Seizure 19 (2010) 650–655

Contents lists available at ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Review

Antiepileptic drug therapy the story so far

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ARTICLE INFO

Keywords:
Antiepileptic drugs
Mechanism of action
Epilepsy
Pharmacoresistance
Prognosis

ABSTRACT

The story began on 11th May 1857 when Charles Locock commented in the Lancet on his use of potassium bromide in 15 cases of "hysterical" epilepsy in young women. The next development was the serendipitous discovery of the anticonvulsant properties of phenobarbital by Alfred Hauptmann in 1912. This predated by more than 20 years the screening of potential therapeutic agents against "electrical seizures" in cats by Houston Merritt and Tracy Putnam. The result was the launching of phenytoin in 1938. Next came primidone, ethosuximide, carbamazepine and valproic acid, all of which can be regarded as first generation antiepileptic drugs (AEDs). Shortly after their synthesis, the benzodiazepines were rapidly recognised as having anticonvulsant activity. The modern era focused on the systematic screening of many thousands of compounds against rodent seizure models under the Anticonvulsant Drug Development Program in the US. This resulted in the global licensing, in chronological order, of vigabatrin, zonisamide, oxcarbazepine, lamotrigine, felbamate, gabapentin, topiramate, tiagabine, levetiracetam, pregabalin and lacosamide. Rufinamide is available in the US and Europe for Lennox-Gastaut syndrome and stiripentol has been made available for Dravet syndrome under the European orphan drug scheme. Eslicarbazepine can be prescribed in Europe for partial seizures, but not in the US. Has all this activity improved the lives of people with epilepsy? The short answer is—probably yes, but not by very much! This paper will conclude with a précis of the views of a selected group of paediatric and adult epileptologists on the advances in pharmacological management achieved over the last 20 years.

1. Introduction

The modern treatment of epilepsy began with potassium bromide. The first mention of bromide in the English literature can be found on pages 327–328 in the Lancet of 23rd May, 1857 during the discussion of a paper presented at the Royal Medical and Chirurgical Society by Dr Edward Sieveking entitled "Analyses of 52 cases of epilepsy observed by the author". The chairman Sir Charles Locock, obstetrician to the highly fertile Queen Victoria, shared with the audience his enthusiasm for potassium bromide in young women with "hysterical epilepsy connected with the menstrual period". Could this have been catamenial epilepsy? Although there are no randomized trials with bromide, there is enough clinical data to support its claim to be the first effective antiepileptic drug.[1] Indeed, bromide has support to this day as a potential "drug of tertiary choice in the treatment of children with epilepsy".[2]

2. Established drugs

The pharmacological age of AED therapy began with the serendipitous discovery by Alfred Hauptmann of the anticonvulsant properties of phenobarbital (PB). The story goes that as a young resident psychiatrist he lived over a ward of people with epilepsy. They kept falling out of bed during the night in the throes of tonic–clonic seizures, thereby keeping him awake. PB had been marketed the previous year as a hypnotic (Luminal) by F. Bayer and Company. Hauptmann sedated his patients with Luminal so that he could get a good night's sleep. Not only did his patients have fewer episodes during the night, but they did not seize the following day. He published his observation and the rest is history.[3] PB is still the most widely prescribed AED in the developing world and remains a first popular choice in many industrialized countries partly because of its modest cost.[4]

When Tracy Putnam was appointed to the directorship of the neurological unit at the Boston City Hospital in 1934, he set out to discover a less sedative AED than PB. With the help of Frederic Gibbs, he established the first electroencephalophic laboratory for the routine study of "brain waves". A makeshift piece of apparatus was assembled to demonstrate that PB markedly raised the convulsive threshold in cats. Parke, Davis, and Company supplied Putnum's research team with a number of non-sedative phenyl compounds. Only one of these, phenytoin (PHT), was not too toxic for routine administration. Luckily it was markedly effective in protecting cats from electrically induced convulsions. Putnam gave PHT to one of his young assistants, Houston Merritt, for clinical evaluation in 1936. The first patient to receive the drug had suffered daily seizures for

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doi:10.1016/j.seizure.2010.10.027

many years and became permanently seizure free on commencing treatment with PHT. The subsequent publication established this new drug in the therapeutic armamentarium.[5] PHT is probably still the most widely used AED in the United States.

