New avenues for anti-epileptic drug discovery and development

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Abstract | Despite the introduction of over 15 third-generation anti-epileptic drugs, current medications fail to control seizures in 20–30% of patients. However, our understanding of the mechanisms mediating the development of epilepsy and the causes of drug resistance has grown substantially over the past decade, providing opportunities for the discovery and development of more efficacious anti-epileptic and anti-epileptogenic drugs. In this Review we discuss how previous preclinical models and clinical trial designs may have hampered the discovery of better treatments. We propose that future anti-epileptic drug development may be improved through a new joint endeavour between academia and the industry, through the identification and application of tools for new target-driven approaches, and through comparative preclinical proof-of-concept studies and innovative clinical trials designs.

Epilepsy
A chronic brain disorder that is characterized by partial or generalized spontaneous (unprovoked) recurrent epileptic seizures and, often, comorbidities such as anxiety and depression.

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Epilepsy is a life-shortening brain disorder affecting approximately 1% of the worldwide population[1]. Although repeated epileptic seizures are the clinical hallmark of epilepsy, the disease process (epileptogenesis) begins before the first seizure and may also lead to the progression of epilepsy after the onset of seizures. Epilepsy is diverse, with over 15 different seizure types and over 30 epilepsy syndromes[2], and is associated with substantial comorbidity, including depression, anxiety and increased mortality[3].

During the past three decades, the introduction of over 15 third-generation anti-epileptic drugs (AEDs) has provided physicians and patients with more options for the treatment of many types of seizures[4]. However, although approximately 70–80% of patients with new-onset epilepsy eventually enter remission with current AEDs, these medications fail to control seizures in 20–30% of patients[5,6]. Furthermore, no AED has been shown to prevent the development of epilepsy in patients prior to the first seizure; these drugs seem to purely act to symptomatically suppress seizures once they occur[7,8]. For some AEDs, an anti-epileptogenic effect has actually been suggested in certain preclinical epilepsy models[9,10], but this has not been proven in humans. Indeed, with the exception of traumatic brain injury[7], none of the therapies found to be effective in preclinical studies has been adequately tested using an appropriately designed clinical trial in humans.

Unfortunately, there are few aetiologically relevant

been validated at the clinical level — a fact that obviously hampers clinical trial design using the appropriate patient population.In addition, there is no compelling evidence that third-generation AEDs are generally much better tolerated[11–13]. However, individual modern AEDs such as gabapentin (Neurontin; Pfizer) or levetiracetam (Keppra; UCB Pharma) cause fewer or no dermatological hypersensitivity reactions. Also, non-enzyme-inducing modern AEDs such as gabapentin or levetiracetam do not induce the drug interactions seen with older AEDs that have been reported to substantially lower the efficacy of other medications, including other AEDs given in combination[14].

AEDs are also unable to prevent or reverse the development of drug-resistant epilepsy, to treat comorbidities or to reduce the burden of disease in a holistic sense[4]. A particularly disquieting aspect of current epilepsy treatments is that we have not made substantial progress in seizure control over the past 40–50 years since the introduction of carbamazepine and valproate to the market[4,15].

The consequences of the standstill in the development of more efficacious drugs for the treatment of epilepsy are several-fold. Patients and physicians are increasingly disappointed and have thus become less interested in using recently developed, pricier AEDs. Payers are hesitant to pay premium prices for drugs that do not differentiate from established low-cost generic medications, and the pharmaceutical industry is losing interest in developing

Box 1 | **Business challenges and opportunities for anti-epileptic drug development**

In the 1990s, epilepsy presented an opportunity to enter a therapeutic space in which there was a good chance for return on investment. Drivers for this included a significant unmet need with few treatment options (especially for patients with refractory epilepsy), good potential for reimbursement at competitive pricing with few competitors in the field, as well as manageable technical and regulatory hurdles.

The adjunctive or add-on treatment paradigm in the clinical management of refractory epilepsy was well suited for bringing forward new agents to the market. The placebo-controlled adjunctive model for evaluating the efficacy of a test compound in refractory patients established efficacy and tolerability at an early stage and could be performed using cost-efficient short-term clinical studies. Furthermore, following the introduction of felbamate (Felbatol; MedPointe) to the market, a new regulatory path existed for the clinical development and labelling of anti-epileptic drugs (AEDs).

