Current and future treatment of epilepsy

H Scott

Abstract

Epilepsy is a common disease with a complex range of aetiological factors; this is mirrored by the diverse classification systems in use. This article considers current supportive, pharmacological and surgical management in the context of epilepsy classification and casts a critical eye towards the possible contributions of new drug discoveries, pharmacogenetic and neurosurgical developments in the future management of epilepsy.

INTRODUCTION

A seizure is defined as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. Epilepsy is a disorder of the brain that is clinically defined. The international league against epilepsy (ILAE) definition requires an enduring predisposition to generate epileptic seizures that are not provoked by other illness. The definition also requires the occurrence of at least one epileptic seizure but most clinicians require two or more before labelling a patient as epileptic [1] .

The prevalence of epilepsy is common both world wide and in the UK. It affects around 45 million people worldwide, this equates to a lifetime risk of around 3% [2] . The classification of epilepsy is notoriously difficult and mirrors the diverse aetiology and polygenicity of different types of epilepsy. The most widely accepted and clinically useful classification is that produced by the ILAE, this attempts to define an individual's particular clinical manifestation of epilepsy into a distinct group based on seizure type or seizure syndrome [3] . Accurate classification is important for determining aetiology, pathology, research themes, appropriate treatment and prognostic prediction [4] .

The treatment of epilepsy is (or arguably should be) inseparably bound to the underlying cause. In the majority of cases this is still unknown and ergo labelled as 'idiopathic', however there are a significant proportion (up to a third) that are due to identifiable precipitants. Common known causes include cerebrovascular, ischaemic or haemorrhagic events, trauma, malignancy, infections, neurodegenerative diseases or toxins [5] . It is important to identify these cases as they may not fulfil the diagnostic criteria of epilepsy and there

may be specific and sometimes curative treatments that will often differ markedly from the idiopathic varieties.

This article will consider current treatments of epilepsy including supportive and pharmacological management. We will briefly consider drug initiation and choice in epilepsy, then for each of the commonest seizure types we will look in more detail at one popular pharmacological agent. An analysis of the current role and efficacy of curative and palliative surgical intervention will follow. The essay will conclude by looking at where future advances in epilepsy treatment may come from. This will include an analysis of the potential roles of new drug discoveries, pharmacogenetics and targeted neurosurgical developments.

CURRENT TREATMENTS OF IDIOPATHIC EPILEPSY
SUPPORTIVE MANAGEMENT

The management of epilepsy has become a multidisciplinary effort that is patient centred and holistic in its ethos. It is important not to forget the importance of allied health professionals and social support in the treatment of epilepsy. Epilepsy is not just a physical disease, the social implications are extremely important in a patient's quality of life and the role of the wider health care team including psychological support and epilepsy nurse specialists are well established in patient care. Simple social measures such as providing free bus passes for patients unable to drive can have a profound impact on quality of life. The National Service Framework for Long-Term (neurological) medical conditions along with the National Institute for Health and Clinical Excellence (NICE) set out an overview for the standard of care in the United Kingdom for management of epilepsy [2, 6-8] .

This review will mainly focus on the pharmacological and surgical management of epilepsy but the reader is directed to the following articles for a deeper discussion of these important areas of quality of life and non-medical treatment particularly in the paediatric and elderly populations [7-11] .

PHARMACOLOGICAL MANAGEMENT

The natural history of epilepsy varies between individuals and epilepsy syndromes. It is difficult to generalize the course of the disease and accurately predict prognosis on a generic level [4] . In terms of pharmacology, one of the most important questions in symptomatic treatment of epilepsy is "when should I start treatment"? There are different views as to the correct answer but evidence suggests that after a single unprovoked seizure (and therefore before a definitive diagnosis of epilepsy) the recurrence rate without pharmacological intervention is around 25% [12] . A large randomized controlled trial showed that early treatment after a single seizure affects short but not longer-term chances of being seizure free [13] . However, the risk of those with a second or third unprovoked seizure suffering from a further ictal episode is around 75%, therefore prophylactic treatment is generally justified in this group [2, 14] . Pharmacological management is a complex area that has variable efficacy and must be tailored to the individual patient.

