



CONSENSUS GUIDELINES ON THE MANAGEMENT OF EPILEPSY 2017



EPILEPSY COUNCIL

Malaysian Society of Neurosciences (Persatuan Neurosains Malaysia)

Statement of Intent

This guideline is not intended to be construed or to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns evolve. These parameters of practice should be considered as guidelines only. Adherence to them will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care aimed at the same results. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the health care provider in the light of the clinical data presented by the patient and the diagnostic and treatment options available.

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Glossary

ACDR	Adverse Cutaneous Drug Reaction
ACTH	Adrenocorticotropic Hormone
AED	Antiepileptic Drug
BCECTS	Benign Childhood Epilepsy with Centro-temporal Spikes
BDZ	Benzodiazepines
BOEC	Benign Occipital Epilepsy of Childhood
BP	Blood Pressure
CBZ	Carbamazepine
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CT	Computed Tomography
DNET	Dysembryoplastic Neuroepileptical Tumour
ECG	Electrocardiogram
EEG	Electroencephalogram
FDA	Food and Drug Administration, United States of America
FLAIR	Fluid-attenuated Inversion Recovery
GLUT1	Glucose Transporter 1
GTCS	Generalised Tonic-clonic Seizures
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HLA-B	Human Leukocyte Antigen B
HRT	Hormone Replacement Therapy
ICU	Intensive Care Unit
ILAE	International League Against Epilepsy
IPTA	Institut Pengajian Tinggi Awam (Public Institute of Higher Education)
IQ	Intelligence Quotient
IRPF SPGR	Inversion Recovery Prepared Fast Spoiled Gradient Echo
IV	Intravenous
JME	Juvenile Myoclonic Epilepsy
JPJ	Jabatan Pengangkutan Jalan (Road Transport Department Malaysia)
MAE	Myoclonic-Astatic Epilepsy
MPRAGE	Magnetization Prepared Rapid Gradient Echo
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
MSN	Malaysian Society of Neurosciences
NCSE	Non-convulsive Status Epilepticus

NEAD	Non-epileptic Attack Disorder
NTD	Neural Tube Defects
OCP	Oral Contraceptive Pill
PCOS	Polycystic Ovarian Syndrome
PET	Positron Emission Tomography
SE	Status Epilepticus
SJS	Stevens Johnson Syndrome
SMEI	Severe Myoclonic Epilepsy in Infancy
SPECT	Single Photon Emission Computerised Tomography
STIR	Short T1 Inversion Recovery
SUDEP	Sudden Unexpected Death in Epilepsy
TEN	Toxic Epidermal Necrolysis
TIA	Transient Ischaemic Attacks
UK	United Kingdom
USA	United States of America
VEMP	Vestibular evoked myogenic potential
WHO	World Health Organization

1 INTRODUCTION

The Epilepsy Council, Malaysian Society of Neurosciences was established in February 2002 to complement the activities organised by the Malaysian Epilepsy Society. In 2005, the Council published a set of guidelines for the management of epilepsy in the country and a revised edition was published in 2010. It had sufficient expertise to make strong recommendations to family physicians, internists, paediatricians, psychiatrists, neurologists, and all relevant healthcare providers pertaining to the management of epilepsy. Local specialists who have national, regional and/or international recognition in the field of epilepsy wrote the chapters in the guidelines. This is the third edition of the guidelines. Most of the chapters have been written and updated by the same authors as the first edition. The chapter on epilepsy classification is written with the knowledge that a new classification is still under construction. The recommendations in the guidelines are based on recent publications as well as the expert opinions of the panel.

2 CLASSIFICATION OF EPILEPSY

2.1 Introduction

The ILAE (International League Against Epilepsy) defines an *epileptic seizure* as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. On the other hand, *epilepsy* is a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures. The diagnosis of epilepsy normally requires the occurrence of at least two seizures more than 24 hours apart. The diagnosis of epilepsy can also be made after one unprovoked seizure if there is at least a 60% risk of further seizures, such as in patients with a past history of stroke, brain infection or brain trauma. However, seizures arising from an acute brain insult that has a low risk of seizure recurrence, such as hyperglycaemia or hypoglycaemia, do not qualify as epilepsy and are termed “acute symptomatic seizures”.

Classification of epilepsy is firstly a scientific taxonomy to reflect the natural order and classes of the different illnesses that manifest as seizures. It thus reflects the scientific community’s current understanding of epilepsy. Classification is also a diagnostic scheme as a practical clinical guide to prognosis and management.

The first major internationally accepted classification of epileptic seizures was the 1981 ILAE Classification of Epileptic Seizures (Table 1), which is still widely used worldwide. It is based on clinical and EEG features. Seizures are primarily divided into partial (focal) or generalised. Partial seizures are those where initial activation is limited to a part of one cerebral hemisphere. Generalised seizures are those where the initial involvement is in homologous areas of both hemispheres. Auras are simple partial seizures that precede complex partial or generalised seizures.

1. Partial seizures
1.1 Simple partial seizure
1.1.1 Motor signs
1.1.2 Sensory symptoms
1.1.3 Autonomic symptoms or signs
1.1.4 Psychic symptoms
1.2 Complex partial seizure
1.2.1 Simple partial at onset (with or without automatism)
1.2.2 With impairment of consciousness (with or with automatism)
1.3 Partial seizures evolving into generalised seizures
2. Generalised seizures
2.1 Absence seizure
2.1.1 Typical
2.1.2 Atypical
2.2 Myoclonic seizure
2.3 Clonic seizure
2.4 Tonic seizure
2.5 Tonic-clonic seizure
2.6 Atonic seizure
3. Unclassified epileptic seizures

Consciousness is maintained in simple partial seizures but impaired in complex partial seizures. The symptomatology of partial seizures (seizure semiology) reflects the anatomical origin of the seizures. Hence, partial seizures may be characterised by motor, special sensory, autonomic or psychic symptoms. In addition, complex partial seizures are typically accompanied by automatisms; consisting of involuntary movements, e.g. lip smacking, chewing, fidgeting and wandering.

The next major classification effort was that of the 1989 ILAE Classification of Epilepsies and Epilepsy Syndrome (Table 2). An epileptic syndrome is an epileptic disorder characterised by a cluster of signs and symptoms customarily occurring together. In contradistinction to a disease, a syndrome does not necessarily have a common aetiology.

In this classification, the epilepsies are also divided into “idiopathic”, “symptomatic” and “cryptogenic”. The idiopathic epilepsies are genetically determined and have no structural cause, no associated clinical signs, normal brain imaging and normal EEG background. The symptomatic epilepsies have known causes. The cryptogenic epilepsies are probably symptomatic, where the seizures are believed to be symptomatic of an underlying cause, but no aetiology has yet been identified.

Table 2: International Classification of Epilepsies and Epileptic Syndromes (1989)

<p>1. Localisation-related (focal, local, partial) epilepsies and syndromes</p> <p>1.1 Idiopathic (with age-related onset)</p> <ul style="list-style-type: none"> • Benign childhood epilepsy with centrotemporal spikes • Childhood epilepsy with occipital paroxysms • Primary reading epilepsy <p>1.2 Symptomatic</p> <p>1.2.1 Characterised by simple partial seizures*</p> <p>1.2.2 Characterised by complex partial seizures*</p> <p>1.2.3 Characterised by secondarily generalised seizures*</p> <p>1.3 Unknown as to whether the syndrome is idiopathic or symptomatic</p>
<p>2. Generalised epilepsies and syndromes</p> <p>2.1 Idiopathic</p> <ul style="list-style-type: none"> • Benign neonatal familial convulsions • Benign neonatal convulsions • Benign myoclonic epilepsy in infancy • Childhood absence epilepsy (pyknolepsy) • Juvenile absence epilepsy • Juvenile myoclonic epilepsy • Epilepsy with generalised tonic-clonic seizures on awakening <p>2.2 Cryptogenic or symptomatic</p> <ul style="list-style-type: none"> • West syndrome • Lennox-Gastaut syndrome • Epilepsy with myoclonic-astatic seizures • Epilepsy with myoclonic absences <p>2.3 Symptomatic</p> <p>2.3.1 Non-specific aetiology</p> <ul style="list-style-type: none"> • Early myoclonic encephalopathy <p>2.3.2 Specific syndromes</p> <ul style="list-style-type: none"> • Epileptic seizures complicating disease states
<p>3. Epilepsies and syndromes undetermined, whether focal or generalised</p> <p>3.1 With both generalised and focal seizures</p> <ul style="list-style-type: none"> • Neonatal seizures • Severe myoclonic epilepsy in infancy • Epilepsy with continuous spike and wave EEG during slow-wave sleep • Acquired epileptic aphasia (Landau-Kleffner syndrome) <p>3.2 Without unequivocal generalised or focal features</p>
<p>4. Special syndromes</p> <p>4.1 Situation-related seizures</p> <ul style="list-style-type: none"> • Febrile convulsions • Isolated seizures or isolated status epilepticus • Seizures occurring only when there is an acute metabolic or toxic event

*With the characteristics of seizures arising from frontal, parietal, temporal, occipital, or multiple lobes; or the locus of onset is unknown.

2.2 Idiopathic epilepsies:

Idiopathic focal epilepsies/idiopathic localisation-related epilepsy:

The two common types of benign focal epilepsy seen in childhood are those with benign centrotemporal spikes (BCECTS) and those with occipital paroxysms (Table 2). The syndrome of BCECTS accounts for 15% of seizures in children aged <15 years. Seizures usually start during primary school. Seizures are often nocturnal during sleep with hemi-facial jerks and salivation. The EEG shows numerous centrotemporal (rolandic) spikes. Spontaneous remission occurs in adolescence.

Idiopathic generalised epilepsies:

These syndromes are genetically determined, and patients have a normal neurological examination and normal intelligence. The EEG shows generalised epileptic discharges and may show photosensitivity (Table 3).

Table 3: EEG features of generalised epileptic seizures

- Absence seizures - generalised 3Hz spike-wave activity
- Myoclonic seizures - generalised polyspikes or polyspike and wave activity
- Clonic seizures - generalised spike-wave activity
- Tonic seizures - paroxysmal fast activity
- Tonic-clonic seizures - combination of the two seizure types
- Atonic - spikes or spike-wave activity or abrupt flattening of EEG

Childhood absence epilepsy, previously known as petit mal epilepsy, is characterised by an age of onset between 4 and 10 years, typical absences, generalised tonic-clonic seizures (GTCS) in about 50% of patients, myoclonic seizures in a minority of patients, and generalised 3Hz spike-wave activity on EEG. Juvenile absence epilepsy usually starts at a later age.

Patients with juvenile myoclonic epilepsy (JME) tend to be older (onset in adolescence), and have myoclonic jerks usually in the morning on awakening with or without GTCS. The seizures and myoclonic jerks respond to sodium valproate. The seizures are often lifelong.

2.3 Non-idiopathic epilepsies:

Symptomatic focal epilepsies

These seizures arise from a localised region of the brain. Mesial temporal lobe epilepsy is most commonly caused by hippocampal sclerosis. Other causes include cortical dysgenesis and low-grade tumours (DNET). The seizures are characterised by auras (typically a rising epigastric sensation or psychic auras), complex partial seizures with orofacial and manual automatisms that may secondarily generalise.

The causes of temporal, occipital, frontal and parietal neocortical epilepsy are more diverse, and include traumatic scars, neoplasm, vascular malformation, infarct, haemorrhage and cortical malformations. Seizure semiology, consisting of simple partial or complex partial seizures, depends on the area of neocortex affected.

Symptomatic generalised epilepsies

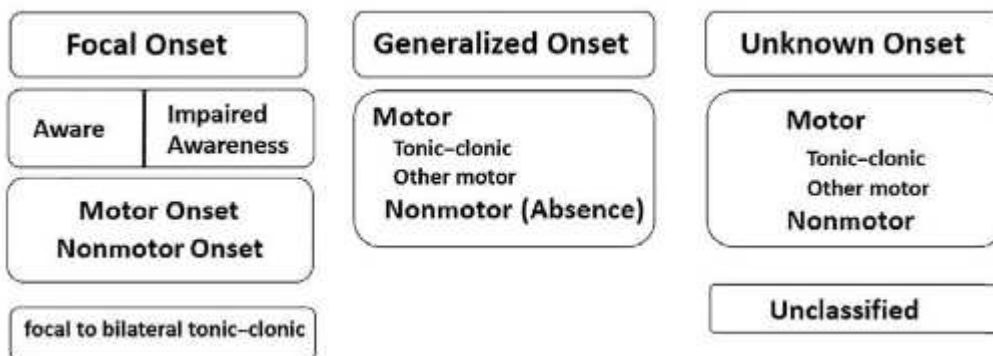
These epilepsies are associated with diffuse brain dysfunction. Common causes include previous anoxic birth injury, underlying metabolic derangement or a chromosomal defect. There is usually clinical evidence of intellectual deficiency and/or developmental delay. The clinical and EEG findings are usually abnormal and age-dependent.

2.4 Revised terminology and concepts for organisation of seizures and epilepsies

In the recently revised terminology and concepts for the organisation of seizures by the ILAE (*Berg AT, et al. 2010*), it is recommended that the terms “idiopathic”, “symptomatic”, and “cryptogenic” be replaced by “genetic” (for idiopathic), “structural/metabolic” (for symptomatic), and “unknown” (for cryptogenic).

In 2017, the ILAE published an update of the 1981 classification of the seizure types. (Fisher et al. 2017) The 2017 version remains largely similar to the 1981 classification. The main changes include “partial” becomes “focal”, awareness is used as a classifier of focal seizures, “focal aware seizure” instead of “simple partial seizure”, and focal impaired awareness seizure” instead of “complex partial seizure”.

Figure 1 ILAE 2017 Classification of Seizure Types Basic Version



3 DIFFERENTIAL DIAGNOSIS OF EPILEPSY

Recurrent episodes of altered consciousness or involuntary jerks pose a diagnostic challenge to the physician. Making the correct diagnosis leads to important implications to the patient, family and society. The evaluation of patients with transient attacks entails careful history taking, which is most important in the workup. The differential diagnosis of seizures may be divided according to different age groups (Table 4).

Table 4: Differential diagnosis of epileptic seizures

Neonates and infants

- Jitteriness and benign myoclonus
- Apnoea
- Shuddering attacks
- Gastro-oesophageal reflux
- Hyperekplexia

Young children

- Breath holding spells
- Reflex syncope
- Parasomnias
- Benign positional vertigo
- Tics and ritualistic movements
- Rage attacks

Adults

- Syncope
- Migraine
- Transient global amnesia
- Transient ischaemic attacks
- Narcolepsy and other sleep disorders
- Paroxysmal movement disorders and ataxias

Any age

- Endocrine/metabolic diseases and toxins
- Drug induced dystonia
- Cardiac dysrhythmias
- Delirium

- Non-epileptic attack disorder

Table 5: Causes of syncope

Neurally mediated reflex syncope

- Vasovagal syncope- central, postural
- Situational (specific triggers)- micturition, defecation, coughing, sneezing, laughing, weight lifting, post exercise, trumpet playing
- Carotid sinus syndrome

Cardiac syncope

- Arrhythmias
- Structural heart disease / mechanical

Syncope due to orthostatic hypotension

- Autonomic failure- multiple system atrophy, diabetes, amyloidosis, hereditary polyneuropathy
- Drug induced- antihypertensives, diuretics, antianginal, tricyclic antidepressants, levodopa, alcohol
- Hypovolemia- anaemia, failure to thrive, malnutrition
- Postural orthostatic hypotension syndrome

Syncope is the most common cause of altered consciousness in adults (Table 5). It can be dramatic, presenting with loss of postural tone that results from an acute reversible global reduction in cerebral blood flow. Important features that favour vasovagal syncope rather than epileptic seizure include a clear precipitating stimulus, the fall that occurs in stages, presence of prodromal symptoms, brief period of unconsciousness, rapid recovery and absence of postictal phase. Identifiable precipitants are getting up quickly, prolonged standing, frightening, emotional or unpleasant scenes, painful stimuli and Valsalva manoeuvres. Syncopal episodes begin with the premonitory phase where the person feels light headed and complains of pallor, sweating, nausea and visual blurring before losing consciousness.

Syncope has potentially important implications, especially when there are preexisting medical conditions. Cardiac syncope is often associated with prodromal symptoms, which include palpitations, chest pain, shortness of breath or features of cardiovascular insufficiency. Patients with an arrhythmia may present with a near syncope but not actual blacking out. Syncope can easily be mistaken for seizures as there is a high percentage of syncope that is associated with abnormal involuntary movements. When the perfusion to the brain is reduced, convulsive, or twitching-type muscle activity may be observed. Tongue biting and urinary incontinence may also occur.

Transient ischaemic attack (TIA) refers to a reversible neurologic deficit of presumed vascular origin that usually resolves in 24 hours, typically within 10 to 15 minutes. Typically the patient has a focal (negative) neurological deficit associated with the event whereas a seizure presents with positive symptoms such as automatisms, paraesthesiae, or visual hallucinations. Posterior circulation TIA may produce altered consciousness associated with the signs of brainstem dysfunction, such as vertigo, diplopia, facial weakness and dysarthria.

The characteristic feature of transient global amnesia is retrograde amnesia without focal signs or symptoms. The patient remains conscious but has no recollection of the events. The patient is often confused and disorientated during the event for less than 24 hours. The patient keeps repeating the same question several times even though is still able to carry out normal daily activities. These clinical features are attributable to

transient ischaemia of the hippocampus, during which, the patient is unable to store the memory of current events.

Movement disorders that may mimic seizure disorders include dystonia, dyskinesias, tics and paroxysmal kinesogenic choreoathetosis. Sleep disorders such as narcolepsy may potentially be mistaken for seizures. The features of narcolepsy include excessive daytime sleepiness, sleep paralysis, hypnagogic hallucinations and cataplexy. In the latter, the patient typically falls to the ground due to lack of muscle control, which is precipitated by emotions. Parasomnias, particularly REM sleep behaviour disorder is a condition where the patient is unable to inhibit movements that are typically suppressed during REM sleep. During an episode, the patient typically acts out his dreams during sleep such as walking and running, or exhibits inappropriate behaviour. Other common parasomnias that have the potential to be mistaken for epilepsy include nightmares, somnambulism and night terrors.

Non-epileptic attack disorder (NEAD), previously known as psychogenic or pseudoseizures can be divided into two broad types: a) attacks involving motor phenomena and b) attacks of lying motionless. Features useful in distinguishing NEAD from epileptic seizures are the triggers (frustration, suggestion, in company), duration (often prolonged), erratic movements (flailing, pelvic thrusting, head rolling), remaining pink and breathing, resisting eye opening and eye contact and often prompt recovery. The attacks may last from several minutes to several hours without resolution, whereas typical epileptic seizures last a minute or two and then resolve. A rapid onset and rapid cessation of the event with rapid reorientation post ictally, also favour NEAD.

KEY MESSAGE

The differential diagnosis of seizures needs careful evaluation in patients presenting with recurrent episodes of altered consciousness.

4 INVESTIGATIONS IN EPILEPSY

4.1 Purpose of investigations

The diagnosis of epilepsy is essentially a clinical one, based on a good and reliable history from the patient or an eyewitness of the epileptic event. One thing that the investigations do not do is to confirm the diagnosis of epilepsy. However, investigations may help define the epileptic syndrome and its possible aetiologies. Clinicians should have an individualised and rational approach when requesting investigations for people with epilepsy, so as to avoid unnecessary investigations and include essential ones. When the clinical presentation of a non-epileptic event (e.g syncope) is probable, investigations such as an EEG should not be requested. Therefore when requesting an investigation, clinicians should have in mind: what is the purpose of the investigations and what difference does it make?

Investigations in epilepsy are aimed at:

- 1) Excluding alternative diagnoses, especially if the clinical diagnosis of epilepsy is in doubt. For example, video EEG monitoring is useful in diagnosing non-epileptic attack disorder.
- 2) Defining an epileptic syndrome, in particular whether it is focal or generalised.
- 3) Determining the aetiology of the epilepsy- whether it is idiopathic (genetic), symptomatic (structural or metabolic cause) or unknown.
- 4) Prognosticating the epilepsy. Certain epilepsy syndromes are associated with poorer seizure control.
- 5) Identifying suitable candidates for epilepsy surgery. Epilepsies that are medically intractable may be treated with epileptic surgery.
- 6) Assessing the suitability of AED withdrawal. A repeat EEG is capable of stratifying the risk of seizure recurrence following AED withdrawal and influence the decision to continue or withdraw the AED.

4.2 Who should be investigated?

Patients with a first epileptic seizure should be investigated for common causes, including hypoglycaemia, hyponatraemia, hypercalcaemia, alcohol intoxication and withdrawal, drug intoxication and head injury.

When red flags are present (new neurological deficits, persistent altered consciousness, focal seizures, fever, persistent headache, neck stiffness, history of malignancy, compromised immunity, HIV positivity, recent head trauma, and anticoagulant use), urgent neuroimaging of the brain should be requested. In an acute setting, CT is preferable to MRI due to its wider availability. All other patients who require neuroimaging (see indications below) may be scheduled for a brain MRI as an outpatient.

