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Measuring the efficacy of antiepileptic drugs

RAJIV MOHANRAJ & MARTIN J. BRODIE

Epilepsy Unit, Division of Cardiovascular and Medical Sciences, Western Infirmary, Glasgow, Scotland, UK

Correspondence to: Professor Martin J. Brodie, Epilepsy Unit, Division of Cardiovascular and Medical Sciences, Western Infirmary, Glasgow G11 6NT, Scotland, UK. *E-mail*: Martin.J.Brodie@clinmed.gla.ac.uk

Clinical trials of new antiepileptic drugs (AEDs) include regulatory studies aimed at demonstrating efficacy and reasonable safety, post-marketing open-open label studies and longer term outcome studies. Regulatory trials involve a carefully selected population of patients and are conducted under rigorously standardised conditions. Data from such studies cannot often be translated into clinical practice. Pragmatic post-marketing studies using flexible dosing schedules allow clinicians to better judge the utility of the new drug in a wider population of patients with epilepsy and decide the most appropriate dosing schedules. This paper discusses some of the issues surrounding the measurement of efficacy of new AEDs in both pre- and post-marketing phases of their development.

All of the newer AEDs are initially used in patients with refractory partial seizures as adjunctive treatment. These trials are generally parallel-group studies although cross-over designs have been employed. The use of placebo-control is uncontroversial in this type of study. Efficacy endpoints are generally manipulations of seizure frequency on study drug compared to control. Global outcome measures and health related quality of life scores can also be used to measure efficacy.

As the standard AEDs are associated with a high rate of seizure remission in patients who receive them as monotherapy, demonstration of superior efficacy of a new agent in a comparative trial will require large numbers of patients in a design that takes into account the natural history of treated epilepsy. Comparing investigational agents to a standard AED in an 'active-control' study with demonstration of equivalent efficacy would seem to be an acceptable way of assessing efficacy of new AEDs in this population. Some regulators, however, do not accept equivalence as proof of efficacy and insist on demonstration of superiority compared to a control. The use of placebo alone in the control group is ethically dubious. Several innovative study designs have, therefore, been used to satisfy regulatory requirements, while maintaining patient safety including withdrawal to monotherapy using high versus low dose comparators.

Observational outcome studies provide the best opportunity of exploring the long-term utility of individual AEDs. Such studies largely follow standard clinical practice and need considerable time and resources. They can, however, yield valuable information about the effectiveness of AEDs in everyday clinical practice. Data from regulatory trials should be complemented by postmarketing studies and longer term studies of outcome to help clinicians decide the best way of utilising new AEDs and establishing their role in the therapeutic armamentarium.

Key words: antiepileptic drugs; monotherapy; epilepsies; clinical trials; effectiveness.

INTRODUCTION

The epilepsies are a group of heterogenous, multifaceted disorders that have physical, psychological and social implications[1]. Nine new chemical entities have been licensed world wide for the prevention of seizures since the late 1980s[2,3]. Nevertheless, only 60–65% of patients achieve remission with currently available antiepileptic drugs (AEDs)[4]. There is clearly a need for more new AEDs with novel mechanisms of action[5]. Trials conducted to assess AEDs vary in their design, methodology and end points depending on who wants the information from them. Regulatory authorities look for evidence of efficacy and safety, while patients and doctors seek data on longer term clinical utility and tolerability. The pharmaceutical companies hope to meet the requirements of all parties. Most trials aimed at demonstrating efficacy to meet regulatory demands do not provide clinicians with the information necessary to make treatment decisions[6].

The setting for regulatory clinical trials is necessarily artificial, the findings from which might not be

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reproducible in 'real life'. Nevertheless, stringent patient selection based on strict protocols and exclusion criteria are necessary to safeguard patients in these trials and to provide unequivocal evidence of efficacy for regulatory authorities[7]. Once efficacy in controlling seizures and reasonable safety have been demonstrated, a license is obtained, initially as adjunctive treatment and then as monotherapy, and clinicians can start to gain experience with the drug and decide its place in the therapeutic armamentarium[8]. Indications, titration schedules and recommended doses can change and new adverse effects come to light in the post-marketing period, which may have important implications for the drug's therapeutic usefulness. To adequately evaluate benefits and risks of treatment for chronic diseases, systematic reviews should consider data from observational studies in addition to randomised controlled trials[9].

Observational studies can be useful adjuncts to randomised, controlled trials to see whether the demonstrated efficacy translates into effective treatment in routine clinical practice[10]. This discussion paper will touch on some of pre- and post-licensing efficacy issues that need to be addressed before the value and usage of a drug can be determined with any degree of certainty. Details of the methodology relative to major efficacy studies for the nine newer AEDs licensed since 1989 are provided in Appendices A–I.

REGULATORY ISSUES

While regulatory authorities require proof of efficacy and safety before a license can be granted, there are differences in what is acceptable in different parts of the world. The requirements for licensing an AED as add-on in patients with refractory epilepsy are largely non-controversial. Placebo-controlled, add-on studies usually include a range of randomised doses for the new AED. The aim is to show a clinically useful dose–response relationship, ideally including a non-effective dose, which will help identify the effective dosage range.

When a monotherapy claim for newly diagnosed epilepsy is requested, the Food and Drug Administration (FDA) in the United States usually insists on two randomised double-blind trials showing evidence of superiority of test drug over control as proof of efficacy[11]. As many patients with newly diagnosed epilepsy will have their seizures controlled with the first AED chosen[4], often at modest or moderate dosage[12], a dose–response relationship can be difficult to identify in this population[13,14].

The European Agency for Evaluation of Medicinal Products (EMEA) recommends trials using established AEDs as controls (active-control). Demonstration of 'no difference' between the new drug and established treatment can be accepted as evidence of efficacy. Although no placebo-controlled trials have been carried out using the traditional AEDs, sufficient historical evidence exists to support their efficacy[15]. Active-control trials can, therefore be considered valid if they reproduce the setting in which the comparator has been shown to be effective and for which it has been licensed by the regulatory authority. One advantage of active-control studies is that they allow the new agent to be tested as monotherapy for the population of patients in whom it will later be licensed. The FDA takes the view that 'equivalence' between the test drug and active-control could be simply due to lack of efficacy of both or because the trial lacked sufficient sensitivity to differentiate between them[16]. A number of strategies have been developed to overcome this dilemma, including high dose versus low dose or 'pseudoplacebo' in withdrawal to monotherapy designs.

ADJUNCTIVE TRIALS

All new AEDs are initially studied as adjunctive treatment in patients who continue to have seizures despite treatment with one or more AEDs. The use of placebo in this setting is not considered unethical as patients are already on treatment with conventional drugs and are protected from status epilepticus by their baseline medication. They are required to have a defined number of seizures per unit time (e.g. four per month) to be eligible for inclusion in a regulatory trial. In the pre-treatment phase, existing therapy remains stable and baseline seizure frequency is recorded usually over 8 weeks. Modern studies tend to follow a parallel-group design. Cross-over studies have largely gone 'out of fashion' because they are regarded as methodologically less sound. Patients with partial seizures with or without secondary generalisation are recruited initially, since there still is substantial need for effective treatment in this patient population[17,18]. Similar studies in the generalised epilepsies are sometimes undertaken later although these are often slow to recruit[19]. Efficacy against typical absences or myoclonic jerks can be difficult to demonstrate.

Cross-over studies

This design involves patients receiving the drug and placebo randomly in two separate treatment phases separated by a washout period. Vigabatrin[20] and lamotrigine[21] underwent European regulatory programmes based on randomised, placebo-controlled, cross-over studies. This design allows the effects of

drug and placebo to be studied within subjects and can be particularly useful early in the development programme[22]. There is a fundamental requirement for seizure numbers to remain stable and predictable. Only if seizure frequency returns to baseline when the first treatment is stopped can the second be evaluated under identical conditions. This can be a problem as many patients tend to be recruited during a period of exacerbation of their seizures which may remit over time irrespective of therapy. Furthermore, if there has been a clear beneficial effect during the first period of treatment, there are ethical concerns about switching patients and consent for the second period might not be forthcoming. Carry over effects can also influence results from the second period. In addition, if the response to or toxicity with the test drug is clearly different from that of placebo, blinding can be difficult to maintain. For these reasons, regulatory authorities are unlikely to accept cross-over trials as primary proof of efficacy. However, useful information on dose-ranging, pharmacokinetic interactions, and side-effect profiling can be obtained using this design[23].

