

Newer drugs for epilepsy in children

Technology Appraisal Guidance 79

Newer drugs for epilepsy in children

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This guidance is written in the following context:

This guidance represents the view of the Institute, which was arrived at after careful consideration of the available evidence. Health professionals are expected to take it fully into account when exercising their clinical judgement. This guidance does not, however, override the individual responsibility of health professionals to make appropriate decisions in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

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1 Guidance

- 1.1 The newer antiepileptic drugs gabapentin, lamotrigine, oxcarbazepine, tiagabine, topiramate, and vigabatrin (as an adjunctive therapy for partial seizures), within their licensed indications, are recommended for the management of epilepsy in children who have not benefited from treatment with the older antiepileptic drugs such as carbamazepine or sodium valproate, or for whom the older antiepileptic drugs are unsuitable because:
- there are contraindications to the drugs
 - they could interact with other drugs the child is taking (notably oral contraceptives)
 - they are already known to be poorly tolerated by the child
 - the child is currently of childbearing potential or is likely to need treatment into her childbearing years (see Section 1.5 below).
- 1.2 Vigabatrin is recommended as a first-line therapy for the management of infantile spasms (West's syndrome).
- 1.3 It is recommended that children should be treated with a single antiepileptic drug (monotherapy) wherever possible. If the initial treatment is unsuccessful, then monotherapy using another drug can be tried. Caution is needed during the changeover period.
- 1.4 It is recommended that combination therapy (adjunctive or 'add-on' therapy) should only be considered when attempts at monotherapy with antiepileptic drugs (as in Section 1.3) have not resulted in seizure freedom. If trials of combination therapy do not bring about worthwhile benefits, treatment should revert to the regimen (monotherapy or combination therapy) that has proved most acceptable to the child, in terms of the balance between effectiveness in reducing seizure frequency and tolerability of side effects.
- 1.5 In girls of childbearing potential, including young girls who are likely to need treatment into their childbearing years, the risk of the drugs causing harm to an unborn child, and the possibility of interaction with oral contraceptives, should be discussed with the child and/or their carer, and an assessment made as to the risks and benefits of treatment with individual drugs. There are currently few data on which

to base a definitive assessment of the risks to the unborn child associated with newer drugs. Specific caution is advised in the use of sodium valproate because of the risk of harm to the unborn child.

- 1.6 It is recommended that all children who have had a first non-febrile seizure should be seen as soon as possible by a specialist in the management of the epilepsies to ensure precise and early diagnosis and initiation of therapy as appropriate to their needs.
- 1.7 Treatment should be reviewed at regular intervals to ensure that children with epilepsy are not maintained for long periods on treatment that is ineffective or poorly tolerated and that concordance with prescribed medication is maintained.
- 1.8 The recommendations on choice of treatment and the importance of regular monitoring of effectiveness and tolerability are the same for specific groups, such as children with learning disabilities, as for the general population of children with epilepsy.

2 Clinical need and practice

- 2.1 Epilepsy is a neurological disorder characterised by unprovoked recurring seizures. An epileptic seizure is a sudden stereotypical episode with changes in motor activity, sensation, behaviour, emotion, memory or consciousness due to an abnormal electrochemical discharge in the brain. Seizures that are the result of an acute reversible systemic or neurological condition – for example, febrile seizures – are not considered to be epilepsy because they usually abate once the underlying condition has resolved. Epilepsy is not usually diagnosed unless the person has had at least two non-febrile seizures.
- 2.2 Seizures are broadly categorised into two types: partial and generalised seizures. Some children have seizures that cannot be categorised in this way.
- 2.3 Partial seizures (also categorised as ‘focal’ or ‘localisation-related’ epilepsies) are epileptic seizures in which the abnormal neuronal discharge begins in or is restricted to a localised part of the brain. The phenomena associated with a partial seizure depend on the location of the abnormal neuronal discharge. If there is no loss of consciousness, the seizure is known as a simple partial seizure. If consciousness

is impaired, the seizure is classified as a complex partial seizure. Simple or complex partial seizures may evolve to become secondarily generalised seizures if the neuronal discharge spreads to involve the entire brain.

2.4 Generalised seizures are characterised by more diffuse neuronal discharges involving both hemispheres of the brain at the onset of the seizure. They are classified according to the presence or absence of different phenomena.

- Absence seizures consist of a short cessation of physical movement and loss of attention. The onset and termination are abrupt, and the seizure normally lasts only a few seconds. Mild absence seizures may pass unnoticed by others and the child may be unaware that anything has happened. 'Atypical' absence seizures have a slower onset and longer duration. Both typical and atypical absence seizures occur predominantly in childhood, usually between 3 and 12 years of age.
- Tonic–clonic seizures involve a tonic phase, in which the muscles suddenly contract, causing the person to fall and lie rigidly. Up to a minute later, the seizure enters the clonic phase, when the muscles begin to alternate between relaxation and rigidity. The person may lose bowel or bladder control. The seizure usually lasts for 2–3 minutes, after which the person remains unconscious for a while. On waking, the person is likely to have a headache and to be confused and tired.
- Clonic seizures are characterised by loss of consciousness, autonomic symptoms and rhythmic contractions of all muscles.
- Tonic seizures involve autonomic symptoms, rigid contraction of the muscles in the limbs and altered consciousness for a number of seconds but the seizures do not progress to the clonic phase.
- Myoclonic seizures are brief jerky contractions of specific muscle groups, such as the face, trunk or limbs.
- Atonic seizures are characterised by a loss of postural tone: the person goes limp and may fall to the ground.

2.5 Clinicians often consider epilepsy in children in terms of the 'epileptic syndrome' – that is an epileptic disorder characterised by a set pattern of seizure type(s) possibly associated with other features, such as a particular physical

appearance or learning disability. If a syndrome can be identified, this allows clarification of the cause, severity and prognosis of the epilepsy. However, for 30% of children with epilepsy, it is not possible to designate a specific syndrome. Some syndromes evolve with time; it may therefore be some months before they can be diagnosed. The most common are benign childhood epilepsy with centrotemporal spikes, juvenile myoclonic epilepsy (JME), childhood absence epilepsy and localisation-related epilepsies categorised as symptomatic (known underlying cause) or cryptogenic (symptomatic cause suspected but not found). Less common syndromes include Lennox–Gastaut syndrome and West’s syndrome.

- 2.6 Benign childhood epilepsy with centrotemporal spikes (also called benign rolandic epilepsy) involves partial seizures arising in the rolandic (centrotemporal or midtemporal) area of the brain. Secondary generalisation to tonic–clonic seizures may occur. Seizures are most frequent on falling asleep and more than half of children have seizures only during sleep. The condition most commonly arises between the ages 7 and 9 years. The child does not usually have a learning disability and the condition has a good prognosis – seizures almost always resolve during puberty. Drug treatment may or may not be used to treat this type of epilepsy; the decision depends on the frequency and severity of the seizures.
- 2.7 Juvenile myoclonic epilepsy (JME) is the most common generalised seizure syndrome in young people. It is characterised by myoclonic seizures which commonly affect the arms and/or trunk, typically on waking. Tonic–clonic seizures are associated with the myoclonic jerks in 90% of people with JME, and about 25% have brief absence seizures. Photosensitivity (in which seizures are provoked by flickering light) occurs in around 50% of people with JME. The onset of the condition is most commonly between 10 and 16 years. JME does not usually remit in adulthood and lifelong treatment is usually required.
- 2.8 Childhood absence epilepsy involves brief (4–20 seconds) and frequent (50–100 per day) absence seizures with abrupt loss of consciousness. It may be associated with learning problems. Other types of epileptic seizures are not part of childhood absence epilepsy. In particular, generalised tonic–clonic seizures or myoclonic jerks do not occur in childhood absence epilepsy, although a proportion of children will develop them later. Most children enter a permanent remission before puberty, but a significant proportion continue to have absences or go on to develop tonic–clonic or myoclonic seizures that persist into adult life.

