**BACKGROUND**

Epilepsy is the second most common neurological disorder after stroke.\(^1\)\(^4\) It is a heterogeneous and serious disorder of the brain characterised by a predisposition to recurrent unprovoked seizures.\(^4\)\(^5\) It is estimated that worldwide approximately 50 million people have epilepsy;\(^6\) the two highest peaks in incidence occur in children and the elderly (>65 years).\(^3\)\(^5\)\(^6\) The prevalence of epilepsy varies by population; the incidence is higher in resource-poor countries.\(^5\) In Ireland it is estimated that up to 37,000 people >5 years of age have epilepsy;\(^6\)\(^7\) a general practitioner provides care to an average of 13 patients with epilepsy.\(^7\) In developed countries more than 60% of patients achieve long-term remission from epilepsy, usually within 5 years of diagnosis; the possibility of remission decreases the longer the epilepsy is active.\(^2\) Predictors of good outcome include earlier age of onset, fewer early seizures and early response to drug treatment.\(^2\)

In addition to psycho-social disabilities and seizure-related injuries, *epilepsy is associated with other co-morbidities* (such as depression) and increased mortality.\(^1\)\(^3\)\(^8\) The overall mortality in people with epilepsy is estimated to be 2 to 3 times the rate expected in the general population;\(^1\)\(^3\)\(^9\) the increased risk is due to the underlying cause of the epilepsy, an increased risk of accidents, status epilepticus (prolonged seizures) and sudden unexpected death in epilepsy (SUDEP).\(^3\)

It is estimated that mortality in patients with epilepsy due to SUDEP and status epilepticus account for between 48 and 162 deaths per year in Ireland.\(^8\) The highest risk of SUDEP is in male teenagers and young adults with epilepsy; other risk factors include generalised tonic-clonic seizures, high seizure frequency and anti-epileptic polytherapy.\(^5\)\(^9\)\(^10\) This bulletin will review current drug treatment of epilepsy in adults; the next bulletin will review some of the frequently asked questions on epilepsy received by the NMIC.

**CLASSIFICATION OF SEIZURES**

Seizures can be defined as transient signs and/or symptoms, which occur as a result of abnormal excessive or synchronous activity in the brain.\(^4\)\(^11\) *The presentation of a seizure is determined by the origin of the hyper-excitability and its degree of spread in the brain.*\(^4\) The classification of epilepsy is evolving. The most recent classification as proposed by the International League Against Epilepsy (ILAE), classifies seizures as generalised, focal and unknown as shown in Table 1.\(^11\)

**Table 1: Classification of seizures**\(^11\)

<table>
<thead>
<tr>
<th>Generalised seizures</th>
<th>Focal seizures</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tonic-clonic</td>
<td>Includes simple partial, complex partial and partial seizures with secondary generalisation</td>
<td>Epileptic spasms</td>
</tr>
<tr>
<td>Absence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myoclonic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tonic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atonic</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Generalised seizures, which represent approximately 20% of cases,\(^12\) originate within neural networks and rapidly spread bilaterally throughout cortical and subcortical structures.\(^11\) Focal seizures, which represent 60% of cases,\(^12\) originate within networks in one hemisphere.\(^11\) Up to 20% of patients at initial presentation have seizures which may be difficult to classify; the classification can change over time and as the patient gets older.

**CAUSES OF EPILEPSY**

Epilepsy occurs as a result of: (1) a known or suspected genetic defect in which seizures are the primary symptom of the disorder and/or (2) a structural or metabolic condition (such as stroke, trauma, infection), or the underlying cause may be unknown.\(^11\)\(^13\) Risk factors for epilepsy vary with age and geographical location.\(^5\) Epilepsy associated with head trauma, central nervous systems (CNS) infections and tumours occur at any age, while cerebrovascular disease is the most common risk factor in people >60 years.\(^5\) The majority of the epilepsies which occur in paediatrics are age-dependent syndromes, where the presentation is affected by on-going brain maturation; these syndromes include West syndrome/Infantile spasms and Lennox-Gastaut syndrome.\(^12\)

