

Newer drugs for epilepsy in adults

Technology Appraisal Guidance 76

Newer drugs for epilepsy in adults

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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, levetiracetam, oxcarbazepine, tiagabine, topiramate and vigabatrin, within their licensed indications, are recommended for the management of epilepsy in people 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 person is taking (notably oral contraceptives)
 - they are already known to be poorly tolerated by the individual
 - the person is a woman of childbearing potential (see Section 1.4 below).
- 1.2 It is recommended that people 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.
- 1.3 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 1.2) 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 patient, in terms of providing the best balance between effectiveness in reducing seizure frequency and tolerability of side effects.
- 1.4 In women of childbearing potential, the possibility of interaction with oral contraceptives and the risk of the drugs causing harm to an unborn child should be discussed and an assessment made as to the risks and benefits of treatment with individual drugs. There are currently few data upon which to base a definitive assessment of the risks to the unborn child associated with the newer drugs. Specific caution is advised in the use of sodium valproate because of the risk of harm to the unborn child.

- 1.5 It is recommended that all people having a first 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.
- 1.6 Treatment should be reviewed at regular intervals to ensure that people with epilepsy are not maintained for long periods on treatment that is ineffective or poorly tolerated and that concordance with prescribed medication is maintained.
- 1.7 The recommendations on choice of treatment and the importance of regular monitoring of effectiveness and tolerability are the same for specific groups such as older people and those with learning disabilities as for the general population.

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, alcohol-withdrawal 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 unprovoked seizures.
- 2.2 On the basis of data from the General Practice Research Database, the prevalence of epilepsy in England and Wales in 1998 was estimated to be 7.7 cases per 1000 in men and 7.6 cases per 1000 in women. The estimated number of people with epilepsy in England and Wales in 1998 was 400,000. The incidence of epilepsy in developed countries has been estimated to be around 50 cases per 100,000 people per year (range 40–70/100,000 people/year).
- 2.3 Epilepsy is not a uniform condition, but comprises many different seizure types and epilepsy syndromes. The severity of the condition and the prognosis vary according to the type of epilepsy. The impact of the condition also depends upon the characteristics of the person experiencing it. The adverse consequences vary according to the person's needs and priorities, for example, with regard to education, employment, pregnancy and child rearing, and independent

living. The condition is also associated with an increase in the risk of premature death; the diagnosis of epilepsy carries an excess mortality that is 2–3 times higher than that of the general population. Those with uncontrolled seizures have the highest excess risk. One study reported that people who had not been seizure-free in the previous year had a 23-fold increase in the risk of sudden unexplained death relative to those with controlled seizures.

- 2.4 Seizures can be broadly categorised into two types: partial seizures (also categorised as ‘focal’ or ‘localisation-related’ epilepsies) are epileptic seizures in which the neuronal discharge begins in or is restricted to a localised part of the brain; generalised seizures are characterised by more diffuse neuronal discharges involving both hemispheres of the brain at once. Some people have seizures that cannot be categorised in this way.
- 2.5 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. More than half of seizures in adults are of the complex partial type. Simple or complex partial seizures may evolve to become secondarily generalised seizures if the neuronal discharge spreads to involve the entire brain.
- 2.6 Generalised seizures 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. Absence seizures may pass unnoticed by others but the person loses consciousness and may experience attacks as often as 50 to 100 times a day. ‘Atypical’ absence seizures have a slower onset and longer duration. Both typical and atypical absence seizures occur predominantly in childhood, usually between the ages of 3 and 12 years.
 - Tonic–clonic seizures involve a tonic phase, in which the muscles suddenly contract, causing the person to fall and lie rigid. 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 usually for a number of seconds, but the seizures do not progress to the clonic phase.
- Myoclonic seizures are a series of brief jerky contractions of specific muscle groups, such as the face or trunk.

2.7 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.

2.8 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. Up to 30% of individuals continue to have seizures on monotherapy; these people are sometimes prescribed a second drug long-term.

2.9 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, absences 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.

- 2.10 A variety of other drugs also are occasionally used in the management of various types of seizure. Phenobarbital is used for tonic–clonic and partial seizures and may also 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 adjunctive therapy in the treatment of 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.
- 2.11 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. However, it can be difficult to distinguish between drug side effects and the consequences of the epileptic condition.
- 2.12 The older antiepileptic drugs have the potential to interact with numerous drugs. Carbamazepine, phenytoin and barbiturates induce hepatic enzymes. This means that they can accelerate the metabolism of drugs that are metabolised by these enzymes and higher doses will be needed or the drugs will be less effective. For example, carbamazepine, phenytoin and barbiturates reduce the effectiveness of oral contraceptives, necessitating the use of alternative methods, or special high-dose regimens of oral contraceptives, the effectiveness of which is less certain. Sodium valproate is a hepatic enzyme inhibitor and therefore slows the metabolism of some drugs, but it does not interfere with oral contraceptives.
- 2.13 The effects of these drugs on the unborn child are also a matter for concern. All the older antiepileptic drugs have been associated with malformations (see Section 4.1.15). 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 technology