About 15% of children with childhood absence epilepsy later exhibit JME. Childhood absence epilepsy is classified as an idiopathic (probable genetic cause) generalised epilepsy.

- 2.9 Symptomatic or cryptogenic localisation-related epilepsies involve partial (focal) seizures. The clinical features, accompanying disabilities and prognosis of these epilepsies depend on the cause and location of the brain abnormality.
- 2.10 West's syndrome (or infantile spasms) is a type of generalised epilepsy which may have a known underlying cause such as tuberous sclerosis (symptomatic), or may have no known cause (idiopathic/cryptogenic). The seizures usually begin in infancy, at around 4–6 months of age. The characteristic seizure type is a brief, sudden contraction of flexor, extensor, or mixed flexor extensor muscles. The features of the spasms depend on the muscle groups affected. Spasms typically happen in clusters of 3–20 occurring several times a day in untreated infants. The prognosis is poor. Most children have evidence of neuropsychological disabilities before the onset of spasms, but even those who do not can develop problems such as loss of visual awareness, loss of social interaction, and loss of hand grasping skills. Although West's syndrome does not usually persist beyond the age of 3 years, more than half of these children will go on to develop other types of seizures and epileptic syndromes, such as Lennox–Gastaut syndrome. Most will have lifelong learning disabilities.
- 2.11 Lennox–Gastaut syndrome is a severe epileptic disorder. It is characterised by very frequent seizures of multiple types, usually including atonic or tonic seizures. It is classified as a cryptogenic or symptomatic generalised epilepsy syndrome. Most children with this syndrome develop learning disabilities, which may be severe. Children with Lennox–Gastaut syndrome usually continue to experience seizures in adulthood.
- 2.12 It has been estimated that there are between 4000 and 14,000 new consultations for children aged 0–14 years with epilepsy in the UK each year. The variation in the figures reflects in part the difficulty in diagnosing epilepsy. Defining the prevalence of epilepsy is also difficult because of the intermittent nature of the condition and the fact that a significant proportion of cases achieve permanent remission. A study in which active antiepileptic drug therapy was used to define active epilepsy showed that the reported prevalence rate increased with age, from 3.9 per 1000 population at the age of 7 years, to 4.9 per 1000 population at 16 years.

- 2.13 Epilepsy in children differs from adults in a number of important respects.
- There are more epilepsy syndromes and causes of epilepsy.
 - There is greater heterogeneity with respect to syndrome type, causes and prognoses.
 - The usual refractory seizure type is generalised rather than partial.
 - The condition may change with age, with one syndrome evolving into another (for example, West's syndrome evolving into Lennox–Gastaut syndrome).
 - There is greater potential for impact on social, educational and behavioural spheres of life.
- 2.14 There is evidence of increased risk of accidents and other illnesses in children with epilepsy, but this is from hospital-based cohorts. Children with epilepsy face an increased risk of premature death, but the excess risk is concentrated in children with symptomatic epilepsy and in children with learning or physical disabilities, or both. Sudden unexpected death in epilepsy (SUDEP) can occur, but it is extremely rare in childhood.
- 2.15 The impact of epilepsy on children is wide ranging. It can delay their educational and social development. In the long term it may limit their choices of employment and thus their opportunities in later life. The impact of the adverse effects of treatment is also different in childhood. The potential effects of drug therapy on behaviour and cognitive function are of particular concern in children because of the possible impact on learning and development.
- 2.16 Existing guidelines recommend that a paediatrician or a paediatric neurologist oversee the management of epilepsy in children, under shared care protocols with primary care.
- 2.17 Drug therapy is the mainstay of management of the epilepsies. The decision to treat is based on a careful evaluation of the balance between the likelihood of further seizures and the risk of adverse effects of treatment. In the UK, treatment is not normally offered after a single seizure except where the person is believed to be at particularly high risk of further seizures. The aim of treatment is to abolish seizures completely, while at the same time keeping the side effects of treatment to a minimum so that the person can lead as normal a life as possible.

- 2.18 Treatment with a single drug is generally preferred to minimise the risk of adverse effects. Monotherapy is initiated by increasing the dose gradually until seizures are controlled or adverse effects become unacceptable. If treatment fails, it is considered preferable to try alternative monotherapies before moving on to combination treatment. Switching between antiepileptic drugs must be carried out cautiously, slowly withdrawing the first drug only after the second drug has reached an adequate therapeutic dosage. Children who continue to have seizures on monotherapy are sometimes prescribed a second drug long-term.
- 2.19 The most commonly prescribed antiepileptic drugs in the UK are sodium valproate and carbamazepine. Phenytoin is also still widely used. Carbamazepine is licensed for the treatment of partial seizures and generalised tonic-clonic seizures and is used as a first-line option in these types of seizure. Sodium valproate is a broad-spectrum antiepileptic drug that is licensed for the complete range of seizure types. It is used as a first-line option in primary generalised seizures, absence and myoclonic seizures, and may be tried in atypical absence, atonic and tonic seizures. Phenytoin is licensed for tonic-clonic seizures, partial seizures, or a combination of these, and for the prevention and treatment of seizures occurring during or following neurosurgery and/or severe head injury.
- 2.20 A variety of other drugs are occasionally used in the management of various types of seizure. Phenobarbital is used for tonic-clonic and partial seizures and also may be tried in atypical absence, atonic and tonic seizures. Ethosuximide is primarily used for absence seizures but, when other types of seizure co-exist, sodium valproate is generally preferred because of its broader spectrum. Clonazepam is licensed for use in tonic-clonic or partial seizures, while the related drug clobazam is licensed for use as combination therapy for epilepsy. Acetazolamide is a carbonic anhydrase inhibitor with a weak diuretic activity. It is licensed for use in conjunction with other antiepileptic drugs in a variety of seizure types, including partial, tonic-clonic and absence seizures.
- 2.21 Each antiepileptic drug has its own set of adverse effects, but some are common to all of them. All antiepileptic drugs have adverse effects on the central nervous system (CNS), although some drugs are more likely to cause troublesome effects than others. CNS side effects are dose-related, and may be apparent at therapeutic doses. There is particular concern surrounding the effects of antiepileptic drugs on

cognitive function. The drugs may have subtle effects on mood, cognition and memory that may not be apparent without testing. Children may be particularly susceptible to these effects and this has consequences in terms of difficulties with behaviour, learning and development. However, it can be difficult to distinguish between drug side effects and the consequences of the epileptic condition.

- 2.22 The older antiepileptic drugs have the potential to interact with numerous drugs. Sodium valproate is a hepatic enzyme inhibitor. This means that it slows the metabolism of drugs that are metabolised by these enzymes so dose reduction may be needed to avoid toxicity. Carbamazepine, phenytoin and barbiturates induce hepatic enzymes. This means that they can accelerate the metabolism of some drugs (including oral contraceptives), and higher doses will be needed or the drugs will be less effective. The influence of antiepileptic drug selection on current or future choices of contraceptive methods needs to be borne in mind when choosing an antiepileptic drug for girls who are likely to continue treatment into their childbearing years.
- 2.23 The effects of antiepileptic drugs on the unborn child are also a matter for concern when selecting treatment for girls who are likely to need to continue treatment into their childbearing years. All the older antiepileptic drugs have been associated with congenital malformations (see Section 4.1.7). Multiple drug therapy is associated with a greater risk, although this may be related to the severity of the mother's epilepsy. The Summary of Product Characteristics for sodium valproate (Epilim) recommends that women of childbearing potential should not be started on sodium valproate without specialist neurological advice and that, for partial seizures, sodium valproate should be used only in women found to be resistant to other treatments.