**DIAGNOSIS**

Historically the diagnosis of epilepsy required that the patient had a history of at least two *unprovoked* seizures.\(^3\)\(^4\) The ILAE recently altered the practical definition for cases that do not meet the 2 unprovoked seizures criteria.\(^13\) Experts considered there was a need to address circumstances for patients with a high risk of future seizures after a first unprovoked seizure.\(^13\)\(^14\) The risk of recurrence after a first seizure might be similar to the average risk after two seizures for patients with risk factors such as epileptiform electroencephalogram (EEG) discharges, an abnormal neurological examination, or other evidence of a structural CNS abnormality presumed to be responsible for the seizure.\(^1\)

**Patients with a first non-febrile seizure should be seen as soon as possible by a specialist with training and expertise in epilepsy, to ensure precise and early diagnosis and initiation of therapy as appropriate to the patient's needs.**\(^15\)

Misdiagnosis of epilepsy can have significant physical, psychosocial and economic consequences for patients.\(^16\) Currently the diagnosis of epilepsy is made on the basis of a description of the seizure (by the patient and witness), clinical examination and specific investigations as indicated (including EEG, neuroimaging, electrocardiogram and appropriate blood tests, such as plasma electrolytes, glucose, calcium).\(^3\)\(^6\)\(^17\)\(^18\)
MANAGEMENT

The management of epilepsy requires a long-term, multidisciplinary, co-ordinated care approach that empowers patients towards pro-active management of their condition.\textsuperscript{15,17,18} Patients and their carers should be given the appropriate information and education about all aspects of their epilepsy and in addition have structured self-management plans.\textsuperscript{15,19} The National Epilepsy Clinical Care Programme has developed a care pathway for epilepsy in Ireland which is currently being implemented (further information is available on the HSE website www.hse.ie). Useful patient information on epilepsy is available from voluntary organisations such as Epilepsy Ireland (www.epilepsy.ie).

Pharmacotherapy

The ultimate goal of epilepsy treatment is freedom from seizures without adverse effects.\textsuperscript{1} Anti-epileptic drugs (AEDs) are the mainstay of epilepsy treatment, which should be initiated by a specialist.\textsuperscript{19} AEDs prevent seizures by acting on diverse molecular targets to selectively modify the excitability of neurons so that seizure-related firing is blocked without disturbing non-epileptic activity.\textsuperscript{1,5} The choice of AED needs to be individualised to the patient and factors such as the seizure type, epilepsy syndrome, the patient’s age, concomitant medication and co-morbidity must be considered.\textsuperscript{1,15} Ideally AEDs should fully control seizures, be well tolerated with no long-term safety problems (including teratogenicity, hypersensitivity reactions or organ toxicity) and be easy for clinicians to prescribe and patients to take.\textsuperscript{1,2,4,20}

First and Second Generation AEDs

Conventionally, AEDs have been divided into the older AEDs (so called first and second generation) and newer AEDs (third generation) according to when they first became available.\textsuperscript{5} Table 2 summarises the indications, special precautions and common undesirable effects associated with the older AEDs. The older AEDs in particular are prone to drug-drug interactions (DDI). The Summary of Product Characteristics (SmPC) should be consulted for complete prescribing information on the individual AEDs. DDI with AEDs will be covered in the next bulletin (NMIC 2014, Vol 20, No.5).

Table 2: Characteristics of first and second generation AEDs authorised in Ireland\textsuperscript{2,4,20-32}