- 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: lamotrigine, oxcarbazepine and topiramate. All seven drugs are licensed for use in combination therapy.
- 3.2 The main advantage proposed for the newer drugs over their predecessors is that they are associated with better quality of life, which has been attributed to various factors such as more acceptable adverse-effect profiles. Some of them also have other potential advantages, such as lower propensity for interactions with other drugs or more convenient dosage regimens, particularly in the initial stages of treatment.
- 3.3 The effects of newer drugs on the unborn child are also a matter for concern. There are fewer 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 more recently, or those which have not been widely prescribed.
- 3.4 Lamotrigine was launched for combination 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 Lennox-Gastaut syndrome. Monotherapy is not licensed in children younger than 12 years; combination therapy 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 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 Topiramate is licensed for combination therapy for adults and children older than 2 years who are inadequately controlled with 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 who have 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 Gabapentin is licensed for use in 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 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. It 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 Levetiracetam is licensed for the combination treatment of partial seizures with or without secondary generalisation. It is not recommended for children younger than 16 years. It has no reported drug interactions. For full details of side effects and contraindications, see the Summary of Product Characteristics.

- 3.9 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, 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.
- 3.10 The indications for vigabatrin are limited to use in combination therapy 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 infantile spasms (West's syndrome) where it remains a first-line therapy. It should be initiated only by an epilepsy specialist. For full details of side effects and contraindications, see the Summary of Product Characteristics.
- 3.11 The newer antiepileptic drugs are more expensive than the older drugs. At average doses, the costs of 28 days' treatment with the newer drugs are as follows:
- lamotrigine 150 mg twice daily, £101.68
 - oxcarbazepine 450 mg twice daily, £33.60
 - topiramate 150 mg twice daily, £94.23
 - gabapentin 400 mg three times daily, £51.52
 - levetiracetam 1 g twice daily, £88.20
 - tiagabine 15 mg twice daily, £76.22
 - vigabatrin 1 g twice daily, £50.23.

For comparison, the most widely used older drugs (carbamazepine, sodium valproate and phenytoin) cost between £2 and £12 per month at average doses, while modified release versions of carbamazepine and sodium valproate cost between £9 and £15 per month at average doses. All costs exclude VAT and are taken from the British National Formulary, 46th edition. However, costs may vary in different settings because of negotiated procurement discounts.

4 Evidence and interpretation

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

4.1 Clinical effectiveness

4.1.1 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).

4.1.2 The Assessment Report included randomised controlled trials and systematic reviews comparing newer antiepileptic drugs with placebo, older antiepileptic drugs, or other newer antiepileptic drugs in the review of clinical effectiveness. In addition, non-randomised, experimental studies and observational studies were included in the review of serious, rare and long-term adverse events.

4.1.3 Most of the trials investigating the effectiveness of newer antiepileptic drugs as monotherapy have compared the newer drugs with older drugs. The Assessment Group found only two studies comparing monotherapy using a new drug with placebo. Both studies involved oxcarbazepine: one in previously untreated people with newly diagnosed epilepsy (n = 67), and another in people with refractory epilepsy who were being evaluated for surgery for their seizures (n = 102). In the study in people with newly diagnosed epilepsy, the primary endpoint was the time to first seizure over the 90-day duration of the study. The median time to first seizure was statistically significantly longer in the oxcarbazepine group. The study in refractory epilepsy (potential candidates for surgery) also found that oxcarbazepine was effective in terms of the primary efficacy variable (time to exit, based on the person meeting one of the following criteria: experiencing four partial seizures, two new-onset secondarily generalised seizures, serial seizures or status epilepticus). However, the duration of this study was only 10 days, and the population was not typical of the general population of people with epilepsy.

4.1.4 Almost all studies comparing newer drugs with older drugs have found no statistically significant differences in terms of seizure-related outcomes (proportion of people seizure-free, proportion with a 50% reduction in seizure frequency, or time to first seizure). However, it cannot be concluded that the drugs have been shown to be equivalent in terms of

efficacy. Overall, the trials were not large enough or were not analysed appropriately to allow this conclusion to be drawn. Most of the studies recruited people newly diagnosed with either partial seizures or generalised seizures.

