

What clinical trial designs have been used to test antiepileptic drugs and do we need to change them?*

Emilio Perucca

Clinical Pharmacology Unit, Department of Internal Medicine and Therapeutics, University of Pavia and National Neurological Institute IRCCS C Mondino Foundation, Pavia, Italy

ABSTRACT – Designs used to evaluate the efficacy and safety of antiepileptic drugs (AEDs) have evolved considerably over the years. A major impulse to develop methodologically sound randomised controlled trials dates back to the Kefauver-Harris Drug Amendment of 1962, through which the US congress introduced the requirement of substantial evidence for proof of efficacy in a new drug application. The mainstay for the initial approval of most new AEDs has been, and still is, the placebo-controlled adjunctive therapy trial, which evolved over the years from the cross-over to the parallel-group design. In the early days, when few AEDs were available, enrolment of patients into these trials was relatively easy and prolonged placebo exposure could be justified by lack of alternative treatment options. With more than 20 drugs now available to treat epilepsy, however, exposing patients to placebo or to a potentially ineffective investigational agent faces practical and ethical concerns. Recruitment difficulties have led sponsors to markedly increase the number of trial sites, but there is evidence that this may adversely affect the ability to differentiate between effective and ineffective treatments. Methodological and practical difficulties are also encountered with monotherapy trials. Because regulatory guidelines for monotherapy approval differ between Europe and the US, sponsors need to pursue separate and costly development programs on the two sides of the Atlantic. Moreover, the scientific validity of the monotherapy trial paradigms currently used in Europe (the non-inferiority design) and in the US (the conversion to monotherapy design with historical controls) has been questioned. This article will review these issues in some detail and discuss how trial designs and regulatory approval processes may evolve in the future to address these concerns.

Key words: epilepsy, antiepileptic drug, trial design, regulatory guideline, randomised controlled trial, review

Correspondence:
Emilio Perucca
Clinical Pharmacology Unit,
University of Pavia,
Via Ferrata 9,
27100 Pavia, Italy
<perucca@unipv.it>

* Updated following presentation and discussion at the 2011 *Progress in Epileptic Disorders Workshop* on “Antiepileptic Drug Trials: will the future challenge the past” held at the Chateauform’ La Maison des Contes, Dareizé, 69490, France. The workshop was partly supported by an educational grant from UCB. The program was under the exclusive responsibility of a Scientific Committee composed by Prs. Philippe Ryvlin (France), Emilio Perucca (Italy), Jackie French (USA), Steve White (USA), Graeme Sills (UK) and Alexis Arzimanoglou (France).

doi:10.1684/epd.2012.0511

The modern treatment of epilepsy can be dated back to the introduction of phenobarbital in 1912, but the methodology that led to the identification of phenobarbital's therapeutic value was all but modern. After making the serendipitous observation that administration of phenobarbital as an hypnotic led to disappearance of seizures in people with epilepsy, a young physician from Freiburg, Alfred Hauptmann, tested it systematically in patients resistant to high-dose bromides (Hauptmann, 1912). He followed them for many months to account for potential random seizure fluctuations and eventually concluded that phenobarbital is effective to treat epilepsy, resistant to bromides. Later, he applied similar observations to determine that the compound could also be recommended for milder cases and status epilepticus (Hauptmann, 1919). Similar uncontrolled observations in a few hundred patients led to the marketing of phenytoin in 1938, less than two years after its first administration in humans (Merritt and Putnam, 1938). Based on the above historical notes, one wonders why over the years it has become so difficult to demonstrate the efficacy of a novel antiepileptic drug (AED). At least two factors need to be considered. The first is that lack of highly effective medications in the early days could make it easier to show unequivocal improvement in seizure control. The second, and far more important factor, is that uncontrolled testing led not only to the marketing of valuable AEDs, but also to the introduction of a plethora of "remedies" that have not withstood the judgement of time. For example, medicines cited as of "definite benefit" for epilepsy in 1940 in the influential *Textbook of Neurology* by Samuel Alexander Kinnier Wilson included not only bromides and barbiturates, but also belladonna, borax, nitroglycerine and dialacetin (Shorvon, 2009). A striking illustration of the pitfalls of relying solely on uncontrolled observations is provided by crotalin, a rattlesnake venom used to treat epilepsy in the US at the same time as phenobarbital was started to be used in Germany. As with phenobarbital, crotalin utilisation stemmed from serendipity, in this case a patient with epilepsy who became seizure-free for two years after being bitten by a rattlesnake. By 1913, Spangler reported as many as 250 patients treated with crotalin in Philadelphia, indicating that "not only were the virulence and number of epileptic fits favourably influenced" but also that "the general health of the patient, their mental faculties and metabolism in every respect are considerably improved" (Spangler, 1913). Despite the claim that there was "no danger in the use of crotalin", subsequent reports of deaths from anaphylaxis and bacterial contamination led to a rapid decline in the popularity of this venom.

