The evolution of antiepileptic drug development and regulation

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ABSTRACT – The early years of antiepileptic drug development were characterised by observation and serendipity, rather than a rational, targeted approach to drug development. Control of seizures was seen as the primary aim of therapy, with much less focus on safety and tolerability. However, experience with thalidomide in the 1960s brought safety to the fore, resulting in an era of much tighter regulatory control that still persists today. A direct consequence of this was an increased emphasis on the importance of evidence from randomised controlled trials. Despite the continuing reliance on randomised controlled trials for regulatory approval and the formulation of evidence-based guidelines, the modern era has seen an increasing acknowledgment of their limitations and the need for complementary sources of ‘real-world’ evidence. Such sources include registries and studies that are designed to provide a much broader assessment of a drug’s overall effectiveness; for example, by incorporating patient-reported outcomes to assess the effects of treatment on quality of life or functional status. Such changes reflect a more patient-centric approach to treatment, since it is now recognised that epilepsy can only be effectively managed if patients’ individual real-life needs are addressed, since a key to successful treatment is long-term compliance. Alongside these changes in approach, the modern era has witnessed important advances in antiepileptic drugs themselves, either through development of novel molecules, or targeted, structural improvements of older agents. [Published with video sequences and a set of slides]

Keywords: antiepileptic drugs, clinical trials, drug development, regulation, QOL, patient-reported outcome

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2009 marks the centenary of the formation of the International League Against Epilepsy (ILAE) and provides a timely opportunity to reflect upon the progress of epilepsy management over this period. A fundamental aim of epilepsy therapy has always been seizure control, but other goals have evolved over time and treatment has become more individualised and patient-focused. This article reviews the evolution of antiepileptic drug (AED) therapy (see video sequence), discusses how some of the key regulatory changes came about and how these impacted on AED development, and also assesses how a more patient-focused approach may improve epilepsy management in the future.

**Early years of AED development**

**The value of observation (slides 3-10)**

In the modern era, potassium bromide was the first drug considered to have value for treating people with epilepsy. On 11th May 1857, Sir Charles Locock presided at a meeting of the Royal Medical and Chirurgical Society at which Dr. Edward H. Sieveking presented an analysis of his care of 52 patients with epilepsy. In the subsequent discussion, Locock commented that he had successfully used potassium bromide to treat women with what he called hysterical epilepsy (catamenial epilepsy). At the time it was believed that bromide could dampen the sexual excitement thought to cause these seizures (Williams, 1866; Pearce, 2002). Subsequent reports of its efficacy eventually led to widespread use of bromides for the treatment of seizures, often in combination with other agents such as digitalis, belladonna, zinc and iron (Gowers, 1881; Friedlander, 2000). Bromides remained the foundation of epilepsy treatment for many years. Their use was, however, associated with dermatological conditions, such as severe rash, and psychological symptoms, such as irritability, emotional instability and even a schizophrenic-like psychosis in many patients ("bromism").

Serendipity then played a key role in the discovery of the antiepileptic efficacy of phenobarbital. Barbiturates were already widely used as hypnotics and sedatives in 1912, when Albert Hauptmann, a young clinical assistant in Freiburg, Germany, gave phenobarbital to his epilepsy patients as a tranquilizer and observed that the frequency of their seizures was reduced (Hauptmann, 1912). Subsequent studies revealed that phenobarbital was more efficacious than bromides and, since it was not associated with their 'bromism' problems, phenobarbital eventually became a widely used AED.

Animal models: a great leap forward (slides 11-14)

The next major advance in AED discovery was the introduction of epilepsy animal models; these models allowed for the screening of multiple compounds for antiepileptic activity prior to testing in humans. The pioneering work of Drs. Houston Merritt and Tracy Putnam focused on screening compounds for antiepileptic activity using electrically induced seizures in cats. Their team subsequently discovered the anticonvulsant properties of the molecule diphenylhydantoin, later known as phenytoin (Merritt and Putnam, 1938). The identification of phenytoin’s antiseizure activity through animal models was a significant event for several reasons. Phenytoin was subsequently shown to be beneficial for a large number of epileptic patients in whom barbiturates and bromides were ineffective. Secondly, clinically efficacious doses of phenytoin were not associated with the sedative effect of these other agents. Thirdly, the success of testing using an animal model demonstrated that a systematic approach to screening could be utilised to discover compounds with clinical efficacy. This meant that subsequent costly and time-consuming clinical trials could be reserved for the most effective compounds identified by these animal experiments. Lastly, the compounds screened by Merritt and Putnam were provided by Parke-Davis; this was probably the first successful industry-academia collaboration in AED discovery, a relationship that has subsequently flourished up to the present day (Krall et al., 1978).