Overall, antiepileptic drug management is effective in controlling seizures in around 60-70% of individuals although this is often achieved through a prolonged course of trial and error "popgun" pharmacy [15] . The choice of first line agent is a complex but important one. The initial selection requires the clinician to consider the individual patient and their wishes. The need for therapeutic monitoring, side effect profile, teratogenicity and even cost are all important considerations but the final aim is usually to achieve a quick, effective seizure control with a minimum of adverse effects [16] . A large randomized controlled trial (the SANAD study) by Marson et al investigated the drug of choice for newly diagnosed epilepsy of either the generalized or partial seizure type. This study has received much attention and despite its high power and good follow-up it been the subject of extensive critiques, mainly for the lack of syndromic classification and its lack of blinding. The findings, if accepted, suggest sodium valproate as first line for generalized seizures and lamotrigine for partial seizures [17, 18] . Notably there have been three new antiepileptics released since this study began (levetiracetam, zonisamide and pregabalin) and these are obviously not considered [19] . Final choices of pharmacologic agent are generally made individually and there is no universally accepted algorithm for therapeutic management, one example of first line drug selection is provided by French et al [2] .

IDIOPATHIC GENERALIZED EPILEPSY

When considering pharmacological actions a popular first line agent for use in idiopathic generalized adult epilepsy is sodium valproate (Fig.1). The benefits of this drug were serendipitously discovered in 1963 when valproic acid was used as a solvent to dissolve various compounds that were being investigated for antiepileptogenic properties in electrical seizure models of mice [20] . The exact mode of action has never been fully elucidated but what is known is that it seems to inhibit the action of succinic semialdehyde dehydrogenase ergo reducing succinic acid concentration and thus removing inhibition of L-glutamic acid decarboxylase (GAD). The GAD is then free to convert L-glutamic acid to the inhibitory neurotransmitter gamma amino butyric acid (GABA) [21] . More recent work has shown that it could also act via an increase in neuropeptide Y in the thalamus and temporal lobe and ergo reducing epileptiform oscillations [22] . The concept of antiepileptic agents simply increasing inhibitory factors and ergo reducing paroxysmal epileptiform discharges is almost certainly a gross simplification. Although sodium valproate is useful in a wide variety of epilepsy types including tonic-clonic, myoclonic and absence seizures, the main limitations are its teratogenicity and the wide side effect profile. Dose related effects include tremor, thrombocytopenia and weight gain while idiosyncratic reactions include hair loss and impaired liver function [23] .

Figure 1

Figure 1. The structure of sodium valproate
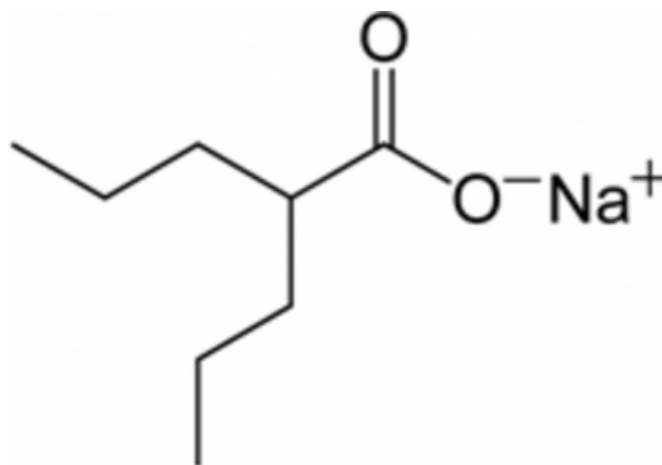
PARTIAL SEIZURES

Lamotrigine is a common initial monotherapy for partial seizures and this is supported by NICE guidance [6] (Fig.2). Its discovery in the early 1980's came from a search for folate antagonists as this property was proposed to underlie the efficacy of the available agents. Although lamotrigine was found to be a very weak inhibitor of dihydrofolate reducatase it was efficacious in animal seizure models [24]. The mode of action seems to be related to stabilization of neuronal membranes and blocking of excitatory glutamate release by sodium channel blockade although this remains controversial. Side effects are noticeably less than many antiepileptic agents, common problems include headaches and nausea. Rarer but more serious effects include cutaneous effects along the spectrum from a simple rash through to erythema multiforme and Steven-Johnson syndrome [23].

