

# Current and future aspects of the drug therapy of epilepsy

By CHARLES TUGWELL, MSc, MRPHARMS

*The second article in this  
month's special feature  
discusses current  
anti-epileptic drugs,  
looks ahead to possible  
therapeutic developments  
and emphasises the  
opportunities for  
clinical pharmacists to  
improve medicines  
management  
in patients with epilepsy*

*Abnormal neuronal discharge in the brain (pictured here conceptually as light trails) causes seizures, which can often be controlled using anti-epileptic drugs*

**T**he first documentation of epilepsy was made around 400 BC in the book "On the sacred disease," attributed to Hippocrates. The condition was considered magical and contagious — caused by intervention of the gods. Treatments included exorcism, bleeding, castration and drinking

the blood of fallen gladiators. Although perfect treatments still elude us today, we have come a long way in terms of the therapy we can offer patients. This article discusses currently available anti-epileptic drugs and outlines possible developments we should look forward to in the future.

the patient. The aim is to achieve control of seizures and improve quality of life while keeping the occurrence of adverse drug effects to a minimum. Clearly, within the health care setting, we need to achieve these goals in the most pharmacoeconomic manner.

A proportion of patients will continue to have seizures despite treatment. However, even if complete freedom from seizures cannot be achieved, a reduction in frequency and severity is achievable in most patients. Even attaining this lesser goal can result in a substantial improvement in a patient's quality of life.

## GOALS OF THERAPY

**I**t is important to set targets when planning the approach to treatment for individual patients with epilepsy. Therapeutic goals should be clearly defined and discussed with

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Adverse reactions are a major issue with anti-epileptic drugs, although they may be less problematic with some of the newer agents. Careful attention to choice of drug for the individual, dosing and rigorous monitoring help to minimise the problems of adverse effects while maximising the potential benefits from therapy.

## — APPROACH TO DRUG THERAPY

Although a significant proportion of patients will require treatment with two or more anti-epileptic drugs, monotherapy should always be used if a satisfactory level of seizure control can be achieved. The likelihood of adverse drug reactions and the complication of drug interactions increases substantially with polytherapy. Studies suggest that approximately 70–80 per cent of patients are adequately controlled with monotherapy. Initial choice of drug is influenced by the nature of the epilepsy syndrome. An accurate diagnosis is therefore a prerequisite to appropriate choice of drug. Indeed, certain anti-epileptic drugs can exacerbate some seizure types. As discussed in the first article in this feature (p288), the distinction between focal (localisation related) and generalised epilepsies is crucial.

A decision also needs to be made on whether to treat if the patient has only experienced one seizure. Overall, the risk of further seizures is 30–40 per cent,<sup>1</sup> falling to less than 10 per cent after two years.<sup>2</sup> However the probability of recurrence can be as high as 90 per cent and as low as 13 per cent, depending on the cause and nature of the seizure and EEG findings.

Primary generalised seizures are usually treated with either sodium valproate or lamotrigine. These two drugs are also considered first-line treatments when there is some doubt about the type of seizure the patient has had. In female patients of child-bearing age, lamotrigine is considered the most appropriate choice.

Partial (focal) and secondary generalised seizures respond to a range of drugs: carbamazepine, sodium valproate, lamotrigine and oxcarbazepine are all appropriate first-line agents. Again, lamotrigine is considered the most appropriate choice in female patients of child-bearing age.

There are now around ten anti-epileptic drugs commonly used in the UK; brief details of these, including typical dosages, are given in Table 1 (p300).

The dosage of anti-epileptic drug should be increased gradually to minimise the risk of troublesome adverse effects and to titrate dosage according to the patient's response. If the chosen first-line drug fails to produce a satisfactory effect, another agent from the first-line group should be added. After this has been titrated to an appropriate dose, an attempt can be made to withdraw the initial drug. This withdrawal should be carried out cautiously since rebound seizures may occur. Unfortunately, despite optimising therapy with a single agent, approximately 30 per cent of patients will not achieve adequate seizure control and will require polytherapy.

## — ADVERSE EFFECTS

Some of the newer anti-epileptic drugs appear to cause fewer problems with adverse effects. Common adverse effects are mostly dose-related, and gradual increase in dosage helps to minimise these. Common adverse effects such as drowsiness, headache, fatigue, dizziness and nausea can occur with most of the drugs. However, more specific concerns exist with a number of agents, the more serious of which deserve special mention.