<table>
<thead>
<tr>
<th>Drug (Indication: type of seizure)</th>
<th>Special precautions include: (= indicates that patient should be monitored)</th>
<th>Common undesirable effects include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital (Focal #, generalised ##)</td>
<td>Risk of dependence (gradual withdrawal needed), risk of severe skin reactions including SJS and TEN\textsuperscript{=}, risk of suicidal ideation\textsuperscript{=}, use with great caution in children, elderly, malnourished and patients with renal or hepatic dysfunction or Addisons’ disease</td>
<td>Sedation, mood changes, behavourial changes, blood dyscrasias, osteoporosis (long-term therapy), cognition impaired, respiratory depression</td>
</tr>
<tr>
<td>Phenytoin (Focal #, generalised [tonic-clonic] # status epilepticus [IV])</td>
<td>Abrupt withdrawal may precipitate status epilepticus (gradual withdrawal needed), risk of severe skin reactions including SJS and TEN (especially with HLA-B<em>1502 allele), risk of hypersensitivity reactions</em>, risk of suicidal ideation\textsuperscript{=}, may affect metabolism of vitamin D and associated with risk of osteoporosis (long-term use), high levels of phenytoin may produce convulsional states, risk of anticonvulsant hypersensitivity syndrome</td>
<td>Dizziness, headache, nystagmus, ataxia, blurred vision, behaviour disorders, somnolence, rash, GI upset</td>
</tr>
<tr>
<td>Primidone (Focal #, generalised ##)</td>
<td>Risk of dependence (gradual withdrawal recommended), use with caution in children, elderly, debilitated and patients with marked renal, hepatic or respiratory dysfunction, risk of megaloblastic anaemia, risk of suicidal ideation\textsuperscript{=}, may affect vitamin D metabolism and predispose to bone disease, risk of hepatic damage</td>
<td>Drowsiness, dizziness, GI disturbances, listlessness, ataxia, visual disturbances, nystagmus, allergic reactions</td>
</tr>
<tr>
<td>Carbamazepine (Focal #, generalised [tonic-clonic] ##)</td>
<td>Risk of agranulocytosis and aplastic anaemia (rare) – discontinue if evidence of bone marrow depression occurs, rash and risk of SJS and TEN (especially with HLA-B<em>1502 allele), risk of hypersensitivity reactions</em>, exacerbation of seizures, risk of liver toxicity (monitor LFTs), risk of suicidal ideation\textsuperscript{=}, risk of hyponatraemia, hypothyroidism\textsuperscript{=}, abrupt withdrawal may precipitate seizures (gradual withdrawal recommended)</td>
<td>Leucopenia, thrombocytopenia, eosinophilia, GI upset, ↑ weight, hyponatraemia, dizziness, ataxia, blurred vision, headache, dry mouth, urticaria, allergic dermatitis, fatigue, ↑ gamma-glutamyltransferase, ↑ alkaline phosphatase</td>
</tr>
<tr>
<td>Sodium valproate (Focal #, generalised)</td>
<td>Risk of liver toxicity\textsuperscript{=}, risk of pancreatitis (rare), risk of suicidal ideation\textsuperscript{=}, teratogenic (not to be used in women of childbearing potential unless absolutely necessary)</td>
<td>GI upset (may be transient), sedation, ↑ weight, mood disorders, sedation, confusion, thrombocytopenia, rash</td>
</tr>
<tr>
<td>Ethosuximide (Absence only)</td>
<td>Risk of SLE (cases reported), risk of suicidal ideation\textsuperscript{=}, risk of blood dyscrasias\textsuperscript{=}, use with extreme caution in presence of impaired hepatic or renal dysfunction</td>
<td>↑ appetite, headache, ataxia, dizziness, somnolence, GI upset, rash, urticaria</td>
</tr>
<tr>
<td>Clonazepam (Focal #, generalised status epilepticus [IV])</td>
<td>Risk of suicidal ideation in patients with depression, risk of dependence (gradual withdrawal required), concomitant use with alcohol or other CNS depressants should be avoided, use with extreme caution in patients with history of alcohol/substance abuse</td>
<td>Somnolence, tiredness, dizziness, allergic reactions, impaired concentration, confusion, paradoxical reactions, anterograde amnesia, nystagmus, muscle weakness, fatigue</td>
</tr>
<tr>
<td>Clobazam (Adjunctive therapy: focal &amp; generalised)</td>
<td>Risk of dependence (gradual withdrawal required), risk of suicidal ideation\textsuperscript{=}, concomitant use with alcohol or other CNS depressants should be avoided, risk of paradoxical reactions</td>
<td>Somnolence, fatigue dizziness, cognition impaired, anterograde amnesia, weight gain</td>
</tr>
<tr>
<td>Diazepam (Focal &amp; generalised, status epilepticus)</td>
<td>Risk of dependence (gradual withdrawal required), risk of suicidal ideation\textsuperscript{=}, concomitant use with alcohol or other CNS depressants should be avoided, risk of paradoxical reactions</td>
<td>Sedation, dizziness, confusion, fatigue, anterograde amnesia</td>
</tr>
</tbody>
</table>

