[Frontiers in Bioscience 5, e124-152, November 1, 2000]

TREATMENT OF EPILEPSY: EXISTING THERAPIES AND FUTURE DEVELOPMENTS

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1. ABSTRACT

Epilepsy is a major public health issue, not least because of the aging population in many developed nations and the known increase in the frequency of epilepsy and seizures in later life. Despite the massive scale of the problem and much research, epilepsy remains poorly understood. Despite more than 20 approved drugs in the developed nations and several non-pharmacological options, up to 30% of patients are still refractory to treatment. Despite over a century of pharmacotherapy and neuroscience research, rational design of anti-epileptic drugs (AEDs) is only now starting to yield results, because of the heterogeneity of the disease and our still limited understanding of it. Discovery and development of AEDs has been especially difficult, because of the regulatory issues of satisfactorily proving safety and efficacy, ethical constraints on placebo-controlled trial designs, the fact that seizures are typically widely spaced in time, and the fact that the person undergoing the seizure is typically in no state to remember, let alone assess, what happened. Several non-pharmacological therapies have been developed: brain surgery was first used more than a century ago; the ketogenic diet was first developed 80 years ago; and the vagus nerve stimulator was introduced recently. Pharmacotherapy remains the mainstay of treatment and is effective in most patients. AEDs can be roughly divided according to their time on the market. The first generation extends from the bromides and the barbiturates (the first of which was phenobarbital), to sodium valproate and carbamazepine. The second generation begins with felbamate and includes drugs approved from 1993 to 2000. "Next generation" drugs are still in clinical development and may reach the marketplace in the near future. Intensive research is being conducted both by pharmaceutical and biotech companies and by academic scientists and clinicians; our understanding of the condition is advancing rapidly but many challenges remain in discovering and developing better AEDs.

2. INTRODUCTION TO EPILEPSY AND RELATED DISORDERS

2.1. Incidence and prevalence

Epilepsy is a chronic brain disorder characterized by recurrent seizures that affects 1-3% of the U.S. and Canadian populations (1-3). Epilepsy occurs with a prevalence of about 0.5% and a cumulative lifetime incidence of 3% (4-6). Consequently, as many as one person in 20 will experience a seizure during his or her lifetime (2, 6). Epilepsy is thus the second leading neurological disorder, exceeded only by stroke. Approximately 50 million people worldwide suffer from the condition (3), and more than 5 five million experience at least one seizure per month; almost three-quarters of those receive no treatment for their seizures (7).

'Seizures' and 'epilepsy' are often used as if they are synonymous, and yet they are not; seizures are a symptom of epilepsy. While all epilepsies are characterized by seizures, not all seizures are epileptic. Epilepsy is the underlying neurological condition that can lead to brief disturbances in the brain's electrical functions.

Worldwide, there are considerable differences in the epidemiology of epilepsies and seizures. In Latin America, for example, two incidence studies have shown that in Chile and Ecuador, incidence rates approach double those of the industrialized nations (see 4, 5, 8-10). Clearly, this raises the question as to whether epilepsies and/or seizures could represent a marker of some endemic disease or socioeconomic condition. A high prevalence of epilepsy in several African countries is believed to be associated with parasitic infections, particularly neurocysticercosis (11-15). Other possible etiological factors include intracranial infections, perinatal brain damage, head injuries, toxic agents, and hereditary factors (see 16-20).

Many studies have concluded that the onset of epilepsy occurs at the extremes of life; children under 10 and seniors over 60 years are represented disproportionately in patients with epilepsy (see 4, 6, 21-34). This is a particularly important observation given the aging of the post second world war "Baby Boomers," especially in the U.S. The boomers are a cohort of approximately 75 million Americans born between 1946 and 1964; they will reach the age of 65 in 2010 and beyond (35-38). As a result, a large increase in the number of patients with epilepsy can be expected in the first few decades of this century. Similar demographic patterns are evident throughout the developed and even much of the developing world.

While few people die during seizures, the large number of people suffering them, high costs associated with the condition, and lifestyle limitations make epilepsy a major medical problem (39-43). Patients with epilepsy do have a mortality rate higher than that of the general population (see 44). This is partly due to what is referred to as "sudden unexpected death in epilepsy" (SUDEP; 45-51). Furthermore, patients are subject to considerable risk of physical injury during seizures (52-61).

In addition to the medical condition itself, the psychosocial consequences of poorly controlled seizures can be severe (62-65). Patients with epilepsy are generally undereducated and underemployed in relation to their level of ability (66-70). Additionally, some people still consider the condition to be associated with mental illness, and even demonic possession (71-74). Thus, many epilepsy sufferers feel stigmatized by their condition (73, 74).

2.2. Causes of epilepsy

There are believed to be over 100 underlying causes of epilepsy; however, in as many as 70% of cases no cause is ever found. Some of the known causes include brain injuries, infections that lead to brain damage (*e.g.* cerebral malaria, cysticercosis), tumors and abscesses, disturbances in blood circulation to the brain (such as stroke), certain metabolic disorders, high fevers, lead or other poisoning, and intrauterine injury (see 16-20, 75).

2.3. Types of seizure

While there are more than 40 different types of epilepsy-related seizures, they fall into 3 broad categories. The distinction depends largely on the part of the brain affected (76-78). The 3 categories are:

- generalized seizures (occurring in 46% of patients),

- partial seizures (occurring in 32% of patients), and
- partial seizures that secondarily generalize (occurring in 20% of patients) (76-78).

Generalized seizures cause loss or alteration of consciousness, involve the entire brain, and affect the whole body. They include *grand mal* (tonic-clonic) seizures, where typically the person falls down unconscious as the body stiffens (tonic) and then jerks (clonic), as the skeletal muscles alternate between relaxation and rigidity, and *petit mal* ('absence') seizures, where there is a momentary alteration of consciousness without abnormal movements. Such absence seizures are typically brief (3-30 seconds), only involve a short cessation of physical movement and/or loss of attention, and may even go unnoticed by others. Partial seizures occur when abnormal electrical activity involves only one area of the brain. There are also two kinds of partial seizure: simple seizures, where the person remains conscious; and complex seizures, in which consciousness is lost or altered. It is also possible for simple or complex partial seizures to evolve into generalized seizures. In fact, in some patients, the progression may be so quick that the partial stage is hardly noticeable. While the type and nature of seizures vary widely between individuals, they are typically stereotyped within individuals.

2.4. Types of epilepsy

Following this categorization of seizures, the International League Against Epilepsy (ILAE) classifies epilepsies as either local or generalized. Seizures from local epilepsies originate from a discrete cortical site; seizures from generalized epilepsies originate from both cerebral hemispheres (79). The ILAE also distinguishes between idiopathic and symptomatic epilepsies. Those associated with a known or suspected brain disease or lesion are referred to as symptomatic. Epilepsies that are inherited without identifiable pathology are labeled idiopathic. Idiopathic epilepsies often carry a better prognosis than symptomatic disorders.

Clinically, the distinction between partial (or secondarily generalized) seizures and primary generalized seizures is meaningful because the two types respond differently to anti-epileptic drugs (AEDs). For example, partial seizures frequently respond to carbamazepine, phenytoin, phenobarbital, primidone, or valproic acid. Similarly, valproic acid or ethosuximide control generalized seizures in many patients who experience absence attacks, and valproic acid also controls seizures in many patients with generalized seizures.

Most epileptic seizures last only a minute or two and are not life-threatening. However, repeated seizures (*status epilepticus*; 80, 81) without regaining consciousness between attacks and prolonged seizures can lead to permanent brain damage (82, 83). *Status epilepticus* is defined as a seizure that lasts at least 30 minutes or is repeated at sufficiently brief intervals to produce a continued epileptic condition lasting a total of 30 minutes without the patient fully regaining consciousness (80, 83-86).

2.5. Related disorders

2.5.1. Severe myoclonic epilepsy of infancy

Severe myoclonic epilepsy of infancy (SMEI) is a recently recognized epileptic syndrome. It is characterized by multiple febrile seizures (often prolonged), subsequent development of uncontrollable mixed-myoclonic seizures, and, eventually, by psychomotor retardation (87-90).

2.5.2. West syndrome

West syndrome is a rare form of infantile spasm occurring early in neonatal development. It is associated with hypsarrhythmias (abnormal EEG recordings) and sometimes with mental retardation. The spasms vary from violent 'jackknife' movements of the body to no more than mild twitching of the nose or mouth. There may be more than one underlying cause of West syndrome (91-94).

2.5.3. Lennox-Gastaut syndrome

Lennox-Gastaut syndrome is a childhood disorder characterized by several kinds of seizures, mental retardation, resistance to most AEDs (95), and characteristic EEG features (96-100). Felbamate was the first drug shown to be effective in treating Lennox-Gastaut syndrome in controlled trials and remains the drug-of-choice for this condition (see 101).

2.5.4. Landau-Kleffner syndrome

Landau-Kleffner syndrome is another rare childhood epilepsy, usually beginning between the ages of 3 and 8. It is characterized by severe language difficulties, particularly involving comprehension. Patients may also be unable to recognize environmental sounds, such as a ringing telephone. Whilst all Landau-Kleffner patients have abnormal temporal lobe EEGs, only about two-thirds suffer seizures. The seizures are typically responsive to AEDs (102-104).

2.5.5. Hemifacial spasm

Hemifacial spasm is characterized by chronic involuntary twitching or spasm on one side of the face, usually starting around the eye and progressing down the face. The most common cause is a blood vessel pressing against the facial nerve. The condition is sometimes treated with a neuromuscular blocker, such as botulinum toxin, or by surgery (105-107).

2.5.6. Trigeminal neuralgia

Patients suffering from trigeminal neuralgia (or *tic douloureux*) experience sudden electric shock-like pains on one side of the jaw or chin. These acute pains generally last for a few seconds at a time, and may occur for days, weeks or months, followed by a longer period that is symptom-free. The cause involves damage to the trigeminal nerve that innervates the jaw and face, and may be traced to a blood vessel pressing against the nerve or a tumor. Treatment of trigeminal neuralgia is generally with AEDs, such as carbamazepine or phenytoin. Baclofen, clonazepam or valproic acid may also be used, and surgery may be an option in some cases (108-111).

