and long-term AEs is summarised in Appendix 20. The quality assessment tools are given in Appendix 10.

Although formal critical appraisal tools were used where possible, the poor description of study design in many reports made assessment of internal validity problematic. This was particularly true of cohort-type studies, most of which were basically observations on groups of patients rather than studies based on a sound design.

The tables of included studies provide comments on the exclusion criteria where these were reported; exclusion criteria were not mentioned at all in 40% of the reports. A comment is also given on how and when AEs were recorded in each study; only half the studies provided this information, an additional 37% reported when or how and 13% gave no information. Even studies that claimed safety, tolerance or toxicity as their

primary objective failed to report either exclusion criteria or how and when the outcomes were measured.

#### **Gabapentin**

Two reports of PEM in the UK were identified<sup>170,171</sup> (Appendix 25, *Tables 99 and 108*). These studies were conducted by the Drug Safety Research Unit, whose methods are reported elsewhere.<sup>172</sup> PEM of 3100 patients (85.4% with epilepsy) found no previously unrecognised AEs. Two cases of hyponatraemia were possibly related to GBP, 17 patients took overdoses and three cases of hair loss were reported after  $\geq 6$  months of treatment. Mortality was comparable to that in published studies of severe epilepsy.<sup>170</sup> The focus of the other PEM study was congenital abnormality. No congenital anomalies were observed among 11 births exposed to GBP in the first trimester.<sup>171</sup>

One RCT of rapid versus slow initiation,<sup>173</sup> eight uncontrolled trials (four in epilepsy ( $n = 2986$ )<sup>174-177</sup> and four in bipolar disorder (BPD) ( $n = 60$ ),<sup>178,181,451</sup> four open-label extension studies in epilepsy<sup>182-185</sup> and one uncontrolled cohort study of patients with spinal cord injury<sup>186</sup> were identified. These studies are summarised in Appendix 25, *Table 100*. Another uncontrolled cohort study of several AEDs included some patients on GBP and is summarised in Appendix 25, *Table 109*.<sup>187</sup>

In the RCT, reporting of serious AEs and withdrawals lacked clarity; the randomisation method was unclear and blinding of outcome assessment was not stated. Two patients out of 781 were hospitalised. One was a 13-year-old girl randomised to rapid initiation (900 mg/day from day one) who developed generalised oedema on day six. The other was an 85-year-old man; the nature and timing of the serious AE that he experienced are not clear.<sup>173</sup>

The largest of the uncontrolled trials in epilepsy reported that convulsion was the most common serious AE (20/2216).<sup>174</sup> In an assessment of tolerability, in which patients served as their own control, serious AEs were reported by 2/278 patients on  $<1800$  mg/day and by 4/278 patients on  $>1800$  mg/day. The maximum dose used exceeded 2400 mg/day. The AEs included infection, overdose, sudden death, grand mal convulsion and hostility, but details of which patients experienced these events and when were lacking. A study in which the maximum reported dose was 2400 mg/day reported serious AEs in

eight out of 110 patients, possibly related to GBP in two patients who experienced headache and accommodation difficulty. One patient was withdrawn owing to an overdose.<sup>175</sup> New-onset myoclonic jerking (2/50) was reported at doses >3600 mg/day in one study.<sup>176</sup> In the fourth uncontrolled trial in epilepsy ( $n = 610$ ), the dose of GBP was within the recommended range and the nature of AEs was similar to those reported in RCTs.<sup>177</sup> The uncontrolled trials in patients with BPD did report the time at which AE-related withdrawals occurred, although the nature of the events was similar to those commonly reported in controlled trials. Reasons for discontinuation after longer periods of treatment included exacerbation of migraine at 10 months and excessive activation or sedation at up to 11 months.

The four open-label extension studies followed patients who had achieved a successful response to GBP adjunctive or monotherapy in previous studies of 2–3 months' duration. In the monotherapy study 23 patients were followed for up to 106 weeks. Myoclonic jerks was reported as a rare adverse event (1/23) in this study in which the mean maximum dose was 3900 mg/day.<sup>182</sup> The largest of the adjunctive studies ( $n = 240$ ) followed up patients, originally treated in an RCT, for up to 784 days.<sup>185</sup> The dose of GBP exceeded the recommended maximum. Of 10 withdrawals due to adverse events three were occurrences of brain tumours, two of which were recurrences. The next largest study ( $n = 203$ ) used recommended doses and followed patients for a mean of 385 days. It reported one case of non-Hodgkin's lymphoma and a case of pneumonia and increased platelets in a patient with pleural disorder.<sup>183</sup> The dose used in the smallest study ( $n = 25$ ) was unclear, patients were followed for a median of 54 months and AEs were similar to those commonly reported.<sup>184</sup>

The uncontrolled cohort study in patients with spinal cord injury ( $n = 27$ ) reported that six patients discontinued owing to AEs including muscle twitching and oedema. Ten patients who were evaluable continued to gain analgesic benefit from GBP throughout the 3-year study period on doses ranging from 500 to 3600 mg/day.<sup>186</sup> The uncontrolled cohort study that included epilepsy patients treated with GBP ( $n = 158$ ), and also patients treated with other AEDs, reported that 10% continued to take GBP for 3 years. Unspecified AEs led to withdrawal of 37%.<sup>187</sup> Neither report stated how exposure was ascertained or determined whether AEs were dose related.

### Lamotrigine

Two reports of PEM conducted by the Drug Safety Research Unit in the UK were identified.<sup>171,188</sup> These reports are summarised in Appendix 25, Tables 101 and 108. PEM of 11,316 epilepsy patients identified seven cases of Stevens–Johnson syndrome (SJS) in adults, four on concomitant VPA.<sup>188</sup> Other rare serious events possibly associated with LTG are summarised in Table 101. The focus of the other PEM study was congenital abnormality. Among 39 births exposed to LTG in the first trimester, four babies had a congenital anomaly; concomitant drug exposure is summarised in Table 108.<sup>171</sup>

Three reports of PMS data were identified, two from the UK<sup>189,190</sup> and one from the USA.<sup>191</sup> These reports are summarised in Appendix 25, Table 101. A UK study of 1050 epilepsy patients showed that LTG was strongly associated with rash compared with GBP or VGB ( $p < 0.001$ ). The LTG dose ranged from 12.5 to 900 mg/day. Four patients experienced serious and unexpected adverse reactions to LTG between 7 days and 1 month of treatment. The events were life-threatening hepatic failure, renal failure, disseminated intravascular coagulation and acute exacerbation of ulcerative colitis. Other AEs associated with LTG ( $p < 0.05$ ) that were not already recognised or listed on the manufacturers' data sheets included pruritus, nightmares and hallucinations. The incidence of hospitalisation due to adverse drug reactions was significantly higher in the first 4 months of treatment than in the following 4 months. The study was funded by GlaxoSmithKline.<sup>189</sup> The USA study determined the rate of rash among patients treated with LTG adjunctive to VPA as 13% (14/108). Half of the patients who discontinued treatment because of AEs did so as a result of rash. Rash appeared between 1 day and 10 weeks of treatment. Other serious AEs reported were hallucinations (two patients), hepatic enzyme elevation and low white cell count (one patient each).<sup>191</sup> The second UK study focused on the risk of birth defects in pregnancies exposed to LTG in the first trimester. Using data from a prospective registry maintained by GlaxoSmithKline, no birth defect was found in association with monotherapy (0/40). The risk of birth defect with polytherapy was reported as 6.5% (95% CI: 3 to 13), but the denominator used was the number of first trimester exposures to either polytherapy or monotherapy.<sup>190</sup> Using only the polytherapy-exposed denominator gives a risk of 9.6% (8/83).

One multicentre case–control study,<sup>192</sup> five uncontrolled trials<sup>193–197</sup> and four uncontrolled

cohort studies<sup>198–201</sup> met the inclusion criteria. These studies are summarised in Appendix 25, *Table 102*. Two other uncontrolled cohort studies that included some patients treated with LTG are summarised in *Table 109*.<sup>187,202</sup>

The case–control study was of good quality considering its design; only the selection of controls was unclear. The study examined 136 cases of SJS, 216 cases of toxic epidermal necrosis (TEN) and 1579 controls. The majority were adults. Dissimilarities in age and gender proportion were evident between cases and controls overall. Of 73 cases who reported use of AEDs, three reported intake of LTG (for  $\leq 8$  weeks) and comedication (CBZ, VPA). Confounding factors were considered to be present in one of the three cases. Univariate analysis identified short-term LTG as a risk factor for SJS/TEN, RR 25 (95% CI: 5.6 to infinity). The small numbers precluded further analysis.<sup>192</sup>

Overall, the uncontrolled trials included 200 patients with epilepsy and 75 with bipolar disorder (BPD), and the majority were adults. One trial with 10 epilepsy patients reported one withdrawal due to SJS after 2 weeks of treatment and one additional withdrawal due to macrocytic anaemia after 23 months of treatment.<sup>195</sup> Another trial ( $n = 75$ ) reported a serious rash in two BPD patients and one patient on LTG monotherapy needed hospitalisation and steroid treatment.<sup>194</sup> Other hospitalisations ( $n = 8$ ) in the same study were due to mania-related AEs at 14–190 days on treatment. Other reasons for withdrawal from uncontrolled trials were similar to those commonly reported in RCTs (including rash, insomnia, headache, diplopia, nystagmus and behavioural disturbance).

One large ( $n = 4700$ ) uncontrolled cohort study examined the rate of SUDEP in a well-defined cohort of adults and children.<sup>199</sup> The estimated rate of SUDEP (definite, probable and possible) was 3.5/1000 patient-years of exposure to LTG. Two adult cases of possible SUDEP were not included in the rate calculation because LTG was discontinued before their deaths. The study reported that there is no conclusive evidence that LTG alters the risk of SUDEP in patients with epilepsy as the rate observed was comparable to the expected rate among young adults with severe epilepsy.

One of the other three uncontrolled cohort studies of LTG ( $n = 125$ ) was conducted in adults with intellectual and/or neurological deficits.<sup>198</sup> Five of

11 withdrawals were due to negative psychotropic effects and three to exanthema. Another study of adults and children ( $n = 200$ ) reported rash in six patients, profound agitation in one and LTG intoxication in 17. Which events contributed to the 13 withdrawals were unclear.<sup>200</sup> A smaller study ( $n = 17$ ) of adults reported five out of nine withdrawals due to rash.<sup>201</sup> One uncontrolled cohort study of mixed AEDs reported on 78 patients treated with LTG, although it was unclear if this was the number originally included in the study. Eight LTG patients changed treatment owing to AEs, although when the events occurred was not reported. Rash was the most common reason for withdrawal of LTG (3/8). The dose taken by patients who experienced intolerable AEs ranged from 150 to 375 mg/day.<sup>202</sup> The other study of mixed AEDs focused on retention rates; for LTG this was 29% of 424 patients at 3 years, but ascertainment of exposure to the drug was not described.<sup>187</sup> There may be an overlap of patients between the latter study and the PMS study by Wong and colleagues.<sup>189</sup>

### **Oxcarbazepine**

Of two open-label extension studies that met the inclusion criteria (Appendix 25, *Table 103*), one included epilepsy patients who had participated in a placebo-controlled RCT of monotherapy. Data were only available from a poster presentation.<sup>203</sup> The dose of OXC used in the extension phase was not stated, and the use of concomitant AEDs was at the discretion of the investigators. Fifty-six of the 97 patients remained on OXC throughout the 52-week extension phase; 12 withdrawals were due to AEs but their nature and timing were not stated. The other study followed patients from a previous RCT, although how many eligible patients chose to continue was not clear. Nine patients experienced severe AEs that were probably or definitely related to OXC. With monotherapy the events included diarrhoea, dizziness, nausea and rash. With polytherapy they were vomiting, abnormal dreams, flatulence, headache and insomnia. The dose range used reached 3000 mg/day.<sup>204</sup> Neither of these study reports gave a clear description of dose or duration of treatment for all participants, and only one gave an adequate description of who was included.

A controlled cohort study of the effects of various AEDs in pregnancy included three babies born to mothers exposed to OXC polytherapy in the first trimester (Appendix 25, *Table 109*). One baby (exposed to OXC 3000 mg/day, VPA 1800 mg/day, clobazam (CLB) 22 mg/day) was born with spina bifida cystica and clubfoot.<sup>205</sup>



**Tiagabine**

One RCT of different dosing schedules,<sup>206</sup> one uncontrolled trial,<sup>207</sup> one controlled cohort study<sup>208</sup> and one open-label extension study<sup>209</sup> met the inclusion criteria. These studies are summarised in Appendix 25, *Table 104*.

In the RCT ( $n = 347$ ), doses of TGB up to 70 mg/day were given to patients with partial epilepsy. Serious adverse events thought to be due to TGB led to withdrawal of the drug from seven patients. The events included one case of central nervous system (CNS) neoplasia. Two patients experienced abnormal vision after 12–24 weeks of treatment.<sup>206</sup> The trial was not blinded and the method of randomisation was not reported.

AEs reported in the uncontrolled trial ( $n = 23$ ) were similar to those commonly reported in RCTs.<sup>207</sup> The duration of treatment was reported to be at least 1 year.

The cohort study tested visual function in 15 adults with epilepsy who had achieved monotherapy with TGB (mean treatment duration 38 months).<sup>208</sup> None of the TGB patients showed loss of concentric visual field although 7/14 had colour vision defects compared with the healthy controls who had no visual abnormalities. Although the study methodology was flawed in several aspects, the small sample size in itself might not be representative of the larger TGB-exposed population of epilepsy patients.

The open-label extension study reported no signs of concentric VFDs among 34 patients who entered the open-label period on TGB monotherapy, but it is unclear when these tests were performed and on which patients. Eighteen patients completed 96 weeks of follow-up on monotherapy; it was not clear why the other 16 stopped treatment.<sup>209</sup>

**Topiramate**

One open-label extension of a double-blind placebo-controlled RCT<sup>210</sup> and six reports of uncontrolled trials<sup>211–216</sup> met the inclusion criteria. These studies are summarised in Appendix 25, *Table 105*. One uncontrolled cohort study that included some patients treated with TPM is summarised in Appendix 25, *Table 109*.<sup>187</sup>

The open-label extension study reported continuation of adjunctive TPM up to 2.5 years in 107 out of 131 adults and children with epilepsy. Although follow-up went as far as 909 days, the low end of the range was only 14 days, and the

only dose reported was that recorded at the last study visit. Commonly reported AEs were similar to those reported in RCTs.<sup>210,217</sup>

The majority of the 1217 patients included in the six uncontrolled trials were adults. One uncontrolled trial ( $n = 277$ ) reported two cases of SUDEP over a treatment period of up to 2.2 years and renal stones in two other patients.<sup>213</sup> The dose of TPM used went as high as 1600 mg/day. The other studies reported around 20% withdrawal due to AEs, the events being similar to those commonly reported. The smallest trial ( $n = 15$ ) reported withdrawal of one patient as a result of metabolic acidosis. The latter possibly overlaps with multicentre data reported in another study that reported metabolic acidosis (but not as a cause of withdrawal) in six of 67 patients.<sup>215</sup> The time at which withdrawals occurred as a result of AEs was reported in only one of the uncontrolled trials, this being between 1 and 8 months of adjunctive therapy at recommended doses.<sup>212</sup> One of the uncontrolled trials was conducted in patients with mental retardation; one of the 19 patients was withdrawn because of unsteadiness, disorientation and pneumonia.<sup>211</sup>

An uncontrolled cohort study of various AEDs focused on retention rates; for TPM this was 30% of 393 patients at 3 years, but ascertainment of exposure to the drug was not described. Unspecified adverse events led to withdrawal of TPM from 40% of patients.<sup>187</sup>

Some PMS data on adverse pregnancy outcomes, based upon the Johnson & Johnson Pharmaceutical Research and Development drug safety database, were reported in the Janssen–Cilag submission prepared for NICE.<sup>218</sup> Of 34 prospectively recorded pregnancies exposed to TPM that provided outcome information on live births, there were two definite and one possible congenital anomalies. In all three cases TPM had been used as adjunctive therapy. No congenital abnormalities were noted among 11 pregnancies exposed to monotherapy.

**Vigabatrin**

Two reports of PEM by the Drug Safety Research Unit in the UK were identified; one focused on the incidence of VFDs,<sup>219</sup> and the other on congenital abnormality.<sup>171</sup> These reports are summarised in Appendix 25, *Tables 106* and *108*, respectively. PEM of 10,178 patients detected four cases with objective evidence of bilateral persistent VFDs during the 6-month observation period (incidence 0.4/1000 patients). Long-term follow-up of patients

who continued VGB treatment beyond 6 months and who had been referred for eye tests or for whom changes in vision (including VFDs) had been reported identified 77 cases out of 4762 survivors who were being followed up by ophthalmologists. Interim data reported are 12 cases of VFD confirmed by formal perimetry tests, 10/12 probably or possibly related to VGB use (incidence 2.0/1000 patients). The study was not designed to determine the incidence of asymptomatic VFD.<sup>220</sup>

The other PEM study identified a congenital anomaly in two full-term babies out of 47 births exposed to VGB in the first trimester; concomitant drug exposure is summarised in *Table 108*.<sup>171</sup>

One non-randomised placebo-controlled study in which patients acted as their own control,<sup>221</sup> seven controlled cohort studies,<sup>222–228</sup> four uncontrolled cohort studies,<sup>229–232</sup> six uncontrolled trials,<sup>233–238</sup> five open-label extension studies<sup>239–243</sup> and six follow-up studies of patients who completed previous studies, one of which was an RCT,<sup>244–249</sup> met the inclusion criteria. These studies are summarised in Appendix 25, *Table 107*.

A small ( $n = 19$ ) study of patients treated with VGB for up to 15 months following placebo reported AEs similar to those commonly reported in RCTs.<sup>221</sup>

The duration of VGB treatment in the seven controlled cohort studies was as long as 11 years, although all but one study ( $n = 60$ ) included no more than 25 participants. All of these studies looked at effects of VGB on vision and all showed a much higher incidence of VFDs with VGB compared with controls. The effects were most often asymptomatic. Six of the studies gave an adequate description of how the VGB cohort was selected and used similar but VGB-unexposed epilepsy patients as controls.<sup>222,223,225–228</sup> One study failed to describe patient selection and used healthy volunteers as controls.<sup>224</sup> None of the studies gave a clear description of how exposure to VGB was ascertained in either the experimental or control groups.

The four uncontrolled cohort studies also all looked at effects of VGB on vision.<sup>229–232</sup> The duration of VGB treatment in these studies was as long as 12 years. All the studies found VFDs in 60% or more of the patients examined; one study assessed 155 patients and the other three studies less than 30 patients. Two studies demonstrated a dose–response relationship, but none of the studies gave a clear description of how exposure to

VGB was ascertained. Among both the controlled and uncontrolled cohort studies, correlation between visual defects and the duration or dose of VGB was inconsistent between studies. Other outcomes reported in these studies are summarised in Appendix 25, *Table 107*.

AEs commonly reported in the uncontrolled trials ( $n = 734$ ), including those associated with withdrawal of VGB, were similar to those commonly reported in RCTs. Where reported these tended to occur in the first few weeks or months of treatment. One withdrawal due to profound oedema was reported in one study but the time at which this occurred was not reported.<sup>236</sup> There is possibly overlap of patients between two of the reports.<sup>237,238</sup> A study conducted in a group of patients who had behavioural problems or mental retardation reported withdrawal of one patient after 9.5 months of treatment due to depression/aggression, one patient after 12 months due to irritability/aggression and one patient after 24 months due to irritability. All of these patients were in tertiary care.<sup>235</sup> Three of the six uncontrolled trials did not provide an adequate description of the eligibility criteria, none clearly stayed within the recommended dose of VGB or mentioned compliance and four failed to account for all participants.

The largest of the follow-up studies ( $n = 254$ ), and also the earliest published, reported that 10.5% of reports of AEs attributed to VGB were severe (the total number of events was not reported). Seven patients had VGB withdrawn because of AEs, including a severe psychotic reaction and severe schizophrenic symptoms; when these occurred was not stated. The VGB dose went as high as 9 g/day.<sup>249</sup> An open-label extension study of adults with intractable epilepsy ( $n = 97$ ) who received up to 4 g/day VGB reported 12 withdrawals due to neurological/psychiatric AEs, one patient was hospitalised with delirium and another with suicidal ideation probably related to VGB, both after 2–6 weeks of treatment; one patient was hospitalised with psychosis definitely related to VGB after 11 weeks.<sup>239</sup> Another follow-up study reported withdrawal of one patient after 7 months of treatment due to depression and two patients because of psychotic reactions at 12 and 22 months. The maximum VGB dose was 4 g/day.<sup>247</sup> Psychosis was the reason for withdrawal in a follow-up study of patients described as mentally retarded, which also reported that psychiatric AEs often appeared during the second year of treatment (up to 3 g/day VGB).<sup>248</sup>

Psychosis was the reason for withdrawal of one patient after 1 year in an open-label extension study in which two more patients experienced dose-related psychotic symptoms. The dose range reached 5 g/day.<sup>243</sup> In the same study, visual disturbance later diagnosed as optic neuritis caused two patients to be withdrawn; these and one other withdrawal for depression had occurred by the 2-year follow-up point. Commonly reported AEs were similar to those reported in short-term RCTs, although one open-label extension study did report that such events continued to emerge during the long-term phase of 12–18 months among patients treated with up to 3 g/day VGB.<sup>242</sup> In that study, two patients were withdrawn because of depression during the first 8 weeks. Ten of the 33 patients originally recruited had a neurological or mental handicap but these co-morbidities were not mentioned further in the report.<sup>242</sup>

Three of the follow-up studies concentrated on AEs on the eyes, all three gave an adequate description of who was studied and follow-up exceeded 24 months.<sup>244–246</sup> One study examined patients ( $n = 32$ ) who were still using VGB following an RCT of VGB versus CBZ, and compared them with CBZ patients and healthy controls. The study found that 13/32 VGB patients had concentrically restricted visual fields (compared with none of the CBZ patients or healthy controls), but no statistically significant correlation was found between the extent of visual field and the duration, dose or cumulative amount of VGB (the actual doses were not stated). Only one VGB patient complained of visual problems.<sup>246</sup> In one study, 15 patients who completed serial testing every 3 months for 1 year, while continuing to take VGB, showed no worsening of visual field constriction (VFC), visual acuity or colour vision (six had constricted visual fields on initial testing). The dose of VGB used was as high as 6 g/day.<sup>245</sup> The third study compared 29 patients who had received VGB (up to 4 g/day) to 31 patients who received another AED. Development of clinically relevant VFC was significantly more common in VGB patients. Among the patients with VFC who received adjunctive VGB ( $n = 23$ ), the median duration of treatment was significantly longer than those who received VGB but did not have VFC (41 versus 20 months,  $p = 0.04$ ). No significant difference was shown in the maximum dose of VGB received by these two groups. VFC was also shown not to be related to type and severity of epilepsy, type and number of concomitant AEDs or length of follow-up.<sup>244</sup>

#### Summary of serious, rare and long-term adverse events

Oedema and myoclonic jerking might be a consequence of higher than recommended doses of GBP. Hyponatraemia might be a rare event, and hair loss could be a long-term effect of GBP treatment, although not listed by the manufacturer. Cancers and infections observed in a few patients were not positively linked to GBP.

Rash associated with LTG is listed in the manufacturer's information and was reported in the RCTs and additional studies. The latter provided additional reports of very serious skin reactions. The additional studies also suggest that life-threatening systemic reactions including hepatic and renal failure and intravascular coagulation are possibly rare events associated with LTG. Lowering of white blood cell counts and hallucinations were observed in the additional studies. Reactions such as mania and agitation could be a particular risk for predisposed people.

The few data available for OXC indicate that serious AEs do occur with OXC but are similar in type to those commonly reported in RCTs. Although diarrhoea was not reported in the RCTs, the manufacturer does list it and one severe case led to withdrawal of the drug in one of the additional studies.

Possible TGB-related serious AEs appear to be mostly neurological, as is evident from the RCTs, additional studies and the manufacturer's information. One report of a CNS neoplasia, not positively linked to the TGB, came from the additional studies. Effects on vision might be a rare AE.

The additional studies suggest that metabolic acidosis (the causes of which include renal failure) and renal stones could be rare events associated with TPM; these are not listed in the manufacturers' information.

The manufacturer's information on VGB includes a caution about VFDs. A number of the additional studies specifically investigated the effect of VGB on vision and consequently provided more evidence for this than the RCTs. Many of the additional studies provided evidence of asymptomatic VFDs in patients treated with VGB at both recommended and higher doses. Follow-up studies suggest that the

extent of VFDs could depend on the duration of treatment. There is evidence from the RCTs and the additional studies of psychological AEs with VGB noted in the manufacturer's data. The additional studies suggest that these effects occur in patients with and without underlying mental disabilities, and that their emergence can be long term. Based on the additional studies data, aggression (not specifically reported in the RCTs) could be significant for patients with underlying behavioural problems.

#### **Summary of data regarding pregnancy**

Regarding pregnancy, the PEM and PMS data included in this review provide indicators of events but are not sufficient to assess or compare risks associated with specific AEDs. A full assessment of AEs in pregnancy should include a comprehensive overview of prospective surveillance data, such as that maintained by the Medicines and Healthcare Products Regulatory Agency (MHRA) and similar agencies, and data registered in specialist collaborative databases. In addition, a comprehensive systematic review of research evidence specific to pregnancy is needed. Both of these were beyond the scope of this review.

#### **Unlicensed indications**

Eleven studies were identified which reported unlicensed usage of four of the drugs (GBP, LEV, TGB, and VGB). Brief details of these studies and the reason for the unlicensed use of the drug are shown in *Table 61*.

### **Results of assessment of cost-effectiveness**

#### **Results of assessment of published cost-effectiveness evidence**

The economic evaluations addressed monotherapy (four studies) and adjunctive therapy (seven studies). Results are reported separately for these two types of antiepileptic therapy. Full details of these studies are presented in Appendix 26.

#### **Monotherapy studies**

A summary description of the four studies of monotherapy can be found in *Table 62*. All the studies compared newer and older AEDs.<sup>252-255</sup>

#### **Design**

All the studies of monotherapy were designed as CMAs. In a CMA, the economic evaluation is based on a comparison of costs and not effects;

consequently, no cost-effectiveness ratio is calculated. The justification for undertaking a CMA is that there is no clinical evidence for a significant difference in the relative effectiveness of the interventions under comparison.

#### **Treatment of effectiveness**

All four studies based their assumptions of therapeutic equivalence on findings of effectiveness reported in the published literature. Shakespeare and Simeon<sup>255</sup> based their assumption on findings from a single trial. The remaining three monotherapy studies took estimates of effectiveness from several trials. Bryant and Stein cited three RCTs as evidence that outcomes with LTG are similar to those with the older AEDs.<sup>252</sup> Heaney and colleagues reviewed the evidence from eight RCTs in their UK study.<sup>253</sup> The same authors, in collaboration with others, assessed five RCTs for a European study that was published in 2000.<sup>254</sup>

#### **Treatment of costs**

The economic studies drew on several sources for cost estimates. All used expert opinion to inform resource use estimates and all but one<sup>252</sup> also drew on clinical trial data, where available. In every study, unit costs were derived from the literature. All four studies confined their analysis to direct healthcare costs: although the existence of indirect costs (lost productivity) and non-medical costs borne by patients was acknowledged, these categories of cost were not included in the analyses. All four monotherapy studies included the cost of AEDs, GP visits, neurologist consultations, laboratory safety monitoring and plasma tests. Shakespeare and Simeon focused their cost analysis on the treatment of AEs, arguing that the principal difference between the newer and older AEDs lay in their side-effect profile.<sup>255</sup> Comparing CBZ with LTG, these authors based the incidence of AEs and withdrawal on clinical trial data and modelled the corresponding treatment pathways according to expert opinion. In addition to costing neurologist consultations, Shakespeare and Simeon also estimated the cost of consultations with dermatologists and psychiatrists; the costs of switching drugs and of additional drug therapy were also evaluated. Only one other monotherapy study estimated the cost of AEs,<sup>253</sup> but this study included only the cost of GP visits and plasma monitoring. Two studies included the cost of emergency room visits.<sup>253,254</sup>

#### **Combining costs and effectiveness**

Since the studies were all CMAs, costs were not combined with any unit of effectiveness. However,

**TABLE 61** Summary details of studies of unlicensed indications

Drug	Author/year/country/ID	Study design	Unlicensed use	Outcomes measured
GBP	Chadwick, 1996, <sup>74</sup> Study Group 945-077 Multinational	Parallel trial of GBP vs placebo	Used in seizures of generalised onset	Change in seizure frequency; proportion of responders (at least 50% or other specified criteria); response ratio; AEs
	Chadwick, 1998, <sup>250</sup> Multinational	Parallel trial of GBP vs CBZ	Used as monotherapy in newly diagnosed patients	Proportion of patients completing treatment; exit/withdrawal rate; time to exit/withdrawal; AEs
	Lopes-Lima, 1999, <sup>46</sup> Spain and Portugal	Parallel trial of GBP (3 different doses) vs VPA	Used as monotherapy	Time to exit/withdrawal; AEs
	Brodie, 2002, <sup>93</sup> Multinational	Parallel trial of GBP vs LTG	Used as monotherapy in newly diagnosed patients	Time to exit/withdrawal; proportion of participants completing the trial; time to first seizure; proportion of seizure-free patients; AEs
LEV	Ben-Menachem, 2000, <sup>144</sup> Europe	Parallel trial of LEV vs placebo	Used as monotherapy	Proportion of patients completing study, remaining seizure-free, and responding; change in seizure frequency; AEs
TGB	Schachter, 1999, <sup>251</sup> UK	Parallel trial of TGB vs placebo	Used as monotherapy	Change in seizure frequency; AEs
	Aikia, 1999, <sup>52</sup> Finland	Parallel trial of TGB vs CBZ	Used as monotherapy in newly diagnosed patients	Proportion of responders (at least 50% or other specified criteria); AEs
VGB	Tanganelli, 1996, <sup>53</sup> Italy	Crossover trial of VGB vs CBZ. Only participants with persisting seizures or intolerable AEs were crossed over to the alternative treatment	Used as monotherapy in newly diagnosed patients	Proportion of seizure-free patients; AEs
	Kälviäinen, 1995, <sup>71</sup> Riekkinen, 1997, <sup>59</sup> Finland	Parallel trial of VGB vs CBZ	Used as monotherapy in newly diagnosed patients	Proportion of responders (at least 50% or other specified criteria); proportion of seizure-free patients; cognitive function; change in functional capacity; AEs
	Chadwick, 1999, <sup>92</sup> UK	Parallel trial of VGB vs CBZ	Used as monotherapy in newly diagnosed patients	Time to exit/withdrawal; proportion of seizure-free patients; time to achieve 6 months of remission (seizure freedom); time to first seizure; AEs
	Czapinski, 1997, <sup>45</sup> Argentina	Parallel trial of VGB vs LTG	Used as monotherapy	Proportion of responders (at least 50% or other specified criteria); AEs

**TABLE 62** Summary description of monotherapy studies (n = 4)

Study	Status and source	Study design	Comparators
Bryant, 1998 <sup>252</sup>	Review/synthesis of previous studies	CEA; adult patients with epilepsy; proportion of patients seizure free after 24 weeks of maintenance therapy	CBZ monotherapy, 600 mg/day; LTG monotherapy, 100 mg/day; LTG monotherapy, 200 mg/day; PHT monotherapy, 300 mg/day
Heaney, 1998 <sup>253</sup>	Review/synthesis of previous studies	CMA; patients aged over 12 years, with newly diagnosed epilepsy (partial and generalised onsets); health outcomes were not included in the economic evaluation	CBZ monotherapy, 600 mg/day; LTG monotherapy, 150 mg/day; PHT monotherapy, 300 mg/day; VPA monotherapy, 1000 mg/day
Heaney, 2000 <sup>254</sup>	Review/synthesis of previous studies	CMA; adults with newly diagnosed epilepsy (partial and generalised onsets); health outcomes were not included in the economic evaluation	CBZ monotherapy, 600 mg/day; LTG monotherapy, 150 mg/day; PHT monotherapy, 300 mg/day; VPA monotherapy, 1000 mg/day
Shakespeare, 1998 <sup>255</sup>	Single study	CMA; patients aged $\geq 13$ years with newly diagnosed tonic-clonic seizures (partial and generalised onsets); health outcomes were not included in the economic evaluation	CBZ monotherapy, 600 mg/day; LTG monotherapy, 150 mg/day

Bryant and Stein reported their findings as a cost per patient seizure free after 24 weeks of maintenance therapy,<sup>252</sup> although there was no between group difference in this measure. The remaining three studies reported per patient costs.

### Study population

As can be seen in *Table 62*, there was some variation in the study population within these four monotherapy studies. Bryant and Stein assessed adult patients with epilepsy,<sup>252</sup> but the remaining studies included only newly diagnosed patients with either partial or generalised onset epilepsy. Two studies included adolescents<sup>253–255</sup> and one focused on patients with tonic-clonic seizures.<sup>255</sup>

### AEDs compared in the monotherapy studies

The AEDs included in the studies are presented in *Table 63*. All four studies compared LTG with CBZ, three studies compared these drugs with PHT and two studies also considered VPA. No study was found that examined the economic impact of the following older AEDs: AZM, ethosuximide or any barbiturates or benzodiazepines. With regard to the newer drugs, we found no evaluation of GBP, LEV, OXC, TGB, TPM or VGB as monotherapy; of these, only OXC is currently licensed for use as monotherapy in the UK.

### Adjunctive studies

A summary description of the seven studies of adjunctive therapy can be found in *Table 64*.

**TABLE 63** Monotherapy studies by AED (n = 4)

AED	CBZ	LTG	PHT	VPA
CBZ	NA	4	3	2
LTG	4	NA	3	2
PHT	3	3	NA	2
VPA	2	2	2	NA
No. of studies	4	4	3	2
No. of comparisons	9	9	8	6
NA, not applicable.				

Two of the seven economic evaluations involved a comparison of newer AEDs only,<sup>256,257</sup> three trials included older drugs only as a baseline for the evaluation of adjunctive therapy with newer drugs<sup>258–260</sup> and the remaining two studies compared newer and older AEDs.<sup>261,262</sup>

### Design

Designs for the economic studies of adjunctive treatment included CMA,<sup>256</sup> CEA,<sup>257,258,260,262</sup> and CUA.<sup>261</sup> Reinharz and colleagues examined the costs and consequences of introducing VGB as an adjunctive therapy, relative to current practice.<sup>259</sup> Although benefits were not evaluated, this study cannot be classified as a CMA because the authors neither assert nor assume that the two treatment strategies are therapeutically equivalent.