Vigabatrin can cause irreversible visual field defects. Onset varies from a few weeks to several years after starting treatment. Visual field testing is essential before treatment is started and should be carried out regularly thereafter. Patients should be asked to report any visual symptoms urgently; however, development of visual field defects can be asymptomatic.

Lamotrigine commonly causes skin rashes. These are usually not serious, but patients should always report them since life-threatening

skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis, can occur. Serious reactions are more common in patients who are also receiving sodium valproate and those who are prescribed initial doses of lamotrigine higher than recommended.

Topiramate may increase the risk of renal stone formation in some patients. It is thought that this results from its inhibitory effect on carbonic anhydrase. This adverse effect is more likely in patients with a predisposition to nephrolithiasis. Patients should ensure adequate fluid intake to reduce the risk of this problem.

Sodium valproate can cause hepatic failure and this has resulted in a number of deaths. Patients should be advised to report immediately symptoms that might indicate hepatic failure (loss of seizure control, malaise, weakness, lethargy, oedema, anorexia, vomiting, abdominal pain, drowsiness, jaundice).

Sodium valproate can also have teratogenic effects and should only be used in women of child-bearing age when there is no satisfactory alternative.

This is by no means a comprehensive review of the serious adverse effects which can result from the use of anti-epileptic drugs.

## — DRUG INTERACTIONS

The potential for drug interactions with anti-epileptic drugs is enormous.<sup>3</sup> Furthermore, interactions are sometimes complex and to some extent unpredictable.

Anti-epileptic drugs not only interact with many other types of drug, they also interact with each other (Table 2, p301). Phenytoin, carbamazepine and phenobarbital induce liver enzymes and thereby reduce levels of sodium valproate, topiramate, lamotrigine, tiagabine and oxcarbazepine, as well as reducing their own blood levels. Sodium valproate inhibits liver enzymes which can result in increased levels of carbamazepine, lamotrigine and tiagabine.

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The interaction between sodium valproate and phenytoin is an example of one which can be complex. Initially, sodium valproate may produce a fall in total serum phenytoin levels. This is a result of sodium valproate displacing phenytoin from protein binding sites and more unbound drug subsequently becoming available for metabolism. However, the rise in free active phenytoin increases the potential for toxic effects. After a while, liver enzyme inhibition caused by sodium valproate leads to a reduction in the metabolism of phenytoin and levels then rise. The situation is further complicated since phenytoin induces liver enzymes and this can cause the levels of sodium valproate to fall.

A thorough understanding of pharmacokinetics and the significance of changes in total and unbound (free) drug is needed to assess the likely consequences of such interactions and to decide on the most appropriate management of drug therapy.

This links in with good interpretation of the results from drug level monitoring. Other clinical conditions may similarly call upon these skills. Significant hypoalbuminaemia, for example, may affect the pharmacokinetics of phenytoin, necessitating calculations to take account of the changes in the proportion of unbound to bound drug. The appropriate interpretation of blood level results (which normally report total drug) is important.

Levels of gabapentin and levetiracetam are unlikely to change as a result of the administration of other anti-epileptic drugs and these drugs do not themselves significantly alter the levels of other drugs. Table 2 summarises the most important interactions between anti-epileptic drugs.

### — PREGNANCY

It is generally acknowledged that there is an increased risk of major fetal

malformations in women taking anti-epileptic drugs. This is in the order of 5–6 per cent for women receiving monotherapy, although with sodium valproate and carbamazepine the risk increases to 6–7 per cent. It is worth remembering that this still means there is more than a 90 per cent chance the women will have a healthy baby. However, risk is further increased if the patient has high plasma levels of drug, or if more than one anti-epileptic drug is used.

Since between 0.5 and 1 per cent of pregnant women have epilepsy and the vast majority of those take anti-epileptic drugs, this is an important issue. In particular, there is a link between folate levels and the development of neural tube defects, and some anti-epileptic drugs reduce folate levels. Women with epilepsy who are planning pregnancy should take folic acid 5mg daily starting pre-conception and continuing throughout pregnancy. Pre-conception counselling and review of therapy should be

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regarded as essential in women with epilepsy considering pregnancy.