- 4.1.5 The main advantages of the newer drugs over the older drugs are thought to be in dimensions of health-related quality of life. However, only nine of the 19 studies comparing monotherapy using newer drugs versus older drugs assessed quality of life. Six of the studies compared lamotrigine with older drugs (one comparison with carbamazepine, one with phenytoin, two with sodium valproate and two with physician's choice of older drug), and used a total of 10 different measuring instruments. Three studies included people newly diagnosed with epilepsy, two included people with refractory epilepsy, and one included both people with refractory epilepsy and people newly diagnosed with epilepsy. The Assessment Group rated these studies as poor quality. Four of the six studies found statistically significant differences in favour of lamotrigine on at least one measure of quality of life. Three studies comparing oxcarbazepine with older drugs (carbamazepine in one study, phenytoin in another and sodium valproate in the third) assessed quality-of-life outcomes. The Assessment Group rated these studies as reasonable quality. Only one of the three (the comparison with phenytoin) found statistically significant differences in favour of oxcarbazepine. These studies do not provide strong evidence of improved quality of life with the newer drugs.
- 4.1.6 Another endpoint that might reflect differences in quality of life associated with these drugs is the time to exit or withdrawal from the study. It might be anticipated that people who were achieving inadequate benefit or who found the adverse effects of the drug intolerable would be more likely to withdraw in the early stages. Eight of the 19 studies comparing newer antiepileptic drugs with older drugs reported time to exit/withdrawal. Five of these were comparisons of lamotrigine with older drugs, two were comparisons of oxcarbazepine with older drugs, and the remaining study was a comparison between topiramate and either sodium valproate or carbamazepine. Three of the lamotrigine studies (one comparison with carbamazepine, one with sodium valproate and one with the physician's choice of older drug) reported statistically significant differences in favour of lamotrigine. One of the oxcarbazepine studies (a comparison with phenytoin) found a statistically significant difference in favour of oxcarbazepine, but the other study (a comparison with

sodium valproate) did not. The topiramate study found a difference between topiramate (100 mg and 200 mg dose groups pooled) and the pooled carbamazepine and sodium valproate groups, but it was not statistically significant.

- 4.1.7 The effects of antiepileptic drugs on cognitive function are of particular concern. Two of the 19 monotherapy studies evaluated aspects of this. One study was a comparison of lamotrigine with carbamazepine in people with either partial or generalised seizures. This study used six measures of cognitive function and found a statistically significant difference in favour of lamotrigine for each of them on at least one of four follow-up visits. 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. These problems, and other deficiencies in the quality of this study, led the Assessment Group to conclude that there may be a differential effect in favour of lamotrigine, but the data should be interpreted with caution. The other study that looked at cognitive function was a comparison of oxcarbazepine and phenytoin in people with partial or generalised onset seizures. This study found no statistically significant differences between the two drugs, but it was small ($n = 37$) and was probably underpowered.
- 4.1.8 Clinical trials of combination therapy are usually conducted in people who continue to have seizures despite treatment with one or more antiepileptic drugs. Seizure freedom, the ultimate goal of therapy, is usually an infrequent outcome in this group. Therefore, for pragmatic reasons relating to the power of the clinical studies to detect differences between the comparators, the primary outcome measure used in most studies of combination therapy is the proportion of people who achieve a 50% reduction in their seizure frequency (50% responders). All seven drugs have been used in trials showing an increase in 50% responder rate versus the addition of placebo to baseline treatment, although the difference was not always statistically significant in individual studies. The duration of the studies was relatively short (mostly 3–6 months or less).
- 4.1.9 Twenty-five of 55 placebo-controlled studies of combination therapy with newer drugs reported the proportion of seizure-free participants. Data on seizure freedom have been reported in at least one placebo-controlled trial for each of the seven drugs. Four studies of lamotrigine reported this endpoint, and in one the difference in proportion of

seizure-free participants between lamotrigine at a daily dose of 300 mg and placebo was statistically significant. Three studies of combination therapy using levetiracetam reported the proportion of seizure-free participants, but the difference reached statistical significance only for the 3 g/day dosage group in one trial. A fourth study that included a 12-week placebo-controlled add-on phase also found that a statistically significantly greater proportion of patients became seizure-free on levetiracetam 3 g/day than on placebo during this period. Only one placebo-controlled trial of oxcarbazepine reported the number of seizure-free participants. This compared three doses (600, 1200 and 2400 mg/day) with placebo. The differences in proportion of seizure-free participants were only statistically significant for two of the doses (1200 and 2400 mg/day). Ten studies of topiramate reported seizure freedom, although only three showed statistically significant differences compared with placebo. Pooled data from two 20-week trials involving patients with generalised seizures favoured topiramate (175–400 mg/day) over placebo but this was not statistically significant. Pooling of data from two trials that used topiramate 400 mg/day in patients with partial seizures showed statistically significant differences in favour of topiramate. Similarly, pooled data from three trials that used topiramate 600 mg/day were also statistically significant in favour of topiramate. Randomised trial data for seizure freedom with combination therapy using gabapentin were extremely limited. Only one trial reported this endpoint, and in this study only two individuals (both in the gabapentin group) were seizure-free. Two crossover trials of tiagabine reported the number of seizure-free participants, but both were of limited applicability because only participants achieving specific reductions in seizure frequency while receiving tiagabine treatment were allowed to enter.

