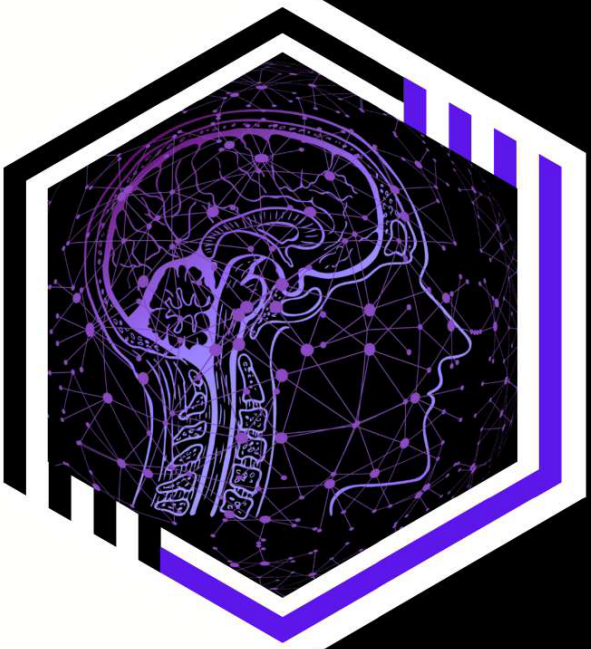
CONSENSUS GUIDELINES ON THE MANAGEMENT OF EPILEPSY

2024



EPILEPSY COUNCIL

Malaysian Society of Neurosciences (Persatuan Neurosain 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 healthcare 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
AE	Adverse Event
ARV	Antiretroviral
ASM	Antiseizure Medication
ATP1A2	ATPase Na+/K+ Transporting Subunit Alpha 2
BCECTS	Benign Childhood Epilepsy with Centrotemporal Spikes
BDZ	Benzodiazepines
BOEC	Benign Occipital Epilepsy of Childhood
BP	Blood Pressure
CACNA1A	Calcium Voltage-gated Channel Subunit Alpha 1A
CBZ	Carbamazepine
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CYP	Cytochrome P450
DNET	Dysembryoplastic Neuroepithelial Tumour
DRE	Drug-resistant Epilepsy
DRESS	Drug Reaction with Eosinophilia and Systemic Symptoms
ECG	Electrocardiogram
EEG	Electroencephalogram
EURAP	International Registry of Antiepileptic Drugs and Pregnancy
FDA	Food and Drug Administration, United States of America
^{18}F-FDG	^{18}F-fluorodeoxyglucose
FLAIR	Fluid-attenuated Inversion Recovery
fMRI	Functional MRI
GABA	Gamma-Aminobutyric Acid
GBP	Gabapentin
GCS	Glasgow Coma Scale/Score
GLUT 1	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
IBE	International Bureau for Epilepsy
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
IVIG	Intravenous Immunoglobulin
JME	Juvenile Myoclonic Epilepsy
JPJ	Jabatan Pengangkutan Jalan (Road Transport Department Malaysia)
KCNQ2	Potassium Voltage-gated Channel Subfamily Q Member 2
LTG	Lamotrigine
MAE	Myoclonic-Astatic Epilepsy
MEG	Magnetoencephalography
MCM	Major Congenital Malformations
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
NIHSS	National Institute of Health Stroke Scale
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NPRA	National Pharmaceutical Regulatory Agency (Malaysia)
NTD	Neural Tube Defects
OCP	Oral Contraceptive Pill
PCOS	Polycystic Ovarian Syndrome
PET	Positron Emission Tomography
Pg-Protein	p-Glycoprotein

PPI	Proton Pump Inhibitor
PSE	Post-stroke Epilepsy
PSS	Post-stroke Seizure
PTE	Posttraumatic Epilepsy
PTS	Posttraumatic Seizure
PWE	People with Epilepsy
SCN1A	Sodium Voltage-gated Channel Alpha Subunit 1
SE	Status Epilepticus
SeLEAS	Self-limited Epilepsy with Autonomic Seizures
SeLECTS	Self-limited Epilepsy with Centrotemporal Spikes
SJS	Stevens-Johnson Syndrome
SLE	Systemic Lupus Erythematosus
SMEI	Severe Myoclonic Epilepsy in Infancy
SPECT	Single Photon Emission Computerised Tomography
STIR	Short T1 Inversion Recovery
SUDEP	Sudden Unexpected Death in Epilepsy
TBI	Traumatic Brain Injury
TEN	Toxic Epidermal Necrolysis
TIA	Transient Ischaemic Attacks
UGT	UDP-Glucuronosyltransferase
UK	United Kingdom
USA	United States of America
VEMP	Vestibular Evoked Myogenic Potential
VNS	Vagus Nerve Stimulation
WHO	World Health Organization

1.0 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 revised editions were published in 2010 and 2017. 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 fourth edition of the guidelines. Many of the chapters have been written and updated by the same authors as the third 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. The Council would like to thank Dr Ahmad Rithauddin Mohamad and Ms Denise Tan Sin Shen for their assistance in formatting the references, as well as, Dr Alina Arulsamy for designing the cover for this Guidelines and for editing the entire document.

2.0 CLASSIFICATION OF EPILEPSY

2.1 Introduction

Epilepsy classification is an undeniably pivotal clinical tool in evaluating someone with seizures. It provides a framework to understand the seizure type and inform the risks of comorbidities and prognosis. It is also critical for epilepsy research and communication around the globe.

Tremendous efforts have been made to revise the classification of the epilepsies by the International League Against Epilepsy (ILAE) as our understanding about epilepsy has changed significantly over the last few decades. Since the last ratified classification that was introduced in 1989, there have been intense debate and an exigent need to call for a revised version due to acquisition of new knowledge and major scientific discoveries in epilepsy. Originated from a draft submitted for public comments in 2013, a new classification of the epilepsies was published in 2017 after incorporating experts' criticism and consultation by the ILAE Commission for Classification and Terminology.

The 2017 ILAE Classification of the Epilepsies defines three levels, starting with seizure type, followed by epilepsy type, then determining epilepsy syndrome, emphasizing the need to consider aetiology and comorbidities along each level.

The term "benign" is replaced by the terms "self-limited" and "pharmacoresponsive" to be used where appropriate. A new term "developmental and epileptic encephalopathy" is introduced and can be applied to individuals of any age.

2.2 Classification of the Epilepsies

The 2017 ILAE Classification of the Epilepsies (Fig. 1) is a multilevel classification considering that epilepsies are disorders with diverse aetiologies, highly varied electroclinical manifestations and clinical outcomes. Before attempting to make a diagnosis of epilepsy or classify a seizure, it is imperative to determine whether the paroxysmal event is an epileptic seizure. There is a plethora of events that can mimic seizures, such as convulsive syncope, movement disorders, parasomnias to name a few.

2.2.1 Seizure Type

An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. The seizure is classified according to the new operational classification of seizure types published in 2017. Figures 2 and 3 depict the basic and expanded seizure classifications, respectively. Seizures are classified into focal, generalized, and unknown onset. This practical classification differs from the 1981 Classification in the following: (1) "partial" is replaced by "focal"; (2) awareness is used as a

classifier of focal seizures; (3) the terms dyscognitive, simple partial, complex partial, psychic, and secondarily generalized are no longer in use; (4) new focal seizure types include automatisms, behaviour arrest, hyperkinetic, autonomic, cognitive, and emotional; (5) atonic, clonic, epileptic spasms, myoclonic, and tonic seizures can be of either focal or generalized onset; (6) secondarily generalized seizure is replaced by focal to bilateral tonic-clonic seizure; (7) new generalized seizure types include absence with eyelid myoclonia, myoclonic absence, myoclonic-atonic, myoclonic-tonic-clonic; and (8) seizures of unknown onset may have features that can still be classified.

2.2.2 Epilepsy Type

Epilepsy is a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition. The definition of epilepsy requires the occurrence of at least one epileptic seizure.

This level includes combined generalized and focal; and unknown categories in addition to the well-established generalized and focal epilepsies.

The diagnosis of generalized epilepsy is made on clinical grounds, supported by typical interictal generalized epileptiform discharges. Focal epilepsies include unifocal or multifocal disorders as well as seizures involving one hemisphere. Typically, the interictal EEG shows focal epileptiform discharges. Patients who have both focal and generalized seizures are classified under the category of combined generalized and focal epilepsy. The interictal EEG may show both generalized spike-wave and focal epileptiform discharges, however, epileptiform activity is not necessary to make a diagnosis. Lennox-Gastaut syndrome and Dravet syndrome are examples of this type of epilepsy. This epilepsy type may also be the final level of diagnosis where the physician is unable to make an epilepsy syndrome diagnosis. The term “unknown” is used where the clinician is unable to conclude if the epilepsy type is focal or generalized because there is limited clinical information available.

2.2.3 Epilepsy Syndrome

Although epilepsy syndromes had been recognized as distinct electroclinical entities long before the first ILAE Classification and Epilepsies and Epilepsy Syndromes, there was never a formal classification of syndromes accepted by the ILAE. An epilepsy syndrome is defined by the Nosology and Definitions Task Force as a characteristic cluster of clinical and EEG features, often supported by specific etiological findings (structural, genetic, metabolic, immune, and infectious). The diagnosis of a syndrome carries both prognostic and therapeutic implications.

2.2.3.1 Idiopathic Generalized Epilepsies

The idiopathic generalized epilepsies (IGEs) encompass four syndromes, namely childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and epilepsy with generalized tonic-clonic seizures alone. Idiopathic was regarded as an imprecise term given the increasing recognition and discovery of many genes involved in epilepsies, including monogenic or complex inheritance. It is therefore meaningful to remove the term idiopathic and refer this group of syndromes to genetic generalized epilepsies (GGEs). However, the Nosology and Definitions Task Force proposed that the term IGE should be retained and pertains to a subgroup of GGEs, for a number reasons, namely they are the most common syndromes within GGEs with a more favourable prognosis and do not evolve into epileptic encephalopathy. The EEG typically shows 2.5 – 6 Hz generalized spike-wave and/or polyspike-wave discharges arising from a normal background, which may be activated by hyperventilation or intermittent photic stimulation. Figure 4 shows a concept of GGEs versus IGEs.

2.2.4 Aetiology

It is always crucial to determine the aetiology of a patient with epilepsy. There are mainly six causes, which include structural, genetic, infectious, metabolic, and immune, as well as unknown (Fig. 1). A patient's epilepsy may have more than one cause; and the causes are not hierarchical. For instance, a patient with tuberous sclerosis has both a genetic and structural cause. Identifying both aetiologies is instrumental in determining the therapeutic options.

2.2.5 Self-limited and Pharmacoresponsive Epilepsies

The term "benign" underestimates the disease burden of epilepsy to some extent. There are significant cognitive effects and associated comorbidities in even milder epilepsy syndromes, for instance, benign epilepsy with centrotemporal spikes and childhood absence epilepsy. It is thus proposed to replace "benign" with "self-limited" and "pharmacoresponsive". "Self-limited" is used to denote the likelihood of spontaneous resolution of a syndrome; whereas "pharmacoresponsive" refers to a syndrome that is likely to be controlled with appropriate therapy.

2.2.6 Developmental and Epileptic Encephalopathies

Developmental encephalopathy refers to developmental impairment without frequent epileptic activity associated with regression or further slowing of development. Epileptic encephalopathy means that there is no preexisting developmental delay and the genetic mutation is unlikely the cause of the slowing. If both factors play a role, it is then called

developmental and epileptic encephalopathy. It is often impossible to discern which component is more important in contributing to the patient's progress.

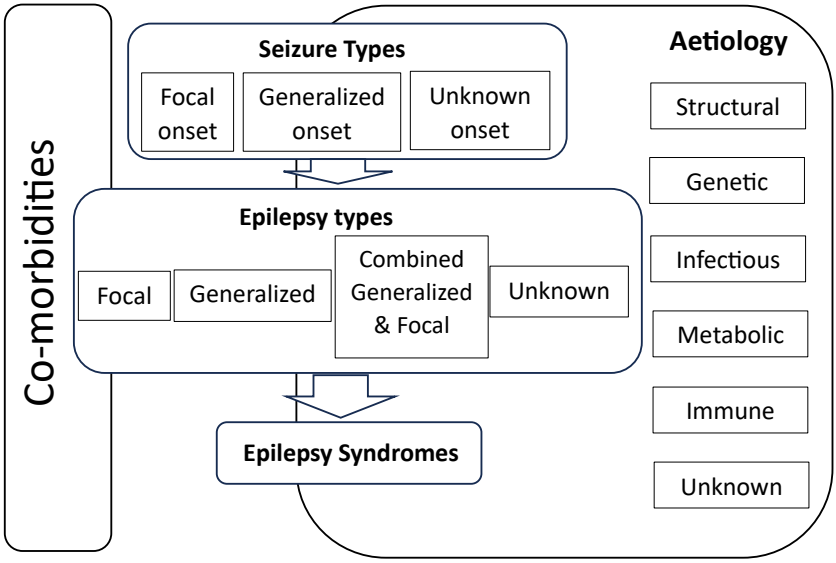

Figure 1: The 2017 ILAE Classification of the Epilepsies. (Adapted from Scheffer IE, *et al.*, Epilepsia. 2017;58:512–521).

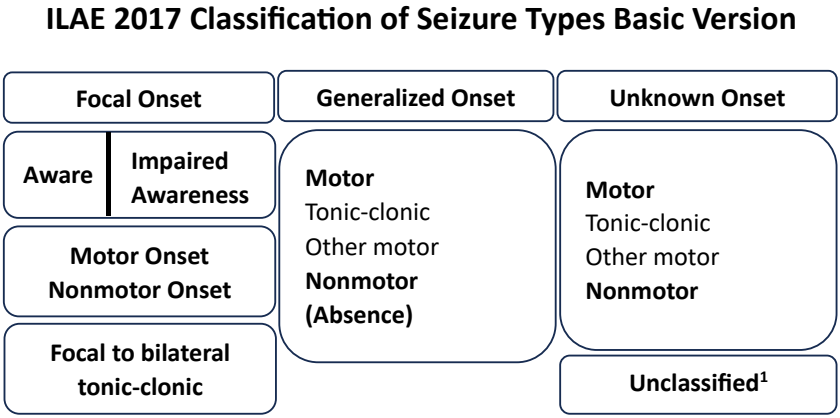

Figure 2: The basic ILAE 2017 operational classification of seizure types. [1]Due to inadequate information or inability to place in other categories. (Adapted from Fisher RS, *et al.*, Epilepsia. 2017;58:522–530).