3 The technologies

- 3.1 Seven drugs have been defined as 'newer' antiepileptics for the purposes of this appraisal. However, some of them have been on the market for several years and are already in widespread use. Vigabatrin was first marketed in the UK in 1989, lamotrigine in 1991, gabapentin in 1993, topiramate in 1995 and tiagabine in 1998. The newest – levetiracetam and oxcarbazepine – were launched in 2000. Three of the newer drugs are licensed for use as monotherapy in partial seizures with or without secondary generalisation: lamotrigine, oxcarbazepine and topiramate. Lamotrigine and topiramate

are also licensed for use as monotherapy in primary generalised seizures. Vigabatrin is licensed for monotherapy in the treatment of West's syndrome only. All seven drugs are licensed for use in combination therapy.

- 3.2 Levetiracetam is only licensed for the treatment of adults and young people aged 16 years or older; therefore, it has been considered as part of the Institute's parallel appraisal of newer antiepileptic drugs in adults (see Section 8).
- 3.3 The main advantage proposed for the newer drugs over their predecessors is that they are associated with better quality of life because of various factors such as more acceptable adverse-effect profiles. Some of them also have other potential advantages such as lower propensity for interacting with other drugs, or more convenient dosage regimens, particularly in the initial stages of treatment.
- 3.4 There are few data on which to base an assessment of the risk of these drugs causing harm to the unborn child, particularly for drugs that have been introduced very recently, or have not been widely prescribed.

3.5 Lamotrigine

- 3.5.1 Lamotrigine was launched for adjunctive treatment of epilepsy in 1991 and was licensed for use as monotherapy in 1995. Its indications include partial seizures and primary and secondarily generalised tonic-clonic seizures. It is also used for seizures in the Lennox-Gastaut syndrome. Lamotrigine is not licensed as monotherapy for children younger than 12 years; as combination therapy, it is licensed for both adults and children older than 2 years. Lamotrigine does not reduce the effectiveness of oral contraceptives. For full details of side effects and contraindications, see the Summary of Product Characteristics.
- 3.5.2 At an average adult dose (suitable for children over 12 years of age) of 150 mg twice daily, 28 days' treatment with lamotrigine using 100 mg and 50 mg tablets costs £101.68. For a 5-year-old child weighing 20 kg, a dose of 25 mg twice daily (2.5 mg/kg/day) using dispersible tablets would cost £21.95 for 28 days' treatment.*

* Costs exclude VAT and are taken from the *British National Formulary*, 45th edition. Costs may vary in different settings because of negotiated procurement discounts.

3.6 Oxcarbazepine

- 3.6.1 Oxcarbazepine is a carbamazepine analogue. It is licensed as monotherapy or combination therapy for the treatment of partial seizures with or without secondary generalisation in adults and in children aged 6 years and older. It has a lower potential for drug interactions than carbamazepine, but it does interact with oral contraceptives. For full details of side effects and contraindications, see the Summary of Product Characteristics.
- 3.6.2 For a child weighing 20 kg, a maintenance dose of 300 mg twice daily using oral suspension would cost £44.80 for 28 days' treatment. *

3.7 Topiramate

- 3.7.1 Topiramate is licensed for combination therapy for adults and children older than 2 years who are inadequately controlled on conventional first-line antiepileptic drugs and who have partial seizures with or without secondary generalisation, seizures associated with Lennox–Gastaut Syndrome, or primary generalised tonic–clonic seizures. It is also licensed as monotherapy in adults and children aged 6 years and older with newly diagnosed epilepsy with generalised tonic–clonic seizures, or partial seizures with or without secondarily generalised seizures. It appears to have a low potential for drug interactions, but it does interact with oral contraceptives. For full details of side effects and contraindications, see the Summary of Product Characteristics.
- 3.7.2 For a child weighing 20 kg, a combination therapy maintenance dose of 75 mg twice daily, using sprinkle capsules, would cost £62.46 for 28 days' treatment. A monotherapy maintenance dose of 45 mg twice daily, using sprinkle capsules, would cost £26–£47 for 28 days' treatment.*

3.8 Gabapentin

- 3.8.1 Gabapentin is licensed for use as combination therapy for partial seizures and partial seizures with secondary generalisation in people who have not achieved satisfactory control with, or who are intolerant of, standard anticonvulsants used alone or in combination. Gabapentin does not interact with other drugs, including other

* Costs exclude VAT and are taken from the *British National Formulary*, 45th edition. Costs may vary in different settings because of negotiated procurement discounts.

antiepileptic drugs and oral contraceptives. The Summary of Product Characteristics recommends that, in children between the ages of 6 and 12 years, gabapentin treatment is supervised by a neurologist. Gabapentin is not licensed for use in children younger than 6 years. For full details of side effects and contraindications, see the Summary of Product Characteristics.

- 3.8.2 A maintenance dose of 300 mg three times a day (suitable for a child weighing 26–36kg) would cost £44.52 for 28 days' treatment.*

3.9 Tiagabine

- 3.9.1 Tiagabine is licensed for the combination treatment of partial seizures with or without secondary generalisation in adults and children older than 12 years. It does not affect the plasma concentrations of oral contraceptives or other antiepileptic drugs to a clinically significant extent, although antiepileptic drugs that induce hepatic enzymes can enhance the metabolism of tiagabine. For full details of side effects and contraindications, see the Summary of Product Characteristics.

- 3.9.2 For a child aged over 12 years, a maintenance dose of 15 mg twice daily, as adjunctive therapy with enzyme-inducing drugs, would cost £76.22 for 28 days' therapy. A maintenance dose of 10 mg twice daily, as adjunctive therapy without enzyme-inducing drugs, would cost £50.81 for 28 days' therapy.*

3.10 Vigabatrin

- 3.10.1 The indications for vigabatrin are limited to adjunctive use only when all other appropriate antiepileptic drug combinations have proved ineffective or poorly tolerated. These restrictions were applied after it was found that about one-third of those using vigabatrin had characteristic visual field defects which varied from asymptomatic to severe and potentially disabling. Vigabatrin should not be initiated as monotherapy except in West's syndrome, where it remains as one of the first-line treatments. Vigabatrin should be initiated by a specialist in epilepsy, a neurologist or a paediatric neurologist. For full details of side effects and contraindications, see the Summary of Product Characteristics.

* Costs exclude VAT and are taken from the *British National Formulary*, 45th edition. Costs may vary in different settings because of negotiated procurement discounts.

- 3.10.2 For an infant weighing 5 kg, maintenance therapy of 500 mg daily for West's syndrome would cost £13.62 for 28 days' treatment. *

4 Evidence and interpretation

The Appraisal Committee considered evidence from a number of sources (see Appendix B).

4.1 Clinical effectiveness

The evidence considered by the Committee included the Assessment Report, submissions by consultees and views put forward at the meeting by clinical experts and representatives of patient/carer organisations (see Appendix B).

4.1.1 Lamotrigine

- 4.1.1.1 Evidence from five randomised controlled trials including children was reviewed in the Assessment Report. These were: a placebo-controlled trial of lamotrigine adjunctive therapy in partial seizures (n = 199); a 'response-mediated' crossover trial of continued lamotrigine adjunctive therapy compared with withdrawal to adjunctive placebo in generalised seizures (n = 30 with 17 randomised); a placebo-controlled trial of lamotrigine adjunctive therapy in Lennox–Gastaut syndrome (n = 169); and a comparison of lamotrigine monotherapy with carbamazepine in newly diagnosed partial seizures (n = 417 randomised to lamotrigine or carbamazepine in a 2:1 ratio). The fifth study was a 'responder-enriched' trial of continued lamotrigine monotherapy compared with withdrawal to placebo in typical absence seizures; however, lamotrigine is not licensed for use in absence seizures.
- 4.1.1.2 As monotherapy in partial seizures, the comparison with carbamazepine found no statistically significant differences in terms of seizure outcomes between the two drugs. This was a mixed age study of patients aged 2 years and older, but results for the children 12 years and younger (n = 233) were reported separately. Although, in the whole trial population, more patients withdrew from the carbamazepine arm as a result of adverse events, this appeared to be mostly due to much worse treatment retention for carbamazepine in the elderly. In the paediatric subpopulation, there was a much smaller difference in withdrawals due to adverse effects (5% for lamotrigine and 7% for carbamazepine), which was not

statistically significant. This study provides evidence for the effectiveness of lamotrigine monotherapy in partial seizures, but it cannot be concluded that lamotrigine and carbamazepine are equivalent.