Together, these commercial, scientific, technical and regulatory factors drove confidence and reduced the risk associated with developing and obtaining a value-returning marketable product for epilepsy. This template provided an incentive for several companies to confidently invest in bringing new AEDs to the market.

Loss of industry interest in AEDs

Prior incentives for investment in AED development are now negatively balanced by the drug development challenges facing industry overall[144–146]. Payer reimbursement requires that future AEDs bring additional value or differentiation (principally an improvement in efficacy) to an already crowded, highly generic AED field. No AED to date has convincingly been demonstrated to be superior in efficacy to any other AED in adjunctive therapy for partial seizures, and differentiation by safety profile for new AEDs is not a principal component for optimizing pricing and reimbursement.

New regulatory hurdles have also evolved over the past 15–20 years. A generally lower risk tolerance for new drugs and recent class labelling regarding safety signals (that is, suicide) have affected opportunities in non-epilepsy indications and had an impact on the overall value proposition for AEDs. New AEDs can require commitments for long-term safety data in a variety of age populations, and paediatric investigational plans necessitate the development and testing of new formulations in very young patients (babies who are ≥1 month old). Commercialization models indicate that the adjunctive indication alone for a marginally differentiated product is not adequate. Product promotion for additional uses requires those specific indications to be established in the label. A monotherapy indication can move an AED earlier into the epilepsy treatment paradigm. However, the approval of a monotherapy has so far required the prior approval of an adjunctive therapy and this causes a considerable time delay.

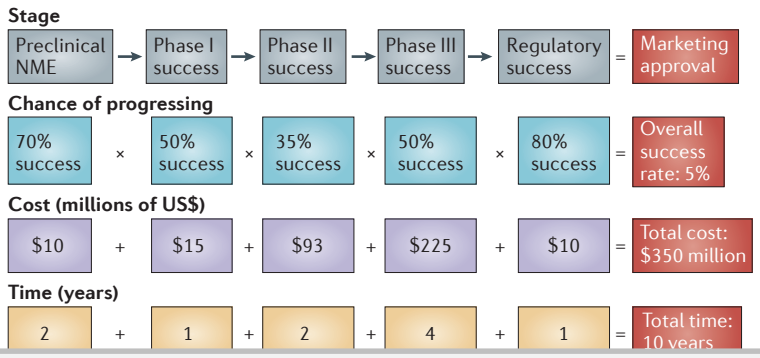
Future business opportunities for AED development

Interesting business cases seem to exist for the very disabling epilepsy syndromes — which are associated with an increased risk of premature death — such as infantile spasms and Lennox–Gastaut syndrome. These may present viable business opportunities for orphan indications, for which tax incentives are provided, investments are smaller and there is a potentially less demanding path for approval.

Another more immediate business opportunity may involve the repurposing of drugs from other therapeutic areas that possess either relevant disease-modifying properties for epilepsy or a novel mechanism of action that provides substantial synergistic efficacy against drug-resistant epilepsy when combined with an existing AED therapy. This would markedly reduce the level of investment necessary for discovery and development, and also potentially lower the technical hurdles and regulatory data requirements, thereby improving the premises for a very positive business case.

A substantial level of investment, beyond that required for traditional AED development, will be necessary for the future development of new AEDs that have evidence of superior efficacy against a relevant standard of care for the treatment of drug-resistant epilepsy, or that have the ability to markedly alter the course or the prognosis of epilepsy. However, as these types of new epilepsy therapies address a major unmet medical need, they also offer a promising business case to drive incentive for future AED development.

The figure illustrates a hypothetical investment example for the development of an AED: a new molecular entity (NME) transitions from discovery into clinical development to be ultimately approved for marketing authorization. From discovery, the lead molecule passes through late-stage preclinical toxicology testing and chemistry scale-up into clinical testing at a cost of US$10 million and a success rate of 70%. The NME passes through each stage with an overall success rate of about 5% at a total cost of $350 million. A key inflection point is at the Phase II stage prior to the most significant spending investment in Phase III. A reduction of risk at this stage can greatly influence the overall success rate and total expenditure for the development of an AED. Note that a cost-effective proof-of-differentiation step early in Phase II can further reduce the investment risk, cost and time. Sales and marketing costs add to the investment and can be of a similar magnitude to the development costs. Following marketing approval, there are costs for sales and marketing, launch, sales force, Phase IV medical affairs studies and post-marketing regulatory commitments. Investments in the initial monotherapy indication and an alternative non-epilepsy indication could add up to approximately



Epileptogenesis
The gradual process (also termed latent period) by which epilepsy develops in the normal brain following brain insults or gene mutations.