- 4.1.10 There were some studies directly comparing newer drugs as adjunctive therapy with older drugs, or with other newer drugs. Ten studies compared newer drugs with older drugs. These were comparisons of gabapentin, tiagabine, topiramate or vigabatrin with carbamazepine, phenytoin or sodium valproate. Only one, a comparison of tiagabine with carbamazepine and phenytoin, found a statistically significant difference in 50% responder rate in favour of phenytoin versus tiagabine. Only two of the studies reported the proportion of seizure-free participants, and neither found statistically significant differences between the drugs.

- 4.1.11 There were four studies directly comparing newer drugs used in combination therapy (the first comparing gabapentin and vigabatrin, one comparing lamotrigine and tiagabine, another comparing gabapentin and lamotrigine, and a fourth study comparing lamotrigine, vigabatrin and gabapentin). The first study found a statistically significant difference in the proportion of 50% responders in favour of vigabatrin over gabapentin, but none found a statistically significant difference in the proportion of people who were seizure-free. Overall, there was very little evidence to draw conclusions about the relative effectiveness of different antiepileptic drugs in combination therapy.
- 4.1.12 Twelve placebo-controlled trials of combination therapy with antiepileptic drugs assessed aspects of cognitive function while on therapy. Six of the studies involved vigabatrin, three involved tiagabine, two involved lamotrigine and one involved gabapentin. Overall, however, there was little evidence that adjunctive therapy had either a positive or a negative effect on cognitive function. Three studies comparing newer drugs with older drugs assessed cognitive function (two comparisons of topiramate with sodium valproate as an adjunct to carbamazepine, and one study comparing tiagabine with phenytoin as an adjunct to carbamazepine or with carbamazepine as an adjunct to phenytoin); none provided strong or consistent evidence of a difference between the drugs in terms of effects on cognitive function.
- 4.1.13 Thirty-one of the 55 placebo-controlled studies of adjunctive therapy included an assessment of quality of life. About half of the studies found improvements in quality of life in favour of drug therapy versus placebo, but even the best of these studies were judged to be of limited quality by the Assessment Group. There were 10 direct comparisons of newer drugs with older drugs for combination therapy (see Section 4.1.10), four of which reported quality-of-life measurements, but none found any significant differences between newer and older drugs for these outcomes. Of the four direct comparisons between newer drugs used in combination therapy, three reported quality-of-life assessments. One comparative study of lamotrigine and gabapentin, which included people with learning disabilities, found statistically significant differences in favour of gabapentin, but overall there was insufficient evidence to assess the relative impact of the different adjunctive therapies on quality of life.

- 4.1.14 Generally, little evidence was found on the use of these agents in specific subgroups, such as older people or those with learning disabilities. Older people are poorly represented in studies. One randomised comparison of lamotrigine and carbamazepine as monotherapy exclusively included people over the age of 65 years, but most trials were in mixed populations. No monotherapy studies in people with learning disabilities were found, and only three studies of adjunctive therapy reported results exclusively from this population. There was some evidence from one study that both lamotrigine and gabapentin have some beneficial effects on behaviour in people with learning disabilities.
- 4.1.15 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 older drugs, the risk in women taking carbamazepine was 2.3% (95% CI, 1.4% to 4.0%), and the risk with sodium valproate was 7.2% (95% CI, 5.2% to 10.0%). The risk with lamotrigine was 3% (95% CI, 1.5% to 5.7%), but no risks were reported for any of the other newer agents. These data suggest that sodium valproate is associated with a statistically 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 The evidence on cost effectiveness considered by the Committee included an integrated cost-effectiveness analysis developed by the Assessment Group and economic evaluations submitted by the manufacturers of five of the drugs (lamotrigine, levetiracetam, oxcarbazepine, tiagabine and topiramate). The Assessment Group also provided a review of the published literature on the cost effectiveness of newer antiepileptic drugs.

- 4.2.2 The Assessment Group found four economic evaluations of monotherapy with newer antiepileptic drugs and seven evaluations of adjunctive therapy in the literature. All the studies of monotherapy were designed as cost-minimisation analyses (that is, the economic evaluation is based on a comparison of costs only). All four made the assumption that the effectiveness of the various antiepileptic drugs was equivalent. Despite differences in methodology between the studies, the findings were similar. Even when the most optimistic treatment scenario for the newer drugs was compared with the worst-case treatment scenario for the older drugs, monotherapy with the older drugs was considerably less costly. For adjunctive therapy, the Assessment Group found three comparisons of adjunctive therapy with existing therapy (without adjunct), two comparisons of older and newer adjunctive therapies (lamotrigine or vigabatrin compared with clobazam, and tiagabine compared with carbamazepine or phenytoin), and two comparisons between newer antiepileptic drugs (a cost-minimisation analysis of gabapentin and lamotrigine, and a cost-effectiveness comparison of topiramate and lamotrigine). None of the published economic evaluations satisfied all of the criteria for a robust economic evaluation of antiepileptic drugs (that is, one that considers all the treatment alternatives, takes a sufficient time horizon, and uses a systematic method to collect evidence).
- 4.2.3 The Assessment Group produced an integrated cost-effectiveness analysis that attempted to compare all the therapies on an equal basis. The model considered the treatment of a cohort of newly diagnosed people and followed them over a simulated treatment-lifetime of 15 years. The analysis incorporated available information on the costs and effects associated with the various newer and older epileptic drugs to allow comparisons between drugs despite the limitations in the data from clinical trials. The benefits of treatment were expressed in terms of quality-adjusted life years (QALYs). The model assumed that utility was based on seizure control, and did not differentiate between the drugs in terms of other effects that might have an impact on quality of life (for example, the acceptability of different side-effect profiles). The analysis was based on evidence from randomised controlled trials reporting the proportions of people having partial (> 50% reduction in seizure frequency) and complete responses, and the proportions discontinuing treatment. In the absence of more appropriate studies, the estimate of the impact of seizure control on utility was based on a single study of people receiving adjunctive therapy. There is uncertainty as to

