9 Epilepsy
The incidence of epilepsy is highest in the first two decades of life. It falls after that only to rise again in late life. Epilepsy is one of the most common chronic neurological condition in children with approximately 5000-7000 children having active epilepsy in Scotland. It is therefore a condition that pharmacists will encounter regularly, enabling them to contribute to, and improve patient care. The pharmacological management of childhood epilepsy can present many challenges and pharmacists have an important role in using their knowledge and expertise to help address or overcome these.

Objectives

On completion of this chapter you should be able to:

- list the most common types of childhood epilepsies and their symptoms
- describe the pharmacological management of epilepsy in children
- describe the pharmacological management of status epilepticus
- outline the main pharmaceutical care issues when managing epilepsy in children.
1. The disease

Epilepsy is defined as a condition characterised by recurrent epileptic seizures. An epileptic seizure is the result of an abnormal and excessive discharge of a set of neurones in the brain.

Seizures occur in approximately 10% of children. Most seizures in children are provoked by somatic disorders originating outside the brain, such as high fever, infection, syncope, head trauma, hypoxia, toxins or cardiac arrhythmias. Less than one third of seizures in children are caused by epilepsy.

1.1 Classification of epileptic seizures

There are international classifications for both seizure type and epilepsy syndrome. There are two main categories of epileptic seizures; generalised and focal. The tables below describe this classification and details the most common symptoms associated with generalised and focal seizures. Classification is important as this may help identify the epilepsy syndrome which will help refine the choice of medication to maximise benefit and minimise adverse effects.

- **Generalised seizures** involve large areas of brain from the outset, usually both hemispheres and are associated with early impairment of consciousness. These range from absences (impairment of consciousness), which are mainly seen in children and adolescents, to generalised tonic clonic seizures with loss of consciousness.

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>Common symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generalised seizures</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Tonic clonic (grand mal) | Tonic phase  
Loss of consciousness  
Rigidity  
Cyanosis  

| | Clonic phase  
Convulsions  
Saliva frothing at mouth  
Incontinence |
| Absence seizures (petit mal) | Loss of awareness  
Loss of motor activity  
Motionless, unresponsive  
Repetitive movements e.g. fluttering of eyelids |
| Myoclonic | Single or repetitive jerks  
Falls (with almost immediate recovery) |
| Tonic | Falls due to increase in muscle tone |
| Clonic | Repetitive jerks which lessen as seizure progresses |
| Atonic (drop attacks) | Sudden loss of muscle tone  
Falls with immediate recovery |
• **Focal seizures** account for a large proportion of childhood seizures. They arise in specific locations of the cerebral cortex (usually frontal or temporal lobes) and carry with them identifiable clinical features. Focal seizures can develop into generalised seizures. Consciousness may or may not be impaired.

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>Common symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Focal (partial) seizures</strong></td>
<td>No loss of consciousness, Jerks/spasms (motor centre), Tingling/numbness (sensory centre)</td>
</tr>
<tr>
<td><strong>Simple partial seizures</strong></td>
<td>Impairment or loss of consciousness, Dizziness, Altered perceptions, hallucinations, Lip smacking, Facial movements or fidgeting</td>
</tr>
</tbody>
</table>

**Status epilepticus**
Status epilepticus is a condition characterised by frequent and prolonged epileptic seizures. Convulsive status epilepticus (CSE) is currently defined as epileptic activity persisting for 30 minutes. Status epilepticus can be fatal because of complications of the convulsion, aspiration of vomit, or overmedication. Mortality is lower in children than in adults at about 4%. Neurological outcome following CSE is age dependent. Sequelae such as persistent epilepsy, motor deficits, and behavioural or learning difficulties occur in 6% of those over three years but in 29% of infants under one year. (See also Section 3 Convulsive status epilepticus on page 114.)

**Epileptic syndromes**
Epilepsy can also be classified by syndrome. Epileptic syndromes have been defined as a complex of signs and symptoms that define a unique epilepsy condition. This must involve more than just the seizure type; thus frontal lobe seizures per se, for instance, do not constitute a syndrome. Examples of epilepsy syndromes include infantile spasms (West syndrome), benign myoclonic epilepsy of infancy and the Lennox-Gastaut syndrome.