Anti-epileptic drugs
(AEDs). Also termed anticonvulsant or anti-seizure drugs. Compounds that, when administered systemically in animal models or to patients, inhibit or control seizures that are associated with epilepsy

In this Review we briefly examine the experimental and clinical strategies for AED discovery and development over the past few decades and discuss why these approaches may have failed to address unmet medical needs. We also outline the challenges for the pharmaceutical industry that have had an impact on its attitude towards the discovery and development of AEDs. Given the serious unmet clinical needs in epilepsy treatment, we present new ideas on how to revitalize the pharmacological and clinical development of better AEDs that could provide the foundation for a new, joint endeavour between academia and the industry.

Previous AED discovery and development

Until recently, the discovery and development of a new AED almost exclusively relied on preclinical testing in animal seizure models to establish anti-seizure efficacy prior to conducting clinical trials in humans[16]. This approach has been successful and crucially contributed to the development of numerous clinically effective AEDs[4,17]. Indeed, animal models with a similarly high predictive value do not exist for other central nervous system (CNS) disorders, such as bipolar disorders or migraine[18].

Since Merritt and Putnam[19] first described the use of an electroshock seizure model to assess drugs for anti-seizure properties in 1937 (FIG. 1 (TIMELINE)), simple models of acute seizures — such as the MES seizure test and the subcutaneous pentylenetetrazole (PTZ) seizure test in mice and rats — have been widely used in AED discovery. These models were considered to be ideal for AED discovery, which necessitates the screening of large numbers of compounds; acute seizure models should therefore be easy to perform, time- and cost-efficient, and predictive of clinical activity. The rodent MES test created by Toman, Swinyard and Goodman[20] in 1946 is still the most commonly used first screen in the search for new AEDs and is quite effective in identifying drugs that block generalized tonic–clonic seizures in patients[17]. The MES test has also repeatedly been proposed to identify drugs that are active against partial seizures in patients, but this test failed to detect several AEDs (for example, levetiracetam and vigabatrin (Sabril; Lundbeck)) that are effective against partial seizures in patients; therefore, other models such as amygdala kindling are better for identifying anticonvulsant effects against partial seizures[21].

Following the report of Everett and Richards[22] in 1944 that the PTZ test can identify the anti-absence efficacy of AEDs, two simple animal models — the MES and PTZ tests — were thought to be sufficient for differentiating among AEDs with different clinical effects. This subsequently formed the basis for the proposal made by Swinyard and colleagues[23,24] that the MES and subcutaneous PTZ tests in mice and rats be used as standard procedures for predicting the clinical anticonvulsant activity of investigational drugs (FIG. 1 (TIMELINE)). However, because of false-positive and false-negative findings in these models, more complex chronic epilepsy models that were developed in the 1980s and later-stage screening to further characterize anti-epileptic efficacy — the most notable of these models being the kindling model and genetic models of epilepsy, such as the absence-epilepsy-prone GAERS rat. More recently, the 6-Hz psychomotor seizure model in mice has been introduced for differentiating an investigational AED from existing AEDs. This model is resistant to some of the old AEDs and enables the screening of a large number of compounds[17,25], which is not possible with more elaborate models such as the kindling model.

Preclinical strategies. Three strategies have been used in AED discovery: first, the random, phenotypic screening of newly synthesized compounds of diverse structural categories with as yet unknown mechanisms; second, the structural variation of known AEDs; and third, hypothesis-driven, target-based drug design[4,17,18]. All three strategies have generated clinically useful AEDs but only very few AEDs have been identified by rational, target-based strategies. These have been based on previously presumed mechanisms of seizure generation: that is, impaired GABA (γ-aminobutyric acid)-ergic inhibition and increased glutamatergic excitation, resulting in AEDs that either potentiate GABA transmission (such as vigabatrin and tiagabine) or inhibit glutamate receptors (such as perampanel (Fycompa; Eisai))[17]. However, the old reductionistic view that seizures or epilepsy are due to an imbalance between GABAergic inhibition and glutamatergic excitation ignores the complexity of the alterations within these neurotransmitter systems in the brain of a patient suffering from epileptic seizures[26].