ILAE 2017 Classification of Seizure Types Expanded Version

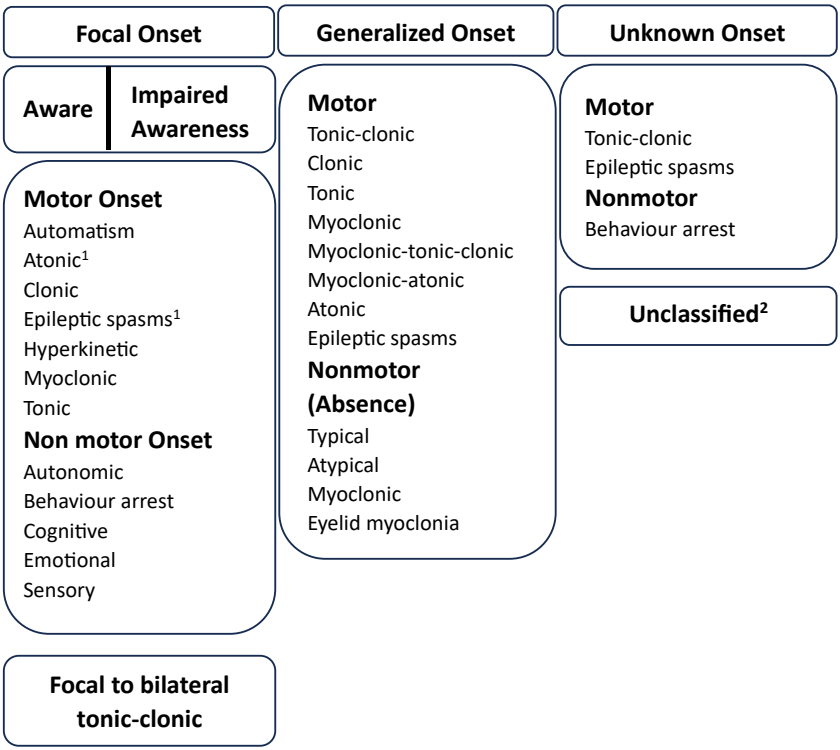

Figure 3: The expanded ILAE 2017 operational classification of seizure types. [1]Degree of awareness is usually not specified. [2]Due to inadequate information or inability to place in other categories. (Adapted from Fisher RS, *et al.*, Epilepsia. 2017;58:522–530).

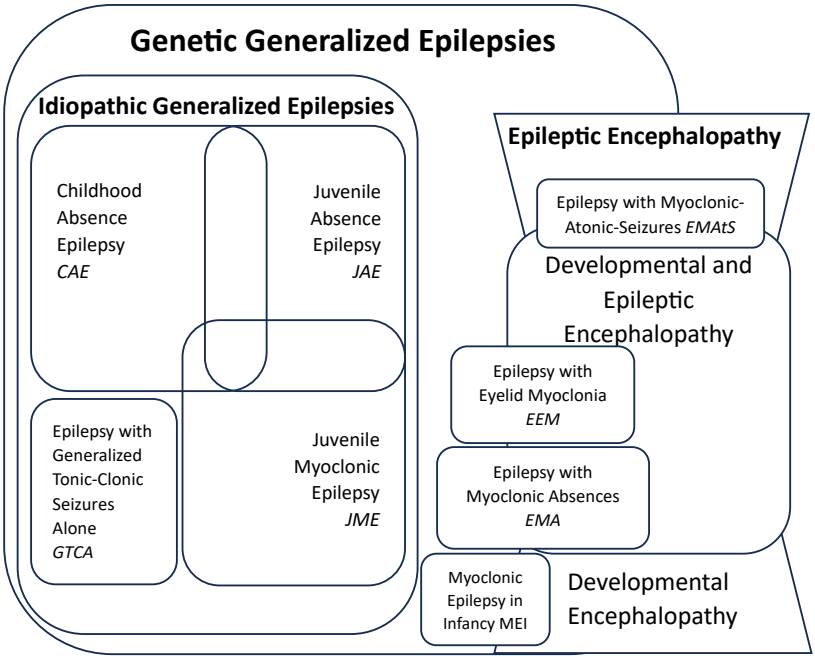

Figure 4: Concept of genetic generalized epilepsy versus idiopathic generalized epilepsy. (Adapted from Hirsch E, *et al.*, Epilepsia. 2022;63:1475–1499).

3.0 DIFFERENTIAL DIAGNOSIS OF SEIZURES

Children and adults who present with recurrent episodes of altered consciousness or involuntary movements may be subjected to a wide range of investigations. Obtaining a detailed history and examination is paramount in the diagnostic process to avoid the consequences of misdiagnosis. Differentiating features of a true epileptic seizure include stereotypic attacks with altered awareness, which may be preceded by an aura in focal seizures and postictal confusion depending on the seizure type. The differential diagnosis of seizures can be subdivided into different age groups. This chapter highlights the differential diagnosis of seizures (Table 1) and the classification of syncope (Table 2).

Table 1: Differential Diagnosis of Seizures

Neonates and infants	Young children	Adults
• Benign myoclonus of infancy • Paroxysmal dystonia • Hyperekplexia • Cardiac arrhythmias • Shuddering attacks • Gastro-oesophageal reflux • Benign sleep myoclonus	• Reflex anoxic seizures • Breath holding spells • Hyperekplexia • Paroxysmal dyskinesias • Benign positional vertigo • Migraine • Cataplexy • Stereotypies/ritualistic behaviour • Confusional arousal • Night terrors • Tics • Parasomnias	• Syncope • Transient ischaemic attack • Migraine • Transient global amnesia • Paroxysmal movement disorders • Metabolic and endocrine disorders • Sleep disorders • Non-epileptic attack disorders

Table 2: Classification of Syncope

Types of Syncope	Examples
Cardiac Syncope	
Arrhythmia	Bradyarrhythmia, ventricular tachyarrhythmia, supraventricular tachyarrhythmia, pacemaker dysfunction, channelopathies
Obstructive cardiomyopathy	Hypertrophic cardiomyopathy
Structural heart disease	Acute myocardial infarct, right ventricular cardiomyopathy, infiltrative, valvular disease
Other structural disease	Acute aortic dissection, cardiac masses, cardiac tamponade, pulmonary hypertension, saddle pulmonary embolus
Neurally Mediated (Reflex) Syncope	
Carotid sinus syndrome/ hypersensitivity	Head rotation or pressure on the carotid sinus
Situational	Coughing, defaecation, gastrointestinal stimulation, micturition

Vasovagal	Mediated by fear, heat, noxious stimuli or stress.
Orthostatic Hypotension Syncope	
Drug-induced	Alcohol, antianginal agents, antidepressants, antidiabetic agents, antihypertensives, antiparkinsonian agents, diuretics
Postural tachycardia syndrome	Severe orthostatic intolerance with marked tachycardia
Primary autonomic failure	Multiple sclerosis, multiple system atrophy, Parkinson disease/ parkinsonism, Wernicke encephalopathy
Secondary autonomic failure	Amyloidosis, chronic inflammatory demyelinating polyneuropathy, connective tissue diseases, diabetes mellitus, Lewy body dementia
Hypovolaemia	Acute blood loss, diarrhoea, inadequate fluid intake, vomiting

Breath-holding spells affect children when a clear trigger is typically present with the child being upset and crying. At the end of expiration, the child is unable to relax and inhale and becomes apnoeic, cyanotic and loses consciousness. Tics are common in children and occur sporadically rather than repetitive, stereotyped, and disappear in sleep. They are preceded by an irresistible urge to move and followed by a sense of relief.

Syncope is a sudden, brief and transient loss of consciousness caused by cerebral hypoperfusion. Syncope is classified as neurally mediated (reflex), cardiac syncope and orthostatic hypotension. Neurally mediated syncope is the most common type and has a benign course. It can be vasovagal, situational, or secondary to carotid sinus hypersensitivity. The important differentiating features of syncope include a clear trigger, presence of prodromal symptoms, transient period of loss of consciousness, rapid recovery phase and absence of postictal phase. Precipitating factors include rapid positional change, prolonged standing, fear, painful stimuli, emotional distress, and activities such as coughing, defaecation or micturition. Characteristic prodromal symptoms include lightheadedness, sweatiness, a sense of receding sound and vision and nausea.

Cardiac related syncope due to arrhythmias or structural disease may be preceded by palpitations, shortness of breath and chest pain. Patients with hypertrophic cardiomyopathy may present with exertional syncope and have a positive family history of sudden death. Acute aortic dissection may manifest as hypotension and severe chest pain with or without radiation to the back.

Vasovagal syncope may include prodromal symptoms (sweating, dizziness, nausea) and often mediated by fear, heat, noxious stimuli, pain, or stress. Specific situations (defaecation, micturition, coughing) may trigger reflex syncope. Unexplained falls following head rotation or pressure on the carotid sinus result from carotid sinus syndrome.

Orthostatic hypotension syncope is typically characterised by posturally induced hypotension, which is most often related to impaired increase in systemic vascular resistance.

Transient ischaemic attack (TIA) is a clinical syndrome characterised by an acute loss of focal cerebral function with symptoms lasting less than 24 hours. The patient often has a

focal neurological deficit in TIA compared to a seizure, which has positive symptoms such as automatisms and jerking movements. Transient global amnesia (TGA) consists of episodes of anterograde amnesia that can last up to 24 hours. Patients are alert and cognitively intact but are unable to form new memories which results in them asking questions repetitively. These episodes are self-limited and resolve within 24 hours with the recovery of memory function.

Paroxysmal movement disorders are a clinical and genetically heterogeneous group characterised by episodic involuntary movements that include dystonia, dyskinesia, chorea, and ataxia. Narcolepsy is characterised by excessive daytime sleepiness, sleep paralysis, hypnogogic hallucinations, and cataplexy. These episodes may be mistaken for seizures as the patient falls to the ground due to a lack of muscle tone and can be triggered by emotions. Parasomnias are a group of sleep disorders characterized by abnormal, unpleasant motor verbal or behavioural events that occur during sleep or wake to sleep transitions. They can be seen in both non-rapid eye movement (NREM) and rapid eye movement (REM) sleep states. REM sleep behaviour disorders is a parasomnia characterized by dream-enactment behaviour that emerge during a loss of REM sleep atonia.

Non-epileptic attack disorders (NEAD), often also known as psychogenic non-epileptic seizures (PNES) are episodic alterations of function that are not caused by epileptic activity with a possible psychological cause. Distinguishing features of NEAD include the triggers (frustration, suggestion, in company), prolonged duration, erratic movements (flailing, pelvic thrusting, head rolling), resistance of eye opening and prompt recovery. Following the exclusion of organic causes, there are three categories of psychiatric diagnoses including dissociative seizures, factitious disorders and other psychiatric disorders (panic disorder, psychosis, attention deficit hyperactivity disorder and depersonalisation).

KEY MESSAGES

Patients with recurrent episodes of altered consciousness need to be carefully evaluated for a detailed history and clinical examination to determine the underlying cause.

4.0 INVESTIGATIONS IN EPILEPSY

4.1 Introduction

The most important aspect of the evaluation of an individual with a suspected seizure disorder is the clinical assessment by the neurologist. This clinical assessment typically involves obtaining a detailed description of the patient's episodes, medical history, development, learning and behaviour (see Appendix). The aim of the assessment is to determine:

1. If episodes of altered behaviour, movement, consciousness etc. are epileptic or non-epileptic in origin.

2. The type of epileptic seizures that a patient experiences, most importantly whether the seizures are focal or generalised.

3. The type of epilepsy that a patient has and its underlying cause (genetic, brain abnormality or unknown)

4. Any associated medical, physical, learning, behavioural and psychosocial problems that may accompany seizures in a patient with epilepsy.

4.2 Purpose of Investigations

The need for tests is determined following the detailed clinical assessment by a neurologist or a paediatrician experienced in seizure disorders. Tests are generally performed to:

a) confirm a clinical suspicion.
b) determine the type of seizure or epilepsy.
c) determine the underlying cause of epilepsy.
d) assess the severity or monitor treatment of a patient with epilepsy.
e) assess associated medical or psychological problems.
f) or determine the most appropriate treatment of a child's condition.
g) prognosticate epilepsy. Certain syndromic epilepsies are associated with poorer seizure control.
h) assess suitability for antiseizure medication withdrawal.

Tests are not performed to determine if a patient has epilepsy or not. This is a clinical judgement made by a specialist. Patients presenting to a doctor or an emergency department with a first major seizure will usually have a blood test to check the glucose, calcium,

magnesium and electrolyte levels, as abnormalities of body chemistry can lead to seizures. Some patients with seizures may have an examination of the spinal fluid (lumbar puncture), metabolic testing of the blood or urine, or genetic tests.

4.3 Who Should Be Investigated?

I. Patients with new onset of seizure should be investigated for common causes including:
    a. hypoglycaemia.
    b. hyponatraemia.
    c. hypercalcaemia.
    d. alcohol intoxication and withdrawal.
    e. drug intoxication and head injury.

II. When red flags (Table 3) are present urgent neuroimaging of the brain should be requested.

III. In an acute setting, CT is preferable to MRI due to its wider availability.

IV. All patients who require neuroimaging (**see indications below**) may be scheduled for a brain MRI as an outpatient.

V. All patients with a first unprovoked seizure should be subjected to an EEG.

VI. Unequivocal interictal epileptiform discharges on EEG are predictive of seizure recurrence and may influence the decision to start ASMs.

Table 3: Red Flags

• **GCS persistently < 15** • **New onset focal neurological signs** • **Sudden onset headache** • **Head injury** • **Signs of meningitis or encephalitis** • **Signs of raised intracranial pressure** • **History of malignancy**	• **Pregnancy/postpartum** • **HIV positive patients** • **Patients on anticoagulants** • **Chronic alcoholic patients** • **Features suggestive of pregnancy-induced hypertension**

4.4 Diagnostic Investigations

4.4.1 Brain Imaging

In the setting of new onset seizures brain imaging should be considered for:

a) The identification of CNS insults responsible for acute symptomatic seizures such as:
   a. intracranial haemorrhage.
   b. ischaemic stroke.
   c. cortical vein thrombosis.
   d. posterior reversible encephalopathy syndrome.
   e. infectious encephalitis and meningitis.
   f. paraneoplastic and non-paraneoplastic autoimmune limbic encephalitis.

b) The identification of underlying aetiology and prediction of risk of recurrence in remote symptomatic seizures thus aiding in the diagnosis of epilepsy.

c) An unprovoked first seizure due to remote symptomatic aetiology, imaging should be considered as part of the routine evaluation in adults (**N.B**. imaging however is not indicated in cases where there is clear evidence of an electroclinical epilepsy syndrome in which imaging is expected to be normal such as in idiopathic/ genetic generalized epilepsy). However, in children, it is indicated in certain circumstances only**.**

4.4.2 Computed Tomography (CT)

In adults:

This is often the recommended first imaging tool used in the acute setting because it is widely available and can be performed quickly. Furthermore, it is also useful in the evaluation of patients who cannot tolerate an MRI (magnetic resonance imaging) examination or who have contraindications to MRI.

I. An abnormal neurologic examination or a focal seizure onset are predictive of an abnormal CT study.

II. Emergent brain CT must be considered in adults with a first seizure with the red flags (Table 3) that may suggest an acute symptomatic aetiology.

III. A non-contrast CT is deemed adequate for this purpose in most cases, as IV contrast is of little benefit and does not definitively improve the sensitivity of CT for emergent findings.

IV. In unprovoked new-onset seizures (non-acute setting) CT may be reasonable in patients without access to MRI or in cases where MRI is contraindicated or in the patient who is intolerant to MRI.

V. It can be useful in excluding pathologies that need urgent intervention (e.g. tumours).

VI. It is important to note that, only 10% of patients have abnormalities revealed by CT and it is less sensitive than MRI which has a detection rate of 30%. Furthermore, the presence of a history of prior CNS insult or focal slowing or focal epileptiform abnormalities on EEG, predict an epileptogenic lesion being identified by MRI when CT is normal.

VII. However, CT is more specific than MRI in the depiction of calcification, which is relevant in populations at risk of calcified lesions, such as vascular malformations, including cavernous malformations.

4.4.3 Magnetic Resonance Imaging (MRI)

MRI is clearly superior to CT in the detection of epileptogenic abnormalities in a patient with a first ever unprovoked seizure, particularly mesial temporal sclerosis and malformations of cortical development. MRI detects a lesion not evident on CT in 1 of 8 patients. However, an undetected lesion in CT being a tumour is seen only in approximately 1 out of 67 patients. Wherever possible, MRI is the preferred method of neuroimaging in adults (due to its higher detection rate) presenting with a new onset remote symptomatic seizure (unprovoked), although MRIs may not be readily available.