SJS = Stevens Johnson Syndrome, TEN = toxic epidermal necrolysis, SLE = systemic lupus erythematosus, ## not useful for absence or myoclonic seizures, * may include drug rash with eosinophilia and systemic symptoms (DRESS)
<table>
<thead>
<tr>
<th>Drug (Indication: type of seizure)</th>
<th>Special precautions include: (≠ indicates patient that should be monitored)</th>
<th>Common undesirable effects include:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamotrigine (Mono/adjunctive therapy: focal &amp; generalised, Lennox-Gastaut syndrome)</td>
<td>Risk of rash including SJS &amp; TEN, risk of hypersensitivity*, risk of suicidal ideation≠, abrupt withdrawal may precipitate seizures (gradual withdrawal recommended)</td>
<td>Mood disorders, headaches, somnolence, dizziness, tremor, insomnia, agitation, GI upset, arthralgia, fatigue, back pain, rash</td>
</tr>
<tr>
<td>Oxcarbazepine (Mono/adjunctive therapy: focal #)</td>
<td>Risk of hypersensitivity* reactions, rash including SJS &amp; TEN (especially with HLA-B*1502 allele), risk of hyponatraemia≠, risk of suicidal ideation≠, abrupt withdrawal may precipitate seizures (gradual withdrawal recommended), risk of blood dyscrasias (very rare)</td>
<td>Hyponatraemia, mood disorders, somnolence, headache, dizziness, ataxia, tremor, nystagmus, amnesia, visual disturbances, vertigo, GI upset, rash, fatigue</td>
</tr>
<tr>
<td>Gabapentin (Mono/adjunctive therapy: focal #,###)</td>
<td>Risk of suicidal ideation≠, abrupt withdrawal may precipitate status epilepticus, hypersensitivity* reactions</td>
<td>Infections including respiratory, leucopenia, ↑↓ appetite, mood disorders, somnolence, dizziness, ataxia, amnesia, visual disturbances, vertigo, hypertension, dyspnoea, GI upset, rash, arthralgia, back pain, impotence, fatigue, fever, asthenia, weight gain</td>
</tr>
<tr>
<td>Topiramate (Mono/adjunctive therapy: focal # &amp; generalised [tonic-clonic], Adjunctive therapy: Lennox-Gastaut syndrome)</td>
<td>Abrupt withdrawal may precipitate seizures (gradual withdrawal recommended), ensure adequate hydration to reduce risk of nephrolithiasis, risk of suicidal ideation≠, caution in patients with renal or hepatic dysfunction, risk of acute myopia associated with secondary glaucoma, visual field defects, risk of metabolic acidosis≠</td>
<td>Nasopharyngitis, anaemia, hypersensitivity, anorexia, mood disorders, somnolence, paraesthesia, dizziness, memory impairment, convulsions, visual disturbances, vertigo, tinnitus, dyspnoea, GI upset, rash, arthralgia, nephrolithiasis, fatigue, irritability, gait disturbance</td>
</tr>
<tr>
<td>Levetiracetam (Monotherapy: focal#, Adjunctive: focal &amp; generalised [tonic-clonic &amp; myoclonic in JME])</td>
<td>Gradual withdrawal recommended, close adjustment may be required in renal impairment, risk of suicidal ideation≠</td>
<td>Nasopharyngitis, anorexia, depression, mood disorders, somnolence, headache, convulsion, dizziness, vertigo, cough, GI upset, rash, fatigue</td>
</tr>
<tr>
<td>Zonisamide (Mono/adjunctive therapy: focal #)</td>
<td>Serious rash including SJS≠, gradual withdrawal recommended, risk of sulphonamide reactions, risk of suicidal ideation≠, risk of nephrolithiasis, metabolic acidosis, pancreatitis and heat stroke</td>
<td>Ecchymosis, hypersensitivity*, anorexia, fatigue, psychotic disorder, dizziness, memory impairment, somnolence, paraesthesia, diplopia, GI upset, ↓ bicarbonate, nephrolithiasis</td>
</tr>
<tr>
<td>Vigabatrin (Monotherapy only for West syndrome, Adjunctive therapy only: drug-resistant focal seizures #)</td>
<td>Risk of irreversible visual field defects (VFD), not recommended for patients with pre-existing VFD, visual field assessment required prior to commencing treatment and while on treatment, monitor neurological function, risk of paradoxical reaction, gradual withdrawal recommended, risk of suicidal ideation≠</td>