Clinical strategies. Marketing approval of new AEDs for the treatment of epilepsy has been routinely obtained by adjunctive therapy placebo-controlled Phase III trials in adult patients with refractory seizures[27]. In the 1960s and 1970s, when few AEDs were available[4], the enrolment of patients into these trials was straightforward and the use of placebo treatments was deemed acceptable given the lack of alternative treatment options[28]. This clinical strategy was very successful and has resulted in over 15 new AEDs entering the market since the 1980s (TABLE 1). Many AEDs that are marketed for adjunctive treatment are subsequently tested in monotherapy trials in patients with either refractory or previously untreated epilepsy. Because regulatory guidelines for monotherapy approval differ between Europe and the United States, sponsors need to pursue two separate and costly development programmes. The monotherapy development paradigm currently used in Europe for new-onset epilepsy is the non-inferiority trial design, which establishes a preset limit for the allowed difference in outcome between the test drug and a standard AED[27]. In the United States, the preferred development path is conversion to monotherapy in refractory patients using historical controls. These designs have demonstrated that several AEDs are efficacious as monotherapies, including levetiracetam and zonisamide (Zonegran; Eisai) in Europe and lamotrigine

MES seizure test
(Maximal electroshock seizure test). A model in which a short (0.2-second) transcorneal or transauricular application of a 50 or 60 Hz electrical stimulus in rodents induces generalized tonic–clonic seizures that are mediated by brainstem structures.

Pentylenetetrazole
(PTZ). A chemical convulsant that, when administered systemically to rodents, induces characteristic myoclonic and clonic convulsions that are mediated by forebrain structures.

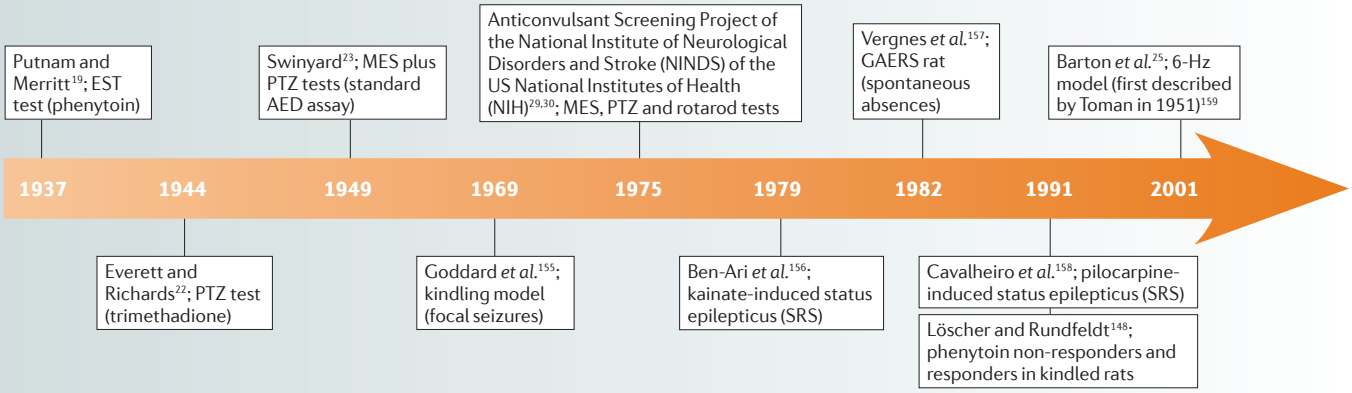
Amygdala kindling
Repeated administration of an initially subconvulsive electrical stimuli via a depth electrode in the amygdala, which induces seizures that progressively increase in severity and duration; once established, the increased susceptibility to the induction of kindled seizures is a permanent phenomenon.