whether these utilities are a good reflection of health-related quality of life in a more general population of people with epilepsy. The utility estimates were common to all the treatments under consideration.

- 4.2.4 For drugs used as first-line monotherapy in the treatment of adults with partial seizures, the results of the simulation suggested that differences between the therapies in terms of the number of QALYs generated were small, and there was a high degree of uncertainty around the estimates. Likewise, over the 15-year time frame of the model, the differences in cost between the initial therapies were small and associated with a high degree of uncertainty. Therefore, this model did not determine the most cost-effective antiepileptic drug with a high degree of certainty.
- 4.2.5 For adjunctive therapy in partial seizures, all the therapies offered a small QALY gain over placebo (that is, no adjunctive therapy). Continued monotherapy was associated with the lowest mean cost overall. Again, the differences in costs and benefits were small and associated with a high degree of uncertainty. The model did not establish the most cost-effective adjunctive therapy with confidence.
- 4.2.6 In considering the cost-effectiveness of monotherapy in generalised seizures, the analysis included only clinical trials that exclusively enrolled adults with generalised seizures. These data were much more limited than for partial seizures. Only lamotrigine and sodium valproate were compared as first-line monotherapy in the assessment group model because of the limitations in the available evidence, although topiramate is also licensed for this indication. As first-line monotherapy, sodium valproate was less costly than lamotrigine and no less effective. Probabilistic analysis showed that sodium valproate is likely to be preferred to lamotrigine across a broad range of acceptable amounts to pay for an additional QALY.
- 4.2.7 Of the newer drugs, only lamotrigine and topiramate are licensed for adjunctive therapy in people with generalised seizures. The cost-effectiveness analysis compared only topiramate with no adjunctive therapy (there were no suitable studies of lamotrigine that exclusively included adults with generalised seizures). This analysis indicated that topiramate might be cost-effective when used as an adjunctive therapy, with an estimated incremental cost-effectiveness ratio of £32,600 compared with continued monotherapy, but this estimate was associated with a high degree of uncertainty.

- 4.2.8 The manufacturer of lamotrigine (GlaxoSmithKline) submitted two cost–utility evaluations: one for monotherapy and one for adjunctive therapy. The monotherapy model compared lamotrigine with carbamazepine or sodium valproate over a time frame of 1 year. Effectiveness was estimated on the basis of clinical trials comparing lamotrigine with sodium valproate or carbamazepine. In the absence of high-quality published data on health-related quality of life associated with these drug treatments, a new study was performed. Members of the general population were asked to value health states representing the side-effect profiles of each drug with either controlled or partially controlled seizures using a standard gamble method. However, it appears that only some aspects of each drug’s side-effect profile were described, and a different aspect was described for each drug. The GlaxoSmithKline model for lamotrigine as adjunctive therapy did not attempt to take account of the side-effect profile of the individual drugs; as in the Assessment Group’s model, published utilities based on seizure control alone were used. Both models concluded that the costs per additional QALY were comparable with other healthcare interventions currently recommended for use by the NHS.
- 4.2.9 The manufacturer of oxcarbazepine (Novartis) supplied two economic analyses of monotherapy (a comparison with carbamazepine, and a cost-minimisation analysis comparing oxcarbazepine with lamotrigine), and one analysis comparing oxcarbazepine with lamotrigine as adjunctive therapy. For the monotherapy comparison with carbamazepine, the model was a decision tree with a 56-week time frame. People who discontinued first-line therapy were assumed to do so during the titration phase and were assumed to go on to lamotrigine for the maintenance period. There was no modelling of progression to third-line monotherapy or combination treatment. According to this analysis, the incremental cost of treating an individual with oxcarbazepine rather than carbamazepine was less than £200 per year.
- 4.2.10 The manufacturer’s comparison of first-line oxcarbazepine with lamotrigine was based on the assumption of equivalent clinical effectiveness of oxcarbazepine and lamotrigine (a cost-minimisation analysis). It was assumed that the second-line treatment was sodium valproate. According to this analysis, oxcarbazepine monotherapy was approximately half the cost of lamotrigine. The comparison of oxcarbazepine and lamotrigine as adjunctive therapy was also a cost-minimisation analysis. This showed that the cost associated with using lamotrigine was higher than that associated with oxcarbazepine.