Phenytoin soon proved its value clinically, showing greater efficacy than phenobarbital in reducing various seizure types without the associated CNS side effects (Mattson et al., 1985; Heller et al., 1995). It became established as a first-choice AED for partial onset seizures, and is still widely used in many markets today. However, phenytoin was also found to have multiple major limitations, including non-linear pharmacokinetics, extensive drug interactions (Richens, 1979), and chronic toxicities such as hirsutism, gingival hyperplasia and the coarsening of facial features, all of which can stigmatise patients (Johnson, 1984; Scheinfeld, 2004). Serious delayed effects, such as carcinogenicity and teratogenicity, have also been associated with its use (Azarbayjani and Danielsson, 2001; Singh et al., 2005).

The discovery of phenytoin was followed by the rapid identification and introduction of several new drugs produced largely by altering the basic chemical moiety of known AEDs. These included analogues of phenytoin such as mephenytoin, and those of phenobarbital such as metharbital and primidone, many of which are no longer widely used.

**Carbamazepine: first of a new generation of AEDs (slides 15-20)**

Carbamazepine (CBZ) was the next major advance in AED development and, to this day, remains the gold standard for partial onset epilepsy in Europe. The anticonvulsant properties of this tricyclic compound were...
discovered by Walter Schindler at Geigy in 1953 during the development of the antidepressant drug imipramine (Schindler and Häfliger, 1954). Animal screening later showed CBZ had potential utility for trigeminal neuralgia, which was confirmed by clinical trials, and it was first marketed for this indication (Blom, 1962). CBZ's anti-epileptic effects were initially reported by two small open-label studies (Bonduelle et al., 1964; Lorge et al., 1963), but confirmed by larger subsequent trials. By the mid-1960s the drug was marketed in most European countries, but approval in the USA for epilepsy was delayed until 1974 because of reports of aplastic anaemia (Fertig and Mattson, 2007). It also emerged that CBZ use was associated with idiosyncratic rash, hyponatraemia, haematological toxicity and hepatic dysfunction, as well as rare adverse events (AEs) such as thrombocytopenia and Stevens-Johnson syndrome (Durelli et al., 1989; Tohen et al., 1991; Dong et al., 2005; Devi et al., 2005). By the mid 1980s, CBZ became the most prescribed AED in Europe and remains a recommended first-line monotherapy for partial seizures in major international guidelines (French et al., 2004; NICE, 2004; Glauser et al., 2006). It is also currently the comparator of choice for non-inferiority trials used to obtain a monotherapy licence for new AEDs (Brodie et al., 2007).

The first Veterans Administration Epilepsy Cooperative Study (VA Cooperative Study) prospectively compared CBZ, phenobarbital, phenytoin and primidone in newly-treated partial and secondarily generalised tonic-clonic seizures (Mattson et al., 1985). CBZ and phenytoin were found to be the most effective in terms of retention and seizure control. The second VA Cooperative Study, comparing CBZ and valproate for partial-onset seizures, also showed unsurpassed efficacy for CBZ (Mattson et al., 1992). However, only one-third of the combined 1,100 patients achieved seizure freedom, and all drugs were associated with multiple AEs. Over time, increasing clinical experience and the emerging availability of brain imagining techniques helped to improve the safety profile of AEDs, since the delineation of specific epilepsy syndromes allowed the identification of the aggravating effects of certain AEDs in specific patient groups. For example, it was discovered that myoclonic seizures are aggravated by CBZ (Horn et al., 1986; Genton et al., 2000). However, there was clearly still a need for effective new AEDs with improved safety profiles.