Figure 2

Figure 2. The structure of lamotrigine
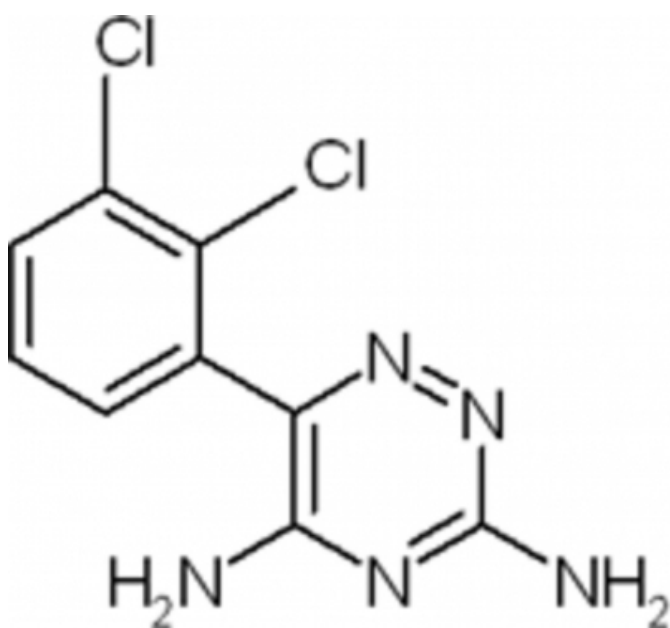
ABSENCE SEIZURES

Absence seizures seem to differ distinctly in their neurophysiological aetiology from other seizure disorders. There is good electophysiological data to show that the pathologic process is driven by abnormal neuronal oscillation in thalmocortical circuits. This circuit is thought to be physiologically important in normal alertness and wakefulness. Abnormalities in absence seizures may be mediated by glutamic overexcitation that becomes phase-locked with inhibition derived from GABAergic neuronal connections [25-27]. This is thought to be the primary reason why many antiepileptic drugs that increase GABA cause an increase in spike-wave propogation and ergo may precipitate seizures of the absence type. The usual first line medication in these cases is ethosuximide, a member of the succinimide class of theraputic agents(Fig.4). The mode of action of this antiepileptic is, yet again, rather controversial. It is efficacious in pentylenetetrazol (PTZ) induced animal convulsion models and classically it has been viewed as a blocker of T-type calcium channels in the thalmocortical circuit. However, some of the experiments that demonstrated this have been criticised for their single neuron methodology and lack of external validity [28]. Safety concerns are limited and mainly centre on idiosyncratic hypersensitivity reactions and the potential to precipitate tonic-clonic seizures in some patients [23].