Indications for MRI:

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 of the 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 self-limited epilepsy with centrotemporal spikes (SeLECTS) [previously called benign childhood epilepsy with centrotemporal spikes (BCECTS)], absence epilepsy and Self-limited epilepsy with autonomic seizures (SeLEAS) [previously benign occipital epilepsy of childhood (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:

a. 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)

b. 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.

c. 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)

d. 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.

4.4.3.1 Neuroimaging in Children:

a) In children the need for urgent imaging may be different. Those with a clinical history and EEG findings consistent with an idiopathic genetic epilepsy (genetic generalized epilepsy), such as childhood absence epilepsy, juvenile absence epilepsy and juvenile myoclonic epilepsy.

b) Similarly, those presenting with self-limited focal epilepsies of childhood do not require imaging, unless there is doubt about the diagnosis during follow up.

c) Brain imaging should, however, be performed in children who have had two or more afebrile epileptic seizures and who do not have the clinical or EEG features of an idiopathic epilepsy, mentioned above.

d) There are two questions regarding imaging; what modality of imaging is recommended and what is the timing of such imaging? Although MRI is superior to CT in demonstrating subtle brain developmental abnormalities, this choice will be influenced by availability of MRI and the need for a general anaesthetic for young children during the procedure. As for the timing, although neuroimaging abnormalities occur in up to one-third of children with a first afebrile seizure, only 2% will demonstrate a clinically significant abnormality that will influence immediate management.

e) It is important to note that seizures are an uncommon presenting symptom of a brain tumour in children. Therefore, routine brain imaging (CT or MRI) in the emergency department following the first afebrile seizure in a child is not usually warranted.

f) However, emergency neuroimaging should be considered in a child in the following instances: emergent head CT for patients with risk factors for abnormal neuroimaging e.g., in paediatric age groups, especially children under the age of six months, those with a focal seizure, a new focal deficit, hydrocephalus, recent cerebrospinal fluid shunt surgery, neurocutaneous disorders, persistent altered mental status or recent head trauma, presenting with afebrile status epilepticus, focal neurological signs that

persist for several hours, history of cancer or on anticoagulation or not returning to baseline within several hours of the seizure[6].

g) Brain MRI is recommended especially in children with atypical features or who do not respond well to antiseizure medications (ASMs).

h) 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.

4.4.4 Functional Neuroimaging

a) Ictal SPECT (single photon emission computed tomography)

b) PET (positron emission tomography)

c) Functional MRI is a functional imaging modality 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.

4.4.5 Electroencephalography (EEG)

4.4.5.1 Standard Non-invasive Scalp EEG Recording in Adults

The EEG is considered as part of the neuro-diagnostic evaluation of an adult or child with an apparent unprovoked first seizure because it has value in determining the risk for seizure recurrence. The sensitivity of scalp EEG in detecting interictal epileptiform discharges that support the diagnosis of epilepsy is approximately 50%. The sensitivity is increased up to 80% if the EEG is repeated up to three times. Interictal epileptiform discharges, and often, ictal discharges, may be provoked by certain procedures: i) Sleep deprivation. ii) Hyperventilation and iii) Photic stimulation. All 21 electrodes and placements recommended by the International Federation of Clinical Neurophysiology (IFCN) should be used. The 10-20 System is the only one officially recommended by the IFCN. A standard EEG should be

recorded for a minimum of 45 minutes. A period of wakefulness followed by provocation procedures of hyperventilation, photic stimulation and natural sleep should be recorded.

a) The EEG may be arranged on an elective outpatient basis, unless there is a concern for non-convulsive status epilepticus often in the acute setting in which provoked seizures are common.

b) Epileptiform abnormalities on the EEG may be useful in confirming that the event was a seizure; however, an EEG abnormality by itself is not sufficient to make a diagnosis of an epileptic seizure, nor does its absence rule out a seizure.

c) An EEG is necessary to determine many of the epilepsy syndromes. The syndromic diagnosis may be helpful in determining the need for specific investigations including imaging studies, specific ASM and predicting the prognosis.

d) An EEG is useful in predicting the prognosis of recurrence of seizures.

e) The abnormalities are of two types: epileptic discharges and focal background slowing. An epileptic discharge can be generalized or focal. Approximately 12–50% of adults and 18–56% of children with a single unprovoked seizure have epileptiform abnormalities on EEG. Generalized epileptiform discharges confer the highest risk of recurrence. Both epileptiform discharges and focal background slowing/paroxysmal slow wave events have been shown to predict the risk of recurrence of seizures, with generalized epileptic discharges offering the greatest predictive ability.

f) An EEG done within 24 hours of a seizure is most likely to show abnormalities.

g) One should be aware that some abnormalities which are transient such as postictal slowing must be interpreted with caution. However, transient focal slowing may be of lateralising value.

h) If a standard EEG is normal, repeated standard EEGs should not be used in preference to sleep or sleep-deprived EEGs. A sleep EEG is best achieved through sleep deprivation. A sleep EEG increases the yield of detecting epileptiform discharges in both children and adults. EEG that includes both wakefulness and sleep should be recommended as it detects a high proportion of abnormalities.

i) 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.

N.B: The use of suggestion and placebo to provoke and terminate an attack involves some element of deception and should be practiced with caution. An EEG should not be performed in the case of probable syncope because of the possibility of a false-positive result.

4.4.5.2 EEG Investigation in Children

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 SeLECTS 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 ASM. 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 electrocardiogram (ECG) should also be performed in cases with diagnostic uncertainty.

4.4.6 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.

4.4.7 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.

4.4.8 Limitations of EEG

A normal EEG does not rule out epilepsy. Interictal epileptiform discharges can only be recorded when the there is a cortical epileptic focus surface area of at least 6 cm^2. 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.

4.5 Other Investigations

4.5.1. Laboratory Investigations in Adults:

a) Routine screening of patients after new-onset seizures for hypoglycaemia, hypocalcaemia, uraemia, drug intoxication, and hyponatremia is recommended for patients seeking care in the emergency setting in which a higher frequency of acute symptomatic seizures occur and should be requested when clinically indicated.

b) Cut off values which can cause acute symptomatic seizures are: serum glucose < 36 mg/dL (2 mmol/L) or > 450 mg/dL (25 mmol/L), serum calcium < 1.2 mmol/L (5 mg/dL), creatinine > 10 mg/dL (884 µmol/L) and serum sodium < 115 mmol/L (264 mg/dL).

c) Routine screening for the above conditions in the outpatient setting is of limited utility and thus not recommended unless there is a strong clinical indication. Seizure-like attacks with a cardiovascular cause may be misdiagnosed as epilepsy. A 12-lead ECG should be performed in adults with a suspected seizure in cases of diagnostic uncertainty.

d) If there is persistent (cause unknown) alteration of mental status or failure to return to baseline following a seizure, or in anyone with meningeal signs and fever, a lumbar puncture (LP) and cerebrospinal fluid (CSF) analysis should be performed.

e) Imaging should precede the LP to exclude any cause of raised intracranial pressure in which case an LP may be contraindicated.

f) 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 focal and absence seizures. Serum prolactin levels may normalise 30 minutes after an attack. Therefore, these tests should not be routinely requested.

g) Serum must be sent for *HLA-B*15:02* testing prior to commencement of carbamazepine. If a screening facility is not available, carbamazepine can still be prescribed, provided the patient is warned of cutaneous ADRs and advised to stop carbamazepine if this occurs.

4.5.2 Laboratory Investigations in Children:

Laboratory tests should be requested based on the history and/or clinical findings. The minimal blood tests required after a first generalised seizure include a full blood count, serum blood glucose, electrolytes and analysis of blood gases, though in children such disturbances remain rare. In any patient with features of CNS infection, or persistent altered level of consciousness, or failure to return to baseline alertness after the seizure a lumbar puncture should be performed following imaging.

4.6 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.

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

However, an ECG is usually unnecessary in children and adolescents with absence epilepsy.

4.7 Specific Investigations in Adults and Children

Cerebrospinal fluid (CSF) studies, HIV testing, and 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 with immunotherapy may lead to a good outcome. Amongst the antibodies that are now identified in this condition are anti-NMDA receptor, anti-LGI 1, anti-Caspr2 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.

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.

4.8 Investigations during Follow Up

a) If there is progressive neurological, cognitive or psychological deficits or poor control of seizure, a repeat EEG or brain MRI may be requested.

b) Neurocognitive testing may be requested in particular in children to assess for cognitive decline, which may be subtle.

c) Investigations should be done to exclude rare neurodegenerative diseases such as progressive myoclonic epilepsy, metabolic disorders and progressive structural disorders.

d) In patients taking enzyme-inducing ASM, a full blood count, liver function test and serum calcium should be done every 1 to 2 years to look for adverse effects.

e) Patients taking sodium valproate should have a full blood count done at least yearly.

f) Patients on topiramate and zonisamide should have an annual renal ultrasound scan.

KEY MESSAGES

- The diagnosis of epilepsy is based on the patient's and/or an eyewitness' account(s) of the attack.
- MRI at a magnet strength of 1.5T/3T is the neuroimaging of choice and is mandatory where the clinical presentation or EEG suggests an underlying brain abnormality
- Routine imaging in children is not always indicated. MRI may be deferred in patients with idiopathic epilepsy.
- An EEG is not diagnostic of epilepsy.
- EEG is useful in predicting the risk of recurrence of seizures.
- Routine blood tests to find the metabolic aetiology of acute symptomatic seizures is indicated in the emergency setting.
- Investigations play a supportive role in determining the aetiology, epilepsy syndrome, prognosis, suitability for surgical treatment and withdrawal of ASMs.
- Specific cut off values to attribute seizures to a metabolic cause are defined by the ILAE.

5.0 GENERAL PRINCIPLES OF THE TREATMENT OF EPILEPSY

5.1 Introduction

Upon establishing the diagnosis of epilepsy, the need for treatment as well as the choice of ASMs must be individualised, with careful consideration given to several factors, including the certainty of the diagnosis of epilepsy, type and severity of seizures, level of function, occupation, patient's age, sex and comorbidities, and family support.

From a patient's perspective, commencement of an ASM confirms the state of 'epilepsy', and this can affect self-esteem, social relationships, education and employment. While benefits of therapy would include lowering the risk of seizure recurrence and of death or injuries, drawbacks would include potential drug side effects, cost, stigmatisation and inconvenience. In addition, special concerns about the safety of ASMs for women and girls need to be considered. Thus, the decision to treat depends on the fine balance between the benefits and drawbacks of the therapy itself. 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, including acute ischaemic stroke, have failed to show any evidence of benefit and is presently not recommended.

5.3 Single Seizure

Patients presenting with a first single unprovoked seizure present a common clinical dilemma. While estimates of recurrence risk vary, the overall risk of recurrence is 30-40%, being the greatest in the first year and dropping to <10% by the 3rd year onwards. The lowest risks (13-24%) were seen in patients with either an acute symptomatic seizure, or those with no identified cause who have a normal EEG, and the highest risk (65% and above) were 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, with the decision made by the patient and the neurologist.

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 EEG shows unequivocal epileptic discharges

3. The patient has a structural cerebral disorder

4. The patient or physician considers the risk of recurrence unacceptable

• The decision to treat focal 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 ASMs. 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 ASM 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 based on the practical (operational) clinical definition of Epilepsy set up by the International League of Epilepsy (ILAE) in 2017 (see Chapter 2).

5.4.1 Newly Diagnosed Epilepsy

Factors influencing the decision to treat include:

1. A firm diagnosis of epilepsy that is 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. The risk reduces by a further 9% and 8% in the following 6 and 12 months respectively. 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: focal seizures are more likely to recur than generalized seizures.

3. Seizures must be sufficiently troublesome. Some seizure types have a minimal impact on quality of life (e.g., focal aware, absence or nocturnal seizures). The disadvantages of ASMs in such seizures may outweigh its benefits. 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 ASM should probably not be prescribed.

4. Epilepsy syndrome - some self-limited epilepsy syndromes have an excellent prognosis without treatment e.g., SeLECTS, and do not require long term therapy.

5. Compliance – ASMs 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 sudden unexpected death in epilepsy (SUDEP) is higher in GTCS 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 ASM.

4. Commencing the patient on a low dose of one (monotherapy) of the 1st line ASMs recommended for their epilepsy syndrome (Table 4). 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.

6. The patient is encouraged to keep a seizure diary to record the date, time and symptoms of their seizures, and show it to their doctor during follow-up.

5.4.2 Treatment of Drug-Resistant Epilepsy

Approximately one-third of patients with epilepsy continue to have poor seizure control despite the use of at least two appropriate and well tolerated ASMs (whether as monotherapy or in combination) and are deemed to have drug-resistant epilepsy (DRE). This may be due to:

1. An incorrect diagnosis of epilepsy
2. An inappropriate choice of ASM for the epilepsy syndrome
3. Poor compliance to the prescribed ASM
4. An underlying metabolic condition, immune process, or cerebral neoplasm.
5. Concurrent drug or alcohol misuse.

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 ASM and lifestyle modification.
4. Review drug history - which ASMs 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

ASMs available and it is important to create a balance between seizure frequency, side effects from ASMs, and quality of life.

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

1. Tolerability and long-term safety are the most important factors in choosing the first drug.

2. If the first ASM is poorly tolerated at low dosage or fails to improve seizure control, an alternative should be substituted.

3. If the first well-tolerated ASM greatly improves but does not completely abolish seizures, combination therapy may be tried. Although the mechanisms of action of many ASMs are not fully understood, this remains a logical basis for choosing combination therapy. Evidence is emerging that certain combinations (preferably ASMs with different mechanisms of action) offer better efficacy than others.

4. Work up for epilepsy surgery should be considered after failure of 2 well-tolerated treatment regimes after a period of 1 to 2 years.

5. If needed, subsequent combinations of 2 or at most 3 ASMs may be effective.

5.5 Decision to Withdraw ASMs

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. juvenile myoclonic epilepsy (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 GTCS or myoclonic seizures.

• with focal seizures.

• with seizures needing > 1 ASM 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 complex 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 SeLECTS.

Discussion of whether to withdraw ASM 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 ASM therapy.

The rate of withdrawal of ASMs should be slow, usually over a few months, and longer with barbiturates and benzodiazepines. One drug should be withdrawn at a time.

5.6 Driving and Epilepsy

The possession of a driver's license 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 licenses. 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 license 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 categories of driver’s license.

• If a licensee has obtained a license before developing this condition, the Pengarah can revoke this license 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, public buses, heavy goods vehicles, as well as flying commercial or military airplanes. As such, obtaining driving licenses 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 license, 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 enroll in an Institute of Higher Learning is required to undergo a medical checkup, including people with epilepsy. People with epilepsy and any other chronic medical conditions are advised to inform the authorities of their condition, 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 ASM regimen

• Indications and risks should be weighed and discussed with the patient.

• Recognise the limits of the efficacy of currently available ASMs. A high level of awareness of drug-resistant epilepsies (DRE) 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, and seizure recurrence.

6.0 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 ASMs

Selection of ASM is highly individualized. Considerations while choosing an ASM include:

1. Effectiveness for specific seizure or epileptic syndrome (Table 4)
2. Pharmacokinetic properties (Table 7)
3. Safety and tolerability profile (Table 7)
4. Patient's circumstances
5. Clinically relevant drug interaction (Table 6)

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 ASMs.
2. Start with a single ASM as monotherapy after deciding on the type of seizure(s) and the epilepsy syndrome (Table 4).
3. Begin at a low dose and increase gradually (Table 5).
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 7)

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 ASM fails to control seizures:

   - Review the diagnosis and seizure pattern.
   - Review compliance (see also "drug monitoring").
   - Ensure that the maximum tolerated dose has been used.