Changing regulatory environment: effect on AED development

Thalidomide: a consequence of poor regulation (slides 22-25)

In the 1950s and 1960s drug development continued in an environment lacking either strict regulatory control or rigid trial designs relating to long-term safety. However, this all changed with one of the most infamous chapters in the history of drug development and regulation. Thalidomide entered the German market in the late 1950s as a sedative to treat insomnia, as well as to reduce nausea associated with pregnancy, and was widely available in Europe by 1960. However, in 1961 Lenz (Lenz et al., 1961) and McBride (McBride, 1961) independently reported that prenatal use of thalidomide was resulting in severe birth defects. By 1961, >8,000 children were born with severe limb abnormalities and other organ defects as a result of prenatal exposure to thalidomide (Annas and Elias, 1999). In the USA, the Food and Drug Administration (FDA) had not granted approval of the New Drug Application submitted by Richardson-Merrill, because of concerns about peripheral neuropathy associated with use of the agent. Although around 20,000 patients received the drug during experimental clinical investigations, only 17 affected infants were reported in the USA, and the company withdrew its application after the effects were widely publicised (Annas and Elias, 1999). It was later discovered that thalidomide possessed anti-inflammatory and immunomodulatory properties, leading to its use for the treatment of erythema nodosum leprosum, a severe dermatological complication of Hansen’s disease (formerly known as leprosy), and for the treatment of multiple myeloma (Annas and Elias, 1999; Palumbo et al., 2008).

At the time of thalidomide, the USA was operating under the 1938 Food, Drug and Cosmetic Act, which did not require demonstration of efficacy for a drug to be approved. In the early 1960s the drug approval process was under considerable criticism, which led to the introduction of the Kefauver-Harris Drug Amendments in October 1962. This legislation included proof of efficacy, “informed consent” from clinical trial participants, and reporting of all adverse reactions. In 1968, the FDA initiated the Drug Efficacy Study Implementation (DESI) programme to retrospectively review the effectiveness of drugs marketed between 1938 and 1962. The thalidomide tragedy also provided the impetus for the introduction in European countries of regulatory control of drugs to be marketed, leading to the EU Council Directive 65/65/EEC. In the United Kingdom, the result was the Medicines Act 1968 and the establishment of the Licensing Authority (Shah and Griffin, 2006).

The new FDA legislation requiring a degree of proof of efficacy resulted in delayed AED development in the USA. This was for several reasons, including lack of appropriate populations for controlled trials, a reluctance from patients to try drugs in clinical trials, and difficulties in designing studies with multiple drugs. Furthermore, there was controversy over definition of specific seizure types, as brain imaging techniques were not yet available and EEG monitoring was not routinely used, and also a
lack of rigorous methodology for measuring response. In fact, between 1961 and 1973 no new drug was marketed in the USA with control of epilepsy as a primary indication (Krall et al., 1978).

The first novel AED in the new regulatory era was valproate (VPA), which was first synthesised in 1881 and used as an organic solvent (Shorvon, 2009b). The anticonvulsant properties of valproate were identified by Pierre Emyard in France in 1962 and it was marketed in France in 1967 (Loiseau, 1999). It then rolled out in other EU countries from 1970 onwards, but did not receive a license in the US until 1978. VPA is a broad-spectrum AED, effective against all seizure types (Perucca, 2002). It became the most widely prescribed AED worldwide, generally regarded as a first-choice agent for most forms of idiopathic and symptomatic generalised epilepsies, many of which are associated with multiple seizure types, including tonic-clonic, myoclonic and absence seizures (Perucca, 2002).

Although the agent was shown to have clear efficacy for the treatment of idiopathic generalised epilepsy, there were concerns over its safety profile, including cognitive problems, teratogenicity and weight gain (Sztajnkrycer, 2002; Wirrell, 2003; Duncan, 2007). It remains the drug of choice for generalised seizures (NICE, 2004; Glauser et al., 2006).