<td>↑ weight, somnolence, headache, dizziness, paraesthesia, memory impairment, visual field defect, GI upset, fatigue, oedema, irritability, mood disorders</td>
</tr>
<tr>
<td>Pregabalin (Adjunctive therapy: Focal #,###)</td>
<td>May have increased risk of falls in the elderly due to dizziness and somnolence, withdrawal symptoms may occur, use with caution in elderly cardiovascular compromised patients, risk of suicidal ideation≠, hypersensitivity, cases of abuse have been reported (caution in patients with a history of substance abuse)</td>
<td>Nasopharyngitis, ↑ appetite, mood changes, somnolence, dizziness, headache, memory impairment, visual field defect, GI upset, arthralgia, erectile dysfunction, fatigue, ↑ weight (monitor diabetic medication)</td>
</tr>
<tr>
<td>Tiagabine (Adjunctive therapy: focal #)</td>
<td>Paradoxical reactions, gradual withdrawal recommended, risk of anxiety, depression and suicidal ideation≠, monitor blood count if ecchymoses occurs, risk of visual field defects (rare) – refer to ophthalmologist if visual symptoms occur</td>
<td>Mood disorders, dizziness, tremor, somnolence, GI upset, ecchymoses, fatigue, ataxia, visual disturbances</td>
</tr>
<tr>
<td>Lacosamide (Adjunctive therapy: focal #)</td>
<td>Risk of suicidal ideation≠, use with caution in patients with known conduction problems or severe cardiac disease, risk of dizziness which may ↑ risk of falls</td>
<td>Mood disorders, dizziness, headache, somnolence, fatigue, memory impairment, nystagmus, visual disturbances, GI upset, rash, gait disturbances</td>
</tr>
<tr>
<td>Eslicarbazepine acetate (Adjunctive therapy: focal #)</td>
<td>Risk of suicidal ideation≠, risk of dizziness (may ↑ risk of falls), gradual withdrawal recommended, rash and possible risk of SJS (especially with HLA-B*1502 allele), risk of hyponatraemia, caution in patients at risk of PR prolongation, caution in patients with renal or hepatic impairment</td>
<td>Hyponatraemia, ↓ appetite, insomnia, dizziness, somnolence, headache, balance disorder, visual disturbances, vertigo, GI upset, rash, fatigue</td>
</tr>
<tr>
<td>Perampanel (Adjunctive therapy: focal #,###)</td>
<td>Risk of suicidal ideation≠, gradual withdrawal recommended, risk of dizziness which may affect ability to drive or operate machinery, ↑ risk of falls especially in the elderly, aggressive behaviour reported≠, caution in patients with history of substance abuse</td>
<td>↑↓ appetite, behaviour disorders, dizziness, somnolence, balance disorder, visual disturbances, vertigo, GI upset, back pain, falls</td>
</tr>
<tr>
<td>Retigabine (Adjunctive: drug-resistant focal #)</td>
<td>Reports of visual impairment (ophthalmological assessment required at baseline and during treatment), caution in patients at risk of urinary retention, risk of QT prolongation, risk of suicidal ideation≠, gradual withdrawal recommended</td>
<td>↑↑ appetite, psychotic disorders, somnolence, dizziness, vertigo, balance impairment, memory impairment, dysarthria, pigment changes of ocular tissues, visual disturbances, GI upset, ↑ liver function tests, blue-grey discolouration of the nails, lips skin, urinary symptoms, fatigue, peripheral oedema</td>
</tr>
<tr>
<td>Rufinamide (Adjunctive therapy: Lennox-Gastaut syndrome)</td>
<td>Cases of status epilepticus reported, gradual withdrawal recommended, ↑ risk of dizziness, somnolence, ataxia (may ↑ risk of falls), hypersensitivity*, rash and SJS≠, risk of ↓ in QTc interval, risk of suicidal ideation≠</td>
<td>Infections including pneumonia, nasopharyngitis, anorexia, anxiety, somnolence, dizziness, headache, status epilepticus, convulsion, nystagmus, visual disturbances, vertigo, epistaxis, GI upset, rash≠, oligomenorrhea, gait disturbance</td>
</tr>
</tbody>
</table>