Major malformations are particularly associated with the use of sodium valproate, carbamazepine and oxcarbazepine.<sup>4</sup> Cleft lip/palate and cardiac malformations are the major effects which most often occur; effects on the brain and spine are also seen. Sodium valproate carries a 1–2 per cent risk of causing neural tube defects.

Less serious congenital abnormalities have been associated with all anti-epileptic drugs, although there is evidence that these abnormalities may occur in women with epilepsy irrespective of therapy.

The early stage of embryogenesis is the time of greatest potential for major malformations. Since the majority of women discover they are pregnant at about six weeks gestation, any harm caused by anti-epileptic drugs may already have resulted. This is an important consideration when deciding whether to modify or stop therapy.

It is also necessary to bear in mind that over 30 per cent of women with epilepsy suffer an increased rate of seizures during pregnancy. There are several reasons for this, including alterations in the pharmacokinetics of the anti-epileptic drug(s) being taken. Drug concentrations may fall because of increases in the volume of distribution and clearance of the anti-epileptic drug, especially in the second half of pregnancy.

Balancing the risk of any toxic effects on the fetus against the risks associated with poor seizure control if therapy is withdrawn, will usually force the decision to manage the pregnant woman with epilepsy by optimally treating the seizure disorder.

#### — BREAST-FEEDING

Except for mothers receiving phenobarbital and some of the newer drugs, there is generally little concern about the risk to infants from breast feeding. Small amounts

of anti-epileptic drug will be present in breast milk, but these are considered unlikely to cause harm. That said, concern has been expressed about the potential effects on long-term development; studies are needed to show if such adverse effects can occur.

#### — FUTURE DEVELOPMENTS

A number of new anti-epileptic drugs have become available in recent years but they have by no means revolutionised the management of epilepsy. There is little evidence that they are significantly more effective than the older agents, and generally the improvement in side effect profile is modest.

Few data exist to allow comparison of the newer agents with the long-established agents. In an attempt to address this, the NHS is funding a trial known as SANAD (Standard And New Anti-epileptic Drugs). This study of the longer-term clinical

**Table 1: Currently available anti-epileptic drugs**

Drug	Indications	Typical starting dose	Typical maintenance dose
Sodium valproate	All forms of epilepsy	300mg twice daily	1–2g daily in divided doses (the modified-release product may be taken once or twice daily)
Phenytoin	All forms of epilepsy except absence	150–300mg daily (single dose or divided)	200–500mg daily (single dose or divided)
Carbamazepine	Partial and some generalised seizures	100–200mg once or twice daily	0.8–1.2g daily in divided doses (the modified-release product is taken twice daily)
Lamotrigine	Monotherapy and adjunctive therapy for partial seizures and generalised tonic-clonic seizures	Monotherapy: 25mg daily Adjunctive therapy with valproate: 25mg on alternate days Adjunctive therapy with enzyme-inducing drug: 50mg daily	Monotherapy: 100–200mg daily (single dose or divided) Adjunctive therapy with valproate: 100–200mg daily (single dose or divided) Adjunctive therapy with enzyme-inducing drug: 200–400mg daily in two divided doses
Topiramate	Adjunctive therapy for partial and generalised tonic-clonic seizures	25mg daily	200–400mg daily in divided doses
Tiagabine	Adjunctive therapy for partial seizures	5mg twice daily	30–45mg daily in divided doses (doses >30mg daily should be taken in three divided doses)
Oxcarbazepine	Monotherapy and adjunctive therapy for partial seizures	300mg twice daily	0.6–2.4g daily in divided doses
Levetiracetam	Adjunctive therapy for partial seizures	500mg twice daily	2–3g daily in two divided doses
Gabapentin	Adjunctive therapy for partial seizures	Day 1: 300mg Day 2: 300mg twice daily Day 3: 300mg three times daily, then according to response	0.9–1.2g daily in three divided doses
Vigabatrin	Adjunctive therapy for partial seizures	1g daily as single or divided dose	2–3g daily as single or divided dose

*Less commonly used drugs, such as phenobarbital, primidone, ethosuximide, clonazepam and clobazam, are not included in this Table. The drug therapy of status epilepticus is not covered in this article.*

outcomes and the cost-effectiveness of agents is expected to be completed by the end of August. It focuses on the two most commonly used first-line treatments in the UK, carbamazepine and sodium valproate, and compares efficacy, tolerability and overall effectiveness with three newer drugs: gabapentin, lamotrigine and topiramate. The aim of the trial is to determine the grounds on which a new drug might reasonably be regarded as first-line treatment. The economic evaluation is an important part of this study since use of the newer drugs has a significant cost implication for the NHS.