2.6. Diagnosis

Diagnosis of the first seizure is still based largely on the patient's medical history (6). Many paroxysmal events may be confused with epileptic seizures, including syncope, movement disorders, parasomnias, and psychogenic seizures (112-116). Syncope is one of the conditions most commonly confused with epileptic seizures. Studies in which volunteers were videotaped during induced syncopal events illustrate the common occurrence of repetitive clonic, myoclonic or dystonic movements on fainting. Such movements rarely persist beyond 5-10 seconds, and do not exhibit the organized progression from tonic to clonic phase typically seen in true convulsive seizures (see 112, 114-116).

Most authorities recommend that patients who experience an unprovoked seizure undergo a brain imaging study in an effort to detect underlying cerebral lesions. Such a scan would likely uncover tumors, abscesses, vascular malformations, stroke, or traumatic injury (see 117-119).

Electroencephalography (EEG) is often helpful in evaluating patients presenting with a seizure (120). Uses of EEG include detection of epileptiform activity, strengthening the putative diagnosis, identification of focal electrocerebral abnormalities (suggesting a focal structural brain lesion), and documentation of specific epileptiform patterns associated with particular epilepsy syndromes (for example, generalized spike-and-wave discharges associated with a generalized epilepsy, or focal discharges associated with a localization-related epilepsy) (120).

While many physicians choose not to prescribe anti-epileptic therapy for patients after a single seizure, the decision to treat initial seizures with medication is controversial and widely debated (see 6, 113, 121-125). Factors of concern include the likelihood of recurrent seizures, the risks of the treatment itself, and the ability of the treatment to decrease the risk of recurrent seizures. In addition, the potential psychological, social, and vocational consequences of further seizures must be considered (62-65).

2.7. Medical management of epilepsy: general principles

The goal of treating epilepsy is to control the seizures completely without causing unacceptable side effects. Pharmacotherapy remains the mainstay of epilepsy treatment (126, 127). In the last decade, several new anti-epileptic drugs have become available, and more are in development (128). The key step is the selection of an AED that is appropriate for the patient's particular type of epilepsy. A specific epilepsy syndrome diagnosis is based on the history of the patient's seizure types, neurological status, and EEG findings. In selecting an AED, the physician must also consider the patient's willingness to tolerate the adverse effects of certain treatments.

2.8. Non-pharmacological treatment of epilepsy

While pharmacotherapy remains the mainstay of epilepsy treatment (129), there are other options for some patients, including brain surgery (130-132), the recently introduced vagal nerve stimulator (133-135), and the much-debated ketogenic diet (136-138). These treatments and the uses of each will now be discussed.

2.8.1. Surgery

Brain surgery is an option in some epileptic patients, though those with progressive metabolic or neurodegenerative conditions are usually poor candidates (see 130, 132). The most common surgical procedures include anterior temporal lobe resection (6, 131, 139) and hemispherectomies (132). Such surgery frequently results in complete seizure control, though the surgery is considered successful even if the patient requires AEDs to remain seizure-free.

2.8.2. Vagus nerve stimulator

The vagus nerve stimulator is a novel, non-pharmacological treatment for epileptic patients whose seizures are uncontrolled by AEDs (140-143). The FDA approved the device in 1997. The device is no panacea and is not appropriate for all patients, but controlled studies have demonstrated efficacy (140, 144).

Effects of vagal nerve stimulation on brain activity have been known since the 1930s (see 145). In the 1950s, it was noted that vagal nerve stimulation caused desynchronization on EEGs (see 145, 146). As seizures represent synchronized electrical activity, it is reasonable to suppose that vagal stimulation might inhibit seizures. Vagal nerve stimulation was indeed shown to decrease the frequency and duration of seizures in animal models (147). In the currently approved product, a bipolar lead is wrapped around the left vagus nerve and tunneled to the infra-clavicular region, where it is connected to the signal generator. This signal generator delivers a precise pattern of stimulation to the vagus nerve. Typically, the device stimulates for 30 seconds every five minutes. In addition, the patient or a caregiver can manually activate the stimulator at the onset of a seizure, with the goal of terminating the seizure before it escalates (134, 140-142).

2.8.3. Ketogenic diet

A hotly debated non-pharmacological treatment for epilepsy is the so-called ketogenic diet, a special high-fat, low-carbohydrate diet that induces ketosis, a condition in which abnormally large amounts of ketones are produced, with a resulting anti-epileptic effect (136, 148-153). Although the diet was developed in the 1920s, it remains unknown how or why ketosis affects seizure activity, so the principles behind the therapy have been developed from years of clinical experience and assumptions, rather than from a mechanistic understanding (154). It seems to work in some animal models of epilepsy (155), but not in others (156).

3. THE CHALLENGE OF DEVELOPING ANTI-EPILEPTIC DRUGS

3.1. Discovery and development of AEDs

Because epilepsy covers a range of disease states and there are many underlying causes, coupled with the difficulty in identifying the cause in many patients and the general lack of understanding of the disease, success with target-based strategies for drug discovery has been limited.

This section discusses some aspects of research and development strategy.

In addition to scientific and clinical problems, regulatory issues have been important in the history of AED discovery and development. In the U.S., the 1938 Food Drug & Cosmetic Act (157) (enacted following the Elixir Sulfanilamide tragedy; 158) required proof of safety before a drug could be approved for marketing. The subsequent 1962 Kefauver-Harris amendments to the Act (enacted after the thalidomide tragedy; 159, 160) required proof of efficacy (161-164). These two pieces of legislation effectively stopped the introduction of new AEDs in the U.S., because of the difficulties in proving the safety and efficacy of an AED (165, 166). The regulatory requirements were rather less stringent in Europe, carbamazepine and valproate being introduced as first-line AEDs in 1963 and 1974, respectively (167). They were subsequently introduced in the U.S. in 1974 and 1978, respectively (128).

No new AED was introduced in the U.S. between 1978 and 1993. Despite that, a greater understanding of pharmacokinetics lead to a more efficient use of existing drugs and, more importantly, it was recognized that the development of drugs on an empirical basis was no longer sensible. As a result, more effort was devoted to understanding the molecular and chemical bases of epilepsy and the rational development of new AEDs (see 168).

3.2. Rational drug discovery in a perfect world

In a perfect world, four areas of knowledge are required for the effective and efficient discovery and development of new drugs. In this perfect world, drug discovery scientists would:

- know the mechanism(s) of the disease
- possess reliable preclinical animal models of the disease that are representative - or at least indicative - of human results
- have reference compounds, even clinically unusable compounds, after which new drugs can be modeled and against which new drugs can be assessed
- have objective, reliable clinical outcome measures.

Armed with this knowledge, the scientist identifies drug targets (169-171), develops *in vitro* screening assays to be used prior to animal models, designs compounds, perhaps conducts random screening using the *in vitro* assay (172, 173), identifies lead compounds with activity, makes variants and analogs of the lead compounds, and identifies those compounds that are worth carrying forward to animal studies. Promising compounds are then tested in animal models of the disease.

Efficacy is, of course, only half the story. *In vitro* and animal studies to assess *safety* (toxicity, mutagenicity), pharmacokinetics (adsorption, distribution, metabolism, and excretion), and pharmacodynamics (therapeutic profile) are also required. If the drug passes all these tests and is still considered safe and efficacious, applications are made to the appropriate regulatory authorities to begin human studies.

3.3. Etiology of epilepsy

Most forms of epilepsy are associated with synchronous firing by large numbers (hundreds of thousands) of neurons, a phenomenon that is readily detected by EEG in the form of a large 'interictal' spike (see 174-177). Such synchronous firing is thought to result from burst firing of pyramidal cells, which generate synchronous activity in post-synaptic neurons by the process of temporal summation (see 178, 179). The large-scale firing is terminated by the opening of voltage-dependent and calcium-dependent potassium channels, preventing further spread of the seizure (180).

What causes this neuronal discharge in epileptic patients? It is clear that an epileptic seizure is associated with a shift in the balance between excitation and inhibition in the brain, manifested as a large, prolonged depolarization of the neurons. The generation of dendritic potentials may be an underlying cause of this, especially the generation of calcium spikes in the dendrites.

3.3.1. Genes implicated in epilepsy

Genetic research into epilepsy is a very active area; the picture so far is that the inheritance of epilepsy is complex and polygenic, like that of diabetes and cancer (see 181-191). Given the heterogeneity of the clinical condition, it is hardly surprising that more than one gene is involved.

Despite this, some autosomal dominant idiopathic epilepsies with simple inheritance patterns have been identified and genetically characterized (24, 188, 189, 192, 193). An understanding of these epilepsies will aid in understanding the much larger number of epilepsy conditions with complex inheritance. These idiopathic conditions point to single gene defects that can cause epilepsy.

Autosomal dominant nocturnal frontal lobe epilepsy, a rare idiopathic partial epilepsy syndrome, is caused in some families by mutations in the gene encoding the alpha-4-subunit of the neuronal nicotinic acetylcholine receptor (194-204). *In vitro* studies suggest that the mutations lead to impaired function of the acetylcholine receptor, raising the possibility of cholinergic therapy for this condition (see 188, 189, 195, 201).

Benign familial neonatal convulsions is an idiopathic generalized epilepsy in newborns that follows autosomal dominant inheritance. Defects in the genes encoding two homologous voltage-gated potassium channels appear to be the cause of the condition (186, 205).

Generalized epilepsy with febrile seizures appears to result from mutations in a voltage-sensitive sodium channel (206, 207). At least in the family studied, there was a linkage to 19q13.1 and a mutation was identified in the gene encoding the voltage-gated sodium channel beta-1-subunit. The mutation lead to a change in a conserved cysteine residue that disrupted a disulfide bridge, apparently leading to loss of function (206). Other research has suggested an additional locus on chromosome 2 (208).

