

# DIAGNOSIS AND MANAGEMENT OF EPILEPSY

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Epilepsy is the commonest serious chronic disease of the nervous system. One in 200 people has epilepsy and one person in 50 will develop epilepsy at some time in their life. Twenty five percent of people newly diagnosed with epilepsy are under the age of 20 and the same proportion of newly diagnosed patients is over the age of 60. One in 20 people will have a single epileptic seizure in their life time.

## Diagnostic considerations

An epileptic seizure is the result of a temporary physiological dysfunction of the brain caused by a self-limited hypersynchronous discharge of cortical neurones.<sup>1</sup> Classification of epilepsy is based on certain clinical and EEG characteristics. (Table 1) For practical purposes it is useful to attempt to classify a patient's epilepsy to determine prognosis and, to decide on the most appropriate anti-epileptic drug (AED).<sup>2</sup>

Whilst it may be difficult to establish with certainty a syndromic diagnosis it is worthwhile being acquainted with some of the commoner epileptic conditions. The majority of patients who have seizures before the age of 20 will have seizures in the context of idiopathic generalised epilepsy.<sup>3</sup> The most readily identified manifestation of this is juvenile myoclonic epilepsy (JME). The cardinal features of this are myoclonic jerks of the upper limbs and trunk which occur in the early morning or after sleep dep-

rivation, generalised tonic clonic seizures, generalised, often asymmetric poly spike and wave discharges on EEG and other features such as absences and photosensitivity.<sup>4</sup> This important constellation is often missed with inappropriate treatment (exacerbation of myoclonus and generalised seizures by carbamazepine) and inadequate counselling concerning prognosis (persistence of epilepsy into adult life).<sup>5</sup> Other patients will have only generalised tonic clonic seizures (Epilepsy with grand mal on waking) or absences (juvenile absence epilepsy) but the presence of a family history of seizures and poly spike and wave discharges on EEG suggests that the syndrome is related to JME.

If generalised seizures occur in the setting of learning disability or some more readily identifiable cerebral pathology then seizures are presumed symptomatic or cryptogenic.<sup>6</sup> Again generalised seizures predominate but a variety of seizures can occur including myoclonic attacks, absences, partial seizures and akinetic /astatic attacks manifesting as drop attacks. The occurrence of multiple seizure types, learning disability and bilateral, frontally dominant, slow spike and wave on EEG is often referred to as the Lennox-Gastaut syndrome and often evolves from the well-recognised infantile spasms or West Syndrome.<sup>7</sup> This is at the opposite end of the spectrum of generalised epilepsies in terms of medical refractoriness.

**Table-1: Classification of epilepsy.**

	<b>Generalised</b>	<b>Localisation-related</b>
Idiopathic (genetic)	Childhood absence epilepsy Juvenile absence epilepsy Juvenile myoclonic epilepsy Epilepsy with grand-mal seizures on awakening Other IG epilepsies	Benign focal epilepsy of childhood Autosomal dominant frontal lobe epilepsy Primary reading epilepsy
Symptomatic or cryptogenic	West's Syndrome Lennox-Gastaut Syndrome Other	Mesio-temporal lobe epilepsy Neocortical focal epilepsy

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Partial or focal epilepsy represents the main type of seizure disorder encountered in adult patients.<sup>8</sup> Temporal lobe epilepsy (TLE) is the most common subtype and is diverse in terms of aetiology. The most typical syndrome of TLE is that associated with pathology in the mesial temporal region, the amygdale, hippocampus and surrounding structures. Seizures are stereotyped and may have an aura (usually an epigastric rising sensation, a non-specific cephalic warning, olfactory hallucination or *deja vu* experience). This may lead to loss of awareness and limb or oro-buccal automatisms.<sup>9</sup> Seizures tend to last for two to three minutes, may cluster and generalise less readily. The most commonly identifiable pathological substrate is gliosis or sclerosis in these structures, the presence of which is correlated in many patients with prolonged or complicated febrile convulsions in infancy.<sup>10</sup> Other frequently identified pathologies include low grade tumours (most typically dysembryoplastic neuroepithelial tumour, DNET) with little or no potential for malignant transformation, and cavernous haemangiomas. All of the lesions should be readily identifiable with high resolution MRI. The presence of these lesions usually implies a high degree of drug refractoriness and early surgical referral should be considered.

Less common forms of focal epilepsy arise extra-temporally especially in the frontal lobes. Frontal lobe seizures have only been well characterised in the last twenty years. The clinical characteristics of these unusual seizures are worth bearing in mind. Seizures are brief (< 1 minute), hypermotor and frenetic but stereotyped, often nocturnal and may be misdiagnosed as parasomnias or non-epileptic seizures.