During the 1940s troxidone became established for the treatment of petit mal. Parke, Davis subsequently initiated a major research project to find a less toxic drug for this indication, which resulted a decade later in the licensing of ethosuximide in 1958. Its current value for absence seizures has been confirmed in a recent double-blind, randomised comparative trial with sodium valproate (VPA) and lamotrigine (LTG).[6]

The next major drug to be licensed was carbamazepine (CBZ), which became widely available in the mid-1960s and is arguably supported by the best evidence base.[7] It was synthesised by Schindler at Geigy in 1953 as a possible competitor for the recently introduced antipsychotic chlorpromazine. The first study with CBZ in epilepsy was not carried out until 1963, after which it was rapidly licensed as an anticonvulsant in 1965 in the UK.

1963 was also the year that the antiepileptic activity of VPA was serendipitously recognised by Pierre Eymard while working as a research student at the University of Lyon. He dissolved a series of insoluble khellin and coumarin derivatives in VPA. Rather surprisingly, all of them appeared to have anticonvulsant properties. The penny dropped and VPA was subjected to extensive clinical investigation. Its sodium salt was first marketed as an AED in France in 1967.[8]

The value of the benzodiazepines for the treatment of epilepsy was rapidly recognised following their synthesis and development by Leo Sternbach, while he was working for the Swiss pharmaceutical company, Roche, in the 1960s.[9] In 1965 Henry Gastaut published a report regarding the efficacy of diazepam in treating status epilepticus.[10] His follow up paper with clonazepam 6 years later was even more positive.[11] Clobazam is probably the most widely used oral benzodiazepine for a range of refractory epilepsies.[12] Rectal diazepam, buccal and intranasal midazolam and intravenous diazepam and lorazepam are drugs of choice for acute repetitive seizures and convulsive status epilepticus.

3. Modern era

The modern era of AED development began in 1975 when the National Institute of Neurological Disorders and Stroke in the United States established the Anticonvulsant Drug Development Programme. More than 28,000 new chemical entities from academic and pharmaceutical chemists have since been screened, resulting in the licensing of an increasing list of AEDs (Fig. 1).

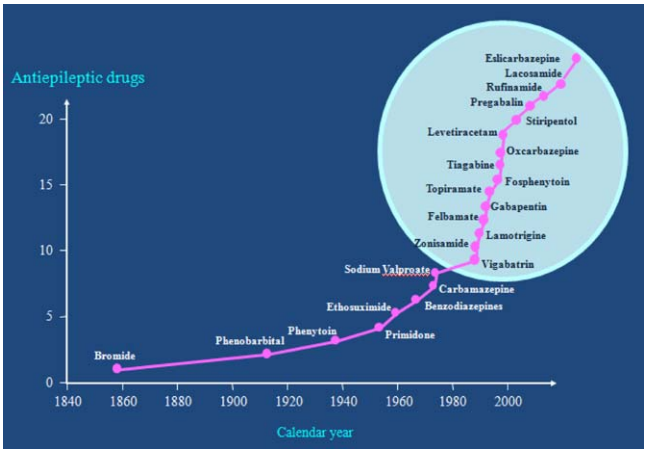

Fig. 1. Chronology of antiepileptic drug introduction over the past 150 years.