For decades, accidents, such as the crotalin saga, did not do much to alert the medical community about

the need for more rigorous testing of new drugs, which explains the recurrent popularity of agents subsequently found to be of little value. For example, in as late as 1952, when phenobarbital and phenytoin were already widely used, the Committee on Research of the American League Against Epilepsy published a table in which the Committee Chairman rated phenylacetylurea as "the best drug now available for all the three major types of epilepsy" (Himwich, 1952). The dismal state of AED assessment deep into the 20th century is best testified by the Coatsworth report, published in 1971 by the US National Institute for Neurological Disorders and Stroke (NINDS). Out of 250 studies published up to 1970 on the efficacy of AEDs marketed in the US, only 110 followed a formal protocol, only three reported blindness as a control for bias, only two had a double-blind design, and only three used a statistical test of hypotheses (Coatsworth, 1971). This situation was largely a consequence of lax regulatory requirements at that time. Although this may be difficult to believe for the modern physician, until the early sixties in the US (and even later in Europe), the marketing of a new drug required demonstration of safety, but not demonstration of efficacy (Coatsworth and Penry, 1972). The major turning point in this scenario was the Kefauver-Harris Drug Amendment of 1962, which introduced in the US the requirement of substantial evidence for proof of efficacy in a new drug application. Evidence of efficacy was defined by Congress as "adequate and well controlled investigations, including clinical investigations by experts..." (Drug Amendments Act, 1962). This act kick-started the era of controlled drug evaluation in epilepsy and it is remarkable how much progress has taken place since that time (Arzimanoglou *et al.*, 2010). This article will review briefly such progress focusing on clinical efficacy trials and will highlight the need for a change in the approaches that are being currently used. For presentation purposes, the history of controlled trial designs in epilepsy will be arbitrarily divided into three periods: (i) before 1970, (ii) 1970 to 1990, and (iii) 1991 to date. It should be understood, however, that transition from one period to another was gradual and that overlap in concepts and methodology occurred across the three periods.

The days of the pioneers (before 1970)

Recognition of the need for a controlled design to evaluate an epilepsy treatment actually pre-dates the Kefauver-Harris Drug Amendment and indeed several randomised trials were conducted prior to the seventies. A review of these studies today identifies a large number of major weaknesses, including

failure to define inclusion criteria, inadequate description of the study population, lack of sample size and statistical considerations, inadequate or unclear control for bias, and inadequate dosing regimens and duration of assessment (Coatsworth, 1971). Some of these weaknesses could be explained by poor understanding of clinical pharmacological principles, and by insufficient knowledge of the pharmacokinetics of the compounds being tested and the role of drug interactions. One illustrative example is a randomised placebo-controlled cross-over comparison of primidone and phenobarbital conducted in the mid fifties (Gruber *et al.*, 1957). Twenty patients with epilepsy and focal brain damage were randomised to receive, in random order, each of as many as eight treatments, which consisted of phenobarbital at 50 mg and 100 mg, primidone at 125, 250, 500 and 1,000 mg, primidone at 125 mg plus phenobarbital at 50 mg, and placebo. Each treatment was given every eight hours for three consecutive days at weekly intervals and the patient's usual medications (not specified) were stopped during the three days of testing. Seizure counts were made by assigning a score of 1 to focal seizures and a score of 2 to generalised seizures. Not surprisingly, primidone at 500 mg and 1,000 mg, at eight hourly intervals, was soon dropped due to intolerability. Interestingly, despite its obvious methodological shortcomings, the study gave rise to the conclusion that phenobarbital and primidone are both effective, that 250 mg primidone is equieffective with 50 mg phenobarbital, and that the combination of the two drugs provides additive, not synergistic, effects.