In several other conditions, genetic linkages have been established, again suggesting single gene defects,

though the specific genes have yet to be characterized. Familial partial epilepsy syndrome with variable foci (FPEVF) has been linked to a 3.8cM region on chromosome 22q11-q12, between markers D22S1144 and D22S685. The syndrome is inherited in an autosomal dominant manner with incomplete penetrance (209). In juvenile myoclonic epilepsy, there is evidence that a locus is located on chromosome 15, in addition to a previously characterized one on chromosome 6 (see 181, 210-212). Interestingly, the GABAB receptor gene is located near the chromosome 6 locus (213-215), and the gene encoding the alpha-7-subunit of the acetylcholine receptor is near the chromosome 15 locus (210).

Thus, at least three autosomal-dominant idiopathic epilepsies are channelopathies and result from mutations in genes encoding ion channels. Benign familial neonatal convulsions result from mutations affecting voltage-sensitive potassium channels (216, 217). Nocturnal frontal lobe epilepsy results from mutations affecting a central nicotinic acetylcholine receptor (216). Generalized epilepsy with febrile seizures result from mutations affecting a voltage-sensitive sodium channel (206, 207). Recently published research suggests that idiopathic generalized epilepsy may result from mutations in gene encoding the calcium channel beta-4-subunit, CACNB4 (218).

At least one idiopathic epilepsy, however, is not a channelopathy. Unverricht-Lundborg disease - an autosomal recessive disorder - is caused by defects in the cystatin B gene (also known as stefin B), leading to the absence, or greatly reduced level, of the gene product. How the absence of this gene product leads to epilepsy is much less clear. The cystatins are a family of cysteine protease inhibitors (219). Unverricht-Lundborg disease is a clinically recognizable form of progressive myoclonic epilepsy. There was no biochemical marker for the disease, but a positional cloning strategy lead to characterization of the gene responsible. In a seminal paper on the condition, two mutations in the cystatin B gene were found in patients with Unverricht-Lundborg disease (220). Since then, an unstable expansion of a 12-base-pair mini-satellite repeat sequence in the promoter region of the gene has been found to be the most common defect (221-223). A series of other mutations has since been characterized (224-228).

3.3.2. Therapeutic strategies suggested by these mechanisms

The most important inhibitory neurotransmitter in the brain is gamma-aminobutyric acid (GABA) (229, 230). It has long been known that downgrading the brain's GABAergic system (for example, with the GABAA antagonist bicuculline or with penicillin) causes epileptiform activity in humans and animals. Many currently available AEDs interfere with GABA neurotransmission in some way (231).

More recently, drugs have been used successful to treat epilepsy by interfering with the excitatory amino acid system. Agonists at all three subclasses of excitatory amino acid receptor (*N*-methyl-D-glutamic acid, NMDA; alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, AMPA; and kainate) cause epileptiform activity. Felbamate is an example of an AED that appears to inhibit NMDA transmission, although it also interacts with the GABA system (101).

Direct or indirect actions of AEDs on ion channels may contribute to their anti-epileptic activity. Felbamate and zonisamide inhibit both calcium and sodium channels. NMDA toxicity in particular is associated with influx of calcium to reach potentially cytotoxic concentrations, and so blocking calcium channels also appears to be a rational approach to the therapy of epilepsy.

3.4. Animal models of epilepsy

The drug discovery scientist needs reliable preclinical animal models of the disease that are representative- or at least indicative - of human results. The availability of animal models has shaped the history of AED discovery and development.

The earliest AEDs resulted from what was hardly a model system of rational drug design! The use of bromide salts and phenobarbital to treat epilepsy was entirely empiric; neither was intended to treat the condition. Bromide salts were being used to inhibit masturbation and sexual behavior (see 128, 216, 232-234). Phenobarbital was a sedative. Both were given to epileptic patients and happened to show some degree of efficacy.

The development of animal models of epilepsy lead to a rather more systematic way of evaluating potential AEDs (235-237). It had been known since the 1880s that electrical stimulation of animals could produce replicable seizures. Later, it was found that certain chemicals, including picrotoxin, bicuculline, strychnine, and pentylenetetrazol, could induce experimental seizures.

Animal seizure models were first used successfully by Merritt and Putnam in the late 1930s. They screened compounds using electrically induced seizures in cats and discovered the anti-convulsant properties of phenytoin (diphenylhydantoin; 238-243).

Better models were to follow. Swinyard and colleagues differentiated between threshold and spread in seizures (see 244). Some AEDs raise the seizure threshold; drugs that operate in this way (such as ethosuximide) are typically effective against absence seizures. This can be assessed using pentylenetetrazol-induced seizures in animals (245). Other drugs limit seizure spread. Drugs that operate in this way (such as phenytoin) are typically effective against partial and generalized tonic-clonic seizures. This can be assessed using the maximal electroshock (MES) animal model (245).

The kindling model of epilepsy in animals resembles psychomotor epilepsy in humans, in which patients experience both illusory phenomena and complex motor actions. The test animal is 'kindled' by repeated high-frequency electrical stimulation to a part of the limbic system (*e.g.* the amygdala) (246-248). Sensitivity of the neuronal circuits increases during the kindling process, until seizures can be produced in response to relatively small stimulation. This phenomenon suggests that epilepsy in humans may be caused by relatively brief electrical events that

chronically alter the properties of the neuronal circuits. Treatment with the non-specific central nervous system (CNS) convulsant pentylenetetrazol (PTZ) can also be used to produce a kindling model of epilepsy, as can treatment with picrotoxin (249).

However, while animal models did advance AED research and essentially lead to the all of the first generation drugs except bromides and phenobarbital, they also created a problem in that they were used so extensively - in fact, almost exclusively. If your screen is the same animal model, it is likely that you will select only closely related drugs, or at least drugs that act in the same way (inhibiting the same seizures in the same way in the same animal model).

Even with the "new generation" of AEDs, despite the benefit of 30 years of neuroscience research, most AEDs were found by screening (*i.e.*, chance, as opposed to rational design), or else they were variations of existing drugs. In fact, to date the only truly rationally designed AEDs are the GABA analogs vigabatrin, tiagabine, gabapentin, and pregabalin, which followed from the "GABA hypothesis" of epilepsy (229, 230).

Today, several animal models of epilepsy are used in drug discovery (247, 250-257). However, these animal models do not necessarily correlate with epilepsy in humans. More than 25 genes have now been identified in mice that lead to epileptic seizures when mutated (258, 259). Many of these genes have been characterized, and they encode voltage- and ligand-gated ion channels. For example, the "tottering" mouse has mutations in the gene encoding the high voltage-activated alpha-1a-calcium channel subunit, and the lethargic mouse has mutations in the beta-4-calcium channel subunit gene (218, 258, 260, 261). Together with results from the human idiopathic epilepsies discussed above, these animal models and the ability to make transgenic animals bearing the human mutations (262) should enable better models to be developed in the near future.

3.5. Known reference compounds

The drug discovery scientist also needs known reference compounds, even those that are clinically unusable, after which new drugs can be modeled and against which new drugs can be tested. As outlined in this review, this is no longer a problem; there is a long history of AEDs, going back to the bromides. There are, of course, many more molecules that have failed at some stage in development. Successes and failures can provide the scientist with insights.

3.6. Objective, reliable clinical outcomes

The drug discovery scientist also needs objective, reliable clinical outcomes to assess drugs. This is a particular problem with epilepsy. What is needed - ideally - is a clinical measure that does not depend on the seizure patient (or their caregiver) remembering or recording what happened.

There is currently no such measure in epilepsy; to assess efficacy, typically careful documentation of changes in ictal activity is used, determined by seizure counts based on patient recall, ideally direct clinical observation, and (at least for absence seizures) EEG monitoring. Assessment of seizure severity is another measure. The choice depends on the design of the trial. In short-term trials, parameters such as time to the n^{th} seizure after randomization have been used as an index of anti-epileptic efficacy, but the clinical relevance of such measures is debatable. In add-on trials, changes in seizure counts and the proportion of patients achieving 50%, 75%, and 100% reduction in seizure frequency can be used. For long-term monotherapy trials in newly diagnosed patients, the proportion of patients achieving prolonged remission (1 year or longer) usually represents the most clinically meaningful efficacy outcome (263). Retention of patients on a treatment can also be a useful measure, although it is a composite endpoint, dependent on both efficacy and tolerability.

3.7. Other challenges in clinical development

Ethical considerations are a challenge in any clinical trial of a putative AED, especially because of the placebo control (264, 265). The use of placebo-only treatment in epileptic patients is discouraged, not just because of the distress associated with seizures, but because severe seizures can result in injury, permanent brain damage, and, in the case of *status epilepticus*, even death (266-270). There is a further problem in that seizures and *status epilepticus* can be induced by withdrawing or altering the dose of an existing AED (271-275), making it difficult to wean a patient from his or her existing AED regimen in order to test a new drug. Quite separately, the placebo effect is well known in epilepsy studies, especially where parents or guardians monitor and report on the patients' seizures, as is typically the case (they are well-meaning, but not very objective) (276).

The now conventional approach to clinical trials of new AEDs is to use concomitant treatment with an established drug and the experimental drug, compared with established drug plus placebo (264, 269, 277-279). While this solves the ethical problem, it creates inevitable difficulties in interpreting results, because of possible drug interactions. Plasma levels of all drugs need to be closely monitored, as different classes of AED can alter each other's metabolism and drastically affect plasma levels (280-282). Despite these obvious problems, most of the current AEDs were tested in this way, beginning with the pioneering work of Rodin and colleagues on carbamazepine (283).

Testing a new drug in this way is not necessarily a bad thing. Polytherapy, the concomitant use of two or more drugs to treat one disease, is indeed common practice in epilepsy (284-288). Many AEDs are developed with the intention of being used in conjunction with existing drugs, and thus clinical trials taking this into account are quite appropriate.