SJS = Stevens Johnson Syndrome, TEN = toxic epidermal necrolysis, JME = juvenile myoclonic epilepsy # partial +/- secondary generalisation, ## not useful for absence or myoclonic seizures, * may include drug rash with eosinophilia and systemic symptoms (DRESS)
PRACTICAL ASPECTS OF MANAGEMENT IN CLINICAL PRACTICE

Approximately 50% of patients with new onset focal or generalised seizures become seizure free with an appropriate first-line AED.2-3 The selection of the first AED needs to be individualised to the patient and include factors such as the type of seizure, the patient's age, co-morbidities and concomitant medications.1,15,58 The AED of choice is gradually titrated to the lowest effective dose to control the seizures.1,10 First-line AEDs for focal seizures include carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, and sodium valproate.15 First-line AEDs for secondary generalised tonic-clonic seizures include carbamazepine, lamotrigine, oxcarbazepine, sodium valproate and levetiracetam.15 First-line AEDs for myoclonic and primary generalised seizures include levetiracetam, lamotrigine and sodium valproate.15 Certain AEDs such as gabapentin, carbamazepine, oxcarbazepine, phenytoin, pregabalin, vigabatrin and tiagabine may induce or exacerbate absence or myoclonic seizures.15

If the first AED is ineffective, the diagnosis of epilepsy needs to be critically evaluated and non-compliance should be considered.1,15 An alternative first-line treatment may be required,15 which is conventionally done by switching gradually to another appropriate AED.1,15 Combination or adjunctive treatment should be considered if a second AED is ineffective.8 A number of newer AEDs are used as adjunctive therapy for focal seizures including lacosamide, retigabine, eslicarbazepine acetate and perampanel.54-57

Uncontrolled epilepsy is associated with an increased risk of mortality, morbidity, seizure-related injuries, psychiatric disorders and poor quality of life.57 Although AEDs achieve symptomatic seizure relief, they do not prevent or reverse the pathological process that underlies epilepsy or other clinical manifestations of epilepsy, such as the co-morbidity of epilepsy.74 Patients who have uncontrolled seizures in spite of treatment with ≥ 2 appropriate AEDs alone or in combination are said to have drug resistant epilepsy.1,2,58 Pseudoresistance should be excluded before AED treatment can be considered to have failed; reasons for pseudoresistance include the wrong diagnosis, wrong drug, wrong dose of AED and non-compliance.58 Drug resistant epilepsy which is estimated to occur in up to 23% of patients with epilepsy is associated with increased risks for premature death, physical injury, psychosocial dysfunction and reduced quality of life.58 These patients require input from a multidisciplinary team involved in managing complex epilepsy.15 Patients with drug resistant epilepsy should be considered for surgical treatment.58