All patients with a first seizure should be subjected to an EEG. Unequivocal interictal epileptiform discharges on EEG are predictive of seizure recurrence and may influence the decision to start AEDs.

4.3 Electroencephalography (EEG)

All patients must be subjected to a standard interictal scalp EEG, where the recording electrodes are attached to the patient's scalp. Rarely an invasive EEG such as a subdural EEG may be needed, where the recording electrodes are surgically implanted just beneath the dura.

4.3.1 Standard interictal scalp EEG

Scalp EEG is useful in detecting interictal epileptiform discharges that support the diagnosis of epilepsy. Rarely, routine scalp EEG may record ictal activity when the patient develops a clinical seizure in the EEG lab.

Every patient with a first seizure should have at least one routine scalp EEG. The sensitivity of scalp EEG in detecting interictal epileptiform discharges is approximately 50%. The sensitivity is increased up to 80% if the EEG is repeated up to three times. However, repeating EEGs may not be cost effective and may not influence clinical decision if the clinical diagnosis of epilepsy has been made and the patient's seizures are well controlled by AEDs.

Interictal epileptiform discharges, and often, ictal discharges, may be provoked by certain procedures: i) Sleep deprivation. The patient is asked to stay awake the night before the EEG is performed. The sensitivity is increased further if a sleep EEG is recorded whilst in the lab; ii) Hyperventilation. The patient is asked to hyperventilate for 3 minutes or more, and iii) Photic stimulation. The patient is asked to look at a stroboscopic light flashed at varying frequencies and with his eyes open and closed alternately. In the case of suspected non-epileptic attack disorder (NEAD), a "motivated" EEG may be performed. In a "motivated" EEG the patient is told beforehand that the purpose of the EEG is to capture the attack on video and EEG so that the appropriate treatment can be determined should the patient get an attack. In a typical NEAD, the patient will have an attack within minutes of the recording or during hyperventilation. The attack is often aborted by an injection of a placebo (normal saline or water for injection).

The use of suggestion and placebo to provoke and terminate an attack involves some element of deception and should be practiced with caution, preferably under the supervision of an experienced neurologist/epileptologists.

4.3.2 Video EEG monitoring

Video EEG monitoring may be short term or long term. Short term monitoring is similar to a standard scalp EEG except that there is simultaneous video recording. Long term monitoring is usually recorded for at least one day and up to 7 days. The purpose of long-term video EEG monitoring is to identify an epileptic focus that may not be picked up on shorter term monitoring. This is often done as part of pre-surgical evaluation. Long-term video EEG monitoring is also done to diagnose NEAD that occurs infrequently and is not picked up on routine EEG. The EEG during an attack in NEAD will show normal alpha rhythm. Approximately 10-20% of patients with epilepsy also have NEAD, and conversely, 5-20% of patients presenting with NEAD have epilepsy. Often, up to 5 video EEG recordings of a non-epileptic attack may be needed before an epileptic seizure is recorded.

4.3.3 Invasive EEG

Invasive EEG such as subdural, sphenoidal or depth electrode EEG are rarely performed. It may be needed in a patient where epilepsy surgery is contemplated and the epileptic focus is ambiguous from scalp EEG.

4.3.4 Limitations of EEG

A normal EEG does not rule out epilepsy. Interictal epileptiform discharges can only be recorded when there is a cortical epileptic focus of at least 6 cm². Epileptic foci that are deep-seated or too small may be missed. In addition, normal variants may be misinterpreted as epileptiform discharges (false positive). Epilepsy should not be diagnosed using EEG in isolation without clinical correlation.

4.3.5 Minimum standard in performing EEG

A standard scalp EEG should have at least 21 electrodes placed using the International 10-20 system. A standard EEG should record at least 3 montages for a minimum of 20 minutes. A period of wakefulness followed by provocation procedures of hyperventilation, photic stimulation and natural sleep should be recorded.

4.3.6 Typical EEG Findings in Common Epilepsy Syndromes

Table 6: Common Epilepsy Syndromes and EEG Findings

Epilepsy Syndrome	Background EEG	Characteristic EEG Findings
Childhood Absence Epilepsy	Normal	Bilateral synchronous and symmetrical 3 Hz spike and wave discharges
Benign Childhood Epilepsy with Centrotemporal Spikes (BCECTS)	Normal	Unilateral or bilateral independent spikes in the centrotemporal region with a horizontal dipole
Benign Occipital Epilepsy of Childhood (BOEC)	Normal	Posterior 1.5-3 Hz spike and wave discharges that attenuates with eye opening
Juvenile Myoclonic Epilepsy	Normal	Photoparoxysmal response, bilateral synchronous polyspike and wave discharges
Mesial Temporal Lobe Epilepsy	Normal	Interictal spikes or sharp waves in anterior temporal region
West Syndrome	Abnormal	Hypsarrhythmia-disorganised high voltage patterns (spikes, polyspikes, slow waves) and electrodecremental response
Lennox-Gastaut Syndrome	Abnormal	Bilateral 2-2.5 Hz spike and wave discharges (atypical absence), generalised paroxysmal fast activity during tonic seizure

4.4 Neuroimaging

4.4.1 Structural neuroimaging

MRI is superior to CT for investigating patients with epilepsy. However, CT is a good initial brain imaging modality in the emergency setting and when MRI is not readily available.

MRI brain is mandatory for certain groups of patients:

- 1) Suspicion of focal onset epilepsy based on history, examination or EEG
- 2) Progressive neurological, cognitive or psychological deficits
- 3) Abnormal EEG background
- 4) Poor seizure control
- 5) Patients with status epilepticus, especially when it is unprovoked
- 6) Following acute head trauma
- 7) Onset of epilepsy before the age of 2 years and after the age of 20 years

MRI brain may be deferred in the following circumstances:

- 1) When the diagnosis of idiopathic generalised epilepsy is made based on clinical history and EEG.
- 2) In pregnant women with no acute problems such as intracerebral haemorrhage or meningoencephalitis.
- 3) In children with BCECTS, absence epilepsy and BOEC.

4) When there is an obvious non-cranial precipitating factor such as hypoglycaemia or alcohol withdrawal.

One of the most important reasons for requesting a brain MRI is the identification of a focal cause of epilepsy that may be treated with epilepsy surgery, such as hippocampal sclerosis, cavernoma, dysembryoplastic neuroepithelial tumour (DNET) and cortical dysplasia. Hippocampal sclerosis is the commonest cause of temporal lobe epilepsy. Hippocampal sclerosis is not visible on CT. On MRI, there is loss of hippocampal volume and the hippocampus appears hypointense on T1-weighted and hyperintense on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images. In addition the adjacent temporal horn of the lateral ventricle may appear larger than the contralateral temporal horn. There may be ipsilateral posterior fornix atrophy as well.

The following MRI protocol is recommended for imaging of patients being evaluated for epilepsy surgery:

- 3.0 Tesla magnet - 1.5 Tesla magnet (in the majority of cases; in selected cases, a 3.0 Tesla magnet may be necessary to better identify or delineate the lesion, particularly if surgical resection is contemplated)
- A volume acquisition (contiguous) T1-weighted coronal data set of the whole brain in 1.5 mm-thick slices using IRPF SPGR(GE) or MPRAGE (Siemens) sequences, allowing reformatting in any orientation or plane, 3D reconstruction or surface rendering.
- An oblique (heavily) T1-weighted coronal inversion recovery sequence orientated perpendicular to the long axis of the hippocampus (parallel to a line joining the base of the splenium of corpus callosum to the infero-posterior border of the frontal lobe)
- An oblique (heavily) T1-weighted coronal spin echo (VEMP) (GE) or double echo STIR (Siemens) or a FLAIR sequence orientated perpendicular to the long axis of hippocampus.

4.4.2 Functional neuroimaging

Ictal SPECT (single photon emission computed tomography), PET (positron emission tomography) and functional MRI are functional imaging modalities that may be done to localise the epileptogenic area. Functional neuroimaging is done in selected cases where MRI is equivocal and epilepsy surgery is contemplated. In addition, functional MRI may help to localise specific functional areas (e.g motor cortex, language area) prior to surgery to determine the resection margin in order to preserve eloquent areas.

4.5 Other investigations

4.5.1 Ancillary blood tests

Patients with new onset seizures should have serum biochemistry done to exclude metabolic causes of provoked seizures such as hyponatraemia, uraemia, hyper/hypocalcaemia and hypoglycaemia. Drug toxicology test should be requested if there is suspicion of drug abuse. As such, patients should routinely have the following tests done:

- 1) Renal profile
- 2) Liver function test
- 3) Serum corrected calcium and magnesium
- 4) Random blood glucose

Serum creatine kinase and serum prolactin levels may be elevated following a generalised tonic-clonic seizure but these are indirect and unreliable markers of seizures. Serum creatine kinase may be normal in simple or complex partial seizure and absence seizure. Serum prolactin levels may have normalised 30 minutes after an attack. Therefore these tests should not be routinely requested.

Serum or saliva must be sent for HLA B*1502 testing prior to commencement of carbamazepine (see also section 6.6 on page 43 for further information).

4.5.2 Cardiac assessment

An ECG should be performed in all patients with epilepsy for the following reasons:

- 1) Cardiac arrhythmias causing cardiac syncope that mimic seizures
- 2) Cardiac arrhythmias or obstruction to cardiac output may cause generalised seizures
- 3) Conduction block may be exacerbated in patients taking phenytoin and carbamazepine.

An echocardiography and chest radiograph should be requested if cardiac abnormalities are suspected.

4.6 Specific investigations

CSF studies, HIV testing, connective tissue disease screening may be requested if clinically indicated.

Autoimmune limbic encephalitis has been recognised as an emerging cause of poorly controlled seizures. Patients often present with a tetrad of seizures, psychiatric symptoms, movement disorders such as orofacial dyskinesia and cognitive decline. It is crucial to diagnose these conditions as specific treatment such as immunotherapy may lead to a good outcome. Amongst the antibodies that are now identified in this condition are anti NMDA receptor antibodies, anti LG1, anti CASPR and anti VGKC antibodies. These antibody tests are not routinely performed in most centres with the exception of anti NMDA receptor antibodies, which can be tested at the Institute of Medical Research (IMR). Given the complexity of these conditions, patients with poorly controlled seizures with progressive neurological symptoms are best managed and investigated in a tertiary referral centre.

4.7 Investigations during follow up

If there is progressive neurological, cognitive or psychological deficits or poor control of seizure, a repeat EEG or MRI brain may be requested. Neurocognitive testing may be requested in particular in children to assess for cognitive decline which may be subtle. Investigations should be done to exclude rare neurodegenerative diseases such as progressive myoclonic epilepsy, metabolic disorders and progressive structural disorders.

In patients taking enzyme-inducing AED, a full blood count, liver function test and serum calcium should be done every 1 to 2 years to look for adverse effects. Patients taking sodium valproate should have a full blood count done at least yearly. Patients on Topiramate should have an annual renal ultrasound scan.

4.8 Investigation of epilepsy in children

A distinction should be made at the onset between provoked seizures and epilepsy. Seizure or recurrent seizures occurring in close temporal relation with an acute systemic, metabolic or toxic cerebral insult are considered to be provoked or acute symptomatic seizures, which occur commonly in children. In such instances, investigations should be tailored at identifying the aetiology since the seizures will usually resolve with prompt treatment of the underlying cause and long term AED is not required.

In epilepsy, history taking is the main diagnostic tool. Parents can be asked to emulate the seizures or record the seizures with their mobile phone camera, camera or home video recorder if the seizures occur frequently enough to be captured. Caregivers are strongly encouraged to utilise home video recording. Investigative

procedures are performed to support the diagnosis, identify the underlying aetiology and to assist in the management and prognostication of the patient.

The diagnosis of epilepsy is primarily clinical and does not depend on EEG. Epileptiform abnormalities are seen in 5-8% of healthy children. Paroxysmal activity or background changes are seen in 32% of healthy children that could be misinterpreted as abnormal. Conversely a normal EEG does not exclude epilepsy when there is a convincing clinical history. The sensitivity of interictal recording is too low (40%) to be a reliable diagnostic test for epilepsy. Surface EEG can only sample electrical activity arising from the scalp convexity, leaving the mesiobasal and inner cortex unexplored. Thus, EEG should not be used to confirm or refute a diagnosis of epilepsy.

The yield of EEG abnormalities is increased by sleep recording, photic stimulation and hyperventilation. It is also increased when the EEG is performed within the first 24 hours of an epileptic seizure. Sleep recording achieved spontaneously or by sleep deprivation is preferred over sedated sleep recording. Sleep recording contributes significantly to epilepsy classification, for example benign childhood epilepsy with centrotemporal spikes (benign rolandic epilepsy) and juvenile myoclonic epilepsy.

All children with recurrent epileptic seizures should have an EEG. It is also recommended in children with the first afebrile, unprovoked seizure to assess recurrence risk and make a syndromic diagnosis. However, it should not be used as the sole guide in deciding whether or not to commence AED. An EEG is not recommended for children with recurrent or complex febrile seizures.

In children who present with diagnostic difficulties after clinical evaluation and standard EEG, video-EEG-telemetry is a useful diagnostic tool. Video-EEG-telemetry is also used for evaluation of potential candidates for epilepsy surgery to identify the epileptogenic zone. A 12 lead ECG should also be performed in cases with diagnostic uncertainty.

All children with epilepsy should have a brain MRI done. However, children with the following syndromes (which follow a typical course) *do not* require neuroimaging :

1. Benign childhood epilepsy with centrotemporal spikes
2. Idiopathic generalised epilepsies (eg childhood absence epilepsy, juvenile myoclonic epilepsy)

Brain MRI is recommended especially in children with atypical features or who do not respond well to AEDs.

Neuroimaging is not recommended for children with simple or complex febrile seizures that follow a typical course.

In the first 6 months of life, T2-weighted images help to identify cortical abnormalities while T1-weighted images better appreciate myelination. Subsequently, such sequences have a reverse role and are complemented by inversion recovery and fluid-attenuated inversion recovery (FLAIR) sequences. Children younger than the age of 2 years require different MR imaging sequences, because immature myelination affects the ability to identify certain lesions such as cortical dysplasia. Other neuroimaging modalities such as PET and SPECT scan are sometimes used in presurgical evaluation in potential candidates.

Children with symptomatic epilepsies warrant other investigations such as metabolic and genetic investigations to identify the underlying aetiology. Such investigations have a higher positive yield in children with dysmorphic features, mental retardation, dystonia, epileptic encephalopathy, and recurrent status epilepticus. Targeted genetic testing is recommended for children with typical phenotypic or electroclinical features and when the underlying disease has a well-characterised molecular and genetic basis.

KEY MESSAGES

- The diagnosis of epilepsy is made based on clinical history. An EEG should not be performed where a non-epileptic event is probable (e.g syncope).
- A normal EEG does not rule out epilepsy.
- Investigations play a supportive role in determining the aetiology, epilepsy syndrome, prognosis, suitability for surgical treatment and withdrawal of AEDs.
- All patients with a clinical diagnosis of epilepsy should have a standard scalp EEG.
- MRI is the neuroimaging of choice and is mandatory where the clinical presentation or EEG suggests an underlying brain abnormality. MRI may be deferred in patients with idiopathic epilepsy.

5 GENERAL PRINCIPLES OF THE TREATMENT OF EPILEPSY

5.1 Introduction

Once the diagnosis of epilepsy has been established, its treatment must be individualised. This includes the need for treatment and choice of AEDs. Careful consideration must be given to several factors, including the certainty of the diagnosis of epilepsy, severity of seizures, level of function, occupation and family support. Few decisions are more critical in the management of epilepsy than the decision to initiate drug therapy. As far as the patient is concerned, starting an AED confirms the state of 'epilepsy', which can affect self-esteem, social relationships, education and employment. The benefits of therapy on the other hand, include lower risk of seizure recurrence and of death or injuries. Drawbacks of therapy include potential drug side effects, cost, stigmatisation and inconvenience. The decision to treat essentially depends on the balance between benefits and drawbacks of therapy. Effective treatment also includes proper education and counselling. Important issues like driving, schooling, employment, pregnancy and compliance must be discussed, and advice must be individualised.

5.2 Prophylactic treatment

Prophylactic treatment has sometimes been advocated, notably in patients with head injuries or large haemorrhagic strokes. While immediate treatment may reduce the risk of early post-traumatic seizures (within one week of injury), it does not influence the risk of late post-traumatic epilepsy. Studies done in neurological conditions with high prospective risk of epilepsy have failed to show any evidence of benefit.

5.3 Single seizure

Patients presenting with a first single unprovoked seizure present a common clinical dilemma. A meta-analysis of prospective studies indicates an overall two-year risk of further seizures of 30-40%. The lowest risk (24%) is in patients with no identified cause who have a normal EEG, and the highest risk (65%) is in those with a remote neurological insult and epileptiform abnormalities in the EEG.

Treatment after a first GTCS halves the two-year risk of seizures from about 40% to 20%. However, this is not associated with any improvement in longer-term outcomes such as proportion of patients achieving a one-year remission.

Given the potentially significant social and physical implications, patients with a high risk of recurrence should be given the option to start treatment.

Recommendations:

- Patients with a certain diagnosis of unprovoked GTCS should be treated after the first seizure if:
 1. The seizure is associated with a previous absence and/or myoclonic seizures, and/or
 2. The patient or physician considers the risk of recurrence unacceptable (e.g. if there is an underlying structural brain abnormality)
- The decision to treat simple and complex partial seizures will depend on the seizure frequency and severity and patient preference. Generally, most patients would seek treatment after at least two seizures have occurred.
- Seizures due to alcohol withdrawal or other metabolic or drug-related causes or sleep deprivation should not be treated with AEDs. Treatment should be considered only if there are recurrences suggestive of epilepsy.

- All patients developing seizures within a week of head injury should be treated, but AED withdrawal should subsequently be considered.
- Patients should not be treated if there is uncertainty about the diagnosis.

5.4 Recurrent seizures

The decision is more straightforward in patients with recurrent seizures and a clear-cut diagnosis of epilepsy.

5.4.1 Newly diagnosed epilepsy

Factors influencing the decision to treat include:

1. A firm diagnosis of epilepsy based on a good first-hand witness account of the attacks. There is no place at all for a 'trial of treatment' to clarify the diagnosis.
2. About 50-80% of all patients who have a non-febrile seizure will have further seizures, the greatest risk being in the first 6 months. There is a further 9% risk in the next 6 months and 8% in the following 12 months. The risk is influenced by the following factors:
 - Aetiology: the risk is greatest with structural cerebral lesions and least in acute symptomatic epilepsy. The risk in idiopathic epilepsy is about 50%. In those with pre-existing learning disability or cerebral damage, the risk approaches 100%.
 - Age: the risk is greater in those under the age of 16 and over 60 years.
 - Seizure type: partial seizures are more likely to recur than generalised seizures.
3. Seizures must be sufficiently troublesome. Some seizure types have a minimal impact on quality of life e.g. simple partial, absence or nocturnal seizures. The benefits of AEDs in such seizures may be outweighed by their disadvantages. If the baseline seizure frequency is very low e.g. less than once every 2 years, the disadvantages of chronic drug therapy may be high, and AED should probably not be prescribed.
4. Epilepsy syndrome - some benign epilepsy syndromes have an excellent prognosis without treatment e.g. benign childhood epilepsy with centrotemporal spikes, and do not require long term therapy.
5. Compliance – AEDs need to be taken reliably and regularly to be effective. In circumstances where compliance is doubtful, the decision to treat will need to be re-considered.
6. Reflex seizures and acute symptomatic seizures - seizures precipitated only under specific circumstances, e.g. alcohol or photosensitivity, may be treated by avoiding these precipitants, obviating the need for drug therapy.
7. Patients' wishes - the final decision is left to the patient; the physician's role is to explain the relative advantages and disadvantages of therapy. However, the risk of SUDEP is higher in generalised tonic-clonic seizures and if there are more than 3 attacks a year. Patients and their caregivers should be counselled about the risk of SUDEP when discussing long-term treatment.

Once the diagnosis is clear, and decision to treat is established, the goal of therapy is to achieve complete seizure control, with a drug taken once or twice a day with minimal or no side-effects.

Formulation of a treatment plan at the time of the patient's initial evaluation would include:

1. Identifying precipitating factors such as sleep deprivation, drug abuse, alcohol, excessive fatigue and photosensitivity. Patients and their caregivers should be counselled about their avoidance.
2. Counselling the patient and/or caregiver with respect to the reasons for starting therapy, expectations, limitations and likely duration of therapy, need for good compliance and potential risks of therapy.
3. A detailed documentation of seizure type/types should be made, particularly when the epilepsy syndrome is unclear. This will avoid aggravation/worsening of certain syndrome/ seizures with an inappropriate AED.
4. Commencing the patient on a low dose of one (monotherapy) of the 1st line AEDs recommended for their epilepsy syndrome (Table 8). Single drug therapy provides optimal seizure control in about 70% of patients, and has the advantages of better tolerability and compliance, fewer side effects, simpler regime, and lower teratogenic risk.
5. Titrating the dose upwards to a higher maintenance dose if seizures continue. The ideal dose for a patient is the dose that gives good seizure control without significant adverse side effects.