The idea of ethically acceptable monotherapy trial design has not been forgotten (279, 289-294). In recent years, some monotherapy trials have been conducted, in restricted circumstances (264). For example, felbamate was studied in placebo-controlled monotherapy trials in patients following pre-surgical electroencephalographic and video monitoring (295-297). In these trials, the patients underwent intensive neurodiagnostic monitoring after partial or complete withdrawal from their prior AEDs. In the hospital setting, a true placebo-controlled study is possible; seizures are closely monitored and not allowed to continue or progress to a potentially brain-damaging situation. Additionally, the

monitoring of seizures is likely to be more objective than it typically is when parents, guardians, or others are involved (266).

AED trials are associated with relatively high drop-out rates (264). One reason for this is the rarity of seizures; dosing has to continue for several weeks, which then leads to poor compliance and inaccurate reporting of events by patients and caregivers. Additionally, the disturbance of a patient's established drug regime may result in seizures serious enough to force discontinuation of the test drug (or placebo) (271, 298). In the treatment of most epileptics, care must be taken to achieve a suitable dose (balancing toxic effects against seizure prevention), and this individual approach to treatment further complicates a clinical trial.

One final problem is that a large proportion of patients entering a clinical trial represent 'atypical' epileptics who have responded poorly to existing drugs. In some cases then, a clinical trial may underestimate the true efficacy of a new AED.

3.8. Toxicity issues

Toxicity data for AEDs are often difficult to interpret, because many patients will be taking more than one drug. Plasma levels of one drug may be affected by the presence of another (280-282), and so toxicity should be correlated with plasma level and not dose. Some investigators have queried whether even that is valuable (299).

Neurological adverse effects of AEDs present a particular problem. Not surprisingly with CNS-acting drugs, serious neurological problems may occur. In many of the patients, however, the underlying epilepsy is itself a very serious neurological condition, and ascribing a particular neurological adverse effect to the AED may be unwise or impossible.

Several studies have shown that different classes of AED seem to be associated with teratological effects when taken during pregnancy (300-303). The individual drugs with the highest incidences were primidone, valproate, phenytoin, carbamazepine, and phenobarbital. Why these distinct classes of drug should all be associated with teratological effects is both intriguing and worrying. The incidence of malformations increased in polytherapy, and certain combinations (e.g. valproate plus carbamazepine, or primidone plus phenytoin plus phenobarbital) were associated with significantly greater susceptibility.

Another problem is that some AEDs may exacerbate seizures in certain patients (304-307). This phenomenon is poorly understood (305).

3.9. Conclusion

Discovery and development of new AEDs presents special challenges to the pharmaceutical industry; the researcher does not live in the perfect world outlined above. Rational, target-based research is hampered by our still limited understanding and the heterogeneity of epilepsy. While animal models are now available and have been important in the development of AEDs, they are only models and may not correlate well with the many forms of human epilepsy. Additionally, clinical trials are inevitably more complex than with most drugs, and have to be conducted with extreme care. Again, because of the heterogeneity of the condition, patient selection criteria add another variable into any clinical trial.

4. PHARMACOTHERAPY OF EPILEPSY

Epilepsy has been recognized for at least 3000 years; the earliest recorded account is in an Akkadian (Babylonian) text known as the Sakikku, dating from around 1050 BC (71, 308, 309). Since then, there have been many attempts to control epilepsy. The evolution of effective drug treatment for epilepsy has been a gradual and erratic process. There have been both scientific and regulatory reasons for this over the last decades.

Modern pharmacotherapy of epilepsy goes back as far as the introduction of phenobarbital in 1912 in the U.S. (see 310), and back to the 1860s if the use of bromide salts is included (128, 216, 234). Phenytoin (Dilantin) was introduced in 1938, and is still widely used (240). Despite this long history, successful pharmacotherapy remains a major challenge to this day, the disease being chronic and often life-long.

There are now more than 20 different drugs approved for the treatment of epilepsy in the developed nations, but the currently available drugs are far from perfect. Up to 30% of patients with epilepsy remain refractory to medical management with current AEDs (6, 311-316). Seizure control in many of these patients is achieved by polytherapy, and at the expense of serious side effects, complications from drug interactions (317), and a resulting decrease in quality of life.

The AED market can be crudely categorized according to the length of time drugs have been on the market: first-generation AEDs, new-generation AEDs, and what we will term the "next generation" (*i.e.* those drugs in development but not yet approved or marketed). We will now discuss the currently marketed AEDs and those likely to be approved soon.

4.1. First generation drugs

4.1.1. Bromide salts

The introduction of bromide in 1857 by Sir Charles Locock for the treatment of seizures can be considered the start of modern anti-epileptic pharmacotherapy (see 128, 216, 234). Despite its use for well over a century, the mechanism of action is still poorly understood, but presumably involves blockade of chloride transport. Bromide is also an inhibitor of carbonic anhydrase, a key enzyme in active chloride transport. The main problem with bromide therapy was always the very narrow therapeutic index (232-234). CNS side effects are the most common and most severe, including dizziness, emotional changes, and frequently psychosis. The very long half-life of elimination (approximately 12 days) contributes to the danger of chronic toxicity. Bromides also cause dermatological side effects (232-234).

4.1.2. Barbiturates

4.1.2.1. Phenobarbital

Several barbiturates are effective in treating epileptic disorders (318, 319). Phenobarbital (5-ethyl-5-phenyl barbituric acid; Figure 1) was the first

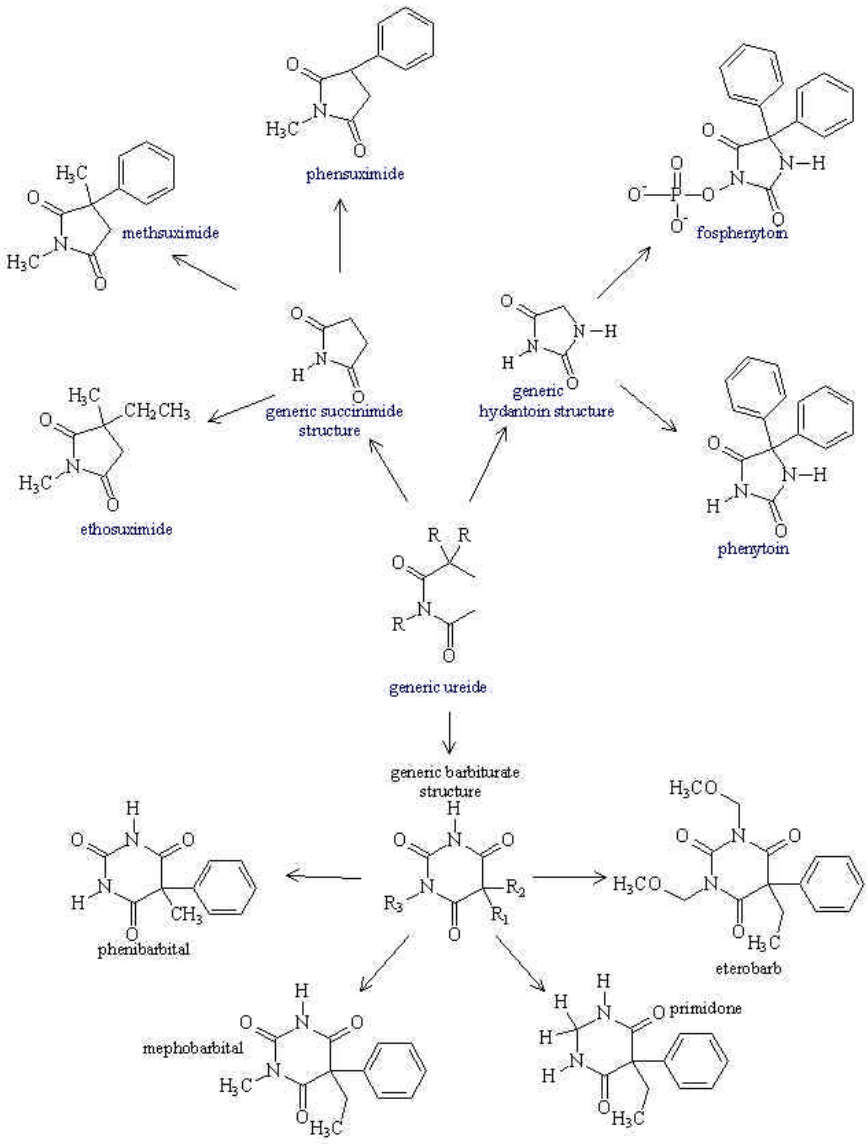


Figure 1. AEDs structurally related to phenobarbital.

AED of real clinical value. It was introduced in 1911 as a sedative and hypnotic, but was soon found to be useful as an anti-convulsant, though it was - at the time - erroneously believed that the anti-epileptic effect was simply a consequence of sedation. It has been in continuous use as a sedative and anticonvulsant ever since; it remains one of the best available drugs for the treatment of certain seizure types, especially *grand mal* and focal seizures (310). Following its development, more than 50 other barbituric acid analogs and derivatives have been and are still being developed and tested (see 318-324; Figure 1).

4.1.2.2. Mephobarbital

Mephobarbital (methylphenobarbital; Figure 1) was introduced in the U.S. in 1935; it is less sedating than phenobarbital. Its anticonvulsant action is due to its slow conversion in the liver to phenobarbital; it remains unclear whether mephobarbital itself contributes to the pharmacological effect. Some neurologists suggested that mephobarbital caused fewer behavioral side effects than phenobarbital in children, although this has been disputed (see 325).

4.1.2.3. Eterobarb

Eterobarb (N,N' dimethoxymethyl phenobarbital (DMMP); 5-ethyl-1,3-bis(methoxymethyl)-5-phenyl-barbituric acid; Zipnotic; Figure 1) is also structurally related to phenobarbital; it is an alkoxymethyl derivative. Eterobarb is reportedly equipotent with phenobarbital in preventing seizures, and causes less sedation. It shows efficacy in treating *grand mal*, psychomotor, or focal epilepsy (326-330), and is approved in some countries, but other clinical trials were abandoned and development was stopped.