A landmark among early controlled trials was the study conducted in the sixties by White and co-workers at the Indiana University Medical Center (White *et al.*, 1966). These authors divided 20 patients with focal seizures into groups of two and randomised them to receive, according to a 10 × 10 Latin square crossover double-blind design, 10 different treatments consisting of full doses of three AEDs (600 mg phenytoin, 300 mg phenobarbital and 1,500 mg primidone), half-doses, combination of half-doses, and a placebo, each given for 14 days. Interestingly, the study incorporated well defined criteria for using rescue medication (oral phenobarbital and rectal amobarbital) and exiting criteria for seizure deterioration and adverse effects. Treatments were compared by calculating demerit scores, based on seizure numbers and exit rates for seizures or drug toxicity. The study concluded that the three AEDs were effective at all doses tested, that full doses were generally more effective than half-doses, that half-doses of two agents combined were about as effective as a full dose of either agent, and that none of the three medications was statistically superior to the others. Remarkably, there was no mention of side effects, in spite of the large doses used. Despite clear

weaknesses, this study pioneered approaches used at later times, such as the use of composite response scores, the application of escape criteria due to seizure deterioration or side effects, and the interest in comparing the relative value of monotherapy and specific drug combinations.

The “middle period” (1970-1990)

From the viewpoint of AED development, the “middle period” can be divided into two parts. In the first part, up to the early eighties, there was little innovation in terms of new drug discovery, but improved clinical trial methodology was applied to better assess the comparative value of already available AEDs, most notably phenobarbital, primidone, phenytoin, carbamazepine and valproic acid. Except for a subset of studies conducted to support the licensing of carbamazepine and valproic acid in the US, these trials were not generally designed to address regulatory requirements. A careful review of the studies done in this period showed that cross-over designs and fixed-dosage schedules were extensively used and that less than half of the trials included a washout period between treatments, complicating the interpretation of the results (Gram *et al.*, 1982). Other common methodological problems were identified, including marked heterogeneity in patient selection and seizure type, non-systematic assessment of adverse effects, and suboptimal duration of follow-up. A number of comparisons involved monotherapy in newly diagnosed epilepsy. Many of these had significant methodological weaknesses, including lack of blinding, limited duration of follow-up, and a sample size insufficient to detect potential differences in outcomes between treatments. Still, this period also saw the completion of a landmark high-quality study, the double-blind VA randomised trial comparing phenobarbital, primidone, phenytoin, and carbamazepine in patients with newly diagnosed or previously under-treated focal epilepsy (Mattson *et al.*, 1985).

The second part of the “middle period” saw the development and the licensing in Europe of the first wave of second generation AEDs, namely oxcarbazepine, vigabatrin, and lamotrigine. Except for oxcarbazepine, which received fast approval in Denmark in 1989, based mostly on the results of a monotherapy comparison with carbamazepine (Dam *et al.*, 1989), an add-on, placebo-controlled, double-blind, cross-over, fixed-dose design was used in the development of these agents. Adults were enrolled in the trials with (mostly) focal seizures; the active treatment period was about eight weeks and seizure frequency or responder rate (proportion of patients with at least 50% seizure reduction) was used as an endpoint. The first two

published trials of vigabatrin, conducted in a total of 24 and 21 patients, respectively, are paradigmatic of this approach (Rimmer and Richens, 1984; Gram *et al.*, 1985). The vast majority of lamotrigine add-on trials, including all those published in 1990 or earlier and which led to approval in many European countries, also followed a two-period, cross-over design (Goa *et al.*, 1993; Matsuo and Riaz, 2009).

The modern era (1991 to date)

The last 20 years have seen a flurry of activity in AED development, resulting in the marketing of over a dozen novel AEDs (Fattore and Perucca, 2011). The same period also witnessed a continuous evolution in trial design, both for adjunctive therapy and for monotherapy.