Suitable compounds were identified by target-orientated design, structural modification of existing molecules and, most importantly, by laborious and systematic screening against a range of seizure models in rodents.[13] The most commonly used tests include maximal electroshock, subcutaneous pentylenetetrazole, 6 Hertz test and a battery of other screening options.[14] Interesting, many newly identified AEDs appear to have unique mechanisms of action despite demonstrating efficacy against a similar range of similar seizure models. They all have in common the ability to decrease neuronal excitation or increase neuronal inhibition by one or more of pharmacological processes, including modulation of voltage-gated cation channels, potentiation of GABA-ergic activity, inhibition of glutamatergic processes and modification of neurotransmitter release.[15]

A number of AEDs bind to the inactivated state of the sodium channel to produce a voltage- and frequency-dependent reduction in conduction (Table 1). PHT, CBZ, LTG, oxcarbazepine and eslicarbazepine all fall into this category. Lacosamide, interestingly, selectively affects slow inactivation of the sodium channel, whereas all the other sodium blockers modulate fast inactivation.[16] These AEDs have varying effects on the pharmacology of the channel and so can be given together if necessary. Whether or not this represents a "rational" strategy is a matter of substantial debate.[17] What is clear, however, is that combining some of these mechanistically similar AEDs is more likely to result in neurological side effects such as headache, dizziness, diplopia and ataxia. Some of the broader spectrum AEDs, such as felbamate, topiramate, zonisamide and rufinamide also bind to sodium channels, although the relevance of this to their pharmacological action remains unclear.[18] Rufinamide is a sodium channel blocker with modest efficacy for partial seizures.[19] It is more effective for generalised seizures in children with Lennox-Gastaut syndrome.[20]

Some AEDs block low or high voltage-activated calcium channels, thereby preventing depolarisation and neurotransmitter release. Ethosuximide has its specific action on T-type calcium channels. Gabapentin and pregabalin bind to the alpha$_2$ delta subunit of high voltage activated calcium channels, which appears to be responsible for their beneficial effects on epileptic seizures, neuropathic pain and anxiety.[21] Some of the broad spectrum AEDs, such as lamotrigine, topiramate, levetiracetam and zonisamide also appears to bind to voltage-activated calcium channels in different ways.

A number of AEDs have their pharmacological action at the GABA$_A$ receptor, either by enhancing the response to synaptically released GABA (barbiturates, benzodiazepines) or by altering its synthesis (sodium valproate), metabolism (vigabatrin) or reuptake (tiagabine) at the synapse.[22] Stiripentol, licensed in Europe for Dravet's syndrome, facilitates GABA-ergic inhibition.[23] Felbamate, topiramate and levetiracetam also modulate responses at the GABA$_A$ receptor.

There are a number of broad spectrum AEDs that have multiple mechanisms of action accompanied by a broad spectrum of activity across a range of seizure types.[24] These include sodium valproate, felbamate, topiramate, zonisamide, and, presumably, rufinamide. Some of these (felbamate, topiramate, and zonisamide) block specific subtypes of the glutamate receptor leading to a reduction in fast excitatory neurotransmission.[21] Levetiracetam, another broad spectrum AED, binds to synaptic vesicle protein 2A (SV 2A) interfering with recycling of synaptic vesicles and thereby the release of a range of neurotransmitters.

The pipeline for the development of new AEDs with novel mechanisms of action is narrowing with only a few interesting compounds on the immediate horizon.[25] Only retigabine (opens potassium channel), perampanel (modulates AMPA mediated neurotransmission) and brivaracetam (binds to SV2A protein and sodium channel) are likely to reach the market-place in the next 5 years.[26]

Table 1
Mechanisms of action of antiepileptic drugs.