- 4.1.1.3 The clinical trial of adjunctive lamotrigine in partial seizures included children between the ages of 2 and 16 years. This study provided evidence that lamotrigine was superior to placebo in suppressing seizures in patients who had not become seizure-free on their existing therapy. There was a greater reduction in median seizure frequency in the lamotrigine group than in the placebo group: a 36.1% reduction compared with a 6.7% reduction in the placebo group over the 18-week follow-up period (6 weeks' dose titration plus a 12-week maintenance period). This was statistically significant, $p = 0.008$.
- 4.1.1.4 In Lennox–Gastaut syndrome, adjunctive lamotrigine was superior to adjunctive placebo in reducing the frequency of major motor seizures in one placebo-controlled study in people between the ages of 3 and 25 years. These results were to some extent supported by a small crossover trial in children and adolescents with refractory generalised seizures (two-thirds of whom had Lennox–Gastaut syndrome), although this trial's unusual design makes comparison difficult. All participants initially received lamotrigine and the 'responders' (those experiencing a reduction of 50% or more in seizure frequency and/or a reduction in seizure severity) were randomised to continue lamotrigine or withdraw to placebo. After 12 weeks' follow-up (plus a 'wash-out' period), the participants were 'crossed over', so that those who initially received lamotrigine withdrew to placebo, and lamotrigine was reintroduced in those who initially received placebo. The study initially included 30 patients (including 20 with Lennox–Gastaut syndrome), 17 of whom were randomised (2 later withdrew). No patients experienced more seizures on lamotrigine than on placebo and 9 of the 15 experienced a reduction of more than 50% in seizure frequency on lamotrigine compared with the placebo phase.

4.1.2 Oxcarbazepine

- 4.1.2.1 Two trials were considered: one placebo-controlled trial of oxcarbazepine adjunctive therapy in previously diagnosed seizures ($n = 267$) and one comparison of oxcarbazepine with phenytoin as monotherapy in a population of newly diagnosed patients with either partial seizures or generalised tonic-clonic seizures.

- 4.1.2.2 The placebo-controlled trial of combination therapy with oxcarbazepine was conducted in children and adolescents (age range 3–17 years) with inadequately controlled partial seizures on one or two concomitant antiepileptic drugs. Oxcarbazepine led to a statistically significantly better response rate (proportion of patients with >50% reduction in seizures) and a significantly greater reduction from baseline in seizure frequency than placebo.
- 4.1.2.3 The monotherapy comparison with phenytoin was conducted in children and adolescents aged 5–18 years with newly diagnosed partial seizures or generalised tonic–clonic seizures. There was no statistically significant difference in the proportion of patients who remained seizure-free on oxcarbazepine monotherapy compared with phenytoin, although the premature discontinuation rate for phenytoin was higher.
- 4.1.2.4 The trials provided good evidence that oxcarbazepine adjunctive therapy was superior to placebo in partial seizures, and limited evidence for similar efficacy with better retention on therapy when oxcarbazepine monotherapy was compared with phenytoin in partial and generalised tonic–clonic seizures.

4.1.3 Topiramate

- 4.1.3.1 Two placebo-controlled trials of combination therapy with topiramate and one active controlled trial of topiramate as monotherapy were considered.
- 4.1.3.2 The first trial examined combination therapy with topiramate in 86 children (age range 2–16 years) with uncontrolled partial seizures. This study found that topiramate reduced the frequency of seizures from baseline to a significantly greater extent than placebo (median percentage reduction 33.1% compared with 10.5%, $p = 0.03$).
- 4.1.3.3 The second trial examined combination therapy with topiramate in 98 children and adults (age range 1–30 years) with Lennox–Gastaut syndrome. Topiramate was associated with a greater reduction from baseline in seizure frequency than placebo (median percentage reduction 20.6% compared with 8.8%) but this was not statistically significant. However, for atonic seizures ('drop attacks'), the median percentage reduction from baseline in seizure rate was 14.8% for the topiramate group, compared with an increase of 5.1% for the placebo group ($p = 0.041$). This trial also reported improvements in parental global evaluation of seizure severity compared with placebo.

- 4.1.3.4 The monotherapy trial compared topiramate monotherapy with either carbamazepine or sodium valproate in the management of epilepsy in a mixed age population (6 years or older) with newly diagnosed partial or generalised tonic-clonic seizures (n = 613). The participants were recruited to either the carbamazepine or the valproate branch of the trial according to the investigator's preferred treatment for that person. They were then randomised to one of two dose levels of topiramate (100 mg or 200 mg per day) or the chosen active control. For a small proportion of patients in this trial (about 2.5%) there was no epilepsy classification. This trial found that there was no statistically significant difference between the pooled topiramate groups and either carbamazepine or sodium valproate in any of the efficacy measures. An analysis of the paediatric subgroup of this trial (age range 6–16 years, n = 119), reported as a conference abstract only, found no statistically significant difference between topiramate and either carbamazepine or sodium valproate.
- 4.1.3.5 The trials provide evidence that topiramate is more effective than placebo in combination therapy in children with refractory partial seizures or people with Lennox–Gastaut syndrome. Topiramate appears to have similar effectiveness to carbamazepine and sodium valproate as monotherapy in newly diagnosed partial seizures or generalised tonic-clonic seizures.

4.1.4 Gabapentin

- 4.1.4.1 Three randomised controlled trials of gabapentin were identified: two placebo-controlled trials of combination therapy with gabapentin in poorly controlled partial seizures and one placebo-controlled trial of gabapentin monotherapy in benign epilepsy with centrotemporal spikes (gabapentin is not licensed for use as monotherapy in this indication).
- 4.1.4.2 The larger of the two studies of combination therapy with gabapentin (n = 247) included children aged 3 to 12 years with refractory partial seizures. This study suggested a slight advantage in response rate for gabapentin compared with placebo, but this did not reach statistical significance. The smaller study (age range 1–36 months, n = 76) found no difference in response rates between the gabapentin and placebo groups. This was a very short trial in which seizure rate was monitored by continuous video-EEG recording over 72 hours.

4.1.4.3 The trials of gabapentin in children provided weak evidence of an advantage over no therapy (placebo). No evidence comparing gabapentin with alternative active therapies was identified.

4.1.5 Tiagabine

4.1.5.1 No studies of tiagabine conducted exclusively in children were found. Two placebo-controlled trials of adjunctive tiagabine primarily conducted in adults included some children (the inclusion criteria specified an age range of 12–75 years). Both found that the proportion of responders (those with a reduction of at least 50% in seizure frequency) was significantly greater in the tiagabine group. However, only one published any specific information on the paediatric subgroup and this was reported only in the form of an abstract, which did not reproduce results. Thus the Committee received no additional evidence on the efficacy or effectiveness of tiagabine in children rather than adults.

4.1.6 Vigabatrin

4.1.6.1 Seven randomised controlled trials were included in the assessment report: two placebo-controlled trials of combination therapy with vigabatrin in children with previously diagnosed partial seizures; one placebo-controlled trial of combination therapy with vigabatrin in a mixed seizure-type population; one trial of vigabatrin monotherapy compared with carbamazepine in children with newly diagnosed partial seizures; one placebo-controlled trial of vigabatrin monotherapy in infantile spasms; and two active-controlled trials of vigabatrin monotherapy in West's syndrome.