8. If the first ASM continues to be ineffective at the maximum tolerated dose, introduce an alternative ASM slowly (Table 5) without tapering the first.

9. If the patient has a good response to the second ASM, consider withdrawing the original ASM gradually.

10. Consider long-term two-drug therapy if monotherapy has not achieved remission or good seizure control.

11. If the first add-on ASM is ineffective, or produces undesirable side effects, withdraw it slowly, and simultaneously replace it with a second add-on ASM from the remaining choices. This process can be repeated for other possible add-on ASMs.

12. If the seizures are still not adequately controlled on two ASMs, some patients may benefit from an additional third ASM.

13. An ASM 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 an ASM 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 NEAD (PNES) 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 focal seizures, and surgery may be an option. Consider VNS if surgery is not an option. In patients who remain refractory to ASMs, with or without surgery and VNS, precision medicine, for example, targeted gene therapies in the genetic epilepsies are being evaluated extensively. An example is the FDA-approved everolimus in the treatment of the Tuberous Sclerosis Complex with focal seizures. However, everolimus is registered in Malaysia, but currently only indicated for the treatment of breast cancer.

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 4: Recommended ASM 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 topiramate**	clobazam gabapentin perampanel lacosamide levetiracetam##	eslicarbazepine phenobarbitone phenytoin pregabalin tiagabine vigabatrin felbamate****
Generalised Tonic Clonic seizure *only*	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	levetiracetam###	clobazam clonazepam piracetam zonisamide
Tonic or Atonic Seizures	sodium valproate#	lamotrigine	rufinamide topiramate
Infantile spasm	steroid vigabatrin (1st for tuberous sclerosis $\mathcal{F}$)		
Epilepsy Syndrome			
Dravet Syndrome	sodium valproate# topiramate	clobazam stiripentol cannabidiol****	
Lennox–Gastaut syndrome	sodium valproate#	lamotrigine cannabidiol****	rufinamide topiramate felbamate****
Self-limited epilepsy with centrotemporal spikes, Self-limited epilepsy with autonomic seizures and Childhood occipital visual epilepsy	carbamazepine lamotrigine levetiracetam oxcarbazepine sodium valproate#	clobazam gabapentin (carbamazepine and oxcarbazepine may exacerbate or unmask CSWS, which may occur in BCECTS.)	eslicarbazepine lacosamide phenobarbital phenytoin pregabalin tiagabine vigabatrin zonisamide
Idiopathic Generalised Epilepsy	sodium valproate# lamotrigine levetiracetam topiramate	perampanel	clobazam clonazepam zonisamide

Juvenile myoclonic epilepsy (JME)	sodium valproate# lamotrigine (may exacerbate myoclonic seizures) 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.

** In patients > 10 years old

*** 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.

**** Not marketed in Malaysia.

ϕ Cannabidiol was approved by the FDA for tuberous sclerosis for children > 1 year old

Use of sodium valproate in female of childbearing age need special considerations and is discussed separately (refer to Chapter 9).

FDA-approved as adjunct ASM in focal onset seizures in children > 4 years old

FDA-approved as adjunct ASM for JME

Table 5: Dosing Frequency

ASM	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
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
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
Eslicarbazepine**	Initial: 400 mg/day (adults); Maintenance: 800-1200 mg/day (adults)	1
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
Ezogabine**	Initial: 300 mg/day (adults); Maintenance: 600-1200 mg/day (adults)	3
Felbamate**	Initial: 1200 mg/day (adults), 15 mg/kg/day (children); Maintenance: 2400-3600 mg/day, 45 mg/kg/day (children)	3-4
Gabapentin	Initial: 300 mg/day (adults). Maintenance: 900-2400 mg/day (adults);	2-3
Lacosamide	Initial: 100 mg/day (adults); Maintenance: 200-400 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
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
Oxcarbazepine	Initial: 600 mg/day (adults); 10 mg/kg/day (children) Maintenance: 1200-2400 mg/day (adults); 20-40 mg/kg/day (children)	2
Perampanel	Initial: 2 mg nocte, 4 mg nocte if concurrent enzyme inducer (adults); Maintenance: 8-12 mg nocte (adults)	1
Phenobarbitone	Initial: 30 mg/day. Maintenance: 30-180 mg/day (adults); 3-5 mg/kg/day (children).	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
Pregabalin	Initial: 150 mg/day (adults); Maintenance: 150-300 mg/day (adults)	2
Primidone	Initial: 100-125 mg/day (adults); Maintenance: 750-1500 mg/day (adults)	1-3
Rufinamide	Initial: 400 mg/day (adults), 10 mg/kg/day (children); Maintenance: 1800 mg/day (adults), 45 mg/kg/day (children)	2
Tiagabine**	Initial: 4 mg/day, Maintenance: 32-56 mg/day	1-4
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

Zonisamide	Initial: 100 mg/day (adults), 1 mg/kg/day (children); Maintenance: 300-400mg/day (adults), 12 mg/kg/day (children)	1-2

*Refer to chapter 9 for the recent update on the use of sodium valproate in women
** Not marketed in Malaysia yet
***May start as low as 250 mg/day in 2 divided doses

Table 6: Clinically Relevant Drug Interactions

ASM	Induction	Interaction with ASM	Inhibition	Interaction with Other Therapeutic Class	Level of Importance	Added Drug	Clinical Consequence
Carbamazepine	CYP3A4 CYP1A2 CYP2B6 CYP2C9 CYP2C19 Pg-Protein UGT	Decreased level of		Decreased level of	Level 1 (should be avoided)	Oral contraceptives	Induction of oestrogen metabolism, reduction in serum concentrations and loss of contraceptive effect
		Clobazam Clonazepam Carbamazepine (autoinduction) Felbamate Lamotrigine Oxcarbazepine Perampanel Phenobarbitone		Calcium-channel blockers Hormonal contraceptives Lapatinib Maraviroc Methadone Nefazodone		Antibiotics (clarithromycin, erythromycin, troleandomycin):	Inhibition of carbamazepine metabolism, elevated serum concentration, potential serious toxicity
		Phenytoin Primidone Rufinamide Tiagabine Topiramate Valproic acid Zonisamide Increased level of phenobarbitone from primidone and phenytoin		NNRTIs Phenothiazines PPIs Lovastatin, simvastatin, cerivastatin & atorvastatin Tricyclic antidepressants Telapravir Theophylline Vitamin D Warfarin		Dextropropoxyphene	Inhibition of carbamazepine metabolism, elevated serum concentration, potential serious toxicity
Clobazam	CYP3A4 (weak)	Increased level of	CYP2D6 (weak)	Decreased level of			
		CYP2D6 substrates (fluoxetine, dextromethorphan)		Hormonal contraceptives			
Eslicarbazepine	CYP3A4 (weak)	Increased level of	CYP2C19 (moderate)	Decreased level of	Level 1	Oral contraceptives	Reduced effectiveness of oral contraceptives levonorgestrel and

		Clobazam Phenytoin		Hormonal contraceptives Simvastatin Rosuvastatin			ethinyloestradiol
Felbamate	CYP3A4 (weak)	Decreased level of Carbamazepine Increased level of CBZ-10,11-epoxide, phenobarbitone, phenytoin, valproic acid	CYP2C19 Beta Oxidation (moderate)	Decreased level of Hormonal contraceptives	Level 1	Oral contraceptives	Use of OCP and low dose of oestrogen is not advised
Lamotrigine	UGT (weak)	Decreased level of Lamotrigine Valproic acid		Decreased level of Levonorgestrel	Level 1 (Should be avoided)	Oral contraceptives	Induction of lamotrigine metabolism, reduction of serum concentration by 50% and reduced seizure control
Oxcarbazepine	CYP3A4/5 (dose dependent, moderate at >1200 mg/day)	Decreased level of Perampanel Increased level of CBZ-10,11-epoxide, phenobarbitone, phenytoin	CYP2C19 (dose dependent, moderate at >1200 mg/day)	Decreased level of Calcium-channel blockers Cyclosporin, hormonal contraceptives			
Perampanel	CYP3A4 (weak)			Decreased level of Levonorgestrel			
Phenobarbital & Primidone	CYP2C9 CYP2C19 CYP2E1 CYP1A2 CYP3A4 UGTs	Decreased level of		Decreased level of	Level 2 (Dosage adjustments and monitoring are needed)	Oral anticoagulants (Warfarin) *This is also for Carbamazepine and phenytoin	Induction of warfarin metabolism, increasing risk of coagulation that may be fatal

		Carbamazepine and monohydroxy derivate Clonazepam Felbamate Lamotrigine Oxcarbazepine Perampanel Phenytoin Rufinamide Zonisamide Tiagabine		Beta-blockers Ca-channel blockers Digoxin Hormonal contraceptives Lovastatin, simvastatin, cerivastatin & atorvastatin Vitamin D		Immunosuppressants (Cyclosporin, tacrolimus) *This is also for Carbamazepine and phenytoin	Induction of immunosuppressant metabolism, potential therapeutic failure
Phenytoin	CYP3A4 CYP2C9	Decreased level of		Decreased level of			
	CYP2C19 CYP1A2 UGT	Carbamazepine and monohydroxy derivate metabolites Clonazepam Felbamate Lamotrigine Oxcarbazepine Perampanel Phenobarbitone Primidone Rufinamide Tiagabine Topiramate Valproic acid Zonisamide		Calcium-channel blockers Digoxin Hormonal contraceptives Ibrutinib Nilotinib PPIs Quinidine Sirolimus Lovastatin, simvastatin, cerivastatin & atorvastatin Tacrolimus Telaprevir Vit D and folic acid Warfarin (prolonged phenytoin)			
Rufinamide	CYP3A4 (weak)	Increased level of Phenytoin	CYP2E1 (weak)	Decreased level of Hormonal contraceptive Triazolam			
Topiramate	CYP3A4 Beta oxidation (mild)	Increased level of Phenytoin	CYP2C19 (mild)	Decreased level of Hormonal contraceptives	Level 1	Oral contraceptives	Doses up to 400 mg/ day increase oral clearance of OCPs, ethinyloestradiol and norethindrone

Valproic acid		Increased level of	CYP2c9 UGTs Epoxide hydrolase		Level 2 (Dosage adjustments and monitoring are needed)	Lamotrigine	Inhibition of lamotrigine metabolism, skin rashes or neurotoxic effect
		CBZ-10,11-epoxide Ethosuximide					A synergistic effect pharmacological effect and improved seizure control
		Lamotrigine Phenytoin free level Rufinamide				Phenobarbitone	Inhibition of phenobarbitone metabolism, risk of intoxication

Table 7: Pharmacokinetics and Adverse Reactions of ASMs

Oral ASM	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, paradoxical increase in seizures if overdose, hypotension, arrhythmias, purple glove syndrome in IV form.
Carbamazepine	Good	Interme-diate	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-B*15:02*)
Oxcarbazepine	Good	Low	Extensive	1-4H, 8-10H (active metabo-lite, prolonged in renal impair-ment)	Present	Drowsiness, headache, fatigue, dizziness, blurred vision, diplopia, nausea, vomiting, 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, thrombocytopaenia, encephalopathy and hyperammonaemia if combined with topiramate and zonisamide); idiosyncratic hepatotoxicity and pancreatitis.
Ethosuximide	Good	Low	Extensive	30-60H	Present	GI adverse effect, neuropsychiatric disturbances, idiosyncratic reaction includes rash, SJS, SLE, aplastic anaemia, thrombocytopaenia, agranulocytosis,and rarely autoimmune thyroiditis.
Clobazam	Good	High	Extensive	36-42H, 71-82H (active metabolite)	Present	Drowsiness, nystagmus, incoordination, unsteadiness, dysarthria, DRESS syndrome.
Clonazepam	Good	High	Extensive	17-60H	Present	Same as clobazam (except for DRESS syndrome)
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	Interme-diate	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, depression, kidney stones 1.5%, paraesthesia, weight loss, glaucoma, oligohidrosis, hyperthermia, metabolic acidosis may occur in children.
Tiagabine#	Good	High	Extensive	7-9H	Present	Dizziness, asthenia, nervousness, tremor, depression, and emotional lability, dose-related non-convulsive status epilepticus or encephalopathy.
Levetiracetam	Good	Low	~30%, Non hepatic	6-8H	Absent	Somnolence, dizziness, asthenia. Irritability and hostility (esp. children), depression, DRESS syndrome.
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	Interme-diate	Extensive	6-10H	Present	Dizziness, fatigue, somnolence, and headache, short QT interval.
Perampanel**	Good	High	Extensive	105H	Present	Dizziness, somnolence, headache, fatigue, ataxia, blurred vision; aggression and hostility (high dose, adolescent)

Not marketed in Malaysia yet.

*LTG Black Box Warning: On 31 March 2020, FDA announced that a review of study findings showed a potential increased risk of arrhythmia in patients with heart diseases who are taking LTG. Lab testing performed at therapeutically relevant concentration, has shown that LTG can increase the risk of serious, life threatening arrhythmias in patients with clinically important structural or functional cardiac disorders. These include heart failure, valvular heart disease, conduction system diseases, congenital heart disease, ventricular arrhythmias, cardiac channelopathies e.g. Brugada syndrome and coronary artery disease. Assessment of risk-benefit should be done in such patients.

**Concomitant use of carbamazepine, and comorbidities of underlying insomnia, anxiety and amnesia, were significantly associated with increased risk of psychiatric and behavioural disorders.

6.3 Drug Monitoring

ASM 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. Serum levetiracetam levels can be tested in some private laboratories in Malaysia.

The major indications for assaying serum ASM levels are:

- to check compliance.
- to determine if signs or symptoms are the result of ASM toxicity.
- as a guide to dosing of certain ASMs (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 ASM 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 ASMs 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 8).

Table 8: Drug Monitoring

ASM	Time to peak concentration (H)	Time to steady state (Days)	Comment	Reference range (mg/L)
Carbamazepine	2–9	2–4	Active 10, 11 epoxide metabolite contributes to clinical effects	4–12
Clobazam	1–3	7–10	Active N- desmethyl metabolite contributes to clinical effects	0.03–0.3 (clobazam); 0.3–3 (desmethyl metabolite)
Clonazepam	1–4	3–10	7-amino metabolite retains some pharmacologic al activity	0.02–0.07
Ethosuximide	1–4	7–10		40–100
Felbamate	2–6	3–4		30–60
Gabapentin	2–3	1–2		2–20
Lamotrigine	1–3	3–6 (5–15 with valproic acid comedication)		2.5–15
Levetiracetam	1	1–2		12–46
Oxcarbazepine	3–6	2–3		3–35
Phenobarbitone	0.5–4	12–24		10–40
Phenytoin	1–12f	5–17		10–20
Pregabalin	1–2	1–2		Not Established
Primidone	2–5	2–4	Metabolically derived phenobarbitone contributes largely to clinical effects	5–10
Tiagabine	0.5–2	1–2		0.02–0.2
Topiramate	2–4	4–5		5–20
Valproic acid	3–6	2–4		50–100
Vigabatrin	1–2	1–2		0.8–36
Zonisamide	2–5	9–12		10–40

6.4 ASM Toxicity

Important points pertaining to ASM toxicity include:

- Acute dose-related toxicity is common and predictable although the dose required to produce symptoms varies between individuals.
- Inappropriate rapid introduction of ASMs 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 ASM.