**TABLE 64** Summary of economic evaluations of adjunctive therapy included in the review (n = 7)

Study	Status and source	Study design	Comparators
Hughes, 1996 <sup>256</sup>	Review/synthesis of previous studies	CMA; patients aged > 12 years with intractable partial epilepsy; health outcomes were not included in the economic evaluation	GBP adjunctive, 1200 mg/day; LTG adjunctive, 200 mg/day; VGB adjunctive, 2000 mg/day
Markowitz, 1998 <sup>258</sup>	Review/synthesis of previous studies	CEA; patients with refractory epilepsy (uncontrolled by any single older AED or by any combination of the older AEDs); seizure-free days gained	LTG adjunctive, 400 mg/day; No adjunctive therapy (monotherapy with older AEDs)
Messori, 1998 <sup>261</sup>	Single study	CUA; patients aged 18–65 years with refractory partial seizures; short-term clinical outcomes were assumed to remain stable over subsequent years. These outcomes were converted into QALYS: trial data were extrapolated to produce survival curves, which were adjusted using utility data taken from a separate prospective study	LTG adjunctive, 500 mg/day; no adjunctive therapy (monotherapy with older AEDs)
O'Neill, 1995 <sup>262</sup>	Review/synthesis of previous studies and expert opinion	CEA; patients with intractable epilepsy (patient age range not reported); treatment success was defined as the achievement of both the following conditions: (1) long-term seizure control (at 12 months follow-up); (2) duration of seizure control of at least 9 months of the 12-month period	COZ adjunctive, 20 mg/day; LTG adjunctive, 150 mg, b.d.; VGB adjunctive, 2000 mg/day
Reinharz, 1995 <sup>259</sup>	Single study	Cost and consequences of introducing VGB as an adjunctive therapy	VGB adjunctive (2000, 3000 or 4000 mg/day); no adjunctive therapy (monotherapy)
Schachter, 1999 <sup>260</sup>	Single study	CEA; patients with at least 4 complex partial seizures per month, refractory to monotherapy with older AEDs; a reduction in complex partial seizure rate of at least 50%	PHT + CB, adjunctive, doses not stated; PHT + TGB adjunctive, doses not stated; CBZ + PHT adjunctive, doses not stated; CBZ + TGB adjunctive, doses not stated
Selai, 1999 <sup>257</sup>	Single study	CEA; adult patients with refractory epilepsy (partial) (uncontrolled by monotherapy with older AEDs); patients were deemed to be 'satisfied' if they met all 4 of the following conditions: (1) still on drug at 6 months follow-up; (2) experiencing no side-effects; (3) had no AEDs; (4) had a >50% reduction in seizure frequency; QoL was assessed, but findings not reported	LTG adjunctive, dose not stated; TPM adjunctive, dose not stated

### Treatment of effectiveness

Three of the economic evaluations of adjunctive therapy based their measure of effectiveness on a review or synthesis of previously published studies<sup>258–260</sup> and one of these was also informed by expert opinion.<sup>262</sup> A single trial was the basis for effectiveness data in three of the economic evaluations<sup>257,260,261</sup> and, in two of these, the economic data were collected prospectively alongside the trial.<sup>257,260</sup> Schachter and colleagues reported as their outcome measure a reduction in seizure rate of at least 50%;<sup>260</sup> Selai and colleagues<sup>257</sup> also used this measure, but also used a more stringent measure of ‘patient satisfaction’, incorporating treatment retention at 6 months, a reduction in seizure rate of >50% and no experience of side-effects or of AEs. The CUA study reported QALYs, based on clinical trial data, utility data from the authors’ own prospective study and assumptions regarding the duration of treatment effects, extrapolated from short-term trial data.<sup>261</sup> The remaining CEAs used seizure-free days gained<sup>258</sup> and ‘treatment success’,<sup>262</sup> defined as long-term seizure control (i.e. control at 12 months follow-up after initiation of therapy) with a duration of at least 9 months.

### Treatment of costs

As in the monotherapy studies, the economic studies of adjunctive therapy drew on several sources for cost estimates. Four evaluations used expert opinion to inform resource use, three used data from a single study and two drew on evidence from a review or synthesis of previous studies. Reinharz and colleagues used data from three Canadian databanks to inform their estimates of resource use.<sup>259</sup> All seven studies confined their analysis to direct healthcare costs.

In some studies, it was unclear which costs had been included in the analysis. For example, although Selai and colleagues estimated the cost of treating AEs, the types of healthcare resources used (e.g. GP visit, neurologist consultation) were not specified.<sup>257</sup> All studies included the cost of the AEDs. Three analyses included the cost of surgery (and of evaluation for surgery).<sup>258,259,261</sup> In the absence of direct clinical trial data on surgery rates associated with LTG, Markowitz and colleagues justified their assumption that LTG was associated with a reduction in surgery rates with reference to the published literature.<sup>258</sup> The authors cited particular studies that found LTG reduced seizure severity, particularly for certain types of epilepsy, although the comparator used in these studies was not reported. Messori and colleagues<sup>261</sup> also evaluated costs associated with

surgery, using rates based on a cost of illness study. Reinharz and colleagues<sup>259</sup> also included the cost of surgery in their analysis, but explored the impact of changes in the duration (and hence the cost) of surgery, rather than changes in surgery rates associated with adjunctive treatment. All three economic evaluation assessed the cost effectiveness of adjunctive therapy with a newer drug, relative to current practice (i.e. monotherapy with an older drug). No study assessed the impact on surgery rates of adjunctive therapy with an older drug.

### Combining of costs and effectiveness

All but two<sup>256,259</sup> of the studies combined costs and effects in their analysis.

### Study population

All but one study,<sup>259</sup> which considered adult patients with any type of epilepsy, focused on refractory patients. However, the definition of ‘refractory’ varied between authors: in some studies it included patients who had not responded to monotherapy with the older drugs,<sup>257,260</sup> whereas another study defined ‘refractory’ patients as those who were unresponsive to both monotherapy and adjunctive therapy with the older drugs.<sup>258</sup> It is also possible that some studies included patients unresponsive to monotherapy with any (older or newer) drug, although this was not explicitly stated. One study included adolescent patients,<sup>256</sup> three studies included only adults<sup>257,259,261</sup> and in the others the patient age range was not specified.

### AEDs compared in the adjunctive studies

The AEDs included in the studies are presented in *Table 65*. The AED that was most frequently compared in the economic studies was LTG: this drug was reported in five studies and was the subject of seven comparisons. In two studies, there was no active comparator for adjunctive LTG; instead, LTG was compared against ‘no adjunctive therapy’ (or ‘monotherapy with older drugs’),<sup>258,261</sup> and two other studies compared LTG against VGB.<sup>256,262</sup> Hughes and Cockerell also compared LTG with GBP<sup>256</sup> and Selai and colleagues compared LTG with TPM.<sup>257</sup> Of the seven comparisons with LTG, just one study employed an older drug (CLB).<sup>262</sup> For patients taking PHT as the base drug, Schachter and colleagues<sup>260</sup> compared adjunctive CBZ with adjunctive TGB; for another group of patients taking CBZ as the base drug, the same study compared adjunctive PHT with adjunctive TGB. No other comparison of older and newer adjunctive therapy was found.



**TABLE 65** Adjunctive studies by antiepileptic drug (n = 7)

AED	CBZ	CLB	GBP	LTG	PHT	TGB	TPM	VGB	No adjunctive therapy
CBZ	NA	0	0	0	0	1	0	0	0
CLB	0	NA	0	1	0	0	0	1	0
GBP	0	0	NA	1	0	0	0	1	0
LTG	0	1	1	NA	0	0	1	2	2
PHT	0	0	0	0	NA	1	0	0	0
TGB	1	0	0	0	1	NA	0	0	0
TPM	0	0	0	1	0	0	NA	0	0
VGB	0	1	1	2	0	0	0	NA	1
No. adjunctive therapy	0	0	0	2	0	0	0	1	NA
No. of studies	1	1	1	5	1	1	1	3	3
No. of comparisons	1	2	2	7	1	1	1	5	3

NA, not applicable.

### Findings of the published evaluations

#### Monotherapy

Appendix 26 summarises the results of the published economic evaluations. Bryant and Stein<sup>252</sup> reported the costs of drug therapy and medical management per patient per day to be £552 for LTG 100 mg/day, £805 for LTG 200 mg/day and £242 for CBZ 600 mg/day. Heaney and colleagues<sup>253</sup> report the costs in the first 2 years of initiating therapy, based on the trials and from an ITT perspective, to vary between £795 and £829 for CBZ, £736 and £768 for PHT, £868 and £884 for VPA and £1525 and £2076 for LTG. Heaney and colleagues<sup>254</sup> estimate that treating a patient with LTG as first-line therapy is between two and four times as expensive as treatment with CBZ, PHT or VPA, which share similar costs, over the first year. These results are consistent in all countries considered despite variations in the medical management of epilepsy. Shakespeare and Simeon<sup>255</sup> estimated the cost of 1-year of treatment on CBZ followed by VPA second line for the proportion of patients intolerant to CBZ as £179. They estimate the cost of LTG followed by CBZ second line as £522. Therefore, all four studies found that treatment with a newer AED was more costly than with older AEDs, and assumed equivalent effectiveness.

#### Adjunctive therapy

O'Neill and colleagues<sup>262</sup> estimated drug costs over the first year at a dose recommended by a clinical expert, including titration costs. These were £94 for CLB, £650 for VGB and £648 for LTG. The proportion of successfully treated patients was 56.6% on CLB, and 59.3% on VGB and LTG. The authors conclude that the results strongly favour the less costly AED, although they do not use a conventional CEA to make this

inference. Schachter and colleagues<sup>260</sup> estimated adjunctive TGB added to existing treatment of phenytoin to cost US\$719 over 16 weeks including the cost of managing AEs. This compared with US\$784 for adjunctive CBZ. CBZ was clinically more efficacious (50% reduction in seizure freedom) but more detailed results are not provided. Within the baseline CBZ arm, add-on PHT cost US\$810 compared with US\$958 for add-on TGB. Add-on phenytoin and add-on tiagabine had similar efficacy. Compared with current medication only, Messori and colleagues<sup>261</sup> found adjunctive LTG cost an additional US\$1,612,370 for a cohort of 100 patients over the patients' lifetimes, gained an additional 39 QALYs, and calculated an incremental cost-effectiveness ratio (ICER) of US\$41,343 per QALY. Costs and benefits were discounted at 6%. Markowitz and colleagues<sup>258</sup> found that LTG therapy cost an additional US\$728 compared with the patients' current monotherapy only, discounted at 3% over 10 years. LTG therapy gained 106 additional seizure-free days (undiscounted) and an ICER of US\$6.90 per seizure-free day gained. Hughes and Cockerell<sup>256</sup> found that GBP saved £18.52 per patient in the first year compared with LTG and £47.18 compared with VGB, and assumed equivalent effectiveness. Selai and colleagues<sup>257</sup> found that 15% (7/47) of patients receiving TPM and 11% (3/26) of patients receiving LTG were satisfied with their treatment. The cost per patient was £472 for TPM and £587 for LTG if the costs of telemetry were excluded from the analysis.

### Results of critical review of company submissions

#### Types of submissions

Table 66 summarises the types of submission received.

**TABLE 66** Types of study

Company	Drug	Treatment and comparator				
		Monotherapy		Adjunctive therapy		
		Newer–older	Newer–newer	Newer–placebo	Newer–older	Newer–newer
Novartis <sup>263</sup>	OXC	Yes	Yes			Yes
GSK <sup>264</sup>	LTG	Yes		Yes		
Janssen <sup>218</sup>	TPM		Yes			Yes
Cephalon <sup>265</sup>	TGB				Yes	Yes
UCB <sup>266</sup>	LEV			Yes		

**TABLE 67** Types of analysis submitted and measures of outcome used in the models

Therapy	Comparator	Type of study	Primary measure of outcome
OXC mono <sup>263</sup>	Older AED	CEA	AE avoided
LTG mono <sup>264</sup>	Older AED	CUA	QALY
OXC mono <sup>263</sup>	Newer AED	CMA	–
TPM mono <sup>218</sup>	Newer AED	CUA	QALY
TGB adj <sup>265</sup>	Older AED	CCA	50% reduction in seizure and incidence of AEs
TGB adj <sup>265</sup>	Newer AED	CEA	50% reduction in seizure
TPM adj <sup>218</sup>	Newer AED	CUA	QALY
OXC adj <sup>263</sup>	Newer AED	CMA	–
LEV adj <sup>266</sup>	Placebo	CEA	Seizure freedom
LTG adj <sup>264</sup>	Placebo	CUA	QALY

CCA, cost–consequences analysis.

### Types of analysis and measures of outcome

The evaluations provided a diverse range of health outcome measures and types of analysis (Table 67). The CMAs assume equivalence of effectiveness between the drugs. The evidence to support this assertion was generally limited, being based on a small number of studies, of heterogeneous design and without appropriate statistical analysis. There were three CEAs. Each chose a different measure of health outcome as their primary measure of benefit, which restricts comparability between the models. Four evaluations used QALYs as a measure of health benefit. However, comparability is again limited since none of the four evaluations considered the same study question, that is, the same type of therapy and comparator. QoL in the treatment of epilepsy cannot be adequately measured by considering AEs or seizure freedom alone. A composite measure is therefore needed. QALYs have the further advantage that they allow comparisons of health outcomes with other treatments and disease groups.

### Treatment pathways

The models differed in their approach to possible treatments if the first study drug failed (Table 68). Four evaluations did not allow for the possibility

that the patient would withdraw from the drug.<sup>263–265</sup> This approach limits the applicability of the model to the clinical decision problem, since withdrawal is the main mechanism by which the patient will register dissatisfaction with the performance of the therapy with respect to seizure control or side-effects. Only one company submitted evaluations that allowed for more than one change of therapy over the lifetime of the model and allowed for a choice of second-line treatment.<sup>218</sup> Since there are a large number of permutations of possible treatment pathways in the treatment of the disease, it is important that the model is flexible, including consideration of the ‘monotherapy only’ alternative in the model for adjunctive treatment. None of the adjunctive therapy submissions allowed comparison of newer AEDs with all relevant alternatives, that is, other newer AEDs, older AEDs or monotherapy only.

### Sources of effectiveness data

No evaluations stated that they used a systematic search strategy to look for effectiveness data concerning either the therapy of interest or the comparators. Table 69 shows the number of RCTs used in each model as a source of effectiveness data and how the results of these RCTs were synthesised. These results show that in general

**TABLE 68** Maximum possible number of changes of treatment considered by the models

Therapy	Monotherapies		Adjunctive therapies		
	One change	Two changes	No changes	One change	Two changes
OXC mono <sup>263</sup>	Yes				
LTG mono <sup>264</sup>	Yes				
OXC mono <sup>263</sup>	Yes				
TPM mono <sup>218</sup>		Yes			
TGB adj <sup>265</sup>			Yes		
TGB adj <sup>265</sup>			Yes		
TPM adj <sup>218</sup>					Yes
OXC adj <sup>263</sup>			Yes		
LEV adj <sup>266</sup>			<b>[Data have been designated commercial-in-confidence and have been removed]</b>		
LTG adj <sup>264</sup>			Yes		

**TABLE 69** Sources extent of and sources of short-term effectiveness data

Model	Therapy	No. of trials	Method of synthesis of trials
Novartis <sup>263</sup>	Mono	1	None needed: based on one trial
GSK <sup>264</sup>	Mono	5	None: separate model presented for each trial
Novartis <sup>263</sup>	Mono	2	None: CMA
Janssen <sup>218</sup>	Mono	2	None needed: one trial per treatment
Cephalon <sup>265</sup>	Adj	1	None needed: based on one trial
Cephalon <sup>265</sup>	Adj	30 <sup>a</sup>	Meta-analysis from systematic review
Janssen <sup>218</sup>	Adj	4	Weighted averages
Novartis <sup>263</sup>	Adj	12 <sup>b</sup>	Meta-analysis from systematic review
UCB <sup>266</sup>	Adj	3	<b>[Data have been designated commercial-in-confidence and have been removed]</b>
GSK <sup>264</sup>	Adj	10 <sup>c</sup>	Weighted averages

<sup>a</sup> Results of published systematic review.  
<sup>b</sup> One RCT and one published systematic review.  
<sup>c</sup> One published systematic review plus an additional trial identified by the company.

the number of sources of evidence used by the companies was limited. In cases where a published systematic review was used, very few further studies were identified by the companies. There is, therefore, a risk that the estimates of effectiveness used in the models are incomplete.

### Synthesis of trial results

Very few RCTs have compared one newer AED directly against another. If indirect comparisons are made using a common comparator there is a potential for bias. Differences in outcome between trials may be caused by different study designs and implementation rather than differences between the therapies. One study found trials that compared the study drug with different older AED comparators.<sup>264</sup> The authors avoided making indirect comparisons by presenting the incremental costs and QALYs for each trial separately. The analysis then calculated a 'mean' of the ICERs as a 'composite measure of cost

effectiveness'. However, this approach is not the preferred method of handling the second-order uncertainty surrounding the estimates of the interventions' expected health effects and costs.<sup>267</sup>

### Extrapolation beyond trial period

One company submitted evaluations that only modelled the treatment decision for the 12–16-week time horizon of the clinical trials.<sup>265</sup> Six models extrapolated with varying degrees of sophistication beyond the trial periods for up to 1 year<sup>264,266,268</sup> and one company submitted models that extrapolated 15 years beyond the trial.<sup>218</sup> The models with a time horizon of >1 year discounted costs and benefits. *Table 70* shows the methods of extrapolation used by each evaluation. These methods were:

1. Assume that outcomes at the end of the trial period continued to the end of the modelling time horizon.

**TABLE 70** Methods of extrapolation used by evaluation

Model	Time horizon	Method 1	Method 2	Method 3
Novartis mono <sup>263</sup>	1 year	Yes		
GSK mono <sup>264</sup>	1 year	Yes		
Novartis mono <sup>263</sup>	1 year	Yes		
Janssen mono <sup>218</sup>	15 years			Yes
Cephalon adj <sup>265</sup>	16 weeks	Yes		
Cephalon adj <sup>265</sup>	12 weeks	Yes		
Janssen adj <sup>218</sup>	15 years			Yes
Novartis adj <sup>263</sup>	1 year	Yes		
UCB adj <sup>266</sup>	1 year		[Data have been designated commercial-in-confidence and have been removed]	
GSK adj <sup>264</sup>	1 year	Yes		

**TABLE 71** Types of costs included in each study

Model	Drug costs	Routine care <sup>a</sup>	Adverse events <sup>b</sup>	Other side-effects	Seizures
Novartis <sup>263</sup>	Yes	Yes	Yes		
GSK <sup>264</sup>	Yes	Yes			
Novartis <sup>263</sup>	Yes	Yes			
Janssen <sup>218</sup>	Yes	Yes	Yes		Yes
Cephalon <sup>265</sup>	Yes	Yes	Yes	? <sup>c</sup>	? <sup>c</sup>
Cephalon <sup>265</sup>	Yes				
Janssen <sup>218</sup>	Yes	Yes	Yes		Yes
Novartis <sup>263</sup>	Yes				
UCB <sup>266</sup>	Yes	Yes	Yes	Yes	Yes
GSK <sup>264</sup>	Yes				

<sup>a</sup> Routine care: costs of GP and outpatient attendances for routine care.  
<sup>b</sup> Adverse events: costs of AEs leading to withdrawal.  
<sup>c</sup> This study was reported only as a poster abstract and few details of the analysis were available.

- Assume that a fixed percentage of patients who were successful at the end of the trial fail by the end of the year.
- Patients who were successful at the end of the trial fail over the subsequent follow-up period according to a constant hazard rate using a Markov chain model.

No submissions considered that the transition probabilities might change over time.

### Resource use

Table 71 shows the types of costs included in each study. There is considerable variation in the types of costs included and the methods used to obtain estimates of these costs. [Text deleted owing to references to commercial-in-confidence data.]

Two evaluations used published data on the costs incurred following seizures.<sup>218</sup> The remaining evaluations used 'expert opinion' or the authors' assumptions.

### Sensitivity analysis

The scope of sensitivity analyses varied widely between submissions. One company submitted (two) models with no sensitivity analysis.<sup>265</sup> Most companies provided one-way analyses based on varying key parameters, with the upper and lower limits set by their 95% CIs. Typical parameters varied were the probability of success (seizure reduction or seizure freedom), the probability of withdrawal from the therapy and the utility weights. One company submitted two models that undertook probabilistic sensitivity analysis and presented results on the cost-effectiveness plane and as cost-effectiveness acceptability curves (CEACs).<sup>218</sup> This was repeated for a large number of different combinations of first-line drugs, second-line drugs and comparators. However, the company opted to use selected pairwise comparisons of certain treatment pathways, rather than comparing all the treatment options head-to-head on a single CEAC plot, which is appropriate when there are multiple interventions under

**TABLE 72** Results of the submissions – monotherapy

Company	Therapy	Comparator	Result
Novartis <sup>263</sup>	OXC 1st line and LTG 2nd line	CBZ 1st line and LTG 2nd line	ICER £1600 per AE avoided
Novartis <sup>263</sup>	OXC	LTG	OXC cheaper than LTG
GSK <sup>264</sup>	LTG	VPA or CBZ	'Mean' of ICER's £13,000 per QALY
Janssen <sup>218</sup>	TPM 1st line and CBZ 2nd line	CBZ 1st line and TPM 2nd line	ICER £38,000 per QALY. Dominates LTG 1st line

**TABLE 73** Results of submissions – adjunctive therapy

Company	Therapy	Comparator	Result
Novartis <sup>263</sup>	OXC	LTG	OXC cheaper than LTG
GSK <sup>264</sup>	LTG	Placebo	ICER £16,000 per QALY
Janssen <sup>218</sup>	LEV 1st line and TPM 2nd line	TPM 1st line and LEV 2nd line	ICER £32,000 per QALY. Dominates LEV + LTG
Cephalon <sup>265</sup>	TGB	Older AEDs	TGB lower cost
Cephalon <sup>265</sup>	TGB	Other newer AEDs	Similar costs and efficacy
UCB <sup>266</sup>	LEV	Placebo	ICER £5000 per seizure-free patient per year

consideration. Probabilistic sensitivity analysis is preferred to univariate sensitivity analysis alone because there is a great deal of uncertainty in the measurement of the model parameters, and changing the values of one of these parameters will affect the sensitivity other parameters have on the decision.<sup>269</sup>

### Results of the analyses

Tables 72 and 73 summarise the results of the submissions, as described by the authors, for partial seizure types. Each manufacturer claims that its product is either cheaper than its rivals or superior and the additional cost represents good value. As anticipated by the protocol, no manufacturers address the same study question with the same measure of economic benefit, so it is not appropriate to summarise these results on a cost-effectiveness plane.

### Assessment of suitability of company submissions to provide an integrated economic evaluation of AED therapies

All of the submissions claimed that the intervention in question was cost-effective. Because of the range of outcome measures, interventions and comparators evaluated, it is not possible to compare the results directly with one another. A summary of the industry evidence of cost-

effectiveness can be found in Appendix 26. This section summarises the suitability of the company submissions to provide an integrated economic evaluation. A suitable model should include a number of important features of the treatment of epilepsy. There are a wide range of available therapies, and all alternatives should be compared head-to-head. Three analyses allowed a comparison of the intervention in question with several other AEDs.<sup>218,265</sup> Four of the analyses incorporated QoL in the measure of health benefit.<sup>218,264</sup> Five of the analyses allowed the substitution of second- or third-line therapies should the intervention in question fail.<sup>218,263,264</sup> Two used a meta-analysis to synthesise evidence.<sup>263,265</sup> Two used a time horizon of >1 year.<sup>218</sup> Three used a broad NHS perspective for use of resources<sup>218,266</sup> and two used probabilistic sensitivity analysis to handle second-order uncertainty in the estimates of parameter values.<sup>218</sup> The main weakness of even the more sophisticated evaluations was a lack of a systematic approach to obtaining and synthesising effectiveness data and not comparing all the relevant alternative therapies with one another. This indicates the need for an integrated economic analysis that incorporates all the available information on the costs and effects associated with new and old AEDs and which

allows direct comparisons to be made on estimated long-term costs and benefits.

## Integrated analysis of cost-effectiveness

The integrated analysis was intended to address the following questions:

1. What is the incremental cost-effectiveness of the treatment of newly diagnosed patients with individual drugs used as monotherapy?
2. What is the incremental cost-effectiveness of the treatment of refractory patients with individual drugs used as monotherapy?
3. What is the incremental cost-effectiveness of individual drugs used as adjunctive therapy for refractory patients?

## Methods

### Overview of the model

In order to determine the cost-effectiveness of the newer AEDs, all of the relevant available treatments must be directly compared. In addition, an estimate must be made of the long-term costs and benefits of treatment. As described in the section 'Results of assessment of cost-effectiveness' (p. 95), the various published evaluations and industry submissions used a variety of analytic methods, comparators and outcomes. Therefore, a decision-analytic model was developed which incorporated the available information on the costs and effects associated with the various newer and older AEDs and which allowed direct comparisons to be made based on estimated long-term costs and benefits.

To allow the cost-effectiveness of the various AEDs under consideration to be compared with therapies for other conditions, a CUA was undertaken. QALYs were calculated using utility weights estimated from EQ-5D responses and UK public valuations. An NHS costing perspective was adopted and all costs are expressed in 2001–02 UK sterling. The following cost items were included in the model: healthcare costs associated with starting a newer therapy; additional healthcare costs required for the treatment for a seizure-free epileptic patient (compared with a non-epileptic patient); additional healthcare costs required for the treatment for an epileptic patient who is not seizure free (compared with a non-epileptic patient); and the cost of AEDs. Although in principle there could be costs associated with the treatments of AEs, we considered these to be small given the nature of these events. The more

important impact of AEs is the time to withdrawal from therapy.

To enable direct comparisons of treatments to be made based on the individual clinical trial results, a meta-analysis of the response and withdrawal rates from randomised trials was performed. This used a hierarchical Bayesian model incorporating random study effects and fixed treatment effects.

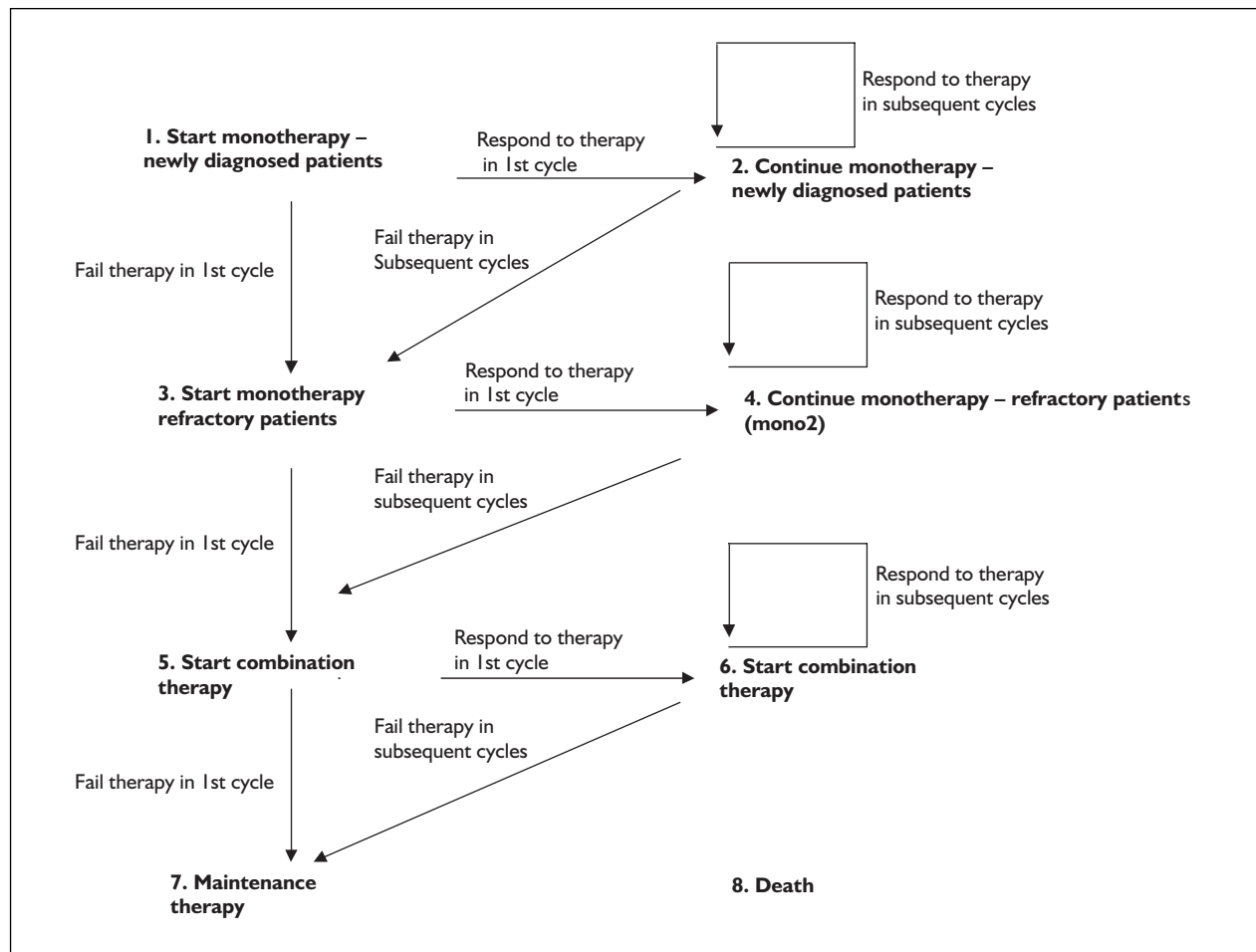
To provide a policy-relevant estimate of incremental cost-effectiveness estimates, the long-term costs and outcomes of treatment have to be considered, including estimates of the future cost and outcomes associated with those patients who do not respond to the treatment under consideration. Therefore, the analysis reported here considered a time horizon of 15 years. The randomised trial evidence available provided comparative data on the rates of response and failure over a short period of time, typically up to 6 months. Observational and open-label clinical trial data were available for a limited range of drugs for periods of several years. It was clear from these data that the rate of withdrawal varied with time, with patients becoming less likely to withdraw from a drug as time progressed. The short-term comparative trial data and the long-term observational data were combined in a semi-Markov process model which allowed for this time dependence in withdrawal. In addition, the model incorporated estimates of mortality rates for seizure-free and non-seizure-free patients.

Second-order uncertainty in model parameters was incorporated by running a Monte Carlo simulation where values for the model parameters were sampled from defined distributions.

The structure of this analytic model, the information used to parameterise it and the results of the analysis are described in detail below.

### Treatment pathways

The following potential treatment sequence was considered in the decision-analytic model: treatment of newly diagnosed patients with a single AED (referred to later as 'mono1'); followed by treatment of those patients who remain refractory with an alternative single AED (referred to later as 'mono2'); followed by treatment of those patients who still remain refractory with a combination of AEDs (referred to later as 'comb'). Those patients who are still refractory at the end of this treatment sequence were assumed to be maintained on monotherapy using older AEDs (referred to later as 'maint'), although in practice



**FIGURE 30** Semi-Markov process model of AED treatment

further therapy or surgery would be considered for these patients. This treatment sequence was felt to represent the most common sequence currently used.<sup>270</sup> However, there were insufficient data available regarding the efficacy of AED therapy conditional on specific prior treatments to allow a more detailed consideration of alternative general sequences such as the use of combination therapy following initial monotherapy or the sequential use of various combination therapies.

#### **Model structure**

The expected costs and effects for each treatment sequence were estimated using a probabilistic semi-Markov process model which is illustrated in *Figure 30*.

The states considered in the model were:

1. Newly diagnosed patient starts monotherapy (one cycle only).
2. Newly diagnosed patient continues monotherapy

3. Refractory patient starts monotherapy (one cycle only).
4. Refractory patient continues monotherapy.
5. Patient starts combination therapy (one cycle only).
6. Patient continues combination therapy.
7. Patient on 'maintenance' therapy.
8. Death.

In this model, the probabilities of patients being in defined states are estimated at discrete time intervals (cycles) over a simulated treatment lifetime. The probability of a patient making a given transition during a model cycle is dependent on the time spent in the current state; hence this is a semi-Markov process model according to the classification used by Billingham and colleagues.<sup>271</sup> Thirty cycles, each of 6 months, were modelled, giving a time horizon for the analysis of 15 years. The probability of a patient remaining on treatment after the first cycle on each drug in the treatment sequence was estimated from clinical trial data specific to the

**TABLE 74** Parameters used to determine transition probabilities

Model parameter	Parameter name	Source	Distribution for probabilistic analysis
Probability of a response to 'monotherapy for newly diagnosed patients' during the 1st cycle	$P_{\text{Mono1 response}}(1)$	Meta-analysis of clinical trial data	1 <sup>a</sup>
Probability of treatment failure for 'monotherapy for newly diagnosed patients' during the tth cycle	$P_{\text{Mono1 failure}}(t)$	NGPSE <sup>270</sup>	2 <sup>b</sup>
Probability of a response to 'monotherapy for refractory patients' during the 1st cycle	$P_{\text{Mono2 response}}(1)$	Meta-analysis of clinical trial data	1
Probability of treatment failure for 'monotherapy for refractory patients' during the tth cycle	$P_{\text{Mono2 failure}}(t)$	NGPSE <sup>270</sup>	2
Probability of a response to 'monotherapy for refractory diagnosed patients' during the 1st cycle	$P_{\text{Comb response}}(1)$	Meta-analysis of clinical trial data	1
Probability of failure for 'combination therapy' during the tth cycle	$P_{\text{Comb failure}}(t)$	Tiagabine Study No. M91-604/M91-604C <sup>272</sup>	2
Probability of death during the tth cycle if patient is seizure free	$P_{\text{Mort.SF}}(t)$	NGPSE, <sup>43</sup> UK Mortality Statistics <sup>273</sup>	3 <sup>c</sup>
Probability of death during the tth cycle if patient is not seizure free	$P_{\text{Mort.NSF}}(t)$	NGPSE, <sup>43</sup> UK Mortality Statistics <sup>273</sup>	3

NGPSE, National General Practice Study of Epilepsy  
<sup>a</sup> 1, Samples from the posterior distribution from the Bayesian meta-analysis of trial data.  
<sup>b</sup> 2 ~Beta ( $\alpha, \beta$ ) where  $\alpha$  = number of discontinuations at time  $t$  and  $\beta$  = number at risk -  $\alpha$ .  
<sup>c</sup> 3, Constant.

drug under consideration. The probability of a patient remaining on treatment for subsequent cycles on each drug in the treatment sequence was based on observational data, which was not specific to the drug under consideration.

### Model parameters

#### Transition probabilities between states

Patients can move through states 1–7 in sequence (depending on the initial state). Patients spend only one cycle in states 1, 3 and 5. Patients may move from any state to state 8 (death).

The parameters determining transition probabilities which were included in the model are shown in *Table 74*.

The transition probabilities for the 'monotherapy for newly diagnosed patients' states which are estimated as functions of the parameters described above are shown in *Table 75*. Transition probabilities for 'monotherapy for refractory patients' and 'combination' therapy states were estimated in a similar fashion.

#### Estimation of response to treatment during the first cycle

The probabilities of treatment success and failure

during the first cycle of treatment for each of the three elements of the treatment sequence were estimated from clinical trial data. Only patients who achieved a response to therapy during the clinical trial continue the therapy after the first cycle of treatment. For 'monotherapy for newly diagnosed patients' a 'response' was defined as a patient achieving seizure freedom and remaining on the study drug until the end of the trial. For 'monotherapy for refractory patients' and 'combination therapy' a 'response' was defined as a patient achieving a 50% reduction in seizure frequency compared with a baseline period and remaining on the study drug. These outcomes reflected those most commonly measured in the clinical trials. The response rates were not corrected for differences in trial duration as a satisfactory model of the relationship between trial duration and response rates could not be determined.

The absolute probability of response was determined from a meta-analysis of clinical trial ITT data.