Figure 3

Figure 3. Schematic showing the normal thalmocortical relay circuit. Thalamic relay neurones are labelled (TR), thalamic reticular nucleus neurones (NRT) and cortical pyramidal neurones (cortex). Glutaminergic neocortical layer VI pyramidal neurones project onto the glutaminergic thalamic relay neurones, setting up a positive feedback loop. Inhibition of this loop is provided by GABAergic reticular nucleus neurones. Cortical pyramidal cells also project onto the reticular nucleus neurons that then connect to thalamic relay neurones. Inherited ion channelopathies in this circuit are thought to underlie circuit hyperexcitability and epileptiform rhythmic spike-wave discharges .
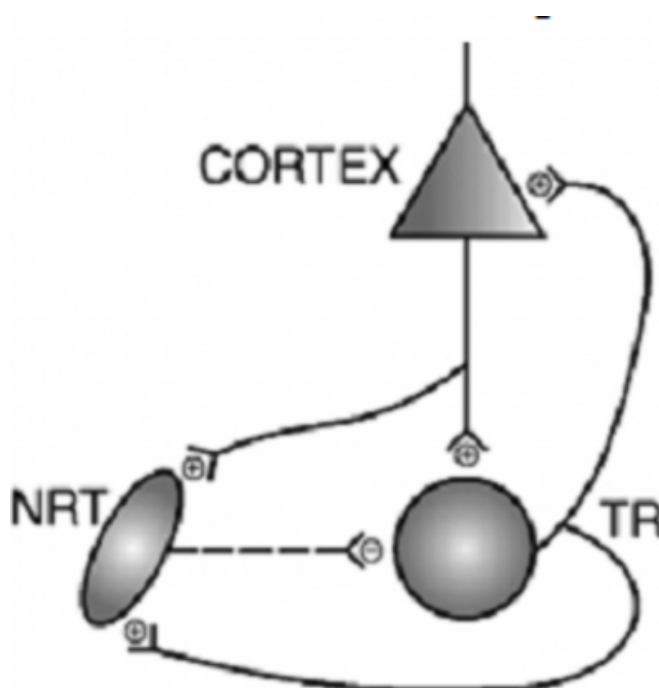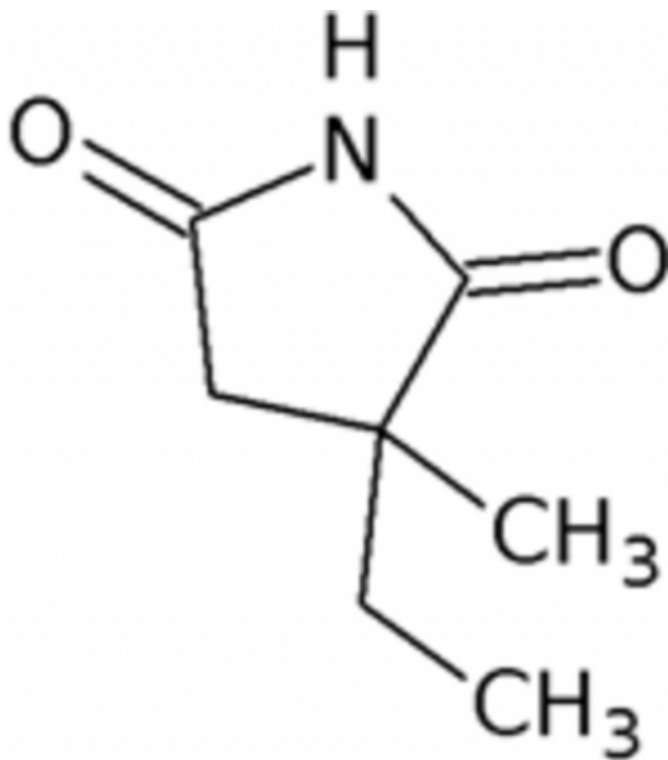
Figure 4

Figure 4. The structure of ethosuximide

OTHER SEIZURE TYPES AND EPILEPSY SYNDROMES

There are numerous other epilepsy syndromes and over 20 antiepileptic agents licensed in the United Kingdom. Many of the inherited childhood epilepsy syndromes have very particular phenotypes and seem to encompass a wide range of underlying pathology. Likewise, treatment for these syndromes differs significantly. It is beyond the scope of this article to cover the details of all antiepileptic drugs, ergo the reader is referred to a review article by Duncan et al for a summary of the other licensed antiepileptic agents. This article provides details of the agent's putative modes of action, elimination, year of introduction, dosing and main safety issues [29].