Parallel-group studies

This is regarded as the design of choice for the regulatory assessment of efficacy of new AEDs as adjunctive therapy in difficult-to-control epilepsy. Patients are randomised to receive one of several doses of drug or matched placebo. Groups are compared for measures of efficacy and tolerability. This design has the advantage that it is suitable for all stages of drug development and a range of dose levels can be included in the same study. The necessity for the seizure disorder to be stable is not vital in this design because the comparison is between rather than within subjects. Dose–response studies need to be carried out with compounds seeking approval as adjunctive therapy and demonstration of a clear-cut dose–response relationship reassures all concerned that efficacy has been demonstrated.

Results from these trials can be complicated by potential pharmacokinetic and pharmacodynamic drug interactions. Some limitations may be placed on the number and types of baseline AEDs to help minimise these problems, but they cannot be wholly eliminated. It can be argued, indeed, that such studies assess the efficacy and tolerability of AED combinations rather than the drug under study. Giving lamotrigine to patients already taking sodium valproate will produce a better response than those established on carbamazepine or phenytoin[24]. Indeed, synergism between sodium valproate and lamotrigine has been confirmed in an open, response-conditional, cross-over design employing concentration measurement[25]. The combination of carbamazepine and lamotrigine, on the other hand, is more likely to produce neurotoxic side-effects due to an adverse pharmacodynamic interaction between the drugs[24,26]. Combination effects may also explain the substantial efficacy of the GABA-ergic AEDs, vigabatrin and tiagabine, as add-on therapy in refractory epilepsy[27,28], which was less impressive when the drugs were used as monotherapy in newly diagnosed localisation-related epilepsy[29,30].

MONOTHERAPY TRIALS

Evidence of efficacy from add-on studies has to be available before such studies can be contemplated. Most patients with untreated epilepsy can expect to have their seizures controlled with one AED[4]. The use of placebo-control in patients with newly diagnosed epilepsy can be regarded, therefore, as ethically dubious[31]. For regulatory purposes, the FDA accepts only evidence of superiority over control as proof of efficacy. There are difficulties in designing clinically relevant monotherapy trials that meet their requirements. Randomising patients to placebo alone could be interpreted as being at odds with the Declaration of Helsinki which stated that, “In any medical study all patients—including those in the control group, if any—should be assured of the best proven diagnostic and therapeutic method”. A revised version, issued in October 2000, included a new section (section 29) which stated “The benefits, risks, burdens and effectiveness of a new method should be tested against the best current prophylactic, diagnostic and therapeutic methods”[32]. If interpreted literally, this would appear to rule out placebo-controlled trials, whenever licensed therapeutic options already exist. However, judicious use of placebo is sometimes essential to establish the efficacy of new treatments[33]. A further ‘clarification’ of this section issued in October 2001 stated that placebo-controlled trials may be justifiable even when effective treatments are available if there are compelling and scientifically sound methodological reasons for their use with the caveat that patients subjected to placebo treatment are assured of no serious or long-lasting harm. In the context of epilepsy, this could be interpreted to mean that the use of placebo alone is justified only when genuine doubt exists as to the effectiveness of the treatment being evaluated (e.g. following first unprovoked seizure), or when the risks from further seizures are low (e.g. absence seizures).

In an attempt to avoid the ethical problems of using placebo controls, low doses of the study drug or suboptimal doses of a standard AED have been used as a ‘pseudoplacebo’. The rationale for this has been

that while a low dose will protect against catastrophic seizures, it will have little effect on the overall number of partial seizures[34]. There is, however, no evidence to support this. In addition, it can be argued that the using a drug at a dose intended to be ineffective is equivalent to using a placebo. A number of innovative study designs have been used to satisfy regulatory requirements while maintaining patient safety. These 'therapeutic failure' paradigms require the demonstration of worse seizure control in the low dose compared to the high dose group[35]. Even with tightly defined exit criteria, ethical concerns remain with such approaches[36].

Pre-surgical withdrawal

These studies are carried out in patients who have had their AEDs discontinued as part of seizure localisation investigations prior to possible epilepsy surgery. Patients are randomised to the study drug or placebo-control and are monitored until they meet pre-defined exit criteria. These can include a specified number of seizures, worsening of seizure severity, or completion of a period on treatment. Primary efficacy variables are usually time to exit and the percentage of patients completing the study. This design can be used as 'proof of concept' for AED efficacy.

Such protocols tend to last short periods (hours to days) and yield little clinically relevant information. Drugs that exhibit delay in onset of full clinical effect (e.g. sodium valproate) and those that show tolerance (e.g. benzodiazepines) may not be suitable for this design. Once the patient has had sufficient number of seizures for the purpose of localisation and video-monitoring has been discontinued, any further episodes will be for the benefit of the study alone. Modifications have been suggested to address such remaining ethical issues[37,38].

Conversion to monotherapy

Patients with difficult-to-control epilepsy taking AEDs are randomised to receive active drug or control. The original AEDs, usually one or two, are then tapered off and patients maintained, if possible, on the new monotherapy. The use of placebo would be unacceptable in this population of patients and, therefore, suboptimal comparators (low dose of study drug or of another AED) are used instead as controls. The aim is to show that significantly more patients can be maintained on monotherapy with the study drug at high than on low dosage[39]. Exit criteria are defined in terms of number and severity of seizures. This follows clinical practice to a limited extent inasmuch as it seeks to withdraw concomitant AEDs in patients whose seizures are controlled when a new drug is added[40]. However, target doses of the study drug are usually fixed and the substitution protocol is often rigid. Maintaining responders on monotherapy for an extended period can yield valuable safety information. These studies have a variable track record in demonstrating efficacy of new AEDs as monotherapy and ethical concerns surrounding the use of pseudo-placebos remain. A recent proposal under discussion is to drop the low dose comparator and compare the withdrawal rate on high doses of new AEDs with 'historical' controls from previous trials.

Active-control

These trials are carried out in drug-naïve patients with newly diagnosed epilepsy. The study drug is compared to standard doses of an established AED using a randomised, double-blind design. This approach has the advantage of comparing the new drug head-to-head with standard treatment without the confounding effect of comedication withdrawal. As the majority of newly diagnosed patients experience seizure remission with the first AED chosen[4], often at low or moderate dosage[12], demonstrating superior efficacy will require large numbers of patients followed-up over long periods of time using a flexible dosage design. Demonstrating 'equivalence' is usually accepted as evidence of efficacy by European regulators. These active-control studies aim to show that the study drug is not inferior to the standard AED which has historically been shown to be effective for the seizure type under study. Although the scientific validity of this design has been questioned[41], it would seem to be a logical method of assessing the effectiveness of AEDs drugs as potential first choice treatment in newly diagnosed epilepsy. Furthermore, there are fewer ethical implications in these types of studies, which are largely acceptable to patients and doctors[42].

Methodological integrity is important in equivalence studies. It is not acceptable to carry out the trial as a comparative study and interpret the lack of statistically significant difference as definite proof of equivalence[43]. The null hypothesis is that there exists a difference between the treatments (delta—the confidence interval around equivalence). If this is rejected, the alternative hypothesis, i.e. that the treatments are equivalent, is accepted. In demonstrating clinical equivalence, the limits of difference with respect to important outcomes such as seizure remission should be decided at the design stage. For AEDs, this is usually taken as 10%. If the study drug is shown to be no more than 10% different from the active comparator, it can be assumed that it is at worst 10% inferior to standard treatment[44]. Sample sizes need to be large,

although optimal numbers can be guaranteed by using a sequential design[45]. Intention to treat analysis is no longer conservative and per protocol analysis should also be presented[46]. European regulators have ruled that the delta should be set as far as possible from the placebo zone and that the natural history of the disorder should be taken into account when deciding it.

Active-control trials have been criticised in the past over choice of doses and titration schedules. If the established comparator is started at a low dose and titrated to moderate dosage in accordance with normal clinical practice, this may be interpreted as introducing bias in favour of the efficacy of the trial drug. If, however, more aggressive regimes are employed, the tolerability of the new AED can appear exaggerated.