Although, in general, focal epilepsies have a worse prognosis in terms of drug responsiveness than seizures of idiopathic generalised epilepsy, there are many patients with focal seizures who are easily controlled with small doses of AEDs.<sup>11</sup> Benign focal epilepsy of childhood with centro-temporal spikes presents with infrequent nocturnal seizures which may secondarily generalise.<sup>12</sup> These seizures always remit by the late adolescence and many patients will not require AED treatment. Many adult patients are also encountered with temporal lobe seizures that are exquisitely sensitive to small doses of AEDs, usually carbamazepine.<sup>13</sup>

It is apparent then that a basic knowledge of the range of epileptic conditions is extremely useful in equipping the treating clinician with a certain degree of confidence and minimising the potential for diagnostic error. Yet even in specialist centres up to 20% of patients with intractable seizures do not have epilepsy. The most frequent diagnostic error in general practice and in the A & E setting is the misdiagnosis of syncope. It is worth recapping the major

features of syncope at this point. Attacks are usually infrequent and occur in the typical settings of erect posture, hot and stuffy environments aided by the vasodilatory effects of alcohol and often triggered by intercurrent illness and physical fatigue.<sup>14</sup> The patients often helpfully state that they fainted which is rarely described in the context of an epileptic seizure. There is a prodrome of dizziness, frank vertigo, a feeling of weakness in the legs, progressive dimming of vision and sometimes discomfort in the back of the neck (related to progressive hypoperfusion of the occipital lobes and paracervical muscles, respectively).<sup>15</sup> The patient then loses consciousness and collapses often with clonic activity of the limbs which can be prolonged particularly if the patient does not fall supinely. Recovery of consciousness is swift but often subject to emotional elaboration appropriate to the context of collapse. True urinary incontinence is unusual and post-ictal confusion is short-lived. If the clinical description is consistent with the above features then it does no service to the patient to label the episode as "Collapse, uncertain cause, rule out epilepsy." It is in fact not a fit but a faint. In general no specific investigations need to be pursued except for the detection of anaemia and a 12-lead ECG which will detect the majority of AV conduction defects.

It follows from the above discussion that a confident clinical diagnosis of epilepsy is most securely derived from the clinical characteristics of the described event and classification then determines the choice of investigations.<sup>16</sup> The idiopathic generalised epilepsies based on clinical and EEG (generalised spike and wave activity) grounds do not require structural neuroimaging as the brain is structurally normal. Any patient with onset of fits under 25 years of age whose seizures cannot be definitely classified as partial or generalised, should have neuroimaging. All older patients should have imaging to exclude any structural pathology. The choice of imaging clearly depends on local resources but as a minimum should consist of contrast enhanced CT of the brain, which will disclose most of the small vascular malformations. MRI is, however, the investigation of choice and will also avoid exposure of the young people to ionising radiations.<sup>17</sup> There is little point in obtaining emergency CT scan of the brain on healthy young patients who present with single seizures as the scans are almost always normal and insensitive to relevant epileptogenic pathology. Timely access to EEG is perhaps more useful in this context.

### **Management Issues**

Once the occurrence of an epileptic seizure is reasonably established, the decision to start drug treatment should not be taken lightly.<sup>18</sup> Widely varying estimates of the risk of seizure recurrence exist.<sup>19</sup>

Meta-analysis of respective studies indicate an overall two-year risk of 30-40%, the risk being lowest in patients with no identified cause and a normal EEG (24%), and highest in those with a remote neurological insult and an epileptiform EEG. Treatment after a first tonic-clonic seizure halves the two year risk of seizures from 40% to 20%. The decision to treat, therefore, will depend on individual factors. Apart from recurrence risks these factors also include the potential risks of AEDs, which range from acute idiosyncratic reactions (2-4%) to chronic toxicity. As approximately 40% of patients with epilepsy are women of childbearing age, teratogenic concerns of medications are of concern. Increasing information from the international pregnancy registries suggest that majority of medications if used as monotherapy and at modest doses are reasonably safe in pregnancy. Carbamazepine and lamotrigine seem to be the safest with an increase in neural tube defects associated with valproate, the highest risks being seen with polytherapy involving valproate.

Factors influencing the decision to begin medication include social and professional reasons, typically the requirement to be one year seizure free for light vehicle driving. The avoidance of physical injury associated with seizures is of real concern but, in reality, the majority of patients with mild epilepsy rarely sustain serious injury during seizures. In recent years the concept of sudden unexplained death in epilepsy (SUDEP) has been highlighted. This certainly should be considered in weighing the pros and cons of treatment. SUDEP, however, is a rare occurrence in patients with mild epileptic disorders and, whilst we raise the concept with patients in discussing treatment, undue emphasis is not placed on it.