The major evolution in adjunctive therapy trials included the adoption of stricter eligibility criteria (most notably, selection of patients with a predefined target seizure type and a minimum seizure frequency), a switch from the cross-over to the parallel-group design, and a prolongation of the double-blind evaluation period to include a maintenance period of at least 12 weeks (Committee, 2000, 2010; Marson and Williamson, 2009; Rheims *et al.*, 2011). The main reason for abandoning the cross-over design was the deepening concerns of regulatory agencies for the analysis and interpretation of these trials, most notably in relation to the difficulties in controlling for potential carry-over effects (Hills and Armitage, 1979). One important consequence of switching to the parallel-group design was the requirement of a larger sample size. For example, the number of patients enrolled in the 10 add-on cross-over trials of lamotrigine in focal epilepsy ranged from 18 to 88, whereas those enrolled in the three parallel-group trials in the same indication ranged from 116 to 191 (Matsuo and Riaz, 2009). Another concern that has emerged recently with the classic adjunctive therapy designs is that responder rates associated with placebo seem to have increased over time (Rheims *et al.*, 2011) and that the effect size associated with newer and promising AEDs seems to have become smaller than expected (see discussion below in this article). The most recent studies with brivaracetam and carisbamate are cases in point (Bialer *et al.*, 2010).

The designs of monotherapy trials also evolved in the same period, both in Europe and in the US. In the early nineties, oxcarbazepine, gabapentin, and lamotrigine received monotherapy approval in some European countries based on relatively small double-blind trials in newly diagnosed epilepsy that showed seizure freedom rates similar to those associated with a comparator, usually carbamazepine (Perucca

and Tomson, 1999). However, most of these trials were not powered to exclude potentially important differences in efficacy between the investigational drug and the comparator (Glauser *et al.*, 2006). All this changed at the turn of the century, when the European Medicines Agency (EMA) introduced specific guidelines to obtain approval for a monotherapy indication. According to these guidelines, an investigational agent may be approved for the monotherapy indication, subject to demonstration that its efficacy in patients with newly diagnosed epilepsy (in terms of seizure freedom for no less than six months) is at least non-inferior by a predefined margin to the best available active comparator used at optimised doses (Committee, 2000). These guidelines place considerable burden on the sponsor, investigators, and patients, because non-inferiority trials require a very large sample size. Moreover, the requirement for patients to be followed for at least one year after dose optimisation, in order to confirm maintenance of the therapeutic response, implies that completion of such studies typically requires two years or longer (Perucca, 2008). The first trial conducted according to these guidelines enrolled 579 patients with newly diagnosed epilepsy and led to a European monotherapy license for levetiracetam (Brodie *et al.*, 2007). An attempt to reduce trial duration using an initial dose which was not found to be optimal, however, resulted in pregabalin failing to meet the non-inferiority limit in a subsequent trial that used lamotrigine as comparator (Kwan *et al.*, 2011).

The monotherapy trial designs required to obtain regulatory approval in the US differed, and still differ, from those used in Europe because the Food and Drug Administration (FDA) believes that non-inferiority AED trials lack assay sensitivity (Perucca, 2008). As a result, monotherapy approval in the US is dependent on demonstration of superiority over a comparator. For a number of years, the design preferentially used was the so-called “conversion to monotherapy” design, in which patients with uncontrolled seizures were randomised to be switched to either monotherapy with a full dose of the investigational drug or a suboptimal dose of an active comparator (Sachdeo, 2007). Patients whose seizures deteriorated during the switch were required to exit the trial and the investigational agent was considered to have superior efficacy if it was associated with an exit rate lower than that associated with the suboptimal comparator (Perucca, 2008). Over the years, however, these trials ran into increasing criticism due to ethical concerns of randomising patients to a treatment deliberately chosen to be suboptimal (Chadwick, 1997; Karlawish and French, 2001; Perucca, 2008). In view of these concerns, the FDA has lately accepted an alternative conversion to monotherapy design in which the investigational agent given at a full