The meta-analysis of partial seizure-type data consisted of a hierarchical Bayesian model incorporating random study effects and fixed treatment effect, and was conducted using



**TABLE 75** Transition probabilities

Current state	Newer state	Transition description	Transition probability
1	2	'Monotherapy for newly diagnosed patients' is successful during the first cycle	$P_{\text{MonoI response}(1)} \times (1 - P_{\text{Mort.SF}})$
1	3	'Monotherapy for newly diagnosed patients' is unsuccessful	$[1 - P_{\text{MonoI response}(1)}] \times (1 - P_{\text{Mort.NSF}})$
1	8	Patient dies while on monotherapy during the first cycle	$P_{\text{Mort.SF}} + [1 - P_{\text{MonoI response}(1)}] \times (P_{\text{Mort.NSF}} - P_{\text{Mort.SF}})$
2	2	'Monotherapy for newly diagnosed patients' is successful during the subsequent cycle $t$	$(1 - P_{\text{MonoI failure}(t)}) \times (1 - P_{\text{Mort.SF}})$
2	3	'Monotherapy for newly diagnosed patients' fails during the subsequent cycle $t$	$P_{\text{MonoI failure}(t)} \times (1 - P_{\text{Mort.NSF}})$
2	8	Patient dies while on first monotherapy during the subsequent cycle $t$	$P_{\text{Mort.SF}} + P_{\text{MonoI failure}(t)} \times (P_{\text{Mort.NSF}} - P_{\text{Mort.SF}})$

Winbugs version 1.3.<sup>274</sup> This assumed that the individual treatments had a specific fixed effect on the log OR ( $\beta_{\text{treatment}}$ ) compared with placebo, the intercept term ( $\alpha$ ) corresponded to the rate in the placebo arms on the log-odds scale and was allowed to vary randomly between trials:

$$P(\text{event}) = \text{logit}^{-1}(\alpha_j + \beta_{\text{treatmentA}} T_{Aj} + \beta_{\text{treatmentB}} T_{Bj} \dots)$$

$$\alpha \sim N(\mu_R, \sigma_R^2)$$

where  $T_{Aj}, T_{Bj} \dots \in [0,1]$  are indicator variables for the treatments A, B, ... for the  $j$ th data point.

Because very few clinical trials were available for generalised seizure types, the meta-analysis for generalised seizure data used a fixed study effects model (that is, a common  $\alpha$  is assumed for all studies).

A meta-analysis was conducted for the outcomes of response for each of the three indications considered in the model: monotherapy for newly diagnosed patients, monotherapy for refractory patients and combination therapy. The uncertainty in these probabilities of response and withdrawal were incorporated into the model using sampled values from the Markov chain Monte Carlo simulation of the posterior distribution. A 'burn-in' period of 10,000 samples was used to allow the estimates to converge and the subsequent 10,000 samples were incorporated into the decision-analytic model. Plots of the simulated values were monitored to gauge convergence.

Clinical trials, identified during the systematic review, which met the following criteria were included in the meta-analyses:

- The dose of AED employed was within the range specified in the BNF.
- The drug was licensed as used in the trial.
- The study was a parallel group design.
- The trial outcomes required for the meta-analysis were reported.

One trial<sup>117</sup> was excluded as it was limited to elderly patients and was felt to be confounding. The trial data for patients diagnosed as suffering from partial seizures are shown in *Tables 76–78*. The differential diagnosis of partial and generalised epilepsy may be difficult and some of these trials did include some patients with generalised seizures. The results of the meta-analyses for these trials are shown in *Table 79*.

Results are shown for the outcomes of both response and withdrawal, although only response was used as a parameter in the decision-analytic model.

The combined results from the various meta-analyses are given in *Table 79*.

A separate analysis was also conducted including the limited trial data for patients diagnosed with generalised seizures. The trial data are given in *Tables 80 and 81* and the results of the meta-

**TABLE 76** Clinical trial data for monotherapy for newly diagnosed patients experiencing partial seizures

Study	Newer AED	Week	Newer AED			CBZ			VPA			PHT		
			N	NW (%)	NR (%)	N	NW (%)	NR (%)	N	NW (%)	NR (%)	N	NW (%)	NR (%)
Brodie, 1995 <sup>121</sup>	LTG	48	131	46 (35)	34 (26)	129	63 (49)	37 (29)						
Nieto Barrera, 2001 <sup>119</sup>	LTG	24	259	58 (22)	126 (49)	126	35 (28)	63 (50)						
Biton, 2001 <sup>116</sup>	LTG	32	65	19 (29)	19 (29)				68	30 (44)	18 (26)			
Reunanen, 1996 <sup>120</sup>	LTG	24	226	79 (35)	126 (56)	117	41 (35)	64 (55)						
Steiner, 1999 <sup>75</sup>	LTG	48	86	45 (52)	19 (24)							95	50 (53)	22 (24)
Aikia, 1992 <sup>58</sup>	OXC	52	19	5 (26)	9 (47)							18	3 (17)	11 (61)
Bill, 1997 <sup>124</sup>	OXC	48	143	56 (39)	70 (49)							144	61 (42)	69 (48)
Christe, 1997 <sup>123</sup>	OXC	48	128	52 (41)	60 (47)				121	41 (33)	57 (47)			
Privitera, 2002 <sup>94</sup>	TPM	26	264	134 (51)	128 (48) <sup>a</sup>	126	63 (50)	56 (44) <sup>a</sup>						
Privitera, 2002 <sup>94</sup>	TPM	26	145	83 (57)	62 (43) <sup>a</sup>				78	48 (63)	34 (44) <sup>a</sup>			

NR, number responding, defined as seizure freedom; NW, number withdrawn for any reason.  
<sup>a</sup> Seizure freedom during the last 6 months of the double-blind phase.

**TABLE 77** Clinical trial data for monotherapy for refractory patients experiencing partial seizures

Study	Week	LTG		CBZ		VPA				
		N	No. of patients withdrawing <sup>a</sup>	No. of patients responding <sup>b</sup>	N	No. of patients withdrawing <sup>a</sup>	No. of patients responding <sup>b</sup>	N	No. of patients withdrawing <sup>a</sup>	No. of patients responding <sup>b</sup>
Gilliam, 1998 <sup>112</sup>	12	76	48 (63%)				80	67 (84%)		
Kerr, 2001 <sup>122</sup>	28	181	85 (47%)	93 (51%)	123	58 (47%)	67 (55%)			
Kerr, 2001 <sup>122</sup>	28	316	191 (60%)	114 (36%)			257	180 (70%)	94(37%)	

<sup>a</sup> Withdrawn for any reason.  
<sup>b</sup> Defined as >50% reduction in seizure frequency compared with baseline or seizure freedom.

**TABLE 78** Clinical trial data for combination therapy for partial seizures

Active treatment	Study	Week	Active treatment arm			Placebo		
			N	No. of patients withdrawing <sup>a</sup>	No. of patients responding <sup>b</sup>	N	No. of patients withdrawing <sup>a</sup>	No. of patients responding <sup>b</sup>
GBP	UK Gabapentin Study Group, 1990 <sup>73</sup>	14	61	16 (26%)	12 (20%)	66	9 (14%)	6 (10%)
GBP	US Gabapentin Study Group No. 5, 1993 <sup>138</sup>	12	101	10 (10%)	18 (18%)	98	3 (3%)	8 (8%)
LEV	Shorvon, 2000 <sup>145</sup>	12	212	31 (15%)	53 (25%)	112	15 (13%)	11 (10%)
LEV	Cereghino, 2000 <sup>143</sup>	14	199	20 (10%)	70 (35%)	95	6 (6%)	10 (11%)
LEV	Betts, 2000 <sup>139c</sup>	24	42	14 (33%)	13 (31%)	39	10 (26%)	5 (13%)
LTG	Matsuo, 1993 <sup>142</sup>	12	143	19 (13%)	33 (23%)	73	6 (8%)	12 (16%)
LTG	Schachter, 1995 <sup>56</sup>	28	332	51 (15%)		112	19 (17%)	
LTG	Veendrick-Meekes, 2000 <sup>137</sup>	16	44	4 (9%)	17 (39%)	24	3 (13%)	6 (25%)
OXC	Barcs, 2000 <sup>70</sup>	24	521	241 (46%)	205 (39%)	173	41 (24%)	22 (13%)
TGB	Sachdeo, 1997 <sup>140</sup>	12	211	37 (18%)	54 (26%)	107	10 (9%)	9 (8%)
TGB	Uthman, 1998 <sup>163c</sup>	16	149	24 (16%)	22 (15%)	91	13 (14%)	4 (4%)
TGB	Kälviäinen, 1998 <sup>164</sup>	22	77	21 (27%)	11 (14%)	77	8 (10%)	5 (6%)
TPM	Guberman, 2002 <sup>150</sup>	4	171	23 (13%)	87 (51%)	92	3 (3%)	29 (31%)
TPM	Yen, 2000 <sup>165</sup>	8	23	3 (13%)	11 (48%)	23	2 (7%)	3 (13%)
TPM	Sharief, 1996 <sup>148</sup>	11	23	6 (26%)	8 (35%)	24	2 (7%)	2 (9%)
TPM	Faught, 1996 <sup>67</sup>	16	136		54 (37%)	45		8 (18%)

<sup>a</sup> Withdrawn for any reason.  
<sup>b</sup> Defined as a >50% reduction in seizure frequency compared with baseline.  
<sup>c</sup> Excludes results for unlicensed doses.

**TABLE 79** Results of meta-analysis for AEDs used in the treatment of partial seizures

Indication	Drug	Proportion withdrawn			Proportion responding		
		Mean	95% CI		Mean	95% CI	
Monotherapy for newly diagnosed patients (mono1)	LTG	0.35	0.26	0.44	0.40	0.30	0.50
	OXC	0.43	0.32	0.54	0.43	0.31	0.55
	CBZ	0.41	0.32	0.51	0.41	0.31	0.51
	VPA	0.43	0.33	0.54	0.42	0.31	0.53
	PHT	0.41	0.30	0.53	0.42	0.30	0.55
Monotherapy for refractory patients (mono2)	TPM	0.43	0.31	0.54	0.44	0.32	0.56
	LTG	0.58	0.40	0.75	0.44	0.23	0.67
	CBZ	0.57	0.37	0.76	0.47	0.24	0.71
Combination therapy (comb)	VPA	0.71	0.53	0.84	0.44	0.23	0.68
	Placebo	0.11	0.08	0.15	0.12	0.09	0.16
	GBP	0.21	0.12	0.34	0.23	0.13	0.35
	LEV	0.14	0.09	0.21	0.32	0.23	0.43
	LTG	0.12	0.07	0.18	0.23	0.13	0.34
	OXC	0.28	0.18	0.39	0.39	0.27	0.52
	TGB	0.20	0.14	0.29	0.27	0.18	0.37
TPM	0.23	0.13	0.36	0.33	0.23	0.43	

**TABLE 80** Clinical trial data for monotherapy for newly diagnosed patients experiencing generalised seizures

Study	Week	N	LTG		VPA		
			No. of patients withdrawing <sup>a</sup>	No. of patients responding <sup>b</sup>	N	No. of patients withdrawing <sup>a</sup>	No. of patients responding <sup>b</sup>
GlaxoSmithKline, 2001 <sup>62</sup>	24	211	49 (23%)	131 (62%)	102	21 (21%)	69 (67%)

<sup>a</sup> Withdrawn for any reason.  
<sup>b</sup> Defined as seizure freedom.

**TABLE 81** Clinical trial data for combination therapy for patients experiencing generalised seizures

Study	Week	N	TPM		Placebo		
			No. of patients withdrawing <sup>a</sup>	No. of patients responding <sup>b</sup>	N	No. of patients withdrawing <sup>a</sup>	No. of patients responding <sup>b</sup>
Barrett, 1997 <sup>76</sup>	12	40	9 (23%)	16 (41%)	40	11 (28%)	8 (20%)
Biton, 1999 <sup>79</sup>	12	39	5 (13%)	18 (46%)	41	3 (7%)	7 (17%)

<sup>a</sup> Withdrawn for any reason.  
<sup>b</sup> Defined as >50% reduction in seizure frequency compared with baseline.

**TABLE 82** Results of meta-analysis for AEDs used in the treatment of generalised seizures

Therapy	Drug	Proportion withdrawing		Proportion responding	
		Mean	95% CI	Mean	95% CI
Monotherapy	LTG	0.23	0.18 to 0.29	0.62	0.55 to 0.68
	VAP	0.21	0.14 to 0.29	0.68	0.58 to 0.76
Combination	Placebo	0.17	0.06 to 0.37	0.19	0.07 to 0.39
	TPM	0.18	0.06 to 0.38	0.43	0.22 to 0.67

**TABLE 83** NGPSE long-term follow-up data for monotherapy<sup>270a</sup>

Duration of therapy (months)	0–12	12–24	24–48	48–72	72–96
No. of patients at risk at start of period	564	508	474	440	412
No. of discontinuations of first treatment	56	34	34	28	11

<sup>a</sup> These results were interpolated from the published graph.

analyses in *Table 82*. The trials included in the meta-analysis and an evaluation of their quality are presented in Appendix 13.

The combined results for patients experiencing generalised seizures are shown in *Table 82*.

#### **Estimation of response to treatment during the subsequent cycles**

The probabilities of treatment failure subsequent to the first cycle for monotherapy for 'newly

diagnosed' and 'refractory' patients were estimated from the NGPSE data<sup>270</sup> (*Table 83*).

The probabilities of treatment failure during subsequent cycles for combination therapy were determined from the results of the TGB open-label follow-up study (Study No. M91-604/M91-604C)<sup>272</sup> (*Table 84*). The uncertainty in the probabilities of treatment failure were incorporated using a beta distribution parameterised using the observed data.

**TABLE 84** Study No. M91-604/M91-604C long-term follow-up data for adjunctive therapy<sup>272</sup>

**[Data have been designated commercial-in-confidence and have been removed]**

#### **Estimation of costs associated with states**

Unit cost estimates were obtained from the BNF, March 2002, Personal Social Services Research Unit (PSSRU), 2002,<sup>275</sup> and NHS Reference Costs, 2001–02.<sup>276</sup> The uncertainty in the doses of drug treatment was incorporated using a gamma distribution with parameters based on the minimum and maximum doses recommended in the BNF, March 2002. The other costs were treated as constants. *Table 85* shows the parameters used to determine the costs incurred in each state in the model. Further details of how these values were derived are included in Appendix 27. Costs in the model were discounted at an annual rate of 6% (Department of Health<sup>276</sup>)

The costs incurred in each state, described as functions of the parameters listed in *Table 85* are shown in *Table 86*.

The costs of the individual AEDs used in the model are shown in *Table 87*.

#### **Estimates of QALYs**

The QALYs gained for patients in each state were calculated based on estimates of the QoL weights (utilities) associated with being seizure free, having a 50% or greater reduction in seizure frequency or not responding to therapy (being uncontrolled). Uncertainty in these estimates was incorporated using a gamma distribution parameterised as a function of the mean and standard deviation of these estimates. *Table 88* shows the parameters used to estimate the expected utilities for the specific states. The utility weights were derived from Selai and colleagues.<sup>467</sup> These results were based on a non-randomised audit of 125 patients starting a new adjunctive AED, who completed the EQ-5D questionnaire after 6 months. Further details are included in Appendix 27.

The utility associated with each state, as functions of the parameters described in *Table 88*, are shown in *Table 89*.

The mortality rate for patients who are seizure free is estimated to be 28 deaths per 1000 patients per year. The mortality rate for patients who experience seizures is estimated to be 40 deaths per 1000 patients per year.<sup>273,277</sup> Further details are included in Appendix 27.

#### **Potential comparisons**

The various AEDs that might be used at the various stages in the treatment sequence for generalised and partial epilepsy are illustrated in *Table 90*. This table is based on the indications as listed in the BNF, March 2002. VGB is not included in these tables as its toxicity excludes it from routine use.<sup>278</sup> According to the BNF, CBZ is the treatment of choice for partial seizures and VPA is the drug of choice for generalised seizures.

This corresponds to the recommendations made in the NHS North West Clinical Neuroscience Partnership's *Clinical Framework for the Management of Adults with Epilepsy*,<sup>279</sup> which recommended:

1. For generalised seizures:
  - (a) For newly diagnosed patients: VPA or LTG (for child-bearing females) as monotherapy.
  - (b) In addition for intractable patients: LTG, VPA, TPM, CLB, PB as adjunctive therapy.
2. For partial seizures:
  - (a) For newly diagnosed patients: CBZ or LTG as monotherapy.
  - (b) In addition for intractable patients: OXC as monotherapy, TPM, VPA, GBP, LEV, CLB, TGB as adjunctive therapy.

The specific drugs included within the analysis were determined by the availability of clinical trial data regarding the efficacy of specific drugs at the various stages in the treatment sequence. In addition, PHT was excluded from the final analysis owing to its narrow therapeutic window and VGB was excluded owing to its toxicity.<sup>278</sup>

#### **Incremental cost-effectiveness analysis**

Standard decision rules were followed for the deterministic cost-effectiveness analysis.<sup>280</sup> ICERs were calculated based on mean costs and effects as estimated by the Monte Carlo simulation described above. Strategies which were either subject to dominance (i.e. those that were more costly and less effective than alternate strategies) or were subject to extended dominance (i.e. where a linear combination of other strategies could produce greater benefit at lower cost) were eliminated. ICERs were then calculated by comparing each treatment strategy with the next most costly and most effective option. The effect of uncertainty on the results of the analysis were illustrated in two ways. First, 95% confidence ellipses were constructed for the differences in costs and effects for the various treatments based on the results of the Monte Carlo simulation performed, and assuming a joint normal bivariate

**TABLE 85** Parameters used to determine cost

Parameter description	Parameter name	Value <sup>a</sup>	Distribution <sup>b</sup>
Cost of starting a newer AED	$C_{\text{switch}}$	£149 (1 outpatient attendance at £128, 1 GP visit at £21)	1 <sup>b</sup>
Additional healthcare costs (excluding AEDs) for a seizure-free patient	$C_{\text{HC seizure-free}}$	£98 (includes estimates of inpatient, outpatient, A&E and GP visits, see Appendix 26 for details of items included)	2 <sup>c</sup>
Additional healthcare costs (excluding AEDs) for a patient who is not seizure free	$C_{\text{HC not seizure-free}}$	£469 (as above)	2
Cost of specific AED treatment	$C_{\text{drug}}$	See Table 95 for cost estimates for individual drugs	2
Cost of concomitant drug used during combination therapy	$C_{\text{conc}}$	£153 (mean cost of older AED)	2
Cost of AED treatment during maintenance therapy	$C_{\text{main}}$	£153 in base case	2

<sup>a</sup> See Appendix 26 for full details.  
<sup>b</sup> 1, Gamma (shape, scale), where shape = mean<sup>2</sup>/SD<sup>2</sup>, scale = mean/SD<sup>2</sup>, mean = (max. cost + min. cost)/2, SD = (max. cost – min. cost)/(1.96 × 2).  
<sup>c</sup> 2, Constant

**TABLE 86** Calculation of costs for each state in the model

State	Cost
1. Newly diagnosed patient starts monotherapy	$C_{\text{drug}} + C_{\text{switch}} + [1 - P(\text{therapy fails})] \times C_{\text{HC seizure-free}} + P(\text{therapy fails}) \times C_{\text{HC not seizure-free}}$
2. Newly diagnosed patient continues monotherapy	$C_{\text{drug}} + C_{\text{HC seizure-free}}$
3. Refractory patient starts monotherapy	$C_{\text{drug}} + C_{\text{switch}} + C_{\text{HC not seizure-free}}$
4. Refractory patient continues monotherapy	$C_{\text{drug}} + C_{\text{HC not seizure-free}}$
5. Patients starts combination therapy	$C_{\text{drug}} + C_{\text{conc}} + C_{\text{switch}} + C_{\text{HC not seizure-free}}$
6. Patients continues combination therapy	$C_{\text{drug}} + C_{\text{conc}} + C_{\text{HC not seizure-free}}$
7. Patient on 'maintenance' therapy	$C_{\text{HC not seizure-free}} + C_{\text{main}}$
8. Death	Cost = 0

**TABLE 87** Costs of individual AEDs

AED	Recommended minimum dose (mg/day)	Recommended maximum dose (mg/day)	Cost/mg (£)	Implied minimum cost per year (£)	Implied maximum cost per year (£)
LTG	100	200	0.0121	442	884
OXC	600	2400	0.0013	285	1140
CBZ	800	1200	0.0003	88	131
VAP	1000	2000	0.0003	110	219
PHT	200	500	0.0013	95	237
LEV	1000	3000	0.0016	584	1753
TGP	15	30	0.0907	497	994
GBP	900	1200	0.0016	526	701
TPM as monotherapy	100	500	0.0108	789	1578
TPM as adjunctive therapy	200	400	0.0108	395	1973

**TABLE 88** Parameters used to estimate utilities based on data from Selai and colleagues<sup>467</sup>

Parameter description	Parameter name	Value: mean (SE)	Distribution
Utility for a seizure-free patient	$U_{\text{seizure-free}}$	0.94 (0.024)	$1^a$
Utility for a patient who has a 50% reduction in seizure frequency	$U_{\geq 50\% \text{ reduction}}$	0.90 (0.020)	1
Utility for a patient who does not respond to therapy	$U_{\text{no response}}$	0.84 (0.029)	1
Utility associated with dead state	$U_{\text{death}}$	0	$2^b$

SE, standard error.  
<sup>a</sup> 1,  $\sim 1$  – Gamma (shape, scale), where shape =  $(1 - \text{mean})^2/\text{SD}^2$ , scale =  $(1 - \text{mean})/\text{SD}^2$ .  
<sup>b</sup> 2, Constant.

**TABLE 89** Calculation of utilities

State	Utility
1. Newly diagnosed patient starts monotherapy	$[1 - P(\text{fail monotherapy})] \times U_{\text{seizure-free}} + P(\text{fail monotherapy}) \times U_{\text{no response}}$
2. Newly diagnosed patient continues monotherapy	$U_{\text{seizure-free}}$
3. Refractory patient starts monotherapy	$[1 - P(\text{fail monotherapy})] \times U_{\geq 50\% \text{ reduction}} + P(\text{fail monotherapy}) \times U_{\text{no response}}$
4. Refractory patient continues monotherapy	$U_{\geq 50\% \text{ reduction}}$
5. Patient starts combination therapy	$[1 - P(\text{fail combination therapy})] \times U_{\geq 50\% \text{ reduction}} + P(\text{fail combination therapy}) \times U_{\text{no response}}$
6. Patient continues combination therapy	$U_{\geq 50\% \text{ reduction}}$
7. Patient on 'maintenance' therapy	$U_{\text{no response}}$
8. Death	Utility = 0

**TABLE 90** AEDs indicated for the three stages of the treatment sequence

Drug type	AEDs	Monotherapy – newly diagnosed patients	Monotherapy – refractory patients	Combination therapy
For generalised seizures	Potential older AEDs	CBZ VPA PHT	CBZ VPA PHT	
	Potential newer AEDs	LTG	LTG	LTG TPM
For partial seizures	Potential older AEDs	CBZ VPA PHT	CBZ VPA PHT	
	Potential newer AEDs	LTG OXC	LTG OXC	LTG GBP LEV OXC TGB TPM

distribution. In order to remove the additional 'noise' associated with the covariation in costs and outcomes between the therapies, the ellipses show the costs and effects relative to LTG. Second, uncertainty is illustrated by CEACs.<sup>281,282</sup>

These indicated the probability of each treatment having the greatest net benefit for a range of maximum values that the NHS might be willing to pay for an additional QALY in this patient population.

**TABLE 91** CEA of 'monotherapy for newly diagnosed patients'<sup>a</sup>

Therapy	Cost: mean (95% CI) (£)	QALY: mean (95% CI)	ICER (£)
CBZ	4428 (4071 to 4782)	9.392 (9.000 to 9.737)	NA
VPA	4572 (4180 to 4949)	9.404 (9.002 to 9.751)	11,731
LTG	6133 (5500 to 6892)	9.382 (8.983 to 9.723)	Dom
OXC	6294 (5133 to 7902)	9.415 (9.010 to 9.766)	Ex Dom
TPM	7838 (5733 to 10,895)	9.430 (9.024 to 9.780)	126,519

Dom, dominated; Ex Dom, extendedly dominated.  
<sup>a</sup> Excluding PHT (narrow therapeutic window).

**Implementation of the model**

The semi-Markov process model used required transition probabilities to be a function of both the initial state and the time spent in the initial state. This was incorporated in the model by defining a three-dimensional transition matrix with dimensions corresponding to current state, time spent in current state and potential future state. The progress of a cohort through the model was tracked using a three-dimensional matrix with dimensions corresponding to current state, total time since model started and time in current state.

The model was implemented using R, a statistical programming language which has the ability to manipulate *n*-dimensional matrices. In addition, the model code can be presented as a script, a full listing of which is given in Appendix 28. It was felt that an implementation of the model in Excel would have been extremely difficult and hard to audit.

**Results of integrated economic model****Results for partial seizure-type patients****Monotherapy for newly diagnosed patients**

In order to model the costs and effects of monotherapy for newly diagnosed patients, the analysis needs to include potential second-line (monotherapy for refractory patients) and third-line (combination) therapies should the first-line therapy (monotherapy for newly diagnosed patients) fail. Patients who fail first-line therapy were assumed to receive a common set of drugs for second and third lines. CBZ and GBP were chosen as second-line and third-line therapies, respectively, because based on the assumptions made about dosing, these therapies have the least expected acquisition cost among the available alternatives. Other second- and third-line therapies were considered in sensitivity analyses. All costs are expressed in UK sterling at 2001–02 prices.

**Deterministic results** The results of the deterministic CEA, based on mean costs and QALYs, of 'monotherapy for newly diagnosed patients' are shown in Table 91. The lowest expected QALY gain is achieved by CBZ (9.392 years) and the highest expected QALY gain is achieved by TPM (9.430 years), but the difference between these expected values is only 0.038 years, or 14 days, reflecting the similarity in efficacy between drugs in the meta-analysis. The differences in costs between therapies are more substantial. The therapy with the lowest expected cost is CBZ, mainly owing to its low acquisition cost. Based on an analysis of expected costs and benefits, LTG and OXC are dominated or extendedly dominated by CBZ, VPA and TPM therapies. TPM is cost-effective if the threshold willingness to pay for an additional QALY is in excess of £126,000.

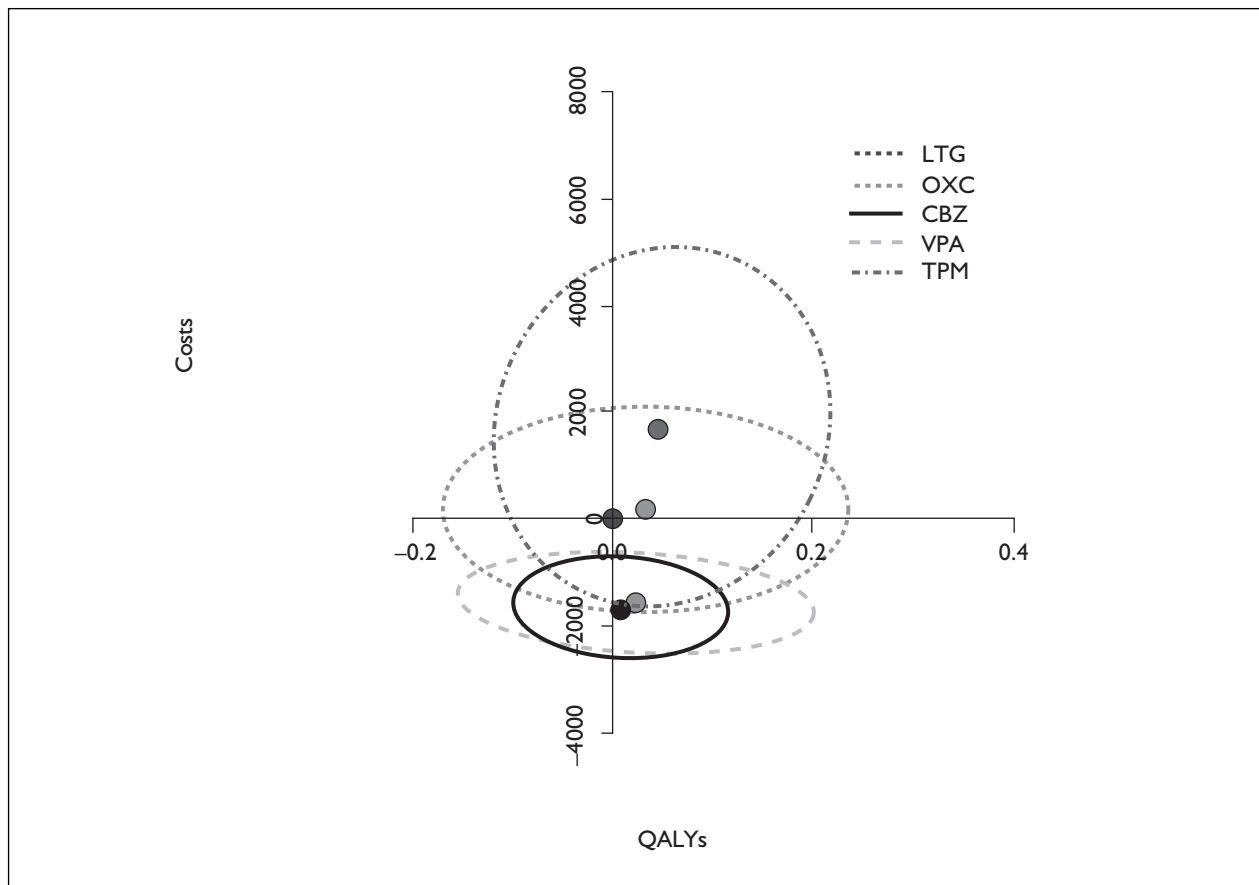
**Allowing for uncertainty** The 95% CIs for costs and effects are shown in Table 91. The 95% confidence ellipses for differences in cost and effects for the various treatments are shown in Figure 31. The ellipses show there is considerable overlap in the estimated mean cost and effects for the various treatments based on the available data. Figure 32 shows the CEACs for monotherapies for newly diagnosed patients. At a threshold willingness to pay for an additional QALY of £30,000, the older AEDs have a probability of 36–41% and the newer AEDs 2–16% of being the most cost-effective option.

**Monotherapy for refractory patients**

Only two trials were identified that considered the effectiveness of monotherapy for refractory patients (see Table 92).<sup>112,122</sup> For this reason, the AEDs considered in this analysis are limited to CBZ, VPA and LTG.

**Deterministic results** Mean costs and QALYs and the deterministic CEA are shown in Table 92. CBZ and VPA therapies are both significantly less costly





**FIGURE 31** Expected values and 95% confidence ellipses for incremental costs and benefits of first monotherapy AEDs compared with LTG

than LTG, owing to lower costs of the AEDs. CBZ therapy delivers slightly higher QALY gains on average and, therefore, dominates VPA and LTG.

*Allowing for uncertainty* The 95% confidence ellipses for incremental costs and benefits, relative to LTG, are shown in *Figure 33*. The CEACs in *Figure 34* show that CBZ is the preferred second-line monotherapy compared with LTG in more than 75% of simulations with a threshold willingness to pay of £30,000. However, if a patient has previously failed to respond to CBZ, or CBZ were contraindicated for any reason, LTG may well be cost-effective as a monotherapy for refractory patients. Comparative data were not available to estimate the cost-effectiveness in this situation.

#### **Combination (adjunctive) therapy for refractory patients**

*Deterministic results* *Table 93* shows the results of the deterministic CEAs for combination therapies for refractory patients. Monotherapy (placebo) has the lowest mean cost overall and GBP the lowest mean cost among the newer AEDs. All AEDs offer

slightly higher mean QALY gains than monotherapy. Based on estimated means, treatment of all (or a proportion) of the patient population with OXC dominates (or extendedly dominates) other therapies. The ICER is £17,095 per QALY gained compared with monotherapy.

*Allowing for uncertainty* *Figure 35* shows expected values and 95% confidence ellipses for the incremental costs and benefits of the treatments compared with no concomitant drug therapy (placebo). This shows the uncertainty in the cost-effectiveness estimates. This is also demonstrated in the CEAC (*Figure 36*), which shows that OXC is the most cost-effective therapy in 65% of simulations when the willingness to pay for an additional QALY is £30,000. However, this does mean that 35% of simulations showed that one of the other treatments was more cost-effective.

*Excluding oxcarbazepine and lamotrigine* *Table 94* represents the situation where LTG and OXC have already been tried as monotherapy and probably would not additionally be considered for as an adjunctive therapy. In these circumstances, other

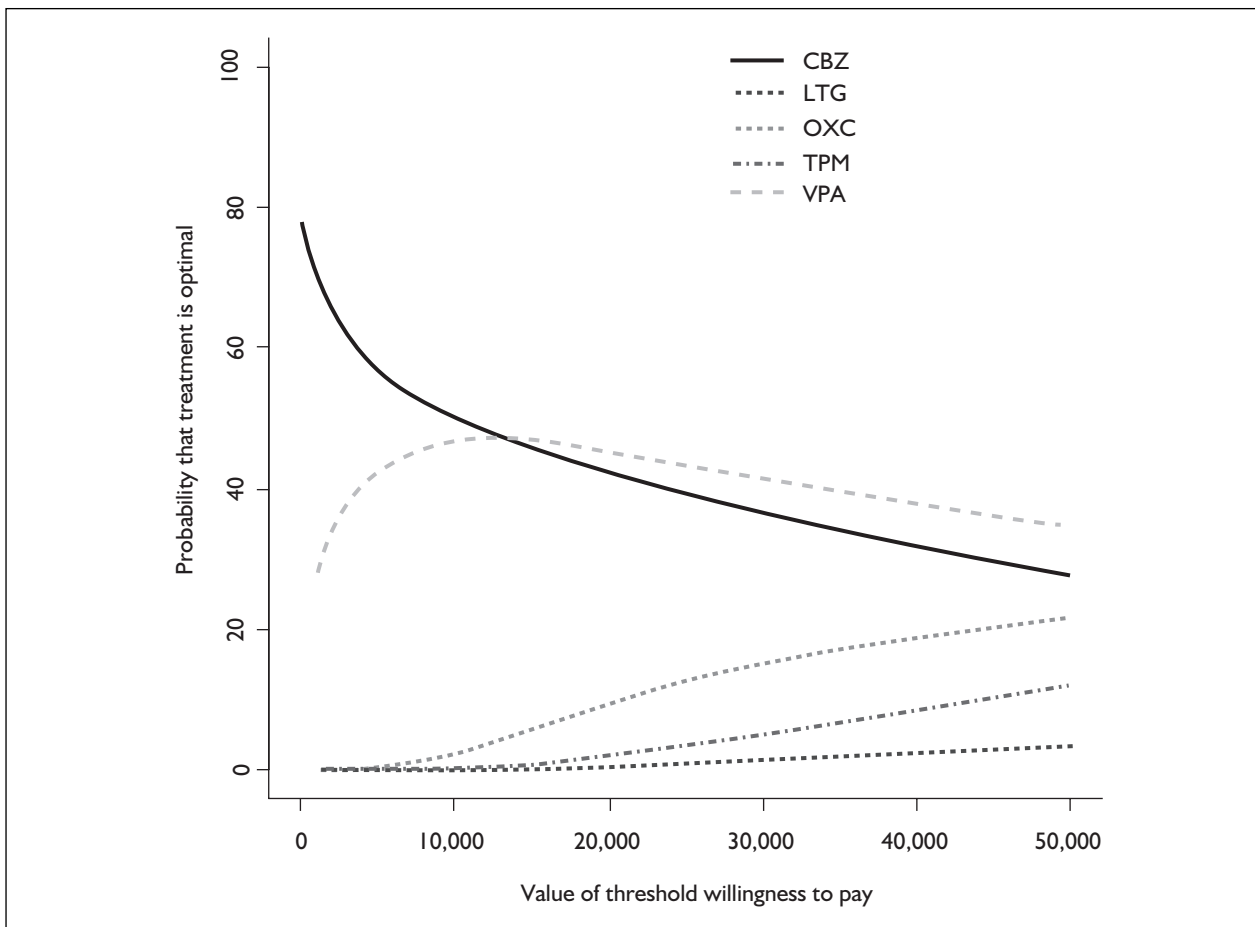


FIGURE 32 CEACs of monotherapy AEDs for newly diagnosed patients

TABLE 92 CEA of 'monotherapy for refractory patients'

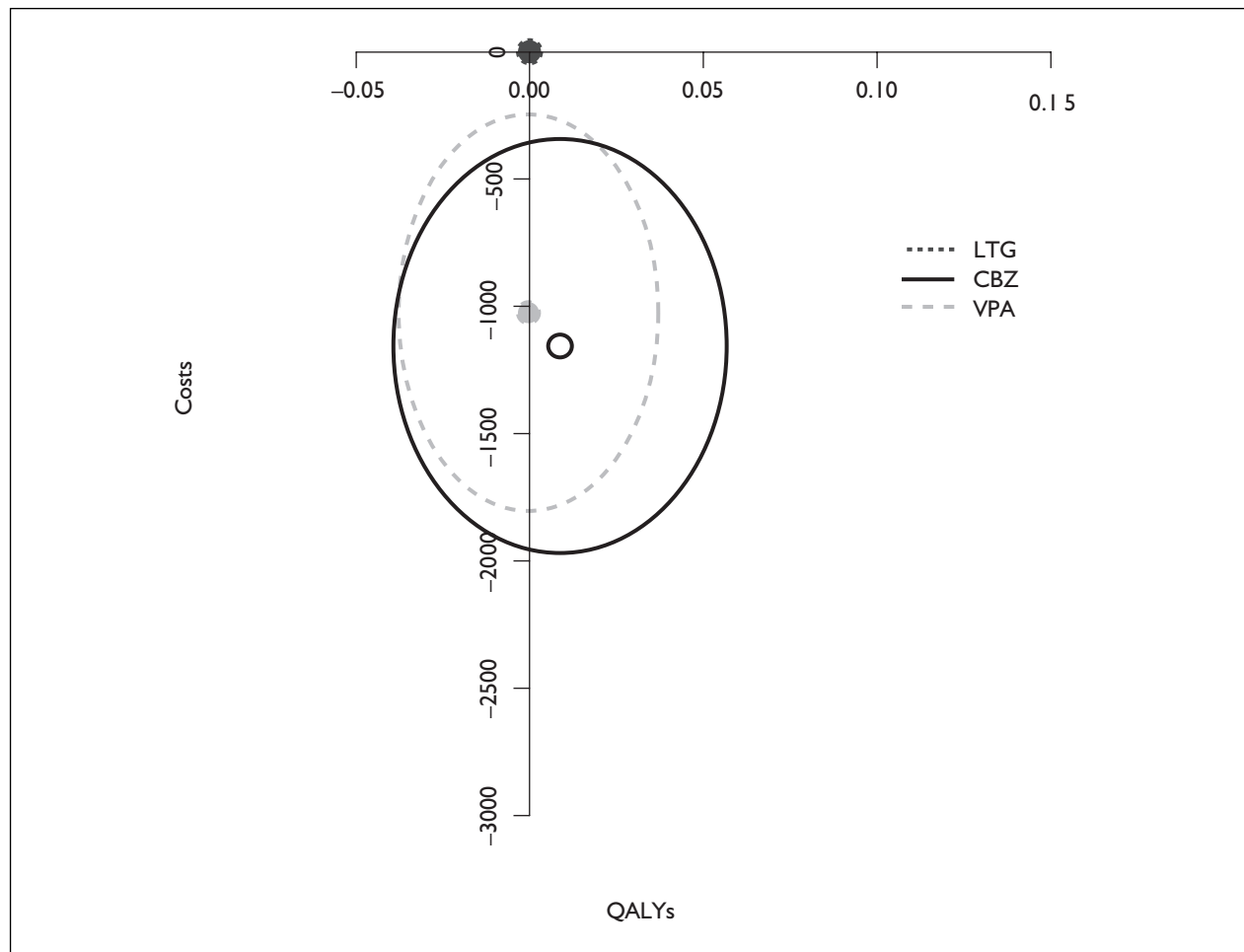
Therapy	Cost: mean (95% CI) (£)	QALY: mean (95% CI)	ICER (£)
CBZ	5599 (5407 to 5833)	8.865 (8.393 to 9.265)	–
VPA	5728 (5526 to 5966)	8.856 (8.380 to 9.261)	Dom
LTG	6749 (6245 to 7410)	8.856 (8.380 to 9.261)	Dom
Dom, dominated.			

therapies are more cost-effective. TGB has an ICER of £25,473 compared with placebo and TPM has an ICER of £47,528 compared with TGB. Other therapies are extendedly dominated. Figure 37 shows the CEACs for these options. There is greater uncertainty about the treatment decision compared with the situation where OXC was an option for combination therapy. At low values of willingness to pay for an additional QALY, placebo is most likely to be cost effective (i.e. patients would be continued on their monotherapy alone). When the willingness to pay is £30,000, the probability that placebo is cost-effective is 31%

and the probability any given adjunctive AED is cost-effective is between 15 and 22%.