CLINICAL END POINTS

All new AEDs are initially evaluated as add-on treatment for patients with seizure disorders not controlled with one or more standard agents. Once adjunctive studies have proven the efficacy of the trial drug, a monotherapy programme can be initiated. Complete seizure control is not regarded as a realistic end point for the majority of patients with refractory epilepsy. Standard end points are manipulations in the number of seizures between the baseline and treatment periods. Seizures can be difficult to count especially if they occur in clusters[47]. Distinguishing between the various types can also be problematic. The non-parametric nature of the data can make analysis challenging. While seizure frequency can only be decreased by 100%, it can be increased infinitely. Several non-parametric paradigms have been devised to address this problem. The response ratio, for example, allows for normalisation of the percent change in seizure frequency which always falls in the range of -100 to $+100$[48,49].

Changes in seizure frequency

Seizures are counted over a defined period of time, e.g. 1 or 3 months, and the number occurring in patients receiving the test drug is compared with that in controls. When analysed as a continuous variable, seizure frequency is the most sensitive measure of efficacy and should be used whenever possible[50]. However, skewed distribution can make data handling difficult using standard statistical methods without transformation. Percentage reduction in seizure frequency between baseline and treatment periods, although superficially an attractive alternative, is prone to be unduly influenced by outliers. Analysis using seizure frequencies during baseline and treatment periods (transformed if necessary) as covariates can be regarded as a better option.

Proportion of responders

When patients exhibit seizures within a wide range suggesting non-normal or multimodal distribution, frequency has to be assessed as a dichotomous (binary) variable. Percentage of subjects with 50% (or some other arbitrary figure) reduction in seizure frequency can be compared among groups. One advantage of such an analysis is that it has been used frequently and, therefore, allows comparisons with previous studies using different AEDs[51]. A minimum of 50% reduction in seizure frequency is the dichotomous cut off point usually quoted in clinical trials. This is arbitrary, however, and may miss important differences between treatments. Categorisation of seizure frequencies can be used instead of a single cut off point; e.g. 0–19%, 20–39%, 40–59%, >75% reductions, etc.[50]. Seizure freedom is not generally quoted as a primary outcome measure, because of the refractoriness of epilepsy in this population and the use of predetermined titration schedules and fixed doses of AEDs. Nevertheless, this observation is probably underused.

Seizure-free days

In studying the effect of levetiracetam in patients with refractory epilepsy, French *et al.*[52] reported an analysis of seizure-free days to determine efficacy. This was carried out by evaluation of seizure diaries. In contrast to standard analyses, where the total number of seizures in a set period of time are counted, this approach looks at each day individually to see whether or not a seizure has occurred. Such day by day evaluation can allow seizure patterns and response timings to be addressed. One aim of this approach is to obtain a flavour of the time-to-effect with the test drug compared to placebo-control.

Time to nth seizure

Time to first seizure is a commonly quoted end point for monotherapy trials especially in pre-surgical withdrawal studies. Pledger and Sahlroot[53] have shown that this type of analysis can be applied equally to adjunctive trials with fixed treatment periods. This outcome measure has also been used in active-control monotherapy comparisons[29,54]. One potential pitfall in newly diagnosed epilepsy is excluding the possibility that any difference between the new and

established agent in time to first seizure was a consequence of differences in titration schedules or maintenance dosing. These values are usually well known for the older agents, but not necessarily for the new AED at the time of the study. Time to second, third, fourth seizure, etc. can be more useful endpoints[54].

Seizure severity

Even if a treatment does not abolish seizures completely, reduction in severity can be often achieved. Examples are fewer secondary generalised seizures in relation to numbers of complex partial seizures or fewer complex partial compared to simple partial events with awareness retained. Shortening of the post-ictal recovery period could allow patients to return to normal activity sooner following a seizure. Three scales are available to measure the severity of seizures. These are the Veterans Administration Seizure Severity and Frequency Rating Scale[55], the Liverpool Seizure Severity Scale[56] and the National Hospital Seizure Severity Scale (formerly known as the Chalfont Seizure Severity Scale)[57]. Each has its strengths and weaknesses[58,59]. New instruments addressing their shortcomings are in development[60]. Seizure severity scales need to be reliable, valid and sensitive. Although the psychometric properties of these scales are well established, there is little evidence to support their clinical utility. Until more data become available, seizure severity scales cannot be recommended as standard outcome measures in evaluating the efficacy of AEDs[61].

Electroencephalography (EEG)

Once a drug has demonstrated anti-seizure activity in animal models, the decision whether to proceed with clinical development is a commercial one. Pivotal studies in man require prolonged administration over months in many patients with several types of seizures. This programme takes years to complete and demands considerable resources. Preliminary evidence of efficacy is valuable to help with decision-making. Surrogate endpoints, such as electroencephalographic changes, can provide indications of potential efficacy. Generally, epileptiform discharges do not correlate with the severity of the seizure disorder[62]. Nevertheless, under standard recording conditions meaningful effects of AEDs may be demonstrable in patients with suitably high and stable rates of epileptiform EEG discharges[63]. Acute experiments require a rapidly effective formulation of the drug (preferably intravenous) tested under rigorously standardised conditions. The drug is usually compared to both placebo and an active-control (e.g. diazepam) employing a cross-over design. The primary outcome measure is the spike count per minute or the percentage of the total recording occupied by discharges. Subacute experiments can be carried out over longer time periods (e.g. 24–48 hours) using telemetry or ambulatory EEG monitoring. These reduce problems with spontaneous variation in the rate of epileptiform discharges. This can also be achieved by measuring evoked responses such as the photoparoxysmal response in photosensitive subjects. Reduction in photosensitivity can be demonstrated after a single dose of various AEDs at clinically relevant plasma concentrations[64]. However, less than 1% of patients with epilepsy are suitable for such studies and the scarcity of subjects is a major limitation in recruitment[65].

Surrogate measures of efficacy using EEG techniques have not been widely used in the development of new AEDs, with the possible exception of lamotrigine, which underwent assessment for interictal spikes[66] and photosensitivity[67]. While suppression of epileptiform discharges may encourage further development of the drug, lack of such efficacy should not be grounds for termination of development. The decisive test of efficacy for any AED is whether it prevents seizures and the earlier that this is demonstrated the better. Attempts to use intensive EEG monitoring to support efficacy claims in absence epilepsy and severe epilepsy syndromes in infants have been tried with variable success[68–72].

EFFECTIVENESS

The effectiveness of an AED is a function of its efficacy and tolerability. The single most relevant outcome measure that reflect both these factors is the life table that expresses the retention of patients on a particular treatment over a length of time[73]. A similar table including just seizure-free patients has the potential to refine further this outcome measure. Patients are withdrawn from treatment when a predetermined combination of insufficient seizure control and/or poor tolerability is reached. This approach conforms to everyday practice and can provide useful clinical information.

Regulatory authorities seek, over and above everything else, evidence of efficacy. Retention time alone does not provide this and, hence, life table analysis alone is less suitable for regulatory trials. A drug that is only modestly efficacious but has excellent tolerability might fare better than one that is more efficacious but is more prone to produce side effects[74]. In addition, if patients are withdrawn from the trial for reasons other than those related to efficacy and tolerability (e.g. inappropriate titration schedule, poor compliance, lost

to follow up, etc.) the results can be misleading. In such circumstances, the analysis can be done excluding these data (evaluable population) in addition to including all randomised patients (intention to treat)[45].

Measures of efficacy

The main objective of treatment with antiepileptic medication is control of seizures with acceptable tolerability. Therefore, an essential outcome measure is the proportion of patients achieving a predefined period of seizure freedom[73]. Depending on the syndrome and the patient population under study, remission may or may not be a realistic goal. As the majority of newly diagnosed adult patients with epilepsy can expect to have their seizures completely controlled, seizure freedom from initiation of treatment or after titration is a sensitive end-point for this population. This would not be the case if the study population were, for instance, infants with Lennox-Gastaut Syndrome.