Seizures are more common in infants and certain seizures in the paediatric population are age specific (e.g. infantile spasms). This observation suggests that the underdeveloped brain is more susceptible to specific seizures than the more developed brain of an older child or adult.
1.2 Diagnosis

There is evidence that misdiagnosis of epilepsy is a significant problem. It is important that the correct epilepsy syndrome (or seizure type if syndrome cannot be diagnosed) is known to ensure the appropriate management.

An accurate history and description of clinical features is very important in making a diagnosis. Often the patient cannot describe what happened as they are unaware of their experience or may have lost consciousness. An eyewitness account is therefore useful.

Details of the frequency, time of day, precipitating factors, and alternation in the type of convulsive disorder are also important.

Clinical classification may be difficult because different seizure types may manifest themselves in similar ways. For example, the clinical features of a child with absence seizures may be almost identical to those of another with complex partial epilepsy. Electroencephalogram (EEG), electrocardiogram (ECG), computed tomography (CT) and magnetic resonance imaging (MRI) are all useful tools in diagnosis when clinical features are inconclusive.

For children with epilepsy, the prognosis is generally good, but 10-20% have persistent seizures that are difficult to control with drugs. These cases pose a diagnostic and management challenge for healthcare staff caring for them.
2. Management of epilepsy

The decision to start antiepileptic medication should be based on the type of epileptic seizure or syndrome and the risks-benefits of drug therapy for the individual and their family. The potential adverse effects of antiepileptic drugs (AEDs) should be a major determinant of the choice of drug in the individual child.

Generally monotherapy is preferred and it will control seizures in most children. Drugs should be introduced slowly to reduce the incidence of adverse effects and to ensure the lowest effective dose is used. If the initial drug therapy is partially or totally ineffective then a second agent should be added and the first may be gradually withdrawn.

If monotherapy is ineffective in controlling seizures then two drugs (but rarely more) may be required. Combination therapy may increase adverse effects and reduce compliance.

Most AEDs used in children are licensed (either in all ages, for those over two years or those over six years), apart from some of the newer agents such as tiagabine and pregabalin. However, as seizures and epileptic syndromes are common in infants and young children, drugs often have to be used off-label. The introduction of appropriate dosage forms for children is improving and many of the widely used anti-epileptic drugs are available in either liquid or powder form for ease of use in children.

Activity 9.1

Using the BNF or BNF-C, list the antiepileptic drugs that are licensed for use in children. Of those, which are available in appropriate dosage forms?

workbook page 18

2.1 Choice of antiepileptic drug

The choice of antiepileptic drug (AED) should be individualised for each patient based on seizure type, as well as clinical and social parameters of the patient and family. Evidence has shown that involving parents and/or family in decisions about the different choices of treatment improves adherence to medication regimens. Children and parents should be informed of the main risks and benefits of each AED so that an informed choice can be made.

SIGN Guideline 81 Diagnosis and Management of Epilepsies in Children and Young People gives evidence-based advice on the most appropriate anti-epileptic agent for the seizure type or syndrome. The table on the following page provides a summary. The National Institute for Clinical Excellence (NICE) has also published treatment recommendations, although they concentrate on the newer AEDs (the clinical effectiveness and cost effectiveness of newer drugs for epilepsy in children).

Dose recommendations can be found in the current BNF and BNF-C.

Combination therapy should only be considered when two appropriate AEDs (at appropriate dosages) have failed as monotherapy.
## Epilepsy

### Generalised epilepsies

<table>
<thead>
<tr>
<th>Choice of AED (monotherapy)</th>
<th>Comments / other drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tonic clonic</strong> (grand mal)</td>
<td>Sodium valproate, lamotrigine, carbamazepine</td>
</tr>
<tr>
<td><strong>Absence seizures</strong> (petit mal)</td>
<td>Sodium valproate, lamotrigine, ethosuximide</td>
</tr>
<tr>
<td><strong>Myoclonic</strong></td>
<td>Sodium valproate</td>
</tr>
<tr>
<td><strong>Infantile spasms</strong> (West syndrome)</td>
<td>Vigabatrin, corticosteroids corticotrophin (ACTH), nitrazepam, sodium valproate (high dose)</td>
</tr>
<tr>
<td><strong>Lennox Gastaut Syndrome</strong></td>
<td>Sodium valproate</td>
</tr>
</tbody>
</table>