EPILEPSY SURGERY

The classic aim of epilepsy surgery was a complete removal of the epileptogenic focus without neurological deficit [30]. This goal fails to consider more complex psychosocial and quality of life issues inherent in most patient encounters. There have been various outcome measures applied to surgical management of epilepsy syndromes. Classically seizure frequency and overall mortality were the markers used, but over time the importance of morbidity and patient quality of life have become more recognised. The efficacy of surgery, like antiepileptic drugs, must take these complex factors into account [31].

There are two main divisions of epilepsy surgery; that taken with curative intent and that performed as a palliative procedure.

The selection criteria vary between centres but patients are generally considered for surgical intervention when they fulfil the core criteria of:

- Focal seizures with a lesion identifiable on imaging (in most cases) that is amenable to surgical intervention

- Supportive electrophysiological data, often in the form of an scalp or invasive electroencephalogram (EEG)

- Refractory to medical therapy or intolerable side effects

- No contraindications to surgery

CURATIVE SURGERY

The commonest and best-studied forms of epilepsy surgery are anteromesial or localized neocortical resection for mesial temporal sclerosis (MTS). This accounts for up to 75% of adult epilepsy surgery [32, 33]. The focal removal of a unilateral sclerotic hippocampal lesion with an anteromesial resection in well-selected patients has a seizure free success rate of around 60-70%. The results for neocortical resections are slightly less encouraging with a seizure free rate of around 50% but with an overall improvement rate of 85%. Surgical morbidity and mortality is generally small in this group [34]. The results at one year seem to predict the long-term outcome accurately [35]. The commonest permanent deficit is a disruption of Meyer's loop causing a superior homonymous quadrantanopic visual field defect that excludes the patient from being eligible to hold a United Kingdom driving license. Improved localization of lesion and eloquent cortex has occurred with the introduction of intracranial electroencephalography with depth electrodes and judicious use of functional magnetic resonance imaging to localize language and other important cortical regions [36-38]. The general trend with surgical refinement and experience is towards improvement and it is hoped that advances such as in vivo white matter bundle identification with diffusion-weighted tractography the risk of inadvertent field defects will be further reduced. The use of surgery in this class of

patients is widely accepted and on a population level this intervention appears beneficial, certainly there is no appropriate medical therapeutic alternative.

Other important curative surgical procedures include removal of space occupying lesions that are epileptogenic or for focal cortical dysplasias. It is difficult to interpret outcomes in these groups due to the diverse range of pathologies and expected prognoses depending on the underlying cause. A recent retrospective study analysed 120 cases of focal cortical dysplasia (including MTS) and found that histological subtype and age of onset was not prognostic [39]. It seems that patients with dysembryoplastic neuroepithelial tumours (DNETs), cystic lesions and vascular malformations have at least as high refraction rates as in MTS [40].

PALLIATIVE SURGERY

In patients with epilepsy that is beyond medical or surgical cure the option of palliation is profoundly important. Radical resections may benefit patients with refractory epilepsy from vascular defects, acquired dysfunction, malformations or developmental abnormalities beyond the remit of lesionectomy [41, 42]. These operations can be quite radical and may extend to complete hemispherectomy in children. In the complex multiseizure Lennox-Gastaut syndrome corpus callostomy is sometimes used with moderate success although no clinical trials have assessed this efficacy of this technique [43]. One interesting method of ameliorating the frequency of seizures is to create a series of cortical incisions below the pia mater with the aim of inhibiting paroxysmal cortical depolarizations. The efficacy of this technique is still being questioned but advocates report good rates of success [44]. The apparent benefits of palliative surgery are often only counted in terms of reduced seizure frequency. Clinical decisions and eligibility criteria in these areas are often difficult with minimal evidence to guide best practice [40].