- 4.2.11 The manufacturer of topiramate (Janssen-Cilag) presented a cost–utility analysis based on a Markov model that simulated a cohort of 1000 people through 3-monthly cycles over a period of 15 years. For partial seizures, topiramate was compared with carbamazepine and lamotrigine. For generalised seizures, topiramate was compared with sodium valproate and lamotrigine. For partial seizures, carbamazepine first-line and topiramate second-line therapy dominated other treatment strategies. First-line topiramate and second-line carbamazepine was the most cost-effective alternative. According to this model, first-line sodium valproate followed by second-line topiramate was the least costly option for generalised seizures.
- 4.2.12 The Janssen-Cilag evaluation of combination antiepileptic therapy found that first-line topiramate and second-line levetiracetam dominated other treatment combinations.
- 4.2.13 The manufacturer of levetiracetam (UCB) submitted a cost-effectiveness analysis of adjunctive levetiracetam compared with continued standard therapy alone for outcomes of seizure freedom and reduction in seizure frequency. The model was a decision tree with a 1-year time frame. No attempt was made to compare levetiracetam with other adjunctive therapies. According to this analysis, the cost per additional seizure-free individual per year was estimated to be £5300.
- 4.2.14 The manufacturer of tiagabine (Cephalon) submitted a cost-effectiveness analysis in which the measure of health benefit was the success rate (success was defined as absolute difference between the active and the placebo groups in the proportion of people achieving 50% reduction in seizure frequency). Tiagabine was compared with other new antiepileptic drugs (lamotrigine, topiramate, gabapentin and vigabatrin) as adjunctive treatment over a 12-week period. The authors concluded that the adjunctive cost of tiagabine was similar to that of topiramate and gabapentin, and less than half that of lamotrigine.
- 4.2.15 The manufacturers' submissions used a range of outcome measures, made different comparisons, and were conducted over different time frames. It is therefore not possible to make direct comparisons between them. Only one of the manufacturers (Janssen-Cilag) presented models that allowed for multiple comparisons between several treatment options over a time horizon of more than 1 year. The main weakness of this model was the lack of a systematic approach to obtaining and synthesising effectiveness data.

4.3 Consideration of the evidence

- 4.3.1 The Committee reviewed the evidence available on the clinical and cost effectiveness of the newer antiepileptic drugs, having considered evidence on the nature of the condition and the value placed by users on the benefits of the newer antiepileptic drugs from people with epileptic disorders, 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 effectiveness in seizure control. There was also insufficient evidence to distinguish between the different newer antiepileptic drugs for seizure control. Although side-effect profiles of the 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 integrated cost-effectiveness analysis showed a high degree of uncertainty around the costs and benefits of these treatments. Thus, given the higher cost of the newer antiepileptic drugs, the Committee recommended that first-line monotherapy should be initiated with one of the older antiepileptic drugs, such as carbamazepine or sodium valproate, unless these drugs are not suitable because there are contra-indications or the potential for interactions with other drugs the person is taking, because they have been poorly tolerated by the person in the past, or because the person is a woman of childbearing potential.
- 4.3.3 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 and concluded that a significant proportion of people who do not achieve seizure freedom on monotherapy could derive worthwhile benefit from combination therapy. The Committee was also persuaded by the experts' evidence that before combination therapy is considered, people should be given a trial of appropriate monotherapy, and that caution is needed during changeover periods between drugs. Because of the relatively short duration of the studies of combination therapy (most were 3–6 months or less) and the limited number of direct comparisons between the newer drugs, 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.

- 4.3.4 The Committee was persuaded that, irrespective of which adjunctive therapy was used, people 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. Therefore the Committee felt that if, after sequential trials of combination therapies, none proves to be beneficial, then following discussion the person should revert to treatment with the regimen that had proved most effective for him or her and has the least side effects.
- 4.3.5 The Committee considered that the available trial evidence did not allow it to draw firm conclusions as to the relative effectiveness of the various drugs in terms of the likelihood of seizure freedom, particularly over the longer term. These issues add to the considerable uncertainty surrounding the relative cost-effectiveness of these drugs.
- 4.3.6 The Committee heard from the experts that some people may be maintained for long periods on medication that is ineffective or not well tolerated. The experts highlighted the importance of regular monitoring to review and optimise treatment.
- 4.3.7 The Committee noted that clinical experts were concerned that the clinical studies did not take account of the heterogeneity of the epilepsies. Entry to the studies was usually determined by seizure type (partial or generalised seizures or a mixed population) and therefore may have inappropriately mixed individuals with different epilepsy disorders and varied prognoses. These studies are not helpful when tailoring antiepileptic drug treatment to the needs of the individual, and often decisions are based upon less robust sources of evidence and an individual clinician's opinions and experience. The Committee recognised the importance of having a range of therapies available for the treatment of epilepsies in the light of variation in individuals' responses. It recognised that these responses to individual drugs could not be predicted in advance, and, in the absence of compelling evidence of advantages in terms of effectiveness, a cost minimisation approach was appropriate for deciding in which order the drugs should be tried.
- 4.3.8 The Committee noted that the issue of whether antiepileptic drugs may be harmful to the unborn child if taken during pregnancy is a major concern. The Committee specifically took note of the particular concern regarding the risks to the unborn child associated with the use of sodium valproate and that, because of this, the Summary of Product Characteristics for sodium valproate (Epilim) warns that, for