GAERS rat
(Genetic absence epileptic rat from Strasbourg). A genetic rat model that displays characteristic 6–7 Hz spike-wave electrographic seizures and a pharmacological profile that is consistent with generalized absence epilepsy.

6-Hz psychomotor seizure model
A seizure model in which a prolonged (4-second) transcorneal application of a 6-Hz electrical stimulus in mice induces limbic seizures that are characterized by a stun, vibrissae chomping, forelimb clonus and a Straub tail; these seizures are resistant to phenytoin and some other anti-epileptic drugs.

Non-inferiority trial design
A clinical trial design that determines whether a test compound is inferior to another compound; the lower limit (95% confidence interval) of a test compound's treatment efficacy or effectiveness is to be compared to a preset lower boundary of efficacy or effectiveness relative to the adequate comparator's point estimate of efficacy

Timeline | **Milestones in the development of animal models for AED discovery and development***



AED, anti-epileptic drug; EST, electroshock threshold; GAERS, genetic absence epilepsy rat from Strasbourg; MES, maximal electroshock; PTZ, pentylenetetrazole; SRS, spontaneous recurrent seizures. *All animal models shown (except for the SRS models described by Ben-Ari *et al.*[156], Vergnes *et al.*[157] and Cavalheiro *et al.*[158]) are those in which seizures are electrically or chemically induced. All models, except for the EST method in cats described by Putnam and Merritt[19], are still used in the development of new epilepsy therapies[21]. Various models are important for different purposes in epilepsy research[21] and can be assigned to four major categories: first, acute seizure models in which single seizures are electrically or chemically induced in healthy, neurologically intact rodents, such as the MES, subcutaneous PTZ or 6-Hz tests; second, chronic seizure (or epilepsy) models in which single or multiple seizures are electrically or chemically induced in rodents with chronic brain alterations, such as amygdala kindling; third, genetic animal models with inborn chronic epilepsy, such as the GAERS rat (which is better suited than the PTZ test to identify drugs that are active against absence seizures); and fourth, chronic epilepsy models in which epilepsy with SRS is induced by brain insults, such as status epilepticus (for example, induced by pilocarpine or kainate) or traumatic brain injury[21]. The MES and subcutaneous PTZ tests, which were developed more than 60 years ago, have been widely used in the search for new AEDs but they obviously do not predict efficacy against difficult-to-treat (or pharmacoresistant) seizures[4]. Löscher and Rundfeldt[148] were the first to describe a chronic model of pharmacoresistant seizures in which AED-resistant rats were selected from large groups of amygdala-kindled rats by repeated testing with phenytoin. Later, Löscher *et al.* also described the selection of AED-resistant subgroups of rats for post-status epilepticus models of temporal lobe epilepsy with SRS[21,160].

Limitations of previous strategies

Despite the development of various new AEDs since the early 1990s, the available evidence indicates that there has been a failure to deliver drugs with improved efficacy[4]. What are the reasons for this apparent failure to discover drugs that can effectively control drug-refractory seizures and comorbidities as well as prevent or modify the disease?

Problems with preclinical models. Simple seizure models such as the MES and PTZ tests in rodents have been instrumental in the identification of most AED candidates. The advantages of such acute seizure models are their technical simplicity and the ability to screen large numbers of compounds. A disadvantage is that the seizures do not mirror epilepsy (that is, spontaneous seizure occurrence) and occur in 'normal', non-epileptic brains. Furthermore, older AEDs provide complete seizure suppression in these tests, hampering the identification of new AED candidates with greater efficacy, including those that might be effective in patients who are resistant to the older drugs.

More recently, large AED screening programmes such as the Anticonvulsant Screening Project (ASP) of the National Institute of Neurological Disorders and Stroke (NINDS) of the US National Institutes of Health (NIH), which was initiated in 1975 to stimulate the discovery and development of new chemical entities for the symptomatic treatment of human epilepsy[29,30], have included models for pharmacoresistant partial seizures in drug screening. One particular model is the 6-Hz

the identification of compounds like levetiracetam; levetiracetam is ineffective in the MES and PTZ models but is among the most effective AEDs in the clinic[16,25,31]. However, although several novel AEDs — including brivaracetam, retigabine (Potiga; Valeant Pharmaceuticals/GlaxoSmithKline) and carisbamate — are highly effective in the 6-Hz mouse model, they are not more effective in patients with pharmacoresistant partial seizures[21].