4.1.6.2 There was no statistically significant difference in seizure control between vigabatrin monotherapy and carbamazepine monotherapy in children with newly diagnosed partial seizures. This is not a licensed indication for vigabatrin.

4.1.6.3 The evidence for vigabatrin adjunctive therapy in previously diagnosed partial seizures was limited but supported superior efficacy compared with placebo. Both studies are only published in abstract form, so details are limited. One study compared vigabatrin (dose 1.5–4 g daily) with placebo in 88 patients with uncontrolled complex partial seizures. More patients in the vigabatrin group had a 50% or greater reduction in their seizure rate than in the placebo group

(55.8% compared with 26.7%, $p = 0.009$). The other study ($n = 126$) was a dose ranging study that reported a statistically significantly greater reduction in seizure frequency in the highest of the three vigabatrin dose-groups (100mg/kg/day) than in the placebo group ($p = 0.014$). However, the actual reduction in seizure frequency was not reported and it is not clear how many patients were randomised to each of the treatment groups.

- 4.1.6.4 The remaining placebo-controlled study of adjunctive vigabatrin recruited people who had been treated with vigabatrin in various clinical trials for a variable length of time and with limited effect ($n = 18$). The participants were randomised to continue vigabatrin or withdraw to placebo. Fewer patients in the continued vigabatrin group were withdrawn from the study because of a worsening of seizure frequency or severity (7% compared with 54% in the placebo group). This indicates that people who benefit to a modest extent from vigabatrin therapy initially may continue to benefit while they remain on therapy.
- 4.1.6.5 The placebo-controlled trial of vigabatrin monotherapy for West's syndrome was well conducted and reported and provided strong evidence that vigabatrin is superior to placebo. This study was conducted in 40 infants (age 1 to 20 months) with newly diagnosed and previously untreated West's syndrome. However, the short duration (5 days) gave limited opportunity to identify side effects.
- 4.1.6.6 The two active-controlled trials of vigabatrin monotherapy indicated that vigabatrin may be superior to adrenocorticotrophic hormone (ACTH) and hydrocortisone. Both studies used a 'response-mediated' cross-over design in which patients who did not respond well to the allocated treatment were switched to the alternative treatment. This design is not well suited to comparing drugs. Taking the results from the first (parallel) period of the studies allows comparisons to be drawn. In the comparison with ACTH ($n = 42$), ACTH abolished spasms in a marginally greater proportion of patients (difference not statistically significant) but vigabatrin appeared to be better tolerated. The comparison with hydrocortisone ($n = 22$) found that all the patients in the vigabatrin group were spasm-free at one month compared with 5 out of 11 in the hydrocortisone group ($p < 0.01$). Limitations in the design and analysis of these studies mean that they do not provide strong evidence.

4.1.6.7 The evidence suggests that vigabatrin is better than placebo in the treatment of partial seizures and West's syndrome. However, there is no convincing evidence of its superiority to the alternative therapies in either of these patient groups. There is concern over the significant risk of visual field defects associated with its use. The licence for vigabatrin reflects this concern. However, the risk of visual field defects must be balanced against the adverse effects of alternative therapies. In the case of hormone (steroid) treatment for West's syndrome, this includes a risk of serious infection and mortality.

4.1.7 Newer antiepileptic drugs and childbearing potential

4.1.7.1 In selecting antiepileptic drugs for girls who are likely to need continued treatment into adulthood, safety in pregnancy needs to be considered. Few data are available on the use of newer antiepileptic drugs in pregnancy, and it is not yet possible to fully assess the risk of teratogenicity associated with them. Preliminary data from the UK Epilepsy and Pregnancy Register presented in 2002 (based on the outcomes of 2028 pregnancies) suggest that the crude rates for risk of major congenital malformation were 4% (95% confidence interval [CI], 3.2% to 5.3%) in women taking one antiepileptic drug and 6.3% (95% CI, 4.3% to 9.1%) in women taking more than one. There are also data for a small group of women with epilepsy (5.9% of the total) who were not exposed to antiepileptic drugs during pregnancy. The crude malformation rate in this group was 0.9% (95% CI, 0.2% to 4.7%). For the individual drugs, the risk in women taking carbamazepine was 2.3% (95% CI, 1.4% to 4.0%), the risk with sodium valproate was 7.2% (95% CI, 5.2% to 10.0%) and the risk with lamotrigine was 3% (95% CI, 1.5% to 5.7%). These data suggest that sodium valproate is associated with a significantly higher risk of malformations than carbamazepine. Although the crude rate for lamotrigine was lower than for sodium valproate, the difference was not statistically significant.

4.2 Cost effectiveness

4.2.1 Lamotrigine

4.2.1.1 The manufacturer submitted two economic analyses of lamotrigine in children. One was a simple decision tree with a 1-year time horizon comparing lamotrigine, carbamazepine and sodium valproate. The results indicated that the incremental cost-effectiveness ratio (ICER) for lamotrigine as first-line monotherapy was £13,045 per QALY gained. The

second cost-effectiveness analysis considered lamotrigine as add-on therapy in children aged 2 years and over. The analysis did not consider a formal model of the management of epilepsy, but rather applied utility weights to outcomes observed in a placebo-controlled randomised controlled trial in order to produce cost-utility estimates. This approach estimated the ICER for lamotrigine add-on therapy to be £16,456 per QALY gained.

- 4.2.1.2 Neither of these analyses considered the chronic nature of epilepsy. In addition, the model for the monotherapy analysis considered first- and second-line therapy only, although significantly more therapeutic strategies are available; and the trial-based analysis had placebo as the comparator therapy.
- 4.2.1.3 The Assessment Group constructed a patient-level simulation model of the cost effectiveness of the newer anti-epileptic drugs in children. They used the model to examine the long-term cost effectiveness of adding lamotrigine to the portfolio of older antiepileptic drugs available. Patients were modelled as following a treatment algorithm starting with sequential monotherapy followed by adjunctive therapy, with progression based on the failure to achieve seizure freedom or the presence of unacceptable side effects. The analysis considered its cost effectiveness as first-line monotherapy, second-line monotherapy and first-line adjunctive therapy. The incremental costs were always positive, but the incremental benefits were sometimes negative and sometimes positive. The credible ranges for the ICERs on lamotrigine were: for first-line monotherapy, -£29,238 to + £44,118; for second-line monotherapy, -£41,628 to +£57,714; and for first-line adjunctive therapy, -£15,581 to +£22,500. These analyses indicated that there is significant uncertainty about the cost effectiveness of lamotrigine in each of these indications. Positive incremental costs were identified, as were a mixture of both positive and negative incremental QALYs.
- 4.2.1.4 It is plausible that lamotrigine is cost effective in all three indications. However, there is insufficient evidence for this to be stated with confidence.

4.2.2 Topiramate

- 4.2.2.1 Janssen-Cilag submitted three cost-effectiveness analyses of topiramate in children: combination therapy with topiramate compared with combination therapy with lamotrigine in partial seizures; monotherapy with topiramate compared with monotherapy with carbamazepine for partial seizures; and monotherapy with topiramate compared with monotherapy with sodium valproate in generalised seizures. The model reported that topiramate dominates lamotrigine as combination therapy; however, the comparison of topiramate with lamotrigine does not address the value of adding topiramate to the portfolio of older antiepileptic drugs.
- 4.2.2.2 The ICER for topiramate monotherapy was estimated to be £734 per QALY gained compared with carbamazepine and £635 per QALY gained compared with sodium valproate. The model used an efficacy estimate taken from an analysis of a small subgroup of children in one trial, which had only been published as a conference abstract. The sub-group analysis suggested a substantial efficacy advantage for topiramate monotherapy over sodium valproate and carbamazepine. The advantage is not consistent with the main trial results and the sensitivity analysis did not examine this issue.
- 4.2.2.3 The Assessment Group used the patient-level simulation model to examine the cost effectiveness of adding topiramate as a first-line adjunctive therapy to the portfolio of older antiepileptic drugs. These analyses indicated that there is significant uncertainty about the cost effectiveness of topiramate in children. The credible range for the incremental cost effectiveness ratio was –£48,431 to +£666,000. The Assessment Group did not examine the cost effectiveness of adding topiramate monotherapy to the portfolio of older antiepileptic drugs.
- 4.2.2.4 The assessment group also modelled the cost effectiveness of gabapentin and oxcarbazepine as first-choice adjunctive therapy. The model structure was the same as for the analyses of lamotrigine and topiramate. The incremental costs of gabapentin were always positive and the credible range for the ICER was –£273,000 to +£25,045 per QALY gained. The credible range for the incremental costs of oxcarbazepine included cost savings. The credible range for the ICER was –£22,352 to +£80,000.