**Sensitivity analyses**

*Discount rate* The probabilistic nature of the analyses above deals with parameter uncertainty, that is, the results reflect the imprecision in parameter estimates. There is uncertainty in other variables the importance of which is assessed using standard sensitivity analysis. Univariate sensitivity analyses were carried out by changing the discount rate for benefits from 1.5% to 0% and 6%. Table 95 shows the sensitivity of the ICER of monotherapy



**FIGURE 33** Expected values and 95% confidence ellipses for incremental costs and benefits of second-line monotherapy AEDs compared with LTG

for newly diagnosed patients and the ICER of combination therapy for refractory patients to changes in the discount rate. The decision about whether the therapies are cost-effective is robust to changes in the discount rate.

*Choice of monotherapy for refractory patients and combination therapies* The sensitivity analysis also considered how different choices of second- or third-line therapy would affect the cost-effectiveness of the monotherapies. The base case used monotherapy CBZ as second-line and adjunctive GBP as third-line therapies. Results are presented for the alternative scenarios of VPA as second-line, LMT as third-line or no adjunctive therapy (placebo) as third-line therapy. Using VPA as second line increases the expected costs by about £85–107 per patient over the lifetime of the model and reduces the QALYs gained by 0.006 for each therapy compared with the base case (Table 96). Using LMT as third-line therapy increases costs by about £68–89 and increases

QALYs by about 0.005. Using placebo as third line reduces costs by about £334–372 and reduces QALYs by 0.013. In each scenario, the ranking of first monotherapies seen in Table 96 does not change. Therefore, the choice of VPA as first monotherapy is robust to subsequent decisions about second- and third-line therapies in this model.

*Treatment costs for patients who fail combination therapy* Lhatoo and colleagues<sup>270</sup> estimate that 30% of patients who start third-line therapy will fail on this treatment. The base case assumes that these patients receive a treatment whose cost is equivalent to monotherapy with an older AED. Sensitivity analysis tested the robustness of the results to this assumption by maintaining patients who failed combination therapy with a new adjunctive therapy costing £1753 per year, but maintaining patients who failed third-line monotherapy (placebo) with a subsequent monotherapy. This alternative assumption does

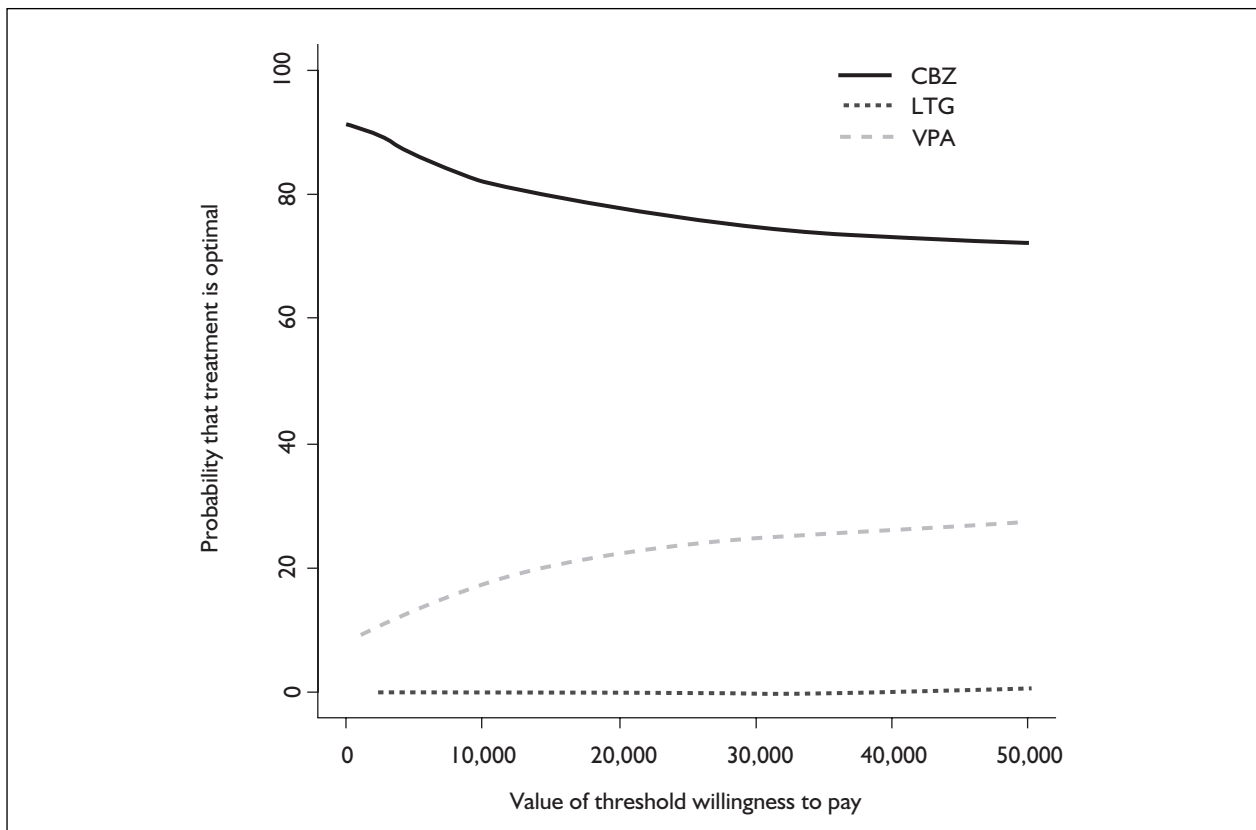


FIGURE 34 CEACs of monotherapy AEDs for refractory patients

TABLE 93 Cost-effectiveness of combination therapies for refractory patients

Therapy	Cost mean (95% CI) (£)	QALY: mean (95% CI)	ICER (£)
PLA	5064 (5064 to 5064)	8.716 (8.111 to 9.229)	–
GBP	5861 (5637 to 6156)	8.747 (8.176 to 9.238)	Ex Dom
LTG	5926 (5601 to 6358)	8.746 (8.172 to 9.234)	Ex Dom
TGB	6133 (5748 to 6624)	8.758 (8.195 to 9.240)	Ex Dom
OXC	6400 (5699 to 7423)	8.794 (8.266 to 9.247)	17,095
LEV	6984 (6094 to 8173)	8.775 (8.232 to 9.243)	Dom
TPM	7026 (6324 to 7902)	8.777 (8.236 to 9.243)	Dom

Dom, dominated; EX Dom, extendedly dominated.

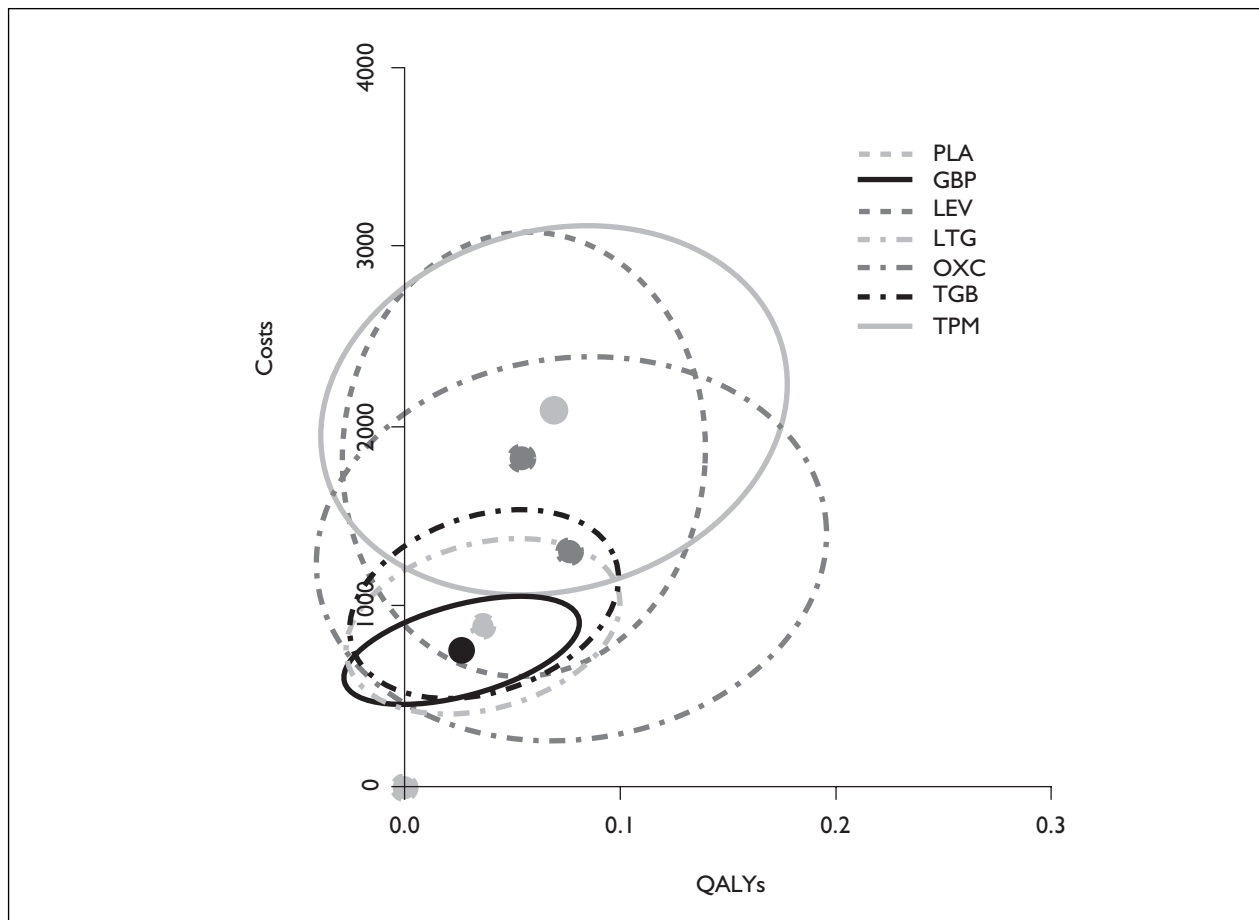
not change the ranking of the results for combination therapy compared with the base case. Costs for all adjunctive therapies increase by £10,800 over the time horizon of the model, whereas costs for monotherapy only remained unchanged. The ICER for adjunctive OXC compared with monotherapy increased from £17,095 to £158,432.

*Annual cost of healthcare for patients who are not seizure free* The base case assumes healthcare costs of £469 per year for patients who are not seizure free. This may be a conservative estimate. Janssen-

Cilag<sup>218</sup> estimated mean annual healthcare costs of up to £1533 for these patients. The costs of monotherapy increased by between £5500 and £5800 for all therapies, but the ranking of monotherapy AEDs for cost-effectiveness remained unchanged compared with the base case.

#### Results for generalised seizure-type patients

Results are presented for monotherapy for newly diagnosed patients and for combination therapy. There were no clinical trial data available for monotherapy for 'refractory' patients. Only trials



**FIGURE 35** Expected values and 95% confidence ellipses for incremental costs and effects of adjunctive therapies for refractory patients compared with no concomitant therapy (placebo)

that exclusively considered patients experiencing generalised seizures were included in the analysis.

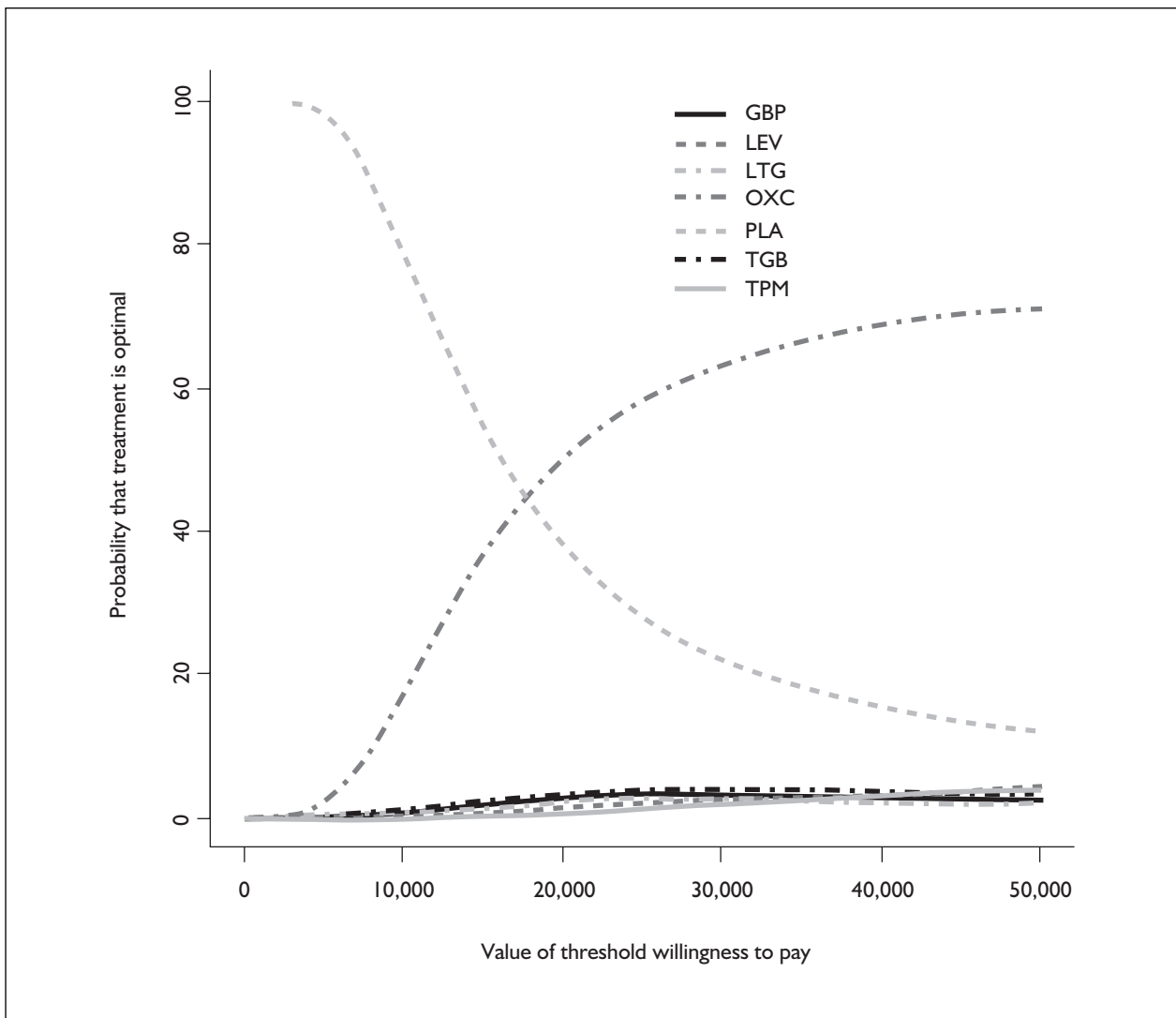
#### Monotherapy for newly diagnosed generalised seizure patients

Table 97 shows the CEA of LTG versus VPA, assuming that TPM was used as the adjunctive therapy for patients who failed monotherapy. Based on the mean estimates of cost and effects, VPA is cheaper and no less effective and, therefore, dominates LTG therapy. The ranking of the monotherapies was not changed when it was assumed that combination therapy was not used for treatment failures. Figure 38 shows the 95% confidence ellipse for the incremental cost and effect of VPA compared with LTG. The CEACs for the two therapies (Figure 39) show that VPA is preferred to

LTG in at least 94% of simulations if the willingness to pay for an additional QALY is less than £50,000.

#### Combination therapy for refractory generalised seizure patients

Table 98 shows the CEA of combination therapy for refractory patients. Based on the estimated means, TPM is significantly more costly than placebo but is more effective. The ICER of TPM compared with placebo is £34,417. Figure 40 shows the 95% confidence ellipse of incremental costs and effects of TPM compared with placebo. Figure 41 shows the CEACs for combination therapy. If the willingness to pay for additional QALYs is about £30,000, then there is a 41% probability that TPM is cost-effective, showing that the decision is highly uncertain.

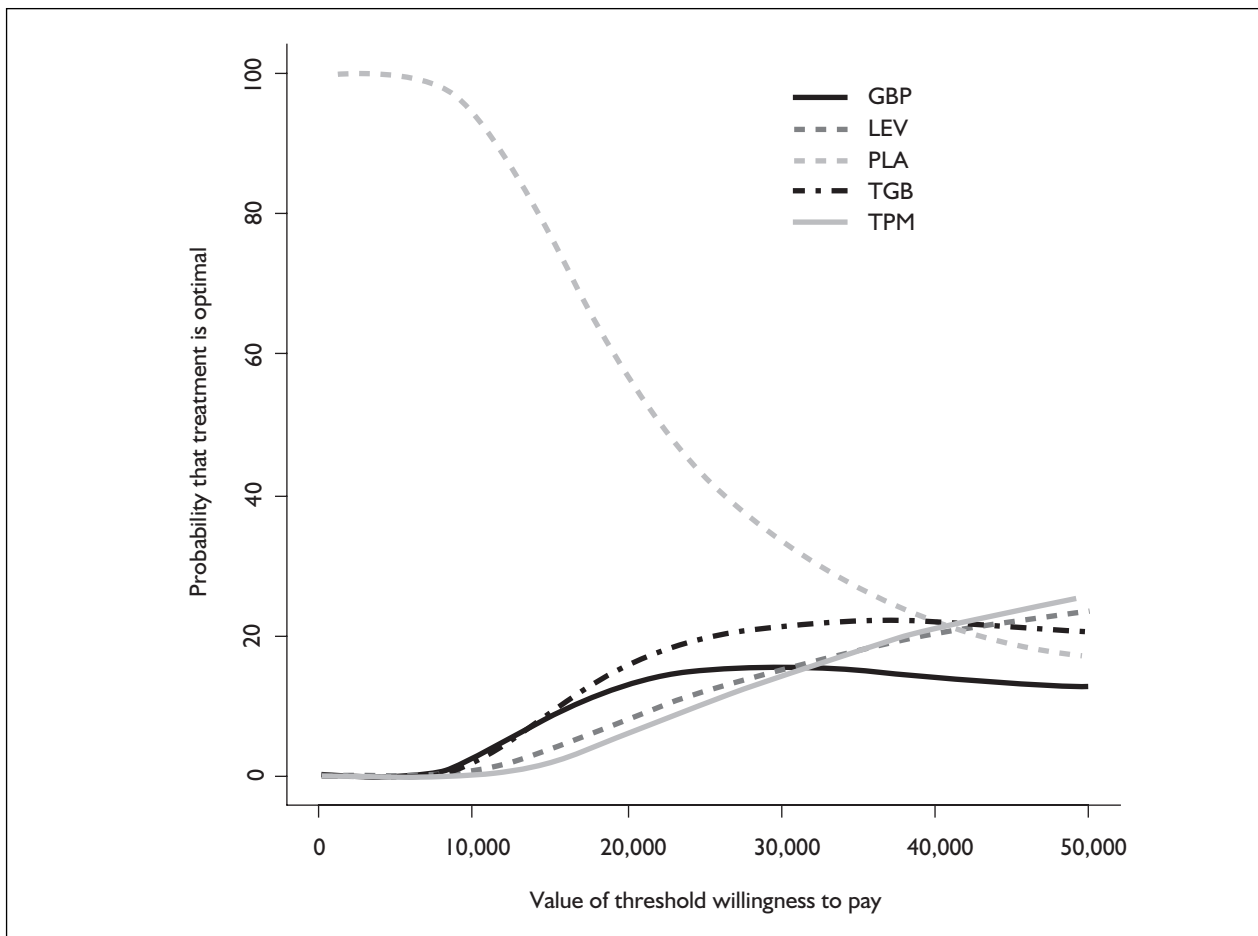


**FIGURE 36** CEACs for adjunctive therapy AEDs

**TABLE 94** Cost-effectiveness of combination therapies for refractory patients (assuming OXC and LTG are excluded because they have been previously used as monotherapies)

Therapy	Cost: mean (95% CI) (£)	QALY: mean (95% CI)	ICER (£)
PLA	5064 (5064 to 5064)	8.716 (8.111 to 9.229)	–
GBP	5861 (5637 to 6156)	8.747 (8.176 to 9.238)	Ex Dom
TGB	6133 (5748 to 6624)	8.758 (8.195 to 9.240)	25,473
LEV	6984 (6094 to 8173)	8.775 (8.232 to 9.243)	Ex Dom
TPM	7026 (6324 to 7902)	8.777 (8.236 to 9.243)	47,528

Ex Dom, extendedly dominated.



**FIGURE 37** CEACs for adjunctive therapy AEDs assuming LTG and OXC are excluded because they have been previously used as monotherapies

**TABLE 95** Sensitivity of ICERs of ‘first monotherapy’ and ‘combination therapy’ to changes in discount rate for QALYs

Discount rate (%)	First monotherapy	Combination
	ICER of TPM vs VPA (£)	ICER of OXC vs placebo (£)
0	113,907	15,963
Base case (1.5)	126,519	17,095
6	170,114	20,750

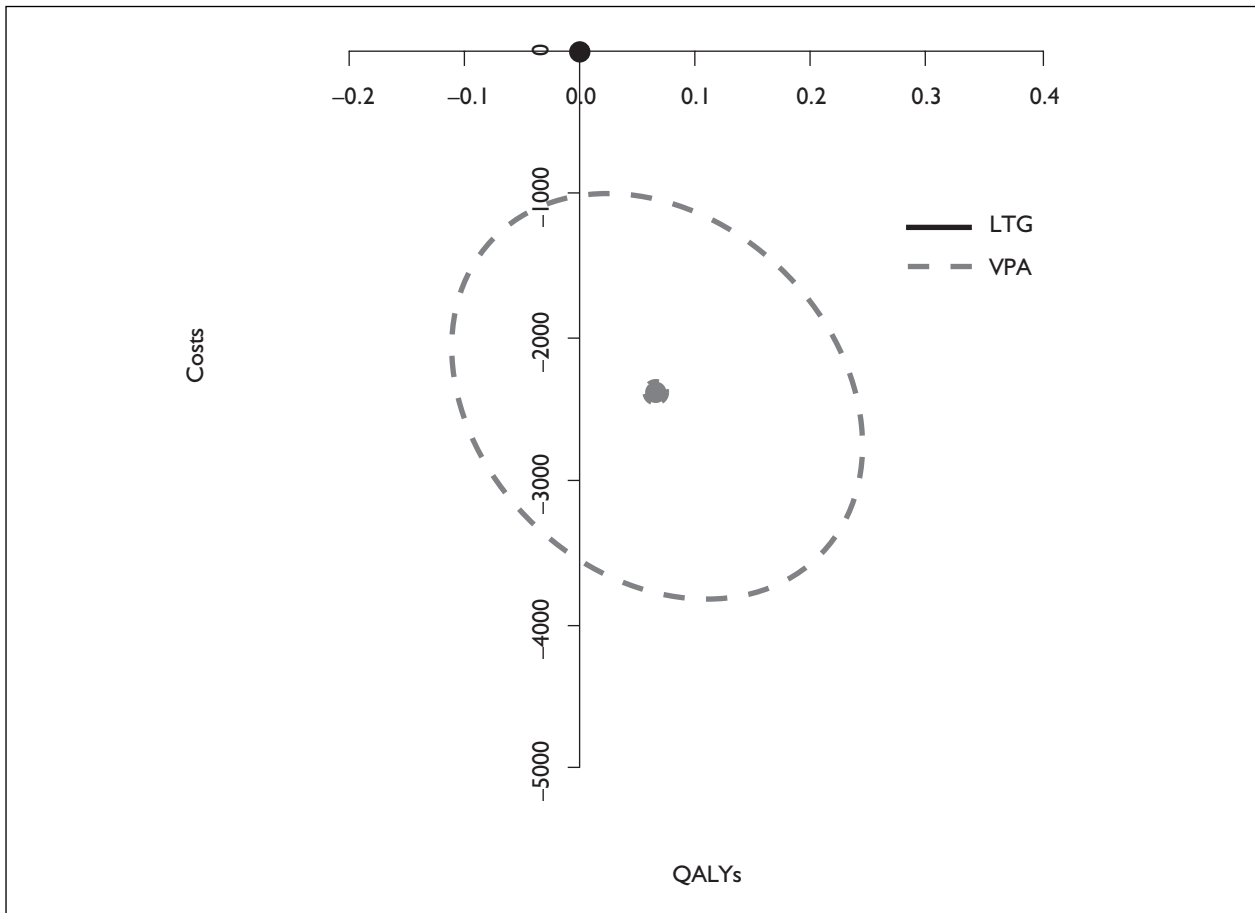
**TABLE 96** Changes to cost-effectiveness (ICER) of monotherapy for newly diagnosed patients compared with base case assuming alternative second- and third-line therapies

Drug	Base case (£)	Monotherapy VPA 2nd line (£)	Monotherapy 3rd line (£)	Adjunctive LMT 3rd line (£)
CBZ	–	–	–	–
VPA	11,731	11,483	11,838	11,967
LMT	Dom	Dom	Dom	Dom
OXC	Ex Dom	Ex dom	Ex dom	Ex dom
TPM	126,519	126,383	123,435	126,142

Dom, dominated; Ex Dom, extendedly dominated.

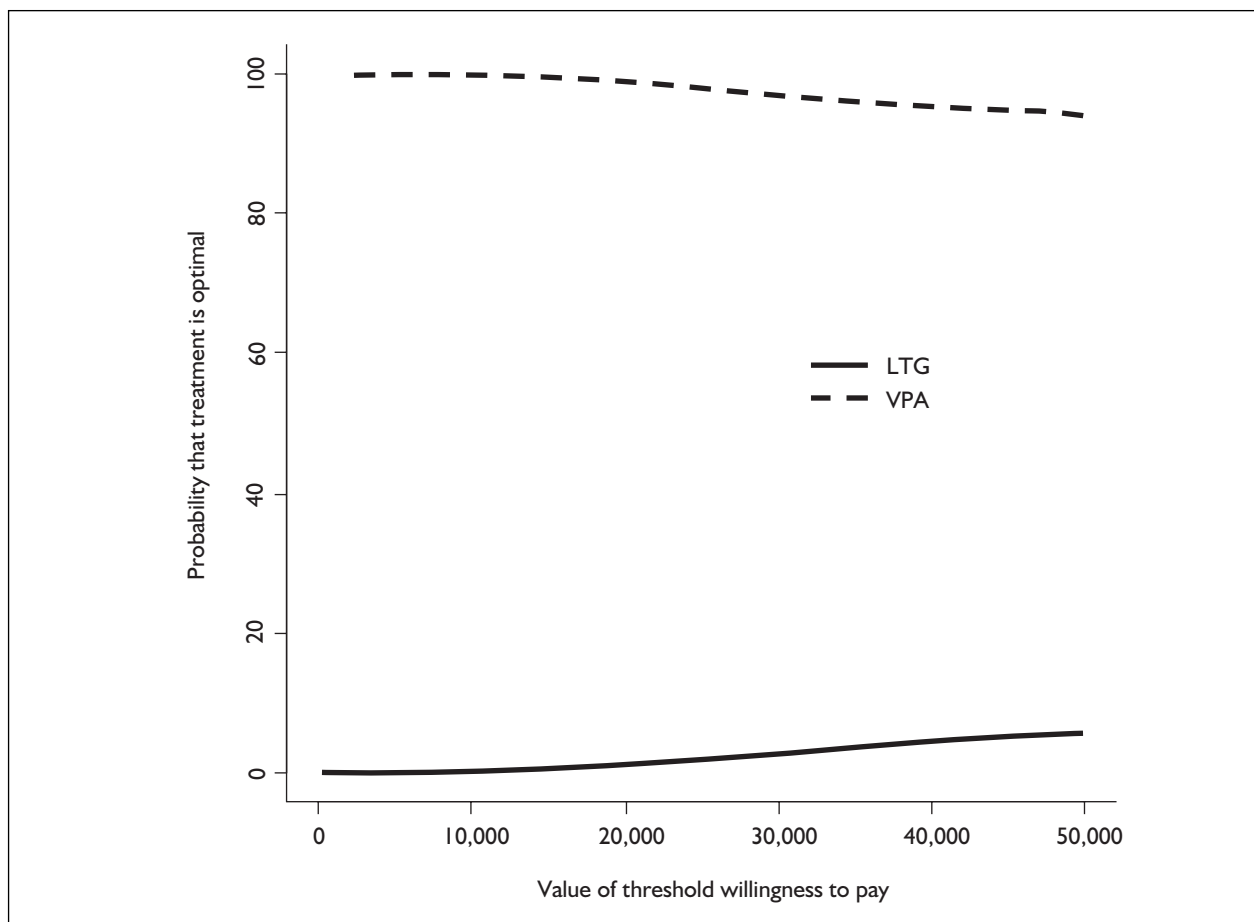
**TABLE 97** CEA of monotherapy in newly diagnosed patients with generalised seizure type

Therapy	Cost: mean (95% CI) (£)	QALY: mean (95% CI)	ICER (£)
VPA	4288 (3817 to 4808)	9.814 (9.357 to 10.178)	–
LTG	6675 (5729 to 7754)	9.748 (9.307 to 10.101)	Dom
Dom, dominated.			