4.1.3. Primidone

Primidone (5-ethyldihydro-5-phenyl-4,6(1H,5H)-pyrimidinedione; 2-deoxyphenobarbital; Figure 1) is also a

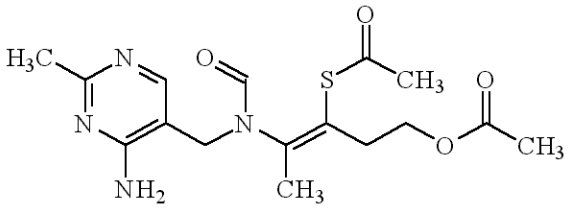


Figure 2. Structure of acetazolamide.

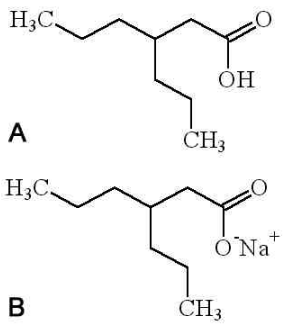


Figure 3. Structure of A: valproic acid and B: sodium valproate.

structural analog of phenobarbital, in which the carbonyl group at the 2 position is replaced with a methylene group. This drug seems better tolerated in some patients than phenobarbital. Primidone is slowly metabolized in the liver and is excreted in urine as phenylethylmalonamide (PEMA), phenobarbital, and p-hydroxyphenobarbital (331). Primidone's pattern of activity is similar to that of phenytoin, though its action is at least partly due to its metabolic conversion to phenobarbital and PEMA, both of which have anticonvulsant activity (332-334).

4.1.4. Phenytoin

Phenytoin (5,5-diphenylhydantoin; Figure 1) is also structurally related to phenobarbital (243, 335, 336). Phenytoin was one of the first AEDs to be tested in animal models of epilepsy (238, 240-243). It was first introduced for the treatment of epilepsy in the U.S. in 1938 (128, 239, 337), and remains one of the most commonly prescribed anti-epileptics in the U.S. It is believed to act by blocking voltage-sensitive sodium channels (336). Its anti-convulsant effect is approximately equal to that of phenobarbital, but it does not cause sedation. It is effective in treating *grand mal*, focal sensory and motor, and psychomotor seizures. In parenteral form, the drug is also used to treat *status epilepticus.*

4.1.5. Fosphenytoin

Fosphenytoin (Cerebyx) is a water-soluble parenteral phenytoin prodrug (a disodium phosphate ester; Figure 1), and has several advantages over phenytoin. It is better tolerated, and can be administered intravenously or intramuscularly (338-345). Uses for fosphenytoin include intravenous administration for the treatment of *status epilepticus* (341), and treatment of patients who are unable to take oral medication or in whom a more rapid attainment of a therapeutic drug level is required. Fosphenytoin has a short half-life (8-15 minutes) and is converted to phenytoin. Being water-soluble, it does not require a propylene glycol solvent and, as a result, causes less hypotension, bradycardia, thrombophlebitis, and fewer local skin reactions than does intravenous phenytoin (340, 341, 343). Fosphenytoin has been used for some years in the U.S. and has recently been licensed in the U.K. (341).

4.1.6. Ethosuximide

Subsequently, further derivatives and analogs of phenytoin and phenobarbital were synthesized by manipulating the cyclic ureide moiety from which both are derived. These include the hydantoins and diones, as well as the succinimides methsuximide (346; Figure 1) and phensuximide (Figure 1). Ethosuximide (2-ethyl-2-methylsuccinimide; Figure 1) is a T-type calcium channel blocker, used in treating absence seizures. It was introduced in 1958. It is absorbed from the gastrointestinal tract and extensively hydroxylated in the liver to an inactive metabolite (347). Ethosuximide is generally free of serious adverse effects, and continues to be used to this day.

4.1.7. Acetazolamide

Acetazolamide (Diamox; Figure 2) is an unsubstituted sulfonamide that inhibits carbonic anhydrase. It was approved for the treatment of epilepsy in 1953 (348). It non-competitively inhibits brain carbonic anhydrase, leading to accumulation of carbon dioxide that seems to decrease the spread of seizure activity and increase the seizure threshold (348). In recent years it has fallen from favor somewhat, but does have a broad spectrum of anti-epileptic activity and a long track record of generally safe and successful use, especially in patients with refractory seizures.

4.1.8. Sodium valproate / valproic acid

Although valproic acid (dipropyl acetic acid or 2-propylvaleric acid; VPA; Figure 3) was first prepared by Burton in 1882 (349), its anti-epileptic properties were not appreciated until 80 years later by Meunier (see 350). Valproic acid is chemically distinct from other AEDs. It was developed as an anti-epileptic drug in Europe during the 1960s and was subsequently introduced in the U.S. Valproate is a major broad-spectrum anti-epileptic drug effective against many different types of epileptic seizures, especially in simple and complex absence seizures.

The incidence of toxicity associated with the clinical use of valproate is generally low, but two rare side effects, idiosyncratic fatal hepatotoxicity and teratogenicity (351, 352), necessitate caution. Pancreatitis is also a rare though serious adverse effect (353). Animal studies indicate that the mechanisms leading to hepatotoxicity and teratogenicity are distinct and differ from the mechanisms of the anticonvulsant action of valproate.

As a result of its wide spectrum of anticonvulsant activity against different seizure types, it is believed that valproate acts through several mechanisms. There is evidence that valproate up-regulates GABA synthesis and release, potentiating GABAergic function in some brain regions. Valproate also appears to alter dopaminergic and serotonergic function. One disadvantage of valproate is its short half-life, making steady plasma levels of the drug

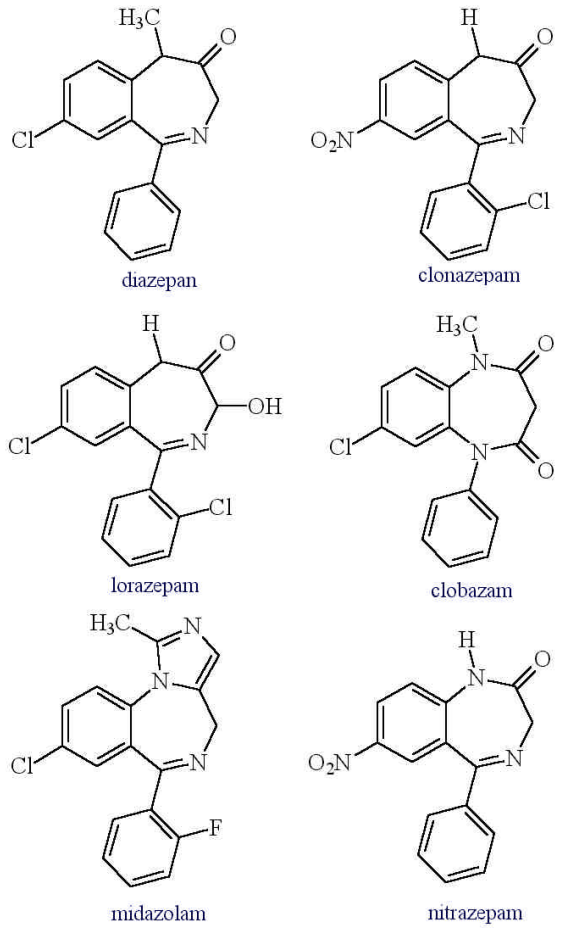


Figure 4. Benzodiazepines used as AEDs.

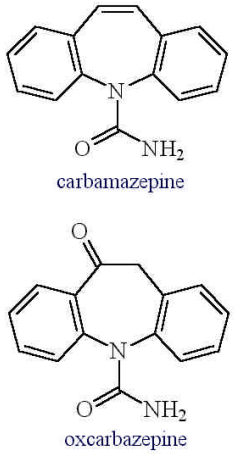


Figure 5. Structures of carbamazepine and oxcarbazepine.

difficult to achieve, although the recent introduction of sustained release formulations has reduced this problem. More recently, divalproex sodium, a stable coordination compound of valproic acid and sodium valproate in a 1:1 molar ratio, has been developed. It is believed to act essentially as a prodrug, dissociating into valproate in the GI tract.

4.1.9. Benzodiazepines

Benzodiazepines have long been used to treat convulsive seizures, though some are not suitable for routine use because tolerance develops rapidly; they are also typically sedatives (354, 355). They are very useful in emergencies: diazepam (Figure 4) and lorazepam (Figure 4) remain first-line drugs for the control of *status epilepticus* (85, 356, 357). Other benzodiazepines in use as AEDs include clonazepam (358; Figure 4), clobazam (359; Figure 4), nitrazepam (360; Figure 4), and midazolam (361-364; Figure 4). It is believed that the benzodiazepines act as enhancers of GABA receptor binding, which causes increased stability of the cell membrane and a reduction in the synaptic response to excitatory stimulation (354). Thus, benzodiazepines facilitate the actions of GABA in the brain.

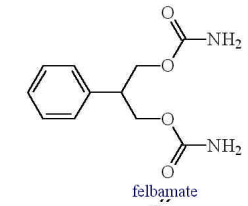
4.1.10. Carbamazepine

Carbamazepine (5H-dibenz[b,f]azepine carboxamide) is an iminostilbene derivative (Figure 5), structurally related to the tricyclic antidepressants, such as amitriptyline and imipramine. The anticonvulsant activity of carbamazepine appears to involve limitation of seizure propagation, by reducing post-tetanic potentiation of synaptic transmission. Carbamazepine was first synthesized in 1960 by Schindler, who had a decade earlier patented the structurally closely related imipramine. Carbamazepine was later found to have anti-epileptic properties (365). It was introduced in 1962 for the treatment of trigeminal neuralgia. It has some structural similarity to phenytoin; its anticonvulsant activity has been associated with the carbamoyl group.

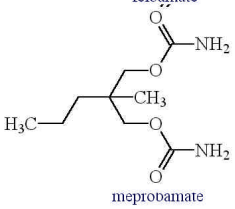
In recent years, extended release carbamazepine formulations have been developed, allowing twice daily dosing. These formulations provide increased convenience, better patient compliance, and more constant serum levels of the drug, reducing peak level toxicity problems and trough level seizures.