6.5 HLA Issues

More than half (58.8%) of patients prescribed ASMs experience adverse reactions. In Malaysia, ASMs were among the top 10 most reported drugs for ADRs that contributed to 2.2% of all reported adverse drug reactions (ADRs), and cutaneous and subcutaneous disorders accounted for 67.9% of the reported ADRs from all drugs. Serious cutaneous adverse reactions (SCARs) such as toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome (SJS), and drug reaction with eosinophilia and systemic symptoms (DRESS) are potentially life-threatening SCARs, which could be due ASMs.

6.5.1 Risk of ASM-induced SCARs in Asians

Asians are at 2- to 3- fold increased risk for SJS/TEN compared to Caucasians. The post-marketing individual case safety report data in VigiBase® under the World Health Organization (WHO) showed that ASMs accounted for 17.6% of all reported cutaneous and subcutaneous reactions in the Asian population, of which 16.1% were severe. This is attributed to the higher prevalence of *HLA-B*15:02* in the Asian population. Reports across Asia have shown that the prevalence of *HLA-B*15:02* is high among the Han Chinese (5.7-14.5%) in Taiwan, Hong Kong, Malaysia, and Singapore; 12.0 to 15.7% among Malays in Malaysia and Singapore; 8.0-27.0% among the Thais, and 13.5% among the Vietnamese. There is a strong association between *HLA-B*15:02* and carbamazepine induced SJS/TEN in Asians. The overall odds ratio for this relationship was found to be 79.84, 95% CI [28.45-224.06]. The racial/ethnic subgroup analyses also showed that the odds ratio was 115.32 for Hans-Chinese, 54.43 for Thais, and 221.0 for Malaysians.

6.5.2 United States Food and Drug Administration (FDA) Recommendation

In view of the high prevalence of the *HLA-B*15:02* allele and its strong association with carbamazepine-induced SCAR among certain Asian populations, the US FDA has recommended *HLA-B*15:02* screening prior to initiating treatment with carbamazepine for all Asians patients since 2008. It should be noted that patients who are tested positive for *HLA-B*15:02* may also be at increased risk of SJS/TEN not only to carbamazepine but also to other aromatic ASMs, notably lamotrigine, phenytoin, and phenobarbitone. Other HLA alleles such as HLA-A*31:01 among the Northern Indians and Malaysian Indians, HLA-B*15:13 among the Malay population and HLA-A*24:02 among the Hans Chinese in Southern China were also found to be strongly associated with SJS/TEN in carbamazepine users.

*6.5.3 Incidence of ASM-induced SCARs in Malaysia and HLA-B*15:02 screening in Malaysia*

There was an upward trend in the incidence of ASM-induced SCAR from 2006 to 2019 in Malaysia, especially for the aromatic ASMs, phenytoin, carbamazepine, and lamotrigine. Carbamazepine was the ASM with the highest incidence of SCARs, averaging 11 per 1,000 persons-year, followed by phenytoin (10.4 per 1,000 persons-year) and lamotrigine (9.0 per 1,000 persons-year). As *HLA-B*15:02* screening is only available in limited centres in Malaysia, there was also a 4.8% and 5.5% increase in prescription of sodium valproate and levetiracetam between 2006 and 2016, respectively, to avoid *HLA-B*15:02* screening as these ASMs have lower risk of SCARs. However, sodium valproate is less effective in focal epilepsy, and levetiracetam is more expensive than carbamazepine and not available in certain hospitals.

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

The effects of carbamazepine dosage on the likelihood and timing of cutaneous ADRs are uncertain. 2. The exact mechanism of how carbamazepine modulates cytotoxic activity via the HLA gene is poorly understood.

Recommendations:

a. All patients should be screened for *HLA-B*15:02* before initiation of carbamazepine. If a screening facility is not available, carbamazepine can still be prescribed provided the patient is warned of cutaneous ADRs and advised to stop carbamazepine if this occurs.

b. There is also a need to set up national or regional laboratory support to provide nationwide *HLA-B*15:02* alleles screening reliably and rapidly for decision making in carbamazepine prescription

c. The latency of carbamazepine-induced SJS/TEN is 25 to 90 days. Therefore, patients who are already on carbamazepine after 3 months without cutaneous ADR should continue the treatment.

d. Patients who are tested positive for *HLA-B*15:02* should not be treated with carbamazepine.

e. Patients who are tested negative for *HLA-B*15:02* 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.

6.6 Generic Drug Issues

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

A generic ASM is considered as bioequivalent to the original ASM as long as the drug's maximum concentration (*Cmax*) in 12-16 healthy volunteers is within 80-125% to that of the reference drug. The drug levels in the actual epilepsy population and patients on multiple ASMs are not tested. There are pharmacokinetic and pharmacodynamic variations between original and generic ASMs as well as between different generic brands of the same ASM. 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 ASMs among clinicians and patients.

Recently, studies comparing generic and original ASMs have been published. Initiating a patient with epilepsy on generic ASM can provide similar efficacy, tolerability and safety to that of the originator ASM. 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 ASMs could be used as an alternative to original ASMs. This will allow easier and wider accessibility to various ASMs.

Although, there is emerging data supporting the use of generic ASMs, there is no data regarding the response to generic ASMs 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 ASMs studied abroad. Therefore, care must be taken for patients with DRE and those who are on polytherapy. These patients are best maintained on their original ASMs to prevent seizures.

KEY MESSAGES

1. ASM should be started after establishing the diagnosis and need for long term ASMs; the patient and the caregiver must participate in the discussion process.

2. Choice of ASM is highly individualised based on the efficacy, safety, mode of actions, cost and pharmacokinetics of the ASM, the seizure type(s) and epilepsy syndrome as well as the patient's preference.

3. Monotherapy with the appropriate ASM is preferred. If uncontrolled, adjunctive ASM is added, and sometimes even a third ASM 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 ASM monitoring are:
   - to check compliance.
   - to determine if signs or symptoms are the result of ASM toxicity.
   - as a guide to dosing of certain ASMs (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 ASMs after a period of remission should be clearly discussed with patients and their caregivers.

8. All patients should be screened for the *HLA-B*15:02* allele, before initiation of carbamazepine. Patients who are tested positive, should not be treated with carbamazepine.

9. The latency of carbamazepine-induced SJS/TEN is 25 to 90 days.

10. Special care must be taken when using generic ASMs in patients with DRE and those who are on polytherapy. These patients are best maintained on patented ASMs to prevent seizures.

11. Physicians must be cognisant of the myriad of manufacturers of the same ASM when prescribing generic ASMs.

7.0 SURGICAL TREATMENT OF EPILEPSY

7.1 Introduction

Epilepsy is the most common serious disorder of the brain and the lifetime prevalence of epilepsy varies greatly from 1.5-14.0 per 1000 persons among the Asian countries. A population-based door-to-door survey revealed a lifetime epilepsy prevalence of 7.8 in 1000 population, and the adjusted prevalence for active epilepsy of 4.2 in 1000 population in Malaysia. About 1.5% of people newly diagnosed with epilepsy may eventually require epilepsy surgery. Two thirds of those who develop epilepsy will have their condition controlled with currently available ASMs. Of those who develop epileptic seizures, 47% will be controlled with the first ASM prescribed, 32% with the second ASM, and 9% with the third. Fourth and subsequent ASMs have at most a 5% chance of producing long-term remission. Given the rapidly diminishing chances of becoming seizure-free after trying three ASMs those continuing to have focal seizures should be considered for surgical treatment at an early stage. About 30%–40% whose seizures continue despite medication, clinicians should consider other options, such as epilepsy surgery, vagus nerve stimulation or ketogenic diet in individuals with focal DRE. Epilepsy surgery offers a 60–70% chance of long-term remission and these patients should be referred to a specialised centre for evaluation. Those who are potential candidates for epilepsy surgery should have this option considered much earlier, after trying two or three ASMs, which will usually take about 2–3 years after starting ASM. DRE is the failure to achieve sustained seizure freedom despite adequate trials of two tolerated, appropriately chosen ASM schedules, either as monotherapy or in combination.

The standard evaluation includes clinical review, brain imaging with magnetic resonance imaging, recording of seizures with prolonged scalp EEG and video, and neuropsychological and psychiatric assessments. The aim is to establish converging evidence that there is a single epileptic focus and that the rest of the brain is functioning normally. In some individuals, further evaluation with functional imaging and intracranial EEG recordings may be necessary. The most commonly performed resective operation is an anterior temporal lobe resection to remove a sclerotic hippocampus, followed by lesionectomies and neocortical resections. Palliative manoeuvres, to reduce seizure frequency and severity include corpus callosotomy, subpial transection and vagal nerve stimulation.

Surgical success may be defined as the complete cessation of seizures without post-operative cognitive, psychiatric, or neurological dysfunction. The outcome of surgery typically represents a balance between seizure control and post-operative deficit. Attaining seizure freedom is also associated with reduced mortality, for example, from SUDEP. The delay between onset of focal epilepsy and epilepsy surgery is about 15–20 years, indicating delay and under-referral for this potentially life-changing treatment. Most patients with focal DRE can be appropriately considered for surgery. Over half of those referred will not be suitable for current resective options, but they may be suitable for a palliative procedure or implantation of a stimulator. In general, about 50% of those who undergo initial, non-invasive, pre-surgical investigations do not proceed further; 25%–40% are offered a resection without needing further investigations, and 10%–30% require intracranial EEG recordings.

7.2 Who Should be Considered for Epilepsy Surgery?

a. All adults with focal DRE (after adequate trials of two or more appropriately selected ASMs) should be considered for resective/curative surgery.

b. All adults with focal or generalised DRE who are not candidates for resective surgery should be considered for palliative procedures, such as vagus nerve stimulation.

c. A low IQ or memory impairment is not a contraindication to resective surgery.

d. Older patients should be considered for surgery, but the risk of complications is higher.

e. A history of long-term psychiatric disorder does not exclude a patient from resective surgery but close psychiatric supervision post-operatively would be mandatory.

f. Bilateral interictal epileptiform activity is not a contraindication to resective surgery; unilateral onset seizures often have bilateral interictal epileptiform activity.

g. People with focal DRE and a normal structural MRI of the brain should be considered for surgery; other investigations may identify a single epileptogenic zone amenable to surgical resection.

h. Multiple or diffuse lesions on MRI are not a contraindication to surgery; seizures may arise from only one of the visible abnormalities or from a part of the lesion.

i. People whose seizure semiology suggests involvement of primary eloquent cortex should be considered for surgery; essential functions can be localised and the symptomatic zone may be distinct from the epileptogenic zone due to seizure propagation.

7.3 Benefits and Risks of Surgery

Potential Benefits

a. Seizure freedom
b. Reduced seizure severity
c. Reduced medication load
d. Cognitive gains from reduction of both medication load and seizure activity
e. Reduced risk of SUDEP and injury
f. Possible improved long-term psychiatric outcomes
g. Improved quality of life

Risks

h. Perioperative mortality and morbidity
i. Post-operative neurological and cognitive deficits particularly if seizures continue post-operatively
j. Possible short-term and de novo long-term psychiatric complications

7.4 Pre-surgical Evaluation

The principal aim of pre-surgical evaluation is to determine the epileptogenic zone and its relationship to eloquent areas of the brain. The epileptogenic zone is a theoretical construct, defined as the minimum amount of cortex that must be resected (inactivated or completely disconnected) to give seizure freedom. No single pre-operative investigation can characterise the epileptogenic zone completely and reliably, and even when combining various investigative modalities there may still be variable concordance. When pre-operative non-invasive investigations have a high degree of congruence between these zones, it may be possible to recommend surgery with predictable levels of benefit and risk. However, if non-invasive investigations are discordant, proceeding directly to resective surgery may be rejected in favour of establishing more definitive localising data using, for example, invasive EEG recordings (Figure 5).

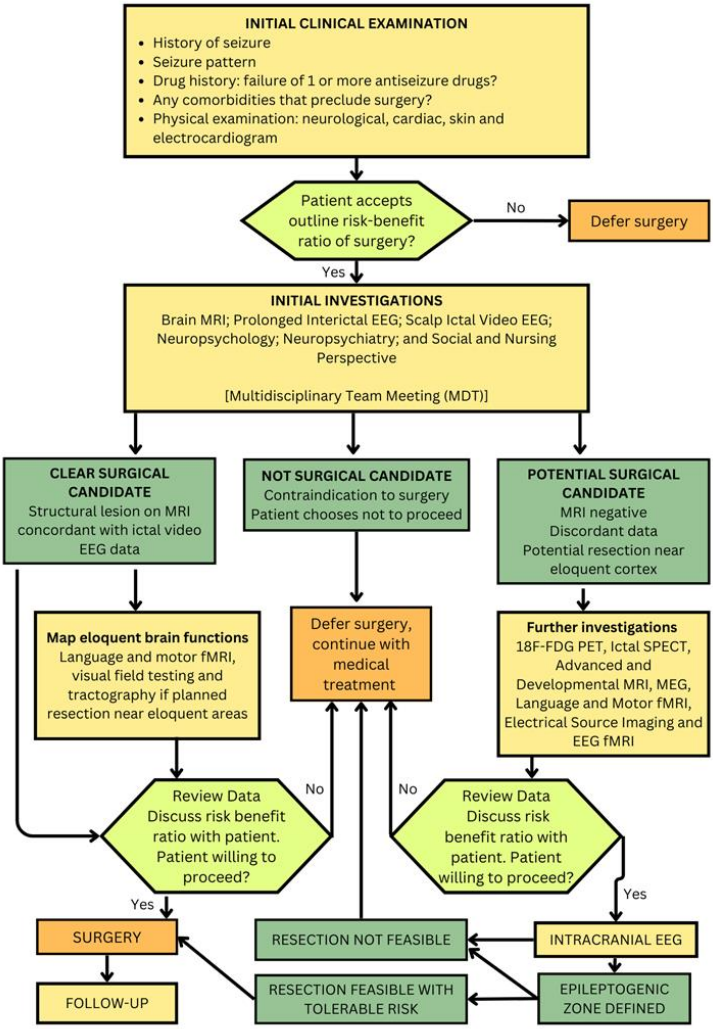

Figure 5: The pathway of assessment for epilepsy surgery. (Adapted from Duncan JS., Epilepsy Behav. 2011;20:230-232).

7.4.1 Identifying the Seizure Focus:

Non-invasive Techniques

I. Identifying the epileptogenic zone starts with a detailed elucidation of the seizure semiological characteristics.

II. Interictal and ictal EEG recordings (Figure 5).

III. High-resolution anatomical MRI with an epilepsy-dedicated protocol should be performed (ideally on a 3-Tesla MRI scanner) and evaluated by an expert neuroradiologist. Up to 86% of cases of hippocampal sclerosis may remain undetected using a standard MRI sequence reported by a non-expert radiologist. A 3-Tesla MR scanner improves the identification of structural lesions by up to 20% compared with a 1.5-Tesla scanner.

IV. Prolonged video-EEG telemetry is mandatory, often with ASM reduction to increase the number of seizures recorded within a reasonable time frame.

V. During and immediately after seizures, it is important to perform neurocognitive testing to establish functional deficit, to aid localisation.

VI. If the initial investigations are discordant or, if the brain MRI is normal or non-definitive, nuclear medicine studies such as fluorodeoxyglucose-positron emission tomography and ictal single photon emission CT are used to generate a hypothesis that may then be tested with intracranial EEG recordings.