**FIGURE 38** Expected values and 95% confidence ellipse for incremental costs and effects of VPA relative to LTG for monotherapy in newly diagnosed patients with generalised seizures

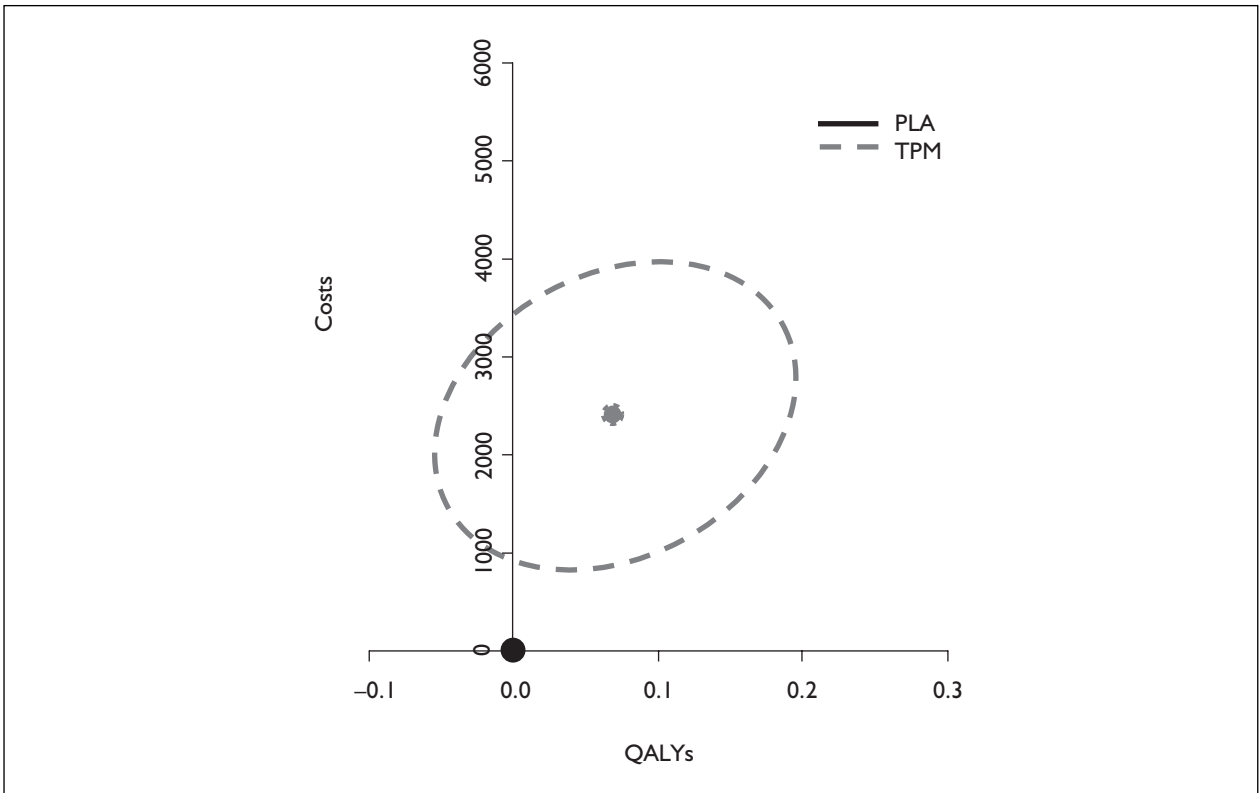




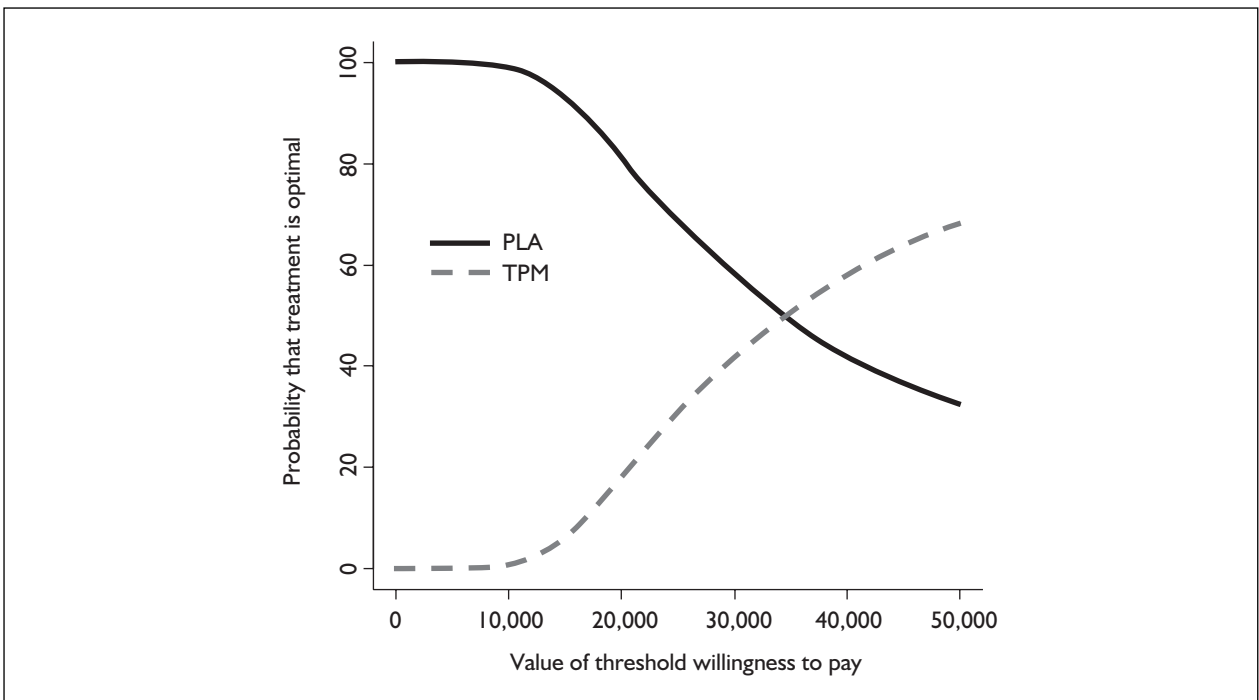
**FIGURE 39** CEACs of monotherapy for generalised seizure patients

**TABLE 98** CEA of combination therapy in refractory generalised seizure type patients

Therapy	Cost: mean (95% CI) (£)	QALY: mean (95% CI)	ICER (£)
PLA	5064 (5064 to 5064)	8.737 (8.164 to 9.231)	–
TPM	7471 (6388 to 8877)	8.807 (8.286 to 9.246)	34417



**FIGURE 40** Expected values and 95% confidence ellipse of incremental costs and effects of TPM combination therapy compared with placebo in refractory generalised seizure-type patients



**FIGURE 41** CEACs of combination therapy in generalised seizure-type patients

**Summary of results of integrated economic evaluation***Partial seizure type*

For the treatment of newly diagnosed patients with monotherapy, the analysis showed similar health benefits for the various AEDs and that the newer AEDs were more expensive than the older therapies. CBZ or VPA was cost-effective up to a threshold willingness to pay per QALY of £127,000, above which TPM was the most likely, although only by a small margin, therapy to be cost-effective. There was considerable uncertainty in these results.

There were few data available about the use of AEDs as monotherapy for refractory patients. The analysis showed that the various AEDs had similar effectiveness and that the newer AEDs were more expensive than the older AEDs. The analysis suggested that, compared with VPA and LTG, CBZ, when indicated, was the treatment most likely to be cost-effective for refractory patients.

The analysis indicated that the newer AEDs used as adjunct therapy for refractory patients were more effective and more costly than continuing with the patients' existing treatment alone. Combination therapy may be cost-effective at a

threshold willingness to pay per QALY greater than £20,000 provided that patients revert to monotherapy should adjunctive therapy prove ineffective. The exact value of this threshold depends on the patients' previous treatment history. There was considerable uncertainty about this conclusion.

Univariate sensitivity analysis showed that the results were robust to different assumptions about discount rates, different second- and third-line therapies should monotherapy fail and the cost of maintenance therapy for highly refractory patients.

*Generalised seizure type*

There were few data available to determine the effectiveness of treatments for patients experiencing generalised seizures. LTG and VPA showed similar health benefits when used as monotherapy. VPA is less costly and found likely to be cost-effective compared with LTG. TPM used as an adjunct therapy for refractory patients was found to be more effective and more costly than continuing with current treatment alone. TPM may be cost-effective as adjunct therapy if the threshold willingness to pay is greater than £35,000, but there was considerable uncertainty in these results.

# Chapter 4

## Discussion

The aim of this review was to assess the clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults. Epilepsy is a complex disease that is responsible for considerable morbidity and mortality, affecting over 400,000 individuals and causing over 1000 deaths per year within the UK.<sup>7</sup> Implications of the disease and the subsequent impact of treatment often have serious consequences for the individuals affected and their families.<sup>12</sup>

Initial treatment approaches focus on drug therapy, either monotherapy or adjunctive. In the event of drug treatment failure, surgery might be considered but is limited to a very specific group of patients. Drug therapy is, therefore, the mainstay of treatment. Because many individuals can require many years', if not lifelong, treatment with AEDs, the clinical effectiveness, tolerability and cost-effectiveness of drug therapy are major considerations.

A number of drug therapies are licensed for the treatment of epilepsy in adults, although many are limited to specific types of epilepsy and therapy regimens.<sup>4,5</sup> Treatment with a number of older AEDs, including CBZ, PHT and VPA, has been available for a number of years. In recent years, newer AEDs have emerged. This review focused on seven of the newer drugs with the aim of determining their clinical effectiveness, tolerability and cost-effectiveness compared with conventional older drug therapies and to each other.

### Clinical effectiveness and tolerability

#### The evidence

##### Monotherapy

Monotherapy is currently recommended for the initial treatment of patients with newly diagnosed epilepsy. Only after subsequent monotherapies have failed are adjunctive therapies considered, as this increases the chance of drug interactions and toxicities. Of the newer AEDs, only LTG and OXC are currently licensed for monotherapy in newly diagnosed patients. TPM should become licensed for monotherapy in newly diagnosed patients in

spring 2003 and hence has also been considered in this review. LTG is licensed for the treatment of both POSs and generalised onset seizures; OXC is only licensed for POSs.

One important clinical question for the treatment of newly diagnosed patients is whether LTG, OXC and TPM are more effective than older AEDs. This review found insufficient evidence from good-quality clinical trials to answer this question. Evidence to support the use of OXC over older AEDs such as VPA, CBZ and PHT was limited and few significant findings from good-quality trials were reported with regard to any of the outcome measures considered in this review. Similarly, there was insufficient evidence from good-quality trials to assess clinical effectiveness and tolerability of newer AEDs compared with older AEDs: only one poor-quality RCT compared TPM monotherapy with older AEDs. A greater number of studies focused on the use of LTG in monotherapy, but only one considered the treatment of generalised onset seizures. The greater number of LTG trials probably reflects the fact that this drug has been available for a longer period of time. However, this review found few consistent statistically significant differences between LTG and the older AEDs, with the exception of a small number of differences in QoL. It remains unclear whether LTG is more or less effective, especially in the treatment of generalised onset seizures.

As to whether one newer drug is more effective than another for treating newly diagnosed patients, only one study investigated this question by comparing LTG monotherapy with GBP monotherapy. Given that GBP is not licensed for use in monotherapy, the clinical applicability of this study is limited. Otherwise, evidence to support the use of one monotherapy AED over another is lacking.

A trend was observed in favour of OXC monotherapy compared with placebo for the proportion of seizure-free patients and the time to event outcomes. However, the significance of this finding to clinical practice is unclear as no treatment is an unlikely option for the majority of adult patients.

### **Adjunctive therapy**

Patients who fail successive monotherapy treatments are classified as refractory and the options for AED therapy switch to adjunctive therapy. All seven of the newer AEDs under investigation in this review are licensed for adjunctive therapy in POSs. Over half of the trials of adjunctive therapy specifically considered the treatment of POSs. Only LTG and TPM are licensed for generalised onset seizures. However, only one trial of adjunctive LTG specifically considered the treatment of generalised onset seizures. No trials of adjunctive TGB specifically recruited patients with generalised onset seizures. The remaining trials considered mixed populations of seizure types.

This review found insufficient evidence from good-quality clinical trials to support the use of any of the newer AEDs versus older AEDs. Evidence was limited both by the amount of data and by the lack of any consistent statistically significant differences between newer and older AEDs in most of the outcome measures considered in this review. There was limited evidence to suggest that both LTG and GBP may have some beneficial effect on behaviour in people with learning disabilities. Very few trials compared newer AEDs with other newer AEDs and so there was insufficient evidence to determine whether one newer drug is more effective than another. A trend was evident in favour of newer drugs compared with placebo.

### **Strength of the evidence**

Extensive literature searches were used to identify both published and unpublished data for inclusion in the clinical effectiveness and tolerability sections of this review. Owing to the difficulties in identifying data concerning serious, rare and long-term AEs, some data may have been omitted. Similarly, owing to time limitations data from non-English language publications could not be included in any part of this review.

The strength of the clinical evidence relating to newer AEDs is reflected not only in the quantity and findings of studies but also in the methodological quality of the studies. Reporting of methods of randomisation, allocation concealment and blinding was often inadequate; therefore, it is not possible to be sure that adequate measures were taken to minimise bias. A feature noted in some trials was that the investigators decided which baseline treatment each participant would take before randomisation to the experimental treatment or control. This practice may be open to

manipulation, however well intended. In addition, a small number of studies compared newer AEDs with lower than recommended doses of older comparator AEDs. This may bias the data in favour of the newer AED.

The majority of trials included in the review were parallel superiority trials. Crossover designs were also used but appropriately confined to adjunctive therapy in refractory patients, although some studies failed to incorporate an adequate washout period. Data from crossover studies were largely not reported in such a way that data from both the first and second phases could be used. This resulted in a loss both of statistical power and of the advantage of within-patient comparisons.

Few of the included studies recruited sufficient numbers of participants to fulfil ILAE recommendations (at least 100–150 participants). Numbers of participants in the included studies ranged from 10 to 877; only one-third of the trials included at least 150 patients. A sample size calculation sufficient to demonstrate a defined treatment effect was not always reported. Similarly, the duration of most trials also failed to meet ILAE recommendations (6 months to 1 year); only 10 studies reported a follow-up of at least 1 year. Some of the included trials continued into a single-treatment open-label extension phase; however, these data were beyond the scope of this review but some may have been included in the review of AEs.

Often study results were based on per protocol populations or were reported as ITT data when they were not based on true ITT populations. Data based on ITT populations presents a more conservative picture of the treatment effect, except in equivalence trials where they may suggest false equivalence. In order to allow all of the studies, regardless of the type of data they presented, to be considered in an equivalent manner, all data considered in this review were based on true ITT populations (i.e. all randomised participants analysed according to the treatment group to which they were originally allocated). This necessitated the recalculation of data in many cases. Recalculation was based on the assumption that missing patients were non-responders. Ideally, the impact of this assumption would be explored further in a sensitivity analysis using both worse-case (i.e. all missing patients considered as non-responders) and best-case (i.e. all missing patients considered as responders) scenarios. However, this was not possible in the time frame available.

Cognitive function and QoL were considered in both monotherapy and adjunctive therapy trials. However, both of these outcomes used a number of different assessment measures and scales, some of which were more rigorous than others. Some measures used to assess QoL were based on subjective evaluations, e.g. physician, investigator and patient global evaluations, and are therefore open to biases associated with subjective reporting. There are currently no guidelines as to which measures are the most appropriate in trials of epilepsy treatments.

Additional issues associated with the strength of evidence relating to cognitive effects were differences in dealing with practice effects (i.e. where there is improvement in performance due to increased familiarity with a test); a standard order of test administration (i.e. fatigue may affect performance in later tests); failure to report postictal status during assessments (i.e. postictal effects may confound test results) and failure to report impact of mood on cognitive performance (i.e. depression and anxiety can have a detrimental effect on cognitive performance); problems in interpreting multiple statistical comparisons when using a large number of cognitive measures. All of these issues may bias the results from cognitive assessments.

### **Applicability**

The included trials varied in the characteristics of the participants, the interventions and the outcome measures reported.

### **Population**

ILAE guidelines recommend that trials recruit sufficient numbers of participants with clinically relevant characteristics.<sup>283</sup> Monotherapy is recommended for the initial treatment of patients with newly diagnosed epilepsy and adjunctive therapy for refractory epilepsy.<sup>279</sup> In this respect, the majority of trials included in this review were conducted with appropriate patient populations. All of the newer AEDs are licensed for the treatment of POSSs. However, only LTG and TPM are licensed for the treatment of generalised seizures. Many of the trials did not solely recruit participants with seizure types appropriate to current licensed practice. In many cases trials of drugs licensed only for the treatment of POSSs, recruited mixed populations of POSSs and generalised onset seizures types. Outcome data were often not reported according to seizure type and so the clinical relevance of these trials is unclear.

A feature of any review of summary data is the limited capacity to explore the effects of individual patient characteristics on outcomes. Epilepsy is not a uniform condition and clinical trials recruit heterogeneous populations. Meta-analysis of individual patient data would better inform treatment of individual patients. However, collection and analysis of individual patient data require collaboration and commitment from those who conduct clinical trials.

A number of trials included in this review used a conditional response design, which is likely to affect the clinical relevance and applicability of the data. Such trials require that participants achieve a specified reduction in seizure frequency while undergoing AED treatment in the pretrial phase, in order to be included in the main assessment phase of the trial. Therefore, the trial only assesses patients who have a good chance of responding well to treatment. This is unlikely to apply to populations in clinical practice. Similarly, a small number of trials in this review included participants who were undergoing evaluation for surgical treatment. Surgery is a treatment option for some patients where AED treatment has proved particularly unsuccessful and problematic; however it is only appropriate for a very specific group of patients. Therefore, the applicability of data from such populations is limited.

This review focused on the treatment of adults (i.e.  $\geq 18$  years old). However, younger patients were often also included in some trials and it was not always possible to separate data according to age. Where data were available, this review also considered the treatment of certain subgroups of patients including the elderly, people with intellectual disabilities and pregnant women. The treatment of epilepsy in these groups of individuals is often problematic and in some cases the use of many AEDs is cautioned owing to potentially toxic effects. Only one study of LTG monotherapy considered elderly patients, although additional studies that addressed AEs did include these patient subgroups. Patients with intellectual disabilities were only considered in trials of adjunctive therapies and the majority did not report data separately for these patients. All of the identified RCTs excluded pregnant and breastfeeding women and women at risk of pregnancy. Overall, this review cannot comment on treatment within these specific groups of patients with epilepsy.

### **Treatment**

Various clinical practice guidelines recommend

treatment pathways for monotherapy and adjunctive therapy of epilepsy including which AEDs should be used. However, this review did not find convincing evidence to inform decisions as to which is the most appropriate AED to use. With regard to clinical practice, it is important that trials use doses of drugs that are clinically appropriate and within licensed ranges. In this review, studies of LTG and TGB sometimes used doses that exceeded those recommended in the UK. Use of lower than recommended doses was unusual. In addition, many trials involved a titration period during the whole of which time patients may not have been receiving an effective dose of the drug. This makes interpretation of the data difficult, but does reflect clinical practice. Ideally, the impact of different doses of drugs would have been explored further in a logistic regression analysis. However, this was not possible within the time frame of this review.

### **Treatment effect**

The aim of most monotherapy AED regimens is freedom from seizures. ILAE guidelines for monotherapy trials recommend time to trial exit/withdrawal because of inadequate drug efficacy and/or poor tolerability as the most useful measure of effectiveness to inform clinical practice.<sup>284</sup> However, the most commonly reported outcome measure reported in the studies included in this review was the proportion of seizure-free participants. Less than half of the monotherapy trials provided data for time to exit/withdrawal. Time to first seizure was more commonly reported; however, the ILAE argue that the time to achieve 6 months, 1 year or 2 years of remission has greater clinical significance (unless the population has infrequent seizures, as in newly diagnosed epilepsy). None of the trials reported these outcomes.

In adjunctive therapy, time to exit/withdrawal for the study is also the most satisfactory measure of effectiveness. However, change in seizure frequency (percentage responders) may also be a useful measure for refractory patients. The majority of the included trials did provide data for this outcome.

Outcomes such as the proportion of participants seizure free were recorded at different time points in different studies. It is possible that investigators could have selected the time point that best illustrated the effectiveness of the favoured treatment. Where possible, the actual time points used in each study were stated, and pooling of

data collected at widely varying follow-up points was avoided.

### **Benefit versus harm**

This review has shown no evidence of significant benefit in epilepsy outcomes with LTG, OXC and TPM monotherapy compared with older AEDs and with other newer AEDs. Only one newer drug (OXC) showed any evidence of improved effect over placebo. There was limited evidence that LTG and OXC improved some aspects of QoL and cognitive function compared with older drugs.

This review showed evidence of some benefit in epilepsy outcomes with LEV, OXC, TGB, TPM or VGB added to existing therapy versus placebo, but studies of QoL and cognitive function did not reflect similar benefits. There was no evidence that any newer drug in adjunctive therapy conferred more benefit in any outcome than the other newer drugs or older drugs.

Less can be concluded about the risks of harm because evidence from RCTs was lacking and observational studies rarely included comparisons between drugs. Observations of serious AEs were not generally convincing of causality, with the exception of some effects of which both manufacturers and clinicians are already aware.

### **Comparison with previous reviews**

All of the previous systematic reviews considered in this current review were Cochrane reviews. The evidence available from the Cochrane reviews was limited to comparisons of adjunctive treatment with placebo in refractory patients with POSs. Similar outcomes were reported in the Cochrane systematic reviews, but they did not address serious, rare and long-term AEs. However, in the majority of cases previous reviews did consider the effects of dose (logistic regression analysis) and included sensitivity analyses to test best- and worst-case scenarios with respect to missing data, which was not done in this review. In the majority of cases, worst and best-case scenarios showed similar effects, although discrepancies were observed with GBP. Planned regression analyses were often not performed owing to lack of data, but where available dose effects were reported for GBP and LEV.

Overall, the previous Cochrane reviews reported similar findings to this review, that is, that newer adjunctive AEDs appeared to be more effective than placebo, but evidence regarding long-term efficacy was limited.

## Cost-effectiveness

### The evidence

#### Published monotherapy studies

Despite the differences in methodology between the four studies, the findings were remarkably similar: even if the most optimistic treatment scenario for the newer drugs is compared against the worst-case treatment scenario for the older drugs, monotherapy with the older drugs is considerably less costly.

All four studies concluded that the newer drugs should not be used as first-line therapy for the treatment of newly diagnosed patients. However, one study indicated that LTG might be a good option for patients whose epilepsy is poorly controlled or who are unable to tolerate the older drugs.

All of the published studies considering monotherapy used a CMA design. The *a priori* assumption that therapies are equally effective is not appropriate since the effect of the drugs on QoL requires consideration of the interaction between seizure control and AEs. This is taken into account in the integrated analysis presented above.

#### Published adjunctive therapy studies

Just two studies compared older and newer adjunctive drugs head to head.<sup>260,262</sup> Both studies were CEAs, comparing both costs and outcomes. O'Neill and colleagues<sup>262</sup> found a clear cost-effectiveness advantage for the older drug (CLB) against the newer drugs (LTG and VGB). Schachter and colleagues<sup>260</sup> found that adjunctive TGB was less expensive (including the cost of managing AEs) but less effective than CBZ; compared with adjunctive PHT, TGB was more expensive and of similar clinical effectiveness. This study was reported only as a poster abstract and few details of the analysis were available. Therefore, it is not possible to perform a satisfactory assessment of its quality.

Three published evaluations compared newer adjunctive drugs with patients' current medication only. One of these considered VGB versus no adjunctive therapy. The paper was published before the serious side-effects associated with VGB were known. In the UK, the use of VGB is currently restricted to patients in whom all other combinations of AEDs are inadequate or not tolerated. Messori and colleagues<sup>261</sup> concluded that LTG was cost-effective if the threshold willingness to pay was greater than US\$41,000 per QALY. Markowitz and colleagues<sup>258</sup> estimated that the

ICER of adjunctive LTG was US\$7 per seizure-free day gained compared with continuing monotherapy. The main weakness of both of these evaluations was that they were based on the results of one or two randomised trials and extrapolated forward over the patients' lifetime using the assumption that outcomes at the end of the trial are maintained over the time horizon of the model.

Two published studies compared newer adjunctive AEDs with other newer AEDs. Hughes and Cockerell<sup>256</sup> presented a CMA that was not appropriate. Selai and colleagues<sup>257</sup> estimated that 15% of patients using TPM and 11% of patients using LTG were 'satisfied' with their treatment after 6 months, and that the cost per patient of TPM was £472 and LTG £587. The study was based on a small sample size and patients were not randomised to treatment.

None of the published economic evaluations satisfied all of the criteria for a robust economic evaluation of AEDs, one that considers all the treatment alternatives, takes a sufficient time horizon and uses a systematic method to collect evidence.

#### Company submissions

All of the submissions claimed that their therapy was cost-effective. The submissions used different comparators and a diverse range of health outcome measures; therefore, it was not possible to compare the results directly with one another. The main features felt to be essential to model the treatment decision were to provide a comparison between all of the relevant treatments, to incorporate QoL in the measure of health benefits, to allow for the possibility that the first- or even second-line therapy might fail, to use a systematic method to identify and synthesise evidence, to use an adequate time horizon, to take a broad NHS perspective and to use probabilistic sensitivity analysis to handle second-order uncertainty surrounding model parameters. Only two analyses achieved most of these criteria. The main weaknesses of even these more sophisticated evaluations was a lack of a systematic approach to obtaining and synthesising effectiveness data, and none of the models provided a comparison between all of the relevant drugs. This indicated the need for a model based on a comprehensive review of the evidence that allowed comparisons to be made between alternative therapies.

## Integrated economic model

The various published evaluations and industry



submissions used a variety of analytic methods, comparators and outcomes. A majority of the evaluations were based on CMAs which assumed equality of benefits and did not fully consider uncertainty in outcomes, or were CEAs that used a variety of outcome measures and therefore could not be compared. A small number of CUAs were conducted; these considered only a limited number of alternative treatments and trial results and did not fully consider uncertainty, especially in the extrapolation of the results of short-term trial data to longer periods of treatment.

Given the limitations in submitted and previously published economic evaluations, an integrated CEA was conducted. This analysis incorporated available information on the costs and effects associated with the various newer and older epileptic drugs and allowed direct comparisons to be made despite the limited number and scope of 'head-to-head' trials. To allow the cost-effectiveness of the various AEDs under consideration to be compared with therapies for other conditions, a CUA was undertaken.

The integrated CEA extrapolated from the individual short-term clinical trials to allow direct comparisons to be made between the various treatments based on predicted long-term benefits and costs. In order to allow these comparisons, data from a variety of sources were combined in the analysis and a number of assumptions were required. These are summarised below and should be borne in mind when considering the results of the analysis.

The first assumption relates to outcomes. AEDs may alter the intensity, frequency and pattern of occurrence of epileptic seizures. The impact of drug treatment on the QoL experienced by a patient will be a complex function of these various effects. The integrated economic analysis was limited to those reported clinical trial outcomes, seizure freedom and 50% reduction in seizure frequency that were common to all drugs and which could be interpreted in light of the available quality of life evidence. The estimates of the impact of seizure control on utility were based on a single small study.<sup>467</sup> An estimate of uncertainty was made based on the observed study data, but this does not account for potential variability between studies. As these utility estimates were common to all treatments being considered, the effect of this uncertainty on the estimates of differences in cost-effectiveness between treatments is likely to be limited.

A second assumption is that, in the absence of specific comparative long-term clinical trial data, we estimated the short-term effectiveness based on specific clinical trial data and the longer term effectiveness based on generic open-label study data. Although an estimate of uncertainty based on the observed trial data was incorporated in the analysis, no account was made of uncertainty arising from potential variability between studies and drugs. The generalisability of the clinical trial data should also be considered when reviewing the results of the analysis.

A third assumption is that, in the absence of direct 'head to head' comparisons between all the drugs included in the analysis, estimates of relative short-term effectiveness were based on data resulting from indirect comparisons which were incorporated into a statistical model. When making direct comparisons based on such indirect comparisons, it is not possible to exclude the effects of systematic differences between studies on the estimates of effectiveness. Although an estimate of uncertainty based on the observed differences between trials was incorporated in the analysis, uncertainty due to potential unobserved differences was not. To an extent, the effects of unobserved heterogeneity cannot be excluded from standard meta-analysis, and this form of evidence synthesis was felt to produce the best estimates of relative efficacy, which were required for the incremental CEA, based on the available clinical trial data.

A fourth assumption is that, owing to a lack of detailed observational and experimental data, our analysis included the use of a limited range of healthcare resource items, and the unit costs were assumed to be common to all drugs investigated. Most of the serious AEs are known to be rare so this should not affect the validity of any conclusions drawn. VGB and PHT were excluded from the analysis as it was felt that the side-effect profile of VGB and the narrow therapeutic index of PHT would not be adequately accounted for in the analysis.

A fifth assumption is that, given the lack of data regarding the mean dose of the AEDs used in normal practice, the uncertainty in dose was modelled based on plausible assumptions. A gamma distribution based on the maximum and minimum recommended dose in the BNF was used to reflect uncertainty. As, in general, the various treatments were found to have similar efficacy, the CEA will be sensitive to the assumptions drawn regarding drug price.

Finally, in the absence of sufficient specific data, the safety of the various drugs during pregnancy was not considered in our analysis.

Although it is important for these assumptions to be explicit and to be considered in interpreting results, the objective of the integrated analysis was to provide the most reasonable synthesis of available evidence and to quantify the uncertainty associated with existing evidence. The analysis of the treatment of patients experiencing partial seizures indicated that the various drugs used in monotherapy for newly diagnosed patients produced similar health benefits and that the newer AEDs were more expensive. Consequently, older AEDs were found most likely to be cost-effective. It is important to bear in mind that there is a great deal of uncertainty in this conclusion owing to the imprecision in the estimate of benefits. As the threshold willingness to pay increases above £30,000, it is not possible to determine which is the most cost-effective AED with any great degree of certainty. It is also possible that, even at low values of the willingness to pay per QALY, the newer AEDs may be cost-effective as monotherapy for the treatment of patients who have failed to respond to older AEDs. There were insufficient clinical trial data regarding the treatment of refractory patients to evaluate this.

The very limited trial data regarding monotherapy for refractory patients with partial seizures indicated that LTG, VPA and CBZ had similar effectiveness and that LTG was more expensive. The CEA indicated that CBZ was the most cost-effective treatment. However, LTG or VPA monotherapy may be cost-effective for patients who have failed to respond to CBZ. There were insufficient data on the use of other alternative newer or older AEDs for patients who are refractory to specific drugs to allow this to be investigated further.

The analysis of combination therapy for refractory patients with partial seizures indicated that the newer treatments were more effective and more costly than continuing with the patients' existing therapy alone. At low values of the threshold willingness to pay, combination therapy with newer AEDs was found not to be cost-effective. Combination therapy may be cost-effective, however, given a threshold willingness to pay for a QALY of £20,000 or more, provided that patients are discontinued from adjunctive drugs should they prove to be unsuccessful. The precise value depends on which treatment options would be

appropriate for an individual patient based on their previous treatment history. Sensitivity analysis showed it is not cost-effective to retain patients on an adjunctive therapy if seizure control proves to be inadequate. The analysis indicates that there was a great deal of uncertainty in this conclusion owing to the lack of precision in the estimate of treatment benefits. Although OXC had the greatest probability of being cost-effective compared with other adjunctive AEDs, the estimate for its effectiveness was based only on a single clinical trial.

The analysis of the treatment of patients experiencing generalised seizures indicated that LTG and VPA had similar efficacy and that treatment with VPA was less costly. The incremental analysis suggested that treatment with VPA was cost-effective compared with treatment with LTG. LTG monotherapy may be cost-effective, however, if VPA is contraindicated, or if patients have failed to respond to previous VPA treatment. There were insufficient data available to consider other alternative newer or older AEDs. The analysis indicated that TPM might be cost-effective when used as an adjunctive therapy, with an estimated ICER of £34,500 compared with continuing current treatment alone. The analysis did, however, indicate that there was a great deal of uncertainty in this estimate.

The integrated economic analysis presented may form the basis of further evaluations as more clinical trial evidence becomes available. In addition, value of information methods based on this model may provide a useful framework for setting priorities for future research in this area and for appropriately designing trials.

## Relevance to the NHS

At present there are a number of guidelines and recommendations for the treatment of epilepsy in adults.<sup>279,283,285-287</sup> NICE has recently issued guidelines about the diagnosis and management of epilepsy in adults. These recommend that monotherapy with an older AED should be the therapy of first choice and if seizures continue adjunctive therapy should be considered. Newer AEDs are recommended for those who have not responded to older drugs or where older AEDs are not suitable due to AEs, contraindications, interactions with other medications or where women are of childbearing age. The guidelines do not make recommendations about the selection or

sequence of AED therapy with regard to specific drugs within the classes of older and newer AEDs.

This review found no clear evidence from clinical trials to support the use of newer AEDs over older AEDs in first-line monotherapy or in adjunctive therapy. Similarly, there was little evidence to support the use of one newer AED over another.

Monotherapy using the newer AEDs is more expensive than monotherapy using the older AEDs, and the treatment of refractory patients with the new AEDs as adjunct therapy appeared to be more expensive than treatment with the patients' existing treatment alone. However, owing to the uncertainty in the estimates of clinical benefit, there is considerable uncertainty over whether any given therapy can be considered more cost-effective than another. Based on the economic evaluation, it may be reasonable to suggest the use of the older AEDs in preference to the newer AEDs unless there are clinical indications to the contrary. The newer AEDs may have a role where treatment with the older AEDs is contraindicated or where patients do not respond to the older AEDs.

Further research is ongoing to help clarify the clinical and cost-effectiveness of the newer AEDs. This may offer clearer evidence for the design of treatment pathways in clinical practice.

## Implications for further research

- More direct comparisons of newer versus newer and of newer versus older AEDs within clinical trials, taking into account different treatment sequences within both monotherapy and adjunctive therapy. An example of such a trial may be the SANAD trial, which is under way.
- Future trials of AEDs should be of good quality and appropriate design. In particular, adequate consideration needs to be given to the type of study design used, the interventions compared, the types of outcome measures used and the size and duration. Ideally, trials should adopt the ILAE guidelines on the design of trials.
- Trials should specifically recruit patients with either partial or generalised seizures. Only a limited number of the newer AEDs are licensed for the treatment of generalised onset seizures and the applicability of data relating to mixed groups of patients is unclear.
- More good-quality trials are required to investigate the effectiveness and cost-

effectiveness of monotherapy and adjunctive therapy in patients with generalised onset seizures. Very few trials considered this group of patients and the relevance of data relating to mixed groups of patients with different seizure types are unclear, especially where outcome data are not presented separately for the two groups.

- More good-quality trials are required to investigate the effectiveness of monotherapy and adjunctive therapy in specific populations of epilepsy patients. Caution is advised when using some of the newer AEDs in certain populations of patients, such as the elderly and pregnant/breastfeeding women. There was very little evidence to support the assessment of effectiveness and tolerability of the newer AEDs in these populations.
- Studies using cognitive outcome measures should use more stringent testing protocols, which consider practice effects, and the possible effects of emotional state on cognitive functioning. There is also a need for studies to adopt a more consistent approach to assessment of cognitive outcomes and the choice of measure should be based on evidence to support the validity of the measurement tool in epilepsy patients.
- Further research into the assessment of patient QoL within trials of epilepsy therapy is required. Future trials should aim to adopt any measure shown to have validity in the assessment of epilepsy patients, but there is also a need to use preference-based measures of outcome, which generate appropriate utilities for CEA.
- Future RCTs should be adequately reported according to CONSORT guidelines.
- Value of information analysis should be undertaken, perhaps as an extension to the integrated modelling work presented here, to help prioritise newer trials in this area and to aid their optimal design.
- Observational data are required to provide information on the use of AEDs in actual practice, including details of treatment sequences and doses.

## Updating the review

This review identified several ongoing studies, including the SANAD trial,<sup>288</sup> which address some but not all of the areas suggested by the recommendations for further research. In order to incorporate these data, any future update of this review should not be considered prior to 2006.

## Chapter 5

# Conclusions

There was little good-quality evidence from clinical trials to support the use of newer monotherapy or adjunctive AEDs over older drugs or to support the use of one newer AED in preference to another. In general, the available data relating to clinical effectiveness, safety and tolerability failed to demonstrate consistent and statistically significant differences between the drugs. The exception was comparisons between newer adjunctive AEDs and placebo, where significant differences favoured the newer AEDs. However, trials often had only relatively short-term treatment durations and often failed to limit recruitment to either partial or generalised onset seizures, thus limiting the applicability of the data.

The lack of difference in clinical effectiveness was also reflected in the integrated economic model, which allowed for direct comparisons between all of the newer AEDs and permitted extrapolation of clinical outcomes to long-term health benefits and costs. The estimated benefits of treatment were similar, but differences were evident in the estimated costs of treatment. The older

monotherapies appeared to be cost-effective when compared with newer AEDs for the treatment of newly diagnosed patients experiencing either partial or generalised seizures.

There was, however, a great deal of uncertainty in this conclusion. In addition, the newer AEDs, used as monotherapy, may be cost-effective for the treatment of patients who have experienced AEs with older AEDs, who have failed to respond to the older drugs or where such drugs are contraindicated. For patients experiencing partial seizures, the integrated economic model also suggested that newer adjunctive AEDs might be cost-effective compared with current treatment alone for a given threshold willingness to pay of about £20,000 per QALY. The precise value depends on the particular treatments that are indicated for a patient. For patients experiencing generalised seizures, the analysis indicated that TPM might be cost-effective when used as an adjunctive therapy, with an estimated ICER of £34,500 compared with continuing current treatment alone. Again, there was considerable uncertainty in this conclusion.





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### Contributions of authors

Mike Drummond carried out the overall management of the economics section of the review; assisted in the selection, quality assessment and data extraction of previously published economic evaluations; and provided comments on the protocol and final report.

David Epstein assisted in developing the economic model, extracting data and appraising the economic sections of the industry submissions; and was involved in preparing the final report.