Randomised controlled studies: “Gold standard” evidence? (slides 25-33)

Sir Austin Bradford Hill, an English statistician, is credited with developing the first randomised controlled trial (RCT), which examined streptomycin in patients with pulmonary tuberculosis (Streptomycin in Tuberculosis Trials Committee, 1948). He also demonstrated the link between smoking and lung cancer (Doll and Hill, 1954) and published the landmark paper “The environment and disease: association or causation?” (Hill, 1965). Medical researchers were initially slow to undertake RCTs, but they have subsequently become the “Gold standard” of evidence: properly conducted, they provide a means of assessing the specific effects of an intervention, since randomisation ensures that, on average, all other possible causes of effect are equal between groups. By the late 1980s there were approximately 5000 RCTs published each year (Devereaux and Yusuf, 2003). RCTs have evolved in design and outcomes from the first small RCTs, primarily in the area of infectious disease, to large simple RCTs that evaluate major clinical outcomes and form the basis of clinical practice guideline development (figure 1). In the field of epilepsy, the VA Cooperative Study Group was the first to develop a modern clinical

**Figure 1.** Evolution of randomised controlled trials.

CONSORT: consolidated standards of reporting trials; FDA: Food and Drug Administration; ILAE: International League Against Epilepsy; QUOROM: Quality of Reporting of Meta-analyses; RCT: randomised controlled trial; TB: tuberculosis.
trial with quantifiable endpoints, using long-term retention as well as seizure severity and adverse effects scales (Mattson et al., 1985).

However, there are limitations to RCTs. They are relatively short in duration, while chronic diseases, such as epilepsy, require long-term treatment, and they are difficult to conduct in patients with rare conditions, due to low patient numbers. RCTs provide evidence of short-term efficacy and safety for regulatory purposes, and follow set protocols which contain inclusion/exclusion criteria and a set dosing schedule. However, in the clinic treatment is tailored to ensure that individual patients receive an AED at a dose that they find both effective and tolerate well, as this encourages medication compliance. There are also methodological issues associated with conducting RCTs. The majority of regulatory RCTs are placebo-controlled, but the use of placebo can itself be problematic. For example, in RCTs of AEDs, placebo response – but not response to active treatment – has been shown to be higher in children than in adults, leading to age-dependent differences in treatment effects that are accounted for in the design of paediatric trials (Rheims et al., 2008). However, despite increasingly stringent recommendations on how AEDs and other drugs should be developed for use in paediatric populations, the design of pivotal paediatric trials is typically based on extrapolations from trials conducted in adult populations (Caldwell et al., 2004; Garofalo, 2006; Chiron et al., 2008).

The limitation of RCTs can be illustrated by the case of vigabatrin, the first in a new class of AED that selectively inhibits gamma aminobutyric acid (GABA) transaminase, the enzyme responsible for the metabolism of GABA (Graham, 1989). The agent was undergoing clinical evaluation in the USA, but the trials were halted in 1983 when white matter changes were found to occur in mice, rats and dogs (Laxer, 1994). Since no serious neurological or neurophysiological toxicity was observed in humans, clinical testing subsequently resumed. By the mid-1990s the drug was widely available in Europe, but then reports began emerging suggesting that it caused visual field defects, with up to 50% of patients affected (Lawden et al., 1999). This led to the licensing authorities heavily restricting the use of vigabatrin, and subsequent monitoring of 563 patients in a multinational, prospective, observational study confirmed that there was an increased risk of visual field defects associated with its use (Wild et al., 2007). However, vigabatrin remains an option for partial seizures where other options have failed and where the risks of its use are outweighed by the benefit. It has also become a drug of choice for infantile spasms (Wheless et al., 2007).

Felbamate is another example of where the full toxicological risk of the drug was not evident on licensing with evidence from RCTs. The drug was approved by the US FDA in August 1993 for adult partial seizures, with or without secondary generalisation, and for Lennox-Gastaut Syndrome (LGS), a serious form of childhood epilepsy. Within 1 year, it had been prescribed to 126,000 patients with epilepsy. However, in September 1994 the FDA had to issue a “Dear Doctor” letter, warning of a higher than expected incidence of aplastic anaemia and hepatic failure among patients receiving felbamate (French et al., 1999). The FDA decided to allow it to remain on the market, but with restricted use. It can be considered for use in those patients who respond inadequately to alternative treatments and whose epilepsy is so severe that the risks of aplastic anaemia and hepatic failure are outweighed by the benefits of the drug (Felbamate Prescribing Information, 2008). Similarly, felbamate is available in Europe on a patient-by-patient basis.