The most frequently observed adverse reactions are CNS-related and dose-dependent, including dizziness, drowsiness, ataxia, nystagmus, blurred vision, slurred speech, confusion, headache, and nausea and vomiting. Carbamazepine can also produce more serious adverse effects, including bone marrow suppression (leading to aplastic anemia), granulocytopenia and/or thrombocytopenia, and liver damage (366-372). Carbamazepine is metabolized in the liver to form carbamazepine-10,11-epoxide, which also has anti-convulsant properties. However, the epoxide is reactive and is believed to be responsible for the blood dyscrasias.

Unlike phenytoin, there is a linear relationship between the dose of the drug and its plasma concentration, so carbamazepine has a wider margin of safety, and measurement of the plasma levels is a useful guide to optimum dosage. The anticonvulsant action of the drug appears to be mediated by a selective binding to voltage-dependent sodium channels. After such binding the sodium channels become stabilized and inactive, so further sodium movement is inhibited. However, how such modulation of sodium channels affects epileptic seizures remains unclear.



felbamate



meprobamate

4.1.11. Oxcarbazepine

Oxcarbazepine (10,11-dihydro-10-oxo-5*H*-dibenz(b,f)azepine-5-carboxamide; Figure 5) reportedly has equivalent efficacy to its structural analog carbamazepine, its tolerability is at least equal to that of other AEDs (373, 374), and it is less toxic than carbamazepine (375). It can be considered a prodrug, being rapidly metabolized to a hydroxyl derivative. Although it may cause fewer interactions with other AEDs, it may induce metabolism of oral contraceptives and hence reduce their effectiveness (376, 377). It is thought to act as a sodium channel antagonist (373). Oxcarbazepine has been marketed in many countries since 1990, and has more than 125,000 patient years of experience. A new formulation (Trileptal) has recently been approved by the FDA for monotherapy or for use in conjunctive therapy of partial seizures (with or without secondary generalization).

4.2. New generation drugs

Until the introduction of felbamate in 1993, no new AED had been launched in the U.S. for 15 years. The "new generation" includes felbamate (Felbatol) and gabapentin (Neurontin), both approved in 1993, lamotrigine (Lamictal), approved in 1994, topiramate (Topamax), approved in 1996, and tiagabine (Gabitril), approved in 1997 (378).

4.2.1. Felbamate

Felbamate (2-phenyl-1,3-propanediol dicarbamate; Felbatol; Figure 6) was first synthesized in 1954 (379), although it did not enter serious clinical development until 1982 (380). Felbamate is chemically related to meprobamate (381, 382), an anxiolytic drug (383), both being propanediol dicarbamates (Figure 6). Meprobamate also has anti-epileptic properties in animal models, and in light of the drug's long history of safe use it has been suggested that it be reconsidered as a potential AED (384). The exact details of felbamate's mechanisms of action remain unclear. The drug appears to have two actions in that it enhances the GABAergic system and inhibits excitatory amino acid responses.

Rho and coworkers studied the effect of meprobamate and felbamate at the $GABA_A$ receptor using whole-cell voltage-clamp recordings from cultured rat hippocampal neurons (383). Meprobamate increased GABA-evoked responses and, at higher concentrations, had an independent channel-blocking effect. In fact, meprobamate caused greater potentiation than felbamate at the same concentration. Both drugs prolonged the mean burst duration of GABA-activated currents in excised outside-out membrane patches. Rho and coworkers concluded that both drugs had barbiturate-like actions at $GABA_A$ receptors, and that meprobamate had greater activity and could directly activate the receptor, whereas felbamate could not (383).

In animal models, felbamate blocks PTZ-, MES-, and picrotoxin-induced seizures, but has little effect on strychnine- or bicuculline-induced seizures (383, 385, 386). This spectrum of action is consistent with felbamate acting in a barbiturate-like manner to potentiate $GABA_A$ receptor responses (383, 385, 386).

Felbamate was widely proclaimed as the first new AED in many years when it received FDA approval in 1993 for monotherapy in adults with partial seizures and as an adjunctive therapy in children suffering from Lennox-Gastaut syndrome (383, 385, 387, 388). Within the first year on the U.S. market, as many as 120,000 patients took the drug, and it was judged efficacious in many patients whose epilepsy had been refractory to other AEDs (383, 387, 389). Felbamate has also been used to treat infantile spasms or West syndrome (390-392), hemifacial spasm (393), acquired epileptic aphasia (394), and trigeminal neuralgia (395).

However, because of potentially fatal adverse effects of hepatic failure (396), aplastic anemia (397-401), and other blood dyscrasias (402) associated with the use of felbamate during early 1994, a "black-box" warning was added to the drug's package insert. As a result, use of felbamate is now restricted to patients with severe epilepsy refractory to other therapies (403, 404). Felbamate continues to be used in many patients, though not as a first-line treatment.

Felbamate was the first drug shown to be effective in controlled studies in Lennox-Gastaut syndrome. The Felbamate Study Group reported a double-blind, placebo-controlled add-on trial of felbamate in 73 patients suffering from Lennox-Gastaut syndrome (278). Patients receiving felbamate experienced a 34% decrease in the frequency of atonic seizures and a 19% decrease in total seizure frequency. Additionally, a trial by Avanzini and coworkers included 80 patients suffering from Lennox-Gastaut syndrome, of whom 60% experienced a >50% reduction in seizure frequency. Of these, 6% were seizure-free during treatment (405).

4.2.2. Gabapentin

Gabapentin (Neurontin) was approved in the U.S. in 1993, as an adjunctive therapy in patients 12 years of age or older with localization-related epilepsy. Gabapentin is a 3-alkylated (lipophilic) GABA analog (Figure 7). Although structurally related to GABA (Figure 7), gabapentin does not seem to interact with any known GABA recognition site, nor with a variety of other ligand-binding sites (including excitatory amino acid receptors) (406, 407). *In vivo* autoradiographical studies suggest that there is a binding site for gabapentin in the brain, although its function is unclear.

The efficacy and safety of gabapentin as a monotherapy for treatment of partial onset seizures was evaluated in three large multicenter, double-blind, parallel-group, dose-controlled trials (408, 409). These three trials provided good evidence for the efficacy and safety of gabapentin monotherapy for the treatment of partial-onset seizures. In one trial, outpatients with refractory partial epilepsy (n=275) maintained on stable doses of AEDs were switched to gabapentin monotherapy. Patients exited the study if their seizure frequency increased; only 3% of patients did withdraw because of this (see 408). In another trial, hospitalized patients (n=82) were weaned off their prior AEDs and were assigned to gabapentin monotherapy at 300 mg/day or 3600 mg/day. Patients remained in the trial for a maximum of 8 days, unless they satisfied various exit criteria. Time to exit was significantly longer in patients receiving 3600mg than those receiving 300mg gabapentin (see 408). In a further study, patients with

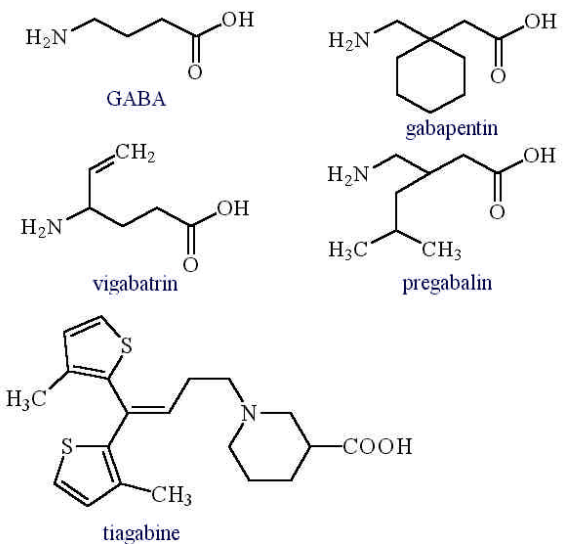


Figure 7. Structures of GABA and of AEDs intended to affect GABA neurotransmission.

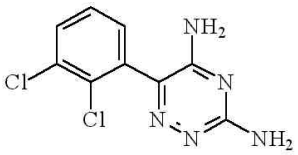


Figure 8. Structure of lamotrigine.

recently diagnosed partial seizures (n=292) received gabapentin (300, 900, or 1800 mg/day) or carbamazepine (600 mg/day). Patients remained in the trial for up to 6 months or until they experienced an exit event. Mean time to exit was significantly longer for patients who received gabapentin at 900 mg/day or 1800 mg/day than those who received 300 mg/day (see 408).

4.2.3. Lamotrigine

Lamotrigine (Lamictal) is a phenyltriazine anticonvulsant agent (Figure 8); the drug is structurally unrelated to any currently available AED. Lamotrigine was approved in 1994 as an adjunctive treatment for localization-related epilepsy in adults. It exhibits a broad spectrum of anti-epileptic activity (410, 411); in animal models, its spectrum is similar to those of phenytoin and carbamazepine. The agent is useful in treating patients with localization-related or generalized epilepsies (412). Its mechanism of action remains unclear, but it appears that the drug may stabilize neuronal membranes by blocking voltage-sensitive sodium channels, thereby inhibiting release of excitatory amino acid neurotransmitters (412).

4.2.4. Topiramate

Topiramate (Topamax), a sulfamate-substituted derivative of D-fructose (Figure 9), is structurally unrelated to any other currently available anticonvulsant. It was approved in the U.S. in 1997, and is indicated for use as an adjunctive therapy in adults with localization-related epilepsy. It also has efficacy in some generalized epilepsies. Topiramate is quickly absorbed, has linear pharmacokinetics, minimal protein binding, and a long half-life (413-415). Some analyses of data from randomized controlled studies suggest topiramate may be the most potent of the new generation of AEDs (416). Its mechanism of action remains unclear, but seems to involve blockade of voltage-sensitive sodium channels, increased GABA activity, and glutamate blockade via non-NMDA receptors. Preliminary clinical research has suggested that topiramate may also be useful in treating mania in patients with bipolar disorder, post-traumatic stress disorder, and frequent migraine and chronic daily headaches.