5.4.2 Treatment of chronic active epilepsy

If seizures continue beyond 2-3 years, the patient is considered to have chronic epilepsy (accounting for about 10-20% of all patients), and the following management steps must be taken:

1. Review the diagnosis and aetiology - history, EEG, neuroimaging, etc. The possibility of pseudoseizures must be considered.
2. Re-classify the epilepsy (seizure type(s) and syndrome).
3. Review compliance to AED and lifestyle modification.
4. Review drug history - which AEDs have or have not been useful in the past, which have not been tried, drug and blood levels of previous therapy.
5. Set a treatment plan - sequence of drug changes, serum level monitoring.
6. Consider surgical therapy.
7. Recognise limitations of therapy; patients with intractable epilepsy must be able to accept their disability and continue with life. There are limits to the effectiveness of AEDs available and it is important to create a balance between seizure frequency, side effects from AEDs, and quality of life.

For both newly diagnosed and chronic epilepsy, a staged approach is advised:

- Tolerability and long-term safety are the most important factors in choosing the first drug.
- If the first AED is poorly tolerated at low dosage or fails to improve seizure control, an alternative should be substituted.
- If the first well-tolerated AED greatly improves but does not completely abolish seizures, combination therapy may be tried. Although the mechanisms of action of many AEDs are not fully understood, this remains a logical basis for choosing combination therapy. Evidence is emerging that certain combinations (preferably AEDs with different mechanisms of action) offer better efficacy than others.
- Work up for epilepsy surgery should be considered after failure of 2 well-tolerated treatment regimes after a period of 1 to 2 years.
- If needed, subsequent combinations of 2 or at most 3 AEDs may be effective.

5.5 Decision to withdraw AEDs

When freedom from seizures has been achieved for a period of at least 2 years, drug withdrawal may be considered. Exceptions occur in certain epilepsy syndromes e.g. JME, which has a high relapse rate. No guarantee of seizure freedom can ever be given when a drug is withdrawn. There is a 40- 50% risk of relapse within the 1st year of cessation. The risk of relapse is higher in patients:

- > 16 years of age.
- whose age at seizure onset was < 3 , or > 30 years.
- with tonic-clonic (primary or secondary) or myoclonic seizures.
- with partial onset seizures.
- with seizures needing > 1 AED for good control at the time of discontinuation.
- with an abnormal EEG - the EEG is not helpful in predicting seizure recurrence, although a normal EEG is reassuring.
- with a past history of status epilepticus.
- with a history of afebrile or atypical febrile seizures in childhood.
- experiencing one or more seizures after the start of treatment.
- with a short duration of seizure-freedom.
- whose duration of treatment exceeds 10 years.
- with a known aetiology of seizures (symptomatic epilepsy) and associated neurological handicap.
- with a fast rate of drug withdrawal.

Patients in whom seizure recurrence is less likely include:

- those who have been seizure-free for five or more years, or at least between three to five years.
- those with benign childhood epilepsy with centrotemporal spikes.

Discussion of whether to withdraw AEDs should take into account:

- the patient's need to work and drive a motor vehicle.
- the patient's fear of seizures and attitude to prolonged AED therapy.

5.6 Driving and epilepsy

The possession of a driver's licence is an important contributor to health-related quality of life in epilepsy, especially denoting independence, and may be a necessity for continued employment. However, epileptic seizures can result in road traffic accidents by causing sudden incapacity at the wheel. Although they do not contribute greatly to the totality of road safety, most countries and states have some laws or guidelines governing fitness to hold both ordinary and vocational licences. There is, however, a worldwide variability from some nations imposing a blanket lifelong prohibition through to systems of individual driver's risk assessment. There is a lack of adequately researched data on relative accident risk in epilepsy compared to a non-epileptic population, which allows for this inequitable variability in regulations.

In Malaysia, the *Akta Pengangkutan Jalan (APJ) 1987* and *Kaedah-Kaedah Kenderaan Motor (Lesen Memandu) 1992* applies, and states:

- Under Section 30 (2) and (3) *APJ 1987*, the *Pengarah* of JPJ may refuse an application for a licence if the licensee is found to have a condition (disease or disability) that may endanger other road users. In this context, *Kaedah 18 dan Kaedah-Kaedah Kenderaan Motor (lesen memandu) 1992* clearly states 'epilepsy' as one such condition; this applies to all and any forms of licences.
- If a licensee has obtained a licence before developing this condition, the *Pengarah* can revoke this licence under *Seksyen 30 APJ 1987* based on a medical report from any medical officer stating the level of disease/disability.

Legally, the doctor is not duty bound to notify *JPJ*. Generally, the decision to drive or not to drive is a choice best made after discussions between the treating physician and patient. Some conditions that may allow for safe driving include:

- Well-controlled epilepsy, and the patient is on treatment.
- Seizure freedom for at least 1 year, off or on treatment.
- Preceding aura – however, auras may not occur with every seizure, or the driver may not have enough space on the road to pull over despite an aura signalling an impending seizure.
- Purely nocturnal seizures.

Someone who is a newly diagnosed epileptic and is being started on medication is advised to stop driving for 6 – 12 months, until the seizures have stabilised and any drug-related side effects have settled. Certain occupations are prohibited for people with epilepsy – these include driving heavy machinery e.g. tractors and public buses, as well as flying commercial or military airplanes. As such, obtaining driving licences in these situations is clearly not possible. Driving is considered a privilege, not a right. If a patient’s epilepsy is against him/her obtaining a driver’s licence, use of public transport or carpooling is encouraged.

5.7 Education and epilepsy

The *Kementerian Pendidikan Malaysia* has confirmed that there are no discriminatory policies or action against any person with epilepsy who wishes to pursue higher education. There are no specific disciplines that are barred for people with epilepsy. Any person who wishes to enrol in an Institute of Higher Learning is required to undergo a medical check up, including people with epilepsy. People with epilepsy and any other chronic medical conditions are advised to inform the authorities of their condition, so as to facilitate any modification to their surroundings or courses as necessary.

KEY MESSAGES

- The diagnosis of epilepsy should be certain before treatment is started. There is no role of ‘trial of therapy’ in uncertain diagnosis.
- Develop a short and long term plan before starting or changing an AED regimen. Indications and risks should be weighed and discussed with the patient.
- Recognise the limits of the efficacy of currently available AEDs. A high level of awareness of drug-refractory epilepsies should be present and appropriate investigations for surgically remediable epilepsies should be part of the management plan.
- Individual factors should not be overlooked such as patient’s lifestyle, attitude towards medication, social and psychological impact of seizures, seizure recurrence and medications, employment, and driving.

6 LONG TERM PHARMACOLOGICAL TREATMENT

6.1 Introduction

Epilepsy is a chronic disease associated with physical, psychological, and socio-economic consequences that may compromise the quality of life. Although achieving seizure control is the main objective of medical management, seizures are not the only cause of concern for patients with epilepsy. Associated neurological, intellectual, psychological and social handicaps need to be equally addressed. Patients and caregivers need to be informed about the nature of the disease, its prognostic implications, the objectives of therapy, the risks and benefits of treatment, including the risks associated with poor compliance and abrupt discontinuation of therapy. Medical treatment should also involve a discussion of factors that could give rise to negative impact on the seizure control but with no undue restrictions on the patient's lifestyle.

6.2 Initiation and continuation of AEDs

Selection of AED is highly individualised.

Considerations while choosing an AED include:

1. Efficacy and effectiveness for specific seizure or epileptic syndrome (Table 7, Table 8)
2. Mode of actions (Table 10, Fig 2, Fig 3)
3. Pharmacokinetic properties (Table 11)
4. Safety and tolerability profile (Table 11)
5. Patient's circumstances
6. Dosing frequency and Cost (Table 9)

A systematic approach to the long-term pharmacological treatment of epilepsy is recommended:

1. Establish the diagnosis of epilepsy and the need for long term AEDs.
2. Start with a single AED as monotherapy after deciding on the type of seizure(s) and the epilepsy syndrome (Table 7, Table 8).
3. Begin at a low dose and increase gradually (Table 9).
4. Counsel and educate the patient and caregivers about his/her epilepsy and treatment. This information can be provided by doctors treating the patient or a nurse trained in epilepsy care.
5. Review the patient within a month to assess compliance, side effects and seizure control (refer to Table 11).
6. Review every 6 to 8 weeks. If the seizures are not controlled and there are no side effects, increase the dose appropriately. In about 60-70% of patients, these steps are sufficient to achieve good seizure control.
7. If the AED fails to control seizures:
 - Review the diagnosis and seizure pattern.
 - Review compliance (see also "drug monitoring").
 - Ensure that the maximum tolerated dosage has been used.
8. If the first AED continues to be ineffective at the maximum tolerated dose, introduce an alternative AED slowly (Table 9) without tapering the first.
9. If the patient has a good response to the second AED, consider withdrawing the original AED gradually.
10. Consider long-term two-drug therapy if monotherapy has not achieved remission or good seizure control.
11. If the first add-on AED is ineffective, or produces undesirable side effects, withdraw it slowly, and simultaneously replace it with a second add-on AED from the remaining choices. This process can be repeated for other possible add-on AEDs.
12. If the seizures are still not adequately controlled on two AEDs, some patients may benefit from an additional third AED.
13. AED from a different mode of action is preferred for add-on therapy to possibly increase the chance of seizure control but more importantly to avoid added side effects by using the AED of similar mode of action.

14. Review the diagnosis if seizures continue despite the above logical approach, and a period of 2-3 years has elapsed. The possibility of pseudoseizures (NEAD) or poor compliance should be considered. When these possibilities have been excluded the patient should be evaluated for a possible progressive structural lesion, especially if the patient has partial seizures, and surgery may be an option.
15. Patients and caregivers must be fully involved in the decision-making process about their treatment. Their views on treatment such as achieving the right balance between side effects and seizure control should be taken into account when considering changes in medication.
16. The importance of compliance should be stressed to patients and caregivers.

Table 7 : Efficacy and safety as Initial Monotherapy

Seizure type or epilepsy syndrome	Level of efficacy and effectiveness evidence (in alphabetical order)
Adults with partial-onset seizures	Level A: CBZ, LEV, PHT, ZNS Level B: VPA* Level C: GBP, LTG, OXC, PB, TPM, VGB Level D: CZP, PRM
Children with partial-onset seizures	Level A: OXC Level B: None Level C: CBZ, PB, PHT, TPM, VPA, VGB Level D: CLB, CZP, LTG, ZNS
Elderly adults with partial-onset seizures	Level A: GBP, LTG Level B: None Level C: CBZ Level D: TPM, VPA
Adults with generalised onset tonic–clonic seizures	Level A: None Level B: None Level C: CBZ, LTG, OXC, PB, PHT, TPM, VPA Level D: GBP, LEV, VGB
Children with generalised onset tonic–clonic seizures	Level A: None Level B: None Level C: CBZ, PB, PHT, TPM, VPA Level D: OXC
Children with absence seizures	Level A: ESM, VPA Level B: None Level C: LTG Level D: None
Benign childhood epilepsy with centrotemporal spikes (BCECTS)	Level A: None Level B: None Level C: CBZ, VPA Level D: GBP, LEV, OXC, STM(sulthiame)
Juvenile myoclonic epilepsy (JME)	Level A: None Level B: None Level C: None Level D: TPM, VPA

The table above summarises the latest evidence for efficacy and effectiveness of different AEDs for specific seizure types or epilepsy syndromes. However in real life, efficacy and effectiveness are just part of the consideration; cost and tolerability are some of the other factors. A more practical recommendation is summarised in table 8.

*Refer to chapter 9 for the recent update on the use of sodium valproate in women

Table 8: Recommended AED according to seizure type or epilepsy syndrome

Seizure types or epilepsy syndromes	Monotherapy	Adjunctive therapy* (other than drugs in monotherapy)	Therapy for resistant cases
Seizure Types			
Focal Seizures	carbamazepine lamotrigine levetiracetam oxcarbazepine sodium valproate# zonisamide	clobazam gabapentin topiramate perampanel lacosamide	eslicarbazepine phenobarbital phenytoin pregabalin tiagabine vigabatrin
Generalised Tonic Clonic seizure <i>only</i>	sodium valproate# lamotrigine carbamazepine** oxcarbazepine**	clobazam levetiracetam topiramate perampanel	
Absence Seizures	ethosuximide sodium valproate# lamotrigine		clobazam clonazepam levetiracetam topiramate zonisamide
Myoclonic Seizures	sodium valproate# levetiracetam topiramate		clobazam clonazepam piracetam zonisamide
Tonic or Atonic Seizures	sodium valproate#	lamotrigine	rufinamide topiramate
Infantile spasm	steroid vigabatrin (1 st for tuberous sclerosis)		
Epilepsy Syndrome			
Dravet Syndrome	sodium valproate# topiramate	clobazam stiripentol	
Lennox–Gastaut syndrome	sodium valproate#	lamotrigine	rufinamide topiramate felbamate
Benign epilepsy with centrotemporal spikes, Panayiotopoulos syndrome or late-onset childhood occipital epilepsy (Gastaut type).	carbamazepine Lamotrigine Levetiracetam oxcarbazepine sodium valproate#	clobazam gabapentin (carbamazepine and oxcarbazepine may exacerbate or unmask CSWS, which may occur in BCEPTS.)	eslicarbazepine lacosamide phenobarbital phenytoin pregabalin tiagabine vigabatrin zonisamide
Idiopathic Generalised Epilepsy	sodium valproate# lamotrigine topiramate	perampanel	clobazam clonazepam zonisamide

Juvenile myoclonic epilepsy (JME)	sodium valproate# lamotrigine (may exacerbate myoclonic seizure) levetiracetam topiramate		clobazam clonazepam zonisamide
Childhood absence epilepsy, juvenile absence epilepsy or other absence epilepsy syndromes	ethosuximide sodium valproate# lamotrigine		clobazam, clonazepam, levetiracetam, topiramate zonisamide

* Medications in the monotherapy column will be suitable adjunctive as well if the first medication effect is suboptimum.

** Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin for patient with idiopathic generalised epilepsy, absence seizures, myoclonic seizures, tonic or atonic seizures, Lennox Gastaut Syndrome, Dravet syndrome.

Use of sodium valproate in female of childbearing age need special considerations and is discussed separately.

*Refer to chapter 9 for the recent update on the use of sodium valproate in women

Table 9: Dosing frequency

AED	Usual daily dose	No. of doses/day
Carbamazepine	Initial: 100 mg nocte (adults); 5 mg/kg/day (children). Maintenance: 400-1600 mg/day (adults); 10-20 mg/kg/day (children).	2-3
Oxcarbazepine	Initial: 600 mg/day (adults); 10 mg/kg/day (children) Maintenance: 1200-2400 mg/day (adults); 20-40 mg/kg/day (children)	2
Eslicarbazepine**	Initial: 400 mg/day (adults); Maintenance: 800-1200 mg/day (adult)	1
Clonazepam	Initial: 0.25 mg/day (adults); 0.02 mg/kg/day (children). Maintenance: 2-8 mg/day (adults); 0.1-0.2 mg/kg/day (children).	1-3
Clobazam	Initial: 5-10 mg/day (adults); 0.1 mg/kg/day (children). Maintenance: 10-20 mg/day (adults); 1 mg/kg/day (children).	2
Ethosuximide*	Initial: 250-500 mg/day (adults); 5-10 mg/kg/day (children). Maintenance: 750-2000 mg/day (adults); 20-40 mg/kg/day (children).	2-3
Gabapentin	Initial: 300 mg/day (adults); 10 mg/kg/day (children). Maintenance: 900-2400 mg/day (adults); 30-60 mg/kg/day (children)	2-3
Pregabalin	Initial: 150 mg/day (adults); Maintenance: 150-300 mg/day (adults)	2
Lamotrigine	Initial: 25 mg EOD (with valproate), 25 mg OD (without valproate) (adults); 0.15 mg/kg/day (with valproate), 0.3 mg/kg (without valproate) (children). Maintenance: 100-200 mg/day (with valproate), 100-400 mg/day (without valproate) (adults); 1-3 mg/kg (with valproate), 4.5-7.5 mg/kg/day (without valproate) (children). Adjunctive therapy with valproate: gradual increment in the dose over one month (adults). Higher doses if concurrent enzyme inducer.	1-2
Phenobarbitone	Initial: 30 mg/day. Maintenance: 30-180 mg/day (adults); 3-5 mg/kg/day (children).	1-3
Primidone	Initial: 100-125 mg/day (adults); Maintenance: 750-1500 mg/day (adults)	1-3
Phenytoin	Initial: 200-300 mg/day (adult.); 5 mg/kg/day (children) Maintenance: 300-400 mg/day (adults), 5-8 mg/kg/day (children)	1
Topiramate	Initial: 25-50 mg/day (adults), 0.5-1 mg/kg/day (children). Maintenance: 200-400 mg/day (adults); 3-9 mg/kg/day (children).	2
Valproate*	Initial: 400-600 mg/day (adults); 10-15 mg/kg/day (children). Maintenance: 400-2500 mg/day (adults); 20-40 mg/kg/day (children under 20 kg); 20-30 mg/kg/day (children over 20 kg).	2
Vigabatrin**	Initial: 1000 mg/day (adults), 50 mg/kg/day (children); Maintenance: 1.5-3g/day (adults), 100-150 mg/kg/day (children)	2
Felbamate**	Initial: 1200 mg/day (adults), 15 mg/kg/day (children); Maintenance: 2400-3600 mg/day, 45 mg/kg/day (children)	3-4

Tiagabine**	Initial: 4 mg/day, Maintenance: 32-56 mg/day	1-4
Rufinamide**	Initial: 400 mg/day (adults), 10 mg/kg/day (children); Maintenance: 1800 mg/day (adults), 45 mg/kg/day (children)	2
Ezogabine**	Initial: 300 mg/day (adults); Maintenance: 600-1200 mg/day (adults)	3
Zonisamide	Initial: 100 mg/day (adults), 1 mg/kg/day (children); Maintenance: 300-400mg/day (adults), 12 mg/kg/day (children)	1-2
Lacosamide	Initial: 100 mg/day (adults); Maintenance: 200-400 mg/day (adults)	2
Perampanel	Initial: 2 mg nocte, 4 mg nocte if concurrent enzyme inducer (adults); Maintenance: 8-12 mg nocte (adults)	1
Levetiracetam	Initial: 500*** mg/day (adults), 14-20 mg/kg/day (children). Maintenance: 1000-3000 mg/day (adults); 40-60 mg/kg/day (children).	2

*Refer to chapter 9 for the recent update on the use of sodium valproate in women

** Not marketed in Malaysia

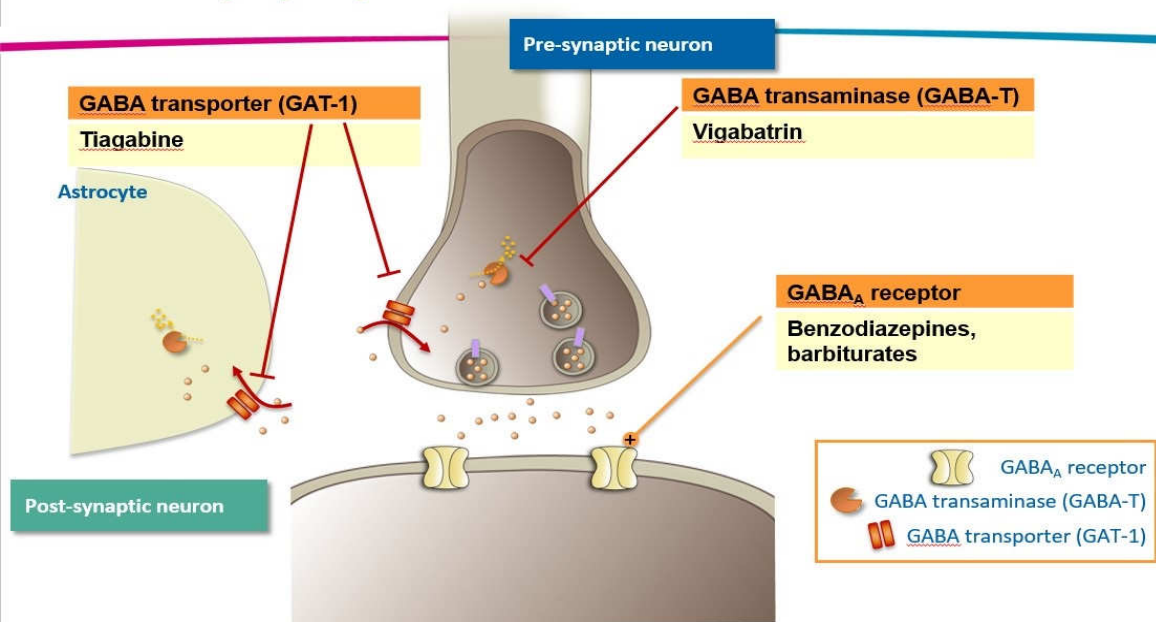
***May start as low as 250 mg/day in 2 divided doses