**Registries vs RCTs (slides 34-40)**

The cases outlined for vigabatrin and felbamate illustrate that RCTs reveal only the top-line impact on short-term seizure reduction and acute tolerability (at specific doses). They cannot monitor safety in the ‘real world’ or naturalistic setting and may not pick up safety signals that are rare or take time to develop. Registries include wider disease populations than RCTs and are useful to confirm whether the safety and efficacy of drugs observed in RCTs translate into everyday clinical practice, after the drug is available for general prescribing. They can also provide supplemental safety data in patients with rare conditions, in circumstances where RCTs are limited due to low patient numbers. Although registry studies may at times be subject to case selection (since they are not randomised), they can produce a wealth of valuable data when properly managed. For example, they can produce long-term data collection with less administrative burden of traditional trials and provide additional data on patient-related outcomes and healthcare resource utilisation. Several AED registries now exist, some requested by regulators, some not, and they now exist to monitor AED effects in pregnancy (Beghi and Annegers, 2001; Vajda et al., 2007; Krishnamurthy, 2008) and also to monitor the effects of adjunctive vagal nerve stimulation (Labar, 2002). A European registry of AED use in patients with LGS has also recently been initiated (Seeruthun et al., 2009).

The Orphan Drug Act of 1983 was passed in the USA, to encourage pharmaceutical companies to target rare conditions, such as LGS. Subsequently, similar legislation was implemented by the European Medicines Agency (EMEA), and in 2007 both regulatory bodies agreed a common application process to simplify orphan drug development. Although Phase III statistical burden for proof of efficacy lessened as a result, there was a requirement for long-term safety monitoring. For example, rufinamide, a triazole derivative structurally unrelated to other marketed AEDs, was licensed for LGS based on data from only one RCT involving 138 patients (Glauser et al., 2008), and European regulators felt a post-marketing registry was appropriate to assess the drug’s safety profile in this
population. The registry will include 100 LGS patients initiating rufinamide and up to 300 LGS patients receiving other AEDs, and will look at the impact of long-term LGS treatment on maturation and development of patients, seizure control, health-related quality of life (QoL) and healthcare resource utilisation (Seeruthun et al., 2009).

For clinical conditions in which RCTs are particularly difficult to perform, the role of “Expert Opinion” has also developed to fill gaps in clinical knowledge; for example, this has been important for certain paediatric epilepsy syndromes (Wheless et al., 2007). Although of limited scientific value, expert opinion can provide valuable guidance to the practicing physician who may otherwise have to rely on their own clinical judgement to select the most appropriate treatment for an individual patient.

Thalidomide changed the landscape of drug development forever, with regulatory emphasis on safety as well as efficacy, and with approval now requiring RCTs controlled down to the finest detail. However, effective epilepsy management is much more than just satisfying regulatory requirements: drug profiles must be optimised to ensure that individual patients can tolerate long-term treatment, since retention is key to success. This became the main focus as AED development entered the modern era.

The modern era of AED development

Focusing on the patient (slides 42-43)

An increasing number of new AEDs have become available over recent years (figure 2; see video sequence), providing patients and physicians with a wealth of alternative treatment options. The availability of more than 15 AEDs has not, however, resulted in a commensurate improvement in patient outcomes. For example, the rate of seizure freedom achieved in the VA Cooperative Study – approximately 30% – has not been improved upon significantly (Mattson et al., 1985; Mattson et al., 1992), and problems with AED tolerability persist. In addition, there has been increasing recognition of the need to evaluate the wider effects of AED therapy on patients, such as the impact of treatment on mood and cognitive function (Loring et al., 2007). There is also a need for therapies that are capable of altering the natural evolution of some epilepsy syndromes, which may necessitate trying new treatments early on during the course of the disease. For example, although it is important to be able to control drop attacks in severely mentally impaired LGS patients, earlier treatment with an appropriate agent might help avoid the development of cognitive impairment.