Carol Forbes carried out the overall management of the project from the data extraction stage; assisted with study selection, data extraction and quality assessment; was involved with data analysis and interpretation; and assisted in writing the final report.

Su Golder was the information officer responsible for developing the search strategies and retrieving references; managed the Endnote library and the ordering of papers; was responsible for writing the

literature search sections of the protocol and report; and also provided comments on both the protocol and the final report.

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## References

1. *Dorland's pocket medical dictionary*. Philadelphia: W. B. Saunders; 2001.
2. WHO Collaboration Centre for International Drug Monitoring. *The UMC – the Global Intelligence Network for Benefits and Risks in Medicinal Products*. Sweden: Uppsala Monitoring Centre, 2003. URL: <http://www.who-umc.org/>. Accessed 21 January 2004.
3. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and EEG classification of epileptic seizures. *Epilepsia* 1981;**22**:489–501.
4. Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia* 1989;**30**:389–99.
5. Sander JWAS, Shorvon SD. Epidemiology of the epilepsies. *J Neurol Neurosurg Psychiatry* 1996; **61**:433–43.
6. Cockerell OC, Johnson AL, Sander JWAS, Shorvon SD. Prognosis of epilepsy: a review and further analysis of the first nine years of the British National General Practice Study of Epilepsy, a prospective population-based study. *Epilepsia* 1997;**38**:31–46.
7. National Statistics Office. Epilepsy prevalence and prescribing patterns in England and Wales. *Health Stat Q* 2002;**15**:23–30.
8. Cockerell OC, Johnson AL, Sander JWAS, Hart YM, Goodridge DM, Shorvon SD. Mortality from epilepsy: results from a prospective population-based study. *Lancet* 1994;**344**:918–21.
9. Hanna NJ, Black M, Sander JW, Smithson H, Appleton R, Brown S, *et al.* *The national sentinel clinical audit of epilepsy – related death: epilepsy-death in the shadows*. Norwich: The Stationery Office, 2002. URL: <http://www.sudep.org>. Accessed February 2003.
10. Sander JWAS, Hart YM, Johnson AL, Shorvon SD. National General Practice Study of Epilepsy: newly diagnosed epileptic seizures in a general population. *Lancet* 1990;**336**:1267–71.
11. Wallace H, Shorvon S, Tallis R. Age specific incidence and prevalence rates of treated epilepsy in an unselected population of 2,052,922 and age-specific fertility rates of women with epilepsy [comment]. *Lancet* 1998;**352**:1970–3.
12. Clinical Standards Advisory Group. *Services for patients with epilepsy*. London: HMSO; 1999.
13. Heaney D, MacDonald B, Everitt A, Stevenson S, Leonardi G, Wilkinson P, *et al.* Socioeconomic variation in incidence of epilepsy: prospective community based study in south-east England. *BMJ* 2002;**325**:1013–16.
14. Hart Y, Shorvon S. The nature of epilepsy in the general population. I. Characteristics of patients receiving medication for epilepsy. *Epilepsy Res* 1995;**21**:43–9.
15. Devinsky O. Patients with refractory seizures. *N Engl J Med* 1999;**340**:1565–70.
16. Kwan P, Brodie M. Early identification of refractory epilepsy. *N Engl J Med* 2000;**342**:314–19.
17. Smith D, Baker GA, Jacoby A, Chadwick DW. The contribution of the measurement of seizure severity to quality of life research. *Qual Life Res* 1995;**4**:143–58.
18. Brodie MJ, Dichter MA. Established antiepileptic drugs. *Seizure* 1997;**6**:159–74.
19. Hart Y, Shorvon, SD. The nature of epilepsy in the general population. II. Medical care. *Epilepsy Res* 1995;**21**:51–8.
20. Association of British Pharmaceutical Industry. *Medicines compendium 2002*. London: Datapharm Communications; 2002.
21. British Medical Association, Royal Pharmaceutical Society of Great Britain. *British National Formulary*. 44th ed. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2002.
22. Battino D, Dukes, G, Perucca E. Anticonvulsants. In: Dukes MNG, Aronson JK, editors. *Meyler's side effects of drugs*. 14th ed. Amsterdam: Elsevier Science; 2000.
23. NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness: CRD's guidance for those carrying out or commissioning reviews*. 2nd ed. York: NHS CRD, University of York; 2001.
24. Scoville B, White B, Cereghino JJ, Porter RJ. Suitability and efficiency of crossover drug trial designs in epilepsy. In Dam K, Gram L, Penry JK, editors. *Advances in epileptology: XIIth Epilepsy International Symposium*. New York: Raven Press; 1981. pp. 113–22.
25. Elbourne D, Altman D, Higgins J, Curtin F, Worthington H, Vail A. Meta-analyses involving cross-over trials: methodological issues. *Int J Epidemiol* 2002;**31**:140–9.



26. Djulbegovic B, Clarke M. Scientific and ethical issues in equivalence trials. *JAMA* 2001;**285**:1206–8.
27. McAlister FA, Sackett DL. Active-control equivalence trials and antihypertensive agents. *Am J Med* 2001;**111**:553–8.
28. Bagett R, Chiquette E, Anagnostelis B, C. M. Locating reports of serious adverse drug reactions. In *7th Annual Cochrane Colloquium Abstracts*, October 1999, Rome. p. B54 (poster).
29. Derry S, Loke YK, Aronson K. *Incomplete evidence: the inadequacy of databases in tracing published adverse drug reactions in clinical trials*. 2001. URL: <http://www.biomedcentral.com/147-2288/1/7>. Accessed February 2003.
30. Loke YK, Edwards J, Derry S. Conventional search strategies cannot easily identify those trials of drug therapy which provide quantitative adverse effects data. In *7th Annual Cochrane Colloquium Abstracts*, October 1999, Rome. p. A19 (poster).
31. Ioannidis JP, Lau J. Completeness of safety reporting in randomized trials: an evaluation of 7 medical areas. *JAMA* 2001;**285**:437–43.
32. Ioannidis JP, Contopoulos-Ioannidis DG. Reporting of safety data from randomised trials. *Lancet* 1998;**352**:1752–3.
33. Loke YK, Derry S. *Reporting of adverse drug reactions in randomised controlled trials – a systematic survey*. 2001. URL: <http://www.biomedcentral.com/1472-6904/1/3>. Accessed February 2003.
34. Ernst E, Pittler MH. Assessment of therapeutic safety in systematic reviews: literature review. *BMJ* 2001;**323**:546–7.
35. Sweetman SC. *Martindale: the complete drug reference*. 33rd ed. London: Pharmaceutical Press, 2002.
36. *AHFSFirst (CD-ROM)*. Bethesda: American Society of Health-System Pharmacists; 2002.
37. Chalmers T, Celano P, Sacks H, Smith HJ. Bias in treatment assignment in controlled clinical trials. *N Engl J Med* 1983;**309**:1358–61.
38. Grunewald RA, Thompson PJ, Corcoran R, Corden Z, Jackson GD, Duncan JS. Effects of vigabatrin on partial seizures and cognitive function. *J Neurol Neurosurg Psychiatry* 1994;**57**:1057–63.
39. Sveinbjornsdottir S, Sander JW, Patsalos PN, Upton D, Thompson PJ, Duncan JS. Neuropsychological effects of tiagabine, a potential new antiepileptic drug. *Seizure* 1994;**3**:29–35.
40. Cordova S, Mendoza U. High or low dose lamotrigine as add-on treatment of medically resistant epilepsy to inducer or valproate medication. *Epilepsia* 1995;**36** (Suppl. 3):S113.
41. Rosenfeld WE, Abou-Khalil B, Reife R, Hegadus R, Pledger G. Placebo-controlled trial of topiramate as adjunctive therapy to carbamazepine or phenytoin for partial onset epilepsy. *Epilepsia* 1996;**37** (Suppl. 5):153.
42. Tassinari CA, Michelucci R, Chauvel P, Chodkiewicz J, Shorvon S, Henriksen O, et al. Double-blind, placebo-controlled trial of topiramate (600 mg daily) for the treatment of refractory partial epilepsy. *Epilepsia* 1996;**37**:763–8.
43. Kälviäinen R, Aikia M, Mervaala E, Saukkonen AM, Pitkänen A, Riekkinen PJ Sr. Long-term cognitive and EEG effects of tiagabine in drug-resistant partial epilepsy. *Epilepsy Res* 1996;**25**:291–7.
44. Meador K, Hulihan J, Kamin R. Topiramate (TPM) and valproate (VPA) added to carbamazepine (CBZ): effect on objective measures of cognitive function in adults with epilepsy. *Epilepsia* 2001;**42** (Suppl. 7):251.
45. Czapinski P, Terczynski A, Czapinska E. Open randomized comparative study of vigabatrin (VGB) and lamotrigine (LTG) efficacy in monotherapy of patients with drug-resistant epilepsy with partial complex seizures resistant to carbamazepine (CBZ) (Abstract). *J Neurol Sci* 1997;**150** (Suppl. 1):S96.
46. Lopes-Lima JM, Pereira H, Sol JM, Morralla C, Hernandez G. Gabapentin vs valproate in partial epilepsy uncontrolled by carbamazepin. *Eur J Neurol* 1999;**6** (Suppl. 3):17.
47. Brodie MJ, Read CL, Gillham RA, Sweet RM, Kane K. Lack of neuropsychological effects of lamotrigine compared to carbamazepine as monotherapy. *Epilepsia* 1999;**40** (Suppl. 2):94.
48. Burt DB, Zembar MJ, Niederehe G. Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. *Psychol Bull* 1995;**117**:285–305.
49. Rimmer EM, Richens A. A double blind study of a new drug, gamma-vinyl GABA, in patients with refractory epilepsy. In: Porter RJ, editor. *Advances in Epileptology: Proceedings of XVth Epilepsy International Symposium*. New York: Raven Press; 1984. pp. 181–5.
50. Binnie CD, Beintema DJ, Debets RMC, Boas WV, Meijer JWA, Meinardi H, et al. 7 day administration of lamotrigine in epilepsy placebo controlled add-on trial. *Epilepsy Res* 1987;**1**:202–8.
51. Gillham RA, Blacklaw J, McKee PJ, Brodie MJ. Effect of vigabatrin on sedation and cognitive function in patients with refractory epilepsy. *J Neurol Neurosurg Psychiatry* 1993;**56**:1271–5.
52. Aikia M, Kälviäinen R, Riekkinen PJ. The cognitive effects of initial tiagabine monotherapy. *Epilepsia* 1999;**40** (Suppl. 7):51.

53. Tanganelli P, Regesta G. Vigabatrin vs. carbamazepine monotherapy in newly diagnosed focal epilepsy: a randomized response conditional cross-over study. *Epilepsy Res* 1996;**25**:257–62.
54. McKee PJ, Blacklaw J, Friel E, Thompson GG, Gillham RA, Brodie MJ. Adjuvant vigabatrin in refractory epilepsy: a ceiling to effective dosage in individual patients? *Epilepsia* 1993;**34**:937–43.
55. Smith D, Baker G, Davies G, Dewey M, Chadwick DW. Outcomes of add-on treatment with lamotrigine in partial epilepsy. *Epilepsia* 1993;**34**:312–22.
56. Schachter SC, Leppik IE, Matsuo F, Messenheimer JA, Faught E, Moore EL, *et al.* Lamotrigine: a six-month, placebo-controlled, safety and tolerance study. *J Epilepsy* 1995;**8**:201–9.
57. Dodrill CB, Arnett JL, Deaton R, Lenz GT, Sommerville KW. Tiagabine versus phenytoin and carbamazepine as add-on therapies: effects on abilities, adjustment, and mood. *Epilepsy Res* 2000;**42**:123–32.
58. Aikia M, Kälviäinen R, Sivenius J, Halonen T, Riekkinen PJ. Cognitive effects of oxcarbazepine and phenytoin monotherapy in newly diagnosed epilepsy: one year follow-up. *Epilepsy Res* 1992;**11**:199–203.
59. Riekkinen SP, Kälviäinen R, Aikia M, Partanen K, Salmenpera T, Vainio P. Prospective neuropsychological and quantitative MRI-follow-up of newly diagnosed patients with epilepsy randomized to either vigabatrin or carbamazepine monotherapy (Abstract). *Eur J Neurol* 1997;**4** (Suppl. 1):S23.
60. Coles H, Baker G, O'Donoghue M. Seizure severity in patients with partial onset (POS) or primary generalised tonic clonic (PGTC) seizures following treatment with topiramate. A comparison of two different methodologies in a randomised controlled trial. *Epilepsia* 1999;**40** (Suppl. 2):285.
61. Specchio LM, La Neve A, Spinelli A, Boero G, Tramacere L, Specchio N. Vigabatrin (VGB), lamotrigine (LTG), and gabapentin (GBP) in refractory partial epilepsy: an open comparative long term study. *Neurology* 1999;**52** (Suppl. 6):A524.
62. GlaxoSmithKline. *An open randomised comparison of lamotrigine with valproate as monotherapy in patients with idiopathic generalised epilepsy*. Critchley Park: Glaxo Wellcome UK; 2001.
63. Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA* 1993;**270**:2598–601.
64. Crombie IK. Appraising clinical trials. In *The pocket guide to critical appraisal: a handbook for health care professionals*. London: BMJ Publishing Group; 1996. pp. 43–9.
65. Cramer J, Ryan J, Chang J, Sommerville K. The short-term impact of adjunctive tiagabine on health-related quality of life. *Epilepsia* 2001;**42** (Suppl. 3):70–5.
66. Brodie MJ, Mumford JP. Double-blind substitution of vigabatrin and valproate in carbamazepine-resistant partial epilepsy. *Epilepsy Res* 1999;**34**:199–205.
67. Faught E, Wilder BJ, Ramsay RE, Reife RA, Kramer LD, Pledger GW, *et al.* Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 200-, 400-, and 600-mg daily dosages. *Neurology* 1996;**46**:1684–90.
68. Privitera M, Fincham R, Penry J, Reife R, Kramer L, Pledger G, *et al.* Topiramate placebo-controlled dose-ranging trial in refractory partial epilepsy using 600-, 800-, and 1,000-mg daily dosages. *Neurology* 1996;**46**:1678–83.
69. Wilensky AJ. *A double-blind, single-center, 3-way crossover study in patients with refractory partial seizures to determine the efficacy and safety of gabapentin monotherapy compared with carbamazepine monotherapy and gabapentin/carbamazepine combination therapy and follow-on open-label safety (Protocols 945-36 and 945-13-14)*. Ann Arbor, MI: Warner-Lambert; 1996.
70. Barcs G, Walker EB, Elger CE, Scaramelli A, Stefan H, Sturm Y, *et al.* Oxcarbazepine placebo-controlled, dose-ranging trial in refractory partial epilepsy. *Epilepsia* 2000;**41**:1597–607.
71. Kälviäinen R, Aikia M, Saukkonen AM, Mervaala E, Riekkinen PJ Sr. Vigabatrin vs carbamazepine monotherapy in patients with newly diagnosed epilepsy. A randomized, controlled study [see comments]. *Arch Neurol* 1995;**52**:989–96.
72. Loiseau P. *Double-blind, multicenter trial in parallel groups comparing the safety and efficacy of Tripleptal and Tegretol as monotherapy in patients with epilepsy*. Camberley: Novartis Pharmaceuticals UK; 1998.
73. UK Gabapentin Study Group. Gabapentin in partial epilepsy. *Lancet* 1990;**335**:1114–17.
74. Chadwick D, Leiderman DB, Sauermann W, Alexander J, Garofalo E. Gabapentin in generalized seizures. *Epilepsy Res* 1996;**25**:191–7.
75. Steiner TJ, Dellaportas CI, Findley LJ, Gross M, Gibberd FB, Perkin GD, *et al.* Lamotrigine monotherapy in newly diagnosed untreated epilepsy: a double-blind comparison with phenytoin. *Epilepsia* 1999;**40**:601–7.
76. Barrett J, Gassman C, Lim P, Hughson C, Zimmerman T. *Topiramate (RWJ-17021-000) clinical trial in primary generalised tonic-clonic seizures*. Report No. YTC-E. New Jersey. R. W. Johnson Pharmaceutical Research Institute; 1997.
77. Gillham R, Kane K, Bryant Comstock L, Brodie MJ. A double-blind comparison of

- lamotrigine and carbamazepine in newly diagnosed epilepsy with health-related quality of life as an outcome measure. *Seizure* 2000;**9**:375–9.
78. Schachter SC, Vazquez B, Fisher RS, Laxer KD, Montouris GD, Combs-Cantrell DT, *et al.* Oxcarbazepine – double-blind, randomized, placebo-control, monotherapy trial for partial seizures. *Neurology* 1999;**52**:732–7.
  79. Biton V, Montouris GD, Ritter F, Riviello JJ, Reife R, Lim P, *et al.* A randomized, placebo-controlled study of topiramate in primary generalized tonic-clonic seizures. Topiramate YTC Study Group. *Neurology* 1999;**52**:1330–7.
  80. Boon P, Chauvel P, Pohlmann-Eden B, Otoul C, Wroe S. Dose-response effect of levetiracetam 1000 and 2000 mg/day in partial epilepsy. *Epilepsy Res* 2002;**48**:77–89.
  81. Richens A. Proof of efficacy trials: cross-over versus parallel-group. *Epilepsy Res* 2001;**45**:43–7.
  82. Yaqub B, Aldeeb S, Cheung CKP, Thomas W, Ahmed R, Khan S, *et al.* Lamotrigine treatment in severe epilepsy. *Epilepsia* 1995;**36** (Suppl. 3):S115.
  83. Loiseau P, Hardenberg JP, Pestre M, Guyot M, Schechter PJ, Tell GP. Double-blind, placebo-controlled study of vigabatrin (gamma-vinyl GABA) in drug-resistant epilepsy. *Epilepsia* 1986;**27**:115–20.
  84. Houtkooper MA, Lammertsma A, Meyer JW, Goedhart DM, Meinardi H, van Oorschot CA, *et al.* Oxcarbazepine (GP 47.680): a possible alternative to carbamazepine? *Epilepsia* 1987;**28**:693–8.
  85. Tassinari CA, Michelucci R, Ambrosetto G, Salvi F. Double-blind study of vigabatrin in the treatment of drug-resistant epilepsy. *Arch Neurol* 1987;**44**:907–10.
  86. Tartara A, Manni R, Galimberti CA, Hardenberg J, Orwin J, Perucca E. Vigabatrin in the treatment of epilepsy: a double-blind, placebo-controlled study. *Epilepsia* 1986;**27**:717–23.
  87. Beran RG, Berkovic SF, Buchanan N, Danta G, Mackenzie R, Schapel G, *et al.* A double-blind, placebo-controlled crossover study of vigabatrin 2 g/day and 3 g/day in uncontrolled partial seizures. *Seizure* 1996;**5**:259–65.
  88. Banks GK, Beran RG. Neuropsychological assessment in lamotrigine treated epileptic patients. *Clin Exp Neurol* 1991;**28**:230–7.
  89. Loiseau P, Yuen AW, Duche B, Menager T, Arne Bes MC. A randomised double-blind placebo-controlled crossover add-on trial of lamotrigine in patients with treatment-resistant partial seizures. *Epilepsy Res* 1990;**7**:136–45.
  90. Leach JP, Girvan J, Paul A, Brodie MJ. Gabapentin and cognition: a double blind, dose ranging, placebo controlled study in refractory epilepsy. *J Neurol Neurosurg Psychiatry* 1997;**62**:372–6.
  91. Schmidt D. *A randomised double-blind placebo controlled crossover add-on trial of lamotrigine in patients with treatment resistant partial seizures (Munich)*. Report No. H34-18. Beckenham: Wellcome Foundation; 1993.
  92. Chadwick D. Safety and efficacy of vigabatrin and carbamazepine in newly diagnosed epilepsy: a multicentre randomised double-blind study. Vigabatrin European Monotherapy Study Group. *Lancet* 1999;**354**:13–19.
  93. Brodie MJ, Chadwick DW, Anhut H, Otte A, Messmer S, Maton S, *et al.* *Gabapentin versus lamotrigine monotherapy: a double-blind comparison in newly diagnosed epilepsy*. Glasgow: Western Infirmary; 2002.
  94. Privitera M, Brodie M, Mattson R, Chadwick D, Neto W, Wang S. *Topiramate, carbamazepine and valproate monotherapy: double-blind comparison in newly diagnosed epilepsy*. High Wycombe: Janssen-Cilag; 2002.
  95. Adab N, Tudur Smith C, Vinten J, Williamson P, Winterbottom J. Common antiepileptic drugs in pregnancy in women with epilepsy. *The Cochrane Database of Systematic Reviews* 2004, Issue 3, CD004848.
  96. Castillo S, Schmidt DB, White S. Oxcarbazepine add-on for drug-resistant partial epilepsy (Cochrane Review). In *The Cochrane Library, Issue 3*. Oxford: Update Software; 2002.
  97. Chaisewikul R, Privitera MD, Hutton JL, Marson AG. Levetiracetam add-on for drug-resistant localization related (partial) epilepsy (Cochrane Review). In *The Cochrane Library, Issue 1*. Oxford: Update Software; 2002.
  98. Jette NJ, Marson AG, Kadir ZA, Hutton JL. Topiramate for drug-resistant partial epilepsy (Cochrane Review). In *The Cochrane Library, Issue 3*. Oxford: Update Software; 2002.
  99. Kälviäinen R, Chadwick DW. Vigabatrin versus carbamazepine monotherapy for epilepsy (Protocol for a Cochrane Review). In *The Cochrane Library, Issue 1*. Oxford: Update Software; 2002.
  100. Marson AG, Kadir ZA, Hutton JL, Chadwick DW. The new antiepileptic drugs: a systematic review of their efficacy and tolerability. *Epilepsia* 1997;**38**:859–80.
  101. Chadwick DW, Marson T, Kadir Z. Clinical administration of new antiepileptic drugs: an overview of safety and efficacy. *Epilepsia* 1996;**37** (Suppl. 6):S17–22.
  102. Chadwick DW. An overview of the efficacy and tolerability of new antiepileptic drugs. *Epilepsia* 1997;**38** (Suppl. 1):S59–62.

103. Marson AG, Kadir ZA, Chadwick DW. New antiepileptic drugs: a systematic review of their efficacy and tolerability. *BMJ* 1996;**313**:1169–74.
104. Marson AG, Hutton JL, Leach JP, Castillo S, Schmidt D, White S, *et al.* Levetiracetam, oxcarbazepine, remacemide and zonisamide for drug resistant localization-related epilepsy: a systematic review. *Epilepsy Res* 2001;**46**:259–70.
105. Marson AG, Kadir ZA, Hutton JL, Chadwick DW. Gabapentin add-on for drug-resistant partial epilepsy (Cochrane Review). In *The Cochrane Library, Issue 3*. Oxford: Update Software; 2002.
106. Muller MM, Marson AG, Williamson PR. Oxcarbazepine versus phenytoin monotherapy for epilepsy (Protocol for a Cochrane Review). In *The Cochrane Library, Issue 3*. Oxford: Update Software; 2002.
107. Pereira J, Marson AG, Hutton JL. Tiagabine add-on for drug-resistant partial epilepsy (Cochrane Review). In *The Cochrane Library, Issue 3*. Oxford: Update Software; 2002.
108. Ramaratnam S, Marson AG, Baker GA. Lamotrigine add-on for drug-resistant partial epilepsy (Cochrane Review). In *The Cochrane Library, Issue 1*. Oxford: Update Software; 2002.
109. Rashid A, Marson AG. Vigabatrin add-on for drug-resistant partial epilepsy (Protocol for a Cochrane Review). In *The Cochrane Library, Issue 3*. Oxford: Update Software; 2002.
110. White S, Marson AG, Williamson PR, Hutton JL, Chadwick DW, Marshall A. Lamotrigine versus carbamazepine monotherapy for epilepsy (Protocol for a Cochrane Review). In *The Cochrane Library, Issue 3*. Oxford: Update Software; 2002.
111. Sachdeo RC. *Safety and efficacy of 1200mg/d of oxcarbazepine monotherapy versus placebo in patients with recent-onset partial seizures*. Camberley: Novartis Pharmaceuticals UK; 1998.
112. Gilliam F, Vazquez B, Sackellares JC, Chang GY, Messenheimer J, Nyberg J, *et al.* An active-control trial of lamotrigine monotherapy for partial seizures. *Neurology* 1998;**51**:1018–25.
113. Bryant-Comstock L, Curtis P, Moorat A, Kerr M. *The impact of switching AED when monotherapy fails on epilepsy-related quality of life: an international, open, randomised comparison study of lamotrigine versus sodium valproate*. North Carolina: GlaxoSmithKline; 2002.
114. Martinez W, Kaminow L, Nanry KB, Vuong A, Varner JA, Hammer AE, *et al.* *Lamotrigine monotherapy compared with carbamazepine, phenytoin, or valproate monotherapy in patients with epilepsy*. Critchley Park: GlaxoSmithKline; 2002.
115. Reinikainen KJ, Keranen T, Halonen T, Komulainen H, Riekkinen PJ. Comparison of oxcarbazepine and carbamazepine: a double-blind study. *Epilepsy Res* 1987;**1**:284–9.
116. Biton V, Mirza W, Montouris G, Vuong A, Hammer AE, Barrett PS. Weight change associated with valproate and lamotrigine monotherapy in patients with epilepsy. *Neurology* 2001;**56**:172–7.
117. Brodie MJ, Overstall PW, Giorgi L. Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. The UK Lamotrigine Elderly Study Group. *Epilepsy Res* 1999;**37**:81–7.
118. GlaxoSmithKline. *An open randomised comparison of Lamotrigine with Valproate as monotherapy in patients with idiopathic generalised epilepsy*. Critchley Park: Glaxo Wellcome UK; 2000.
119. Nieto Barrera M, Brozmanova M, Capovilla G, Christe W, Pedersen B, Kane K, *et al.* A comparison of monotherapy with lamotrigine or carbamazepine in patients with newly diagnosed partial epilepsy. *Epilepsy Res* 2001;**46**:145–55.
120. Reunanen M, Dam M, Yuen AW. A randomised open multicentre comparative trial of lamotrigine and carbamazepine as monotherapy in patients with newly diagnosed or recurrent epilepsy. *Epilepsy Res* 1996;**23**:149–55.
121. Brodie MJ, Richens A, Yuen AW. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. UK Lamotrigine/Carbamazepine Monotherapy Trial Group. *Lancet* 1995;**345**:476–9.
122. Kerr M. *An open randomised comparison of add-on lamotrigine or valproate/carbamazepine withdrawing to monotherapy in patients with treatment resistant epilepsy*. Report No. SCAB3001 (105-133). Critchley Park: Glaxo Wellcome UK; 2001.
123. Christe W, Kramer G, Vigonius U, Pohlmann H, Steinhoff BJ, Brodie MJ, *et al.* A double-blind controlled clinical trial: oxcarbazepine versus sodium valproate in adults with newly diagnosed epilepsy. *Epilepsy Res* 1997;**26**:451–60.
124. Bill PA, Vigonius U, Pohlmann H, Guerreiro CAM, Kochen S, Saffer D, *et al.* A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in adults with previously untreated epilepsy. *Epilepsy Res* 1997;**27**:195–204.
125. Dam M, Ekberg R, Loyning Y, Waltimo O, Jakobsen K. A double-blind study comparing oxcarbazepine and carbamazepine in patients with newly diagnosed, previously untreated epilepsy. *Epilepsy Res* 1989;**3**:70–6.
126. Sackellares C, Kwong W, Vuong A, Hammer A, Barrett P. Lamotrigine monotherapy improves health-related quality of life in epilepsy: a double-blind comparison with valproate. *Epilepsia* 2000;**41**:28. Proceedings of the 54th Annual Meeting of the American Epilepsy Society. Los Angeles: American Epilepsy Society; 2000.
127. GlaxoSmithKline. *A multicentre, double-blind comparison of the efficacy and safety of lamotrigine and*

- carbamazepine monotherapy in patients with newly diagnosed epilepsy. Critchley Park: Glaxo Wellcome UK; 1994.
128. Maton S. *A blinded parallel group comparison of Neurontin (gabapentin) and sodium valproate as add-on therapy in the treatment of partial seizures (Protocol 945-430003, NE003)*. Eastleigh: Parke Davis Medical Division; 1998.
  129. Sommerville K. *Safety and efficacy of tiagabine HCl as adjunctive treatment*. Abbott Park, IL: Abbott Laboratories; 1998.
  130. Aldenkamp AP, Baker G, Mulder OG, Chadwick D, Cooper P, Doelman J, *et al*. A multicenter, randomized clinical study to evaluate the effect on cognitive function of topiramate compared with valproate as add-on therapy to carbamazepine in patients with partial-onset seizures. *Epilepsia* 2000;**41**:1167–78.
  131. Crawford P, Brown S, Kerr M. A randomized open-label study of gabapentin and lamotrigine in adults with learning disability and resistant epilepsy. *Seizure* 2001;**10**:107–15.
  132. Lindberger M, Alenius M, Frisen L, Johannessen SI, Larsson S, Malmgren K, *et al*. Gabapentin versus vigabatrin as first add-on for patients with partial seizures that failed to respond to monotherapy: a randomized, double-blind, dose titration study. GREAT Study Investigators Group. Gabapentin in Refractory Epilepsy Add-on Treatment. *Epilepsia* 2000;**41**:1289–95.
  133. Chmielewska B, Stelmasiak Z. Clinical evaluation of Gabitril and Lamictal for drug-resistant epilepsy in adults. *Ann Univ Mariae Curie Sklodowska [Med]* 2001;**56**:35–42.
  134. Beran RG, Berkovic SF, Dunagan FM, Vajda FJ, Danta G, Black AB, *et al*. Double-blind, placebo-controlled, crossover study of lamotrigine in treatment-resistant generalised epilepsy. *Epilepsia* 1998;**39**:1329–33.
  135. Sander JW, Patsalos PN, Oxley JR, Hamilton MJ, Yuen WC. A randomised double-blind placebo-controlled add-on trial of lamotrigine in patients with severe epilepsy. *Epilepsy Res* 1990;**6**:221–6.
  136. Boas J, Dam M, Friis ML, Kristensen O, Pedersen B, Gallagher J. Controlled trial of lamotrigine (Lamictal) for treatment-resistant partial seizures. *Acta Neurol Scand* 1996;**94**:247–52.
  137. Veendrick-Meekes MJB, Beun AM, Carpay JA, Arends LR, Schlosser A. Use of Lamictal® as adjunctive therapy in patients with mental retardation and epilepsy: final analysis of a double-blind study with evaluation of behavioural effects. Poster presentation. *4th European Congress of Epileptology, Florence, Italy* 2000.
  138. US Gabapentin Study Group No. 5. Gabapentin as add-on therapy in refractory partial epilepsy: a double-blind, placebo-controlled, parallel-group study. *Neurology* 1993;**43**:2292–8.
  139. Betts T, Waegemans T, Crawford P. A multicentre, double-blind, randomized, parallel group study to evaluate the tolerability and efficacy of two oral doses of levetiracetam, 2000 mg daily and 4000 mg daily, without titration in patients with refractory epilepsy. *Seizure* 2000;**9**:80–7.
  140. Sachdeo RC, Leroy RF, Krauss GL, Drake ME Jr, Green PM, Leppik IE, *et al*. Tiagabine therapy for complex partial seizures: a dose–frequency study. *Arch Neurol* 1997;**54**:595–601.
  141. Reynolds EH, Ring HA, Farr IN, Heller AJ, Elwes RD. Open, double-blind and long-term study of vigabatrin in chronic epilepsy. *Epilepsia* 1991;**32**:530–8.
  142. Matsuo F, Bergen D, Faught E, Messenheimer JA, Dren AT, Rudd GD, *et al*. Placebo-controlled study of the efficacy and safety of lamotrigine in patients with partial seizures. U.S. Lamotrigine Protocol 0.5 Clinical Trial Group. *Neurology* 1993;**43**:2284–91.
  143. Cereghino JJ, Biton V, Abou-Khalil B, Dreifuss F, Gauer LJ, Leppik I. Levetiracetam for partial seizures: results of a double-blind, randomized clinical trial. *Neurology* 2000;**55**:236–42.
  144. Ben-Menachem E, Falter U. Efficacy and tolerability of levetiracetam 3000 mg/d in patients with refractory partial seizures: a multicenter, double-blind, responder-selected study evaluating monotherapy. European Levetiracetam Study Group. *Epilepsia* 2000;**41**:1276–83.
  145. Shorvon SD, Lowenthal A, Janz D, Bielen E, Loiseau P. Multicenter double-blind, randomized, placebo-controlled trial of levetiracetam as add-on therapy in patients with refractory partial seizures. European Levetiracetam Study Group. *Epilepsia* 2000;**41**:1179–86.
  146. Richens A, Chadwick DW, Duncan JS, Dam M, Gram L, Mikkelsen M, *et al*. Adjunctive treatment of partial seizures with tiagabine: a placebo-controlled trial. *Epilepsy Res* 1995;**21**:37–42.
  147. Crawford P, Meinardi H, Brown S, Rentmeester Th W, Pedersen B, Pedersen PC, *et al*. Tiagabine: efficacy and safety in adjunctive treatment of partial seizures. *Epilepsia* 2001;**42**:531–8.
  148. Sharief M, Viteri C, Ben Menachem E, Weber M, Reife R, Pledger G, *et al*. Double-blind, placebo-controlled study of topiramate in patients with refractory partial epilepsy. *Epilepsy Res* 1996;**25**:217–24.
  149. Korean Topiramate Study Group. Topiramate in medically intractable partial epilepsies: double-blind placebo-controlled randomized parallel group trial. *Epilepsia* 1999;**40**:1767–74.