	Decreased Na^+ channels	Decreased Ca^{2+} channels[†]	Increased GABA transmission	Decreased glutamate transmission
Established antiepileptic drugs				
Benzodiazepines			++	
Carbamazepine	++			
Ethosuximide		++ (T-type)		
Phenobarbital		?	++	?
Phenytoin	++			
Valproate	?	? (T-type)	+	?
Modern antiepileptic drugs				
Eslicarbazepine	++			
Felbamate	+	?	+	+
Gabapentin	?	++ (alpha2-delta)	+	
Lacosamide	+			
Lamotrigine	++	?		
Levetiracetam[*]		?	?	?
Oxcarbazepine	++			
Pregabalin		++ (alpha2-delta)		
Rufinamide	++			
Tiagabine			++	
Topiramate	+	+	+	+
Vigabatrin			++	
Zonisamide				?
	+	+ (T-type)		

(++) primary action; (+) probable action; (?) possible action.
[†] Unless otherwise stated, action on high voltage activated calcium channels.
[*] Levetiracetam acts by binding to synaptic vesicle protein 2A (SV2A).

4. Drug response

The prognosis for most adults and adolescents with newly diagnosed epilepsy is reasonably good with around 50% controlled on their first ever AED often at a modest or moderate dose.[27] Double-blind, head-to-head randomised trials in this setting find no differences in efficacy among AEDs with differing mechanisms of action.[28,29] It would appear that any appropriate AED that decreases neuronal excitation and/or increases neuronal inhibition will produce long term seizure freedom in these highly drug-sensitive individuals. Pragmatic randomized trials can, however, find differences in effectiveness between AEDs as a consequence of better tolerability.[30,31]

A further 10% of patients with newly diagnosed epilepsy will control on their second or third drug with only a few going into remission on an AED combination.[32] Thereafter, the likelihood of a perfect outcome becomes progressively less likely with around 30% of this population developing refractory epilepsy. The suggestion that many of these patients are pharmacoresistant de novo and never respond to AED therapy from the outset is intriguing and points to important variations in the neurobiology of epilepsy among different individuals.[33] The International League Against Epilepsy task force has recently defined drug-resistant epilepsy as "failure of adequate trials of two tolerated, appropriate chosen and used AED schedules (where as monotherapy or in combination) to achieve sustained seizure freedom".[34] This is a different clinical scenario from that of refractory epilepsy, where all drug choices used singly or in combination have failed to provide complete seizure freedom.[35]

Refractory epilepsy is generally thought to reflect a complex multifactorial phenomenon to which genetic and acquired factors may contribute.[36] Research during the last decade has focused on two major hypotheses, which are related to the assumptions necessary for AED efficacy.[37] First, an AED needs to meet the pharmacodynamic requirements including binding to and induction of specific effects at the target site. Changes at these sites may significantly alter affinity for or efficacy at the target, thereby reducing overall drug-sensitivity (target hypothesis). In addition the drug needs to reach the target site in sufficient concentration to produce its pharmacological effect. Appropriate drug delivery is promoted by the high blood supply to the brain, which may be restricted by the blood–brain barrier (BBB). It has been suggested that enhanced BBB efflux transport may limit brain penetration of AEDs (transporter hypothesis) to epileptic neurones.[38]

Autoimmune responses and inflammation are increasingly recognized to play a role in seizure generation and propagation. A range of autoantibodies to ion channels involved in neuronal excitation and inhibition, including voltage-gated potassium and calcium channels,[39] glutamate N-methyl-D-aspartate (NMDA)[40] and $GABA_B$ receptors[41] have been identified in patients with seizures of otherwise unknown etiology. Other emerging cellular mechanisms responsible for seizures and epileptogenesis include mitochondrial oxidative stress and dysfunction[42] and electrical coupling through gap junctions in neurons or glial cells.[43] These processes represent potential novel targets for future drug development.