4.2.5. Tiagabine

Tiagabine is one of few rationally designed AEDs in that it was designed based on the GABAergic theory of epilepsy (Figure 7). Tiagabine is a potent and selective inhibitor of the synaptosomal uptake of GABA, and it appears to lack benzodiazepine-like sedative effects. The drug is structurally related to nipecotic acid, but crosses the blood-brain barrier to a greater degree, being much more lipophilic. Tiagabine was approved in the U.S. in 1997 as an adjunctive therapy for patients 12 years of age or older with localization-related epilepsy. The inhibition of GABA reuptake allows increased binding of GABA to post-synaptic receptors, and the enhanced GABA activity may prevent propagation of seizure impulses (417). However, it is unclear whether inhibiting GABA reuptake is the drug's only effect (418, 419).

4.2.6. Vigabatrin

Vigabatrin (gamma-vinyl-GABA; Figure 7) is a close structural analog of GABA and operates as an enzyme-activated, irreversible inhibitor of GABA transaminase, an enzyme that degrades GABA (420). Vigabatrin crosses the blood-brain barrier. Once bound to GABA transaminase, the drug is converted into a reactive intermediate that irreversibly inhibits the enzyme, resulting in dose-dependently increased levels of GABA in the brain (420, 421). The product is a racemate, but only the S(+)-enantiomer is pharmacologically active (422). Nuclear magnetic resonance spectroscopy has demonstrated 2-3 fold increases in GABA concentration in the brains of adult epileptic patients treated with standard doses of vigabatrin (423). Increased GABA concentrations are not only neuroprotective in theory, but extensive experimental evidence has shown that they do protect the brain against chemically and electrically induced convulsions (421).

The clinical development of vigabatrin was delayed in the U.S. by findings of microvacuolation in the white matter of brains in rodents and dogs. However, extensive monitoring in humans through autopsy, MRI, and cognitive function tests has confirmed that this does not occur in humans (424). The FDA's external advisory committee has recommended vigabatrin (Sabril) for approval as an adjunctive therapy, but final action is still pending. The drug has been extensively used in more than 45 countries.

4.2.7. Zonisamide

Zonisamide (1-(1,2-benzoxazol-3-yl) methane-sulfonamide; Zonegran; Excegran; Figure 10) is a 1,2-benzisoxazole derivative and the first agent of this class to be developed as an AED. Zonisamide was launched in Japan as early as 1989. In various animal models, zonisamide has considerable activity. It appears to block

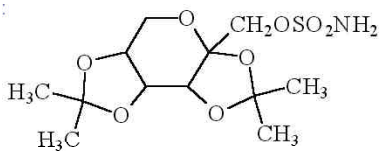


Figure 9. Structure of topiramate.

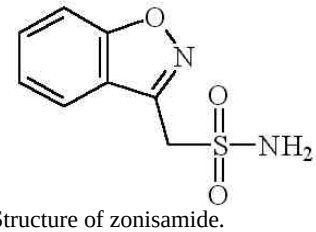


Figure 10. Structure of zonisamide.

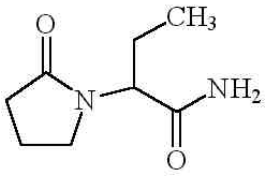


Figure 11. Structure of levetiracetam.

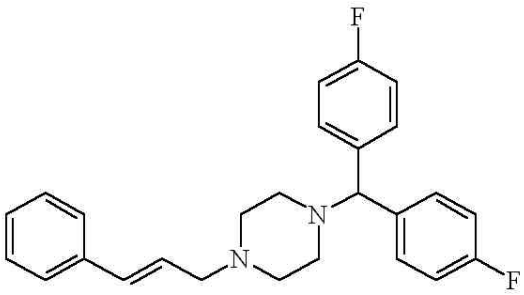


Figure 12. Structure of flunarizine.

the propagation/spread of seizure discharges and to suppress the epileptogenic focus (425).

The marketing of zonisamide in the U.S. was delayed by reports of nephrolithiasis by European and American investigators (426). However, the drug has been used successfully in Japan for a range of epilepsy types, including infantile spasms (427) and myoclonic seizures (428). Efficacy as a neuroprotectant and in the treatment of mania has also been suggested. Zonisamide is active in a wide range of animal models of epilepsy (429), and is efficacious in the treatment of simple and complex partial seizures and (to a lesser extent) generalized seizures. The FDA approved zonisamide in 1999.

The mechanism of action of zonisamide has not been elucidated, but it is known to block sodium channels (429) and T-type calcium channels (430). Block of T-type channels would be expected to shift the channel population toward the inactivation state, thus allowing fewer channels to open upon depolarization. This in turn would inhibit the spread of epileptiform activity.

Zonisamide is generally well-tolerated. The most common side effects are drowsiness, loss of appetite, gastrointestinal problems and CNS toxicity, although the rare occurrence of nephrolithiasis suggests patients should be monitored carefully (426). Interestingly, the incidence of nephrolithiasis in Japanese patients appears to be much lower in than in the U.S. or Europe, and the causative link with the drug has been disputed. The drug was teratogenic in animal models (425).

4.2.8. Levetiracetam

Levetiracetam (Figure 11) is structurally related to piracetam (Nootropil; a cognitive enhancer and anti-myoclonic drug), but unrelated to other AEDs. Levetiracetam was approved in the U.S. in late 1999 for the adjunctive treatment of partial onset seizures with and without secondary generalization in adults. It was also assessed for the treatment of Alzheimer's disease, but development for this indication was discontinued.

Levetiracetam has been evaluated in double-blind, placebo-controlled, phase III clinical studies in the U.S. and in Europe. More patients receiving levetiracetam experienced a reduction in weekly seizure frequency when compared to placebo, and levetiracetam-treated patient groups had significantly more responders (incidence with at least a 50% reduction from baseline in partial onset seizure frequency). More than 900 patients participated in these studies, and over 3000 people received levetiracetam in various clinical studies. Levetiracetam was well tolerated, and most adverse experiences were mild or moderate (431).

4.2.9. Flunarizine

Flunarizine (Figure 12) is a calcium channel blocker with neuronal protective properties. It is effective against migraine, vertebrobasilar insufficiency, epilepsy (432-438), and alternating hemiplegia. Somewhat contradictory results have been obtained as to its efficacy in epilepsy; Durrheim *et al.* reported that as add-on therapy to sodium valproate it was effective in treating reading epilepsy (439), while Alving *et al.* concluded that it showed no statistical advantage over the placebo in reducing total seizure frequency in patients with complex partial seizures (440). Other studies have questioned its value in treating epilepsy (441-443).

4.3. The "next generation"

Other new AEDs in clinical development are summarized below.

4.3.1. Remacemide

Remacemide (Figure 13) acts by blocking NMDA receptors and by prolonging inactivation of sodium channels. The desglycinated metabolite, ARL 12495AA, is approximately twice as potent as the parent drug (444-447). It has been suggested that modulation of the metabolism of remacemide could be of therapeutic use (448).

In binding studies in cerebral cortical membranes (444), ARL 12495AA was shown to have 150 times the

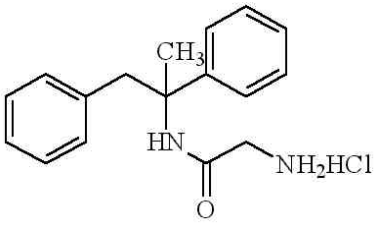


Figure 13. Structure of remacemide hydrochloride.

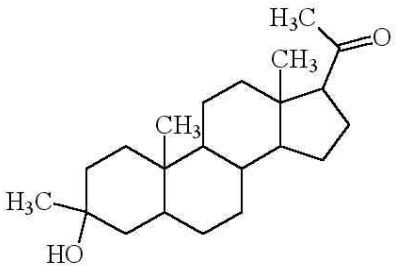


Figure 14. Structure of ganaxalone.

affinity of remacemide for the NMDA receptor (displacement of [^{3}H]MK801). ARL 12495AA reduces NMDA-induced depolarizations in various *in vitro* preparations, and the mechanism of NMDA block probably involves an action at the channel site on the NMDA receptor complex. Unlike MK801 and many other NMDA blockers however, remacemide exhibits low toxicity.

The anti-convulsant effect of remacemide has been demonstrated in the WAG/Rij rat, a genetic model for generalized absence epilepsy (449). Remacemide and its metabolite both decreased the number of spike-wave discharges, without causing major effects on behavior or the EEG spectral content. In the case of the metabolite, the mean duration of spike-wave discharges was prolonged, a unique combination of effects in an AED.

In vitro electrophysiological studies have demonstrated that remacemide and ARL 12495AA increase spike duration and decrease or eliminate spike after-hyperpolarization, in rat CA1 hippocampal neurons (448). Thus, the drugs appear to modulate sodium and/or potassium channel activity. Such multiple mechanisms may contribute to remacemide's anti-epileptic activity.

Clinical trials have shown remacemide to be well tolerated and efficacious in patients with partial and secondary generalized seizures. Remacemide is currently undergoing phase III trials in Europe and the U.S. (450, 451).

4.3.2. Ganaxolone

Ganaxolone (CCD 1042; 3-alpha-hydroxy-3-beta-methyl-5-alpha-pregnan-20-one; Figure 14) is a member of a class of neuroactive steroids that have been termed “epalons” (452, 453). Epalons modulate the $GABA_A$ receptor / chloride ionophore complex in the CNS via a specific steroid-sensitive site, and as a result have anti-epileptic, anxiolytic, sedative, and hypnotic properties. Epalons are structurally related to progesterone but have no hormonal activity; ganaxolone is a 3-beta-methyl-substituted analog of the endogenous neuroactive steroid 3-alpha-hydroxy-5-alpha-pregnan-20-one. It is under development as an AED for treating generalized absence seizures and simple or complex partial seizures.