dose is simply required to show lower exit rates than those historically associated with suboptimal comparators in trials conducted in the past (French *et al.*, 2010a). While the use of historical controls is advantageous in avoiding the ethical problem of allocating patients to a suboptimal treatment, its application is not free of concern (Perucca, 2010). Perhaps the most critical concern stems from difficulties in recruiting in future trials a study population which closely mimics that enrolled in the historical trials, an obvious prerequisite for the comparison with historical controls to be valid. Fulfilling this objective is increasingly challenging, when one considers that critical variables to be mimicked may include not only seizure type and seizure frequency, but also epilepsy aetiology, co-morbidities, and concomitant medications, the utilisation of which has changed over the years. To some extent, the environmental setting in which the study is conducted may also need to mimic the setting of past trials, which adds an additional hurdle to the challenge.

The future: do we need to change currently used designs?

The designs currently used for the clinical testing of novel AEDs have been found to be useful in the past, but there are clear signals that their application is increasingly facing many difficulties. These will be discussed briefly below, separately for adjunctive therapy and monotherapy trials.

Adjunctive therapy trials

Adjunctive therapy trials, as currently performed, face practical and ethical concerns. When only a handful of AEDs were commercially available, it was easy to enrol a sizeable population of patients who had already tried all existing options. These patients were eager to try a potentially useful new treatment and the lack of available therapeutic alternatives justified allocating a control group to a placebo. Clinical trials were typically conducted at specialised centres by experienced investigators and effective recruitment could be completed rapidly at a single site or at a small number of sites.

In the last 20 years, the scenario has undergone fundamental changes. With more than 20 drugs now available to treat epilepsy (Fattore and Perucca, 2011; Perucca and Tomson, 2011), patients who exhausted all treatment options are increasingly difficult to find. When alternative potentially effective treatments exist, patients are less willing to try an investigational agent with an unproven efficacy and safety record, or even a placebo. Under such conditions, there are

also serious ethical concerns of exposing a control group to placebo for several months without changes in underlying medications, particularly since uncontrolled seizures can be associated with morbidity and even mortality risks (Perucca and Tomson, 2011). Such ethical concerns have been reinforced by the results of a recent meta-analysis in which patients randomised to placebo in adjunctive therapy trials suffered significantly higher mortality rates than patients randomised to an active treatment arm (Ryvlin *et al.*, 2011).

The above difficulties are already reflected in a change in the way patients are being enrolled into trials. Unlike the past, when individual centres could recruit 20 or more patients (Rimmer and Richens, 1984; Gram *et al.*, 1985; Grant and Heel, 1991; Goa *et al.*, 1993), it is now not uncommon for centres to be able to recruit, on average, no more than five patients (Faught *et al.*, 2008; Halford *et al.*, 2011). Because the parallel-group design requires a large sample size, sponsors have responded to these difficulties by increasing the number of sites (up to over 100) and by extending enrolment to diverse geographical regions and sites not previously involved in the randomised trials (Faught *et al.*, 2008; Bialer *et al.*, 2010; Brodie *et al.*, 2010; Halford *et al.*, 2011). In parallel with these developments, evidence has been produced that placebo response rates have increased over time (Rheims *et al.*, 2011), whereas our ability to differentiate between efficacious AEDs and placebo may be decreasing. For example, promising efficacy data associated with phase II adjunctive therapy clinical trials of brivaracetam (French *et al.*, 2010b) and carisbamate (Faught *et al.*, 2008) could not be replicated in large phase III confirmatory trials (Bialer *et al.*, 2010; Halford *et al.*, 2011). Along the same lines, in two recent adjunctive therapy trials, well established AEDs such as lamotrigine (Baulac *et al.*, 2010) and levetiracetam (Xiao *et al.*, 2009) could not be statistically differentiated from placebo. The cause for this apparent decline in effect size is unclear, one possibility is the difficulty in diagnosis and recording seizures correctly at sites where investigators and patients are less experienced with participation in controlled trials. If this is the case, attempts to deal with an apparently reduced effect size by increasing sample size and number of study sites is only going to exacerbate the problem.