4.3 Consideration of the evidence

- 4.3.1 The Appraisal Committee reviewed the evidence available on the clinical and cost effectiveness of newer antiepileptic drugs, having considered evidence on the nature of the condition and the value placed by children and/or their carers on the benefits of newer antiepileptic drugs from people with epilepsy, those who represent them, and clinical experts. It was also mindful of the need to ensure that its advice took account of the effective use of NHS resources.
- 4.3.2 The Committee considered that the evidence from randomised trials comparing newer and older antiepileptic drugs as monotherapy did not suggest differences in their overall effectiveness in seizure control. The Committee noted that most of the evidence on the effectiveness of newer antiepileptic drugs as monotherapy in children came from clinical trials in mixed age groups (that is, both adults and children were included in the same trial). There were very few data relating exclusively to children and to the types of epileptic disorder that commonly affect children. In coming to their conclusions, the Committee were persuaded that for the major licensed indications (generalised tonic-clonic seizures and/or partial seizures as appropriate to the individual drugs), the evidence from mixed-age trials could be considered alongside studies conducted principally or exclusively in adults.
- 4.3.3 Although side-effect profiles of newer and older drugs were different, the Committee considered that the evidence was inadequate to support a conclusion that the newer drugs were generally associated with improved quality of life. The Assessment Group's cost-effectiveness analyses showed a high degree of uncertainty around the costs and benefits of these treatments.
- 4.3.4 The Assessment Group had not reported results for all possible comparisons and indications, as there was no evidence for superior efficacy of any of the therapies in any of the indications. However, the Committee considered that the model analyses provided useful insight into the cost effectiveness of all the newer antiepileptic drugs. The Committee considered that it was not possible to conclude that any of the newer anti-epileptic drugs were likely to be more cost effective than the older agents.
- 4.3.5 The Committee was also persuaded by the experts' evidence that, before combination therapy is considered, children should be given a trial of all appropriate monotherapy regimens, with the changeover being carried out cautiously.

- 4.3.6 The experts and patient representatives stressed that the most important outcome for people with epilepsy is seizure freedom. The Committee reviewed the evidence for combination therapy with the newer antiepileptic drugs. While acknowledging that the evidence base on the use of these drugs in children was considerably sparser than that in adults, the Committee concluded that a significant proportion of children who do not achieve seizure freedom on monotherapy could derive worthwhile benefit from adjunctive therapy. The Committee noted that for some of the antiepileptic drugs used in combination therapy in children, there were few or no trials conducted exclusively in children demonstrating a benefit in terms of seizure control. The Committee accepted that, particularly for drugs used in combination therapy in older children and adolescents with partial seizures, it was appropriate to consider evidence from trials in adults and mixed-age populations alongside the evidence from studies in children. Other limitations in the evidence base include the relatively short duration of the studies of combination therapy (most were 3–6 months' duration or less) and the limited number of direct comparisons between the newer drugs (none conducted in children). Because of these limitations, the Committee considered that it was not possible to determine whether any one drug was more likely to bring about seizure freedom over the longer term than any other.
- 4.3.7 The Committee was persuaded that, irrespective of which adjunctive therapy was used, children who do not derive worthwhile benefits in terms of significant seizure reduction or improvement in quality of life should not continue with that regimen in the long term. After sequential trials of combination therapies, if none of the combinations proves to be beneficial, then after discussion with the child and/or their carer, the child should revert to treatment with the regimen that proved most effective for him or her and had least side effects.
- 4.3.8 The Committee noted that, in addition to the general scarcity of well-conducted clinical studies of antiepileptic drugs in children, clinical experts were concerned that the available studies did not take account of the heterogeneity of the epilepsies. There were particular difficulties in assessing the effectiveness of antiepileptic drugs in children with defined seizure syndromes because entry to the studies was usually determined by seizure type (partial or generalised seizures or multiple seizure types). This could have meant that the studies inappropriately mixed patients with different epilepsy disorders and varied prognoses. These

studies are not helpful when tailoring antiepileptic drug treatment to the needs of the child, and often decisions are based on less robust sources of evidence and individual clinician's opinions and experience. However, the Committee recognised the importance of having a range of therapies available for the treatment of epilepsies in the light of variation in children's responses.

- 4.3.9 The Committee noted the lack of high-quality evidence on which to base decisions on the most appropriate treatments for children with learning disabilities. The Committee decided the considerations surrounding choice of treatment and the importance of regular monitoring of effectiveness and tolerability were largely the same as for the general population.
- 4.3.10 The Committee heard from the experts that some people may be maintained for long periods on ineffective medication, or therapy that is not well tolerated. The experts highlighted the importance of regular monitoring of patients to review and optimise their treatment.
- 4.3.11 The experts stressed to the Committee the value of vigabatrin in the management of West's syndrome. Their opinion was based on the balance of the known risks and benefits for the use of vigabatrin in this clinical situation.
- 4.3.12 The Committee noted that the issue of whether antiepileptic drugs may be harmful to the unborn child is a matter of major concern and should be considered in the treatment of girls of childbearing potential (and younger girls who are likely to need continued treatment into adolescence and adulthood). The Committee took specific note of the particular concern regarding the risks to the unborn child associated with sodium valproate and that, because of this, the Summary of Product Characteristics for sodium valproate (Epilim) warns that, for partial seizures, it should be used in women and girls only if they are resistant to other treatments. The experts advised the Committee that despite the concerns highlighted in the Summary of Product Characteristics, sodium valproate may be an appropriate choice for women or girls with some types of generalised seizures. However, when considering the use of sodium valproate in girls of childbearing potential, the risks and benefits must be clearly communicated with both the child and her carer as appropriate to ensure that an informed choice is made. The Committee were persuaded that, as yet, there are few data upon which to base an assessment of the potential risks of teratogenicity associated with newer drugs.

- 4.3.13 Additionally, the Committee took note of the potential for drug interactions with the use of the antiepileptic drugs and, in particular, interaction with oral contraceptives, which may be of relevance in girls of childbearing potential. They concluded that this aspect of therapy should be taken into account in determining the most suitable treatment for any individual patient.
- 4.3.14 The Committee discussed the issue of generic prescribing in relation to antiepileptic drugs. They noted that the experts had particular concerns about the use of generic products, particularly in relation to some of the older drugs, such as phenytoin, where the pharmacokinetics are such that small differences in absorption can result in large differences in therapeutic effect. However, the Committee did not consider that it had adequate evidence to make recommendations on the use of generic products in the treatment of epilepsy.
- 4.3.15 The Committee were aware of the importance of investigation and early accurate diagnosis for children experiencing a first seizure so that an appropriate pathway of care including drug therapy can be put in place efficiently. In addition, the experts emphasised the importance of appropriate follow-up arrangements including, where necessary, shared care arrangements for all children with epilepsy, in order to ensure they were on the most appropriate treatment regimen.