### Generalised epilepsies

| Simple and complex partial seizures | Sodium valproate, carbamazepine, lamotrigine, topiramate, oxcarbazepine | Clobazam, gabapentin, levetiracetam or tiagabine are second-line drugs. |

### 2.2 Adverse effects of antiepileptic drugs

Adverse effects from AEDs are a major cause of drug withdrawal or non-compliance with drug therapy. They also influence the choice of long-term treatment in children. Take carbamazepine and phenytoin, for example; they have a comparable efficacy but carbamazepine is the preferred agent of choice for long-term therapy in children because it has none of the cosmetic adverse effects of phenytoin. Treatment must aim to strike a balance between efficacy and toxicity.

Many adverse effects of AEDs are dose related and can be minimised by gradual introduction of therapy and escalation of dose. Lamotrigine, for example, is known to cause rash if treatment is initiated too quickly. As with all drugs, the potential adverse effects of the AED should be discussed with children and/or parents. This should be accompanied by clear instructions to seek medical attention for serious symptoms.

Adverse effects can be classed in two main groups; idiosyncratic drug reactions and chronic adverse effects.
Idiosyncratic drug reactions
Idiosyncratic drug reactions can manifest at any point during therapy and are potentially serious. They include:

- rash (carbamazepine and lamotrigine)
- pancreatitis (sodium valproate)
- blood dyscrasias† (carbamazepine and sodium valproate)
- hepatotoxicity (enzyme inducing AEDs)
- hyperlipidaemia (carbamazepine).

Chronic adverse effects
Chronic adverse effects are listed in the BNF and BNF-C. One example of an AED associated adverse effect is visual field defects in children taking vigabatrin. Vigabatrin is now recommended for use in the management of infantile spasms and is only used in other types of epilepsy when standard agents have failed. It is not recommended in children who are known to have, or who may be at particular risk of developing, a visual field defect. It is also advised that children receiving vigabatrin have visual field assessment by an ophthalmologist or optometrist. At present, this can only be done in children over nine years as the specifically developed method, for children aged 3 years and above, developed by Sanofi Aventis, has not been validated for detection of vigabatrin attributed visual field defects.

Pregnancy
The potential adverse effects of AEDs during pregnancy are also a matter for concern with girls who are likely to need to continue treatment into their childbearing years. All the older antiepileptic drugs have been associated with congenital malformations and, at present, there is insufficient data on the risks to the unborn child for the newer drugs. Multiple drug therapy is associated with a greater risk, although this may be related to the severity of the mother’s epilepsy. The risk of harm to an unborn child, and the possibility of interaction with oral contraceptives, should be discussed with the young woman and/or their carer, and an assessment made of the risks and benefits of treatment with individual drugs.

Activity 9.2
Based on current recommendations, what is most appropriate AED for a four-year-old girl (16.8kg) with absence seizures? She is taking no other drug therapy and has no relevant medical history. What dose and formulation would be most appropriate?

workbook page 18

2.3 Drug level monitoring
There is evidence that routine monitoring of AED drug levels does not effect clinical management, except to adjust phenytoin dosage. Routine AED level monitoring is not indicated in children.

In hospital, serum drug concentration is usually readily available and pharmacists can have an active role in treatment decisions by interpretation of the reported levels. This is more difficult in community pharmacy as the information required to interpret drug levels is not usually available.
Serum phenytoin drug concentrations are useful in determining whether there is scope for:

- increasing the dose of a drug in a child with poorly controlled epilepsy
- assessing compliance with treatment
- monitoring for drug interactions and adverse effects.

Blood concentrations are only useful if they are interpreted properly by taking into account:

- the clinical parameters of the individual patient
- the dose and timing of the drug.

**Drug interactions**

Drug interactions are common with the use of antiepileptic drugs. Many of the AEDs induce or inhibit enzyme systems used in drug metabolism. An understanding of the enzyme inducing or inhibiting capacity of each antiepileptic drug is important when assessing an individual’s drug therapy in relation to seizure control or adverse effects.