5. Rational polytherapy

The potential choices of AEDs as monotherapy, or, particularly, in combination are now so numerous that it is not possible for a doctor or patient to try every permutation in a single lifetime. How, therefore, are we going to improve the outlook for the 30% or so people with refractory epilepsy? Although we have some reasonable idea of how the majority of AEDs act, what is missing is similar information regarding the neurobiologies underpinning drug response and, in particular, pharmacoresistance in the individual patient. Nevertheless, it seems reasonable to use a drug possessing a different mode of action when an AED fails due to poor tolerability or, perhaps more persuasively, because of lack of efficacy.[17] There are arguments for combining a sodium channel blocker with a drug possessing GABA-ergic properties[44]or one known to have multiple mechanisms of action.[45]

The best evidence for a synergistic interaction between 2 AEDs is with VPA and LTG for partial-onset and generalised seizures. Brodie and his European colleagues undertook a pragmatic trial during which an attempt was made to substitute lamotrigine in patients suboptimally controlled with CBZ, PHT or VPA as monotherapy.[46] Adjustment was made in the LTG dosing schedules for the pharmacokinetic interactions among these drugs resulting in similar LTG concentrations in all 3 treatment groups. When patients were taking both drugs, it was noted that responses were significantly better for the VPA group than in the patients taking LTG with CBZ or PHT. Following up on this observation, Pisani and co-workers performed a crossover study in 20 patients with refractory partial seizures. Among the 13 who did not respond to the consecutive addition of VPA or LTG to their existing regimen, 4 patients became seizure free and an additional 4 experienced ≥50% seizure reduction when both drugs were given in combination despite lower doses and circulating concentrations of VPA and LTG than when they were administered separately.[47]

Other "recommended" combinations are based on anecdotal reports in small groups of patients or studies with modest sample size. These include VPA with ethosuximide for absence seizures,[48] PB with PHT for generalised tonic–clonic seizures,[49] vigabatrin with tiagabine for partial seizure types[50] and LTG with topiramate for a range of seizures.[51] Although none of these reports can be regarded as any more than limited observational evidence in support of the mechanistic hypothesis, it is interesting to note that combinations with different modes of action were universally employed in these reports.

6. Improvement in prognosis

William Gowers made the following statement on p. 201 in his book "Epilepsy and other chronic convulsive diseases" published in 1881:

> "What is the prospect, in any given case, that an arrest of the fits can be obtained by treatment? The indications of the prognosis have been materially changed by the introduction of the bromides as remedies for epilepsy. Not only do they arrest fits far more frequently than any other remedy, but they are effective in many cases which, according to experience previous to the introduction of these remedies, would have been regarded as most unpromising. Hence, by their use, the conditions of the prognosis have been essentially changed".[52]

This clearly gives an early hint that "pharmacoresistance" is a moving target, which may be amenable to the introduction of new AEDs with unique mechanisms of action. There is, in addition, increasing evidence that the global introduction of 13 modern AEDs over the past 20 years is having a small but definite impact in improving the likelihood of a good outcome for the individual patient, even though the overall prognosis for the whole population has not markedly changed.[35,53,54] This is perhaps not too surprising since placebo-corrected efficacy of adjunctive treatment with the same AEDs in randomized double-blind, dose-ranging regulatory trials has been disappointingly small[55] with very few patients becoming seizure-free for even the short duration of these studies.[56] The situation may be a little better for the common childhood idiopathic and localisation related epilepsies.[57,58]

In our own expanding cohort of newly diagnosed epilepsy starting on the first AED and followed for up to 26 years, the outcome has slowly improved over the 3 consecutive analyses relevant to 470, 780 and 1098 newly diagnosed patients, respectively.[32,59,60] Compared with our first analysis, the seizure-free rate 10 years later has increased from 64% to 68.4%. This difference can be explained by a small increase in successful