Table 10: Modes of action of AEDs

AED	Ion Channel	Excitatory Mechanism	Inhibitory Mechanism	Others
<i>First Generation</i>				
Benzodiazepine			Enhances GABA	
Carbamazepine	Na, Ca (L-type) blockade			
Ethosuximide	Ca (T-type) blockade			
Phenobarbitone	Increases chloride ion influx		Enhances and increases GABA	
Phenytoin	Na blockade			
Valproic acid	Na/Ca (T-type) blockade		Enhances GABA	
<i>Second Generation</i>				
Felbamate	Na/Ca blockade	Antagonises NMDA receptors		
Gabapentin	Ca (N-, P/Q-type)			
Lamotrigine	Na/Ca (N-, P/Q-, R-, T-type) blockade		Increases GABA	
Levetiracetam	K ⁺ /Ca (N-type) blockade		Increases GABA	Binds to SV2A protein
Oxcarbazepine	Na/Ca (N- and P-type) blockade			
Pregabalin	Ca (N-, P/Q-type) blockade			
Rufinamide	Na prolonged inactivation			
Tiagabine			Increases GABA	
Topiramate	Na blockade	Antagonises AMPA/kainate glutamate receptor	Enhances GABA	Inhibits carbonic anhydrase enzyme
Vigabatrin			Increases GABA	
Zonisamide	Na/Ca (N-, P-, T-type) blockade			Inhibits carbonic anhydrase enzyme
<i>Third Generation</i>				
Ezogabine/Retigabine	K (enhances M-type current)			
Lacosamide	Increases slow inactivation of Na channels			Binds to collapsin response mediator protein-2
Perampanel		Antagonises AMPA glutamate receptor		

Figure 2

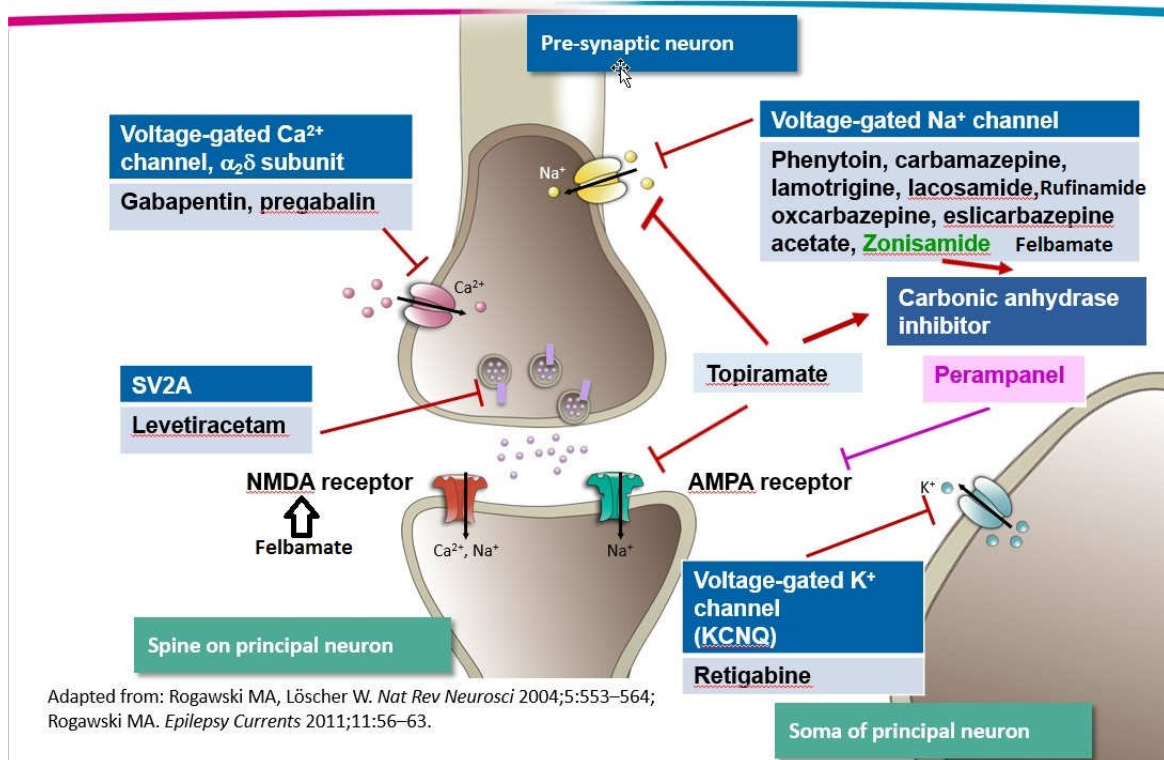
Inhibitory synapse



Adapted from: Rogawski MA, Löscher W. *Nat Rev Neurosci* 2004;5:553–564; Rogawski MA. *Epilepsy Currents* 2011;11:56–63.

Figure 3

Excitatory synapse – AEDs that attenuate excitability



Adapted from: Rogawski MA, Löscher W. *Nat Rev Neurosci* 2004;5:553–564; Rogawski MA. *Epilepsy Currents* 2011;11:56–63.

Table 11: AEDs pharmacokinetics and adverse reactions

Oral AED	Oral Bioavailability	Protein Binding	Metabolism	Half-life	Interaction	Side effects
Phenobarbitone	Good	Low	>70%	80-100H	Present	Sedation, decreased concentration, depression, hyperactivity (children), reduced bone density, plantar fibromatosis, Dupuytren contracture, frozen shoulder.
Primidone	Good	Low	Extensive	10-15H	Present	Similar to phenobarbitone, acute toxic reaction with debilitating drowsiness, dizziness, ataxia, nausea, and vomiting.
Phenytoin	Variable	High	Extensive, Non Linear	9- >42H (dose dependent, longer in toxicity)	Present	Ataxia, incoordination, dysarthria, nystagmus, diplopia, gingival hypertrophy, hirsutism. A paradoxical increase in seizures in overdose. Hypotension, arrhythmias, purple glove syndrome in IV form.
Carbamazepine	Good	Intermediate	Extensive	25-65H (initial use) 8-22H (auto induction)	Present	Blurred vision, diplopia, nystagmus, unsteadiness, incoordination, tremor, hyponatraemia, weight gain, decreased bone, mild leukopaenia, rarely aplastic anaemia. Rash and SJS (increased risk with HLA B1502)
Oxcarbazepine	Good	Low	Extensive	1-4H, 8-10H (active metabolite, prolonged in renal impairment)	Present	Drowsiness, headache, fatigue, dizziness, blurred vision, diplopia, nausea, vomiting, and ataxia, rash (25% cross reactivity with CBZ), more hyponatraemia than CBZ.
Eslicarbazepine	Good	Low	~40%	13-20H	Present	Similar to oxcarbazepine. Less hyponatremia, rash 3%.
Valproate	Good	High	Extensive	13-16H	Present	Gastric irritation with nausea, vomiting, anorexia, fatigue, drowsiness, tremor, weight gain, hair loss, peripheral oedema, thrombocytopenia. Encephalopathy and hyperammonaemia in polypharmacy (TPX, ZNS) Idiosyncratic hepatotoxicity and pancreatitis.
Ethosuximide	Good	Low	Extensive	30-60H	Present	GI adverse effect, neuropsychiatric disturbances. Idiosyncratic reaction includes rash, SJS, SLE, aplastic anaemia, thrombocytopenia,

						agranulocytosis, and rarely autoimmune thyroiditis.
Clobazam	Good	High	Extensive	36-42H, 71-82H (active metabolite)	Present	Drowsiness, nystagmus, incoordination, unsteadiness, dysarthria
Clonazepam	Good	High	Extensive	17-60H	Present	Same as clobazam
Felbamate	Good	Low	~50%	20-23H	Present	GI irritability, insomnia, weight loss, aplastic anemia (1/5000 to 1/8000) , hepatic failure (1/26,000 to 1/54,000)
Gabapentin	Low	Low	None	5-7H	Absent	Drowsiness, dizziness, ataxia, tiredness, , weight gain, myoclonus, cognitive slowing in the elderly, emotional lability in children, peripheral oedema
Pregabalin	Good	Low	None	~6H	Absent	Same as GBP
Lamotrigine	Good	Intermediate	Extensive	~24H, double with valproate	Present	Dizziness, blurred vision, diplopia, unsteadiness, nausea and vomiting, headache, tremor. Rash 3%, TENS and SJS (1/4000)
Topiramate	Good	Low	~30%	~21H	Minimal	Cognitive adverse effects including cognitive slowing, decreased attention and memory, impaired executive function, word-finding difficulty, and reduced verbal fluency. Sedation, fatigue, dizziness, ataxia, and depression. Kidney stones 1.5%. Paresthesia, weight loss glaucoma. Oligohidrosis, hyperthermia, and metabolic acidosis may occur in children.
Tiagabine	Good	High	Extensive	7-9H	Present	Dizziness, asthenia, nervousness, tremor, depression, and emotional lability. Dose-related nonconvulsive status epilepticus or encephalopathy.
Levetiracetam	Good	Low	~30%, Non hepatic	6-8H	Absent	Somnolence, dizziness, asthenia. Irritability and hostility (esp. children) Depression.
Zonisamide	Good	Low	~65%	~60H	Present	Cognitive slowing and difficulty with concentration. Depression and psychosis. SJS, TEN rarely. Kidney stones 4%. Oligohidrosis, hyperthermia, and metabolic acidosis (esp. children), aplastic anaemia.
Lacosamide	Good	Low	~60%	~13H	Minimal	Dizziness, headache, nausea, vomiting,

						diplopia, fatigue, sedation. Cardiac arrhythmias.
Vigabatrin	Good	Low	None	10.5H	Absent	Sedation, fatigue, dizziness, ataxia. Irritability, behaviour changes, psychosis, depression. Weight gain. Progressive and permanent bilateral concentric visual field constriction (30% to 40%)
Rufinamide	Good	Intermediate	Extensive	6-10H	Present	Dizziness, fatigue, somnolence, and headache. Short QT interval.
Ezogabine/retigabine	Limited	Intermediate	Extensive	7-11H	Present	Dizziness, somnolence, fatigue, confusion, blurred vision, tremor, nausea. Weight gain. Urinary retention 2%. Bluish pigmentation in the skin, nails, and retina.
Perampanel	Good	High	Extensive	105H	Present	Dizziness, somnolence, headache, fatigue, ataxia, and blurred vision. Aggression and hostility (high dose, adolescent)

6.3 Drug monitoring

AED concentrations are over-requested and often misinterpreted, leading to injudicious alteration of treatment. When employed as a guide to dosing, serum concentrations of phenytoin are the most useful, given its narrow therapeutic range and zero order kinetics. Assays of carbamazepine, phenobarbitone, and benzodiazepines are moderately helpful. Serum assays for valproate are unhelpful due to large fluctuations in levels and lack of correlation with efficacy. Serum assays for the newer drugs such as lamotrigine, topiramate and gabapentin are not available and generally unnecessary.

The major indications for assaying serum AED levels are:

- to check compliance.
- to determine if signs or symptoms are the result of AED toxicity.
- as a guide to dosing of certain AEDs (in particular, phenytoin).
- to monitor pharmacokinetic interactions.
- as a guide in certain situations e.g. pre-pregnancy planning, during pregnancy, and status epilepticus.

As a general rule, serum AED levels should be measured at steady state, i.e. when at least 5 elimination half-lives have elapsed since the last dose change. Blood should be drawn in the morning before the first daily dose, when the concentration is usually at its trough. The time of sampling is unimportant for AEDs with long half-lives like phenobarbitone. For drugs with significant variation in serum concentrations during the dosing interval (e.g. sodium valproate and carbamazepine), a second sample should be taken a few hours later. If drug toxicity is suspected, peak levels should be taken (Table 12).

Table 12 : Drug Monitoring

AED	Time to peak concentration (H)	Time to steady state (Days)	Comment	Reference range (mg/L)	Conversion factor (F) ($\mu\text{mol/L} = F \times \text{mg/L}$)
Carbamazepine	2-9	2-4	Active 10, 11 epoxide metabolite contributes to clinical effects	4-12	4.23
Clobazam	1-3	7-10	Active N-desmethylmetabolite contributes to clinical effects	0.03-0.3 (clobazam) 0.3-3 (desmethyl metabolite)	3.33 (clobazam) 3.49 (desmethyl metabolite)
Clonazepam	1-4	3-10	7-amino metabolite retains some pharmacological activity	0.02-0.07	3.17
Ethosuximide	1-4	7-10		40-100	7.08
Felbamate	2-6	3-4		30-60	4.20
Gabapentin	2-3	1-2		2-20	5.84
Lamotrigine	1-3	3-6 (5-15 with valproic acid comedication)		2.5-15	3.90
Levetiracetam	1	1-2		12-46	5.87
Oxcarbazepine	3-6	2-3		3-35	3.96
Phenobarbitone	0.5-4	12-24		10-40	4.31
Phenytoin	1-12f	5-17		10-20	3.96
Pregabalin	1-2	1-2		Not Established	6.28
Primidone	2-5	2-4	Metabolically derived phenobarbital contributes largely to clinical effects	5-10	4.58
Tiagabine	0.5-2	1-2		0.02-0.2	2.66
Topiramate	2-4	4-5		5-20	2.95
Valproic acid	3-6	2-4		50-100	6.93
Vigabatrin	1-2	1-2		0.8-36	7.74
Zonisamide	2-5	9-12		10-40	4.71

6.4 AED toxicity

Important points pertaining to AED toxicity include:

- Acute dose-related toxicity is common and predictable although the dose required to produce symptoms varies between individuals.
- Inappropriate rapid introduction of AEDs is a common reason for toxicity and apparent drug failure.
- Carbamazepine, lamotrigine and topiramate produce non-specific central nervous system manifestations, in particular drowsiness.
- Allergic reactions, manifested initially by rash occur in 2-4% of patients exposed to carbamazepine, phenytoin, phenobarbitone, and lamotrigine. This may occur even after a few weeks of starting treatment, with the peak incidence at 10-21 days.
- Chronic toxicity may affect any system. The side effects are quite specific for each AED.

6.5 Epilepsy in remission

Population and cohort studies have shown that 70-80% of patients diagnosed and treated for epilepsy will attain long-term remission in excess of two or more years. The decision to continue the AED despite seizure freedom is critical and potentially more difficult to make. For adults, the penalties for seizure recurrence is high but there may be perceived adverse effects of AED on concentration and cognitive function, as well as unwanted complications in pregnancy in women. In spite of all the studies suggesting various prognostic factors, no factor or model can exactly predict the risk of seizure recurrence in an individual patient and hence each patient needs to be counselled on a case-to-case basis. The "one size fits all" approach is not feasible. However, some guidance may be available from the following frequently asked clinical questions:

1. What Is the Length of the Seizure-Free Period Required to Start Drug Withdrawal? Should We Consider Different Seizure-Free Periods in Children and Adults?

Antiepileptic treatment might be discontinued after a minimum period of 2 years of seizure freedom; shorter seizure-free period should be discouraged because of a higher risk of relapse. Discontinuation of treatment could be considered after 2 years in children because of a marginally higher risk of relapse for early withdrawal).

2. Should We Consider Withdrawing Treatment in Patients with an Abnormal EEG at Time of Discontinuation?

An abnormal EEG (epileptiform abnormalities or specific EEG patterns) at the time of treatment discontinuation is associated with an increased risk of relapse, although of a limited relevance if the abnormal EEG is the only negative prognostic predictor. The decision to stop treatment should be considered in the light of other (concurrent) predictors of relapse and the social and personal complications of a seizure relapse.

3. Should We Consider Withdrawing Treatment in Patients with a Documented Aetiology of Epilepsy (Including Mental Retardation and Perinatal Insults)?

A documented aetiology of seizures, including the presence of mental retardation and/or abnormal neurologic or imaging findings, is also associated with an increased risk of relapse; however, as with an abnormal EEG, the risk is of a limited relevance if this is the only negative prognostic predictor. The decision to stop treatment should also be considered in the light of the social and personal complications of a seizure relapse. However, an abnormal EEG pattern associated with a documented aetiology of seizures warn against treatment discontinuation.

4. Should We Consider Withdrawing Treatment in Patients with Partial Seizures?

The presence of partial seizures should not be considered per se a risk factor for relapse, in absence of other relevant seizure predictors (abnormal EEG and/or documented aetiology). Seizure type should be assessed along with other variables when the decision to stop treatment must be taken.

5. *Should Age at Onset Be a Factor Influencing the Decision to Stop or Withhold Treatment?*

Age at onset of seizures should be considered along with other factors when deciding to stop or withhold treatment. Older age at seizure onset should not affect the decision to stop treatment if other negative prognostic predictors are not present.

6. *Does Sex Matter?*

Although a female patient carries a higher risk of relapse than a male patient, the role of sex should not influence the decision to stop or withhold treatment unless other factors (e.g. epilepsy syndrome) are associated.

7. *Should We Exclude Treatment Withdrawal in Patients with a Family History of Epilepsy?*

Family history of epilepsy should not be a contraindication to treatment discontinuation when all the other variables have been properly weighted (recommendation B).

8. *Should We Exclude Treatment Withdrawal in Patients with a History of Febrile Seizures?*

History of febrile seizures per se should not be a contraindication to treatment discontinuation.

9. *Should We Exclude Treatment Withdrawal in Patients with Some Epilepsy Syndromes?*

The epilepsy syndrome should always be considered in the decision process at the time of treatment discontinuation. In this regard, a case should be made to stop treatment in benign childhood epilepsy with centrotemporal spikes and in most idiopathic generalised epilepsies. In contrast, withholding treatment in seizure-free patients might be an option for cryptogenic or symptomatic generalised epilepsies, juvenile myoclonic epilepsy, and symptomatic partial epilepsies.

10. *Should We Consider Treatment Withdrawal Only in Patients with Lower Seizure Frequency before Entering Remission and/or Shorter Duration of Active Epilepsy and/or Less Difficult Seizure Control?*

Prolonged duration of active disease before and during treatment and high seizure frequency should not be a contraindication to treatment discontinuation.

11. *What Is the Most Appropriate Tapering Period?*

Slow discontinuation of antiepileptic drugs should be encouraged and the duration of the tapering period should be tailored to the patient's needs and preference.

12. *Is a Patient Taking Two or More Drugs at Higher Risk of Relapse Compared to a Patient on Monotherapy?*

The patient should be warned that taking two or more drugs at the time of treatment discontinuation might be associated with an increased risk of relapse. However, discontinuation of AEDs might be considered, in particular when no other concurrent negative prognostic factors occur.

13. *Does the Drug Taken at Time of Discontinuation Matter?*

The decision to stop or withhold treatment in a seizure free patient is not affected by the type of drug to be ceased.

14. Which Combinations of Risk Factors Help the Decision to Withdraw Treatment?

A patient who is age 12 years or older and has seizures after treatment initiation should be cautioned not to stop treatment.

15. How long Should We Monitor Patients after Treatment Discontinuation?

A patient discontinuing treatment for seizure freedom should be followed for no fewer than 2 years.

6.6 HLA issues

There has been much concern about the strong association of HLA-B*1502 genotype with severe adverse cutaneous drug reactions (ACDR), namely, Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) in patients taking carbamazepine (CBZ), but not with the milder maculopapular eruption and hypersensitivity syndrome. This has led to an FDA alert in recommending testing of HLA-B*1502 before starting treatment with carbamazepine.

The overall estimated risk of SJS/TEN associated with carbamazepine in Caucasian populations is fairly low at 1 to 6 per 10,000 new users. However, recently, post-marketing adverse events reported to the World Health Organization (WHO) and carbamazepine manufacturers pointed to a much higher rate of SJS/TEN, (about 10 times higher) in some Asian countries. This is attributed to the higher prevalence of HLA-B*1502 in the Asian population.

HLA-B*1502 is not a universal marker. The prevalence of HLA-B*1502 in the general population is low in Europe, Japan, Korea and Sri Lanka and most ethnic groups in India. However, it is more common among some Asian populations. Reports across Asia have shown that the prevalence of HLA-B*1502 is high among the Han Chinese (5-15%) in Taiwan, Hong Kong, Malaysia, and Singapore; 12-15% among Malays in Malaysia and Singapore; 8-27% among the Thais, and less than 10% among Vietnamese.

To date, the HLA-B*1502 allele as a marker for carbamazepine-induced SJS/TEN is only established among the Han Chinese. A recent study showed that the HLA-B*1502 allele was seen in all 44 patients with carbamazepine-induced SJS, but only in 3% of carbamazepine -tolerant patients, and 8.6% in the normal population. A case control study in Taiwan found that 59 out of 60 patients with SJS/TEN associated with carbamazepine were positive for HLA-B*1502, far higher than the 4% prevalence of HLA-B*1502 in carbamazepine-tolerant controls. Studies in Malay and Thai populations showed a similar but less strong association. Another study showed that there might be other genes that could be responsible for the CBZ-induced rash. It should be noted that patients who are tested positive for HLA-B*1502 may also be at increased risk of SJS/TEN not only to carbamazepine but also to other AEDs, notably lamotrigine, phenytoin, and phenobarbitone.

There are, however, many unanswered questions related to this issue:

1. The effects of carbamazepine dosage on the likelihood and timing of ACDR are uncertain.
2. The exact mechanism of how carbamazepine modulates cytotoxic activity via the HLA gene is also poorly understood.
3. The role of other HLA-B subtypes in carbamazepine-induced SJS/TEN and significance of HLA-B*1502 and other HLA subtypes in ACDR induced by other AEDs, e.g. phenytoin and lamotrigine are unclear.