Patient populations used in RCTs are carefully selected and tightly defined in order to limit the impact of confounding factors, thereby allowing the effects of an intervention to be clearly revealed. In the case of AEDs, regulatory trials focusing solely on the efficacy and safety of the agent in question cannot provide information on how new medications should be used in ‘real life’ for ‘real’ individual patients, who vary in terms of their (often multiple) concomitant medications, co-morbidities, age and other special requirements (e.g. renal function). Moreover, the overall success of an AED is not just depen-
ent on its efficacy and tolerability, but on a global impression of treatment satisfaction that also encompasses a patient’s functional status (independence, ability to work, psychological condition, etc.) and QoL.

It is particularly important to recognise that epilepsy is a chronic condition, requiring long-term – often life-long – treatment, and the key to its effective management is to provide treatment options that patients are able and willing to continue taking long-term. In order to achieve this, a broader, more holistic approach to epilepsy management is required, which is focused on the needs of patients as individuals. There is consequently a need to bridge the gap between clinical trials and clinical practice, and provide physicians and patients with the type of information they require in order to make informed and appropriate treatment choices in the real world.

**Importance of effectiveness studies (slides 44-48)**

RCTs provide a specific type of clinical evidence required for regulatory approval, but clinical evidence can come from a wide variety of sources. At one end of the spectrum, a single-centre, retrospective chart review can reveal certain subjective treatment trends, while, at the other end, RCTs provide statistically robust, objective assessments of efficacy and short-term tolerability in carefully defined patient populations (table 1). In addition to the limitations previously outlined, RCTs may give a false impression of a drug’s tolerability, since they usually involve forced titration schedules and require the reporting of every AE, whereas, in clinical practice, lower and slower titration schedules can be used, which help to provide a better indication of effective clinical doses and thereby minimise the occurrence and impact of AEs. Effectiveness studies provide a balance between the extremes of this spectrum of evidence, allowing the objective evaluation of a drug under typical clinical practice conditions (in terms of patient populations and dosing schedules), together with an assessment of patient-reported outcomes (PROs), such as functional status, global evaluation of patient status, and QoL (table 1).

Effectiveness studies are typically open-label in design and included as part of a drug’s post-approval (phase IV) development. For example, the Zonisamide in the European Union Study (ZEUS) (Dupont et al., 2009) was a prospective, Phase IV, non-comparative study, conducted in nine European countries, which was designed to assess the efficacy and safety of zonisamide (ZNS) add-on therapy for partial-onset seizures in an adult population that was more heterogeneous and less refractory to treatment than the patients included in previous pivotal RCTs (Schmidt et al., 1993; Faught et al., 2001; Sackellares et al., 2004; Brodie et al., 2005). In addition to confirming ZNS’s tolerability and efficacy (in terms of seizure frequency reduction), and identifying the most common daily dose used (300 mg), ZEUS demonstrated improvements in Clinical Global Impression, health-related QoL and seizure severity, in a setting that was reflective of clinical practice (Dupont et al., 2009). Similarly, the Keppra® Epilepsy Evaluation of the Patient timE to Response (KEEPER™) trial was a prospective, Phase IV, open-label, multicentre study, conducted in the USA, which was designed to gather additional information on the safety and efficacy of levetiracetam (LEV) add-on therapy for adult partial-onset seizures in a real-world setting of community-based practice (Morrell et al., 2003), following regulatory approval based on the results of several RCTs (Cereghino et al., 2000; Shorvon et al., 2000; Ben-Menachem and Falter, 2000; Boon et al., 2002). In addition to confirming LEV efficacy