The ultimate goal of complete freedom from seizures with treatment which is free of side effects is still a long way off. In addition to developing new strategies for treating the processes of epilepsy and their consequences (as opposed to merely suppressing seizures), the search for better anti-epileptic drugs continues.

Many compounds have been developed<sup>5</sup> but these can fall by the wayside because of disappointing efficacy or major concerns about toxic effects. Remacemide, for example, is unlikely to be further developed

as clinical trials have produced disappointing results. Work on refinamide, losigamone and ganaxalone has also halted despite initial hopes that these would be useful drugs.

Felbamate and zonisamide are not available for routine use in the UK, although they are marketed in some other countries. Felbamate is an effective drug but was found to cause serious aplastic anaemia and liver failure. It is estimated that one in 4,000 patients treated is affected.

At least three derivatives of valproic acid are currently in clinical trials. These may be more potent and less toxic than sodium valproate.<sup>6</sup> There is hope that they will prove to be less hepatotoxic and teratogenic; some of the *in vivo* data look promising.

Pregabalin is currently at the phase III stage of development. It is a derivative of gabapentin which increases the levels of GABA (gamma-aminobutyric acid) in neuronal tissue and binds to a subunit of Ca<sup>2+</sup> channels.

Retigabine is also undergoing phase III trial evaluation. Results from animal studies suggest it has potent anticonvulsant activity, possibly mediated by increasing K<sup>+</sup> conduc-

tance in neuronal cells. Some of the other drugs in various stages of development are shown in Table 3, p301.

The quest for new drugs that have properties conferring advantages over existing agents is not the only avenue being explored for future treatments. A major advance would be a new drug that not only reduces seizure frequency and severity but also directly affects the changes occurring in the brain which precipitate seizure activity. It has been claimed that some existing drugs do have such antiepileptogenic properties. These include sodium valproate and levetiracetam, but clearly much more work needs to be carried out on this approach to treatment.

For most seizure types, it is not clear to what extent any secondary brain damage results, although there is good evidence that hippocampal and cerebral damage can occur during status epilepticus. Drugs that have a neuroprotective effect may offer advantages in preventing long-term damage. Evidence that this is a significant property for existing drugs is limited.

An alternative to developing anti-epileptic drugs with neuroprotective effects would

be the development of specific neuroprotectant agents that could be taken concomitantly with the anti-epileptic drug.

Magnetic resonance spectroscopy is now sufficiently advanced to measure concentrations of GABA and glutamate in the brain non-invasively. If an appropriate relationship can be determined between concentrations of these compounds and seizure activity, the tailoring of anti-epileptic drug therapy based on pharmacological requirements might be possible. Thus, in the future, a profile of the chemical pattern within a patient's brain might assist in selecting the specific anti-epileptic drug most likely to produce the desired effect.

There are also suggestions that it might become possible to predict responses to individual anti-epileptic drugs based on certain genetic characteristics. Similarly, it might become feasible to identify in advance those patients who are more likely to suffer adverse effects such as allergic reactions to carbamazepine or lamotrigine. As mentioned previously, felbamate is an effective anti-epileptic drug, but it is not licensed in the UK because of the small risk of aplastic anaemia. If it became possible to identify those patients who would not develop the reaction, the drug could be of significant clinical value.

**Localising drug delivery** The idea of delivering an anti-epileptic drug directly to the site of action is attractive. Not only could such an approach increase efficacy, it is also likely to reduce the risk of adverse effects substantially. In some patients with focal seizures it is possible to identify the specific area of the brain where seizure activity is being generated. It is conceivable that micro-systems which deliver minute quantities of drug accurately to a selected site can be designed.