The proportion of patients with complete control of seizures can be measured at 1, 2 or 3 years from treatment initiation. This provides the most clinically meaningful data for predicting the long-term efficacy of an AED[50]. Time to achieving 1-year of seizure-freedom (or some similar end point) focuses directly on the main aim of treatment. It has the advantage that patients, who continue to have seizures for a period after starting on treatment, can also be included[73]. Both the above end points, while lending themselves to statistical and intuitive analyses, can be insensitive. They require complete control of seizures as evidence of efficacy, and discount patients who experience even a single seizure due, for instance, to a lapse in compliance or an intercurrent gastrointestinal infection. Detecting differences in efficacy among patients not fully controlled is possible using seizure rates, i.e. number of seizures over a unit time. This can also be used to compare two treatments. If patients are lost to follow up, this approach becomes less valuable. Although an 'intention to treat' analysis addresses this issue, results can still be distorted.

Measures of adverse effects

While no important differences in efficacy have been shown among AEDs in regulatory trials, differences have been seen in tolerability[75,76], which is assessed by the incidence, prevalence, severity and the impact of side effects[50]. Adverse events include issues relating to tolerability and safety. The most important outcome measure is withdrawal of a drug because of intolerable or life threatening side-effects. Surveillance for organ toxicity is maintained by history, physical examination and laboratory testing. Life threatening idiosyncratic reactions, with the exception of hypersensitivity rash, are extremely rare. Regulatory trials do not involve sufficient number patients to uncover these events. Post-marketing surveillance is more important in detecting these uncommon but potentially serious problems. Major safety concerns with felbamate and vigabatrin were identified in this phase.

Neurotoxic adverse effects such as sedation, dizziness and diplopia tend to resolve with a reduction in dose. This may not be allowable in a fixed dose study and so the patient may drop out and, therefore, not gain efficacy from the drug[30]. These and other systemic adverse effects, including gastrointestinal upsets, may also abate with time. The development of tolerance to initial neurotoxicity may allow higher doses to be used at a later date. An end point that records only the incidence of adverse effects will not make this distinction. Patient based scales have been developed to measure the neurotoxic effects of AEDs[77].

Historically, many clinical trials of AEDs have used incidence reporting of adverse events after passive inquiry. This is now recognised as inadequate[50]. Such studies have relied on spontaneous reporting of adverse effects by patients. While having the advantage of highlighting clinically relevant problems, this method is associated with substantial variability in sensitivity and detection. Spontaneous reporting tends to underestimate side-effects, as patients may not make the association between subtle problems and AED therapy. Patients might also not recall transient mild symptoms. Therefore, some form of standardisation in interview and examination has been recommended to supplement spontaneous reporting[50]. Checklists should be used for recording adverse events during randomised trials.

Why focus on adverse effects in a discussion paper on efficacy? The reason is that efficacy and tolerability cannot be sensibly separated. They combine to form effectiveness. If a patient develops a rash or drops out of a study due to neurotoxicity, data from this individual will not contribute to the drug's efficacy. A major difference in tolerability can distort the clinical or scientific relevance of efficacy end-points. Thus, in a recent double-blind trial of carbamazepine versus lamotrigine in the elderly, no differences in efficacy could be demonstrated even though twice as many patients taking lamotrigine remained seizure-free due to its better tolerability and, therefore effectiveness[78].

Dosage

Doses used in regulatory trials are frequently different from those subsequently found to be effective in routine clinical practice. Thus, gabapentin is now

prescribed in higher amounts (up to 4800 mg daily) than those doses originally studied (900–1800 mg daily) and subsequently licensed (up to 2400 mg daily)[48, 49, 79–83]. On the other hand, the titration schedules (50 mg weekly) and maintenance doses (200–800 mg daily) for topiramate in regulatory studies were more robust than now recommended producing high responder rates but at the expense of numerous adverse events[84–89]. Prospective observational studies have shown that good outcomes can be obtained in many patients with substantially lower amounts of topiramate (50–200 mg daily) than those used in regulatory trials[90, 91]. The recommended titration schedule now starts with 25 mg topiramate daily with weekly or 2 weekly increments of 25–50 mg daily. As the primary aim of a regulatory trial is to demonstrate efficacy, the tendency will be to err on the side of fast titration and higher dosing. Well designed post-marketing studies can allow clinicians to gauge the optimal titration schedules and effective doses for less severely affected patients taking the drug in everyday clinical practice.

Concentration measurement

Serum levels of AEDs can be used to augment the daily dose in controlled clinical trials. Concentration-defined trials were used in the unsuccessful development of flunarizine[92] and with lamotrigine[93]. The basis for this approach is the empirical observation that serum concentrations may correlate better with clinical response than does dose. This could reduce interpatient variability and make the trial statistically more efficient[35]. Drug levels are monitored and controlled in an effort to identify a concentration–effect relationship. Such data were helpful in supporting the license claim for zonisamide as add-on therapy in the US[94]. A concentration–response trial has also been carried out with sodium valproate as monotherapy in partial epilepsy[95]. Many of the newer AEDs, however, do not exhibit clinically relevant concentration–effect–toxicity relationships[81, 90, 96].

Quality of life

Health related quality of life (HRQOL) measurements have been an area of increasing interest in recent years[97]. Several generic instruments measuring HRQOL can be used in patients with epilepsy[61]. In addition, a number of scales specific to epilepsy have been devised. The latter include the Liverpool HRQOL battery[98], Epilepsy Surgery Inventory[99] and QOL in Epilepsy (QOLIE) instruments[100]. These attempt to quantify emotional, functional and psychosocial well-being. They are heavily dependent on seizure freedom, however, and are unlikely to be independent outcome variables in clinical trials of AEDs[101].

OBSERVATIONAL OUTCOME STUDIES

Epilepsy is a chronic condition. Most patients take AEDs for many years and many receive lifelong treatment. Studies that follow patients up over prolonged periods of years can provide an insight into the natural history of treated epilepsy. These data can help identify patients who are likely to enter remission and those who have a more progressive seizure disorder. These studies require substantial resources and do not usually attract the same level of commercial or grant funding as regulatory or comparative trials. However, they can help identify the best way of utilising new treatments. The modern AEDs are, not surprisingly, more expensive than the older agents. A recent cost–benefit assessment of lamotrigine has, for instance, suggested that the costs associated with newer AEDs might be unjustifiably high[102]. The assumptions in this study have been challenged[103], but the fact remains that significant proportion of health care budgets for epilepsy is taken up by the newer AEDs. There seems little doubt that they have helped patients whose seizures might otherwise have remained uncontrolled. In addition, the use of individual drugs can be of substantial value in specific epilepsy syndromes, e.g. vigabatrin for infantile spasms[104]. It would, therefore, make economic sense to invest in studies of sufficient scope and magnitude that could help identify the optimal place and usage of AEDs in clinical practice.

Methodology

The basic requirement for any long-term outcome study is that it follows routine clinical practice as closely as possible. Exclusion criteria should be kept to a minimum. Patients with newly diagnosed epilepsy differ from those with difficult-to-control seizures in terms of expected outcomes, side-effect profiles and quality of life issues. These groups should be studied separately. Patient care should not vary from normal except for closer follow up and more objective assessment of efficacy and tolerability. Rating systems should be used for documenting seizures and side-effects, taking into account their number and severity together with objective assessments of behavioral and cognitive status. Individual seizure types or epilepsy syndromes should be studied separately and rigorous standards applied to

diagnosis and classification. Pre-defined protocols should be followed in investigating and monitoring patients. Sample sizes required to answer specific questions should be calculated prior to commencement, and anticipated losses due to non-drug related events should be taken into consideration. In newly diagnosed epilepsy, the incentive to continue treatment and attend follow up appointments may not be as persuasive as in patients with refractory seizures.

These studies can be observational where each patient's treatment is deliberately chosen or randomly assigned. Dosing schedules should be flexible tailoring therapy for the individual patient. This allows the therapeutic potential of each AED to be maximised. There is an unavoidable risk of selection bias and differences in outcomes might not always be due to differences in treatment. Adjustments for identifiable variation in patient characteristics at the analysis stage can mitigate this. Unsophisticated post-marketing surveillance tends to cause more problems than it solves and these studies are best undertaken for safety than efficacy reasons[105].