VII. Additionally, more advanced developmental MRI or neurophysiological techniques such as magnetoencephalography or electrical source imaging may help to localise the seizure focus.

Invasive Techniques

Up to 20%–30% of surgical candidates need intracranial EEG recordings to define the epileptogenic zone. The aim of invasive EEG recording is to acquire neurophysiological data to support or disprove a hypothesis regarding the site of seizure onset. Typically, this is required for non-lesional focal epilepsy or if non-invasive investigations are non-localising or discordant (Figure 5). The type of intracranial recording depends on the suspected pathophysiological substrate of the epilepsy and its location. Intracranial EEG recording mainly involves two techniques:

I. **Depth electrode implantation** uses multiple electrodes stereotactically implanted into the brain parenchyma via small screws fixed to the skull. This stereo-EEG technique allows recording from both deep and superficial areas. Its overall morbidity is about 1.3%, equating to a risk of 1 in 287 electrodes, including a 1% risk of haemorrhage. The implantation can be performed with

a frame-based stereotactic approach or using frameless image-guidance systems that promise to simplify the pre-surgical planning of electrode placement. Both frame-based and frameless approaches can be robotically assisted.

II. **Subdural electrodes (strips and grids)** are placed directly on to the brain surface. Subdural strips can be placed through simple burr holes, whereas grids require a craniotomy and can record from a larger area of contiguous cortex. They are frequently used when epileptogenic lesions are adjacent to eloquent cortex. Subdural grids enable detailed extra-operative direct cortical stimulation, facilitating the mapping of eloquent cortex. The main advantage of this technique is a more comprehensive cortical stimulation study, compared with stereo-EEG, where cortical sampling is spatially more limited. The duration of invasive monitoring depends on the seizure frequency, the success of any planned stimulation and patient compliance. It may need several weeks of depth electrode recording to characterise a patient's seizure disorder fully. In contrast, subdural grid recordings seldom extend beyond 10–14 days, as these patients often have a higher seizure frequency, and the procedure carries a higher risk of infection.

Invasive monitoring may be stopped at any stage if there is a clinically significant adverse event, such as intracranial haematoma (<5% of cases) or infection resulting from the wires passing through the scalp (2% of studies). These risks can be reduced by careful intra-operative technique, appropriate post-operative nursing care and prophylactic antibiotics. Invasive intracranial EEG studies are time-consuming, expensive, have an inherent risk of complications, and require numerous personnel and access numerous allied investigations. This limits the number of neuroscience centres that can support a comprehensive epilepsy surgery programme. About 40% of patients who undergo invasive recording are deemed unsuitable for resective surgery, for three main reasons: the epileptogenic zone cannot be satisfactorily determined, there are multiple potential seizure foci or the epileptogenic zone is situated in eloquent cortex.

7.4.2 Preservation of Cognitive and Neurological Function

Neuropsychological testing can help to predict the post-operative cognitive outcome and seizure control.

I. Bilateral hippocampal resection results in profound anterograde amnesia.

II. Unilateral temporal lobe resections may result in material-specific memory dysfunction.

III. Approximately 30% of patients undergoing dominant temporal lobe resection develop difficulties in verbal memory processing and word-retrieval.

IV. 30% of patients undergoing non-dominant temporal lobe resection develop difficulties with non-verbal or visual memory processing.

V. A decline in verbal memory is generally more disabling than a decline in visual memory. Those at greatest risk of a troublesome decline in language and verbal memory are high-functioning people who undergo an anterior temporal lobe resection in the speech-dominant hemisphere. A proportion of people note an improved memory after temporal lobe resection, particularly if the resection is on the non-dominant side.

VI. Pre-operative neuropsychological scores, in conjunction with MRI and other clinical data, can be used to predict post-operative neuropsychological change using logistic regression techniques.

VII. Those at high risk of a significant memory decline can be advised pre-operatively and can be trained in compensatory strategies before the surgery.

VIII. Functional MRI (fMRI) can lateralise and localise cerebral areas involved in language function. Language lateralisation assessed using fMRI language tasks correlates well with that assessed using the carotid amytal test. Thus, in most epilepsy surgery centres, language fMRI has largely replaced the amytal test. Resections close to eloquent language cortex require a more detailed and accurate assessment of the anatomical relationship between seizure focus and language areas than can be assumed from an fMRI activation pattern; it may be necessary to perform electro-cortical stimulation or an awake resection.

IX. Awake craniotomy poses significant challenges to both the surgeon and anaesthetic team; seizures may occur during the procedure or patients may become agitated or distressed. There is neither immediate control of blood pressure nor the possibility of hyperventilation to reduce intracranial pressure.

X. Visual pathway tractography can predict the likelihood and extent of a visual field defect following anterior temporal lobe resection. Typically, up to 10% of patients undergoing anterior temporal lobe resection develop a significant superior quadrantanopic field defect post-operatively, which can prevent restoration of driving eligibility Tractography data made available to the surgeon through a visual overlay when using the operating microscope has reduced the incidence of post-operative visual field deficit.

7.5 Epilepsy Surgery Multidisciplinary Meeting

A multidisciplinary and systematic approach to investigations is essential to a surgical pathway (Figure 5). The epilepsy surgery multidisciplinary team meeting is attended by epileptologists, neurosurgical team, neurophysiologists, neuropsychologists, neuropsychiatrists and epilepsy specialist nurses.

I. The seizure history is presented and then each investigation discussed in detail. Having reached consensus on a potentially curative or palliative surgical approach, the team formulates a detailed management plan.

II. Subsequently, this risk benefit analysis is discussed in detail with the patient and along with written information.

III. Patients must be given realistic expectations of what may be achieved, and what may be the negative consequences of epilepsy surgery.

7.6 Surgical Procedures: Curative

I. Lesionectomy

a. The increased anatomical resolution of modern MRI has led to the identification of many more cortically based lesions. Small lesions such as cavernomas, focal areas of cortical dysplasia and indolent tumours such as DNETs are highly epileptogenic, and their resection is associated with a high rate of seizure freedom. Interventional MRI allows documentation of complete lesion resection before completing the surgical procedure. It also enables the surgical navigation software to be recalibrated during the operation, improving its accuracy. Thus, interventional MRI can potentially improve the rate of seizure freedom from surgery, and reduce the risk of neurological deficit.

II. Lobectomy

a. **Temporal lobe: Anterior temporal lobe resection**, including the mesial temporal lobe structures. Contemporary approaches attempt to limit the size of the neocortical resection to minimise neurocognitive sequelae, using either the method described by Spencer or selective amygdalohippocampectomy. Anterior temporal lobe resection that includes removal of up to 4.5 cm of neocortex shows a trend towards improved seizure outcomes compared with selective amygdalohippocampectomy, and with minimal differences in neuropsychological outcome. The initial seizure-free rate following resection of hippocampal sclerosis is approximately 75%–80%, and approximately 70%–75% for resection of other temporal lobe lesions. There is gradual attrition of seizure freedom over subsequent years so that 40%–50% can expect to remain totally seizure free after 20 years. The failure to achieve seizure freedom may be due to insufficient resection of the epileptogenic mesial temporal structures, seizures arising from the contralateral mesial temporal lobe, lateral temporal neocortical epilepsy, dual pathology, secondary epileptogenesis and extra-temporal lobe epilepsy mimicking temporal lobe epilepsy, as with insula or posterior cingulate foci.

b. **Extra-temporal lobe:**

Seizure outcome is typically less good for extra-temporal resections than with temporal lobe resections, particularly in non-lesional cases but may be as high as 50%–60% following careful evaluation with stereo EEG. Depending on the pathology, it may be necessary to make large resections of the epileptogenic zone, thus putting eloquent cortex at risk. Certain post-operative neurological and neuropsychological deficits are often predictable, such as a hemianopic field deficit following occipital lobe resections, or a Gerstmann's syndrome or hemisensory impairment following parietal lobe surgery.

IV Hemispherotomy

Hemispherotomy inevitably leads to profound neurological deficit, including hemiplegia and hemianopia; this is therefore most appropriate for those with a pre-existing deficit. If patients can walk pre-operatively, most remain able to do so. Typically, there is loss of fine motor skills in the contralateral upper and lower limbs, but cognitive function is stable. Hemispherectomy used to cause long-term complications in up to one-third of patients, including superficial cerebral hemosiderosis. As a result, alternative techniques were developed, including a functional hemispherectomy, in which the temporal lobe and central cortex are removed and the corpus callosum and frontal and occipital cortex disconnected. The seizure outcomes remain unchanged, but the complication rate has significantly improved. The success of hemispherotomy depends on the underlying pathology, with excellent outcomes and seizure freedom rates approaching 75%–85% for pathologies such as Rasmussen's encephalitis and focal infarcts, but with a poorer outcome for patients with hemi-megalencephaly.

7.7 Surgical Procedures: Palliative

The objective of these functional procedures is to palliate rather than to cure the epilepsy. They should be offered only if resective surgery is considered to be inappropriate or too risky.

I. Corpus callosotomy

The primary indication for corpus callosotomy is atonic drop attacks, although it is effective for other seizure types. The disconnection slows inter-hemispheric seizure propagation and provides patients with a warning or disrupts a seizure, the expression of which relies on synchrony. About 74% of people have favourable outcomes with corpus callosotomy, including 39% who stop having drop attacks. The operation may cause either immediate or delayed symptoms of disconnection. In order to minimise this risk in adults, the callosotomy is usually carried out in two stages, with the anterior two-thirds of the corpus callosum being divided first and the posterior third divided later.

7.7.1 Stimulation Techniques

I. Vagus Nerve Stimulation

The neurophysiological basis of periodic vagus nerve stimulation has not been fully elucidated but may involve autonomic nervous pathways and augmented function of neurotransmitters such as gamma-aminobutyric acid (GABA). Besides intermittent stimulation, the patient or caregiver can also activate on-demand stimulation. The newest devices are capable of self-activation upon detection of ictal tachycardia. The left vagus nerve is used to avoid cardiac side effects, and the electrode placed around the nerve in the neck between the common carotid artery and the internal jugular vein. Side effects include hoarseness and coughing during stimulation and neck discomfort. The beneficial effect of vagus nerve stimulation may take up to 2 years to emerge. Long-term studies have shown that although very few people become seizure free, up to 43%–64% have their seizure frequency reduced by 50% or more. The efficacy of VNS improves over time, with a 66% seizure reduction at 6 years.

II. Intracranial Stimulation

1. Traditional 'open-loop' deep-brain stimulation techniques use continuous or scheduled stimulation, and so do not depend on the presence of epileptiform activity. In one study of people with focal epilepsy, bilateral stimulation of the anterior nuclei of the thalamus was associated with an immediate mean decrease in seizure frequency of 29%, at 1 year and 56% at 2 years. The procedure was generally well tolerated without symptomatic haemorrhage or infection, but the treatment group developed more depression and memory difficulties·
2. 'Closed-loop' or responsive cortical stimulation has been an important development. Here, the stimulation is activated only after having detected abnormal ictal or interictal epileptiform discharges.
3. The Neuropace responsive neurostimulator (RNS) delivers a pre-symptomatic short train of electrical pulses to the brain through implanted leads, on detection of abnormal electrical activity via an implanted strip electrode on the brain surface. A multicentre, double blind, randomised control trial showed a 38% reduction in mean seizure frequency in the treatment group compared with a 17% reduction in the sham group. Mild adverse events, such as implant site pain, headache and dysaesthesia, were common in both the treated and sham groups·
4. Other implantable responsive devices currently in development use optogenetics, local cooling or drug-delivery systems; trials of these in humans will begin in the next few years.

7.8 Outcome

7.8.1 Seizure Control

The outcome from epilepsy surgery is based on several facets including seizure control, neuropsychological development, neurological deficit, quality of life and psychosocial adjustment. Of these, seizure control is the one most commonly ascertained.

a. In one large cohort study of almost exclusively curative procedures, the average post-operative seizure remission rate was 52% at 5 years and 47% at 10 years, with a range of between 40% for extra-temporal lesionectomy and 64% for hemispherectomy. Early seizure recurrence predicted a worse seizure outcome, in line with other studies.
b. Patients with an identified epileptogenic lesion are two to three times more likely to become seizure free post-operatively than patients with normal imaging.
c. The factors associated with an increased risk of seizure recurrence post-operatively include normal MRI scan of brain, a history of focal-to-bilateral tonic clonic seizures, a psychiatric history, extra-temporal rather than temporal lobe surgery, older age, and having tried a higher number of medications before surgery.

7.8.2 Complications

The neurological complications of epilepsy surgery depend largely on the location and extent of the surgical resection.

a. The overall complication rate is around 7%–8%, though this is higher in people aged over 50 years at 6%–25%.

b. Most neurological deficits are predictable (such as visual field deficit); the risk of new, long-term, unexpected neurological complications is low, at less than 5%.

c. Transient complications such as infection or cerebrospinal fluid collections are more common.

d. Psychiatric disorders are common in people with epilepsy. Having a prior or current history of psychiatric disorders is associated with a lower chance of seizure freedom following surgery, but this is not a contraindication to surgery. Following successful surgery, there may be short-term worsening of psychiatric symptoms, in particular anxiety, but this is often followed by long-term improvement. Nevertheless, de novo psychiatric disorders, such as depression, anxiety or psychosis may develop in up to 26% of people after temporal lobe surgery. Careful post-operative psychiatric supervision is therefore important. [26]

e. Interestingly, new onset of dissociative (non-epileptic) seizures may develop in 4%–8% of people following surgery.

7.8.3 Medication Withdrawal

Patients who become seizure free following surgery may wish to consider subsequent medication withdrawal. However, the risk of seizure recurrence, the nature of prognostic factors, and the timing and rate of medication withdrawal remain unclear. In general, about one-third of people withdraw medication completely after surgery. However, with no clear data or guidelines, maintaining pre-operative medication for at least 12 months after surgery is recommended, before gradually reducing it to monotherapy during the second post-operative year, provided there is ongoing seizure freedom.

7.9 Recent Developments

Minimally invasive lesioning epilepsy surgery techniques offer the possibility of stopping seizures with improved neurocognitive outcomes. One such technique is thermal ablation, also called laser interstitial thermal therapy.

a. A low-voltage laser is introduced via an optic fibre using MRI guidance and a coagulative necrotic lesion is created using MRI thermal maps in real time. This is undertaken as a day case procedure and is becoming widely adopted for hippocampal sclerosis, hypothalamic hamartomas and cortical dysplasia.

b. Compared with gamma-knife radiotherapy, there are no issues with long-term radiation risks and the region of ablation is better demarcated.

c. In terms of outcome, real-time MR stereotactic laser amygdalohippocampectomy generally gives lower seizure free rates (53%–80% at 1–3 years) than open surgery in the small series completed to date.

d. Hippocampal sclerosis on pre-operative imaging predicts a better outcome.

e. Neurological complications, such as visual field defects, intracranial haemorrhage and cranial nerve defects occur at a rate comparable with open surgery, but neuropsychological decline (particularly of verbal memory) is less common. Data on other lesioning techniques (such as **high-frequency ultrasound ablation**) and their potential use for more challenging surgical targets such as periventricular nodular heterotopia or corpus callosotomy should be available soon.

KEY MESSAGES

1. All patients with focal DRE should be considered for resective epilepsy surgery.

2. The purpose of presurgical evaluation is to characterise the epileptogenic zone and to prevent postoperative neurological, psychiatric and cognitive deficits. This requires a multidisciplinary approach with a comprehensive investigative pathway.

3. Surgery carries a risk of permanent neurocognitive or psychological deficit but this needs to be balanced against the risks of ongoing seizure activity.