150. Guberman A, Neto W, Gassman-Mayer C. Low dose topiramate in adults with treatment-resistant partial-onset seizures. *Acta Neurol Scand* 2002; **106**:183–9.
151. Ben-Menachem E, Henriksen O, Dam M, Mikkelsen M, Schmidt D, Reid S, *et al.* Double-blind, placebo-controlled trial of topiramate as add-on therapy in patients with refractory partial seizures. *Epilepsia* 1996;**37**:539–43.
152. Provinciali L, Bartolini M, Mari F, Del Pesce M, Ceravolo MG. Influence of vigabatrin on cognitive performances and behaviour in patients with drug-resistant epilepsy. *Acta Neurol Scand* 1996; **94**:12–8.
153. Bruni J, Guberman A, Vachon L, Desforges C. Vigabatrin as add-on therapy for adult complex partial seizures: a double-blind, placebo-controlled multicentre study. *Seizure* 2000;**9**:224–32.
154. Dean C, Mosier M, Penry K. Dose-response study of vigabatrin as add-on therapy in patients with uncontrolled complex partial seizures. *Epilepsia* 1999;**40**:74–82.
155. French JA, Mosier M, Walker S, Sommerville K, Sussman N, Barry E, *et al.* A double-blind, placebo-controlled study of vigabatrin three g/day in patients with uncontrolled complex partial seizures. *Neurology* 1996;**46**:54–61.
156. Anhut H, Ashman P, Feuerstein TJ, Sauermann W, Saunders M, Schmidt B, *et al.* Gabapentin (Neurontin) as add-on therapy in patients with partial seizures – a double-blind, placebo-controlled study. *Epilepsia* 1994;**35**:795–801.
157. Sivenius J, Kälviäinen R, Ylinen A, Riekkinen P. Double-blind study of gabapentin in the treatment of partial seizures. *Epilepsia* 1991;**32**:539–42.
158. Messenheimer J, Ramsay RE, Willmore LJ, Leroy RF, Zielinski JJ, Mattson R, *et al.* Lamotrigine therapy for partial seizures: a multicenter, placebo-controlled, double-blind, cross-over trial. *Epilepsia* 1994;**35**:113–21.
159. Binnie CD, Debets RM, Engelsman M, Meijer JW, Meinardi H, Overweg J, *et al.* Double-blind crossover trial of lamotrigine (Lamictal) as add-on therapy in intractable epilepsy. *Epilepsy Res* 1989; **4**:222–9.
160. Jawad S, Richens A, Goodwin G, Yuen WC. Controlled trial of lamotrigine (Lamictal) for refractory partial seizures. *Epilepsia* 1989; **30**:356–63.
161. Schapel G, Beran R, Vajda F, Berkovic S, Mashford ML, Dunagan FM, *et al.* Double-blind, placebo controlled, crossover study of lamotrigine in treatment resistant partial seizures. *J Neurol Neurosurg Psychiatry* 1993;**56**:448–53.
162. Stolarek I, Blacklaw J, Forrest G, Brodie MJ. Vigabatrin and lamotrigine in refractory epilepsy. *J Neurol Neurosurg Psychiatry* 1994;**57**:921–4.
163. Uthman BM, Rowan AJ, Ahmann PA, Leppik IE, Schachter SC, Sommerville KW, *et al.* Tiagabine for complex partial seizures: a randomized, add-on, dose-response trial. *Arch Neurol* 1998;**55**:56–62.
164. Kälviäinen R, Brodie MJ, Duncan J, Chadwick D, Edwards D, Lyby K. A double-blind, placebo-controlled trial of tiagabine given three-times daily as add-on therapy for refractory partial seizures. *Epilepsy Res* 1998;**30**:31–40.
165. Yen DJ, Yu HY, Guo YC, Chen C, Yiu CH, Su MS. A double-blind, placebo-controlled study of topiramate in adult patients with refractory partial epilepsy. *Epilepsia* 2000;**41**:1162–6.
166. Cramer JA, Arrigo C, Van Hamme G, Gauer LJ, Cereghino JJ. Effect of levetiracetam on epilepsy-related quality of life. N132 Study Group. *Epilepsia* 2000;**41**:868–74.
167. Dodrill CB, Arnett JL, Sommerville KW, Shu V. Cognitive and quality of life effects of differing dosages of tiagabine in epilepsy. *Neurology* 1997; **48**:1025–31.
168. Dodrill CB, Arnett JL, Sommerville KW, Sussman NM. Effects of differing dosages of vigabatrin (Sabril) on cognitive abilities and quality of life in epilepsy. *Epilepsia* 1995; **36**:164–73.
169. Dodrill CB, Arnett JL, Sommerville KW, Sussman NM. Evaluation of the effects of vigabatrin on cognitive abilities and quality of life in epilepsy. *Neurology* 1993;**43**:2501–7.
170. Wilton LV, Shakir S. A postmarketing surveillance study of gabapentin as add-on therapy for 3,100 patients in England. *Epilepsia* 2002;**43**:983–92.
171. Wilton L, Pearce G, Martin RM, Mackay FJ, Mann RD. The outcomes of pregnancy in women exposed to newly marketed drugs in general practice in England. *Br J Obstet Gynaecol* 1998; **105**:882–9.
172. Mann RD. Prescription-event monitoring – recent progress and future horizons. *Br J Clin Pharmacol* 1998;**46**:195–201.
173. Fisher RS, Sachdeo RC, Pellock J, Penovich PE, Magnus L, Bernstein P. Rapid initiation of gabapentin: a randomized, controlled trial. *Neurology* 2001;**56**:743–8.
174. McLean MJ, Morrell MJ, Willmore LJ, Privitera MD, Faught RE, Holmes GL, *et al.* Safety and tolerability of gabapentin as adjunctive therapy in a large, multicenter study. *Epilepsia* 1999;**40**:965–72.
175. Mayer T, Schutte W, Wolf P, Elger CE. Gabapentin add-on treatment: how many patients become seizure-free? An open-label multicenter study. *Acta Neurol Scand* 1999;**99**:1–7.

176. Wilson EA, Sills GJ, Forrest G, Brodie MJ. High dose gabapentin in refractory partial epilepsy: clinical observations in 50 patients. *Epilepsy Res* 1998;**29**:161–6.
177. Baulac M, Cavalcanti D, Semah F, Arzimanoglou A, Portal JJ. Gabapentin add-on therapy with adaptable dosages in 610 patients with partial epilepsy: an open, observational study. The French Gabapentin Collaborative Group. *Seizure* 1998;**7**:55–62.
178. Mauri MC, Laini V, Scalvini ME, Omboni A, Ferrari VMS, Clemente A, *et al.* Gabapentin and the prophylaxis of bipolar disorders in patients intolerant to lithium. *Clin Drug Invest* 2001;**21**:169–74.
179. Schaffer CB, Schaffer LC. Open maintenance treatment of bipolar disorder spectrum patients who responded to gabapentin augmentation in the acute phase of treatment. *J Affect Disord* 1999;**55**:237–40.
180. Sasanelli F, Amodeo M, Colombo A, Molini GE. Gabapentin versus carbamazepine: monotherapy in newly-diagnosed patients with partial epilepsy: Preliminary results. *Boll Lega Ital Epil* 1996;**95–96**:185–6 (in Italian).
181. McElroy SL, Soutullo CA, Keck PE Jr, Kmetz GF. A pilot trial of adjunctive gabapentin in the treatment of bipolar disorder. *Ann Clin Psychiatry* 1997;**9**:99–103.
182. Beydoun A, Fakhoury T, Nasreddine W, Abou-Khalil B. Conversion to high dose gabapentin monotherapy in patients with medically refractory partial epilepsy. *Epilepsia* 1998;**39**:188–93.
183. Anhut H, Ashman PJ, Feuerstein TJ, Quebe-Fehling E, Saunders M, Baron BA, *et al.* Long-term safety and efficacy of gabapentin (neurontin) as add-on therapy in patients with refractory partial seizures. *J Epilepsy* 1995;**8**:44–50.
184. Sivenius J, Ylinen A, Kälviäinen R, Riekkinen Sr PJ. Long-term study with gabapentin in patients with drug-resistant epileptic seizures. *Arch Neurol* 1994;**51**:1047–50.
185. US Gabapentin Study Group. The long-term safety and efficacy of gabapentin (Neurontin(TM)) as add-on therapy in drug-resistant partial epilepsy. *Epilepsy Res* 1994;**18**:67–73.
186. Putzke JD, Richards JS, Kezar L, Hicken BL, Ness TJ. Long-term use of gabapentin for treatment of pain after traumatic spinal cord injury. *Clin J Pain* 2002;**18**:116–21.
187. Lhatoo SD, Wong IC, Polizzi G, Sander JW. Long-term retention rates of lamotrigine, gabapentin, and topiramate in chronic epilepsy. *Epilepsia* 2000;**41**:1592–6.
188. Mackay FJ, Wilton LV, Pearce GL, Freemantle SN, Mann RD. Safety of long-term lamotrigine in epilepsy. *Epilepsia* 1997;**38**:881–6.
189. Wong IC, Mawer GE, Sander JW. Adverse event monitoring in lamotrigine patients: a pharmacoepidemiologic study in the United Kingdom. *Epilepsia* 2001;**42**:237–44.
190. Tennis P, Eldridge R. Six-year interim results of the Lamotrigine Pregnancy Registry. *Epilepsia* 1999;**40** (Suppl. 2):196.
191. Faught E, Morris G, Jacobson M, French J, Harden C, Montouris G, *et al.* Adding lamotrigine to valproate: incidence of rash and other adverse effects. Postmarketing Antiepileptic Drug Survey (PADS) Group. *Epilepsia* 1999;**40**:1135–40.
192. Rzany B, Correia O, Kelly JP, Naldi L, Auquier A, Stern R. Risk of Stevens–Johnson syndrome and toxic epidermal necrolysis during first weeks of antiepileptic therapy: a case–control study. Study Group of the International Case Control Study on Severe Cutaneous Adverse Reactions. *Lancet* 1999;**353**:2190–4.
193. Pimentel J, Guimaraes ML, Lima L, Leitao O, Sampaio MJ. Lamotrigine as add-on therapy in treatment-resistant epilepsy. Portuguese Lamotrigine as Add-on Therapy in Treatment-resistant Epilepsy Study Group. *J Int Med Res* 1999;**27**:148–57.
194. Calabrese JR, Bowden CL, McElroy SL, Cookson J, Andersen J, Keck PE Jr, *et al.* Spectrum of activity of lamotrigine in treatment-refractory bipolar disorder. *Am J Psychiatry* 1999;**156**:1019–23.
195. Cocito L, Maffini M, Loeb C. Long-term observations on the clinical use of lamotrigine as add-on drug in patients with epilepsy. *Epilepsy Res* 1994;**19**:123–7.
196. Mikati MA, Schachter SC, Schomer DL, Keally M, Osborne-Shafer P, Seaman CA, *et al.* Long-term tolerability, pharmacokinetic and preliminary efficacy study of lamotrigine in patients with resistant partial seizures. *Clin Neuropharmacol* 1989;**12**:312–21.
197. Sander J, Trevisol-Bittencourt PC, Hart YM, Patsalos PN, Shorvon SD. The efficacy and long-term tolerability of lamotrigine in the treatment of severe epilepsy. *Epilepsy Res* 1990;**7**:226–9.
198. Huber B, May T, Seidel M. Lamotrigine in multihandicapped therapy-resistant epileptic patients. *Clin Drug Invest* 1998;**16**:263–77.
199. Leestma JE, Annegers JF, Brodie MJ, Brown S, Schraeder P, Siscovick D, *et al.* Sudden unexplained death in epilepsy: observations from a large clinical development program. *Epilepsia* 1997;**38**:47–55.
200. Buchanan N. Lamotrigine: clinical experience in 200 patients with epilepsy with follow-up to four years. *Seizure* 1996;**5**:209–14.

201. Martin PJ, Millac PAH. Impact of lamotrigine on patients with refractory epilepsy: the Leicester experience. *Seizure* 1994;**3**:209–13.
202. Kwan P, Brodie MJ. Effectiveness of first antiepileptic drug. *Epilepsia* 2001;**42**:1255–60.
203. Schachter SC, Vazquez B, Fisher RS, Beydoun A. Long-term open-label efficacy, safety and tolerability study of TRILEPTAL (oxcarbazepine) in patients with medically intractable partial seizures. *Epilepsia* 2001;**42** (Suppl. 7):176.
204. Beydoun A, Sachdeo WE, Rosenfeld WE, D'Souza J. Long-term safety and efficacy of Oxcarbazepine in patients with refractory partial epilepsy. *Epilepsia* 2001;**42** (Suppl. 7):176.
205. Samren EB, Van Duijn CM, Christiaens G, Hofman A, Lindhout D. Antiepileptic drug regimens and major congenital abnormalities in the offspring. *Ann Neurol* 1999;**46**:739–46.
206. Biraben A, Beaussart M, Josien E, Pestre M, Savet JF, Schaff JL, *et al.* Comparison of twice- and three times daily tiagabine for the adjunctive treatment of partial seizures in refractory patients with epilepsy: an open label, randomised, parallel-group study. *Epileptic Disord* 2001;**3**:91–100.
207. Striano S, Striano P, Boccella P, Nocerino C, Bilo L. Tiagabine in glial tumors. *Epilepsy Res* 2002;**49**:81–5.
208. Nousiainen I, Mäntyjärvi M, Kälviäinen R. Visual function in patients treated with the GABAergic anticonvulsant drug tiagabine. *Clin Drug Invest* 2000;**20**:393–400.
209. Kälviäinen R, Salmenpera T, Jutila L, Aikia M, Nousiainen I, Riekkinen P. Tiagabine monotherapy in chronic partial epilepsy. *Epilepsia* 1999;**40**:258–9.
210. Montouris GD, Biton V, Rosenfeld WE. Nonfocal generalized tonic-clonic seizures: response during long-term topiramate treatment. *Epilepsia* 2000;**41** (Suppl. 1):S77–81.
211. Singh BK, White-Scott S. Role of topiramate in adults with intractable epilepsy, mental retardation, and developmental disabilities. *Seizure* 2002;**11**:47–50.
212. Mecarelli O, Piacenti A, Pulitano P, Vicenzini E, Rizzo C, Rinalduzzi S, *et al.* Clinical and electroencephalographic effects of topiramate in patients with epilepsy and healthy volunteers. *Clin Neuropharmacol* 2001;**24**:284–9.
213. Abou-Khalil B. Topiramate in the long-term management of refractory epilepsy. Topiramate YOL Study Group. *Epilepsia* 2000;**41** (Suppl. 1): S72–6.
214. Pellock J, Kamin M, Kraut L, Wu SC. Adverse events (AEs) when topiramate is titrated to effect: results from an open-label, in-practice study with 800+ patients. *Epilepsia* 2000;**41** (Suppl. 7):105.
215. Canger R, Avanzini G, Tartara A, Durisotti C, Guidolin L, Binelli S, *et al.* Long term efficacy and tolerability of topiramate add-on therapy: Interim analysis after four years treatment. *Boll Lega Ital Epil* 1997;**99**:105–7.
216. Tartara A, Sartori I, Manni R, Galimberti CA, Di Fazio M, Perucca E. Efficacy and safety of topiramate in refractory epilepsy: a long-term prospective trial. *Ital Neurol Sci* 1996;**17**:429–32.
217. Biton V. Preliminary open-label experience with topiramate in primary generalized seizures. *Epilepsia* 1997;**38** (Suppl. 1):S42–4.
218. Janssen-Cilag. *The clinical and cost effectiveness of topiramate (Topomax) in the treatment of epilepsy in adults: A submission prepared for the National Institute for Clinical Excellence*. High Wycombe: Janssen-Cilag; 2002.
219. Wilton LV, Stephens MD, Mann RD. Visual field defect associated with vigabatrin: observational cohort study. *BMJ* 1999;**319**:1165–6.
220. Comaish IF, Gorman C, Galloway NR, Manuchehri K, Midelfart A, Wilton LV. Visual field defect associated with vigabatrin (multiple letters). *BMJ* 2000;**320**:1403–4.
221. Cocito L, Maffini M, Perfumo P, Roncallo F, Loeb C. Vigabatrin in complex partial seizures: a long-term study. *Epilepsy Res* 1989;**3**:160–6.
222. Comaish I, Gorman C, Brimlow G, Barber C, Orr G, Galloway N. The effects of vigabatrin on electrophysiology and visual fields in epileptics: a controlled study with a discussion of possible mechanisms. *Doc Ophthalmol* 2002;**104**:195–212.
223. Jensen H, Sjo Uldall P, Gram L. Vigabatrin and retinal changes. *Doc Ophthalmol* 2002;**104**:171–80.
224. Nousiainen I, Mäntyjärvi M, Kälviäinen R. No reversion in vigabatrin-associated visual field defects. *Neurology* 2001;**57**:1916–7.
225. Toggweiler S, Wieser HG. Concentric visual field restriction under vigabatrin therapy: extent depends on the duration of drug intake. *Seizure* 2001;**10**:420–3.
226. Manuchehri K, Goodman S, Siviter L, Nightingale S. A controlled study of vigabatrin and visual abnormalities. *Br J Ophthalmol* 2000;**84**:499–505.
227. Midelfart A, Midelfart E, Brodtkorb E. Visual field defects in patients taking vigabatrin. *Acta Ophthalmol Scand* 2000;**78**:580–4.
228. Lawden MC, Eke T, Degg C, Harding GF, Wild JM. Visual field defects associated with vigabatrin therapy. *J Neurol Neurosurg Psychiatry* 1999;**67**:716–22.
229. van der Torren K, Graniewski-Wijnands HS, Polak BCP. Visual field and electrophysiological



- abnormalities due to vigabatrin. *Doc Ophthalmol* 2002;**104**:181–8.
230. Malmgren K, Ben-Menachem E, Frisen L. Vigabatrin visual toxicity: evolution and dose dependence. *Epilepsia* 2001;**42**:609–15.
231. Ponjavic V, Andreasson S. Multifocal ERG and full-field ERG in patients on long-term vigabatrin medication. *Doc Ophthalmol* 2001;**102**:63–72.
232. Arndt CF, Derambure P, Defoort-Dhellemmes S, Hache JC. Outer retinal dysfunction in patients treated with vigabatrin. *Neurology* 1999;**52**:1201–5.
233. de Feo MR, Mecarelli O, Marciani MG, Striano S, Ortenzi A, Cerone G, *et al.* Vigabatrin monotherapy in partial epilepsy: Preliminary results of a open collaborative study. *Boll Lega Ital Epil* 1994;**87**:81–2 (in Italian).
234. Arzimanoglou AA, Dumas C, Ghirardi L. Multicentre clinical evaluation of vigabatrin (Sabril) in mild to moderate partial epilepsies. French Neurologists Sabril Study Group. *Seizure* 1997;**6**:225–31.
235. Russ W. Vigabatrin in unsatisfactory controlled epilepsies. *Schweiz Arch Neurol Psychiatr* 1995; **146**:55–9.
236. Buchanan N. Vigabatrin use in 72 patients with drug-resistant epilepsy. *Seizure* 1994;**3**:191–6.
237. Dam M. Long-term evaluation of vigabatrin (gamma vinyl GABA) in epilepsy. *Epilepsia* 1989; **30** (Suppl. 3):S26–30.
238. Pedersen SA, Klosterskov P, Gram L, Dam M. Long-term study of gamma-vinyl GABA in the treatment of epilepsy. *Acta Neurol Scand* 1985; **72**:295–8.
239. Guberman A, Bruni J. Long-term open multicentre, add-on trial of vigabatrin in adult resistant partial epilepsy. The Canadian Vigabatrin Study Group. *Seizure* 2000;**9**:112–18.
240. Michelucci R, Veri L, Passarelli D, Zamagni M, Strumia S, Buzzi AM, *et al.* Long-term follow-up study of vigabatrin in the treatment of refractory epilepsy. *J Epilepsy* 1994;**7**:88–93.
241. Browne TR, Mattson RH, Penry JK, Smith DB, Treiman DM, Wilder BJ, *et al.* Multicenter long-term safety and efficacy study of vigabatrin for refractory complex partial seizures: an update. *Neurology* 1991;**41**:363–4.
242. Reynolds EH, Ring HA, Farr IN, Heller AJ, Elwes RDC. Open, double-blind and long-term study of vigabatrin in chronic epilepsy. *Epilepsia* 1991;**32**:530–8.
243. Sivenius J, Ylinen A, Murros K, Mumford JP, Riekkinen PJ. Vigabatrin in drug-resistant partial epilepsy: a 5-year follow-up study. *Neurology* 1991; **41**:562–5.
244. Schmitz B, Schmidt T, Jokiel B, Pfeiffer S, Tiel-Wilck K, Ruther K. Visual field constriction in epilepsy patients treated with vigabatrin and other antiepileptic drugs: a prospective study. *J Neurol* 2002;**249**:469–75.
245. Paul SR, Krauss GL, Miller NR, Medura MT, Miller TA, Johnson MA. Visual function is stable in patients who continue long-term vigabatrin therapy: implications for clinical decision making. *Epilepsia* 2001;**42**:525–30.
246. Kälviäinen R, Nousiainen I, Mäntyjärvi M, Nikoskelainen E, Partanen J, Partanen K, *et al.* Vigabatrin, a gabaergic antiepileptic drug, causes concentric visual field defects. *Neurology* 1999; **53**:922–6.
247. Tartara A, Manni R, Galimberti C, Sartori I, Murelli R, Marchioni E, *et al.* Long term efficacy and tolerability of Vigabatrin as add-on treatment in adult refractory epilepsy. *Boll Lega Ital Epil* 1997;**99**:23–5 (in Italian).
248. Pitkänen A, Ylinen A, Matilainen R, Luukkainen R, Mervaala E, Seppanen R, *et al.* Long-term antiepileptic efficacy of vigabatrin in drug-refractory epilepsy in mentally retarded patients: a 5-year follow-up study. *Arch Neurol* 1993;**50**:24–9.
249. Remy C, Beaumont D. Efficacy and safety of vigabatrin in the long term treatment of refractory epilepsy. *Br J Clin Pharmacol* 1989;**27** (Suppl. 1): S125–9.
250. Chadwick DW, Anhut H, Greiner MJ, Alexander J, Murray GH, Garofalo EA, *et al.* A double-blind trial of gabapentin monotherapy for newly diagnosed partial seizures. *Neurology* 1998; **51**:1282–8.
251. Schachter SC. Tiagabine monotherapy in the treatment of partial epilepsy. *Epilepsia* 1995; **36** (Suppl. 6):S2–6.
252. Bryant J, Stein K. *Lamotrigine as monotherapy for epilepsy in adults*. Wessex Institute for Health Research and Development; 1998. URL: <http://www.doh.gov.uk/research/swro/rd/publicat/dec/dec80.htm>. Accessed March 2002.
253. Heaney DC, Shorvon SD, Sander JW. An economic appraisal of carbamazepine, lamotrigine, phenytoin and valproate as initial treatment in adults with newly diagnosed epilepsy. *Epilepsia* 1998;**39** (Suppl. 3):S19–25.
254. Heaney DC, Shorvon SD, Sander JW, Boon P, Komarek V, Marusic P, *et al.* Cost minimization analysis of antiepileptic drugs in newly diagnosed epilepsy in 12 European countries. *Epilepsia* 2000;**41** (Suppl. 5):S37–44.
255. Shakespeare A, Simeon G. Economic analysis of epilepsy treatment: a cost minimization analysis comparing carbamazepine and lamotrigine in the UK. *Seizure* 1998;**7**:119–25.

256. Hughes D, Cockerell OC. A cost minimization study comparing vigabatrin, lamotrigine and gabapentin for the treatment of intractable partial epilepsy. *Seizure* 1996;**5**:89–95.
257. Selai CE, Smith K, Trimble MR. Adjunctive therapy in epilepsy: a cost-effectiveness comparison of two AEDs. *Seizure* 1999;**8**:8–13.
258. Markowitz MA, Mauskopf JA, Halpern MT. Cost-effectiveness model of adjunctive lamotrigine for the treatment of epilepsy. *Neurology* 1998;**51**:1026–33.
259. Reinharz DK, W. Contandriopoulos, A. P. Tessier, G. Champagne, F. The economic effects of introducing vigabatrin a new antiepileptic medication. *Pharmacoeconomics* 1995;**8**:400–9.
260. Schachter SC, Sommerville KW, Ryan JE. A cost-effectiveness analysis of tiagabine, phenytoin, and carbamazepine adjunctive therapy for patients with complex partial seizures. *Neurology* 1999;**52** (Suppl. 6):A143.
261. Messori A, Trippoli S, Becagli P, Cincotta M, Labbate MG, Zaccara G. Adjunctive lamotrigine therapy in patients with refractory seizures: a lifetime cost–utility analysis. *Eur J Clin Pharmacol* 1998;**53**:421–7.
262. O'Neill BA, Trimble MR, Bloom DS. Adjunctive therapy in epilepsy: a cost-effectiveness comparison of alternative treatment options. *Seizure* 1995;**4**:37–44.
263. Novartis Pharmaceuticals UK. *Appraisal of Trileptal for treatment of epilepsy in adults: evidence submitted to the National Institute for Clinical Excellence*. Camberley: Novartis Pharmaceuticals UK; 2002.
264. GlaxoSmithKline. *Lamotrigine (Lamictal) for the treatment of epilepsy in adults: a submission to the National Institute for Clinical Excellence*. Critchley Park: Glaxo Smith Kline; 2002.
265. Cephalon UK *The clinical effectiveness and cost effectiveness of new drugs for epilepsy: a submission to the National Institute for Clinical Excellence*. Guildford: Cephalon UK; 2002.
266. UCB Pharma. *Clinical and cost-effectiveness of levetiracetam (Keppra) in the treatment of refractory epilepsy: sponsor submission to the National Institute for Clinical Excellence*. Watford: UCB Pharma; 2002.
267. Stinnett A, Paltiel A. Estimating CE ratios under second order uncertainty: the mean ratio versus the ratio of means. *Med Decis Making* 1997;**17**:483–9.
268. Aldenkamp AP, Mulder OG, Overweg J. Cognitive effects of lamotrigine as first-line add-on in patients with localization-related (partial) epilepsy. *J Epilepsy* 1997;**10**:117–21.
269. Briggs A, Goeree R, Blackhouse G, O'Brien B. Probabilistic analysis of cost-effectiveness models: choosing between treatment strategies for gastroesophageal reflux disease. *Med Decis Making* 2002;**22**:290–308.
270. Lhatoo SD, Sander JWAS, Shorvon SD. The dynamics of drug treatment in epilepsy: an observational study in an unselected population based cohort with newly diagnosed epilepsy followed up prospectively over 11–14 years. *J Neurol Neurosurg Psychiatry* 2001;**71**:632–7.
271. Billingham LJ, Abrams KR, Jones DR. Methods for the analysis of quality-of-life and survival data in health technology assessment. *Health Technol Assess* 1999;**3**(10).
272. Abbott Laboratories. *An open-label extension study of tiagabine HCl in the treatment of patients with partial seizures*. Abbott Park, IL: Abbott Laboratories; 1998.
273. Office for National statistics. *Mortality statistics: general. Review of the Registrar General on deaths in England and Wales, 2000*. London: Office for National Statistics; 2000.
274. Ades A. *A chain of evidence with mixed comparisons: models for multi-parameter evidence synthesis and consistency of evidence*. 2002. URL: <http://www.ihs.ox.ac.uk/herc/DEEM/Ades.pdf>. Accessed February 2003.
275. Netten A, Curtis L. *Unit costs of health and social care*. PSSRU, University of Kent; 2002. URL: <http://www.ukc.ac.uk/PSSRU>. Accessed February 2003.
276. Department of Health. NHS Executive. *The new NHS: 2002 reference costs*. Department of Health; 2002. URL: <http://www.doh.gov.uk/nhsexec/refcosts.htm#spred>. Accessed February 2003.
277. Lhatoo SD, Johnson AL, Goodridge DM, MacDonald BK, Sander JWAS, Shorvon SD. Mortality in epilepsy in the first 11 to 14 years after diagnosis: multivariate analysis of a long-term, prospective, population-based cohort. *Ann Neurol* 2001;**49**:336–44.
278. Wilton LV, Stephens MDB, Mann RD. Visual field defect associated with vigabatrin: observational cohort study. *BMJ* 1999;**319**:1165–6.
279. NHS North West *Clinical Neuroscience Partnership. Clinical framework for the management of adults with epilepsy*. A North West Clinical Framework. Manchester: North West Clinical Neuroscience Partnership; 2001.
280. Johannesson M, Weinstein S. On the decision rules of cost-effectiveness analysis. *J. Health Econ*. 1993;**12**:459–67.
281. Van Hout BA, Al MJ, Gordon GS, Rutten FF. Costs, effects and C/E-ratios alongside a clinical trial. *Health Econ* 1994;**3**:309–19.

282. Briggs AH. Handling uncertainty in cost effectiveness models. *Pharmacoeconomics* 2000; **17**:479–500.
283. Commission on Antiepileptic Drugs of the International League Against Epilepsy. Guidelines for the clinical evaluation of antiepileptic drugs. *Epilepsia* 1989;**30**:400–8.
284. ILAE Commission on Antiepileptic Drugs. Considerations on designing clinical trials to evaluate the place of new antiepileptic drugs in the treatment of newly diagnosed and chronic patients with epilepsy. *Epilepsia* 1998;**39**:799–803.
285. Agency for Healthcare Research and Quality. *Management of newly diagnosed patients with epilepsy: a systematic review of the literature*. Agency for Healthcare Research and Quality; 2001. URL: <http://www.ahrq.gov/clinic/epcsums/epilepsum.htm>. Accessed February 2003.
286. SIGN. *Diagnosis and management of epilepsy in adults*. Guideline. SIGN Publication 21. Edinburgh: SIGN; 1997.
287. International League Against Epilepsy. Guidelines for the care of women of childbearing age with epilepsy: Commission on Genetics, Pregnancy, and the Child. *Epilepsia* 1993;**34**:588–9.
288. Chadwick D. SANAD – a RCT of longer-term clinical outcomes and cost effectiveness of standard and new antiepileptic drugs. (Protocol for a Cochrane Review.) Liverpool: University Department of Neurological Science; ongoing.
289. Bergey GK, Morris HH, Rosenfeld W, Blume WT, Penovich PE, Morrell MJ, *et al.* Gabapentin monotherapy. 1. An 8-day, double-blind, dose-controlled, multicenter study in hospitalized patients with refractory complex partial or secondarily generalized seizures. *Neurology* 1997; **49**:739–45.
290. Betts T, Goodwin G, Withers RM, Yuen AWC. Human safety of lamotrigine. *Epilepsia* 1991; **32** (Suppl. 2):S17–21.
291. GlaxoSmithKline. *Open one-week trial of lamotrigine as add-on therapy in patients with epilepsy*. Beckenham: Wellcome Foundation; 1987.
292. Critchley P. MREC/97/0/44 (SCAB4005) – *Evaluation of the long-term clinical effectiveness of lamotrigine in epilepsy; an open label follow up study of patients established on monotherapy with either lamotrigine, valproate or Carbamazepine*. Leicester: Research and Development Office, Leicester General Hospital NHS Trust; 2000.
293. GlaxoSmithKline. *Evaluation of the long term clinical effectiveness of lamotrigine in epilepsy; an open label, follow up study of patients established on monotherapy with either lamotrigine, valproate or carbamazepine*. Critchley Park: Glaxo Smith Kline; 1998.
294. Akyol A, Yoldas T, Baydas G, Müngen B. Lamotrigine versus valproate as monotherapy in patients with newly diagnosed epilepsy. *Epilepsia* 1998;**39** (Suppl. 2):23.
295. Duchowny M, Pellock JM, Graf WD, Billard C, Gilman J, Casale E, *et al.* A placebo-controlled trial of lamotrigine add-on therapy for partial seizures in children. Lamictal Pediatric Partial Seizure Study Group. *Neurology* 1999;**53**:1724–31.
296. Fakhoury T, Li H, Moorat A. Quality of life in patients switched to monotherapy with lamotrigine or valproate. 24th International Epilepsy Congress, Buenos Aires 2001. *Epilepsia* 2001; **42** (Suppl. 2).
297. Mouzichouk L, Maryek G, Obukhova H. Lamotrigine in patients with treatment-resistant epilepsy. *Epilepsia* 1995;**36**:S114.
298. Bisgaard C. Lamictal as add-on anti-epileptic drug in 210 patients with resistant epilepsy. *Epilepsia* 1994;**35** (Suppl. 7).
299. Marciani MG, Stanzione P, Mattia D, Spanedda F, Bassetti MA, Maschio M, *et al.* Lamotrigine add-on therapy in focal epilepsy: electroencephalographic and neuropsychological evaluation. *Clin Neuropharmacol* 1998;**21**:41–7.
300. French J, Edrich P, Cramer JA. A systematic review of the safety profile of levetiracetam: a new antiepileptic drug. *Epilepsy Res* 2001;**47**:77–90.
301. Krakow K, Walker M, Otoul C, Sander J. Long-term continuation of levetiracetam in patients with refractory epilepsy. *Neurology* 2001;**56**:1772–4.
302. Betts T, Yarrow H, Greenhill L, Barrett M. *Clinical experience of marketed levetiracetam in an epilepsy clinic – a one year follow up study*. 2002. URL: <http://www.harcourt-international.com/journals/seiz/sciencedirect.cfm>. Accessed 4 December 2002.
303. Mohanraj R, Parker P, Kelly K, Stephen L, Sills G, Brodie M. Clinical experience with levetiracetam: a prospective observational study. *Epilepsia* 2002; **43** (Suppl. 7):196.
304. Morrell M, Ferrendelli J, French J, Leppik I, Magnus L, Herbeuval A. Final results from the KEEPER trial: a phase IV community based clinical trial investigating levetiracetam as add-on therapy in partial onset seizures. *Epilepsia* 2002; **43** (Suppl. 7):197.
305. Sachdeo R, Beydoun A, Schachter S, Vazquez B, Schaul N, Mesenbrink P, *et al.* Oxcarbazepine (Trileptal) as monotherapy in patients with partial seizures. *Neurology* 2001;**57**:864–71.
306. Beydoun A, Sachdeo RC, Rosenfeld WE, Krauss GL, Sessler N, Mesenbrink P, *et al.* Oxcarbazepine monotherapy for partial-onset seizures – a multicenter, double-blind, clinical trial. *Neurology* 2000;**54**:2245–51.