In Malaysia, HLA-B*1502 testing is available in only a few centres. It is currently quite costly and the test result may take up to 3 weeks.

Recommendations:

- a. There is a need for further studies to determine the prevalence of HLA-B*1502 among various ethnic groups in Malaysia. One issue to be considered is whether children of inter-racial marriages should be evaluated differently due to their mixed genetic status.
- b. There is a need to have national data on carbamazepine-induced SJS/TEN and HLA-B*1502 in this group of patients.
- c. There is also a need to set up national or regional laboratory support to provide the test reliably.
- d. In view of the significant morbidity and mortality in SJS-TEN, selected patients, especially Han Chinese and Malays, should be screened for HLA-B*1502 before starting carbamazepine.
- e. The latency of carbamazepine-induced SJS/TEN is 25 to 90 days. Therefore, patients who are already on carbamazepine after 3 months without ACDR should continue the treatment.
- f. Patients who are tested positive for HLA-B*1502 should not be treated with carbamazepine unless the expected benefit clearly outweighs the risk of SJS/TEN.
- g. Patients who are tested negative for HLA-B*1502 have a low risk of SJS/TEN from carbamazepine, but SJS/TEN can still occur rarely. Therefore, the physician should still monitor the patient for relevant symptoms.

6.7 Generic Drug Issues

The Malaysian Society of Neurosciences has supported the use of original (patented) AEDs in previous meetings. However, in recent years, many generic AEDs have been approved for use by the National Pharmaceutical Control Bureau, Ministry of Health Malaysia once they have passed the bioequivalence study in healthy subjects. Original AEDs require stringent laboratory and clinical studies to ensure safety and efficacy in epilepsy patients before being approved by the drug authorities whereas generic AEDs only require bioequivalent studies.

A generic AED is considered as bioequivalent to the original AED as long as the drug's maximum concentration (C_{max}) in 12-16 healthy subjects is within 80-125% to that of the reference drug. The drug levels in the actual epilepsy population and patients on multiple AEDs are not tested. There are pharmacokinetic and pharmacodynamic variations between original and generic AEDs as well as between different generic brands of the same AED. These have yet to be taken into consideration. Therefore, there is indeed some concern about the differences between the efficacy and safety of the generic and original AEDs among clinicians and patients.

Recently, studies comparing generic and original AEDs have been published. Initiating a patient with epilepsy on generic AED can provide similar efficacy, tolerability and safety to that of the originator AED. A recent clinical trial published in *Lancet Neurology* 2016 showed that generic lamotrigine products with FDA-approved bioequivalence provide no detectable differences in clinical effects compared with the originator drug, supporting the notion that the US Food and Drug Administration bioequivalence standards are appropriate as long as the patient is consistently given the same formulation. These findings suggest that

generic AEDs could be used as an alternative to original AEDs. This will allow easier and wider accessibility to various AEDs.

Although, there is emerging data supporting the use of generic AEDs, there is no data regarding the response to generic AEDs in our local population, in pregnancy and in special populations such as children and the elderly. The plethora of generic drug manufacturers and distributors in Malaysia makes it difficult to draw conclusions about the clinical efficacy and safety of generic AEDs studied abroad. Therefore, care must be taken for patients with refractory epilepsy and those who are on polytherapy. These patients are best maintained on their original AEDs to prevent seizures.

KEY MESSAGES

1. AED should be started after establishing the diagnosis and need for long term AEDs; the patient and the caregiver must participate in the discussion process.
2. Choice of AED is highly individualised based on the efficacy, safety, mode of actions, cost and pharmacokinetics of the AED, the seizure type(s) and epilepsy syndrome as well as the patient's preference.
3. Monotherapy with the appropriate AED is preferred. If uncontrolled, adjunctive AED is added, and sometimes even a third AED is required for resistant cases.
4. Do not offer carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine or vigabatrin for patients with idiopathic generalised epilepsy, absence seizures, myoclonic seizures, tonic or atonic seizures, Lennox-Gastaut Syndrome and Dravet syndrome.
5. There are special considerations for the use of sodium valproate in women of child bearing age.
6. Major indications for AED monitoring are:
 - to check compliance.
 - to determine if signs or symptoms are the result of AED toxicity.
 - as a guide to dosing of certain AEDs (in particular, phenytoin).
 - to monitor pharmacokinetic interactions.
 - as a guide in certain situations e.g. pre-pregnancy planning, during pregnancy, and status epilepticus.
7. Withdrawal of AEDs after a period of remission should be clearly discussed with patients and their caregivers.
8. Han Chinese and Malays have a higher incidence of the HLA B*1502 allele, which is associated with carbamazepine-induced SJS-TEN; they should be screened before starting carbamazepine.
9. The latency of carbamazepine-induced SJS/TEN is 25 to 90 days.
10. Special care must be taken when using generic AEDs in patients with refractory epilepsy and those who are on polytherapy. These patients are best maintained on patented AEDs to prevent seizures.
11. Physicians must be cognisant of the myriad of manufacturers of the same AED when prescribing generic AEDs.

7 SURGICAL TREATMENT OF EPILEPSY

7.1 Introduction

More than 30% of people with epilepsy will continue to have seizures despite appropriate treatment with AEDs. This figure has not changed much even though many new AEDs have been introduced in the past 20 years. Options available to clinicians when dealing with drug resistant epilepsy (DRE) include changing or adding another (often 'new') AED, trial of dietary therapies (such as the ketogenic diet) and epilepsy surgery. Responder rates (i.e. 50% reduction of seizures) following introduction of a new AED and ketogenic diet are typically between 20-30% and 30-50% respectively. Seizure free rates following a new AED and ketogenic diet are disappointingly low at less than 10% each. In contrast, responder and seizure free rates following epilepsy surgery may be as high as 90% and 70% respectively. In a recent meta-analysis involving 16,253 participants, 10,518 (65%) achieved a good outcome from epilepsy surgery. A randomised controlled trial of adults with mesial temporal lobe epilepsy (MTLE) also showed superiority of temporal lobe surgery compared to continued AED therapy.

Uncontrolled seizures occurring over a prolonged period impact negatively on brain development and function. Neuroimaging studies show progressive neuronal damage and dysfunction that improves following successful surgical treatment. In children, such dysfunction may manifest as developmental delay, learning disability and behavioural impairments while in adults, it can lead to decline of higher cognitive function and limit educational and vocational opportunities. People with uncontrolled seizures have lower social interaction and reduced marriage rates, and are exposed to social stigma and discrimination. Psychiatric comorbidities such as depression and anxiety are much more common in those with uncontrolled seizures. The risk of accidental injury and sudden unexpected death (SUDEP) far exceeds that of the normal population. The use of multiple AEDs is associated with acute (eg. drowsiness and hypersensitivity) and long term adverse effects (eg. osteoporosis and cerebellar atrophy), and carry teratogenic risks. Chronic uncontrolled epilepsy also leads to high dependency on caregivers.

Despite the above data, epilepsy surgery is still much underutilised especially in resource-limited settings. In the UK, it is estimated that epilepsy surgery is performed in less than a quarter of those deemed appropriate for surgery. The surgical treatment gap is even worse in India, where it is estimated that only 1% of epilepsy surgery candidates are operated on. Furthermore, when patients are referred for surgery, there is an average duration of 22 years between the onset of epilepsy and referral. Potential reasons for underutilisation and delayed referrals include resource limitations, misconceptions regarding the risks and benefits of surgery and suboptimal assessment and referral patterns.

7.2 Early diagnosis of candidates for epilepsy surgery

An important development in epileptology is the recognition of “surgically remediable epilepsy syndromes”. These syndromes have a clearly defined clinical and EEG profile as well as a generally predictable natural history and response to currently available AEDs. The types of surgically remediable epileptic syndromes and their characteristics are shown in Table 13.

Table 13: Types of surgically remediable epileptic syndromes and their characteristics

Type of syndrome	Location of epileptogenic lesion	Nature of epileptogenic lesion
Mesial temporal lobe epilepsy	hippocampus parahippocampal gyrus uncus entorhinal cortex (any of the above)	hippocampal sclerosis, low grade tumour*, cavernous malformation, focal cortical dysplasia
Lesional neocortical epilepsy	lateral temporal, frontal, parietal or occipital lobes (any of the above)	low grade tumour*, cavernous malformation, focal cortical dysplasia, cortical tubers, ischaemic lesion
Non-lesional neocortical epilepsy	frontal temporal, parietal or occipital lobes	focal cortical dysplasia
Posterior quadrant epilepsy	multilobar lesion involving parietal, temporal, occipital lobes (sparing motor/sensory cortex)	tumour, cortical malformations, Sturge-Weber syndrome , ischaemic lesion
Hemispheric epilepsy	Diffuse involvement of one cerebral hemisphere with a normal contralateral hemisphere	hemimegalencephaly, Rasmussen’s Syndrome, Sturge- Weber syndrome, hemispheric infarction
Symptomatic generalised epilepsy	Bilateral, multifocal or diffuse lesions	cortical malformation, gliotic lesions

* Tumours with very low growth potential (WHO Grade I) such as dysembryoplastic neuroepithelial tumour (DNET), ganglioglioma, pleomorphic xanthoastrocytoma, and low grade cortical glial tumours

By current guidelines, patients are considered to have ‘medically intractable’ or drug resistant epilepsy after failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom. It is important to note that specific seizure frequency and time interval are not necessarily required. The diagnosis of intractability should also be individualised, with consideration given to age, the seizure type, seizure burden, degree of interference with quality of life, education and employment as well as any adverse effects due to appropriate medication. Patients who have medically intractable seizures should be referred for further investigation to determine if they are candidates for surgical treatment. There is little justification for persisting with prolonged trials of drug therapy in patients with potential surgically remediable syndromes.

7.3 Selection of patients for epilepsy surgery

Patient selection is the most important determinant of a successful surgical outcome. Presurgical evaluation of potential candidates should be carried out at a multi-disciplinary centre by clinicians who are not only sufficiently competent in the investigation and surgical treatment of epilepsy, but who also carry out a sufficient number of evaluations and surgical procedures to maintain their clinical skills. Inexpert evaluation can result in denial of surgery to patients who suffer from surgically remediable lesions or may lead to surgical treatment being undertaken in patients in whom surgery has no prospect of seizure control or in whom unacceptable complications would result from surgery.

The aims of presurgical evaluation are to

- Accurately localise the epileptogenic zone, identify the epileptogenic lesion
- Establish a resection(or disconnection) strategy for optimal seizure control
- Ensure that an unacceptable neurological deficit does not result from the resection(or disconnection)
- Establish that seizure control by surgery would significantly improve the quality of life

It is also important to exclude patients who have pseudoseizures and other non-epileptic attacks. Epilepsy surgery is not an option in patients who have progressive neurological disease (except those with Rasmussen's syndrome). Surgery is also not generally undertaken in those with significant mental retardation (IQ < 70), those with psychiatric disease (except post-ictal psychosis) and in those with dual pathology that cannot be safely removed or disconnected.

7.4 Presurgical evaluation

7.4.1 Localising the epileptogenic zone

Seizure origin and spread is best determined by studying the seizure semiology and ictal EEG. Video-scalp EEG monitoring remains the main tool for seizure localisation, and is used by all centres involved with presurgical evaluation. Additional methods used to directly or indirectly localise the seizure origin include

- Interictal scalp EEG
- Substraction ictal and interictal single photon emission tomography (SPECT)
- Simultaneous EEG and functional MRI (EEG-fMRI)
- Magnetoencephalography (MEG)
- Advanced EEG analysis (electronic source localisation, broadband EEG analyse)

7.4.2 Localising the epileptogenic lesion

MRI is essential in localising the epileptogenic lesion. Minimum sequences should include a volumetric T1-weighted and axial/coronal T2-weighted and FLAIR sequences. An appropriately calibrated and optimised 1.5 Tesla MRI will detect the majority of epileptogenic lesions, while a 3.0 Tesla MRI may additionally detect subtle changes such as those seen in hippocampal sclerosis and small focal cortical dysplasia. MRI post-processing (eg. curvilinear reformatting, quantitative studies with voxel-based morphometry) may assist the detection of lesions. In cases where MRI is negative or the boundaries of the lesion are unclear, positron emission tomography with 18-fluorodeoxyglucose (18-FDG PET) may provide localising information.

The data from all the above are then evaluated at a multidisciplinary conference attended by a team of neurologists trained in epileptology, epilepsy neurosurgeons and radiologists competent in the evaluation of epilepsy imaging. If all the investigations during the presurgical evaluation are completely concordant, a diagnosis of medically intractable seizures due to a surgically remediable epilepsy syndrome is made. Pseudoseizures and surgically irremediable dual pathology are excluded. A surgical treatment plan is then established, that would offer a reasonable prospect for seizure control without an unacceptable neurological deficit. The benefits and risks of a given procedure are patient specific and must be discussed in detail with the patient and family. On the other hand, if the presurgical findings are discordant, the patient will require further investigations including invasive studies.

7.4.3 Invasive Studies

Invasive EEG recording is used to acquire neurophysiological data to further elucidate the epileptogenic zone in a patient with otherwise discordant non-invasive presurgical investigation results. The type of intracranial recording depends on the suspected pathophysiological substrate of the epilepsy and its location. Invasive electrodes may be placed either within the brain parenchyma, in the subdural space, or in the extradural space. Electrodes may be used both for recording and for stimulation, allowing assessment of the relationship between the epileptogenic lesion and eloquent cortex.

Invasive depth electrodes may be placed with the assistance of frame-based stereotaxy or image guidance. The advantage of depth electrode includes precision recording and the ability to record deep cortical lesions. The disadvantages include a higher risk of haemorrhage due to the crossing of pial borders and sampling errors due to the smaller area of recording. Depth electrodes are currently used mainly to determine laterality in seizures of temporal lobe origin and in MRI-negative frontal lobe epilepsy.

Subdural strips and grids are placed onto the cortical surface below the dura. They pose a smaller haemorrhage risk as they do not breach the pial boundaries. Subdural grids are placed via open craniotomy while strips can be placed through simple burr holes. Subdural grids can record from a larger cortical area and are frequently used when epileptogenic lesions are adjacent to eloquent cortex. They can be used to localise and lateralise both temporal and extra temporal epilepsy.

The duration of monitoring varies from a week for subdural grids up to a few weeks for depth electrodes. The main criteria for the determination of the recording duration are seizure frequency, the success of lateralisation and stimulation. This has to be balanced against the risk of inherent infection. This risk can be reduced by proper intraoperative technique and post-operative care.

Invasive intracranial monitoring is increasing in frequency due to advanced neuroimaging techniques like SPECT and PET, which are able to detect small, potentially epileptogenic lesions. In recent years it has become a modality of choice in discordant epileptic cases.

Factors that determine the timing of epilepsy surgery and the outcome are

- a) Seizure burden and the degree of interference with quality of life
- b) Age – eg. the devastating effects of uncontrolled seizures in infants, young children < 5 years
- c) Nature of the epileptogenic lesion (eg. better outcomes with low grade tumour, cavernoma, Type II focal cortical dysplasia, Rasmussen's Syndrome, perinatal infarction)
- d) Proximity of the epileptogenic lesion to eloquent areas and hence the risk of an unacceptable neurological deficit
- e) Location of the epileptogenic lesion (eg. better outcome with temporal lobe lesions)
- f) Preoperative duration of seizures (better outcome with shorter duration of seizures)

It must also be established that control of seizures would make a significant positive impact on the patient's quality of life and that the patient and family are sufficiently motivated.

7.5 Operative procedure

The objective of surgical treatment is complete resection (or complete disconnection) of the epileptogenic zone without the risk of damage to any adjacent eloquent brain tissue (subserving speech, hand motor, visual, and memory function). Recent developments have contributed significantly to the efficacy and safety of epilepsy surgery. The use of the operating microscope and refinement of microneurosurgical techniques have led to significant improvement in surgical outcomes. Image guided surgery and the use of ultrasonic aspiration for tissue dissection and lesion removal have improved the precision and safety of even extensive

resection/disconnection procedures. There has been improvement in defining the relationship of epileptogenic lesions to adjacent eloquent structures with functional MRI, MR tractography, intracranial monitoring and cortical stimulation. The introduction of intraoperative MRI allows for real time assessment of lesion resection prior to the termination of any surgical procedure and also allows the surgical navigation software to be recalibrated during the operation, making the procedure more accurate.

The use of awake craniotomy, when considered suitable, has been proven to be a highly reliable technique to avoid neurological deficit during removal of epileptogenic lesions adjacent to motor and speech areas.

Table 14: Treatment options and expected outcomes for surgically remediable epilepsy syndromes

Epilepsy syndrome	Surgical options	Long term seizure outcomes (Engel’s Class I)
Mesial temporal lobe epilepsy	Anterior temporal lobectomy; selective amygdalohippocampectomy	60-80% (better outcomes for tumours, cavernoma)
Lesional neocortical epilepsy	Lesionectomy (resection of the lesion alone)	70-80%
	Tailored cortical resection (resection of the lesion and epileptogenic peri-lesional cortex)	50-60% (better outcomes for tumours, cavernoma)
Non-lesional neocortical epilepsy	Tailored cortical resection (with intra or extra-operative electrocorticography)	40-60%
Posterior quadrant epilepsy	Posterior quadrant disconnection (less commonly posterior quadrant resection)	60-70%
Hemispheric epilepsy	Functional hemispherotomy	50- 70% (better outcome for Rasmussen’s encephalitis, perinatal infarction; worse for hemimegalencephaly)
	Functional hemispherectomy	
	Endoscopic Functional Hemispherotomy	
Symptomatic generalised epilepsy	Corpus callosotomy VNS	40-50% seizure reduction, rare seizure freedom

Anterior temporal lobectomy involves en-bloc removal of medial temporal structures (head and anterior 2 cm of the body of the hippocampus, adjacent portion of the parahippocampal gyrus, uncus and inferior portion of the amygdala) as well as the overlying temporal neocortex (which may vary from a 3-4 cm segment of the superior, middle and inferior temporal gyri in the dominant hemisphere to a 4-5 cm resection in the non-dominant hemisphere).

Selective amygdalohippocampectomy may be performed anatomically or by the assistance of image guidance. In pure hippocampal sclerosis, the mediobasal resection is the determinant factor of a successful surgical outcome.

Resection of extra-temporal neocortical lesions such as cavernomas, focal cortical dysplasia, and indolent tumours such as dysembryoplastic neuroepithelial tumours is associated with a high rate of freedom from seizures. The extent of neocortical perilesional resection is guided by visual inspection, tactile feel of the surrounding tissue and intra-operative electrocorticography, all of which may be further facilitated by the use of image guidance or intraoperative imaging.

Outcome studies have shown that resection of extra-temporal lesions often result in better seizure control compared to temporal lesions, probably due to the proximity of mesial temporal structures to an associated second pathology, ie mesial temporal sclerosis alongside a structural lesion. In these cases, the potential benefits and risks of lesionectomy and resection of mesial temporal structures must be weighed and discussed with the patient prior to surgery.

In patients who have extensive lesions involving a single hemisphere or the posterior quadrant (multilobar lesions involving the parietal, temporal and occipital lobes but sparing the motor/sensory cortex), the surgical technique has evolved progressively toward more disconnection and less resection, maintaining similar seizure outcomes as resective surgery, and simultaneously reducing perioperative morbidity. With the use of image-guided surgery, the disconnections can be performed with better precision, shorter operative times, less intraoperative blood loss, less eventful postoperative course and less long-term complications as compared with anatomic resections.

Functional hemispherotomy and functional hemispherectomy involve near complete disconnection of hemispheric neural connections (disconnection of the internal capsule, corona radiata, removal of mesial temporal structures, transventricular corpus callosotomy, and disruption of the frontal horizontal fibres) with maximal preservation of cerebral tissue.

Posterior quadrant disconnection involves a medial temporal resection and disconnection of the posterior temporal, parietal and occipital lobes, which are anatomically left in situ but functionally completely disconnected. Recent literature suggests endoscopic functional hemispherotomy may be safely performed, thereby minimising the trauma of access while maintaining similar surgical outcomes to open surgery.

7.6 Risks of surgical treatment

7.6.1 7.6.1 Temporal lobe resections

Risks of mortality and life threatening morbidity (coma, hemiplegia) from medial temporal resections are now reported to be less than 2%. Transient hemiparesis may occur in about 2% of resections. Minor, non-disabling upper quadrantic visual deficits may occur in about 50% of patients due to interruption of lower fibres of the optic radiation. The most significant deficit is a decline of verbal memory with dominant hippocampal resections, in patients who have good preoperative memory function, especially if they do not achieve seizure freedom. Other persistent neurological complications include hemiparesis (2%) and dysphasia (3%).

7.6.2 Lesionectomy

The mortality risk is < 1% and risk of major permanent neurologic morbidity variable (determined by location of lesion, thoroughness of presurgical selection).

7.6.3 Posterior Quadrant Disconnection

Risk of mortality and major morbidity is <1%.