| **Table 1. Effectiveness studies within the spectrum of clinical evidence.** |
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| **Study type** | **Method** | **Drawbacks** | **Advantages** | **Example** |
| Chart review, one centre | Review charts for seizure frequency, AEs | Single site, treatment evolves over time, minimal records | Reveals trends | Kwan and Brodie, 2001 |
| Observational chart study, convenience sample, one centre | Prospective follow-up using standard format | Wide variation in patients, typically small N (even if multicentre) | Proof of concept | |
| Effectiveness study, multicentre, observational | Open-label, flexible-dose treatment, PROs | No control group | Typical clinical practice, less refractory patients, focus on PROs | ZEUS (Dupont et al., 2009) KEEPER™ (Morrell et al., 2003) |
| Interventional study, randomised vs intervention or active treatment | Clinical trial | Specific eligibility, follow-up, planned N | Adequate N, defined primary outcome | VA Studies (Mattson et al., 1985; Mattson et al., 1992) |
| Interventional study, randomised vs placebo treatment | Clinical trial | Specific eligibility, follow-up, planned N | Adequate N, defined primary outcome | Phase III clinical trial |

AE: adverse event; PRO: patient-reported outcome.
and tolerability in a setting reflective of clinical practice, KEEPER™ demonstrated that almost three-quarters of patients improved, either slightly (11.3%), moderately (26.0%), or markedly (37.0%), based on the investigator-completed Global Evaluation Scale (Morrell et al., 2003). Effectiveness studies therefore provide important and unique evidence, by gathering data under conditions more closely mirroring routine clinical practice, using diverse populations that are reflective of the real word (in terms of refractoriness to treatment, concomitant medication and comorbidity) and flexible and clinically relevant dosing schedules. By including patient-reported outcomes, effectiveness studies are also more patient-centric, providing valuable evidence of a drug’s impact on aspects of patients’ lives that are most likely to predict whether or not the treatment will be acceptable (and therefore maintained) long-term (figure 3).

Determining the individual needs of patients (slides 49-50)
The use of patient-reported outcomes in clinical studies provides an important means of assessing what is important to patients in clinical practice, but only effective direct communication between clinician and patient can determine the latter’s specific needs. Physicians should be encouraged to ask their patients at every visit about their functional status, QoL and emerging/ongoing AEs, in terms of both the patient’s condition and their medication. Moreover, it is important that physicians elicit information from patients by asking directed questions, particularly since many epilepsy patients are depressed (Kanner, 2008) and therefore likely to experience difficulty in communication, and to suffer more AEs. To facilitate this process, physicians can use a standard format to obtain information and take notes to chart changes over time. A combination of neurological or physical examination plus interview can be utilised, in order to determine the presence and severity of specific adverse neurological and systemic problems (Cramer et al., 1983; Gilliam et al., 2004). Physicians should always be prepared to consider changing a patient’s dose or AED in order to improve outcomes.

Third-generation AEDs and beyond (slides 51-56)
By tailoring an individual patient’s needs to the treatments available, a more patient-focused approach to epilepsy management will undoubtedly lead to improvements in patient-perceived outcomes, but there is clearly also a need to continue improving and expanding the therapeutic options on offer, since history has shown there to be continued unmet needs with existing AEDs, in terms of both tolerability and seizure control. Hope for the future is provided by the development of new AEDs that are either structural advances of older agents, or completely novel molecules. Importantly, PROs are increasingly being acknowledged as useful endpoints to include, in addition to those for efficacy and tolerability, when assessing the clinically-relevant benefits of new AEDs.