Adverse effects (AEs), including those that are dose-related, idiosyncratic and associated with long-term AED use, occur in approximately 50% of patients treated with first-line AEDs.2 Risk factors for AEs include age, gender, concomitant medication, concurrent medical and neurological conditions.2,30 AEs can be minimised by slow dose escalation up to average daily maintenance doses, by avoiding enzyme inducing agents and polytherapy.54 Full information on the adverse effects associated with each medicine is available in the SmPC. Psychiatric co-morbidity, especially depression is common in people with epilepsy. The association between AEDs and increased risk of suicide is controversial.1,59,60 People of Asian descent and who have the HLA-B*1502 allele have a significantly increased risk of developing Stevens-Johnson syndrome or toxic epidermal necrolysis, especially if they are taking AEDs such as carbamazepine.2 Screening for this allele is recommended before starting carbamazepine in patients with Han Chinese and South East Asian ancestry.2,15 Evidence also suggests that the presence of the HLA-A*3101 allele in patients of Northern European ancestry is associated with carbamazepine induced hypersensitivity reactions.51 Long-term use of enzyme-inducing AEDs is also associated with impaired bone health, endocrine dysfunction and changes in cholesterol concentration.1,62,63 Patients who are taking long-term AEDs (e.g. carbamazepine, phenytoin or phenobarbital), are at increased risk of developing osteoporosis;1,12 Postmenopausal women, in particular on long-term AEDs should be considered at increased risk of fracture.2

Therapeutic drug monitoring is available for a number of AEDs.1,2,4 Interpretation of serum AED levels must take into account the interval since the last dose was taken, the expected pharmacokinetic profile of the AED being monitored and the patient's clinical condition.3,4,44 Drug monitoring of AEDs may be useful to aid in the diagnosis of clinical toxicity, to confirm suspected non-compliance, to evaluate unexplained toxicity or uncontrolled seizures in individual cases, to guide dose adjustments in situations associated with increased pharmacokinetic variability (e.g. elderly, drug formulation changes), when a pharmacokinetic change is anticipated (e.g. pregnancy) and to guide dose adjustments for AEDs with dose-dependent pharmacokinetics (e.g. phenytoin).61

Drug interactions: Many AEDs (particularly the older AEDs such as carbamazepine and phenytoin) are associated with DDIs. The possibility of a DDI occurring must be considered when first commencing the AED in a patient on concomitant medications and when using adjunctive AEDs. This will be discussed in more detail in the next bulletin. Teratogenicity is a factor which must be considered when prescribing AEDs to women of child-bearing potential. Sodium valproate is associated with the greatest risk of major congenital malformations.20 The European Medicines Agency recently recommended that sodium valproate should not be prescribed for epilepsy (or bipolar disorder) in pregnant women, in women who can become pregnant or in girls unless other treatments are ineffective or not tolerated.65,66 This issue will be covered in more detail in the next bulletin.

Non-pharmacological management

Non-pharmacological treatments may be required after AEDs have failed.2 Options include curative surgery, palliative surgical procedures (including vagal nerve stimulation) and the ketogenic diet for severe forms of drug-resistant epilepsy in paediatric practice.5

SUMMARY

- AED treatment should be initiated by a specialist and needs to be individualised to the patient
- The potential for a DDI must always be considered for patients on an AED
- Up to 50% of patients will respond to the first-line AED
- The National Epilepsy Clinical Care Programme has developed a care pathway for epilepsy in Ireland which is currently being implemented (www.hse.ie)
- Useful patient information on epilepsy is available from voluntary organisations such as Epilepsy Ireland (www.epilepsy.ie)

List of references available on request. Date of preparation: November 2014

Every effort has been made to ensure that this information is correct and is prepared from the best available resources at our disposal at the time of issue. Prescribers are recommended to refer to the individual Summary of Product Characteristics (SmPC) for specific information on a drug.