7.6.4 Functional hemispherotomy/Functional hemispherectomy

The mortality risk is <2-4%. Hydrocephalus may occur in 4-16% of patients. Usually, the decision to proceed to hemisphere surgery is taken after the patient has a complete hemiparesis, which may remain unchanged after surgery, or would return to baseline motor function in the contralateral leg within about one year of surgery. However, contralateral hand function does not return to baseline. Most patients are ambulatory after

surgery. Overall, gains in cognition, activities of daily living, and social interactions outweigh the increased motor deficit of the hand, which occurs after hemisphere disconnection.

7.7 Epilepsy surgery in children

Refractory epilepsy has devastating effects on brain maturation (myelination, dendritic branching) that occur during the first 5 years of life. In children with refractory seizures, persistent abnormal epileptiform discharges themselves can contribute to a progressive disturbance in cerebral function – an epileptic encephalopathy. Uncontrolled major seizures in infancy and early childhood have a devastating impact on cognitive and behavioural function in later life.

There is a general misconception that complications related to extensive resection or disconnection procedures such as functional hemispherotomy and posterior quadrant disconnection may be unacceptably high in infants and younger children. However, with current advances in neuroanaesthesia and improved surgical techniques, the risks of such procedures, even in infants and young children compare favourably with the much higher risks of irreversible major morbidity from continued disabling, refractory seizures. It is also important to realise that there is a greater potential for functional recovery following resection of eloquent cortex due to greater plasticity of the developing brain in this age group. In infants and young children with refractory epilepsy due to hemispheric pathology, hemisphere disconnection before the second or third year of life offers the best chance of transfer of neurological function to the opposite hemisphere. Timing of surgery is therefore crucial in infants and young children. Several months of frequent, disabling seizures might be sufficient for consideration of surgery, given the deleterious effects of refractory seizures.

The goals of epilepsy surgery in children are often to stop the harmful effects of severe, disabling seizures, reverse any epileptic encephalopathy and achieve a decrease in the consumption of AED. Successful surgery has been shown to result in a significant improvement in the rate of neurodevelopment, and an enhanced quality of life for both the patients with refractory seizures and their families. In some instances, the persistence of minor seizures postoperatively may be acceptable, when the above goals are achieved.

7.8 Palliative procedures

7.8.1 Corpus callosotomy

Section of the corpus callosum prevents rapid bilateral generalisation of epileptic discharges. Callosotomy is an option in patients with frequent atonic seizures (drop attacks), which may lead to severe and recurrent injuries. Initially a section of the anterior two thirds of the corpus callosum may be performed, with the option of a complete callosal section after an interval, if there is no response. Callosotomy can significantly reduce atonic seizures in 40–50% of patients. Some seizures may persist postoperatively but seizures may become less frequent, less disabling, and less violent. Transient hemiparesis and disconnection syndromes may occur in some patients after callosotomy.

7.8.2 Vagal nerve stimulation

Peripheral stimulation in the form of vagal nerve stimulation has shown some promise as a palliative procedure. Although the mechanism is not fully understood, it is postulated to be due to the stimulation of autonomic nervous pathways. About 40% of patients may achieve at least a 50% seizure reduction. Side effects include hoarseness and coughing on stimulation.

7.8.3 Deep Brain Stimulation

While there has been a lot of interest in extending the utility of deep brain stimulation to epilepsy surgery, the general results have been mixed. Stimulation of the anterior nucleus of the thalamus shows promise with results matching VNS outcomes.

7.8.4 Multiple Subpial Transections

Multiple subpial transection is a technique whereby superficial incisions are made in the cortex to reduce seizure propagation within the eloquent cortex, with the objective of maintaining anatomical function while reducing epileptogenesis. There is not much data available on the efficacy due to this procedure being frequently used as an adjunct to neocortical resection.

7.9 Exploratory interventions

7.9.1 Radiosurgery

Stereotactic radiosurgery of the amygdala and hippocampus offers a potential non-surgical option of epilepsy control. Initial results are quite promising, with a 2 year seizure free outcome similar to surgical resection. There is still the disadvantage of post-procedure swelling, delay to seizure freedom, increase in simple partial seizures one year following treatment, and reported increase in visual field deficits and the unknown long-term risk of radiation.

7.9.2 Laser ablation therapy

This is a minimally invasive stereotactic technique whereby a thermal wire is inserted into the centre of the epileptogenic lesion and heated up with a laser source. The ablation is monitored via intraoperative imaging. Initial outcomes are similar to resection and radiosurgery. Again this technique holds promise, in the form of minimal surgical trauma and precision ablation with the added advantage of immediate results.

7.9.3 Neuropace RNS™

The RNS neurostimulator is a programmable, battery powered, microprocessor-controlled device that delivers a short train of electrical pulses to the brain through implanted leads. The stimulator is designed to detect abnormal electrical activity in the brain and respond by delivering electrical stimulation to normalise brain activity before the patient experiences seizure symptoms. The neurostimulator is implanted in the cranium and connected to one or two leads that are implanted near the patient's seizure focus. The device monitors the patient's electrical activity through a connection to an implanted strip electrode on the brain surface. In theory the device can be taught to recognise the onset of a patient's seizure. This device is still being tested in clinical trials.

7.10 Management after epilepsy surgery

In patients who have cognitive and behavioural impairments before surgery, comprehensive rehabilitative efforts are needed post-surgery, in accordance with goals established during presurgical evaluation. Patients who remain seizure free after surgery have significant improvements in quality of life, employability, ability to drive and marital rates. In addition, there is reduction in mortality rates. The decision to withdraw AED therapy should be made on a patient-to-patient basis guided by age of the patient, preoperative seizure characteristics, nature of the epileptogenic lesion and adequacy of resection/disconnection, as assessed by a postoperative brain MRI. A recent paediatric study suggests that early AED withdrawal does not affect long-term seizure outcome or cure. Early AED withdrawal might unmask incomplete surgical resection sooner, identify those needing long term drug treatment and prevent unnecessary continuation of AEDs in others.

KEY MESSAGES

1. Evaluation for epilepsy surgery should be considered in all patients with drug resistant epilepsy, given the low responder and seizure free rates with further trials of AEDs and potentially good outcome following surgery.
2. Even though surgical outcome is best for those with focal epilepsies and discrete lesions, those with more widespread lesions and generalised seizures may still benefit from surgical interventions.
3. The mortality and morbidity risks associated with epilepsy surgery are low when patients are well selected.
4. Surgical intervention should be considered early in young children due to the potentially devastating effect on neurodevelopment of intractable epilepsy.

8 EMERGENCY TREATMENT OF EPILEPSY

8.1 Introduction

Most seizures are self-limiting and treatment is usually supportive and patients will recover fully after a period of rest of about 30-60 minutes.

8.2 Definition of status epilepticus

The proposed new ILAE definition of SE (2015) is as follows: Status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally, prolonged seizures (after time point t_1). It is a condition, which can have long-term consequences (after time point t_2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures. Time point t_1 indicates when treatment should be initiated, and time point t_2 indicates when long-term consequences may appear. The time points vary with different types of SE (Table 15)

Table 15 : Operational dimensions with t_1 indicating the time that emergency treatment of SE should be started and t_2 indicating the time at which long-term consequences may be expected

Type of SE	Operational dimension 1 Time (t_1), when a seizure is likely to be prolonged leading to continuous seizure activity	Operational dimension 2 Time (t_2), when a seizure may cause long term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits)
Tonic-clonic SE	5 min	30 min
Focal SE with impaired consciousness	10 min	>60 min
Absence SE	10-15 min ^a	Unknown

^aEvidence for the time frame is currently limited and future data may lead to modifications. (Adapted from Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus--Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia* 2015;56:1515-23.)

Refractory SE is defined as on-going seizures following first- and second-line drug therapy. *Super-refractory SE* is SE that continues or recurs 24 hours or more after the onset of anaesthetic therapy, including those cases where SE recurs on the reduction or withdrawal of anaesthesia.

8.3 Initial supportive management

During an acute epileptic seizure, the following measures should be taken:

- Place the patient on a smooth surface, if possible.
- Remove any harmful objects.
- Loosen tight clothing.
- Turn the patient to the left (or right, if left not possible) lateral position, and place the head on a soft support (bundle of cloth or pillow).
- Avoid placing any objects in the patient's mouth.
- Stay with the patient until he or she recovers fully, and gather information about the patient's background and epilepsy history.
- Get the patient to the nearest hospital if the seizure persists beyond 5 minutes, or there is no recovery of consciousness after 30 minutes, significant fever, serious injury, or a recent increase in seizure frequency.

8.4 Pre-hospital treatment

The duration and recurrence rate of seizures may be reduced by proper pre-hospital treatment by paramedical personnel including *buccal/intramuscular midazolam or rectal diazepam* in the case without venous access. Intramuscular midazolam is as effective as intravenous lorazepam. Caregivers of patients with recurrent clusters of seizures or prolonged seizures may be trained to administer rectal diazepam or buccal midazolam at doses predetermined by their medical practitioner.

- Buccal/intramuscular midazolam: 0.2 mg/kg
- Rectal diazepam: 0.5 mg/kg (2-5 years old), 0.3 mg/kg (6-11 years), 0.2 mg/kg (12 years and above)
-

8.5 Treatment of convulsive SE (t_1)

In the event that the seizure does not stop beyond time point (t_1), vital parameters, including the blood pressure, heart rate, oxygen saturation and ECG must be monitored. Oxygen is delivered through a high flow mask. If there is any suspicion of hypoglycaemia as the cause of the seizures, 50 ml of 50% glucose should be given intravenously. In addition, if Wernicke's encephalopathy is suspected, an intravenous bolus of thiamine 100 mg should be given prior to the glucose administration. Prolonged seizures may be aborted with the following AEDs:

8.5.1 First line: Benzodiazepines (BDZ)

Intravenous diazepam is the principal first line AEDs used for prolonged seizures in Malaysia. Intravenous diazepam is given at 0.15 mg/kg (10 mg for 60-70kg adult), repeated once after 10-20 min if seizures continue.

8.5.2 Second line: Phenytoin

For sustained control or if seizures continue, phenytoin can be given at 15-18 mg/kg at an infusion rate of ≤ 50 mg/min. Phenytoin is the preferred AED because it is widely available and is less sedating than the other AEDs. An additional dose of phenytoin at 5-10 mg/kg can be given if the first loading dose is unproductive.

8.5.3 Refractory SE

If the seizures persist, the patient should be referred to an anaesthesiologist for ICU care and administration of barbiturates or other anaesthetic agents, including thiopentone, midazolam, propofol or ketamine. (Table 17) At this point, intubation will be necessary as respiratory depression and hypotension from the seizure as well as the effects of the phenytoin or BDZ are of prime concern. The administration of barbiturates or other anaesthetic agents may cause further respiratory depression. The underlying aetiology needs to be treated. Anaesthetic agent can be tailed down if the patient is seizure-free for 24 hours.

8.5.4 Super-refractory SE

If seizures continue or recur 24 hours or more after the onset of anaesthetic therapy, or recur on the reduction or withdrawal of anaesthesia, the following can be considered:

- Anaesthetic agents and other AEDs e.g. IV/oral levetiracetam, IV sodium valproate and oral topiramate
- Magnesium infusion, pyridoxine
- Steroids and immunotherapy, especially in those suspected to have an autoimmune basis
- Ketogenic diet
- Hypothermia 31–35°C for 20–60 hours

- Surgery: emergency resective neurosurgery and multiple subpial transection, vagal nerve stimulation, deep brain stimulation
- Transcranial magnetic stimulation
- Electroconvulsive therapy

Table 16: Dosages of AEDs used in SE

- | |
|---|
| <ul style="list-style-type: none"> • IV diazepam 0.15 mg/kg, repeated once after 10-20 min • IV lorazepam 0.07 mg/kg (usually 4 mg) bolus • IV phenytoin 15-18 mg/kg at an infusion rate of ≤ 50 mg/min • IV phenobarbitone 10-20 mg/kg at an infusion rate of ≤ 100 mg/min, followed by infusion at 1-10 mg/kg/hour • IV midazolam 0.15-0.2 mg/kg bolus, followed by 0.05- 0.3mg/kg/hour • IV thiopentone 3-5 mg/kg bolus, followed by 3- 5mg/kg/hour • IV propofol 1-3mg/kg, followed by 2-10mg/kg/hour (Beware of propofol infusion syndrome with acidosis and rhabdomyolysis, especially in children) • IV ketamine 1 mg/kg/hour • IV sodium valproate 15-25 mg/kg slow bolus (over ½ hour), followed by infusion at 1 mg/kg/hour for 6 hours • IV/oral levetiracetam 20 mg/kg over 15 min, followed by 500-1500 mg b.d. • Oral topiramate 400mg, followed by 200mg b.d. |
|---|

Continuous/Repeat EEG recording is helpful to detect electrographic seizures as well as monitoring the adequacy of general anaesthesia/AED therapy. The table below is a useful step-by-step guide to the management of convulsive SE in adults. However, it is recommended that each hospital develops its own protocol.

Table 17: Management of convulsive SE in adults

Phase	Steps
Pre-hospital treatment	Buccal/intramuscular midazolam: 0.2 mg/kg Rectal diazepam: 0.5 mg/kg (2-5 years old), 0.3 mg/kg (6-11 years), 0.2 mg/kg (12 years and above)
Early status	Assess and control airway Monitor cardiac function Treat hypoglycaemia and administer IV thiamine 100 mg Intravenous diazepam at 0.15 mg/kg (10 mg for 60-70kg adult), repeated once after 10-20 min if seizures continue.
Established status	IV phenytoin 15 - 18 mg/kg infusion (diluted in 100 ml of normal saline), at a rate not exceeding 50 mg/min. Monitor ECG and BP throughout. An additional dose of phenytoin at 5-10 mg/kg can be given if the first loading dose is unproductive.
Refractory status	Ventilation and anaesthetic agents: <ul style="list-style-type: none"> • IV midazolam 0.15-0.2 mg/kg bolus, followed by 0.05-0.3mg/kg/hour • IV thiopentone 3-5 mg/kg bolus, followed by 3- 5mg/kg/hour • IV propofol 1-3mg/kg, followed by 2-10mg/kg/hour (Beware of propofol infusion syndrome, especially in children But this table is for treatment of adults) • IV ketamine 1 mg/kg/hour <p>Continue anaesthetic agents for 12-24 hours after last clinical or electrographic seizure</p>

8.6 Emergency treatment of other types of SE

SE can be classified into convulsive or non-convulsive, focal or generalised, and with or without impairment of consciousness (Table 18) Alternative non-sedative antiepileptic agents, e.g. IV/oral levetiracetam, IV sodium valproate, oral topiramate or other oral antiepileptic drugs, can be considered prior to anaesthetic agents in certain types of SE, for example:

- Focal motor SE e.g. epilepsy partialis continua
- NCSE without coma

Table 18: Classification of SE

<p>(A) <i>With prominent motor symptoms</i></p> <p>A.1 Convulsive SE (CSE, synonym: tonic–clonic SE) A.1.a. Generalised convulsive A.1.b. Focal onset evolving into bilateral convulsive SE A.1.c. Unknown whether focal or generalised</p> <p>A.2 Myoclonic SE (prominent epileptic myoclonic jerks) A.2.a. With coma A.2.b. Without coma</p> <p>A.3 Focal motor A.3.a. Repeated focal motor seizures (Jacksonian) A.3.b. Epilepsia partialis continua (EPC) A.3.c. Adversive status A.3.d. Oculoclonic status A.3.e. Ictal paresis (i.e., focal inhibitory SE)</p> <p>A.4 Tonic status</p> <p>A.5 Hyperkinetic SE</p> <p>(B) <i>Without prominent motor symptoms (i.e., nonconvulsive SE, NCSE)</i></p> <p>B.1 NCSE with coma (including so-called “subtle” SE)</p> <p>B.2 NCSE without coma B.2.a. Generalised B.2.a.a Typical absence status B.2.a.b Atypical absence status B.2.a.c Myoclonic absence status B.2.b. Focal B.2.b.a Without impairment of consciousness (aura continua, with autonomic, sensory, visual, olfactory, gustatory, emotional/psychic/experiential, or auditory symptoms) B.2.b.b Aphasic status B.2.b.c With impaired consciousness B.2.c Unknown whether focal or generalised B.2.c.a Autonomic SE</p>
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(Adapted from Trinka E, Cock H, Hesdorffer D, et al. A definition and classification of status epilepticus--Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia* 2015;56:1515-23.)

8.6.1 Myoclonic status

In a hospital setting, anoxic brain damage and acute renal deterioration are the commonest causes of myoclonic seizures. Treatment should be aimed at symptomatic control, and the eventual prognosis will depend on the underlying cause. More rapid resolution can be obtained with intravenous BDZ like midazolam/clonazepam or sodium valproate. Levetiracetam is also useful for anoxia-induced myoclonus.

8.6.2 Non-convulsive SE (NCSE) with coma

NCSE is defined as a prolonged state of impaired consciousness without obvious motor signs associated with continuous epileptiform discharges on EEG. Subtle SE may present with subtle eye movement abnormalities

e.g. nystagmoid eye jerks, repeated blinking, and persistent eye deviation. NCSE is seen in up to 8% of patients in coma who have no outward signs of seizure activity.

NCSE should be suspected if the patient does not wake up within 30-60 minutes after cessation of seizure, and can only be diagnosed with EEG. The first line of treatment is an infusion of a BDZ, i.e. midazolam or diazepam, and the simultaneous introduction of oral treatment like carbamazepine, phenytoin, or sodium valproate. In the event that BDZ infusion does not work, infusion of phenytoin or sodium valproate may be tried. Resistant patients may need a barbiturate for control. The risk of brain damage is minimal in comparison to convulsive SE.

KEY MESSAGES

1. Treatment of SE is aimed at preventing prolonged seizure (time point t_1) and long-term consequences (time point t_2)
2. Treatment should be initiated as early as the pre-hospital period
3. Anaesthetic agents should be initiated early with adequate loading dose if first and second line treatment fail.
4. Non-anaesthetic agents can be considered especially in those without impairment of consciousness.

9 SPECIAL ISSUES

9.1 Epilepsy in women

9.1.1 Introduction

In order to optimise the efficiency of treatment in women with epilepsy, the patients and their partners, as appropriate, must be given accurate information and counselling in the following areas:

- Menstruation
- Fertility
- Contraception
- Pregnancy
- Pre-conception management and counselling
- Labour
- Foetal malformations and long term cognition
- Breastfeeding and the puerperium
- Menopause and hormone replacement therapy
- Bone health

9.1.2 Menstruation

Menstrual disturbance had been reported in as high as 20-60% of epileptic women, related to underlying neuroendocrine dysfunction secondary to the seizure disorder. Women with epilepsy have disturbances in luteinising hormone concentration and pulsatile release and abnormalities in prolactin and steroid hormone levels. About one in three women with epilepsy have an abnormal menstrual cycle length (less than 23 days or more than 35 days). Polycystic ovarian syndrome (PCOS) is one of the commonest causes of menstrual disturbance, and has a higher prevalence in patients on valproate as compared to other AEDs. Valproate is an important first line AED in adolescent and young adult epilepsy syndromes e.g. juvenile myoclonic epilepsy and photosensitive epilepsy. Therefore, regular screening for menstrual disturbance is mandatory. Most disturbances will resolve with valproate discontinuation. Between 5% and 12% of women experience catamenial epilepsy in which exacerbation of seizures occur immediately before or during menses, because of the proconvulsant effect of oestrogen. Intermittent clobazam or acetazolamide given during the menstrual period may alleviate catamenial exacerbation of seizures.

9.1.3 Fertility

Women with epilepsy can achieve up to 80% of the expected level of fertility. Infertility in epilepsy is a reproductive endocrine disorder, which is directly related to seizure control or indirectly due to antiepileptic therapy, in particular, valproate and enzyme inducers e.g. carbamazepine and phenytoin. Infertile patients need to be screened for endocrine and menstrual dysfunction, as well as reviewed for antiepileptic therapy.

9.1.4 Contraception

There is an increased risk of oral contraceptive pill (OCP) failure with AEDs that induce hepatic microsomal enzymes (barbiturates, phenytoin, carbamazepine, and oxcarbazepine) (Table 19). These drugs enhance hepatic metabolism of contraceptive steroids and reduce their biologically active compound. Patients on the OCP need to be advised about additional non-hormonal contraceptive measures. If a woman wishes to rely on the OCP alone, she should be prescribed a preparation containing at least 50 µg of oestradiol, as opposed to the commonly available OCPs containing ≤ 35 µg oestradiol. If breakthrough bleeding occurs, the dose of oestrogen should be increased to 75 or 100 µg per day, and 'tricycling' (taking three packs without a break) should be considered. The progesterone-only pill is not recommended as a reliable contraceptive in women

taking enzyme-inducing AEDs. Intramuscular Depo-Provera at a dose of 150 mg should be given at a shorter interval (every 10 weeks instead of 12 weeks) if she is on enzyme-inducing AED. There is no evidence that hormonal contraception adversely affects seizure control, except for those patients treated with lamotrigine whose metabolism is significantly increased by OCP. If emergency contraception is required for women taking enzyme inducing AEDs, the dose of levonorgestrel should be increased to 1.5 mg and 750 micrograms 12 hours apart.