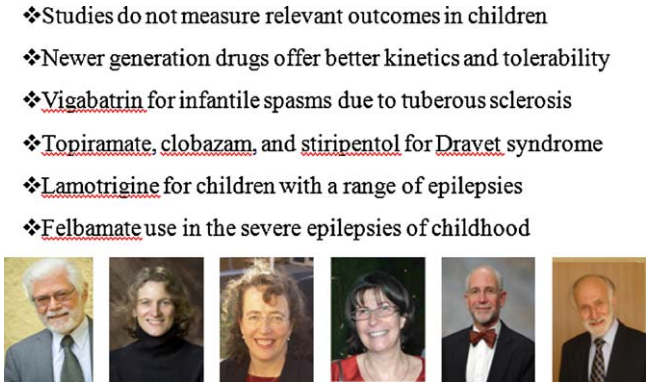

Fig. 2. Quotations from 6 paediatric epileptologists summarising their responses to the question regarding the impact of the introduction of the newer antiepileptic drugs over the last 20 years. Photographs of the contributors are below the quotations with their permission.

Fig. 3. Quotations from 6 adult epileptologists summarising their responses to the question regarding the impact of the introduction of the newer antiepileptic drugs over the last 20 years. Photographs of the contributors are below the quotations with their permission.

combinations (67 out of 70 patients taking just 2 AEDs) rising from 3% to 6.4%. This implicates a modest but positive effect of the introduction of the newer AEDs as add on treatment for the common epilepsies of adulthood. The impact of any new AED will take many years to become apparent since it will be initially used as drug of last choice in the most pharmacoresistant patients who are often taking 2, 3 or 4 other drugs.

In summary, therefore, progress in improving the lives of people with drug resistant epilepsy is slow, but the overall chance of long-term seizure freedom is perhaps a little more likely than it was a decade ago. Figs. 2 and 3 summarise the responses of 6 paediatric and 6 adult epileptologists to the question "What advances have there been in the pharmacological management of epilepsy over the last 20 years?" I will leave it to the reader to match the name and face to each quotation! There have been no "eureka" moments over this time, only a chip-chipping away at the problem with minor insights into which drugs to use and which not to use in specific clinical settings.

7. Conclusions

Where do we go from here? There are few new AEDs in the pipeline and these have largely failed to make people with refractory epilepsy seizure-free in regulatory trials. The long list of drugs licensed over the last 20 years has provided modest improvement in outcome at best. All have been tested in the same rodent seizure models and have the ability to reduce neuronal excitation and/or increase neuronal inhibition. Maybe we

need to change the pharmacological paradigm? The problem has been confounded by the fact that we do not understand how seizures are generated in the brains of individual patients and so we cannot logically apply our knowledge relating to mechanisms of action of the currently available therapeutic armamentarium. Each choice is a guess, sometimes intelligent and sometimes not.

We need treatment strategies based on a better understanding of the various neurobiologies leading to pharmacoresistance, which would help us replace the current empiricism with a more scientific and personalised approach to clinical management.[61] A broader sweep is necessary to identify agents that have the potential not just to prevent seizures, but that will have a positive influence on the process or processes responsible for epileptogenesis.[62] Focus too must be placed on better delineating the phenotypes and genotypes of the individual epilepsy syndromes in order to develop novel therapeutic strategies.[63] We are a long way from identifying these strategies let alone taking the first step down the path leading to truly rational management of refractory epilepsy. Perhaps the increasing availability of genome analysis will provide better insights into AED tailoring for people with epilepsy.[64]

Randomized trials in specific syndromes with similar pathophysiologies are likely to prove more successful in influencing the lives of people with epilepsy than the current expensive, time-consuming, blanket approaches to drug regulation. Not only do we need to hit upon and develop scientific breakthroughs, but we must persuade regulatory agencies to parallel this with a more patient-orientated, cost-effective and imaginative approach to the challenges of treating refractory epilepsy. We are nearing the end of an era. The new one must provide answers to at least some of these questions. "Hope springs eternal in the human breast",[65] but groundbreaking science would also help!

Conflict of interest statement

Professor M Brodie serves on the Scientific Advisory Boards for Pfizer Inc., UCB, Eisai Inc., GlaxoSmithKline, Valeant Pharmaceuticals, Novartis and Medtronic Inc.

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