To some extent, some of the above difficulties could be addressed by investigating carefully the patient- and study site-associated characteristics which influence the ability to differentiate between an efficacious treatment and placebo. Ultimately, however, the solution should come from improved trial designs which minimise duration of exposure to placebo and ineffective treatments. Such improved study designs will address ethical concerns, motivate patients to enrol, and facilitate recruitment at experienced study sites. A possible design that could meet such objectives is the

time-to-event trial, in which patients are required to exit the study when a predefined threshold of poor seizure control (or number of seizures) has been reached, an approach previously used in monotherapy trials (Arroyo *et al.*, 2005).

Monotherapy trials

Current difficulties with monotherapy trials have been discussed above. Because existing regulatory guidelines differ between Europe and the US, sponsors need to pursue separate trial programs to fulfil licensing requirements on the two sides of the Atlantic, which increases development costs and reduces the industry's incentive to invest in a greatly needed search for better AEDs (Perucca *et al.*, 2007). The non-inferiority design favoured in Europe has the advantage of using protocols and endpoints which are relevant to clinical practice, but concerns about the sensitivity of such trials in differentiating between effective and ineffective treatments has been questioned (Perucca, 2008). On the other hand, the conversion to monotherapy design with historical controls is equally open to criticism for the difficulties that are being faced in mimicking closely the conditions in which the historical trials were conducted. Additionally, conversion to monotherapy trials are performed in patients with chronic uncontrolled epilepsy, who (unlike people with newly diagnosed epilepsy) are not the primary population for whom monotherapy is intended. In particular, the high-dose regimens used in conversion to monotherapy trials provide no information about dose requirements in people with newly diagnosed or less severe forms of epilepsy (Chadwick, 1997; Perucca, 2010).

It is unlikely that a study design that addresses the above concerns and is acceptable to regulatory authorities on both sides of the Atlantic could emerge in the foreseeable future. In contrast, the solution may be found by careful appraisal of the rationale for requiring monotherapy studies once efficacy has been demonstrated in the adjunctive therapy setting. In other therapeutic areas, regulatory authorities approve new drugs for use as adjunctive therapy or as monotherapy, irrespective of whether the patients included in the phase II and III trials were taking concomitant medications or not. Based on current knowledge, it is difficult to argue that an AED found to be efficacious as adjunctive therapy can be ineffective when used as the sole medication. Obviously, extrapolation to the monotherapy setting of efficacy data from adjunctive therapy trials will need to be supported by careful scrutiny of the data, including comparative responses in patients receiving different classes of comedications and consideration of dosing issues if pharmacokinetic interactions occur.

Conclusions

This article shows how the process of AED evaluation has evolved from the time phenobarbital came into the market 100 years ago. Challenges have emerged continuously in parallel with advances in knowledge and these difficulties have been successfully overcome in the past, each and every time our colleagues were able to adapt and refine trial designs. In the last 20 years, treatment choices have expanded dramatically in epilepsy, but the need for safer and more effective AEDs remains unaltered. Current trial designs have been highly valuable, but they are proving to be increasingly inadequate to meet the new challenges that are facing us. Once again, it is time for change and for a new step forward. □

Acknowledgements and disclosures.

This work was not supported by any funding source. The author received research grants from the European Union, the Italian Medicines Agency, the Italian Ministry of Health, and the Italian Ministry for Education, University and Research. The author also received speaker's or consultancy fees and/or research grants from Bial, Eisai, GSK, Johnson and Johnson, Novartis, Pfizer, Sepracor, SK Life Sciences Holdings, Supernus, UCB Pharma, Upsher-Smith, Valeant, and Vertex.