Table 19: Antiepileptic Drug Effects On Hormonal Oral Contraceptives (OC)

<p>Liver enzyme inducers – reduce concentration of OC</p> <ul style="list-style-type: none"> - Carbamazepine - Felbamate - Phenytoin - Phenobarbitone - Primidone - Oxcarbazepine - Topiramate
<p>Drugs that are safe to be used with OC</p> <ul style="list-style-type: none"> - Gabapentin - Levetiracetam - Lamotrigine - Tiagabine - Sodium valproate - Zonisamide

9.1.5 Pregnancy

Sixty per cent of women will experience no change in seizure frequency during pregnancy, 30% increased frequency and 10% decreased frequency. Although the increased seizure frequency in some women may be due to pregnancy-related fall in plasma drug concentrations, other factors such as sleep deprivation, poor compliance, inappropriate reduction in AED therapy and vomiting may also contribute.

There is little evidence that seizures adversely affect pregnancy other than increasing the risk of trauma to the developing foetus. There are only anecdotal reports of miscarriage following GTCS. Whether epilepsy is associated with an increased risk of obstetric complications remains controversial.

Pregnancy does not increase the risk of developing new epileptic seizures for the first time. However, if seizures do develop de novo in pregnancy, certain special causes must be considered and appropriately ruled out because they are more common in pregnancy (Table 20). A brain MRI or CT with lead shielding will often be required. The principles of treatment of new epileptic patients in pregnancy are the same as for the non-gravid state. Certain underlying causes need specific treatment. For example, eclampsia, is best treated with magnesium sulphate; it has a lower rate of seizure recurrence, pneumonia, assisted ventilation, and mortality as compared to standard AEDs. It is also safer for the developing foetus.

The serum concentration of most of the standard AEDs often falls during pregnancy, particularly in the first and third trimesters and these include phenobarbitone, phenytoin and valproate. Pregnancy has been shown to increase the elimination of some of the newer AEDs, viz. lamotrigine, levetiracetam and oxcarbazepine metabolite. The International Registry of Antiepileptic Drugs and Pregnancy (EURAP) study group reported a higher risk of convulsive seizures in pregnant mothers on oxcarbazepine monotherapy compared to other regimens. Dose increment should be considered if there is an increase in seizure frequency. Phenytoin and carbamazepine serum levels should be measured every 2-3 months. Serum levels of commonly used AEDs in pregnancy, including lamotrigine and levetiracetam, should be monitored closely during pregnancy to prevent decrease by more than 35% from preconception baseline. However, dose adjustments should not be based on

AED concentrations alone. Other factors such as seizure frequency, drug tolerance and interactions with other medications should be taken into consideration too.

Table 20: Special causes of epilepsy developing in pregnancy

Special causes of epilepsy developing in pregnancy
<ul style="list-style-type: none"> • Enlarging meningioma • Enlarging arteriovenous malformation • Ischaemic stroke • Cerebral venous or venous sinus thrombosis • Vasculitides • Subarachnoid haemorrhage • Eclampsia

Women on AEDs should be monitored throughout pregnancy to detect foetal malformations. Recommended investigations are listed in Table 21.

Table 21 : Prenatal diagnosis of malformations

Malformation	Investigation	Sensitivity/timing
Neural tube defects (NTDs)	Serum alpha-fetoprotein in maternal blood	80% at 16 weeks
	Serum alpha-fetoprotein in amniotic fluid	>80%, but reserved when ultrasound cannot reliably exclude a NTD
	Ultrasound	94% at 16-18 weeks
Major cardiac, facial and limb anomalies	Ultrasound	20-24 weeks

9.1.6 Pre-conception management and counselling

1. Ideally, women should be advised against getting pregnant until they become seizure free and are off AEDs. However, for various personal, cultural or religious reasons, this is seldom possible or practical. Hence, in all women with childbearing potential, the risk of teratogenicity while on AEDs and the risk of recurrent seizures if AEDs were to be withdrawn must be discussed long before they wish to conceive. The latter risk is low if the patient has been seizure-free for more than 2 years and tapering is done gradually. If AED withdrawal is impossible, effort to achieve monotherapy and lowest effective dose should be attempted before conception. Switching to a less teratogenic AED should be done before conception; switching during pregnancy is likely to be pointless because most teratogenic effects take place in the first trimester. For the above reason, contraception should be practiced till AED adjustment is achieved.

In cases where a patient with epilepsy is on AEDs and is seen for the first time in the first trimester, the AEDs should not be stopped or regime modified if the seizure control is good (rare attacks or complete seizure freedom).

9.1.7 Labour

The risk of seizures is greatest during the delivery period; 1-2% of epileptic women suffer a GTCS during labour. This must be made known to the patient and her obstetrician so that necessary precautions can be taken. The patient's regular AEDs must be continued through labour, via a nasogastric tube or intravenously, if

necessary. As pain, emotional stress and hyperventilation may increase the risk of seizures, epidural anaesthesia should be considered early during labour. If frequent GTCS or complex partial seizures do occur during labour, a caesarean section is indicated. An elective caesarean section is also recommended if frequent GTCS or complex partial seizures occur during the last weeks of pregnancy; the treatment of the seizure itself should proceed in the usual manner.

There is insufficient evidence to determine if there is an increased risk of bleeding in infants born to mothers on AEDs (particularly hepatic enzyme-inducing drugs). However, the precautionary measure of giving 20 mg/day of oral vitamin K1 in the last month of pregnancy, and/or their newborns 1 mg of vitamin K1 intramuscularly at birth should be practiced till proven otherwise. If there is evidence of bleeding in the newborn, intravenous fresh frozen plasma should be given.

9.1.8 Foetal malformations and long term cognition

The risk of foetal malformations is 4-8% if one AED is taken (compared with 1-3% in the general population) and 15% if more than one AED is taken. Studies on foetal malformations are limited to results from large prospective registries and these include the North American Antiepileptic Drug Pregnancy Registry (NAAPR), the UK Epilepsy and Pregnancy Register and the EURAP. Data from these registries have consistently shown that valproate is associated with the highest rate of foetal malformations, either as monotherapy or polytherapy, followed by phenobarbitone and topiramate. Valproate doses of ≥ 1500 mg daily carry the greatest risk (>25%) although the risk is still high (approximately 10%) in patients receiving 501-1500 mg daily of valproate. Valproate is associated with NTDs (1-2% risk compared with 0.2-0.5% in the general population). The combination of valproate, carbamazepine and phenytoin, has been associated with up to a 50% risk of foetal malformation. The risk of developing oral clefts is highest with phenobarbitone (2%), topiramate (1.4%) and valproate (1.4%) and the risk with topiramate was further supported by the most recent case-control study from North America. In a large retrospective cohort study, phenytoin monotherapy has not been shown to be associated with an increased risk of major congenital abnormalities. The reported teratogenic effects of commonly used AEDs are summarised in Table 22.

The lowest risks of foetal malformation are reported in patients taking lamotrigine and levetiracetam (2% and 2.4% respectively, compared to 1.1% in the normal population). Lamotrigine at <300 mg daily had the lowest risk. Risk is lower with carbamazepine if prescribed <400 mg daily (3.4%) but goes up to about 8.7% for doses ≥ 1000 mg daily.

Polytherapy carries a higher risk of foetal malformation than monotherapy (6% vs 3.7%) and this is even higher if the combination contains valproate. The recommended practice would be prescribing single-drug therapy at the lowest possible dose that effectively controls seizures. Valproate should be avoided in patients of child bearing age whenever possible unless attempts to control seizures with other AEDs have failed. If valproate is used, the lowest dose is recommended, viz. ≤ 700 mg daily. Levetiracetam and Lamotrigine would be the recommended AEDs to be used in pregnancy although other factors such as drug availability, side effects and cost have to be taken into account.

Studies on the teratogenic effects of the newer AEDs are limited by the small sample size, but animal studies might enable us to predict the teratogenic potential of these AEDs in the future. The beneficial role of folic acid in the prevention of major congenital malformation in newborns of women taking AEDs is questionable. However, a recent evidence-based review concluded that folic acid supplementation is possibly effective and should be recommended for all women of child-bearing age taking AEDs, starting before conception, at a dose of at least 0.4 mg – 4 mg daily.

Table 22: Teratogenic effects of AEDs

AED	Reported major teratogenic effects
Phenytoin	Cleft lip and palate, cardiac defects; craniofacial defects, digital hypoplasia. Recent evidence suggests no increased risk
Valproate	NTDs, cardiac defects, urogenital malformations
Carbamazepine	NTDs
Ethosuximide	Cleft palate
Barbiturates	Cleft palate
Vigabatrin	Cleft palate
Lamotrigine	Oro-facial cleft
Topiramate	Cleft lip and palate, hypospadias
Levetiracetam	No increased risk
Oxcarbazepine	Information not available

Cognitive teratogenesis has been highlighted in the recent Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study, in which valproate, again, has been found to have the highest risk. The study showed that children exposed to valproate in utero had a lower intelligence quotient (IQ) at age 6 compared to carbamazepine, lamotrigine and phenytoin. In addition, the study also showed that those exposed to high doses of valproate of >1000 mg daily had impaired verbal and non verbal ability, executive function and memory. Another study using the Childhood Autism Rating Scale (CARS) found that higher doses of valproate were associated with autistic traits and the scores were higher in valproate polytherapy than monotherapy. Regular assessment of cognitive function for children who had foetal exposure to AEDs, is therefore, recommended.

In 2015, the pharmaceutical company Sanofi added the following recommendation in its information leaflet for Epilim® (patented sodium valproate):

Female children/Female adolescents/ Women of childbearing potential/Pregnancy

Epilim should not be used in female children, in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated because of its high teratogenic potential and risk of developmental disorders in infants exposed in utero to valproate.

This package insert was approved by the National Pharmaceutical Regulatory Agency, Ministry of Health of Malaysia on 5 December 2016

9.1.9 Breast-feeding and the puerperium

Breast-feeding for most women on AED is generally safe. The dose of the AEDs should be reduced to pre-conception levels over the few weeks following delivery if the dose has been increased during pregnancy to avoid drug toxicity. Antiepileptic drug secretion in breast milk is inversely proportionate to the extent of protein binding. Hence AEDs that have no protein binding e.g. gabapentin and levetiracetam will have nearly equivalent concentrations in maternal serum and breast milk. Phenytoin and valproate have very low concentration in breast milk due to their extensive protein binding properties. Carbamazepine, phenobarbitone, lamotrigine, topiramate and zonisamide have low to moderate concentrations in breast milk. If AEDs are secreted in breast milk, the infant may become sedated or hypotonic if breastfed (occurring in 5-10% of babies). If this happens, the breastfeeding can be reduced and supplemented with bottle feeds. A special precaution should be taken if the mother is taking primidone and levetiracetam because these two agents transfer into breast milk in clinically important amounts.

Mothers should breastfeed their babies whilst seated on floor cushions and should not be allowed to bathe their babies in a bathtub unless assisted to avoid dropping their babies in case a seizure occurs.

9.1.10 Important Steps in the Management of Pregnant Women with Epilepsy

- Preconception counselling of the patient about risks of teratogenicity and possible adverse effects of uncontrolled seizures to maternal health and pregnancy
- Preconception review of AEDs; aim for minimal effective monotherapy if active epilepsy; consider drug withdrawal if seizure free
- Commence preconception folic acid supplements
- Screen for malformations
- Monitor condition and AED concentrations throughout pregnancy (refer to section 9.1.5)
- Vitamin K1 in last month of pregnancy, or for neonate
- Reassure patient that >90% pregnancies proceed with no problem in women with epilepsy

9.1.11 Menopause and hormone replacement therapy

Menopause can have quite a variable effect on epilepsy, with the frequency of seizures remaining the same, improving or worsening with menopause. Seizure frequency is more likely to improve during menopause if there was a catamenial relationship of seizure before menopause. Cryptogenic epilepsy accounts for about one-third of the epilepsy in elderly women, usually between the start of menopause and 2 years after complete cessation of menses, probably related to hormonal changes.

Hormone replacement therapy (HRT) has been shown to be associated with increased seizures in women taking the combination of oestrogen and progesterone, but decreased in those taking progesterone only. A dose-effect relationship between HRT and seizure frequency has been demonstrated in a randomised placebo-controlled trial.

9.1.12 Bone health

Women are more likely than men to develop bone health abnormalities, including osteopenia, osteoporosis and osteomalacia, from the hepatic enzyme inducing AEDs (namely phenytoin, carbamazepine, and phenobarbitone) as well as sodium valproate. All patients who have been taking these drugs for more than 5 years should be subjected to bone densitometry, and treated with calcium and vitamin D supplementation as necessary. Weight-bearing exercises, adequate sunlight exposure, cessation of smoking, and avoidance of caffeine should be encouraged. Early treatment of metabolic bone disease will reduce morbidity and mortality from long bone fractures.

KEY MESSAGES

- Patients taking OCP concomitantly with hepatic enzyme inducing AEDs may need an additional non-hormonal contraceptive measure or a higher dose of OCP preparation
- Certain AEDs concentration may fall during pregnancy and may need higher effective dose
- Valproate has been associated with highest risk of fetal malformation and children born with low IQ
- Valproate should be avoided in patients of child bearing age whenever possible. If valproate is used, the lowest dose is recommended, viz. \leq 700mg daily.
- Levetiracetam and Lamotrigine would be the recommended AEDs to be used in pregnancy
- It is generally safe to breastfeed whilst on AEDs but certain AEDs may be secreted in the breastmilk and cause complications to baby. Alternative feeding may be considered.
- The risk of osteopenia and osteoporosis is higher in patients taking hepatic enzyme inducing AEDs.

9.2 Epilepsy in children

9.2.1 Epidemiology

The incidence of epilepsy is highest during the infantile period of all age groups at 70.1 per 100,000. Among the infantile epilepsies, infantile spasms constitute the largest single epilepsy subgroup representing 13 – 45.5% of infantile population-based incidence studies. In developed countries, the prevalence of epilepsy increases as age increases but in developing countries, it generally peaks in adolescence and early adulthood. The aetiology also differs in children. The onset of idiopathic or genetic epilepsy is in childhood. Strokes and tumours are uncommon causes of childhood epilepsy; instead cerebral malformations, especially neuronal migration disorders, are much more common. Nearly all the inherited metabolic disorders responsible for seizures will present in infancy and early childhood, and should be considered when the children do not fit into any of the categories of seizures and epilepsy syndromes described in Chapter 2.

9.2.2 Diagnosis

There are many paediatric paroxysmal events, with and without altered consciousness, that mimic seizures (Chapter 3). Thus, the crucial step in evaluating children with a possible seizure disorder is to take a thorough history from a reliable witness, and whenever possible, review home video-recordings to confirm if the events are actually epileptic seizures rather than non-epileptic events. Great care should be taken to avoid misdiagnosis, resulting in the child being mislabelled as "epileptic" and subjected to unnecessary treatment. It is also important to remember that seizures in children may manifest as a single epilepsy syndrome or evolve through several epilepsy syndromes as their seizure characteristics change with brain maturation.

Epilepsy syndromes are defined as distinctive epilepsy disorders identifiable on the basis of age of epilepsy onset, specific EEG characteristics, seizure types and other features. The paediatric epilepsy syndromes range from benign self-limiting syndromes to severe epileptic encephalopathies. Please refer to Chapter 2 for specific details of the individual epilepsy syndromes. In children with epilepsy, it is important to attempt to make an epilepsy syndromic diagnosis, for appropriate counselling and treatment. If epilepsy syndromic

classification is not possible then the clinician should classify the seizure disorder according to the seizure type whilst always considering a possible underlying aetiology.

9.2.3 Neonatal seizures

Neonatal seizures are often either under- or over-diagnosed as neonates frequently exhibit non-epileptic movements that can be mistaken for epileptic seizures. Movements that are likely to be epileptic include generalised myoclonic jerks, clonic movements of the limbs particularly if it is associated with autonomic features and tonic eye deviation, focal tonic seizures, rhythmic clonic thrusting of the tongue (especially if associated with other clonic movements of the limbs) and spasms. Movements that are not likely to be epileptic include tremor or jitteriness, spontaneous clonus (unlike clonic movements, clonus of the limbs would stop if the position of the affected joint is changed and is provoked by quick movements of the joint), myoclonus in sleep, dystonia and excessive startle. It is important to note that generalised tonic clonic seizures very rarely occur in neonates due to incomplete brain myelination. When there is diagnostic doubt of whether a neonatal movement is epileptic or not, clinicians should consider doing an EEG with surface limb EMG whenever possible for confirmation.

Neonatal epileptic seizures are often acute symptomatic seizures provoked by an underlying condition; examples include hypoxic brain injury, hypoglycaemia, electrolyte imbalance and cerebral infection. A smaller number of neonatal seizures will fall into specific neonatal epilepsy syndromes.

A careful history of the age of onset, preceding antenatal and intrapartum events, family history, physical examination and selective investigations (see Chapter 4) will help in determining the possible aetiology. Neonates with seizures within the first 48 hours of life usually have an underlying acute symptomatic cause. In comparison neonates presenting with seizures after 48 hours usually have an underlying neuro-metabolic cause (apart from pyridoxine dependent/responsive epilepsy which can also present in the first 48 hours) or distinctive infantile neonatal epilepsy syndromes. Investigations should be targeted and depends on the likely differential diagnosis.

Treatment is targeted at correcting the underlying electrolyte disturbance, metabolic disorder or infection. Clinicians should undertake a degree of diagnostic rigour to decide if a neonate truly needs AEDs due to potential side effects of treatment. Animal studies have shown that many AEDs are associated with apoptotic neurodegeneration, which may have potential long-term effects on the developing brain. AEDs should be used if epileptic seizures are recurrent. Currently, phenobarbitone remains the 1st line AED in most countries. Phenytoin also has the same efficacy as phenobarbitone but often requires blood level monitoring and tends to have a worse side effect profile. New generation AEDs like levetiracetam and topiramate are also increasingly being used as 2nd or 3rd line AEDs. Large doses of benzodiazepines should be used with caution in very premature infants or those with severe unconjugated jaundice as bilirubin can be displaced from its binding site. Treatment for vitamin-responsive epilepsies should always be considered early in any neonate with seizures refractory to 1st line AEDs. This includes a trial of intravenous or oral pyridoxine and if no response is seen then a trial of oral pyridoxal-5-phosphate should be considered. Treatment with biotin and folic acid should also be considered. The long-term prognosis depends more on the underlying aetiology than the severity of the seizures during the neonatal period itself.

9.2.4 Antiepileptic drug therapy

Treatment should be started only after the diagnosis of epilepsy is certain. There is no indication for initiation of AEDs for simple febrile seizures. Choosing the most appropriate AED depends on the seizure type, epilepsy syndrome and co-morbidities. In children with associated motor, behavioural, sleep and feeding problems, care must be taken not to use an AED that may exacerbate their symptoms. When an epilepsy syndrome has been identified, treatment should be based on the epilepsy syndrome rather than individual seizure types. Steroids (ACTH or prednisolone) remain the 1st line treatment for infantile spasms that are not due to tuberous sclerosis. Vigabatrin is the recommended 1st line treatment in children with tuberous sclerosis. Infantile

epileptic encephalopathies should be treated with rapid introduction and dose escalation of AEDs. There are established guidelines including the NICE UK and ILAE guidelines for the recommended AEDs for specific paediatric epilepsy syndromes. The recently licensed AED perampanel has also been shown to be well tolerated and can improve seizure control among adolescents with refractory epilepsy.

Age has an effect on AED pharmacokinetics. Neonates tend to eliminate AEDs slower than any other age groups. In addition, birth asphyxia, a common cause of neonatal seizures, may be associated with hepatic and renal dysfunction that also retards drug elimination. After the neonatal period, the rapid growth of children results in higher AED clearance and larger within-group variability in elimination kinetics. Recommended doses based on body weight are often 2-4 times higher than adults. However, drug utilisation remains relatively stable during middle and later childhood, and children tend not to outgrow their doses. The growth spurt at adolescence also does not necessitate drug dose adjustment because of the dramatic change in drug clearance. Hence, if lower levels of AEDs are found in older children, these are more likely to be due to poor compliance or drug interaction than changes in pharmacokinetics.

Some AEDs have specific adverse effects in children that are not common in adults. Sedative AEDs like phenobarbitone and benzodiazepines may cause irritability and hyperactive behaviour in young children. Clonazepam and related AEDs may increase oral secretions and exacerbate hypotonia, compromising respiratory function and oropharyngeal function in those with neuromuscular weakness. Hepatic toxicity has been reported with the use of sodium valproate in infants who have developmental delay and are on multiple AEDs; this appears to be related more to an undiagnosed inborn error of metabolism than to the direct effect of the drug itself. The incidence of rashes with the use of lamotrigine is higher in children than adults, and appears to be related to the rate at which the drug is escalated, especially with concomitant sodium valproate therapy. Agranulocytosis, anaemia and pancytopenia seem to be less common in young children. Levetiracetam may cause behavioural disturbance and hyperactivity in children. Perampanel may cause aggression among adolescents.