Currently, anti-epileptic drug therapy is given systemically, and normally continuously since it has not been possible to forecast when a seizure might occur. However, a paper published in *The Lancet* two years ago showed that it was possible to

**Table 2: Liver enzyme induction/inhibition caused by anti-epileptic drugs — effects on serum levels of other anti-epileptic drugs**

Drug affected	Enzyme inducers	Enzyme inhibitors
	Phenytoin	Sodium valproate
	Phenobarbital	
	Carbamazepine	
Phenytoin	–	/ (see text)
Phenobarbital	–	/
Carbamazepine	–	/
Sodium valproate		–
Gabapentin	no change	no change
Lamotrigine		/
Topiramate		no change
Tiagabine		/
Levetiracetam	no change	no change
Oxcarbazepine	*	*

\* sometimes lowers levels of an active metabolite of oxcarbazepine

anticipate epileptic seizures up to 18 minutes before they occurred.<sup>7</sup>

Again, it is conceivable that systems could be developed which monitor EEG activity (perhaps an implanted sensor) and could trigger therapeutic intervention in advance of the impending seizure. This could take the form of local delivery of drug (see above) or systemic administration to prevent manifestation of the seizure.

### MANAGEMENT ISSUES

This review only touches the surface of a complex area of medicine. Numerous issues affect the management of patients with epilepsy, not only from a drug therapy perspective, but also in terms of the availability of specialists to provide appropriate diagnosis and overall management of the condition. A detailed set of guidelines on the diagnosis and management of epilepsy published earlier this year in Scotland<sup>8</sup> confirms this view, and is

recommended reading for anyone needing a deeper insight than this article is able to give in the space available.

There is little doubt that the standard of care given to this large group of patients needs to be substantially improved. Audit results cited in the recent Department of Health action plan “Improving services for people with epilepsy”<sup>9</sup> were that 54 per cent of adults with epilepsy in hospital had inadequate care, and it was concluded that 39 per cent of adult deaths were potentially or probably avoidable. The incidence of inadequacies in drug management was stated to be 20 per cent. In children, the results were even more alarming. It was concluded that 59 per cent of deaths in children were potentially or probably avoidable and inadequate drug management was reported at a level of 45 per cent.

In the light of these and other findings, the document outlines how the Department of Health intends to make improvements. These include the plan to have a particular focus on neurological conditions (including epilepsy) in the National Service Framework for Long-term Conditions. This NSF is due for publication next year with a proposed 10-year implementation programme starting in 2005. However, the action plan has been described as “fundamentally flawed” by the Joint Epilepsy Council, which stated that it was unlikely to deliver any significant improvement in care for people with epilepsy.<sup>10</sup> This belief is based on the fact that the NSF will not contain specific targets and milestones for epilepsy and on the absence of mechanisms to monitor progress resulting from implementation of the action plan.

The Department of Health strategy document “Pharmacy in the future”<sup>11</sup> aims to ensure patients have easy access to the

**Table 3: Potential future anti-epileptic drugs**

Drug	Class
Valproyl glycinamide	valproic acid derivative
3-Methylbutanamide (isovaleramide)	valproic acid derivative
SDP421 (DP-VPA)	valproic acid derivative
Pregabalin	GABA analogue
Retigabine	carbamic acid derivative
Harkoseride	aceto-propionamide amino acid
Talampanel	AMPA* antagonist
Caraberstat	benzopyran
Safinamide (NW 1015)	methansulfonate
Valroceamide (TV1901)	valproyl derivative of GABA
AWD131-138	imidazolin
NPS 1776	aliphatic amide

\* alpha-amino-3-hydroxy-5-methylisoxazole-4-propionate

medicines they need and to high quality pharmaceutical care. The Department of Health is setting up programmes to support this strategy in relation to patients with epilepsy.

The National Institute for Clinical Excellence (NICE) is looking at the newer anti-epileptic drugs and its appraisal is due in October this year. Clinical guidelines are also being prepared by NICE covering the diagnosis, management and treatment of epilepsy. These are scheduled for publication in June 2004.

Whatever happens from government initiatives, there are clearly many opportunities for clinical pharmacists to bring about a major improvement in the management of medication in patients with epilepsy. There are numerous pharmaceutical issues relating to the use of drugs, including choice of agent, dosing regimens, interaction potential, interpretation of serum levels, therapeutic inequivalency of different formulations, issues during pregnancy and breast feeding and adverse effects.

Pharmacists' long-standing involvement in compliance and concordance issues is also valuable, since the implications of non-compliance may be substantial in these patients. Non-compliance is more likely to occur if a concordant approach has not been taken when drawing up the treatment

plans for patients with epilepsy.

Clinical pharmacists have superb opportunities to optimise therapy for these patients and, as a result, to have significant impact on clinical outcomes and patients' quality of life.

*Credit for learning begins on p309*

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