End points

In monotherapy studies in newly diagnosed epilepsy, the majority of patients can be expected to enter remission with appropriate therapy. Time to first seizure can, therefore, be a relevant end point assuming appropriate AED titration and dosing. The number of patients who have not suffered a first seizure would represent the number who have remained fully controlled. In longer term studies of outcomes, the proportion of patients remaining free of seizures after 1, 2 and 3 years of follow-up will provide a useful indication of effectiveness. These measures, combined with quality of life issues such as employment, driving, etc. reflect the real impact of AED treatment on the lives of people with epilepsy.

As discussed above, the incidence, prevalence and severity of adverse effects is an important determinant in the success of AED treatment. Withdrawal of a drug because of adverse effects is a definitive end point in a clinical study. For patients with difficult-to-control epilepsy, drug burden can significantly impair quality of life. In the VA co-operative study, a complex approach was used to quantify the efficacy and toxicity of phenytoin, carbamazepine, phenobarbital and primidone[75]. Seizure frequency and severity, neurotoxicity, systemic and behavioral toxicity, and retention time on treatment were the primary variables. These were computed into a single composite score which allowed relative effectiveness of each of the four drugs to be compared[55].

META-ANALYSES

In the absence of comparative studies, meta-analyses of individual clinical trials can give clinicians an impression of how these drugs might stack up in terms of efficacy and side-effects. Meta-analyses of adjunctive clinical trials showed no significant differences in efficacy among the various new AEDs studied[27, 51]. These analyses were based on odds ratios, and it has been suggested that number-needed-to-treat might be better suited to demonstrate differences in efficacy[106]. This is the number of patients requiring treatment in order to achieve a single occurrence of a specified outcome. This measure has the advantage of being readily interpretable by clinicians, although it does have some undesirable statistical properties[107]. In meta-analyses of AED trials, it is not possible to compare newer AEDs with traditional ones, as none of the older agents (with the exception of sodium valproate) has been evaluated as add-on treatment in a controlled clinical trial[108]. Moreover, as these trials were restricted to adjunctive treatment for partial onset seizures, few conclusions can be drawn about the use of these drugs as monotherapy or in the treatment of other seizure types.

CONCLUSIONS

The epilepsies are a range of multifaceted disorders that can affect many aspects of a person's life. No single outcome measure can reflect their complex nature and impact in the individual patient. The aim of drug treatment is the prevention of seizures with no or tolerable side-effects. While this is possible for the majority of patients, there remains a significant proportion in whom ongoing seizures and increasing drug burden exact a heavy toll. Efficacy has to be the first consideration in the development of any new AED. However, trials aimed at demonstrating efficacy to meet regulatory requirements rarely produce data that are helpful to doctors who treat people with epilepsy. The outcome measures in these trials, while admirably suited to demonstrating statistical differences, are of dubious clinical relevance. The real test is how a new AED stands up to scrutiny in clinical practice. Well designed observational studies can help doctors decide their value. The end points in these studies should include both global outcome measures, such as the life table of retention on treatment, as well as specific measures of efficacy and tolerability. Analyses should explore effects in different seizures types and epilepsy syndromes. Measures of subjective health status can be used as secondary endpoints. A combination of randomised and observational studies will help decide the eventual place of a new AED in the therapeutic armamentarium.

Appendix A Clinical trials with felbamate.

Study	Design	Number of patients	Duration	Efficacy measures	References
Add-on studies					
Leppik *et al.*, 1991	Add-on Double-blind Placebo-controlled Parallel-group	56	8 weeks	Difference in mean seizure frequency Percentage change in seizure frequency	1
Theodore *et al.*, 1991	Add-on Double-blind Placebo-controlled Three-period Parallel-group	30	15 weeks	Percentage change in seizure frequency	2
Sachdeo *et al.*, 1992	Add-on Double-blind Active-control (VPA) Parallel-group	44	112 days	Number of patients meeting exit criteria Difference in seizure frequency	3
Ritter *et al.*, 1993	Add-on Double-blind Placebo-controlled Parallel-group	73	70 days	Percentage change in seizure frequency	4
Jensen, 1994	Add-on Double-blind Placebo-controlled Parallel-group	76	Not stipulated	Percentage change in seizure frequency >50% seizure reduction	5
Siegel *et al.*, 1999	Add-on (VPA) Double-blind Placebo-controlled Parallel-group	13	14 weeks	Percentage change in seizure frequency	6
Monotherapy studies					
Bourgeois *et al.*, 1993	Monotherapy Pre-surgical Double-blind Placebo-controlled	64	29 days	Time to fourth seizure	7
Faught *et al.*, 1993	Withdrawal to monotherapy Double-blind Active-control (VPA) Parallel-group	111	112 days	Number of patients meeting exit criteria	8
Devinsky *et al.*, 1995	Monotherapy Pre-surgical Double-blind Placebo-controlled	52	10 days	Average daily seizure frequency Time to fourth seizure	9
Theodore *et al.*, 1995	Monotherapy Pre-surgical Double-blind Placebo-controlled Parallel-group	40	18 days	Difference in seizure rates	10
Open-label studies					
Dodson, 1993	Add-on Open-label extension of RCT	73	12 months	>50% seizure reduction Patient rated global evaluation	11
Carmant *et al.*, 1994	Add-on Open-label	30	Not stipulated	Percentage change in seizure frequency >50% seizure reduction	12

Appendix A (*Continued*).

Study	Design	Number of patients	Duration	Efficacy measures	References
Avanzini *et al.*, 1996	Add-on Open-label	351	2 months	Seizure freedom >50% seizure reduction	13
Li *et al.*, 1996	Open-label Add-on	111	4 months (mean)	Seizure freedom >95% seizure reduction >50% seizure reduction	14
De Romanis and Sopranzi, 1997	Add-on Open-label	18	22 months	Percentage change in seizure frequency	15
Canger *et al.*, 1999	Add-on Open-label	36	10 months (mean)	Seizure freedom rate >50%/>75% seizure reduction	16
Cilio *et al.*, 2001	Add-on Open-label	36	Not stipulated	>50% seizure reduction	17

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Appendix B Clinical trials with gabapentin.

Study	Design	Number of patients	Duration	Efficacy measures	References
Add-on studies					
UK Gabapentin Study Group, 1990	Add-on Double-blind Placebo-controlled	127	12 weeks	Percentage change in seizure frequency Response ratio	1
Sivenius *et al.*, 1991	Add-on Double-blind Placebo-controlled	43	12 weeks	Percentage change in seizure frequency	2

Appendix B (*Continued*).

Study	Design	Number of patients	Duration	Efficacy measures	References
The US Gabapentin Study Group No. 5, 1993	Add-on Double-blind Placebo-controlled	306	12 weeks	Response ratio Responder rate (>50% seizure reduction)	3
Anhut *et al.*, 1994	Add-on Double-blind Placebo-controlled	272	12 weeks	Response ratio Responder rate (>50% seizure reduction) Percentage change in seizure frequency	4
Leach *et al.*, 1997	Add-on Double-blind Placebo-controlled	27	24 weeks	Percentage change in seizure frequency Responder rate (>50% seizure reduction) Drowsiness score Composite psychomotor score	5
Shapiro *et al.*, 2000	Add-on Double-blind Placebo-controlled	76	3 days (Video-EEG)	Response ratio Responder rate (>50% seizure reduction)	6
Lindberger *et al.*, 2000	Add-on Double-blind Active-control (VGB) Parallel-group Dose titration	102	8 weeks	>50% seizure reduction Seizure freedom rate	7
Appleton *et al.*, 1999	Add-on Double-blind Placebo-controlled	247 (children)	12 weeks	Response ratio Responder rate (>50% seizure reduction) Percentage change in seizure frequency Investigator and parent assessment of well being	8
Monotherapy studies					
Trudeau *et al.*, 1996	Monotherapy (*de novo*) Double-blind Placebo-controlled	33 children (absence seizures)	2 weeks (6 weeks open-label)	Percentage change in seizure frequency (EEG quantified)	9
Bergey *et al.*, 1997	Monotherapy Pre-surgical Double-blind Placebo-controlled	82	8 days	Time to exit	10
US Gabapentin Study Group 82/83, 1997	Conversion to monotherapy	275	26 weeks	Time to exit Completion rate Mean time on monotherapy	11
Chadwick *et al.*, 1998	Monotherapy (*de novo*) Double-blind Active-control (CBZ)	218	24 weeks	Retention time	12

Appendix B (*Continued*).