References

- Arroyo S, Dodson WE, Privitera MD, *et al.* Randomized dose-controlled study of topiramate as first-line therapy in epilepsy. *Acta Neurol Scand* 2005; 112: 214-22.
- Arzimanoglou A, Ben-Menachem E, Cramer J, Glauser T, Seeruthun R, Harrison M. The evolution of antiepileptic drug development and regulation. *Epileptic Disord* 2010; 12: 3-15.
- Baulac M, Leon T, O'Brien TJ, Whalen E, Barrett J. A comparison of pregabalin, lamotrigine, and placebo as adjunctive therapy in patients with refractory partial-onset seizures. *Epilepsy Res* 2010; 91: 10-9.
- Bialer M, Johannessen SI, Levy RH, Perucca E, Tomson T, White HS. Progress report on new antiepileptic drugs: a summary of the Tenth Eilat Conference (EILAT X). *Epilepsy Res* 2010; 92: 89-124.
- Brodie MJ, Perucca E, Ryvlin P, *et al.* Comparison of levetiracetam and controlled-release carbamazepine in newly diagnosed epilepsy. *Neurology* 2007; 68: 402-8.
- Brodie MJ, Lerche H, Gil-Nagel A, *et al.* Efficacy and safety of adjunctive ezogabine (retigabine) in refractory partial epilepsy. *Neurology* 2010; 75: 1817-24.
- Chadwick D. Monotherapy clinical trials of new antiepileptic drugs: design, indications, and controversies. *Epilepsia* 1997; 38: S16-20.
- Coatsworth JJ. *Studies on the Clinical Efficacy of Marketed Antiepileptic Drugs*. NINDS Monograph # 12. Washington (DC): US Government Printing Office, 1971.