Thus, it seems that the simple acute seizure screening models used in the ASP and other programmes fail to differentiate between compounds with promising potential for efficacy against drug-resistant seizures and compounds that work through mechanisms that are not detected by these models. Importantly, chronic seizure models, such as the lamotrigine-resistant kindled rat[32], in which seizures are induced in animals with chronic brain alterations, were therefore recently included in the ASP. However, none of the emerging models of therapy-resistant epilepsy (FIG. 1 (TIMELINE)) has actually been validated at predicting clinical success in the therapy-resistant patient population. Thus, it remains to be established whether the use of chronic models such as kindling or models with spontaneous recurrent seizures will lead to the identification of more effective anti-epileptic treatments, but we consider this approach to be much more viable than the exclusive use of simple acute seizure models, particularly when testing hypothesis-driven, target-based strategies of drug development[21].

Problems with broad-spectrum approaches. An important aim of previous research and development (R&D)

Table 1 | **Characteristics of clinically approved AEDs***

AED	Companies	Year of approval	Presumed main mechanisms of action	Approved indications	Main utility	Main limitations
First-generation drugs						
Potassium bromide	Dow	1857‡	GABA potentiation?	GTCS, myoclonic seizures	Broad use for focal and generalized seizures	Currently for adjunctive use only, not in wide use anymore; acts as a sedative
Phenobarbital	Bayer	1912‡	GABA potentiation	PGCS, sedation, anxiety disorders, sleep disorders	Broad use for focal and generalized seizures	Enzyme inducer; skin hypersensitivity; no absence seizures
Phenytoin	Parke-Davis/ Pfizer	1938	Sodium channel blocker	PGCS	First-line AED, i.v. use	Enzyme inducer; skin hypersensitivity; NLPK; not useful for absence or myoclonic seizures
Trimethadione	Abbott	1946	T-type calcium channel blocker	Absence seizures	Rare use for absence seizures	Not in wide use anymore; teratogenic
Primidone	Imperial Chemical Industries	1954	GABA potentiation	PGCS	Broad use for focal and generalized seizures	Enzyme inducer; skin hypersensitivity; no absence seizures; acts as a sedative
Ethosuximide	Parke-Davis/ Pfizer	1958	T-type calcium channel blocker	Absence seizures	First-line AED, no skin hypersensitivity	Somnolence, loss of appetite, nausea, vomiting, singultus, depression, psychotic episodes, insomnia, rare aplastic anaemia
Second-generation drugs						
Diazepam	Roche	1963	GABA potentiation	Convulsive disorders, status epilepticus, anxiety, alcohol withdrawal	Broad use for focal and generalized seizures, i.v. use, no clinical hepatotoxicity, no skin hypersensitivity	Currently for adjunctive use only; emergency use only; acts as a sedative; leads to tolerance (loss of efficacy)
Carbamazepine	Novartis	1964	Sodium channel blockade	PGCS, trigeminal pain, bipolar disorder	First-line AED	Enzyme inducer; skin hypersensitivity; not useful for absence or myoclonic seizures
Valproate	Sanofi/Abbott	1967	Multiple (for example, GABA potentiation, glutamate (NMDA) inhibition, sodium channel and T-type calcium channel blockade)	PGCS, absence seizures, migraine prophylaxis, bipolar disorder	Broad use for focal and generalized seizures, first-line AED, i.v. use, no skin hypersensitivity	Enzyme inhibitor; substantial teratogenicity; weight gain
Clonazepam	Roche	1968	GABA potentiation	Lennox–Gastaut syndrome, myoclonic seizures, panic disorders	Broad use for focal and generalized seizures, no clinical hepatotoxicity	Currently for adjunctive use only; acts as a sedative; leads to tolerance (loss of efficacy)
Clobazam	Hoechst Roussel/ Lundbeck/Sanofi	1975	GABA potentiation	Lennox–Gastaut syndrome, anxiety disorders	Broad use for focal and generalized seizures, no clinical hepatotoxicity	Currently for adjunctive use only; acts as a sedative; leads to tolerance (loss of efficacy)

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