Once the decision to commence drug treatment is made, it is necessary to make a choice from a large array of medications whose number has greatly expanded in the last decade. (Table 2) It is probably reasonable to still regard carbamazepine and valproate as the drugs of first choice for partial and generalised onset seizures, respectively. Other drugs have now become available for initial monotherapy (lamotrigine, topiramate and oxcarbazepine) but there is no evidence for superior efficacy. Lamotrigine is now widely used as initial choice of treatment in generalised seizures in young people. In practice it has a very favourable neurotoxic profile, does not interact with the oral contraceptive pill and appears to be very safe in pregnancy. It has, however, relatively weak anti-myoclonic activity and it has been found it to be rather less effective than sodium valproate in controlling the generalised seizures of JME. Topiramate has also useful activity in idiopathic generalised seizures and is available as monotherapy. It is particularly useful if there is coexistent migraine (a common associa-

tion). Cognitive side-effects especially verbal fluency may be affected in up to 20% of patients, limiting its use. Although there is no convincing data to support of the superiority of carbamazepine over valproate in partial epilepsy, in practice we have many patients with partial or secondarily generalised seizures who become seizure free on carbamazepine where valproate has failed. Increasingly, levetiracetam and topiramate are being used successfully in partial epilepsy, the former having a very favourable side effect profile.

**Table-2: Antiepileptic drugs with year of introduction.**

Anti-epileptic drug	Year of introduction
Phenobarbitone	1912
Phenytoin	1938
Primidone	1952
Ethosuximide	1960
Carbamazepine	1962
Sodium Valproate	1973
Vigabatrin	1989
Lamotrigine	1991
Gabapentin	1993
Topiramate	1995
Tiagabine	1998
Oxcarbazepine	2000
Levetiracetam	2000

When a patient is established on drug treatment clinical follow-up is sufficient in the majority. AED blood concentrations are over requested and often misinterpreted leading to injudicious alteration of treatment. A reasonable indication includes where compliance is suspected as poor or erratic especially in someone whose seizure control is much worse than expected. Similarly, there is no place for routine haematology and biochemistry because the minor abnormalities encountered (raised transaminases caused by enzyme induction, thrombocytopenia on valproate, neutropaenia and hyponatraemia on carbamazepine) are rarely of clinical significance.

The withdrawal of AEDs is generally considered after two years of seizure freedom although, in practice, most adult patients who drive will elect to remain on some form of treatment. In other patients individualised estimates of the risk of relapse can be made based on the findings of the MRC AED

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withdrawal study. Planned withdrawal as opposed to patients stopping medication themselves, more than one drug necessary to control seizures, seizure type, EEG findings and duration of remission have been identified as the most relevant indicators.

Once compliance with appropriate AED medication at adequate dose has been ensured, approximately 60 to 70% of patients can expect to become fully seizure free and enter long term remission. As discussed, this depends on the underlying of epilepsy syndrome and further evaluation may require video-EEG telemetry and volumetric MRI studies appropriate to a specialist centre. Some patients will have a surgically remediable syndrome indicated by a focal lesion on MRI. Others will have more complex epilepsies including those associated with malformations of cortical development, the demonstration of which at least explains the refractory nature of the seizure disorder.

### **Women and Epilepsy**

Antiepileptic drugs (AEDs) have the potential to produce both anatomic and behavioral teratogenesis; however, both the magnitude of the effect and the presence of differential AED effects are uncertain. Pregnancy registries provide a powerful tool to investigate pregnancy-related outcomes in women with epilepsy. Several ongoing pregnancy registries throughout the world have been collecting data on the teratogenesis of AEDs. Their most current findings were reported at the Pregnancy Outcomes Forum during the annual meeting of the American Epilepsy Society (AES) in December 2004.

The North American Pregnancy Registry has prospectively enrolled more than 3000 women who are receiving various AEDs<sup>20</sup> The registry's pure, prospective samples have revealed a 6.5% risk of congenital malformations with phenobarbital monotherapy and a 10.7% risk with valproate monotherapy. These rates are statistically greater than the rates for the general population, but confidence intervals are statistically inadequate to differentiate AEDs. However, the results are consistent with higher rates for valproate reported at the same symposium by 2 other registries. The Australian Pregnancy Registry,<sup>21</sup> which has assessed over 500 AED-exposure fetal outcomes, found a malformation rate of 16.5% for valproate monotherapy (significantly greater than no AED), and the United Kingdom Pregnancy Registry,<sup>22</sup> which includes more than 3000 women with full outcome data on a variety of AEDs, reported a rate of 6.1% for valproate (significantly greater than carbamazepine).