partial seizures, sodium valproate should be used in women 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 of childbearing age with some types of generalised seizures, provided that an informed choice has been made. The Committee was persuaded that, as yet, there are few data upon which to base a robust assessment of the risks to the unborn child associated with newer drugs.

- 4.3.9 Additionally, the Committee took note of the potential for drug interactions with the use of the antiepileptic drugs and, in particular, interactions with oral contraceptives, which may be of relevance in women of childbearing potential. It concluded that this aspect of therapy should be taken into account in determining the most suitable treatment for any individual.
- 4.3.10 The Committee noted the lack of high-quality evidence on which to base recommendations on the most appropriate treatments for those with learning disabilities and older people. The Committee noted that the importance of regular monitoring of effectiveness and tolerability was the same for those with learning disabilities and older people as for the general population of people with epilepsy.
- 4.3.11 The Committee discussed the issue of generic prescribing in relation to antiepileptic drugs. It 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.
- 4.3.12 The Committee was aware of the importance of investigation and early accurate diagnosis for people 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 people with epilepsy, in order to ensure patient/carer preferences have been considered and the most appropriate treatment regimen is maintained.

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 about 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. 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.

6 Implications for the NHS

- 6.1 Prescriptions for newer antiepileptic drugs have been steadily increasing as a proportion of the total. Between 1991 (when vigabatrin and lamotrigine were the only newer drugs available) and 1999, newer drugs rose as a proportion of prescriptions for antiepileptic drugs from 0.1% to 11.2%. According to the most recent prescription cost analysis (PCA) data, they had risen to 20% of total items and 69% of total costs (£99 million of £142 million) in 2002. However, some drugs are used for indications other than epilepsy, and such use is likely to account for at least part of the increase. This guidance is expected to have a neutral impact on these prescribing trends.
- 6.2 There will be implications for provision of specialist services if additional clinics are required to ensure that people having a first seizure are seen quickly and reviewed at regular intervals.

7 Implementation and audit

- 7.1 All clinicians with responsibility for treating adults 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 adults with epilepsy should incorporate the guidance.
- 7.3 To measure compliance locally with the guidance, the following criteria could be used and will be applicable to all individuals with epilepsy. Further details on suggestions for audit are presented in Appendix C.

- 7.3.1 A person 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 person is taking (notably oral contraceptives)
 - they are already known to be poorly tolerated by the individual
 - the person is a woman of childbearing potential (see Section 1.4).
- 7.3.2 A person with epilepsy is ordinarily treated with a single antiepileptic drug. If treatment with a single antiepileptic drug (monotherapy) is unsuccessful, then the person is treated using another single antiepileptic drug, exercising caution during the changeover period.
- 7.3.3 A person with epilepsy is prescribed combination (adjunctive) therapy only when attempts at monotherapy with antiepileptic drugs have not resulted in seizure freedom. If trials of adjunctive therapy do not bring about worthwhile benefits, the person's treatment is reverted to the regimen that has proved most acceptable to the patient in terms of its effectiveness in reducing seizure frequency and the tolerability of its side effects.
- 7.3.4 In women of childbearing potential, the risk of the drugs causing harm to an unborn child and the possibility of interaction with oral contraceptives are discussed between the woman and the responsible clinician and an assessment is made as to the risks and benefits of treatment with individual drugs.
- 7.3.5 A person who has had a first seizure is seen as soon as possible by a specialist in the management of epilepsies.
- 7.3.6 Treatment is reviewed at regular intervals.

- 7.4 Local clinical audits also could 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 people 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 a parallel appraisal of the use of newer drugs in children with epilepsy, which will be published in 2004. The Institute also plans to publish a clinical guideline for the diagnosis, management and treatment of epilepsy in 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
March 2004

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 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 and Primary Care Nursing, St Bartholomew School of Nursing and Midwifery

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

Dr John Geddes

Consultant Psychiatrist, University Department of Psychiatrists, Oxford

Ms Bethan George
Interface Liaison Pharmacist,
Tower Hamlets PCT and Royal
London Hospital, Whitechapel

Mr John Goulston
Director of Finance, Barts and
the London NHS Trust

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
Lay Representative; Chief
Executive, Changing Faces,
London

Mrs Kathryn Roberts
Nurse Practitioner, Hyde,
Cheshire

**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.

Janet Robertson
Health Technology Analyst

Eleanor Donegan
Health Technology Analyst

Kathleen Dalby
Technology Appraisal Project
Manager

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 the Centre for Reviews and Dissemination (CRD) and Centre for Health Economics (CHE), University of York.