AED-induced seizure aggravation is also known to occur with specific epilepsy syndromes. Idiopathic generalised epilepsies are particularly prone to seizure aggravation or onset of a new seizure type with AEDs like carbamazepine, vigabatrin, tiagabine and gabapentin. In severe myoclonic epilepsy of infancy (Dravet syndrome), there is a nearly constant aggravating effect with lamotrigine, phenytoin or carbamazepine.

9.2.5 Non-AED drug treatment

For some specific childhood metabolic disorders presenting with epilepsy, particularly in the infantile period, vitamins and co-factors like Vitamin B6, pyridoxal phosphate, biotin and folic acid are the treatment of choice.

For children with AED-refractory epilepsy (children who have failed 2 trials of appropriate AEDs), other non-AED therapeutic options exist which can be very effective in correctly selected children. Epilepsy surgery needs to be considered in all children, particular those with focal-onset epilepsy and a unilateral structural brain abnormality. In appropriately selected candidates; epilepsy surgery can achieve up to 60-70% seizure freedom. Please refer to Chapter 7 for further information.

Regardless of age, seizure type or aetiology, the ketogenic diet can result in seizure freedom in 10-15% children, and more than 50% will experience worthwhile seizure reduction. It should be offered to all children with AED-refractory epilepsy, particularly those who are not epilepsy surgical candidates. This diet is the treatment of choice for two distinct disorders of brain energy metabolism (GLUT1 deficiency and pyruvate dehydrogenase deficiency) and may be useful for particular epilepsy syndromes like SMEI, MAE and West syndrome that have failed steroids and tuberous sclerosis complex. Before starting the diet, inborn errors of metabolism (disorders of fatty acid oxidation and mitochondrial transport) that could lead to a metabolic crisis have to be excluded. There are now consensus guidelines on major issues pertaining to the ketogenic diet, namely, patient selection, counselling of patient and family, supplementation, management of the patient on

the diet with regards to nutrition, laboratory investigations, monitoring of potential side effects and eventual discontinuation.

Palliative surgery for children who are not candidates for focal resection should also be considered as this can also markedly reduce seizure burden. These include callosotomy for children with drop seizures and vagal nerve stimulation. Vagal nerve stimulation has been shown to result in meaningful seizure reduction in 30 – 50% of children with refractory epilepsy.

9.2.6 Prognosis

Regardless of the definition of outcome, across all studies, 60% of children with epilepsy will outgrow their seizure disorder, become seizure free and discontinue AED treatment. Approximately 20% of children show pharmacoresistance to multiple AEDs and would be considered to have AED-refractory epilepsy. The most significant predictor of pharmacoresistant epilepsy is the presence of a neuroimaging abnormality particularly cortical dysplasia and mesial temporal sclerosis, and such children should have a comprehensive presurgical evaluation for possible epilepsy surgery. Other predictors include: symptomatic generalised epilepsy, neonatal seizure, intellectual disability, high initial seizure frequency or failure to respond to AED in the first year. There are also some intractable epilepsy syndromes that begin in childhood and carry a poor prognosis. In most epilepsies, the arbitrary duration for AED therapy is until the patient has been seizure free for two years.

Onset of uncontrolled seizures in early childhood is also associated with a higher incidence of mental retardation, learning difficulties and behavioural problems. While it is likely that uncontrolled seizures contribute to intellectual impairment, very often it is the underlying brain pathology that leads to both mental retardation and epilepsy. The additional problems of polypharmacy (producing increased side effects), pseudoseizures, and paroxysmal non-epileptic movements (e.g. Sandifer's syndrome) often complicate the picture.

9.2.7 The child and family

Parent and patient education is a vital but often neglected aspect of management. Once the diagnosis of epilepsy is made, an explanation of what epilepsy and seizures are, its inheritance (if any), and prognosis are necessary. Treatment considerations (purpose and objectives, compliance and dosing schedule, possible adverse effects, concurrent use with other medications like antipyretics and antibiotics) are discussed, and the caregiver is given specific guidance on the treatment of prolonged seizures (rectal diazepam or buccal midazolam) and intercurrent illnesses in situations where the seizures are exacerbated during febrile illnesses. Epilepsy may adversely affect family relationships and lead to further psychosocial disturbance. Proper counselling and advice for both child and family go a long way towards improving the quality of life in these children.

Schooling and leisure activities also need to be discussed. The need for good communication between the schoolteacher, family and doctor cannot be overemphasised. Teachers need specific instructions on the measures that need to be taken when the child has a seizure at school. Teacher and peer group acceptance is crucial for the child's self esteem. There is a tendency to "overprotect" the child with epilepsy and it is important to emphasise that the child can lead a normal healthy lifestyle like their peers. Studies have shown that people with epilepsy who are active and participate in recreational sports can have a beneficial effect on their epilepsy. In children with ongoing frequent seizures; care and tailored supervision are required for recreational activities including aquatic sports, sports involving high heights (eg: abseiling, mountain climbing) and cycling. Please refer to epilepsy websites (eg: Epilepsy Action UK, Epilepsy Action Australia) for further information on lifestyle advice.

The childhood period is a crucial phase of bone mass development. Long-term AED treatment is a significant risk factor for impaired bone health and vitamin D deficiency. Vitamin D deficiency is prevalent among Malaysian children with epilepsy; particularly those with risk factors of polytherapy (>1 AED), reduced daily

sunlight exposure of < 30 minutes/day, adolescents (> 12 years old), female gender and Indian ethnicity. Vitamin D supplementation and recommendation of healthy sunlight lifestyle exposure behaviour should be given to children with epilepsy on long-term AEDs particularly to those with high risk of having vitamin D deficiency.

Key Messages

- Due to a diverse range of paediatric paroxysmal events; a thorough history (often supplemented with video-recordings) is required when evaluating a child with possible seizure disorder
- Treatment should only be started after the diagnosis of epilepsy is certain
- Treatment of vitamin responsive epilepsies should be considered in any infant with seizures refractory to 1st line AED
- Wherever possible the most appropriate AED treatment should be based on epilepsy syndrome rather than individual seizure type
- In most paediatric epilepsies, the arbitrary duration for AED therapy is until the patient has been seizure free for two years
- Children with AED refractory epilepsy should be evaluated for possible epilepsy surgery and a trial of ketogenic diet
- Holistic education of the epilepsy to the child, parent and teachers are important to improve the quality of life of the child with epilepsy
- Vitamin D supplementation should be given to children on long-term AEDs particularly those with additional risk factors

9.3 Epilepsy in the elderly

The prevalence of active epilepsy in those >70 years of age is 1.5% as compared to 0.5% for the general population. The principal causes of epilepsy among the elderly include cerebrovascular disease (30-40%), degenerative diseases of the CNS (10%), and tumours (10%), but a large proportion of cases remain cryptogenic (30-40%).

Generalised convulsions and complex partial seizures are the main clinical manifestations of the seizures in the elderly. Unlike the complex partial seizures seen in younger patients, the epileptic focus in the elderly more often involve the parietal and frontal lobes rather than the temporal lobe. Thus, orofacial and limb automatisms, olfactory hallucination, and déjà vu are less common among the elderly. On the other hand, altered cognition, periods of staring and unresponsiveness, blackout spells, and “dizziness” are common presentations. Post-ictal confusion may be prolonged. Tonic posturing may be interpreted as paralysis, and thus mistaken for TIA.

The EEG changes are often non-specific. Thus, differentiation from cardiac syncope may be difficult. As far as treatment is concerned, one should note the many differences in pharmacodynamics, which are common in the elderly, resulting in increased side effects to AEDs. Most of the older AEDs are metabolised by the liver and excreted in the kidney. As hepatic and renal functions diminish with age, the required total dose of AED may be lower. Drug interactions are also more important among the elderly, as the elderly often take many other medications. For example, enzyme-inducing AEDs (CBZ, PHT, PHB) can increase the metabolism of warfarin, decreasing its serum level by 25-50%, and thus necessitating warfarin dose escalation to achieve the required INR. Nevertheless, elderly patients with epilepsy often respond well to AED treatment. Thus, as a general rule, it is better to give smaller doses and slower dose increments of the AED in the elderly.

9.4 Social issues in Epilepsy

The psychosocial impact of epilepsy is extensive. Almost all aspects of life are affected, including education, employment, lifestyle and leisure, relationship, and driving. Management of epilepsy should cover both clinical and non-clinical aspects to ensure the best quality of life as possible. The role of healthcare professionals in educating the public as well as related personnel e.g. teacher, parents, spouse etc. is as important as treating the patient. Education and driving will be discussed in the chapter of “general principles of the treatment of epilepsy”.

9.4.1 Employment

Unemployment is a major social problem in epilepsy. In a Malaysian study in 2013, only 70% of people with epilepsy were employed full-time, 13 times more likely to be unemployed as compared to their age-matched siblings. Furthermore, 43% had a monthly income below poverty line, i.e., RM1000. However, despite having uncontrolled seizures, a systematic review reported that 58% were still able to have full-time employment. Although clinical factors were frequently reported to be associated with unemployment, psychological and social factors also play important roles.

Approach to employment issue

Epilepsy and antiepileptic medication are major factors in unemployment. Seizure freedom is associated with improved quality of life. If seizure freedom is not achievable, poor concentration, drowsiness or reduced cognitive function due to AEDs should be avoided. Behavioural changes and affective disorders secondary to AEDs may occur. If all the above possibilities have been excluded, the patient should be screened for the presence of psychosocial problems. These include low self-esteem, poor coping style and low self-efficacy, as well as poor family support and stigma especially at the workplace. There is lack of universal factors affecting employability among people with epilepsy. It is essential to develop a multifactorial assessment and individualised intervention aiming to increase employability in patients with epilepsy.

Disclosure in working place

Disclosure of the diagnosis of epilepsy has been shown to be associated with failure in getting a job and work termination. However, in view of the occupational risk, patients should be encouraged to disclose their diagnosis in their workplace, on a voluntary basis. Unnecessary restriction can be minimised with proper recommendations.

Occupational hazard and recommendations

The magnitude of the occupational hazard among epilepsy patients will depend on both individual factors and the nature of work. Absolute rules in employment for people with epilepsy are not available. Similar rules in driving can be applied in employment. Patients in seizure remission or have only nocturnal seizure should be treated as normal individuals. High-risk jobs such as working with machinery and chemicals should be forbidden for those with seizures affecting consciousness. Patients with simple partial seizures or complex partial seizure with aura should be counselled on the nature of their work on a case-by-case basis. Besides seizure control and type of seizure, medication side effects and patient intellectual ability should always be taken into consideration when choosing a suitable job.

Stigma and discrimination

People with epilepsy are burdened by a multitude of social, psychological and economic consequences of stigmatisation, which lead to poor quality of life. Social stigma in epilepsy is a universal issue. However, the attitudes of those who have a direct impact on people with epilepsy, such as parents, teachers, school counsellors, health care professionals, and employers, are equally important in influencing their life.

Discrimination legislation such as the American Disability Act (U.S.A.) and Disability Discrimination Act of the U.K. were introduced to reduce the social stigma of various medical conditions. Advocacy efforts to institute a similar act in Malaysia would be beneficial.

9.4.2 Lifestyle and leisure

People with epilepsy should maintain a healthy lifestyle as well as active social life including sports and leisure. A normal sexual life should be maintained and sexual dysfunction should be dealt with proactively. Recreational drugs, alcohol and sleep deprivation might aggravate seizures and should be avoided.

Sports

Many epilepsy patients do not participate in sports, and caregivers often discourage epilepsy patients from participating in sports. Steinhoff *et al.* reported that among patients with epilepsy, 41% reported a fear of seizure during sports, and 40% were concerned about seizure-related injuries. However, sport provoked seizures are uncommon. Clinical as well as EEG studies have shown that exercise either leads to fewer seizures or does not change seizure control. Exercise-induced seizure, though rare, does occur in certain individuals. Seizure-related injuries are not unusual, but usually the degree of injury is mild. The risk of drowning or serious injury in water sports is four times that of the general population, but the absolute risk remains small, mostly occurring when unsupervised and without precaution. Decision on sports participation should be based on an individual basis, depending on the type and control of the seizures, presence of aura, the nature of the sports activities and whether there is supervision. Appropriate safety precautions and avoidance of triggers can minimise the risk of injury. Based on present evidence, sports should generally be actively encouraged in people with epilepsy.

Sexual life in epilepsy

Sexual dysfunction can be a significant but often hidden issue in up to 20% of people with epilepsy. The problem is multifactorial, and is related to poor seizure control, temporal lobe epilepsy, interaction between enzyme inducing AEDs and hormones, as well as psychological disorders e.g. anxiety, fear and depression. Proactive open discussion with patients on this issue and proper assessment accordingly may improve their quality of life.

Sexual activity may provoke seizures through hyperventilation and stimulation of the sensory cortex. However, evidence for this is lacking. Exercise induced seizures are rare. People with epilepsy should be encouraged to have a normal sexual life.

9.4.3 Malaysian Society of Epilepsy

Interaction among people with epilepsy will enable the sharing of experiences and emotions and promote patient-initiated support. The Malaysian Epilepsy Society aims to:

- Serve people with epilepsy and others interested in medical science, public health and social care related to epilepsy.
- Establish a register for people with epilepsy in Malaysia.
- Provide information and advice to those living with epilepsy.
- Liaise with international organisations interested in epilepsy.

Regular epilepsy support group meetings are organised by the society to promote interaction among people with epilepsy and for educational purposes. More information can be obtained via Facebook - “Malaysian Society of Epilepsy (Persatuan Epilepsi Malaysia)”.

9.5 Special medical conditions

9.5.1 Introduction

A high proportion of patients with epilepsy have comorbidities. The type of comorbidity is an important factor in determining the most suitable treatment, including acute emergency treatment and chronic management.

9.5.2 Cardiovascular disease

In the acute management of an epileptic seizure, the use of intravenous phenytoin or fosphenytoin is contraindicated in patients with severe heart disease, and second or third degree atrioventricular block. Valproate acid, levetiracetam and benzodiazepine appear safer and are good alternative drugs. In chronic antiepileptic treatment, carbamazepine, oxcarbazepine, and phenytoin should be used with caution in patients with heart disease and should be avoided in the event of atrioventricular conduction dysfunction. The newer AEDs are preferred in patients with concomitant heart disease because interaction with drugs that are commonly used in heart disease (antiplatelets, antiarrhythmics, antihypertensives, oral anticoagulants, diuretics, digoxin and lipid lowering agents) is less likely.

9.5.3 Liver disease

Effective antiepileptic treatment in hepatic diseases require attention to drug pharmacokinetics. In hepatic dysfunction, the impaired cytochrome P450 metabolism and the low albumin binding affinity from the hypoalbuminemia will increase the free AED levels. Drugs with low protein binding and minimal liver metabolism such as gabapentin, pregabalin, topiramate, vigabatrin and levetiracetam are more suitable. Phenobarbitone, phenytoin and carbamazepine induce liver enzymes whereas valproate acid, which is a broad spectrum inhibitor, increases its own concentration. Monitoring of free drug levels are advisable to avoid toxicity and to improve the efficacy of AEDs.

9.5.4 Renal failure

In renal failure, albuminuria and acidosis reduce the plasma albumin level and binding affinity, leading to increased fractions of free drug. Renally excreted drugs such as gabapentin, vigabatrin, topiramate, levetiracetam and phenytoin accumulate in renal failure. Therefore, the dosage of the above AEDs need be adjusted. Water soluble and low protein bound molecules such as gabapentin, pregabalin, vigabatrin, topiramate, phenobarbitone and levetiracetam are easily removed and may require a supplemental dose after haemodialysis. Topiramate and zonisamide should be avoided in patients who have or who may potentially develop nephrolithiasis.

9.5.5 Porphyria

The induction of hepatic haemosynthesis by enzyme-inducing AEDs can exacerbate the symptoms of porphyria. Non-enzyme inducing AEDs such as gabapentin, levetiracetam and pregabalin are recommended.

9.5.6 Endocrine disease-thyroid disease

Enzyme-inducing AEDs such as carbamazepine, phenytoin, barbiturates, and oxcarbazepine, influence thyroid hormone metabolism and may reduce the levels of free and total thyroxine. It may be clinically significant in patients with hypothyroidism who are on replacement therapy. Valproate acid can also cause a subclinical, reversible increase in TSH. However, clinically relevant thyroid dysfunction owing to AEDs treatment is rare.

9.5.7 Organ transplant

The possible presence of hepatic and renal dysfunction as well as pharmacological interactions between enzyme-inducing AEDs (carbamazepine, phenobarbitone, phenytoin) and immunosuppressive drugs need to be addressed. Enzyme-inducing AEDs can reduce plasma levels of cyclosporine, tacrolimus, sirolimus and corticosteroids. Cyclosporine binds largely to plasma proteins and can significantly increase the free fraction of AEDs with high protein binding affinity. Azathioprine, mycophenolate and muromonab-CD3 are not significantly affected by AEDs. Valproate should be avoided in liver transplantation and in the engraftment phase of bone marrow transplantation (the first 2 to 6 weeks). Gabapentin, levetiracetam, pregabalin, topiramate are suitable for liver transplantation patients; benzodiazepine, lamotrigine, valproate are appropriate for kidney transplantation patients whereas gabapentin, levetiracetam and topiramate are most appropriate in bone marrow transplantation.

9.5.8 HIV/AIDS

AED and antiretroviral (ARV) co-administration may be indicated in up to 55% of people taking ARVs. Patients should be counselled that it is unclear whether dosage adjustment is necessary when AEDs and ARVs are combined. Pharmacokinetic interactions may result in virologic failure, which has clinical implications for disease progression and development of ARV resistance. Non-enzyme inducing AEDs that are not metabolised in the liver and newer AEDs such as levetiracetam, pregabalin, gabapentin and topiramate are recommended in patients receiving ARV regimens that include protease inhibitors or non-nucleoside reverse transcriptase.

9.5.9 Stroke

Stroke is the leading cause of symptomatic epilepsy in adults, accounting for up to one-third of newly diagnosed seizure among the elderly. About 3% to 5% of stroke patients will suffer a remote seizure, of which 54% to 66% will develop epilepsy. Although several studies suggested that seizures alter the functional recovery after stroke, it remained difficult to determine whether or not the occurrence of a second seizure in untreated stroke patient might hamper the overall outcome. The decision to initiate AEDs treatment after a first seizure or a second post-stroke seizure should therefore be individualised, primarily based on the functional impact of the first seizure and patient's preference. Short-term prophylactic AEDs for intracerebral haemorrhage, cerebral venous thrombosis and ischemic stroke is not recommended as the benefit is still uncertain. First generation AEDs including phenytoin, phenobarbital, valproate and benzodiazepine are not appropriate choices in view of their potential harmful impact on the functional recovery, bone health and drug interactions especially anticoagulants and salicylates. Low-dose lamotrigine, gabapentin or levetiracetam is recommended as the first-line therapy for post-stroke seizure and epilepsy in elderly patients or younger patients requiring anticoagulants.

Key Messages

- Selection of appropriate AEDs is important in patients with specific comorbidities.
- Drug interaction and elimination of AEDs need be to addressed especially in those with hepatic and renal diseases.
- Monitoring serum levels of AEDs may be necessary.
- Decision to initiate AEDs for post-stroke seizure needs to be individualised.
- Benefit of short-term prophylactic AEDs for stroke is still uncertain.

10 CONCLUSION

Epilepsy is one of the commonest chronic neurological diseases. Definitions and classifications continue to evolve as we learn more about the natural history and aetiology of epileptic seizures and epilepsy syndromes. Many more new AEDs have been developed and new surgical procedures introduced, including implantable devices. The choice of AED must be tailored to the individual patient. Other than age, gender, child-bearing potential, the epilepsy syndrome and psychosocial factors of the patient, pharmacogenetics may also influence the choice of AED. Although the differential diagnosis of epilepsy remains broad, we are now more confident in diagnosing non-epileptic attack disorders (pseudoseizures). Correct diagnosis of the epilepsy syndrome will guide the physician to select investigations judiciously. Not all patients, for instance, require a brain scan, and not all patients are amenable to epilepsy surgery. The growing availability of more powerful MR scanners is expected to further reduce the number of cryptogenic cases.

The mode of action of most of the newer AEDs is poorly understood, but these drugs have proven efficacy in large randomised trials, albeit as add-on therapy in refractory cases. It is now clear that greater efficacy in comparison with the older AEDs is unlikely to be the reason for the change in clinical practice, but rather the improved safety and tolerability profile of the newer AEDs. Long-term, non-pharmacological issues, including driving, employment, pregnancy, and education must feature prominently in the physician's management plan. He or she must also be sensitive to the special needs of children and the elderly as well as the co-existence of comorbidities and special medical conditions. In cases where AEDs fail to control the seizures, or when the side effects are intolerable despite good seizure control, epilepsy surgery may be an option. Epilepsy surgery should be considered early in patients where the MRI-identified lesion per se may be lethal (e.g. a vascular malformation, or a brain tumour with malignant potential). The pre-surgical evaluation of a patient is the single most important pre-requisite of epilepsy surgery. The onus is on the neurologist to ensure that the epileptogenic zone is correctly identified, and that the operation produces a good seizure as well as neurological outcome.

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