4. New techniques, such as laser ablation and responsive stimulation, aim to reduce epileptic activity while preserving neurocognitive function better than with standard resective surgery.

8.0 EMERGENCY TREATMENT OF EPILEPSY

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

8.1 Definition of Status Epilepticus (SE)

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 9)

Table 9: Operational Dimension With t^1 Indicating When Emergency Treatment of SE Should Be Initiated And t^2 Indicating When Long-term Consequences May Appear (Adapted from Trinka E, et al. Epilepsia. 2015;56(10):1515-23).

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
[a]Evidence for the time frame is currently limited and future data may lead to modifications.		

Refractory SE is defined as ongoing 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.

8.2 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 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.

8.3 Pre-Hospital Treatment (Home)

The duration and recurrence rate of seizures may be reduced by proper pre-hospital treatment by paramedical personnel including *intramuscular or buccal midazolam, or rectal diazepam* in the case without venous access. Intramuscular midazolam was proven to be 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.

- Intramuscular midazolam: 0.2mg/kg (max, 10mg for those > 40kg, 5mg for 13-40kg, single dose)
- Buccal midazolam: 0.2 mg/kg (max, 10mg)
- 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)

8.4 Pre-Hospital Treatment (Ambulance)

For prehospital treatment in a hospital ambulance, IV diazepam is the most readily available. However, midazolam should be carried along if accessible, especially for patients without venous access.

All ambulance services including those provided by non-government organisations should be equipped with benzodiazepine (diazepam or midazolam).

8.5 Treatment of Convulsive SE (t_1)

In the event that the seizure does not stop beyond the time point (t_1), vital parameters, including 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 ASMs:

8.5.1 First line: Benzodiazepines (BDZ)

Intravenous diazepam is the principal first-line ASM used for prolonged seizures in Malaysia. Intravenous diazepam is given at 0.15-0.2 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, IV phenytoin can be given at 15-18 mg/kg at an infusion rate of ≤50 mg/min. Phenytoin is the preferred ASM because it is widely available and is less sedating than the other ASMs. An additional dose of phenytoin at 5-10 mg/kg can be given if the first loading dose is unproductive. If IV sodium valproate or IV levetiracetam is available, there is a contraindication to use phenytoin, or seizures fail to respond to phenytoin, one of these two medications should be considered. They can be given fast over 10 minutes at high doses, i.e., sodium valproate at 40mg/kg (max 3000mg) and levetiracetam at 60mg/kg (max 4500mg).

8.6 Refractory SE

If the seizures persist, the patient should be referred to an anaesthesiologist for ICU care and administration of barbiturates or anaesthetic agents including thiopentone, midazolam, propofol or ketamine. (Table 10) Ketamine has an additional advantage of anti-glutaminergic activity that is essential when the synaptic $GABA_A$ receptors are internalized and become functionally inactivated as status epilepticus progresses. 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. The anaesthetic agent can be tailed down if the patient is seizure-free for 24 hours.

8.7 Super-refractory SE

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

- Anaesthetic agents and other ASMs e.g. IV/oral levetiracetam, IV sodium valproate and oral topiramate
- Magnesium infusion, pyridoxine
- Steroids and immunotherapy, especially in those suspected to have autoimmune aetiology
- Ketogenic diet
- Hypothermia 31–35°C for 20–60 hours
- Surgery: emergency resective neurosurgery and multiple subpial transections, vagal nerve stimulation, deep brain stimulation
- Transcranial magnetic stimulation
- Electroconvulsive therapy

Table 10: Dosages of ASMs Used in SE

- IV diazepam 0.15-0.2 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 sodium valproate 40 mg/kg bolus over 10 min, max: 3,000mg
- IV/oral levetiracetam 60 mg/kg over 10 min, max: 4,500mg
- 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
- Oral topiramate 400mg, followed by 200mg b.d.

*Caution: higher doses may lead to delayed respiratory depression

Continuous/repeat EEG recording is helpful in detecting electrographic seizures as well as monitoring the adequacy of general anaesthesia/ASM therapy.

A useful step-by-step guide to the management of convulsive SE in adults is shown in Table 11. However, it is recommended that each hospital develops its own protocol.

Table 11: Management of Convulsive SE in Adults

Phase	Steps
Pre-hospital treatment	Intramuscular or buccal 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. IV sodium valproate 40 mg/kg bolus over 10 min, max: 3,000mg IV levetiracetam 60 mg/kg over 10 min, max: 4,500mg
Refractory status	Ventilation and anaesthetic agents: • 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) • IV ketamine 1 mg/kg/hour Continue anaesthetic agents for 12-24 hours after last clinical or electrographic seizure.

8.6 New-Onset Refractory Status Epilepticus (NORSE) and Febrile Infection-Related Epilepsy Syndrome (FIRES)

NORSE is a rare and devastating condition characterized by de novo onset of refractory status epilepticus (RSE) without an identifiable acute or active structural, toxic, or metabolic cause. FIRES is considered a subcategory of NORSE rather than a separate entity. The FIRES diagnosis requires a prior febrile illness starting between 2 weeks and 24 hours before the onset of RSE (with or without fever at the onset of status epilepticus).

As immunological activation is likely, first-line immunotherapy should be considered within 72 hours of seizure onset in cryptogenic cases without waiting for the results of the autoimmune limbic encephalitis panel. In cases that remain cryptogenic, second-line immunotherapy and ketogenic diet should be considered within 7 days of seizure onset.

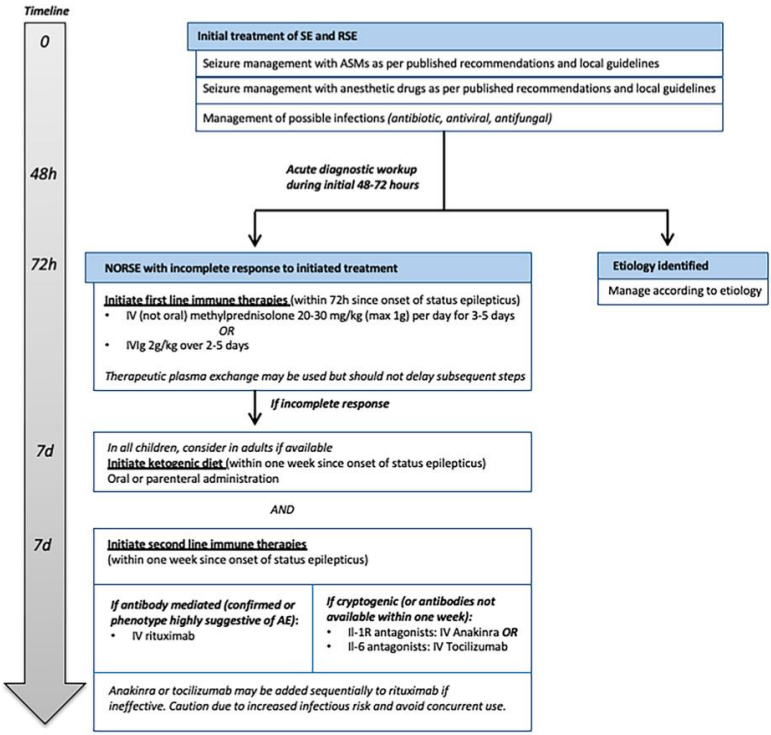

Figure 6: Suggested treatment algorithm for NORSE including FIRES (expert opinion). Adapted from the International Consensus Recommendations for the Management of New-Onset Refractory Status Epilepticus (NORSE) including febrile infection-related epilepsy syndrome (FIRES).

8.7 Emergency Treatment of Other Types of SE

SE can be classified as convulsive or non-convulsive, focal or generalised, and with or without impairment of consciousness. (Table 12) Alternative non-sedative ASMs, 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., epilepsia partialis continua
- NCSE without coma

Table 12: Classification of SE

(A) With prominent motor symptoms
A.1 Convulsive SE (CSE, synonym: tonic–clonic SE)
  A.1.a. Generalized convulsive
  A.1.b. Focal onset evolving into bilateral convulsive SE
  A.1.c. Unknown whether focal or generalized
A.2 Myoclonic SE (prominent epileptic myoclonic jerks)
  A.2.a. With coma
  A.2.b. Without coma
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)
A.4 Tonic status
A.5 Hyperkinetic SE
(B) Without prominent motor symptoms (i.e., nonconvulsive SE, NCSE)
B.1 NCSE with coma (including so-called "subtle" SE)
B.2 NCSE without coma
  B.2.a. Generalized
    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 generalized
    B.2.c.a Autonomic SE

Myoclonic Status

In a hospital setting, anoxic brain damage and acute renal deterioration are the commonest causes of myoclonic seizures and status. 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.

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 a 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 a 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, an 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 aims to prevent 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. The second-line agent should be administered in an adequate dose and fast.

4. Anaesthetic agents should be initiated early with adequate loading doses if first- and second-line treatment fails.

5. Non-anaesthetic agents can be considered especially in those without impairment of consciousness.

6. For those with suspected autoimmune aetiology (NORSE or FIRES) or no other causes identified, early immunotherapy should be considered.

9.0 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

Several reports have demonstrated an increased frequency of menstrual disturbances, fertility problems, polycystic ovaries and hormonal changes in women with epilepsy. The rate of menstrual irregularities among women with epilepsy is usually higher than the normal population and ranges between 20-48%. This can be related to the underlying neuroendocrine dysfunction secondary to the epilepsy itself, seizure frequency, the use of specific ASMs, or the need for polytherapy. The rate of menstrual irregularities is similar regardless of epilepsy type.

Epileptic seizures may influence the release of hormones from the hypothalamic-pituitary-gonadal axis. Women with epilepsy may have low gonadotrophin and oestrogen levels. Patients may have disturbances in luteinising hormone concentration and its 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). Young women with epilepsy are at risk of developing anovulatory menstrual cycles,

hypogonadotropic hypogonadism, polycystic ovarian syndrome (PCOS), hypoandrogenism, premature menopause and functional hyperprolactinaemia. PCOS is one of the commonest causes of menstrual disturbance and has a higher prevalence in patients on valproate as compared to other ASMs. Valproate is an important ASM 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. True catamenial epilepsy is defined as consistent increased or change in the character of the seizures at the same point each month in a regular menstrual cycle. This is thought to be due to the proconvulsant effect of oestrogen. Intermittent clobazam or acetazolamide given during the menstrual period may alleviate catamenial exacerbation of seizures. Hormonal therapy with progesterone supplementation may be an appropriate adjunctive treatment to be given just before the menses (luteal phase) or to stop the menses altogether.

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 ASM, 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 ASM. However, lower reproduction rates among women with epilepsy can also be due to social inhibitions and fear of the effects of epilepsy and treatment on the pregnancy itself.

9.1.4 Contraception

There is an increased risk of oral contraceptive pill (OCP) failure with ASMs that induce hepatic microsomal enzymes (barbiturates, phenytoin, carbamazepine, and oxcarbazepine) (Table 13). 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 ASMs. 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 an enzyme-inducing ASM. 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. The usual recommended

dose for emergency contraception with levonorgestrel is either a single dose of 1.5mg or two doses of 0.75mg taken 12-24 hours apart. However, in women taking enzyme inducing ASM, the dose of levonorgestrel should be increased from a single dose of 1.5mg to a single dose of 3mg to compensate for the reduction in plasma levonorgestrel levels.

Table 13: Antiseizure Medication Effects on Hormonal Oral Contraceptive Pill (OCP)

Liver enzyme inducers – reduce concentration of OCP - Carbamazepine - Eslicarbazepine - Felbamate - Phenytoin - Phenobarbitone - Primidone - Oxcarbazepine - Topiramate
Drugs that are safe to be used with OCP - Gabapentin - Levetiracetam - Lamotrigine - Tiagabine - Sodium valproate - Zonisamide - Lacosamide - Perampanel

9.1.5 Pregnancy

Management of epilepsy in pregnancy can be challenging especially when foetal exposure to ASMs can be associated with a dose-dependent increase in the risk of congenital malformations and neurocognitive deficits. This risk must be balanced against the need for seizure control, as the effect of poor seizure control will affect the well-being of both the mother and foetus.

Most women with epilepsy maintain good seizure control throughout pregnancy. The European and International Registry of antiepileptic drugs in pregnancy (EURAP) reported that about 66.3% of pregnant women with epilepsy remained seizure-free throughout their pregnancies. Among the 3806 pregnancies observed, 70.5% of patients had no change in their seizure frequency during the 2nd and 3rd trimesters compared to the 1st trimester. Only 15.8% of pregnant women had worsening of their seizure frequencies and these women were on lamotrigine and oxcarbazepine. Pregnant women with epilepsy have a higher chance of remaining seizure-free throughout pregnancy if they are able to achieve seizure freedom 9 months prior to being pregnant. 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 the dosage of ASM therapy and vomiting may also contribute.

Maternal death from epilepsy is about 10-fold higher (100 per 100,000) compared to pregnant women without epilepsy, and SUDEP is one of the major causes of death. Focal seizures that do not evolve into GTCS is less likely to be harmful. GTCS can lead to hypoxia and lactic acidosis and can be transferred to the baby leading to asphyxia. There are only anecdotal reports of miscarriage following GTCS. There is also risk of trauma to the foetus during a 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 14). 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 offers a lower rate of seizure recurrence, pneumonia, assisted ventilation, and mortality as compared to standard ASMs. It is also safer for the developing foetus.

The serum concentration of most of the standard ASMs often fall during pregnancy, particularly in the first and third trimesters due to several factors including pharmacokinetic alteration during pregnancy, increased volume of distribution, elevated renal clearance and induction of hepatic metabolism. Pregnancy has been shown to significantly increase the elimination of some of the newer ASMs, e.g. lamotrigine, levetiracetam and oxcarbazepine metabolite. Lamotrigine clearance increment over baseline during pregnancy can range from 65%-230%, peaking in the second and third trimesters. The EURAP study group also reported a higher risk of GTCS in pregnant mothers on oxcarbazepine monotherapy compared to other regimens but the sample size was small. Dose increment should be considered if there is an increase in seizure frequency. Serum levels of commonly used ASMs in pregnancy, including lamotrigine, oxcarbazepine and levetiracetam, if available, should be monitored closely during pregnancy to prevent decrease by more than 35% from preconception baseline. However, dose adjustments should not be based on ASM concentrations alone. Moreover, not all centres provide facilities to check drug levels. Other factors such as seizure frequency, drug tolerance and interactions with other medications, especially in polytherapy, should be taken into consideration too.

Table 14: Special Causes of Epilepsy Developing in Pregnancy

Special causes of epilepsy developing in pregnancy
• Enlarging meningioma • Enlarging arteriovenous malformation • Ischaemic stroke • Cerebral venous or venous sinus thrombosis • Vasculitides • Subarachnoid haemorrhage • Eclampsia

Women on ASMs should be monitored throughout pregnancy to detect foetal malformations. Recommended investigations are listed in Table 15.

Table 15: 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

Ideally, women should be advised against getting pregnant until they become seizure free and are off ASMs. 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 ASMs and the risk of recurrent seizures if ASMs 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 ASM

withdrawal is impossible, efforts to achieve monotherapy and the lowest effective dose should be attempted before conception. Switching to a less teratogenic ASM should be done before conception; switching during pregnancy is likely to be less useful because most teratogenic effects take place in the first trimester. Moreover, the risk of seizures is high in patients during drug tapering process. For the aforementioned reasons, contraception should be practiced until ASM adjustment is achieved.