A rapid and systematic review of the clinical effectiveness, tolerability and cost effectiveness of newer drugs for epilepsy in adults, 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
- Department of Health
- Epilepsy Action
- Epilepsy Bereaved
- Epilepsy Research Foundation
- Epilepsy Specialist Nurses Association
- Epilepsy Wales
- Institute of Neurology
- Joint Epilepsy Council
- National Society for Epilepsy
- Royal College of General Practitioners
- Royal College of Physicians
- Royal College of Psychiatrists
- Welsh Assembly Government

III Commentator organisations (without the right of appeal):

- Fund for Epilepsy
- National Collaborating Centre for Primary Care
- NHS Quality Improvement Scotland
- Dudley South Primary Care Trust
- East Kent Coastal Primary Care Trust

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 adults by attending the initial Committee discussion and/or providing written evidence to the Committee. They were also invited to comment on the ACD.

- Ms Kathy Bairstow, Senior Advice and Information Officer, Epilepsy Action
- Professor David Chadwick, Professor of Neurology and Neurosurgery, Association of British Neurologists
- Dr Morgan Feely, Consultant Clinical Pharmacologist, Leeds General Infirmary
- Ms Julie Hodgson, Member and Accredited Volunteer, Epilepsy Action
- Dr Peter Humphrey, Chairman, Guideline Panel re Epilepsy, Association of British Neurologists
- Mr Jim Oates, Epilepsy Liaison Nurse & Chair, Epilepsy Specialist Nurses Association
- Professor Ley Sander, Professor of Neurology & Clinical Epilepsy and Consultant Neurologist, Institute of Neurology and National Society for 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 adults

Possible objectives for an audit

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

Possible patients to be included in the audit

An audit could be carried out on the care provided to adults with epilepsy, including older people and those with learning disabilities, treated either by specialists or in primary care settings. In the specialist setting, the audit could include all individuals 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 people 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 adults are as follows.

Criterion	Standard	Exception	Definition of terms
<p>1. The person is treated with a newer antiepileptic drug if he or she meets either of the following:</p> <p>a. the person has not benefited from treatment with an older antiepileptic drug or</p> <p>b. an older antiepileptic drug is unsuitable because:</p> <p>1) there are contraindications to the drugs or</p> <p>2) there could be interactions with other drugs the person is taking or</p> <p>3) they have proven to be poorly tolerated or</p> <p>4) the person is a woman of childbearing potential</p>	<p>100% of people in the audit</p>	<p>A. The person chose an older drug based on discussion with the prescribing clinician (see criterion 4)</p>	<p>'Older antiepileptic drugs' include carbamazepine, sodium valproate, phenytoin, phenobarbital, ethosuximide, clonazepam, clobazam and acetazolamide. 'Newer antiepileptic drugs' are gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate or vigabatrin.</p> <p>'Benefited from treatment' 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, childbearing potential and any other exceptions, for audit purposes.</p>

Criterion	Standard	Exception	Definition of terms
2. The individual is treated with a single antiepileptic drug	100% of people 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. Attempts at monotherapy with antiepileptic drugs have not resulted in seizure freedom</p>	<p>Clinicians will need to agree locally on what constitutes 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 and the licensed indications for each drug.</p>
3. If trials of adjunctive therapy do not bring about worthwhile benefits, the treatment of an individual on adjunctive therapy is reverted to the regimen that has proved most acceptable to the patient	100% of people on combination therapy that has not brought about worthwhile benefits	None	<p>Clinicians will need to agree locally on the duration of a trial before a person's therapy is reverted to the one that was most acceptable for the patient. '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. The risk of the antiepileptic drugs causing harm to an unborn child and the possibility of interaction with oral contraceptives are discussed with a woman of childbearing potential	100% of women of childbearing potential who are in the audit	None	Clinicians will need to agree locally on the definition of childbearing potential and on how the discussion will be documented, for audit purposes.
5. A person who has had a first seizure is seen as soon as possible by a specialist in the management of epilepsies	100% of people in the audit	None	<p>Clinicians will need to agree locally on the time frame for seeing people suffering from a first seizure and the definition of a specialist in the management of epilepsies, for audit purposes.</p> <p>Clinicians also will need to agree on the time frame for looking back, for audit purposes, for example, individuals having a first seizure in the past 6 months.</p>
6. Treatment is reviewed at regular intervals	100% of people in the audit	None	Clinicians will need to agree locally on the definition of regular, for audit purposes. It should be obvious from documentation that the review has ensured that a person 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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