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References for NMIC Bulletin Epilepsy No. 1

1. Perucca E, Tomson T, the pharmacological treatment of epilepsy in adults, the Lancet 2011;10:446-56
2. Schmidt D, Schachter S, Drug Treatment in Epilepsy in adults, BMJ 2014;348;2546
7. Linehan C et al, Examining the prevalence of epilepsy and delivery of epilepsy care in Ireland, Epilepsia 2010;51(5):845-852
10. Shorvon S, Tomson T, Sudden unexpected death in epilepsy, lancet 2011;378:2028-38
15. NICE clinical guideline January 2012
18. Fitzsimmons M et al, Evidence-based models of care for people with epilepsy, Epilepsy & behaviour 2012;23:1-6
22. SmPC for Epanutin® capsule downloaded from www.medicines.ie on the 7th July 2014
23. SmPC for Epanutin® inj downloaded from www.medicines.ie on the 7th July 2014
25. SmPC for Tegretol® (carbamazepine) downloaded from www.medicines.ie on the 7th July 2014
27. SmPC for Zarontin® downloaded from www.medicines.ie on the 7th July 2014
28. SmPC for Rivotril tab® (Clonazepam) downloaded from www.medicines.ie on the 7th July 2014
29. SmPC for Rivotril inj/inf® (Clonazepam) downloaded from www.medicines.ie on the 7th July 2014
30. SmPC for Frisium (Clobazam)® downloaded from www.medicines.ie on the 7th July 2014
32. SmPC for diazemuls injection downloaded from www.hpra.ie on the 28th August 2014
33. Trinka E et al, KOMET: an unblinded, randomised, two parallel group, stratified trial comparing the effectiveness of levetiracetam with controlled-release carbamazepine and extended-release sodium valproate as monotherapy in patients with newly diagnosed epilepsy, J Neurol Neurosurg Psychiatry 2013;84:1138-1147
34. Glauser TA et al Ethosuximide, valproic acid and lamotrigine in childhood epilepsy, NEJM 2010;362:790-9
35. French J, Pedley T, Initial management of epilepsy, NEJM 2008;359:166-76
40. SmPC for Trileptal® (oxcarbazepine) downloaded from www.medicines.ie on the 29th August 2014
41. SmPC for Neurontin® (gabapentin) downloaded from www.medicines.ie on the 7th July 2014
42. SmPC for Topamax® (topiramate) downloaded from www.hpra.ie on the 20th November 2014
43. SmPC for Keppra® (levetiracetam) downloaded from www.medicines.ie on the 7th July 2014
44. SmPC for Zonegran® (zonisamide) downloaded from www.medicines.ie on the 29th August 2014
45. SmPC for Sabril® (vigabatrin) downloaded from www.medicines.ie on the 7th July 2014
46. SmPC for Lyrica® (pregabalin) downloaded from www.medicines.ie on the 7th July 2014
47. SmPC for Gabitril (tiagabine) downloaded from www.hpra.ie on the 4th September 2014
48. SmPC for Vimpat® (lacosamide) downloaded from www.medicines.ie on the 7th July 2014
49. SmPC for Zebinix® (eslicarbazepine) downloaded from www.medicines.ie on the 7th July 2014
50. SmPC for Fycompa® (perampanel) downloaded from www.medicines.ie on the 7th July 2014
51. SmPC for Trobalt® (retigabine) downloaded from www.medicines.ie on the 7th July 2014
52. SmPC for Inovelon® (rufinamide) downloaded from www.medicines.ie on the 7th July 2014
56. Plosker G, Perampanel as adjunctive therapy in patients with partial-onset seizures, CNS Drugs 2012;26:1085-1096
57. Rektor I, Perampanel, a novel, non-competitive, selective AMPA receptor antagonist as adjunctive therapy for treatment resistant partial-onset seizures, Expert Opin. Pharmacother 2013;14(2):225-235
60. Arana A et al, Suicide-Related Events in Patients Treated with Antiepileptic Drugs, NEJM 2010;363(6):542-51
63. Mintzer S, Metabolic consequences of antiepileptic drugs, Curr Opin Neurol 2010;23(2):164-9