Newer drugs for epilepsy in adults

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

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Executive summary

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Executive summary

Background

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

Aims of the review

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

Methods

Search strategy

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

Inclusion/exclusion criteria

Studies of newer AED therapies for the treatment of adults with newly diagnosed or refractory epilepsy were included. Relevant comparators included older AEDs, other newer AEDs and placebo. Only randomised controlled trials (RCTs) and systematic reviews were included in the review of clinical effectiveness, and in addition non-randomised experimental studies and observational studies were included in the review of serious, rare and long-term adverse events. The assessment of cost-effectiveness included only cost-minimisation, cost-effectiveness and cost–utility analyses. Two reviewers independently screened all titles and abstracts and made final decisions on the inclusion/exclusion of studies based on full copies of articles. Any disagreements were resolved through discussion.

Data extraction and quality assessment

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

Analysis strategy

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

Results

Included studies

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

Quality of clinical effectiveness studies

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

Quality of economic evaluations

The main weakness of the published economic evaluations was inappropriate use of the cost- ▶

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

Assessment of clinical effectiveness

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

Monotherapy

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

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

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

Adjunctive therapy

Sixty-seven RCTs (10 GBP, 21 LTG, three LEV, two OXC, seven TGB, 14 TPM and 15 VGB) compared adjunctive therapy with placebo (56 studies), older AEDs (seven studies) or other newer AEDs (four studies). Three of the four studies of newer AEDs compared to other newer AEDs investigated two newer AEDs each, and the other study investigated three newer AEDs. For newer AEDs versus placebo, a trend was observed in favour of newer drugs, and there was evidence of statistically significant differences in proportion of responders in favour of newer drugs. However, as the length of follow-up was limited in many trials, it was not possible to assess long-term effectiveness. Most trials were conducted in patients with partial seizures.

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

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

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

Adverse events

Eighty RCTs reported the incidence of adverse events. There was no consistent or convincing evidence from these studies to draw any clear conclusions concerning relative safety and tolerability of newer AEDs compared with each other, older AEDs or placebo. Observational data provided some evidence of possible serious, rare ►

and long-term adverse events beyond those reported in RCTs. However, the evidence reviewed does not provide proof of association between drug and event.

Assessment of cost-effectiveness

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

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

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

Conclusions

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

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

Recommendations for research

There is a need for the following:

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

Publication

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