Study	Design	Number of patients	Duration	Efficacy measures	References
Beydoun *et al.*, 1998	Conversion to monotherapy Open-label	45 (23 converted)	252 days	Percentage change in seizure frequency	13
Brodie *et al.*, 2002	Monotherapy (*de novo*) Double-blind Active-control (LTG)	309	30 weeks	Time to exit	14
Open-label studies					
The US Gabapentin Study Group, 1994	Add-on Open-label	240	10–784 days	Percentage change in seizure frequency Responder rate (>50% seizure reduction)	15
Baulac *et al.*, 1998	Add-on Open-label	610	24 weeks	Life table Percentage change in seizure frequency Responder rate (>50% seizure reduction)	16
Bruni, 1998	Add-on Open-label	141	20 weeks	>50% seizure reduction Seizure freedom QUOLIE 10 score	17
Wilson *et al.*, 1998	Add-on Open-label	50	Not stipulated	>50% seizure reduction Seizure freedom	18
Morrell, 1999	Add-on Open-label Dose–response	1055	16 weeks	Responder rate (>50% seizure reduction) Seizure freedom	19
Meyer *et al.*, 1999	Add-on Open-label	110	26 weeks	Seizure-free rate Percentage change in seizure frequency	20
Morrell *et al.*, 2000	Add-on Open-label	2016	16 weeks	>50% seizure reduction Seizure freedom	21
Herranz *et al.*, 2000	Add-on Open-label	559	24 weeks	Responder rate (>50% seizure reduction) QUOLIE 10 score	22
Beran *et al.*, 2001	Add-on Open-label	176	24 weeks	>50% seizure reduction QUOLIE 10 score	23
Appleton *et al.*, 2001	Add-on Open-label	237 (children)	24 weeks	Percentage change in seizure frequency Responder rate (>50% seizure reduction)	24

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Appendix C Clinical trials with lamotrigine.

Study	Design	Number of patients	Duration	Measure of efficacy	References
Add-on studies					
Binnie *et al.*, 1987	Add-on Randomised Double-blind Placebo-controlled	10	7 days	>50% seizure reduction EEG spike count	1
Jawad *et al.*, 1989	Add-on Randomised Double-blind Placebo-controlled Cross-over	24	12 weeks	Reduction in seizure frequency Total seizure days	2
Binnie *et al.*, 1989	Add-on Randomised Double-blind Placebo-controlled Concentration-defined Cross-over	34	30 weeks	Reduction in seizure frequency	3
Sander *et al.*, 1990	Add-on Double-blind Placebo-controlled Cross-over	23	30 weeks	Seizure count Number of generalised seizures	4

Appendix C (*Continued*).

Study	Design	Number of patients	Duration	Measure of efficacy	References
Loiseau *et al.*, 1990	Add-on Randomised Double-blind Placebo-controlled Cross-over	23	8 weeks	Reduction in seizure frequency >50% seizure reduction	5
Matsuo *et al.*, 1993	Add-on Randomised Double-blind Placebo-controlled Parallel-group	216	24 weeks	Percentage reduction in seizure frequency	6
Smith *et al.*, 1993	Add-on Double-blind Placebo-controlled Cross-over	81	18 weeks	Percentage reduction in seizure frequency HRQOL score	7
Schapel *et al.*, 1993	Add-on Randomised Double-blind Placebo-controlled Cross-over	41	28 weeks	Reduction in seizure frequency >50% seizure reduction	8
Messenheimer *et al.*, 1994	Add-on Randomised Double-blind Placebo-controlled Cross-over	98	28 weeks	Percentage reduction in seizure frequency >50% seizure reduction	9
Stolarek *et al.*, 1994	Add-on (to VGB) Double-blind Placebo-controlled Cross-over	22	28 weeks	Percentage reduction in seizure frequency Seizure freedom	10
Boas *et al.*, 1996	Add-on Randomised Double-blind Placebo-controlled Cross-over	56	12 weeks	Percentage reduction in seizure frequency Total seizure days	11
Motte *et al.*, 1997	Add-on Randomised Double-blind Placebo-controlled Parallel-group	169	16 weeks	Reduction in seizure frequency >50% seizure reduction	12
Eriksson *et al.*, 1998	Add-on Responder-enriched Double-blind Placebo-controlled Cross-over	30	Not stipulated	>50% seizure reduction	13
Beran *et al.*, 1998	Add-on Double-blind Placebo-controlled Cross-over	26	20 weeks	Percentage reduction in seizure frequency >50% seizure reduction	14
Duchowny *et al.*, 1999	Add-on Randomised Double-blind Placebo-controlled Parallel-group	201	18 weeks	Percentage reduction in seizure frequency	15

Appendix C (*Continued*).

Study	Design	Number of patients	Duration	Measure of efficacy	References
Eriksson *et al.*, 2001	Add-on Double-blind Cross-over Placebo-controlled	12	24 hours	Epileptiform discharges during Video-EEG monitoring >50% seizure reduction Behavior and alertness as assessed by medical personnel and parents	16
Monotherapy studies					
Brodie *et al.*, 1995	Monotherapy (*de novo*) Randomised Double-blind Parallel-group Active-control (CBZ)	260	48 weeks	Seizure freedom Retention on treatment	17
Gilliam *et al.*, 1998	Monotherapy Double-blind Double-dummy Parallel-group	156	20 weeks	Life table of retention on treatment	18
Brodie *et al.*, 1999	Monotherapy (*de novo*) Randomised Double-blind Parallel-group Active-control (CBZ)	150 (elderly)	24 weeks	Time to first seizure Seizure freedom Retention on treatment	19
Steiner *et al.*, 1999	Monotherapy (*de novo*) Double-blind Parallel-group Active-control (PHT)	92	48 weeks	Seizure freedom Proportion remaining on treatment Time to first seizure Time to discontinuation SEALS (HRQOL Inventory)	20
Gillham *et al.*, 2000	Monotherapy (*de novo*) Randomised Double-blind Active-control (CBZ)	260	48 weeks	SEALS (HRQOL Inventory)	21
Frank *et al.*, 2000	Monotherapy (typical absence seizures) Responder-enriched Placebo-controlled, Double-blind	45	Not stipulated	Seizure freedom (Video EEG)	22
Neito-Barrera *et al.*, 2001	Monotherapy (*de novo*) Randomised Open-label Active-control (CBZ)	417	24 weeks	Seizure freedom Completion rate	23
Reunanen *et al.*, 1996	Monotherapy (*de novo*) Double-blind Active-control (LTG)	309	30 weeks	Time to exit	24
Open-label studies					
Karlsborg *et al.*, 1996	Monotherapy Open-label Active-control (CBZ)	343	Not stipulated	Seizure freedom	25
Buchanan, 1996	Add-on Open-label	92	Not stipulated	Seizure freedom >50% seizure reduction	26
Farrell *et al.*, 1997	Add-on Open-label	200	1–4 years	Seizure freedom Percentage reduction in seizure frequency	27
Buoni *et al.*, 1998	Add-on Open-label	56	Not stipulated	Seizure freedom >50% seizure reduction	28

Appendix C (*Continued*).

Study	Design	Number of patients	Duration	Measure of efficacy	References
Gericke *et al.*, 1999	Add-on Open-label	63	1–3 years	Percentage reduction in seizure frequency Normalisation of EEG Social and academic performance	29
Pimentel *et al.*, 1999	Add-on and monotherapy Open-label	47	25 months (mean)	Seizure freedom >50% seizure reduction (Video-EEG)	30
Parmeggiani *et al.*, 2000	Add-on Open-label	61	24 months	Reduction in seizure frequency	31
Mauri-Llerda *et al.*, 2001	Add-on Open-label	41	Not stipulated	Percentage reduction in seizure frequency >50% seizure reduction Seizure freedom	32
Brodie *et al.*, 2002	Add-on Open-label	106	3.4 years (mean)	>50% seizure reduction	33

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Appendix D Clinical trials with levetiracetam.