As well as having an awareness of drug interactions between AEDs, it is also important to be alert to interactions that can occur between AEDs and other medication. These are interactions that other health professionals may not be so familiar with and pharmacists have a responsibility to ensure any concomitant drug therapy is safe and effective. As an example, the influence of AED selection on choices of contraceptive methods needs to be borne in mind when choosing an AED for girls who are likely to continue treatment into their childbearing years. Some antibiotics such as macrolides that are commonly used in children can also interact with AEDs and may result in adverse effects.

Pharmacists must consider the significance of the drug interaction in relation to the individual and their clinical condition. When considering erythromycin and carbamazepine for example, it may be decided that the short-term use of erythromycin is unlikely to lead to significant adverse effects and it is sufficient simply to highlight the possible adverse effects to the patient/carer. Conversely, it may be decided that an alternative antibiotic is more appropriate if adverse effects are likely (i.e. the antibiotic course will be prolonged or the patient already has serum concentrations at the top of the target range), or that a small reduction in the carbamazepine dose is advisable.

See the BNF or BNF-C for a list of AED interactions.

**Activity 9.3**

Give four examples of drugs which can lower the seizure threshold and should be used with extreme caution in children with epilepsy.

workbook page 18
3. Convulsive status epilepticus

Convulsive status epilepticus (CSE) is a medical emergency. Early control is a priority as mortality and morbidity are related to the seizure duration. It is important to note that there is little evidence for the management of CSE in children. Treatment is largely based on adult management, adjusted for paediatric doses.

The figure below illustrates the standard management of CSE according to the *Advanced Paediatric Life Support* (3rd edition) and appears in the SIGN guideline as an example of how it might be managed.

Early management of seizures, before admission to hospital, reduces their length. Benzodiazepines are the initial drugs of choice and, as intravenous access is not usually possible at this stage, other routes of administration are necessary. Rectal diazepam was the drug of choice but now midazolam given via the buccal or intranasal route which is more socially acceptable route of administration, is an alternative choice in the older child. As no licensed preparation of midazolam is available for administration via these routes, normal practice is to use intravenous midazolam ampoules or a buccal liquid preparation available as a ‘special’. Patients with epilepsy are normally given a supply of diazepam or midazolam to treat CSE at home or before hospital admission.
Parents or carers require detailed training on the use of these drugs and on administration techniques. Pharmacists are in an ideal position to contribute to this training/education.

If seizures occur while in hospital, the treatment of choice is intravenous lorazepam. Lorazepam is equally as effective as diazepam and possibly produces less respiratory depression. It also has a shorter duration of action than diazepam. When intravenous access is unavailable intramuscular midazolam or rectal diazepam are the preferred choices.

**Continuing seizures**

There is a lack of good evidence on what should be done when seizures continue, despite treatment with benzodiazepines. Generally, a second dose of lorazepam should be given followed by paraldehyde, phenytoin and then phenobarbital. Paraldehyde is given by rectal administration and is made up as a 50:50 solution in olive oil. Arachis oil should be avoided due to the potential reaction in children with peanut allergy. Paraldehyde can cause rectal irritation but this route of administration is preferred to intramuscular use which can cause severe pain and sterile abscess formation.

Phenytoin is another option when CSE persists. As phenytoin has a narrow therapeutic index, it should only be used in children not already taking phenytoin or when a child’s measured phenytoin concentration is suboptimal. Phenytoin can cause dysrhythmias and hypotension. Therefore ECG and blood pressure monitoring should be carried out during the infusion. If phenytoin is not appropriate for an individual then intravenous phenobarbital is an alternative.

If these measures all fail to control CSE, then intubation and general anaesthesia should be considered. This should only be done by experienced staff and normally would require admission to an intensive care unit.

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**Activity 9.4**

Consider the key pharmaceutical care issues in a child prescribed buccal or intranasal midazolam for the first time. What actions would you require to take for the following pharmaceutical care issues?

- Verify dose correct and dose volume is practical for administration purposes.
- Ensure patient’s carer understands how and when to administer the midazolam.
- Ensure continuity of supply of midazolam

workbook page 19
Introduction to paediatric pharmaceutical care