5 Recommendations for further research

- 5.1 A large randomised controlled trial of longer-term clinical outcomes and cost effectiveness of standard and new antiepileptic drugs (SANAD) has been sponsored by the NHS R&D Health Technology Assessment Programme. The study aims to recruit around 3000 people in the UK over 3 years. The study will compare monotherapy with clinicians' first-choice standard drug (carbamazepine or sodium valproate) with appropriate comparators from among the new antiepileptic drugs. Both adults and children of 5 years or older will be included. This study will be the largest randomised controlled trial in epilepsy and is intended to provide robust evidence for the effectiveness of the newer antiepileptic drugs.

- 5.2 It is clear that further high-quality research needs to be undertaken in the paediatric epilepsies. This should include randomised controlled trials of the older and newer antiepileptic drugs in homogeneous epilepsy syndrome populations using a number of clinical outcomes, including seizure freedom, freedom from adverse side effects, and relevant quality of life measures.

6 Implications for the NHS

- 6.1 Prescriptions for newer antiepileptic drugs have been steadily increasing as a proportion of the total. According to the most recent prescribing cost analysis (PCA) data, newer antiepileptic drugs accounted for 20% of total items and 69% of total costs (£99 million of £142 million) in 2002. It is not possible to determine the extent to which these data relate to children. There is some evidence from another source to suggest that children are more likely to receive treatment with a newer antiepileptic drug than adults. It is also not possible to determine from PCA data how much of the prescribing is for the treatment of epilepsy. Some drugs are used for indications other than epilepsy, and such use is likely to account for at least part of the increase in costs and volume. This guidance is expected to have a neutral impact on these prescribing trends.
- 6.2 There might be implications for provision of specialist services if additional clinics are required to ensure that children having a first seizure are seen quickly and reviewed at regular intervals.

7 Implementation and audit

- 7.1 All clinicians with responsibility for treating children with epilepsy should review their current practice and policies to take account of the guidance set out in Section 1.
- 7.2 Local guidelines, protocols or care pathways that refer to the care of children with epilepsy should incorporate the guidance.
- 7.3 To measure compliance locally with the guidance, the following criteria could be used. Further details on suggestions for audit are presented in Appendix C.

- 7.3.1 A child with epilepsy is treated with a newer antiepileptic drug in the following circumstances.
- 7.3.1.1 He or she has not benefited from treatment with the older antiepileptic drugs such as carbamazepine or sodium valproate.
- 7.3.1.2 Older antiepileptic drugs are unsuitable because:
- there are contraindications to the drugs
 - they could interact with other drugs the child is taking (notably oral contraceptives)
 - they are already known to be poorly tolerated by the individual
 - the child is of childbearing potential or is likely to need treatment into her childbearing years (see Section 7.3.5).
- 7.3.2 Vigabatrin is considered as a first-line therapy for a child who has West's syndrome.
- 7.3.3 A child with epilepsy is ordinarily treated with a single antiepileptic drug. If the initial treatment of a child with epilepsy with a single antiepileptic drug (monotherapy) is unsuccessful, then he or she is treated with another single antiepileptic drug, with the changeover being carried out cautiously.
- 7.3.4 A child with epilepsy is prescribed combination therapy only when attempts at monotherapy with antiepileptic drugs have not resulted in seizure freedom. If trials of combination therapy do not bring about worthwhile benefits, the child's treatment is reverted to the regimen that has proved most effective in reducing seizure frequency and has least side effects.
- 7.3.5 In girls of childbearing age, the risk of the drugs causing harm to an unborn child is discussed between the girl and/or her carer and the responsible clinician and an assessment is made as to the risks and benefits of treatment with individual drugs.
- 7.3.6 A child who has had a first non-febrile seizure is seen as early as possible by a specialist in the management of epilepsies.
- 7.3.7 Treatment is reviewed at regular intervals.

- 7.4 Local clinical audits could also include measurement of compliance with issues identified in the National Clinical Audit of Epilepsy-related Death and/or *Improving Services for People with Epilepsy* (the Department of Health response to the National Clinical Audit of Epilepsy-related Death), such as carrying out appropriate investigations to reach a diagnosis of epilepsy, supporting patients who are having problems with their drug regimens, and shared-care arrangements. Local audits may be able to make use of data already being collected for registries on epilepsy.

8 Related guidance

- 8.1 There is an ongoing parallel appraisal of the use of newer drugs for epilepsy in adults. The Institute also plans to publish a clinical guideline for the diagnosis, management and treatment of epilepsy in June 2004.

9 Review of guidance

- 9.1 The review date for a technology appraisal refers to the month and year in which the Guidance Executive will consider any new evidence on the technology, in the form of an updated Assessment Report, and decide whether the technology should be referred to the Appraisal Committee for review.
- 9.2 The guidance on this technology will be reviewed in December 2006.

Andrew Dillon
Chief Executive
April 2004

A version of this guidance written for children with epilepsy, their families and carers, and the public is available from the NHS Response Line (telephone 0870 1555 455 and quote reference number N0550 for a version in English only and N0551 for a version in English and Welsh). It is also available, in English and Welsh, from the NICE website (www.nice.org.uk/TA079publicinfo).

Appendix A

Appraisal Committee members and NICE project team

A. Appraisal Committee members

NOTE The Appraisal Committee is a standing advisory committee of the Institute. Its members are appointed for a 3-year term. A list of the Committee members who took part in the discussions for this appraisal appears below. The Appraisal Committee meets twice a month except in December, when there are no meetings. The Committee membership is split into two branches, with the chair, vice-chair and a number of other members attending meetings of both branches. Each branch considers its own list of technologies and ongoing topics are not moved between the branches.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered that there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each Appraisal Committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Dr A E Ades

MRC Senior Scientist, MRC Health Services Research Collaboration, University of Bristol

Dr Tom Aslan

General Practitioner, Stockwell, London

Professor David Barnett (Chair)

Professor of Clinical Pharmacology, University of Leicester

Professor Rosamund Bryar

Professor of Community & Primary Care Nursing, St Bartholomew School of Nursing and Midwifery

Dr Karl Claxton

Health Economist, University of York

Dr Richard Cookson

Senior Lecturer, Health Economics, School of Health Policy and Practice, University of East Anglia, Norwich

Professor Terry Feest

Clinical Director & Consultant Nephrologist, Richard Bright Renal Unit, & Chair of UK Renal Registry, Bristol

Professor Gary A Ford
Professor of Pharmacology of
Old Age/Consultant Physician,
Newcastle upon Tyne Hospitals
NHS Trust

Professor John Geddes
Professor of Epidemiological
Psychiatry, University of Oxford

Ms Bethan George
Interface Liaison Pharmacist,
Mile End Hospital, London
Mr John Goulston
Director of Finance, Barts and
the London NHS Trust

Professor Philip Home
Professor of Diabetes Medicine,
University of Newcastle upon
Tyne

Dr Terry John
General Practitioner, The Firs,
London

Mr Muntzer Mughal
Consultant Surgeon, Lancashire
Teaching Hospitals NHS Trust,
Chorley

Judith Paget
Chief Executive, Caerphilly Local
Health Board, Torfaen

Mr James Partridge
Chief Executive, Changing Faces,
London

Mrs Kathryn Roberts
Nurse Practitioner, Hyde,
Cheshire

Professor Philip Routledge
Professor of Clinical
Pharmacology, College of
Medicine, University of Wales,
Cardiff

**Professor Andrew Stevens
(Vice-Chair)**

Professor of Public Health,
University of Birmingham

Dr Cathryn Thomas
General Practitioner, & Senior
Lecturer, Department of Primary
Care & General Practice,
University of Birmingham

Dr Norman Vetter
Reader, Department of
Epidemiology, Statistics and
Public Health, College of
Medicine, University of Wales,
Cardiff

Dr David Winfield
Consultant Haematologist, Royal
Hallamshire Hospital, Sheffield

B. NICE Project Team

Each appraisal of a technology is assigned to a Health Technology Analyst and a Technology Appraisal Project Manager within the Institute.