Results were also reported from the Neuro-developmental Effects of Antiepileptic Drugs (NEAD) Study,<sup>23</sup> which is an ongoing, prospective, multi-center study in the United Kingdom and United States

funded by the US National Institutes of Health. This study is designed to determine the effects of in utero monotherapy exposure to the 4 commonly used AEDs (carbamazepine, lamotrigine, phenytoin, and valproate) on the long-term neurobehavioral development of the offspring. More than 300 mothers with epilepsy were enrolled during their pregnancies. A preliminary analysis of AED-related outcomes for serious adverse events (fetal death, major congenital malformation, or developmental delay) revealed significant differences across all these AEDs. The incidence of serious adverse events for each AED was: carbamazepine 8%, lamotrigine 1%, phenytoin 10%, and valproate 25%.

Previous animal studies have demonstrated that in utero AED exposure can produce long-term behavioral deficits, and recent human studies have provided some insight in this regard. In a retrospective Danish study, men exposed in utero to phenobarbital had a 7-point decline in verbal IQ.<sup>24</sup> In a retrospective UK study of school-aged children exposed to in utero AEDs, 30% of children exposed to valproate monotherapy had additional educational needs compared with 3.2% of children exposed to carbamazepine monotherapy and 6.5% for other monotherapy groups.<sup>25</sup> In a follow-up study performed by the same investigators, neuropsychological testing in 249 children showed that children exposed to valproate had a significantly lower verbal IQ compared with children exposed to other AEDs or with children who were not exposed at all.<sup>26</sup> The study included a second cohort comprising children younger than 6 years old. For this cohort, the investigators used a developmental scale because the children were too young for IQ testing. Again, the valproate group achieved worse outcomes. Results from a prospective Finnish study also support the observation of poorer outcomes with valproate.<sup>27</sup> In that study, the mean verbal IQ score following in utero exposure to valproate was 82 compared with 96 for carbamazepine and 95 for healthy controls.

Thus, there have been 7 different investigations of children exposed to AEDs in utero. Outcomes were worse for valproate in all 7 studies even though the investigations evaluated different cohorts from various locations around the world, employed different methodologies, and even had different outcome measures. The likelihood of all 7 studies consistently finding a worse outcome for 1 AED by chance seems doubtful.

At a separate symposium during the AES meeting, a preliminary outline of AED treatment guidelines developed by the International League Against Epilepsy (ILAE) was presented, in which valproate was not listed as a first-line drug for women of child-bearing age because of concerns over similar toxicity issues. Although additional research is needed

to confirm these findings, these initial studies suggest that the risks of in utero AED exposure differ across AEDs and that the risk is higher for valproate.

### **Epilepsy in Elderly**

Fortunately, most elderly patients with epilepsy respond well to antiepileptic drugs (AEDs), including low doses of AEDs.<sup>28</sup> Although not yet well studied in elderly patients, AEDs that are effective in younger patients are usually effective in older patients. Drug tolerability is probably more important than drug efficacy in the elderly. For example, sedating medications, such as benzodiazepines and barbiturates, should be avoided in the elderly. Because many elderly patients have comorbid disorders, such as depression, drugs with mood-stabilizing effects (eg, lamotrigine) may be particularly useful. Elderly patients are often on concomitant drugs, and thus, use of AEDs that do not alter the metabolism of other drugs is particularly practical. For example, neither levetiracetam nor gabapentin alter the metabolism of other drugs or are altered by other drugs.

Although most elderly patients respond well to AEDs as do younger patients, some elderly patients have pharmaco-resistant epilepsy. However, in a retrospective analysis of data from the Veterans Administration Cooperative Study 428, Maa and colleagues<sup>29</sup> identified 22% of elderly patients as having intractable epilepsy. Intractability was related to the presence of neoplasms, complex partial seizures, or medication noncompliance.

### **Medical treatment of pediatric epilepsy**

Because initial trials of new AEDs are almost always confined to adults, similar data on the efficacy, tolerability, and pharmacokinetics must be obtained for children. Glauser and colleagues<sup>30</sup> reported the results of a multicenter trial of levetiracetam for children 4-16 years of age with refractory partial-onset seizures. There was a 27% reduction from baseline in median seizure frequency over placebo. These efficacy data, as well as the adverse effect profile, are similar to the results observed in adult studies.

Appleton and associates<sup>31</sup> reported that buccal midazolam was superior to rectal diazepam in children 6 months and older without intravenous access. The dose of each was from 2.5 mg to 10 mg, and the seizures stopped within 10 minutes in 56% of midazolam-treated and 27% of diazepam-treated patients. This appears to be a reasonable alternative therapy, although it should be noted that the rectal diazepam gel commercially available in the United States was not used in this UK study.

## **CONCLUSION**

It is apparent that algorithms of diagnosis and management in epilepsy are complex with attendant risks of under-treatment, mistreatment and over-treatment. With the current deplorable lack of specialists in Neuropsychiatry in this country services for people with epilepsy fall short of what might be expected in chronic disease management. All physicians who encounter patients with seizures should acquaint themselves with the basic clinical, diagnostic and treatment features of Epilepsy.

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