307. Beydoun A, Sachdeo RC, Rosenfeld WE, D'Souza J. Long-term safety and efficacy of oxcarbazepine in patients with refractory partial epilepsy. *Epilepsia* 2001;**42** (Suppl. 7):176.
308. Van Parys JA, Meinardi H. Survey of 260 epileptic patients treated with oxcarbazepine (Trileptal) on a named-patient basis. *Epilepsy Res* 1994;**19**:79–85.
309. Friis ML, Kristensen O, Boas J, Dalby M, Deth SH, Gram L, *et al.* Therapeutic experiences with 947 epileptic out-patients in oxcarbazepine treatment. *Acta Neurol Scand* 1993;**87**:224–7.
310. Nielsen OA, Johannessen AC, Bardrum B. Oxcarbazepine-induced hyponatremia, a cross-sectional study. *Epilepsy Res* 1988;**2**:269–71.
311. Jensen N. Oxcarbazepine in patients hypersensitive to carbamazepine. Presented at the 16th Epilepsy International Congress, Hamburg, 1985.
312. Novartis Pharmaceuticals. *Trileptal (oxcarbazepine, GP 47680) [150, 300 and 600 mg oral, film-coated tablets]: expert report on the clinical documentation.* East Hanover, NJ: Novartis Pharmaceuticals; 1999.
313. Guerreiro MM, Vigonius U, Pohlmann H, de Manreza ML, Fejerman N, Antoniuk SA, *et al.* A double-blind controlled clinical trial of oxcarbazepine versus phenytoin in children and adolescents with epilepsy. *Epilepsy Res* 1997;**27**:205–13.
314. Ben-Menachem E. Clinical efficacy of topiramate as add-on therapy in refractory partial epilepsy: the European experience. *Epilepsia* 1997;**38**:S28–30.
315. Ben-Menachem E. International experience with tiagabine add-on therapy. *Epilepsia* 1995;**36** (Suppl. 6):S14–21.
316. Biraben A, Beaussart M, Josien E, Pestre M, Savet JF, Schaff JL, *et al.* Comparison of twice- and three times daily tiagabine for the adjunctive treatment of partial seizures in refractory patients with epilepsy: an open label, randomised, parallel-group study. *Epileptic Disord* 2001;**3**:91–100.
317. Arroyo S, Salas Puig J, Alvarez Gutierrez J, Amador Trujillo R, Anciones Rodriguez V, Arribas Bartolome A, *et al.* An open study of tiagabine in partial epilepsy. *Rev Neurol* 2001;**32**:1041–6.
318. Cramer JA, Menachem EB, French J. Review of treatment options for refractory epilepsy: new medications and vagal nerve stimulation. *Epilepsy Res* 2001;**47**:17–25.
319. Kazibutowska Z, Stelmach-Wawrzyczek M. Effects of therapy with new antiepileptic drugs (tiagabine, gabapentin, topiramate) in drug-resistant epilepsy (abstract). *Epilepsia* 2000;**41** (Suppl. 2):S38.
320. Kazibutowska Z, Stelmach-Wawrzyczek M, Solytk J. Efficacy of tiagabine and topiramate as add-on therapy in drug resistant simple or complex partial and secondary generalized seizures (abstract). *Epilepsia* 2001;**42** (Suppl. 2):S38.
321. Baker GA, Currie NG, Light MJ, Schneiderman JH. The effects of adjunctive topiramate therapy on seizure severity and health-related quality of life in patients with refractory epilepsy – a Canadian study. *Seizure* 2002;**11**:6–15.
322. Biton V, Edwards KR, Montouris GD, Sackellares JC, Harden CL, Kamin M. Topiramate titration and tolerability. *Ann Pharmacother* 2001;**35**:173–9.
323. Stephen LJ, Sills GJ, Brodie MJ. Topiramate in refractory epilepsy: a prospective observational study. *Epilepsia* 2000;**41**:977–80.
324. Arroyo S, Squires L, Wang S, R T. Topiramate (TPM) monotherapy in newly diagnosed epilepsy: effectiveness in dose-response study. Presented at the 5th European Congress of Epileptology, 5–10 October 2002, Madrid.
325. Peeters K, Adriaenseen I, Wapenaar R. Topiramate as add-on therapy in refractory partial-onset seizures: pooled analysis of RCTs in adults. Presented at the 5th European Congress on Epileptology, 5–10 October 2002, Madrid.
326. Penry JK, Wilder BJ, Sachdeo RC, Vaughan LV, Ahlbrandt RA, Sommerville KW, *et al.* Multicenter dose-response study of vigabatrin in adults with focal (partial) epilepsy (abstract). *Epilepsia* 1993;**34** (Suppl. 6):67.
327. Drummond MF, O' Brien B, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programmes.* 2nd ed. Oxford: Oxford Medical Publications; 1997.
328. Matsuo F, Gay P, Madsen J, Tolman KG, Rollins DE, Risner ME, *et al.* Lamotrigine high-dose tolerability and safety in patients with epilepsy: a double-blind, placebo-controlled, eleven-week study. *Epilepsia* 1996;**37**:857–62.
329. Baulac M. *Randomized, double-blind, parallel-group, multi-centre study of safety and efficacy of tiagabine versus valproate as monotherapy in patients with newly diagnosed primary generalised tonic-clonic seizures.* Sanofi Synthelabo; 2001.
330. Brodie MJ, Chadwick DW, Anhut H, Messmer S, Garofalo E. Gabapentin versus lamotrigine monotherapy: a double-blind comparison in newly diagnosed epilepsy. *Epilepsia* 2001;**42** (Suppl. 7):177.
331. Chadwick D. Gabapentin (Neurontin) in generalized tonic-clonic seizures. *Neurology* 1994;**44** (Suppl. 4):A321.
332. Jones MW. Topiramate – safety and tolerability. *Can J Neurol Sci* 1998;**25**:S13–15.
333. Anhut H, Greiner MJ, Murray GH. Double-blind, fixed-dose comparison study of gabapentin (Gbp Neurontin(R)) and carbamazepine (Cbz)

- monotherapy in patients with newly diagnosed partial epilepsy. *Epilepsia* 1995;**36** (Suppl. 4):67.
334. Baker GA, Hesdon B, Marson AG. Quality-of-life and behavioral outcome measures in randomized controlled trials of antiepileptic drugs: a systematic review of methodology and reporting standards. *Epilepsia* 1999;**40**:73–4.
335. Patterson V. Gabapentin as an anticonvulsant in partial epilepsy. *Neurology* 1988;**38** (Suppl. 1): 152.
336. Trudeau VL, Dimond KR, Smith FB, Wilensky AJ, Chmelir T, Ricker B, *et al.* Gabapentin (Gbp Neurontin(R)) monotherapy compared with carbamazepine (Cbz) monotherapy and combination Gbp plus Cbz (Gbp/Cbz) therapy in patients with medically refractory partial seizures – a 3-way cross-over trial (94536). *Epilepsia* 1995; **36** (Suppl. 4):68.
337. GlaxoSmithKline. *A multicentre randomised double-blind placebo-controlled crossover trial of lamotrigine as add-on therapy in treatment resistant epilepsy: Australia*. Beckenham: Wellcome Foundation; 1991.
338. Beran RG, Berkovic SF, Dunagan FM, Vajda FJE, Danta G, Black AB. Double-blind placebo-controlled cross-over study of lamotrigine in treatment-resistant epilepsy. *J Clin Neurosci* 1997; **4**:384.
339. Wellcome Foundation. *Double blind, placebo-controlled trial of lamotrigine as add-on therapy in treatment-resistant epilepsy*. Beckenham: Wellcome Foundation; 1989.
340. GlaxoSmithKline. *A randomised double-blind placebo-controlled crossover add-on trial of lamotrigine in patients with treatment resistant partial seizures*. Critchley Park: Glaxo Wellcome UK; 1990.
341. Montouris G, Mirza WU, Biton V, Vuong A, Barrett P, Hammer A. Effects of LAMICTAL (R) and DEPAKOTE (R) monotherapy on body weight in patients with epilepsy: interim analysis of a randomized, double-blind clinical trial. *Neurology* 1999;**52** (Suppl. 6):A523–4.
342. Mirza W, Biton V, Barrett P, Vuong A, Hammer A. Weight gain associated with valproate monotherapy in patients with epilepsy: An interim analysis of a randomized, double-blinded comparative clinical trial with lamotrigine. *Epilepsia* 1999;**40** (Suppl. 2):282.
343. Biton VM, W. Montouris, G. Earl, N. Vuong, A. Hammer, A., Barrett P. Weight gain associated with valproate versus lamotrigine monotherapy in patients with epilepsy: a randomized, double-blind comparative clinical trial. *Eur Neuropsychopharmacol* 2000;**10** (Suppl. 3):S236.
344. Edwards KR, Sackellares JC, Vuong A, Hammer AE, Barrett PS. Lamotrigine monotherapy improves depressive symptoms in epilepsy: a double-blind comparison with valproate. *Epilepsy Behav* 2001; **2**:28–36.
345. GlaxoSmithKline. *A double-blind, double-dummy, parallel-group comparison of lamotrigine and divalproex sodium monotherapy in patients with generalised seizures*. Critchley Park: Glaxo Wellcome UK; 2001.
346. GlaxoSmithKline. *A placebo-controlled, double-blind, crossover trial of lamotrigine as add-on therapy in treatment resistant partial seizures*. Critchley Park: Glaxo Wellcome UK; 1994.
347. Boas J, Cooke EA, Yuen AWC. Controlled trial of lamotrigine (Lamictal) for treatment resistant partial seizures. *Epilepsia* 1995;**36**:S113.
348. Reynolds EH. Lamotrigine versus carbamazepine in epilepsy. *Lancet* 1995;**345**:1300.
349. Richens A. Lamotrigine versus carbamazepine double-blind comparative trial. In *Lamotrigine: A Brighter Future – International Congress and Symposium*; 1996, Series 214. pp. 9–14.
350. Brodie MJ, Giorgi L, The Lamotrigine Elderly Study G. A multicenter double-blind randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. *Epilepsia* 1998;**39** (Suppl. 6):72.
351. Park D. *Multicentre double blind randomised comparative trial of lamotrigine and carbamazepine in elderly patients with new diagnosed epilepsy*, Ongoing.
352. Glaxo Wellcome Research and Development. *A multicentre, double-blind randomised comparative trial of lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy*. Critchley Park, UK.: GlaxoSmithKline, 1998.
353. Bryant-Comstock L, Moorat A. Improvement in quality of life and severity of side effects in patients with epilepsy receiving lamotrigine or valproate. *Epilepsia* 1999;**40** (Suppl. 7):61.
354. Gillham R. Use of SEALS, a quality of life instrument, in evaluating lamotrigine and carbamazepine monotherapy. *Epilepsia* 1995; **36** (Suppl. 3):S186.
355. Panayiotopoulos CP, Gilliam F, Vasquez B, Sackellares J, Chang GY, Messenheimer J, *et al.* An active-control trial of lamotrigine monotherapy for partial seizures [3] (multiple letters). *Neurology* 2000;**54**:777.
356. GlaxoSmithKline. *A multicentre, double-blind, active control evaluation of the efficacy and safety of lamotrigine monotherapy in patients with partial seizures*. Critchley Park: Glaxo Wellcome UK; 1996.
357. Tamhne R. *An open, randomised comparison of lamotrigine with valproate as monotherapy in patients with idiopathic generalised epilepsy*. Leicester: University Hospitals of Leicester; 1997.
358. Stephen LJ. *Changing young women with epilepsy to lamotrigine monotherapy*. Glasgow: North Glasgow University Hospitals NHS Trust; 1999.

359. Critchley P. *An open randomised comparison of Lamotrigine with physicians' preferred choice of valproate or carbamazepine as monotherapy in newly diagnosed epilepsy*. Leicester: University Hospitals of Leicester; 1996.
360. GlaxoSmithKline. *A randomised double-blind placebo-controlled crossover add-on trial of lamotrigine in patients with treatment resistant partial seizures*. Critchley Park: Glaxo Wellcome UK; 1989.
361. Wroe S. Study N138: *Evaluation of the efficacy and tolerability of ucb L059 (1500 mg b.i.d.) monotherapy in responder selected epileptic patients with complex partial onset seizures*. Ipswich: Department of Neurology, Ipswich Hospital NHS Trust; 1998.
362. Kerr M, Kane K, Moorat AM. Switching to monotherapy with Lamictal compared to valproate. *Epilepsia* 1999;**40** (Suppl. 2):284.
363. Bryant-Comstock L, Kane K, Moorat A. Quality of life improvement in patients treated with lamotrigine compared with valproate. *Epilepsia* 1999;**40**:98.
364. Nanry K, Martinez W, Li H, *et al.* Epilepsy patients switched from older antiepileptic drugs to lamotrigine monotherapy show improvement in quality of life. *Epilepsia* 2000;**41** (Suppl. 7).
365. GlaxoSmithKline. *A multicentre, placebo-controlled, parallel design, dose-response evaluation of the safety and efficacy of lamotrigine (LAMICTAL) as add-on therapy in outpatients with partial seizures*. Critchley Park: Glaxo Wellcome UK; 1991.
366. Burroughs Wellcome. *Final study report Lamotrigine 14-01: Chronic dose tolerance of lamotrigine and placebo in epileptic patients: a further evaluation*. Research Triangle Park, NC: Burroughs Wellcome Foundation; 1989.
367. GlaxoSmithKline. *A multicentre, double-blind, placebo-controlled, add-on, crossover study of lamotrigine in epileptic outpatients with partial seizures*. Critchley Park: Burroughs Wellcome; 1990.
368. Dam M. Lamotrigine versus carbamazepine open-label comparative trial. In *Lamotrigine: A Brighter Future – International Congress and Symposium*, 1996, Series 214. pp. 17–21.
369. Yuen AWC, Chapman A. Interim report on an open multicentre lamotrigine (Lamictal) versus carbamazepine monotherapy trial in patients with epilepsy. *Can J Neurol Sci* 1993;**20**:S150.
370. Severi S, Muscas GC, Bianchi A, Zolo P. Efficacy and safety of lamotrigine monotherapy in partial epilepsy. *Boll Lega Ital Epil* 1994;**86–87**:149–51.
371. Severi S, Cantelmi T, Bianchi A, Zolo P. Efficacy and safety of lamotrigine in patients with partial epilepsy: preliminary data. *Boll Lega Ital Epil* 1993;**82–83**:139–43.
372. Severi S, Bianchi A, Zolo P, Muscas GC. Lamotrigine monotherapy in patients with partial epilepsy. *Epilepsia* 1995;**36** (Suppl. 3):S113.
373. Dodrill CB. Problems in the assessment of cognitive effects of antiepileptic drugs. *Epilepsia* 1992;**33** (Suppl. 6):S29–32.
374. Burroughs Wellcome. *A multicenter, placebo-controlled, parallel-design, phase III evaluation of the safety of lamotrigine (LAMICTAL) as add-on therapy in outpatients with partial seizures*. Research Triangle Park, NC: Burroughs Wellcome; 1991.
375. Schmidt D, Ried S, Rapp P. Add-on treatment with lamotrigine for intractable partial epilepsy: a placebo-controlled, cross-over trial. *Epilepsia* 1993;**34** (Suppl. 2):66.
376. Smith D, Chadwick D, Baker G, Davis G, Dewey M. Seizure severity and the quality of life. *Epilepsia* 1993;**34** (Suppl. 5):S31–5.
377. Smith D, Baker G, Davis G, Cook M, Fish DR, Shorvon SD, *et al.* A placebo-controlled, double-blind, crossover trial of lamotrigine as add-on therapy on seizure frequency, severity, mood and quality of life in patients with treatment-resistant epilepsy. *J Neurol Neurosurg Psychiatry* 1992;**55**:416.
378. GlaxoSmithKline. *A randomised double-blind placebo-controlled crossover trial of lamotrigine as add-on therapy on seizure frequency, seizure severity, mood and quality-of-life in patients with treatment resistant epilepsy: Liverpool*. Beckenham: Wellcome Foundation; 1992.
379. Steiner TJ. Comparison of lamotrigine and phenytoin monotherapy in newly diagnosed epilepsy (abstract). *Epilepsia* 1994;**35** (Suppl. 8):31.
380. Steiner TJ, Yuen AWC. Comparison of lamotrigine (Lamictal) and phenytoin monotherapy in newly diagnosed epilepsy. *Epilepsia* 1994;**35** (Suppl. 7):61.
381. GlaxoSmithKline. *A multicentre, double-blind comparison of the efficacy and safety of lamotrigine and phenytoin monotherapy in patients with newly diagnosed epilepsy*. Critchley Park: Glaxo Wellcome UK; 1994.
382. Ben-Menachem E, Falter U. 'Proof of principle' study to evaluate efficacy and safety of levetiracetam (1500 mg, bid) monotherapy in patients with refractory focal epilepsy. *Epilepsia* 1999;**40** (Suppl. 7):218.
383. Ben-Menachem E, Fortpled C, Falter U. Evaluation of the efficacy and tolerability of levetiracetam (LEV) monotherapy in epileptic patients with complex partial onset seizures. *Epilepsia* 1999;**40** (Suppl. 2):249.
384. Crawford P, Danniau A, Waegemans T. Levetiracetam (LEV) for the treatment of refractory epilepsy: tolerability and efficacy as add-on treatment without up-titration period. *Epilepsia* 1999;**40** (Suppl. 2):248.

385. Shorvon S, Otoul C, Selak I. Efficacy and tolerability of levetiracetam (LEV) as add-on treatment in refractory epileptic patients with partial onset seizures: analysis of the crossover part of the European trial. *Epilepsia* 1999; **40** (Suppl. 2):248–9.
386. Penovich P, Cereghino J, Debrabandere L, Gauer L. Levetiracetam: evaluation of efficacy and safety of different dosages in add-on treatment of partial epilepsy. *Epilepsia* 1998;**39** (Suppl. 6):68.
387. Radtke R, Biton V, Abou-Khalil B, Nohria V. Levetiracetam reduces seizure frequency within two weeks of initiating therapy when used as an adjunct to other AEDs in patients with partial-onset seizures. *Epilepsia* 1999;**40** (Suppl. 7):243.
388. Cramer JA, Arrigo C, Gauer L, Cereghino J. Short-term treatment with levetiracetam enhances health-related quality of life in patients with refractory epilepsy. *Epilepsia* 1999;**40** (Suppl. 2):98.
389. Wroe SJ. *Clinical trial protocol OT?PEI-GGB 93031 Trileptal in patients with partial seizures*. Ipswich: Department of Neurology, Ipswich Hospital NHS Trust; 1997.
390. Houtkooper M, Vanoorschot C, Hoppener R. Oxcarbazepine (Gp-47680) versus carbamazepine – a double-blind crossover study in patients with epilepsy. *Acta Neurol Scand* 1984;**70**:221–2.
391. Reimikainen K, Keranen T, Hallikainen E, Riekkinen PJ. Substitution of diphenylhydantoin by oxcarbazepine or carbamazepine: double-blind study. *Acta Neurol Scand* 1984;**69**:89–90.
392. Schachter SC, Vazquez B, Fisher RS, Laxer KD, Combe-Cantrell D, Faught E, *et al.* Oxcarbazepine in a monotherapy trial for partial seizures – placebo-controlled studies in neurology: where do they stop? *Neurology* 1999;**53**:2211–12.
393. Aikia M, Kälviäinen R, Juttila L, Riekkinen P Sr. Cognitive effects of initial tiagabine monotherapy. *Epilepsia* 1999;**40** (Suppl. 2):99.
394. Wroe S. Randomised, double-blind, parallel-group, multi-centre study of safety and efficacy of tiagabine versus valproate as mono-therapy in patients with newly diagnosed primary generalised tonic-clonic seizures. Protocol number: TIA-126/CNS/1. NRR entry.
395. Abbott Laboratories. *Phase II study of tiagabine: efficacy and safety in adjunctive treatment of partial seizures*. Abbott Park, IL: Abbott Laboratories; 1994.
396. Arnett JL, Dodrill CB, Mercante DE, Schaller GA, Sommerville KW. Evaluation of the effects of tiagabine HCl on cognitive functioning and adjustment in patients with epilepsy. *Epilepsia* 1995;**36** (Suppl. 4):55.
397. Dodrill CB, Arnett JL, Sommerville K, Mengel H. Tiagabine. *Epilepsia* 1995;**36** (Suppl. 3):S31.
398. Abbott Laboratories. *Safety and efficacy of three dose levels of tiagabine HCl versus placebo as adjunctive treatment for complex partial seizures*. Abbott Park, IL: Abbott Laboratories; 1994.
399. Riekkinen PJ, Kälviäinen R, Aikia M, Mervaal E, Saukkonen AM, Pitkänen A. Cognitive and electrophysiological effects of tiagabine add-on therapy: a randomised double-blind placebo-controlled study. *Neurology* 1994;**44** (Suppl. 2):A321.
400. Abbott Laboratories. *Safety and efficacy of tiagabine as adjunctive treatment for complex partial seizures*. Abbott Park, IL: Abbott Laboratories; 1993.
401. Sachdeo R, Leroy R, Krauss G, Green P, Drake M, Leppik I, *et al.* Safety and efficacy of bid and qid dosing with tiagabine HCl versus placebo as adjunctive treatment for partial seizures. *Neurology* 1995;**45** (Suppl. 4):A202.
402. Abbott Laboratories. *Safety and efficacy of BID and QID dosing with tiagabine HCl versus placebo as adjunctive treatment for partial seizures*. Abbott Park, IL: Abbott Laboratories; 1994.
403. Vasquez B, Sachdeo RC, Chang G, Lenz GT, Hentz J, Martin J, *et al.* Tiagabine or phenytoin as first add-on therapy for complex partial seizures. *Neurology* 1998;**50** (Suppl. 4):A199.
404. Biton V, Vasquez KB, Sachdeo RC, Lenz G, Deaton R, Sommerville K. Adjunctive tiagabine compared with phenytoin and carbamazepine in the multicenter, double-blind trial of complex partial seizures. *Epilepsia* 1998;**39** (Suppl. 6):125–6.
405. Uthman B, Rowan AJ, Ahmann P, Wannamaker B, Schachter S, Rask C. Safety and efficacy of 3 dose levels of tiagabine HCl versus placebo as adjunctive treatment for complex partial seizures. *Ann Neurol* 1993;**34**:272.
406. Rowan AJ, Uthman B, Ahmann P, *et al.* Safety and efficacy of three dose levels of tiagabine HCl versus placebo as adjunctive treatment of complex partial seizures. *Epilepsia* 1994;**35** (Suppl. 8):54.
407. Aldenkamp AP, Baker G, Mulder OG, Chadwick P, Cooper G, de Haan GJ, *et al.* A randomized observer-blind clinical study comparing the cognitive effects of topiramate versus valproate in a first-line add on design. *Epilepsia* 1999; **40** (Suppl. 2):94–5.
408. Bailey MES. *A randomised, observer blinded, parallel study to evaluate the effect on cognitive function of Topamax (topiramate) compared to valproate as add-on therapy to carbamazepine, in subjects with partial onset seizures (PRI/TOP-INT-10)*. Glasgow: South Glasgow University Hospitals NHS Trust; 2000.
409. Cooper P. *Topiramate cognitive function trial*. Salford: Hope Hospital; 1999.
410. Ben-Menachem E, Dam M, Henriksen O, Schmidt D. Double-blind, placebo-controlled trial

- of 800 mg/day topiramate as add-on therapy in patients with refractory partial epilepsy. *Epilepsia* 1995;**36** (Suppl. 3):S150.
411. Ben-Menachem E, Dam M, Mikkelsen M, Engelskjøn H, Henriksen O, Johannessen SI, *et al.* Topiramate add-on treatment in patients with intractable partial epilepsy: a multicenter study. *Epilepsia* 1993;**34** (Suppl. 2):109.
  412. Faught E, Wilder BJ, Ramsay RE, Reife RA, Kramer LD, Pledger GW, *et al.* Topiramate dose-ranging trial in refractory partial epilepsy. *Epilepsia* 1995;**36** (Suppl. 2):33.
  413. Guberman A, Neto F, Gassman-Mayer C. Topiramate 200 mg/day as the target dose for add-on therapy in adults. *Neurology* 2001; **56** (Suppl. 3):A332.
  414. Guberman A, Neto W, Gassman-Mayer C, Johnson RW. Efficacy of 200 mg/day topiramate in treatment resistant partial seizures when added to an enzyme-inducing antiepileptic drug (AED). *Epilepsia* 2001;**42** (Suppl. 7):179.
  415. Privitera MD, Brodie MJ, Neto W, Wang S. Topiramate, carbamazepine, and valproate in the spectrum of newly diagnosed epilepsy. *Neurology* 2001;**56** (Suppl. 8):A332.
  416. Wheless J, Wang S. Monotherapy in newly diagnosed epilepsy: findings in the pediatric subset of a comparative study of topiramate, carbamazepine, and valproate. *Epilepsia* 2001; **42** (Suppl. 7):57.
  417. Privitera M, Fincham R, Penry JK, Reife R, Kramer L, Pledger G, *et al.* Dose-ranging trial with higher doses of topiramate in patients with resistant partial seizures. *Epilepsia* 1995; **36** (Suppl. 4):33.
  418. Martinez-Lage J, Ben-Menachem E, Shorvon SD, Weber M. Double-blind, placebo-controlled trial of 400 mg/Day topiramate as add-on therapy in patients with refractory partial epilepsy. *Epilepsia* 1995;**36** (Suppl. 3):S149–50.
  419. Tassinari C, Chauvel P, Chodkiewicz J, Shorvon SD, Henriksen O, Dam M, *et al.* Double-blind, placebo-controlled trial of 600 mg/day topiramate as add-on therapy in patients with refractory partial epilepsy. *Epilepsia* 1995;**36**:S150.
  420. Yu H, Yen D, Hing C, Shung M. Double-blind, placebo-controlled trial of topiramate as add-on therapy in patients with refractory partial epilepsy. *Epilepsia* 1999;**40** (Suppl. 2):97–97.
  421. Dodrill CB, Arnett J, Sommerville K, Sussman N. Evaluation of the effects of vigabatrin (Sabril(R), Vgb) upon cognition and quality-of-life in epilepsy. *Neurology* 1993;**43** (Suppl. 4):A306-7.
  422. French J, Pellock J, Ferrendelli J, Sommerville K, Sherry K, Ahlbrandt R, *et al.* Results of a multicenter, placebo-controlled, parallel study of Vigabatrin (Vgb, Sabril(R)) in patients with focal epilepsy whose seizures are difficult to control. *Neurology* 1993;**43** (Suppl. 4):A307.
  423. Grunewald RA, Thompson P, Corcoran R, Corden Z, Jackson GD, Duncan JS. Effects of vigabatrin on seizure frequency and cognitive function. *Neurology* 1993;**43** (Suppl. 4):A307.
  424. Kälviäinen R, Aikia M, Mervaala E, Saukkonen AM, Riekkinen PJ. Prognosis of newly-diagnosed epilepsy and effects of initial vigabatrin monotherapy compared with carbamazepine monotherapy. *Neurology* 1994;**44** (Suppl. 4):A204.
  425. Aikia M, Kälviäinen R, Sivenius J, *et al.* Cognitive effects of vigabatrin and carbamazepine monotherapy. *Epilepsia* 1991;**32** (Suppl. 1):103.
  426. Kälviäinen R, Aikia M, Partanen J, Sivenius J, Mumford J, Saksa M, *et al.* Randomized controlled pilot study of vigabatrin versus carbamazepine monotherapy in newly diagnosed patients with epilepsy: an interim report. *J Child Neurol* 1991; **6** (Suppl. 2):S60–9.
  427. Ring HA, Heller AJ, Farr IN, Reynolds EH. Vigabatrin: rational treatment for chronic epilepsy. *J Neurol Neurosurg Psychiatry* 1990;**53**:1051–5.
  428. Reynolds EH, Ring H, Heller A. A controlled trial of gamma-vinyl-GABA (vigabatrin) in drug-resistant epilepsy. *Br J Clin Pract Suppl.* 1988;**61**:33.
  429. Ring H, Heller A, Reynolds EH. Open and double-blind study of gamma-vinyl GABA in chronic epilepsy. *Neurology* 1988;**38** (Suppl. 1):183.
  430. Rimmer EM, Richens A. Double-blind study of gamma-vinyl GABA in patients with refractory epilepsy. *Lancet* 1984;**1**:189–90.
  431. Tanganelli P, Regesta G. Vigabatrin versus carbamazepine in newly-diagnosed epileptic patients – a randomized-response conditional cross-over study. *Epilepsia* 1995;**36** (Suppl. 3):S104.
  432. GlaxoSmithKline. *A double-blind, placebo-controlled, crossover study of lamotrigine in treatment resistant generalised epilepsy.* Critchley Park: Glaxo Wellcome UK; 1996.
  433. Wellcome Foundation. *A randomised double-blind placebo controlled crossover add-on trial of lamotrigine in patients with treatment resistant seizures: Chalfont.* Beckenham: Wellcome Foundation; 1989.
  434. Abbott Laboratories. *Randomised, double-blind, placebo-controlled, parallel-group study of the safety and efficacy of tiagabine administered tid as adjunctive treatment for partial seizures.* Abbott Park, IL: Novo Nordisk and Abbott Laboratories; 1995.
  435. Boati E, Defanti CA, Franza A, Scaturro M. Vigabatrin versus carbamazepine in patients with newly diagnosed partial epilepsy. *Boll Lega Ital Epil* 1998;**102/103**:123–7.
  436. Canger R, Saltarelli A. Vigabatrin versus carbamazepine as first line monotherapy in newly



- diagnosed patients: a double blind randomized parallel group study. *Boll Lega Ital Epil* 1997; **99**:33–6.
437. de Romanis F, Sopranzi N. Lamotrigine: first experience in Italy. *Clin Ter* 1995; **146**:203–9 (in Italian).
438. Regesta G, Tanganelli P. Vigabatrin monotherapy in newly diagnosed focal epilepsy. *Boll Lega Ital Epil* 1997; **99**:27–32.
439. Sasanelli F, Amodeo M, Colombo A, Molini GE. Gabapentin versus carbamazepine: monotherapy in newly-diagnosed patients with partial epilepsy: Preliminary results. *Boll Lega Ital Epil* 1996; **95–96**:185–6.
440. Thümler R, Kramer G, Besser R. Vigabatrin: Long-term efficacy and tolerability in drug-resistant epilepsy. *Aktuel Neurol* 1992; **19** (Suppl. 1):S46–7.
441. Stephen LJ. *Antiepileptic drug treatment in patients with newly diagnosed epilepsy: a randomised open-label study comparing sodium valproate with lamotrigine alone and in combination in patients failing initial monotherapy*. Glasgow: Epilepsy Unit; ongoing.
442. Faught ER, Hayden CT, Felicetta JV, Marks W, Iragui V, Handforth A, *et al.* *Do gabapentin and lamotrigine have significantly fewer side-effects while providing equal or better seizure control than the current drug choice, carbamazepine, for the treatment of seizures in the elderly*. Alabama: Birmingham VA Medical Center; ongoing.
443. Collins JF. *Treatment of seizures in the elderly population*. Maryland; ongoing. URL: <http://www.controlled-trials.com>
444. Rowan AJ, Ramsay RE, Collins JF. Seizures in the elderly population: interim report of VA cooperative study 428. *Epilepsia* 2001; **42**:143.
445. Read S. *Randomised, double blind, placebo controlled study of add-on TOPAMAX (topiramate) in subjects with seizures (any type) and learning disabilities (mental handicap)*. Huddersfield: LDRU, University of Huddersfield; 2001.
446. Read S. *Add-on topiramate in subjects with epilepsy and learning disabilities*. Huddersfield: University of Leeds, Huddersfield NHS Healthcare Trust, St Luke's Hospital; 2001.
447. Bird JM. *Randomised, double-blind, placebo controlled study of add-on additional therapy in subjects with seizures (any type) and learning difficulties (mental handicap)*. Bristol: Burden Neurological Institute, North Bristol NHS Trust, Frenchay Hospital; 2000.
448. Manga S. *A multicentre study of add-on topiramate in patients with seizure and learning disability*. Hounslow: Hounslow and Spelthorne Community and Mental Health NHS Trust; 2001.
449. Morrell MJ, McLean MJ, Willmore LJ, Privitera MD, Faught RE, Holmes GL, *et al.* Efficacy of gabapentin as adjunctive therapy in a large, multicenter study. *Seizure* 2000; **9**:241–8.
450. Laini V, Mauri MC. Efficacy and tolerability of gabapentin in the prophylaxis of bipolar disorders. *Riv Psichiatr* 1999; **34**:213–16 (in Italian).
451. Knoll J, Stegman K, Suppes T. Clinical experience using gabapentin adjunctively in patients with a history of mania or hypomania. *J Affect Disord* 1998; **49**:229–33.
452. de Feo MR, Mercarelli O, Marciani MG, Striano S, Tata MR, D'Alessandro P, *et al.* Vigabatrin monotherapy in newly diagnosed partial epilepsy: An open multicentre Italian pilot study. *Med Sci Res* 1998; **26**:283–4.
453. Graniewski-Wijnands HS, van der Torren K. Electro-ophthalmological recovery after withdrawal from vigabatrin. *Doc Ophthalmol* 2002; **104**:189–94.
454. Matilainen R, Pitkänen A, Ruutiainen T, Mervaala E, Sarlund H, Riekkinen P. Effect of vigabatrin on epilepsy in mentally retarded patients: a 7-month follow-up study. *Neurology* 1988; **38**:743–7.
455. Cosi V, Callieco R, Galimberti CA, Tartara A, Lanzi G, Balottin U, *et al.* Effect of vigabatrin (gamma-vinyl-GABA) on visual, brainstem auditory and somatosensory evoked potentials in epileptic patients. *Eur Neurol* 1988; **28**:42–6.
456. Cosi V, Callieco R, Galimberti CA, Manni R, Tartara A, Mumford J, *et al.* Effects of vigabatrin on evoked potentials in epileptic patients. *Br J Clin Pharmacol* 1989; **27** (Suppl. 1):S61–8.
457. Tartara A, Galimberti CA, Manni R, Sartori I, Castelnovo G, Perucca E. Usefulness of vigabatrin in the long-term treatment of epilepsy: a 10-year clinical experience. *Boll Lega Ital Epil* 1994; **87**:95–6 (in Italian).
458. Elterman RD, Glauser TA, Wyllie E, Reife R, Wu SC, Pledger G. A double-blind, randomized trial of topiramate as adjunctive therapy for partial-onset seizures in children. Topiramate YP Study Group. *Neurology* 1999; **52**:1338–44.
459. Appleton R, Fichtner K, LaMoreaux L, Alexander J, Halsall G, Murray G, *et al.* Gabapentin as add-on therapy in children with refractory partial seizures: a 12-week, multicentre, double-blind, placebo-controlled study. Gabapentin Paediatric Study Group. *Epilepsia* 1999; **40**:1147–54.
460. Lindberger M. A nordic multicenter, randomized, double-blind, comparative study gabapentin and vigabatrin. *Epilepsia* 1999; **40** (Suppl. 7):98–9.
461. Gupta A. *A blind, parallel group comparison of Neurontin (gabapentin) and sodium valproate as add-on therapy in the treatment of partial seizures*.

- Birmingham: Department of Neurophysiology, City Hospital NHS Trust; 1998.
462. R. W. Johnson Pharmaceutical Research Institute. *Topomax (topiramate) monotherapy comparison trial to standard monotherapy in the treatment of newly diagnosed epilepsy*. Report No. EPMN-105. R. W. Johnson Pharmaceutical Research Institute; 2000.
463. Wong ICK, Mawer GE, Sander J. Factors influencing the incidence of lamotrigine-related skin rash. *Ann Pharmacother* 1999;**33**:1037–42.
464. Tartara A, Manni R, Galimberti CA, Morini R, Mumford JP, Iudice A, *et al*. Six-year follow-up study on the efficacy and safety of vigabatrin in patients with epilepsy. *Acta Neurol Scand* 1992;**86**:247–51.
465. Stavem K, Bjornaes H, Lossius M. Properties of the 15D and EQ-5D utility measures in a community sample of people with epilepsy. *Epilepsy Res* 2001;**44**:179–89.
466. Dolan P. Output measures and valuation in health. In Drummond M, McGuire A, editors. *Economic evaluation in health care*. Oxford: Oxford University Press; 2001. pp. 46–67.
467. Selai CE, Trimble M, Price ML. Evaluation of the relationship between epilepsy severity and utility. Presented at *ISPOR Fifth Annual European Conference*, 3–5 November 2002; Rotterdam.
468. Jacoby AB, D. Baker, G. McNamee, P. Graham-Jones, S. Chadwick, D. Uptake and costs of care for epilepsy: findings from a UK regional study. *Epilepsia* 1998;**39**:776–86.
469. Begley CE, Annegers J, Lairson D, Reynolds T, Hauser W. Cost of epilepsy in the United States: a model based on incidence and prognosis. *Epilepsia* 1994;**35**:1230–43.
470. Wong IC, Chadwick DW, Fenwick PB, Mawer GE, Sander JW. The long-term use of gabapentin, lamotrigine, and vigabatrin in patients with chronic epilepsy. *Epilepsia* 1999;**40**:1439–45.
471. Cockerell O, Hart Y, Sander JWAS, Shorvon SD. The cost of epilepsy in the United Kingdom: an estimation based on the results of two population based studies. *Epilepsy Res* 1994;**18**:249–60.
472. Smith D, Baker G, Davies G, Dewey M, Chadwick DW. Outcomes of add-on treatment with lamotrigine in partial epilepsy. *Epilepsia* 1993;**34**:312–22.
473. Lachin JM, Foulkes MA. Evaluation of sample size and power for analyses of survival with allowance for non-uniform patient entry, losses to follow-up, non-compliance and stratification. *Biometrics* 1986;**42**:507–16.
474. McKee PJ, Blacklaw J, Friel E, Thompson GG, Gillham RA, Brodie MJ. Adjuvant vigabatrin in refractory epilepsy: a ceiling to effective dosage in individual patients? *Epilepsia* 1993;**34**:937–43.
475. Hills M, Armitage P. The two period cross-over clinical trial. *Br J Pharm* 1979;**8**:7–20.
476. Nousiainen I, Kälviäinen R, Mäntyjärvi M. Color vision in epilepsy patients treated with vigabatrin or carbamazepine monotherapy. *Ophthalmology* 2000;**107**:884–8.
477. Matilainen R, Pitkänen A, Ruutiainen T, Mervaala E, Riekkinen P. Vigabatrin in epilepsy in mentally retarded patients. *Br J Clin Pharmac* 1989;**27** (Suppl.):113–18.
478. Ben-Menachem E, Gilland E. Efficacy and tolerability of levetiracetam during one year follow up in patients with refractory epilepsy. 2002. Available from: <http://www.harcourt-international.com/journals/seiz/sciencedirect.cfm> [cited 25 October 2002].
479. Berto P. Quality of life in patients with epilepsy and impact of treatments. *Pharmacoeconomics* 2002;**20**:1039–59.
480. Laird NM, Mosteller F. Some statistical methods for combining experimental results. *Int J Technol Assess Health Care* 1990;**6**:5–30.
481. Brooks, DN, McKinlay, W. Personality and behavioural changes after severe blunt head injury – a relatives view. *J Neurol Neurosurg Psychiatry* 1983;**46**:336–44.



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## Therapeutic Procedures Panel

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***We look forward to hearing from you.***