Ganaxolone has been shown to inhibit binding to the $GABA_A$ receptor / chloride channel complex and also to enhance binding at the benzodiazepine and muscimol binding sites (454). These actions suggest that ganaxolone is a positive allosteric modulator of the $GABA_A$ receptor.

Ganaxolone is an efficacious anticonvulsant agent in a variety of acute seizure models, as well as in electrical and chemical kindling models (455). The drug attenuates seizures in animals resulting from PTZ, bicuculline or aminophylline treatment in rodents, and in the kindling model of epilepsy. Electroshock-induced seizures are attenuated only at doses that produce ataxia (454). In contrast to these results however, Snead (1998) found that PTZ- or gamma-hydroxybutyric acid-induced absence seizures in rats were exacerbated by ganaxolone (456).

In healthy volunteers, ganaxolone was well tolerated after single (up to 1500 mg) and multiple doses (up to 300 mg bid for 10 days). The drug was rapidly absorbed from the gastrointestinal tract after oral administration. Pharmacokinetics were linear and dose-proportional (457). Ganaxolone was in phase II trials in France and the U.S. in 1998, and early results suggest promising activity in patients with infantile spasms.

The difficulty in reaching bioactive concentrations of neurosteroids has caused problems in the pharmacological development of such drugs however. It may be possible to combine therapy with a drug to modify the metabolism of the neurosteroid.

4.3.3. Losigamone

Losigamone (5-(2-chlorophenylhydroxymethyl)-4-methoxy-2(5*H*)-furanone; Figure 15) is a tetronic acid derivative in clinical trials as an AED (458). The drug is being developed as a racemate (459), though its enantiomers have somewhat different properties (56, 460). Although the mechanism of action is unclear, losigamone probably acts via the NMDA system; it also affects the $GABA_A$ receptor-linked chloride channel. Currently, losigamone is in phase III clinical trials in Europe and the U.S. It is being promoted as an adjunct therapy for patients with refractory partial epilepsy, and as an alternative monotherapy for patients with partial epilepsy.

Losigamone significantly reduced NMDA-induced depolarizations in the mouse cortical wedge preparation, without affecting AMPA-induced depolarizations. Furthermore, release of glutamate stimulated by veratridine or potassium was reduced by losigamone in the same preparation (461). Gasior *et al.* (1999) demonstrated losigamone’s efficacy at treating cocaine-induced seizures in the mouse (462).

The pharmacokinetics of losigamone were investigated in healthy volunteers, and were found to be linear (463). Losigamone was rapidly absorbed after oral administration, and is extensively metabolized, predominantly by hydroxylation and conjugation (464). The drug was well tolerated and no serious adverse effects

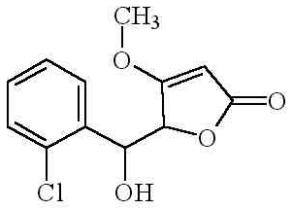


Figure 15. Structure of losigamone.

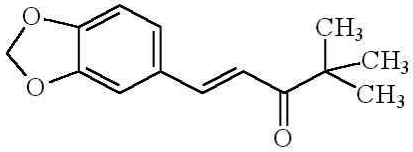


Figure 16. Structure of stiripentol.

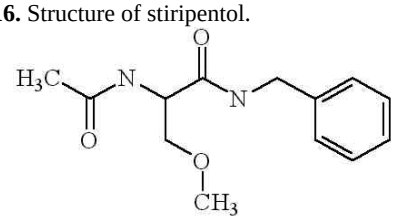


Figure 17. Structure of harkoseride.

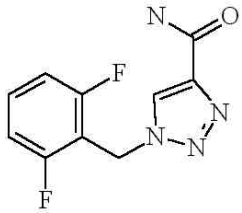


Figure 18. Structure of rufinamide.

occurred, although in some subjects there was a reversible increase in transaminases (463).

4.3.4. Stiripentol

Stiripentol (4,4-dimethyl-1-[3,4-(methylenedioxy)-phenyl]-1-penten-3-ol; Figure 16) is an alpha-ethylene alcohol with multiple effects on GABAergic neurotransmission (465). The drug does not appear to be a GABA agonist, but inhibits GABA uptake (as demonstrated in a synaptosomal preparation) and also inhibits GABA transaminase (466, 467). Stiripentol is an effective anti-convulsant in animal models, including electroshock, PTZ, bicuculline, and strychnine. Stiripentol has a chiral center; when the S-enantiomer was given orally to rats, only the S-enantiomer was found in blood, whereas following administration of the R-enantiomer, both the R and S forms were detected in the systemic circulation (468, 469). Other studies have shown differences in potency and pharmacokinetics between the enantiomers (470, 471).

Stiripentol has shown promise as an adjunctive therapy in uncontrolled atypical absence seizures in children (472). Only one patient out of 10 reported an adverse effect (vomiting) that warranted withdrawal of the drug. Stiripentol has also shown efficacy in patients with partial seizures and refractory epilepsy (438), and in the treatment of cocaine-induced seizures (462).

The inhibition of cytochrome P-450 by stiripentol is worth noting; it results in marked drug interactions with other AEDs, such as phenytoin, carbamazepine, and phenobarbital (438). Finnell *et al.* (1994) demonstrated a significant reduction of the teratogenic effect of phenytoin in mice by the co-administration of stiripentol, an effect that could be explained in terms of reduced production of a teratogenic metabolite of phenytoin (473).

4.3.5. Pregabalin

Pregabalin (4-amino-3-isobutylbutyric acid; isobutyl GABA; Figure 7) is an AED under development; it is currently in phase III trials. Its mechanism of action is unclear. It is chemically related to gabapentin and apparently interacts with the same binding site and has a similar pharmacological profile to gabapentin (474). Pregabalin is claimed to be more potent than gabapentin in preclinical trials of anticonvulsant activity (474, 475). Results from early clinical trials have shown efficacy in treating patients with refractory complex partial seizures (with or without secondary generalization); pregabalin compared favorably to gabapentin. Pregabalin was well tolerated in healthy volunteers and is readily absorbed after oral administration (474, 476).

4.3.6. Harkoseride

In early 1999, a new anti-convulsant agent, harkoseride (ADD 234037; Figure 17), entered phase II clinical trials. Initial safety studies of intravenous harkoseride showed no serious adverse effects in healthy volunteers, and demonstrated a pharmacokinetic profile ideal for an AED following oral dosing. Animal studies of harkoseride have also suggested a wide margin of safety. The drug reduces seizures in mice and rats at oral doses from 0.5 to 5 mg/kg.

4.3.7. Rufinamide

Rufinamide (CGP 331010; Figure 18) is a GABA uptake inhibitor in development. It is in phase III trials in Switzerland and the U.S. and shows promise as a therapy for patients with partial epilepsy and generalized tonic-clonic epilepsy. Rufinamide is orally absorbed and is generally well tolerated (477, 478), although tremor and tiredness have been reported as adverse effects. In a double-blind trial of 50 patients with refractive epilepsy, rufinamide as an adjunct therapy reduced seizure frequency by 42%, compared with an increase of 52% in placebo recipients.

5. CONCLUSIONS

The goal of treating epilepsy is to control seizures completely without causing unacceptable side effects. None of the currently available treatments accomplishes that; many of the drugs reviewed here have unwelcome side effects and complete seizure control is rare under any regimen. Given the heterogeneity of the disease, it is extremely unlikely that there will ever be a single ideal AED. However, as we understand more and more about the condition, patients will be classified into rational groups and will be treated accordingly.

Ideally, the drug discovery scientist knows the mechanism(s) of the disease, possesses reliable preclinical

animal models of the disease that are representative or indicative of human results, has reference compounds after which new drugs can be modeled and against which new drugs can be tested, and has objective, reliable clinical outcome measures. Even after more than a century of pharmacotherapy and research, the scientist really only has one of these, a set of existing AEDs, with varying qualities and properties.

Our understanding of the etiology of epilepsy is advancing rapidly and has entered the genetic age; single gene defects with simple inheritance patterns have been characterized and are providing some insight. Additionally, better animal models can be generated, using transgenic technology and our improving knowledge of these gene defects.

Animal models have lead to significant advances in AED discovery twice before: the work of Merritt & Putnam and then of Swinyard and colleagues. There is every reason to believe that better models, better screening technologies, and the advent of techniques such as combinatorial chemistry for generating lead compounds will similarly advance AED research again.

Even if the drug discovery scientist had all four ideal elements, there remain special problems unique to epilepsy. The use of placebo control in epileptic patients is generally considered unethical, not only because of the distress associated with seizures, but because severe seizures can lead to injury, brain damage, or even death. A further problem is that seizures and *status epilepticus* can be induced by withdrawing or altering the dose of an existing AED, making it difficult to wean a patient from his or her existing AED regimen in order to test a new drug. Even changes in the law have conspired against AED researchers, because of difficulties in satisfactorily proving safety and efficacy!

However, creative scientists and physicians have found ways around these problems. New drugs can be tested without placebo controls using a technique pioneered by Rodin and colleagues on carbamazepine: the new AED is used concomitantly with an established AED and the combination is compared with the established AED plus placebo. It is hardly the perfect solution, given drug-drug interactions, but most AEDs have been tested in this way. True monotherapy placebo-controlled studies have been conducted in special circumstances, specifically in patients undergoing intensive neurodiagnostic monitoring after partial or complete withdrawal from their prior AEDs. In the hospital setting, a true placebo-controlled study may be possible because seizures can be monitored and not allowed to progress to a potentially brain-damaging situation.

The recent introduction of new AEDs with new novel mechanisms of action has opened up the field of epilepsy research. With many new compounds currently in development and the vast amount of ongoing epilepsy and more general neuroscience research, the pharmacotherapy of epilepsy looks set to undergo radical changes in the next decade.

6. ACKNOWLEDGEMENTS

We thank Dr. Philip M. Brown for assistance with the figures.

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Key Words: Epilepsy, Seizure, Anti-Epileptic Drug, Drug Discovery , Development, Etiology, Review

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