Many “third-generation” AEDs have resulted from structural advances of existing agents, including brivaracetam, pregabalin and eslicarbazepine acetate (ESL) (figure 4). In addition, several novel molecules are currently being assessed as potential AEDs in phase III trials. Ganaxolone is a synthetic analogue of the endogenous neurosteroid allopregnanolone (Rogawski, 2006), a metabolite of progesterone that lacks hormonal activity (Monaghan et al., 1997). Ganaxolone acts as potent allosteric modulator of the GABA\(_\text{A}\) complex, binding to a receptor site distinct from that bound by benzodiazepines (Rogawski, 2006; Nohria and Giller, 2007). Preclinical models have revealed no signal for tolerance (Rogawski, 2006) and early open-label clinical studies have indicated that
Ganaxolone is effective in reducing complex partial seizures and infantile spasms (Monaghan et al., 1999). Perampanel is a novel selective α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA)-type glutamate receptor antagonist. Since AMPA receptors play a key role in cortical glutamatergic transmission (Prince et al., 1995), AMPA antagonists might be expected to reduce excessive activity and excitotoxicity, and perampanel has demonstrated antiseizure effects in a broad spectrum of rodent models (Hashizume et al., 2007; Hashizume et al., 2008). In addition, perampanel showed preliminary evidence of efficacy and favourable safety and tolerability in two phase II trials (Krauss et al., 2009). Other agents that have undergone phase III trials are: carisbamate, which is structurally related to felbamate and has been primarily shown to inhibit voltage-dependent sodium channels (Liu et al., 2009); brivaracetam, which, like its parent compound levetiracetam, is thought to act on the synaptic vesicle protein 2A, as well as additionally inhibit voltage-gated sodium channels (Rogawski, 2006; Matagne et al., 2008); and retigabine, a novel potassium channel opener (Rundfeldt and Netzer, 2000). Retigabine has recently been filed for regulatory approval with both the US FDA and EMEA, for use as adjunctive therapy to treat adult patients with partial-onset seizures (GlaxoSmithKline and Valeant Pharmaceuticals International Press Release 2009).

The modern era has been characterised by increasing recognition of the need to assess the effects of any treatment on individual patients, not only in terms of efficacy and tolerability, but also in terms of QoL and other patient-related outcomes. The use of PROs and effectiveness studies is helping to provide a more patient-centric approach to AED development, which is improving patient outcomes and encouraging better patient retention. Since the ultimate aim of epilepsy management – a cure – remains elusive, and since there are still unmet needs (in terms of efficacy and tolerability) in the therapeutic

Figure 4. Development of new antiepileptic drugs as structural advances on existing agents.
options available, the need for new AEDs persists, and is being addressed by the development of third-generation AEDs and novel molecules. AED development is also being assisted by global organisations, such as the Epilepsy Therapy Project (www.epilepsy.com/epilepsy_therapy_project), which aims to accelerate the development of new and better treatments.

Conclusion

The centenary of the ILAE has provided an opportunity to reassess the evolution of AEDs, which mirrors the development and regulation of drugs in general. At its outset, AED development focused primarily on controlling seizures, with less regard for tolerability and safety profile, but experience with thalidomide brought safety to the forefront and the development of all drugs, including AEDs, to a temporary standstill, resulting in an era of much tighter regulation that persists to this day. The development of the RCT and evidence-based medicine is key to the regulatory process, but RCTs have important limitations, which are increasingly acknowledged. These limitations are being addressed in terms of regulatory law (Orphan Drug Act), the type of clinical evidence gathered (e.g. registries and effectiveness studies), and the incorporation of PROs into clinical development programmes. Importantly, AED development has now evolved to the point where the primary focus has shifted from purely efficacy parameters towards individualising treatment related to PROs. It is now recognised that epilepsy can only be managed effectively by addressing each patient’s real-life needs; AED therapy can only help a patient if they are compliant with it. There have been significant improvements in the available AEDs, either through development of novel molecules or structural advances of older agents. Some aspects of the story, however, remain unchanged: there is still a need for new therapies and the search for a cure continues.

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“The times they are a-changing”
Presentation slides and video sequence

Introduction – video sequence

Tracy Glauser
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3 Lessons From The Past
4 Bromide - The Start of the Modern Journey
5 Bromide - The Start of the Modern Journey
6 Bromide - The Start of the Modern Journey
7 Bromide - Efficacy with Toxicity
8 Multiple Combinations Recommended Throughout History to Treat Seizures
9 Barbiturates - A New Class of Sedatives
10 Phenoobarbital - Observation + Serendipity
11 Phenytoin - Great Leap Forward
12 Phenytoin - Unique Pharmacokinetics
13 Phenytoin - Variety of Adverse Events
14 The Era of Look Alike AEDs
15 Carbamazepine - New Generation
16 Comparative Effectiveness Trial: VA Cooperative Study I Overall Results
17 VA Cooperative Study I: Seizure Freedom
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20 Lessons From The Past

Elinor Ben-Menachem
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