Study	Design	Number of patients	Duration	Efficacy measures	References
Add-on/monotherapy studies					
Cereghino *et al.*, 2000	Add-on Double-blind Placebo-controlled Parallel-group	294	30 weeks	Difference in seizure frequency >50% seizure reduction	1
Shorvon *et al.*, 2000	Add-on Double-blind Placebo-controlled Parallel-group	324	28 weeks	Difference in seizure frequency >50% seizure reduction	2
Ben-Menachem and Falter, 2000	Add-on Double-blind Placebo-controlled Responder-enriched Conversion to monotherapy	286 (add-on) 86 (monotherapy)	36 weeks	Double-blind phase >50% seizure reduction Monotherapy phase Study completion rate Percentage reduction in seizure frequency Seizure freedom rate	3
Betts *et al.*, 2000	Add-on Double-blind Placebo-controlled Parallel-group Dose–response	119	32 weeks	>50% seizure reduction Seizure freedom	4
Cramer *et al.*, 2000	Add-on Double-blind Placebo-controlled	246	18 weeks	QUOLIE-31	5
Boon *et al.*, 2002	Add-on Double-blind Placebo-controlled Parallel-group Dose–response	324	32 weeks	Percentage reduction in seizure frequency >50%/>75% seizure reduction Seizure freedom rate	6
Open-label studies					
Grant and Shorvon, 2000	Add-on Open-label/single-blind Dose-ranging	29	16 weeks	Difference in seizure frequency Seizure freedom	7
Glauser *et al.*, 2002	Add-on Open-label	22	18 weeks	Difference in seizure frequency >50% seizure reduction Seizure freedom	8

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Appendix E Clinical trials with oxcarbazepine.

Study	Design	Number of patients	Duration	Efficacy measures	References
Add-on studies					
Barcs *et al.*, 2000	Add-on Double-blind Parallel-group Dose-ranging	694	28 weeks	Percentage change in seizure frequency >50% seizure reduction	1
Glauser *et al.*, 2000	Add-on Double-blind Placebo-controlled	267	112 days	Percentage change in seizure frequency >50% seizure reduction	2
Monotherapy studies					
Reinikainen *et al.*, 1987	Monotherapy (substitution for PHT) Double-blind Active-control (CBZ)	40	50 weeks	Difference in seizure frequency	3
Dam *et al.*, 1989	Monotherapy (*de novo*) Double-blind Active-control (CBZ)	235	48 weeks	Difference in seizure frequency	4
Bill *et al.*, 1997	Monotherapy (*de novo*) Double-blind Parallel-group Active-control (PHT)	287	56 weeks	Seizure-free rates Retention on treatment	5
Christe *et al.*, 1997	Monotherapy (*de novo*) Double-blind Parallel-group Active-control (VPA)	249	56 weeks	Seizure-free rates Difference in seizure frequency Retention on treatment	6
Guerreiro *et al.*, 1997	*De novo* monotherapy Double-blind Parallel-group Active-control (PHT)	193 (adolescents)	56 weeks	Seizure-free rates Retention on treatment	7
Schachter *et al.*, 1999	Monotherapy Pre-surgical Double-blind Placebo-controlled Parallel-group	102	10 days	Time to exit Proportion of patients exiting Difference in seizure frequency	8

Appendix E (*Continued*).

Study	Design	Number of patients	Duration	Efficacy measures	References
Beydoun *et al.*, 2000	Monotherapy (conversion) Double-blind Parallel-group Low dose comparator	87	126 days	Proportion of patients exiting Time to exit	9
Sachdeo *et al.*, 2001	Monotherapy (conversion) Double-blind Parallel-group Low dose comparator	143	210 days	Time to exit Proportion of patients exiting	10
Friis *et al.*, 1993	Monotherapy Open-label Observational	947	Not stipulated	Change in seizure frequency	11
Van Parys and Meinardi, 1994	Open-label Substitution (for CBZ) Add-on and monotherapy	260	Not stipulated	>50% seizure reduction	12
Gaily *et al.*, 1997	Open-label Monotherapy	53 (children)	Not stipulated	Seizure remission >50% seizure reduction	13

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Appendix F Clinical trials with tiagabine.

Study	Design	Number of patients	Duration	Efficacy measures	References
Add-on studies					
Richens *et al.*, 1995	Add-on Responder-enriched Double-blind Placebo-controlled Cross-over	94	35 weeks	Percentage change in seizure frequency >50% seizure reduction	1

Appendix F (*Continued*).

Study	Design	Number of patients	Duration	Efficacy measures	References
Sachdeo *et al.*, 1997	Add-on Double-blind Placebo-controlled Dose–response Parallel-group	351	24 weeks	Percentage change in seizure frequency	2
Uthman *et al.*, 1998	Add-on Double-blind Placebo-controlled Dose–response Parallel-group	297	32 weeks	Percentage change in seizure frequency >50% seizure reduction	3
Kalviainen *et al.*, 1998	Add-on Double-blind Placebo-controlled	154	16 weeks	Percentage change in seizure frequency >50% seizure reduction	4
Uldall *et al.*, 2000	Add-on Single-blind Placebo-controlled Dose–response	52	4 months	Percentage change in seizure frequency	5
Crawford *et al.*, 2001	Add-on Responder-enriched Double-blind Placebo-controlled Cross-over	88 (44 responders)	17 weeks	Percentage change in seizure frequency >50% seizure reduction	6
Monotherapy studies					
Schachter, 1995	Monotherapy Pre-surgical Double-blind Placebo-controlled	11 (pre-surgical), 31 (dose-ranging), 198 (low vs. high dose)	7 days (pre-surgical), 15 weeks (dose-ranging), 29 weeks (low vs. high dose)	Time to exit (pre-surgical) Change in seizure frequency (dose-ranging and high vs. low dose)	7
Open-label studies					
Arroyo and Salas-Puig, 2001	Add-on Open-label	941	Not stipulated	Seizure freedom rate >50% seizure reduction	8
Biraben *et al.*, 2001	Add-on Open-label Parallel-group Dose-frequency	347	24 weeks	Seizure freedom rate >50% seizure reduction	9
Herranz *et al.*, 2001	Add-on Open-label Dose-frequency Parallel-group	247	24 weeks	Discontinuation rate >50% seizure reduction	10

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Appendix G Clinical trials with topiramate.

Study	Design	Number of patients	Duration	Efficacy measures	References
Add-on studies					
Faught *et al.*, 1996	Add-on Double-blind Placebo-controlled Dose-ranging Parallel-group	188	30 weeks	Percentage reduction in seizure frequency >50% seizure reduction Reduction in secondary generalised seizures	1
Tassinari *et al.*, 1996	Add-on Double-blind Placebo-controlled Parallel-group	60	12 weeks	Percentage reduction in seizure frequency >50% seizure reduction Patient and investigator global assessment of treatment	2
Ben-Menachem *et al.*, 1996	Add-on Double-blind Placebo-controlled Parallel-group	56	21 weeks	Percentage reduction in seizure frequency >50%, 75–100% seizure reduction	3
Shareif *et al.*, 1996	Add-on Double-blind Placebo-controlled Parallel-group	47	19 weeks	Percentage reduction in seizure frequency >50% seizure reduction Reduction in secondary generalised seizures	4
Privitera *et al.*, 1996	Add-on Double-blind Placebo-controlled Dose-ranging Parallel-group	190	18 weeks	Percentage reduction in seizure frequency >50% seizure reduction Patient and investigator global assessment of treatment	5

Appendix G (*Continued*).