Eleanor Donegan
Technical Lead,
NICE project team

Chris McCabe
Technical Lead,
NICE project team

Janet Robertson
Technical Lead,
NICE project team

Appendix B

Sources of evidence considered by the Committee

The following documentation and opinions were made available to the Committee:

- A** The assessment report for this appraisal was prepared by West Midlands Health Technology Assessment Collaboration, Department of Public Health and Epidemiology, The University of Birmingham

The clinical and cost effectiveness of newer drugs for children with epilepsy, February 2003

- B** The following organisations accepted the invitation to participate in this appraisal. They were invited to make submissions and comment on the draft scope, assessment report and the Appraisal Consultation Document (ACD). Consultee organisations are provided with the opportunity to appeal against the Final Appraisal Determination.

I Manufacturer/sponsors:

- Aventis Pharma
- Cephalon UK
- GlaxoSmithKline
- Janssen-Cilag
- Novartis Pharmaceuticals
- UCB Pharma

II Professional/specialist and patient/carer groups:

- Association of British Neurologists
- British Branch of the International League Against Epilepsy
- British Neuropsychiatry Association
- British Paediatric Neurology Association
- Department of Health
- Epilepsy Action
- Epilepsy Bereaved
- Epilepsy Research Foundation
- Epilepsy Specialist Nurses Association
- Epilepsy Wales
- Institute of Neurology
- Joint Epilepsy Council
- National Centre for Young People with Epilepsy
- National Society for Epilepsy
- Royal College of General Practitioners
- Royal College of Paediatrics and Child Health

- Royal College of Physicians
- Royal College of Psychiatrists
- Welsh Assembly Government

III Commentator organisations (without the right of appeal):

- Cambridgeshire Health Authority
- Fund for Epilepsy
- National Collaborating Centre for Primary Care
- NHS Quality Improvement Scotland

C The following individuals were selected from clinical expert and patient advocate nominations from the professional/specialist and patient/carer groups. They participated in the Appraisal Committee discussions and provided evidence to inform the Appraisal Committee's deliberations. They gave their expert personal view on newer drugs for epilepsy in children by attending the initial Committee discussion and/or providing written evidence to the Committee. They were invited to comment on the Appraisal Consultation Document.

- Dr Richard Appleton, Consultant Paediatric Neurologist, Royal Liverpool Children's Hospital
- Ms Kathy Bairstow, Senior Advice and Information Officer, Epilepsy Action
- Dr Helen Cross, Consultant Paediatric Neurologist, Great Ormond Street Hospital
- Dr Colin Ferrie, Consultant Paediatric Neurologist, Leeds Teaching Hospital NHS Trust
- Ms Julie Hodgson, Member and Accredited Volunteer, Epilepsy Action
- Mr Jim Oates, Epilepsy Liaison Nurse & Chair, Epilepsy Specialist Nurses Association
- Ms Linda Perry, Director of Medical Services, National Centre for Young People with Epilepsy
- Mr Mark Stephens, on behalf of the National Society for Epilepsy

Appendix C

Detail on criteria for audit of the use of newer drugs for epilepsy in children

Possible objectives for an audit

An audit could be carried out to ensure the appropriate and effective use of newer drugs for epilepsy in children.

Possible patients to be included in the audit

An audit could be carried out on the care provided to children with epilepsy treated by specialists or in primary care settings. In the specialist setting, the audit could include all children treated for epilepsy in a suitable time period for the audit, for example, 3 months. In a primary care setting, the audit could include all children being treated for epilepsy.

Measures that could be used as a basis for audit

The measures that could be used in an audit of newer drugs for epilepsy in children are as follows.

Criterion	Standard	Exception	Definition of terms
<p>1. The child is treated with a newer antiepileptic drug if he or she meets any of the following:</p> <p>a. the child has not benefited from treatment with an older antiepileptic drug or</p> <p>b. an older antiepileptic drug is unsuitable because:</p> <ol style="list-style-type: none"> 1) there are contraindications to the drugs or 2) they could interact with other drugs the individual is taking (notably oral contraceptives) or 3) they are already known to be poorly tolerated by the individual or 4) the child is of childbearing potential or is likely to need treatment into her childbearing years 	<p>100% of children in the audit</p>	<p>A. The child (or carer) chooses an older drug based on discussion with the prescribing clinician (see criterion 4 below)</p> <p>B. Vigabatrin is considered as a first-line therapy for a child with West's syndrome</p>	<p>'Newer antiepileptic drugs' are vigabatrin, lamotrigine, gabapentin, topiramate, tiagabine, levetiracetam and oxcarbazepine.</p> <p>'Older antiepileptic drugs' include carbamazepine, sodium valproate, phenytoin, phenobarbital, ethosuximide, clonazepam, clobazam and acetazolamide.</p> <p>'Benefited from treatment' (1a) means significant seizure reduction, improvement in quality of life and/or least side effects.</p> <p>Clinicians will need to agree locally on what constitutes significant seizure reduction and improvement in quality of life, contraindications to and tolerability of an older antiepileptic drug, and any other exceptions and how consideration of vigabatrin for a child with West's syndrome is documented, for audit purposes.</p>

Criterion	Standard	Exception	Definition of terms
2. The child is treated with a single antiepileptic drug	100% of children in the audit	<p>A. Treatment with a single drug was unsuccessful, the single drug was changed and two drugs were used during the changeover</p> <p>B. The child is prescribed combination therapy when attempts at monotherapy with antiepileptic drugs have not resulted in seizure freedom</p>	<p>Clinicians will have to agree locally on what constitutes lack of success in treatment (see above for indications of success) and seizure freedom, for audit purposes.</p> <p>Also, for audit purposes, see the <i>BNF</i> for reference to the antiepileptic drugs that can be used as monotherapy or as adjunctive therapy, the licensed indications for each drug, and the ages of children referred to in the licences.</p>
3. If trials of adjunctive therapy do not bring about worthwhile benefits, the child on adjunctive therapy is reverted to the regimen that has proved most effective	100% of children on adjunctive therapy which has not brought about worthwhile benefits	None	<p>Clinicians will have to agree locally on the number of sequential trials attempted before a child's therapy is reverted to the one that was most effective. 'Worthwhile benefits' can include significant seizure reduction, improvement in quality of life and/or least side effects. Clinicians will need to agree locally on how benefits are documented, for audit purposes.</p>

Criterion	Standard	Exception	Definition of terms
4. In girls of childbearing age, the risk of the drugs causing harm to an unborn child is discussed between the girl and/or her carer and the responsible clinician and an assessment is made as to the risks and benefits of treatment with individual drugs	100% of children in the audit	None	Clinicians will need to agree locally on how the discussion with the child and/or carer will be documented and any exceptions, for audit purposes.
5. A child who has had a first non-febrile seizure is seen as early as possible by a specialist in the management of epilepsies	100% of children in the audit	None	<p>Clinicians will have to agree locally on the time frame for seeing a child who has had a first seizure and the definition of a specialist in the management of epilepsies, for audit purposes.</p> <p>Clinicians will also need to agree on the time frame for looking back, for audit purposes, for example, children having a first seizure in the last 6 months.</p>
6. Treatment is reviewed at regular intervals	100% of children in the audit	None	Clinicians will have to agree locally on the definition of 'regular', for audit purposes. It should be obvious from documentation that the review has ensured that a child with epilepsy is not maintained for long periods on treatment that is ineffective or poorly tolerated and that concordance with prescribed medication is maintained.

Calculation of compliance

Compliance (%) with each measure described in the table above is calculated as follows.

$$\frac{\text{Number of patients whose care is consistent with the criterion *plus* number of patients who meet any exception listed}}{\text{Number of patients to whom the measure applies}} \times 100$$

Clinicians should review the findings of measurement, identify whether practice can be improved, agree on a plan to achieve any desired improvement and repeat the measurement of actual practice to confirm that the desired improvement is being achieved.



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