- Coatsworth JJ, Penry JK. General principles. Clinical efficacy and use. In: Woodbury DM, Penry JK, Schmidt RP. *Antiepileptic Drugs*. New York: Raven Press, 1972: 87.
- Committee for Proprietary Medicinal Products (CPMP). *Note for guidance on clinical investigation of medicinal products in the treatment of epileptic disorders*. (CPMP/EWP/566/98 rev 1). London: CPMP, 16 November 2000.
- Committee for Medicinal Products for Human Use. *Guidance on clinical investigation of medicinal products in the treatment of epileptic disorders*. (CPMP/EWP/566/98 rev 2). London: Committee for Medicinal Products for Human Use, 22 July 2010.
- Dam M, Ekberg R, Løyning Y, Waltimo O, Jakobsen K. A double-blind study comparing oxcarbazepine and carbamazepine in patients with newly diagnosed, previously untreated epilepsy. *Epilepsy Res* 1989;3: 70-6.
- Drug Amendments Act of 1962 (Public Law 87-781, 21 USC 355).
- Fattore C, Perucca E. Novel medications for epilepsy. *Drugs* 2011; 71: 2151-78.
- Faught E, Holmes GL, Rosenfeld WE, et al. Randomized, controlled, dose-ranging trial of carisbamate for partial-onset seizures. *Neurology* 2008;71: 1586-93.
- French JA, Wang S, Warnock B, Temkin N. Historical control monotherapy design in the treatment of epilepsy. *Epilepsia* 2010a;51: 1936-43.
- French JA, Costantini C, Brodsky A, von Rosenstiel P; N01193 Study Group. Adjunctive brivaracetam for refractory partial-onset seizures: a randomized, controlled trial. *Neurology* 2010b; 75: 519-25.
- Glauser T, Ben-Menachem E, Bourgeois B, et al. ILAE treatment guidelines: evidence-based analysis of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia* 2006;47: 1094-120.
- Goa KL, Ross SR, Chrisp P. Lamotrigine. A review of its pharmacological properties and clinical efficacy in epilepsy. *Drugs* 1993;46: 152-76.
- Gram L, Bentsen KD, Parnas J, Flachs H. Controlled trials in epilepsy: a review. *Epilepsia* 1982;23: 491-519.
- Gram L, Klosterskov P, Dam M. Gamma-Vinyl GABA: a double-blind placebo-controlled trial in partial epilepsy. *Ann Neurol* 1985;17: 262-6.
- Grant SM, Heel RC. Vigabatrin. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in epilepsy and disorders of motor control. *Drugs* 1991;41: 889-926.
- Gruber CM Jr, Mosier JM, Grant P. Objective comparison of primidone and phenobarbital in epileptics. *J Pharmacol Exp Ther* 1957;120: 184-7.
- Halford JJ, Ben-Menachem E, Kwan P, et al. A randomized, double-blind, placebo-controlled study of the efficacy, safety, and tolerability of adjunctive carisbamate treatment in patients with partial-onset seizures. *Epilepsia* 2011;52: 816-25.
- Hauptmann A. Luminal bei Epilepsie. *Münch med Wochenschr* 1912;59: 1907-9.
- Hauptmann A. Erfahrungen aus der Behandlung der Epilepsie mit Luminal. *Münch med Wochenschr* 1919;46: 1319-21.
- Hills M, Armitage P. The two-period cross-over clinical trial. *Br J Clin Pharmacol* 1979;8: 7-20.
- Himwich HE. Report of committee on research 111: anticonvulsant and convulsant agents. *Epilepsia* (3rd series) 1952; 1: 145-52.
- Karlawish JH, French J. The ethical and scientific shortcomings of current monotherapy epilepsy trials in newly diagnosed patients. *Epilepsy Behav* 2001;2: 193-200.
- Kwan P, Brodie MJ, Kalviainen R, Yurkevich L, Weaver J, Knapp LE. Efficacy and safety of pregabalin versus lamotrigine in patients with newly diagnosed partial seizures: a phase 3, double-blind, randomised, parallel-group trial. *Lancet Neurol* 2011; 10: 881-90.
- Marson AG, Williamson PR. Interpreting regulatory trials in epilepsy. *Curr Opin Neurol* 2009;22: 167-73.
- Matsuo F, Riaz A. Lamotrigine. In: Shorvon S, Perucca E, Engel J Jr. *The Treatment of Epilepsy*. 3rd edition. Oxford: Blackwell Publishers, 2009: 535-58.
- Mattson RH, Cramer JA, Collins JF, et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. *N Engl J Med* 1985;313: 145-51.
- Merritt HH, Putnam TJ. Sodium diphenyl hydantoinate in the treatment of convulsive disorders. *J Am Med Soc* 1938;111: 1068-73.
- Perucca E. Designing clinical trials to assess antiepileptic drugs as monotherapy: difficulties and solutions. *CNS Drugs* 2008;22: 917-38.
- Perucca E. When clinical trials make history: demonstrating efficacy of new antiepileptic drugs as monotherapy. *Epilepsia* 2010;51: 1933-5.
- Perucca E, Tomson T. Monotherapy trials with the new antiepileptic drugs: study designs, practical relevance and ethical implications. *Epilepsy Res* 1999;33: 247-62.
- Perucca E, Tomson T. The pharmacological treatment of epilepsy in adults. *Lancet Neurol* 2011; 10: 446-56.
- Perucca E, French J, Bialer M. Development of new antiepileptic drugs: challenges, incentives, and recent advances. *Lancet Neurol* 2007;6: 793-804.
- Rheims S, Perucca E, Cucherat M, Ryvlin P. Factors determining response to antiepileptic drugs in randomized controlled trials. A systematic review and meta-analysis. *Epilepsia* 2011;52: 219-33.
- Rimmer EM, Richens A. Double-blind study of gamma-vinyl GABA in patients with refractory epilepsy. *Lancet* 1984; 1: 189-90.
- Ryvlin P, Cucherat M, Rheims S. Risk of sudden unexpected death in epilepsy in patients given adjunctive antiepileptic treatment for refractory seizures: a meta-analysis of placebo-controlled randomised trials. *Lancet Neurol* 2011; 10: 961-8.

Sachdeo R. Monotherapy clinical trial design. *Neurology* 2007; 69: S23-7.

Shorvon SD. Drug treatment of epilepsy in the century of the ILAE: the first 50 years, 1909-1958. *Epilepsia* 2009; 50: 69-92.

Spangler R. The crotalin treatment of epilepsy. *Epilepsia* 1913; 3: 307-18.

White PT, Plott D, Norton J. Relative anticonvulsant potency of primidone; a double-blind comparison. *Arch Neurol* 1966; 14: 31-5.

Xiao Z, Li JM, Wang XF, *et al.* Efficacy and safety of levetiracetam (3,000 mg/day) as an adjunctive therapy in Chinese patients with refractory partial seizures. *Eur Neurol* 2009; 61: 233-9.