FUTURE DEVELOPMENTS
NEW DRUGS

As already alluded to, many of the anti-epileptic medications on license have come about, at least in part, due to serendipitous circumstances. The vogue in the scientific community is to rely less on fortune and to try and create medicines based on scientific reasoning. In this respect there have been several partial successes. Vigabatrin was the first 'designer' anticonvulsant agent and despite the severe risks of visual field defects and potential to lead to psychiatric disturbances it still has a role in West's syndrome, a rare and particularly severe form of infantile epilepsy [45]. Other examples of newer drugs with varied efficacy include gabapentin, pregabalin, tigabine, topiramate, levetiracetam and zonisamide. Despite the apparent plethora of new drugs it is notable that the new agents seem to be more 'fine-tuning' than 'radical new cure'. This may be related to the relative inaccuracy of current animal seizure models and their inability to identify new therapeutic mechanisms, instead producing 'me too' drugs [46]. The extent to which this is true is debatable, and with better understanding of epileptogenesis there may be scope to develop newer, more accurate models on which to test novel compounds. The alternative of primary in vivo experimentation is generally considered ethically suspect and technically impractical. With these existing barriers and the current scientific framework we are left to join patients in hoping for epiphanic pharmaceutical success, be it by molecular targeting or animal models [46].

PHARMACOGENOMICS

The concept of individually designed and personalised medicines is central to the field of pharmacogenomics. The individual balance of pharmacodynamics and pharmacokinetics markedly affects the efficacy and side-effect profile of drug on each individual. Current dosing strategies and treatment schemes are based on Gaussian concepts of population-based responses. There exists a developing science by which drug treatment could conceivably be more accurately tailored to an individual. Key areas are drug absorption that may be more accurately determined by individual typing of transporters and counter-regulatory enzymatic eliminatory function. Examples include the current research into the expression of P-glycoprotein (pgp) that may determine the initial bioavailability of antiepileptic agents [47, 48]. Drug distribution is a second important part of pharmacogenomics, and knowledge of the extent to which a drug is apparently distributed in individuals should improve dosing accuracy. There have been multiple studies into the ABCB1 gene polymorphism and some have shown clinically significant effects on cerebrospinal fluid levels of antiepileptics [49]. The extent to which the may be important in refractory epilepsy is still not known but further study is certainly warranted. There are many other areas in which pharmacogenetics may improve epilepsy treatment. These range from dosing improvement with better understanding of excretory functions to side effect prediction and event prediction of teratogenicity risk [47].

NEUROSURGICAL PROGRESS

Over the past two decades stereotactic neurosurgical targeting has transformed operative practice and significantly improved patient outcomes. These benefits have come largely from the surgical enhanced accuracy provided by the technique. Analogous new developments include the application of magnetoencephalography and diffusion-weighted tractography to epilepsy surgery. These modalities promise to improve localisation of lesions and improve the resolution of resection margins with the goal of complete lesion removal and greater retention of eloquent cortex [50]. The clinical applications of these technique are still being explored but progress must be made carefully as there are already cautionary tales in the literature where over-reliance on the imaging without other support have lead to detrimental outcomes [51, 52]. The role of white matter tractography is now being investigated specifically in epilepsy surgery [53]. Likewise, transcranial magnetic stimulation and deep brain stimulation in epilepsy are being increasingly studied. They remain in their infancy but the potential for these techniques are significant and results so far are generally positive especially in refractory cases [54, 55]. Other invasive treatments with potentially revolutionary benefits include targeted direct application of stem cells, pharmaceuticals and even viral particulates to epileptogenic foci. Only further time and study will reveal how successful these strategies will be [29].

CONCLUSION

Despite the apparently wide range of treatment modalities available for epileptic syndromes there are still a significant proportion of patients who suffer unacceptable morbidity and mortality from this disease. A greater understanding of the underlying neuropathology involved in different epilepsy syndromes will hopefully lead to improved treatment options. Whether improvements will come from logical scientific developments or from serendipity as so often in the past, it remains to be seen. Regardless, it is important that those involved in epilepsy care and new treatment developments understand the individual nature of the disease. Effective new treatments must aim not only to reduce seizure frequencies but also to improve the patient's quality of life.

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Author Information

HC Scott

Institute of Neurology, Queen Square, London