Study	Design	Number of patients	Duration	Efficacy measures	References
Korean Topiramate Study Group, 1999	Add-on Double-blind Placebo-controlled Parallel-group	177	30 weeks	Percentage reduction in seizure frequency >50% seizure reduction Seizure freedom rate Patient and investigator global assessment of treatment	6
Sachdeo *et al.*, 1999	Add-on Double-blind Placebo-controlled Parallel-group	98	11 weeks	Percentage reduction in seizure frequency >50% seizure reduction Seizure severity	7
Elterman *et al.*, 1999	Add-on Double-blind Placebo-controlled Parallel-group	86	16 weeks	Percentage reduction in seizure frequency >50% seizure reduction >75% seizure reduction Parental global assessment of improvement	8
Biton *et al.*, 1999	Add-on Double-blind Placebo-controlled Parallel-group	80	20 weeks	Percentage reduction in seizure frequency >50% seizure reduction	9
Yen *et al.*, 2000	Add-on Double-blind Placebo-controlled Parallel-group	46	14 weeks	>50% seizure reduction Patient and investigator global assessment of treatment	10
Guberman *et al.*, 2002	Add-on Double-blind Placebo-controlled Dose-ranging Parallel-group	263	12 weeks	Percentage reduction in seizure frequency	11
Monotherapy studies					
Sachdeo *et al.*, 1997	Monotherapy (conversion) Double-blind Low dose TPM control	48	16 weeks	Completion rate Time to exit	12
Open-label studies					
Uldall and Buchholt, 1999	Add-on Open-label	39	13 months (mean)	>50% seizure reduction Seizure freedom rate Retention on treatment	13
Abou-Khalil, 2000	Add-on Open-label	292	413 days (mean)	>50% seizure reduction Seizure freedom rate	14
Stephen *et al.*, 2000	Add-on Open-label	170	24 weeks	Seizure freedom rate >50% seizure reduction	15
Glauser *et al.*, 2000	Add-on Open-label extension of RCT	97	6 months	>50% seizure reduction Retention on treatment	16

Appendix G (*Continued*).

Study	Design	Number of patients	Duration	Efficacy measures	References
Montouris *et al.*, 2000	Add-on Open-label extension of RCT	131	387 days (mean)	>50% seizure reduction >75% seizure reduction Retention on treatment	17
Ritter *et al.*, 2000	Add-on Open-label extension of RCT	87	3 months	>50% seizure reduction Seizure freedom rate Retention on treatment	18
Korean Topiramate Study Group, 2002	Add-on Open-label Dose-ranging	213	Not stipulated	Percentage reduction in seizure frequency Seizure freedom rate >50% seizure reduction	19
Cross, 2002	Monotherapy Open-label	5 (children with absence seizures)	Not stipulated	Seizure freedom rate Percentage reduction in seizure frequency	20
Coppola *et al.*, 2002	Add-on Open-label	18 (SMEI)	11.9 months (mean)	Seizure freedom rate Percentage reduction in seizure frequency	21
Kelly *et al.*, 2002	Add-on Open-label	64	24 weeks	Seizure freedom rate >50% seizure reduction	22

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Appendix H Clinical trials with vigabatrin.

Study	Design	Number of patients	Duration	Efficacy measures	References
Add-on studies					
Rimmer and Richens, 1984	Add-on Double-blind Placebo-controlled Cross-over	24	18 weeks	Reduction in seizure frequency	1
Gram *et al.*, 1985	Add-on Double-blind Placebo-controlled Cross-over	21	12 weeks	Percentage reduction in seizure frequency >50% seizure reduction	2
Loiseau *et al.*, 1986	Add-on Double-blind Placebo-controlled Cross-over	23	10 weeks	Reduction in mean seizure frequency >50% seizure reduction	3
Tartara *et al.*, 1986	Add-on Double-blind Placebo-controlled Cross-over	23	14 weeks	Reduction in mean seizure frequency >50%/>75% seizure reduction	4
Tassinari *et al.*, 1987	Add-on Double-blind Placebo-controlled Cross-over	31	6 months	>50% seizure reduction Percentage reduction in seizure frequency	5
Sivenius *et al.*, 1987	Add-on Double-blind Responder-enriched Dose-ranging	53	3 months	Reduction in mean seizure frequency	6
Luna *et al.*, 1989	Add-on Single-blind Placebo-controlled Parallel-group	61	16 weeks	>50% seizure reduction	7
Browne *et al.*, 1989	Add-on Single-blind Uncontrolled	89	33 months (median)	Reduction in mean seizure frequency >50% seizure reduction	8
Reynolds *et al.*, 1991	Add-on Double-blind Responder-enriched Placebo-controlled	20	8 weeks (open-label), 8 weeks (double-blind)	>50% seizure reduction	9
The Italian Study Group on Vigabatrin, 1992	Add-on Single-blind Placebo-controlled	90	32 weeks	Reduction in mean seizure frequency >50% seizure reduction	10

Appendix H (*Continued*).

Study	Design	Number of patients	Duration	Efficacy measures	References
Dalla Bernardina *et al.*, 1995	Add-on Single-blind Placebo-controlled Cross-over	46 (children)	6 months	Seizure freedom rate >50% seizure reduction	11
French *et al.*, 1996	Add-on Double-blind Placebo-controlled Parallel-group	182	16 weeks	Reduction in mean seizure frequency >50% seizure reduction	12
Beran *et al.*, 1996	Add-on Double-blind Placebo-controlled Cross-over	97	Not stipulated	Reduction in mean seizure frequency	13
Zahner *et al.*, 1999	Add-on Dose-frequency ranging Double-blind Placebo-controlled Responder-enriched Cross-over	50	6 months	Reduction in mean seizure frequency >50% seizure reduction Patient and physician's assessment of well-being	14
Brodie and Mumford, 1999	Add-on (to CBZ) Double-blind Double-dummy Active-control (VPA) Parallel-group	215	6 months	>50% seizure reduction Seizure freedom rate	15
Bruni *et al.*, 2000	Add-on Placebo-controlled Parallel-group	111	36 weeks	Reduction in mean seizure frequency Seizure-free days >50% seizure reduction	16
Monotherapy studies					
Tanganelli and Regesta, 1996	*De novo* monotherapy Double-blind Active-control (CBZ) Response conditional cross-over	51	4 months	Seizure freedom rate	17
Chadwick, 1999	*De novo* monotherapy Double-blind Active-control (CBZ) Parallel-group	459	52 weeks	Time to withdrawal Time to 6 month seizure remission Time to first seizure	18
Elterman *et al.*, 2001	Monotherapy Single-blind Low dose comparator	142	3 months	Seizure freedom rates	19
Open-label studies					
Pedersen *et al.*, 1985	Add-on Open-label	36	9.3 months (mean)	>50% seizure reduction	20
Remy and Beaumont, 1989	Add-on Open-label	254	22.7 months (mean)	Reduction in mean seizure frequency	21
Herranz *et al.*, 1991	Add-on Open-label Dose-ranging	20	9 months	Seizure freedom rate >50% seizure reduction	22

Appendix H (*Continued*).

Study	Design	Number of patients	Duration	Efficacy measures	References
Sivenius *et al.*, 1991	Add-on Open-label	75	6–60 months	Reduction in mean seizure frequency >50% seizure reduction Retention on treatment	23
Lhoir, 1994	Add-on Open-label	102	235 days (mean)	Percentage change in seizure frequency >50% seizure reduction	24
Kalviainen *et al.*, 1995	*De novo* monotherapy Active-control (CBZ)	100	12 months	Retention on treatment Seizure freedom rate	25
Russ, 1995	Add-on Open-label	127	10 months (mean)	>50% seizure reduction	26
Coppola *et al.*, 1997	Add-on Open-label	77	18 months (median)	Percentage change in seizure frequency >50% seizure reduction	27
Zamponi and Cardinali, 1999	*De novo* monotherapy Open-label Active-control (CBZ)	70	2 years	Seizure freedom rate	28
Guberman and Bruni, 2000	Add-on Open-label extension of RCT	97	12 months	>50% seizure reduction Withdrawal of treatment	29

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Appendix I Clinical trials with zonisamide.

Study	Design	Number of patients	Duration	Efficacy measures	References
Add-on studies					
Schmidt *et al.*, 1993	Add-on Double-blind Placebo-controlled Parallel-group	139	12 weeks	Seizure remission >50% seizure reduction	1
Faught *et al.*, 2001	Add-on Double-blind Placebo-controlled Parallel-group	309	16 weeks	Change in median seizure frequency	2
Leppik *et al.*, 1993	Add-on Double-blind Placebo-controlled Parallel-group	203	12 weeks	Change in median seizure frequency	3
Open-label studies					
Wilensky *et al.*, 1985	Monotherapy Open-label Active-control (CBZ) Cross-over	8	32 weeks	Seizure remission Reduction in seizure frequency	4
Kumagai *et al.*, 1991	Add-on Open-label	167	16 weeks	Change in median seizure frequency	5
Yanai *et al.*, 1999	*De novo* monotherapy Open-label	27 (infantile spasms)	Not stipulated	Seizure remission	6
Nakane *et al.*, 1999	Monotherapy Open-label	44	Not stipulated	Seizure remission	7

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