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 ASMs 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 focal seizures do occur during labour, a caesarean section is indicated. An elective caesarean section is also recommended if frequent 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 ASMs (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 until 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 major foetal malformations (MCM) is 4-8% if one ASM is taken (compared with 1-3% in the general population) and 15% if more than one ASM is taken. MCMs are defined as an abnormality of an essential anatomic structure present at birth that interferes significantly with function and/or requires major intervention. The reported teratogenic effects of commonly used ASMs are summarised in Table 16.

Studies on MCM 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 MCM, either as monotherapy or polytherapy, followed by phenobarbitone and topiramate. Valproate doses of $\geq$ 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 MCM. Prenatal exposure to valproate has been associated with an increased risk of autism spectrum disorder.

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 MCM.

The lowest risks of MCM are reported in patients taking lamotrigine and levetiracetam (2% and 2.4% respectively, compared to 1.1% in the normal population). Infants exposed to levetiracetam or lamotrigine during pregnancy experience an MCM risk similar to that seen in infants unexposed to ASM. 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 MCM 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 childbearing potential whenever possible unless attempts to control seizures with other ASMs have failed. If valproate is used, the lowest dose is recommended, e.g. ≤700 mg daily. Levetiracetam and lamotrigine would be the recommended ASMs 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 ASMs e.g. oxcarbazepine, brivaracetam, lacosamide, zonisamide and perampanel are limited by the small sample size. The EURAP registry reported a MCM risk of 3% associated with oxcarbazepine. Data from the UK and Ireland pregnancy registers reported a MCM risk of 13% in the zonisamide monotherapy group compared to 6.9% in the polytherapy group in pregnant women with epilepsy. The NAAPR registry data showed an association between zonisamide and exposure and low infant birth weight compared to infants exposed to lamotrigine prenatally. Animal studies might enable us to predict the teratogenic potential of newer ASMs.

In summary, the MCM prevalence rate is highest with valproate, moderately high with topiramate and phenobarbitone, intermediate with carbamazepine, oxcarbazepine and phenytoin, and lowest with levetiracetam and lamotrigine. Polypharmacy results in higher prevalence rates of MCMs, particularly when the polytherapy includes valproate or topiramate.

The beneficial role of folic acid in the prevention of major congenital malformation in newborns of women taking ASMs is still uncertain. Folic acid (Vitamin B9) is essential in DNA repair, cell division and normal cellular growth. Treatment with cytochrome P-450 enzyme-inducing antiseizure medications and valproate are known to interfere with folate

metabolism. In addition, low blood folate in pregnancy has been associated with spontaneous abortion and developmental anomalies. Recent evidence-based review concluded that folic acid supplementation is possibly effective and should be recommended for all women of child-bearing age taking ASMs, starting before conception, at a dose of at least 0.4 mg – 4 mg daily.

Table 16: Teratogenic Effects of ASMs

ASM	Reported major teratogenic effects
Phenytoin	Cleft lip and palate, cardiac defects; craniofacial defects, digital hypoplasia. Recent evidence suggests no increased risk if used as monotherapy
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	No increased risk

Cognitive teratogenesis has been highlighted in the recent Neurodevelopmental Effects of Antiepileptic Drugs 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 years 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 ASMs, 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".

Hitherto, the package insert has been approved by several regulatory agencies, including the *European Medicines Agency* (EMA), *The Medicines and Healthcare Products Regulatory Agency,* United Kingdom (UK MHRA) and *Therapeutic Goods Administration* (TGA), Australia.

In December 2018, the National Pharmaceutical Regulatory Agency (NPRA), Malaysia, approved this new package insert. However, sodium valproate can still be prescribed for epileptic women **only if there is no suitable alternative medicine available** to treat the patient and the conditions of the pregnancy prevention programme are met. Guidelines on the use of sodium valproate in women of childbearing potential were developed by the Epilepsy Council, MSN, in 2020 and can be downloaded from the MSN website (under "Resources" - **Expert Opinion on the Treatment Approach of Epilepsy**: **Valproate Use in Women of Childbearing Potential**)

All female patients who are considering sodium valproate therapy must be informed about the following:

- There is a risk of congenital malformations and neurodevelopmental problems in children whose mothers are exposed to sodium valproate during pregnancy.
- Pregnancy testing is required before starting sodium valproate and throughout treatment, as necessary.
- The use of effective contraception during the entire duration of treatment is important.
- Consult a doctor if they are planning for pregnancy.
- Continue taking sodium valproate even when pregnancy is suspected or already pregnant, and immediately see their doctor.
- Ensure they have received educational materials (e.g. patient card and patient information leaflet).

If sodium valproate is required for the patient and other treatment options are ineffective or not tolerated, please ensure the following:

- Treatment should only be initiated after pregnancy has been excluded (negative pregnancy test).
- Sodium valproate should be prescribed as monotherapy and at the lowest effective dose. A prolonged release formulation is recommended to avoid high peak plasma concentrations and the daily dose should be divided into at least two single doses.
- Annual review should be carried out, and ad-hoc treatment review conducted when required. The benefit and risk should be carefully reconsidered during every treatment review.

- When patient is planning for pregnancy, all efforts should be made to switch to appropriate alternative treatment at least 6 months prior to conception, if possible.

- If sodium valproate must be used during pregnancy, prenatal monitoring is recommended to detect any malformations.

9.1.9 Breast-Feeding and the Puerperium

Breast-feeding for most women on ASM is generally safe. The dose of the ASMs 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. ASM secretion in breast milk is inversely proportionate to the extent of protein binding. Hence ASMs 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 ASMs 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. Table 17 illustrates the safety of different ASMs during breastfeeding.

Table 17: Safety of ASMs during Breastfeeding

Considered safe	Carbamazepine Phenytoin Valproate
Moderately safe	Gabapentin Lamotrigine Levetiracetam Oxcarbazepine Pregabalin Tiagabine Topiramate Vigabatrin
With possible side effects for infants*	Benzodiazepines Ethosuximide Felbamate Phenobarbitone Primidone Zonisamide

*Side effects may include sedation and poor infant weight gain.

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 ASMs; aim for minimal effective monotherapy if active epilepsy; consider drug withdrawal if seizure free
- Commence preconception folic acid supplementation
- Screen for malformations
- Monitor condition and ASM concentrations throughout pregnancy (refer to section 9.1.5)
- Vitamin K1 in the 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 seizures 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.

KEY MESSAGES

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

9.2 Epilepsy in Children

9.2.1 Epidemiology

The incidence of epilepsy is highest in the infantile period of all age groups with an estimated incidence of 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, whereas it generally peaks in adolescence and early adulthood in developing countries . Paediatric epilepsy is distinct from adult epilepsy and consists of highly variable with age-related electroclinical epilepsy syndromes. The aetiology also differs in children. The highest incidence of idiopathic or genetic epilepsy has its onset in childhood. Strokes and tumours are not common 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 a child with a possible seizure disorder is to take a thorough accurate history and whenever possible to review home video-recordings to confirm if the events are actually epileptic seizures rather that 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 children may manifest a single epilepsy syndrome or evolve through several epilepsy syndromes as their seizure characteristics change with brain maturation.

Electroclinical 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 electroclinical syndromes. An important paediatric electroclinical syndrome that needs to be recognised is the developmental and epilepsy encephalopathies as aggressive seizure treatment may potentially improve their cognitive outcomes. In children with epilepsy, it is important to attempt to make as accurate an electroclinical syndromic diagnosis as possible, to guide further investigations, appropriate counselling and treatment recommendations. If electroclinical syndrome classification is not possible then the clinician should classify according the seizure type whilst always considering the 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 frequently epileptic include generalised myoclonic jerks, clonic jerking of limbs particularly if it is associated with autonomic features and tonic eye deviation, focal tonic seizures, rhythmic clonic thrusting of tongue (especially if associated with other clonic movements of limbs) and spasms. Movements that are not likely to be epileptic include tremors or jitteriness, clonus (as opposed to clonic jerking) whereby clonus of part of the body is evoked by sudden passive movement of the relevant joint and stopped if the position of the relevant joint is changed or the body part is released), myoclonus in sleep, dystonia and excessive startle. It is important to note that GTCS do not occur in neonates due to incomplete brain myelination.

Seizure semiology in neonatal epilepsies may be poorly defined and masked by antiseizure treatment. Neonates with epilepsy will usually have clinically apparent seizures in contrast with neonates with acute symptomatic seizures, who are more likely to have subclinical electrographic seizures. In some circumstances certain electroclinical features can be typical for certain genetic causes like neonates with *KCNQ2* mutation often have migrating epilepsy with seizure semiology of alternating laterality. When there is diagnostic doubt of whether a neonatal movement is epileptic or not, clinicians should consider EEG with surface limb EMG whenever possible for confirmation. Apart from trying to capture ictal events, the EEG background can also be helpful in classifying the epilepsy syndrome with a well-organised background indicating a benign self-limiting epilepsy in contrast to a disorganised and dysmature EEG background indicating a more severe epilepsy syndrome.

Neonatal epileptic seizures are often acute symptomatic seizures provoked by an underlying condition; examples include hypoxic brain injury, hypoglycaemia, electrolyte imbalance or cerebral infections. A smaller number of neonatal epileptic 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 seizure. In comparison neonates presenting with seizures after 48 hours of life 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 guided by the likely differential diagnoses.

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 ASMs given the potential side effects of treatment. Animal studies have shown that many ASMs are associated with apoptotic neurodegeneration which may have potential long-term effects on the developing brain. ASMs should be used if epileptic seizures are recurrent. Currently, phenobarbitone remains to be the first line of treatment 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 ASMs like levetiracetam and topiramate are also increasingly being used as 2nd or 3rd line ASMs. Large doses of BDZ 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 epileptic seizures refractory to first line ASMs. This includes a trial of intravenous or oral pyridoxine and if no response is seen, a trial of oral pyridoxal phosphate. Treatment with biotin and folinic 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 Antiseizure Medication Therapy

Treatment should be started only after the diagnosis of epilepsy is certain. There is no indication for initiating ASMs for simple childhood febrile seizures. Choosing the most appropriate ASM depends on the seizure type, epilepsy syndrome and underlying co-morbidities. In children with associated motor, behavioural, sleep and feeding problems, care must be taken not to use an ASM which 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 as first line treatment for infantile spasms that are not due to tuberous sclerosis. Vigabatrin is the recommended first line treatment in children with tuberous sclerosis. Treatment of infantile epileptic encephalopathies should be considered with rapid introduction of incremental ASM doses. There are established guidelines including the NICE UK and ILAE guidance on the recommended ASMs for specific paediatric epilepsy syndromes.

Age has an effect on ASM pharmacokinetics. Neonates tend to eliminate ASMs slower than children of any other age groups. In addition, birth asphyxia, a common cause of neonatal seizures, may be associated with hepatic and renal dysfunction which also retards drug elimination. After the neonatal period, the rapid growth of children results in higher ASM clearance and larger within–group variability in elimination kinetics. Recommended doses based on 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 lowered levels of ASMs are found in older children, these are more likely to be due to poor compliance or drug interaction than pharmacokinetic changes.

Some ASMs have specific adverse effects in children that are not common in adults. Sedative ASMs like phenobarbitone and benzodiazepines may cause irritability and hyperactive

behaviour in young children. Clonazepam and related ASMs 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 ASMs; 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 seen to be less common in young children. Levetiracetam may cause behavioural disturbance and hyperactivity in children.

ASM-induced seizure aggravation is also known to occur with specific epilepsy syndromes. The idiopathic generalised epilepsies are particularly prone to seizure aggravation or onset of a new seizure type with ASMs like carbamazepine, vigabatrin, tiagabine and gabapentin. In Dravet syndrome, there is a nearly constant aggravating effect with lamotrigine.

As the childhood period is a crucial phase of bone mass development, long-term ASM treatment is a significant risk factor for impaired bone health and vitamin D deficiency. Vitamin D supplementation and recommendation of healthy sunlight lifestyle exposure behaviour should be given to children with epilepsy on long-term ASMs particularly to those with high risk of having vitamin D deficiency.

9.2.5 Non-ASM Drug and Non-Pharmacological 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 folinic acid represent the treatment of choice.

For children with DRE (children who have failed 2 trials of appropriate ASMs), other non-ASM therapeutic options exists which can be very effective in selected children. Epilepsy surgery needs to be considered in all of these children particular those with focal-onset epilepsy and unilateral structural brain abnormality. In appropriately selected candidates; epilepsy surgery can achieve up to 60-70% seizure freedom (see Chapter 7).

Regardless of age, seizure type or aetiology, the ketogenic diet can result in seizure freedom in 10-15% of children and more than 50% would experience worthwhile seizure reduction. It should be offered to children with DRE particularly those who are not epilepsy surgical candidates. The diet is the treatment of choice for two distinct disorders of brain energy metabolism (GLUT 1 deficiency and pyruvate dehydrogenase deficiency) and may be useful for particular epilepsy syndromes like SMEI, MAE, 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 the major issues of 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.

Other non-lesional epilepsy surgeries for children who are not candidates for focal resection should also be considered they can also markedly reduce seizure burden. These include callosotomy for children with drop seizures and VNS. VNS has been shown to result in meaningful seizure reduction in 30 – 50% of children with DRE.

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 ASM treatment. Approximately 20% of children show pharmacoresistance to multiple trials of ASMs and would be considered to have DRE. The most significant predictor of pharmacoresistance epilepsy is the presence of neuroimaging abnormality particularly cortical dysplasia and mesial temporal sclerosis, and such children should have a comprehensive epilepsy evaluation for possible epilepsy surgery. Other predictors include: symptomatic generalised epilepsy, neonatal seizures, intellectual disability, high initial seizure frequency or failure to respond to ASM 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 period for ASM therapy is until the patient has been seizure free for two years.

Uncontrolled seizure onset in early childhood is 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 are a vital but often neglected aspect of management. Once the diagnosis of epilepsy is made, an explanation of what epilepsy and seizures are, as well as its inheritance (if any), and prognosis is necessary. Treatment considerations (purpose and objectives, compliance and dosing schedule, possible adverse effects, concurrent use with other medication 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 disturbances. In addition, behavioural disorders (e.g. attention deficit hyperactivity disorder and autism spectrum disorder) and learning difficulties can also occur among children with epilepsy. Proper counselling, routine behavioural health and cognitive screening, recognition of potential comorbidities and advice for both child and family goes a long way towards improving the quality of life in these children.

Mortality in epilepsy, in particular SUDEP, whilst it may be possibly a sensitive topic, should be discussed with families of children with epilepsy as the vast majority of families would prefer to know about the child's risk of SUDEP. SUDEP is death in a patient with epilepsy not due to accident, drowning, status epilepticus, or other identified cause, but there may be evidence of a concurrent seizure that is unwitnessed and often the patient is found in bed. The overall incidence of paediatric SUDEP is 1 in 4,500 children per year which is much lower than the incidence in adults of approximately 1 in 1,000 per year. The main risk factors associated with SUDEP are frequent (3 or more) GTCSs per month, nocturnal convulsive seizures, and poor medication compliance. The SUDEP risk is lower for benign self-limiting epilepsy syndromes.

Schooling and leisure activities also need to be discussed. The need for good communication between the school teacher, 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 are 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 is required for recreational activities including aquatic sports, sports involving high heights (eg: abseiling, mountain climbing) and cycling. Please refer to epilepsy websites (e.g. Epilepsy Action UK, Epilepsy Action Australia) for further information on lifestyle advice.

9.3 Epilepsy in the Elderly

Epilepsy is the third most common neurological disorder in older people (aged >65 years) after stroke and dementia. An epilepsy prevalence of 5.4 per 100 people in older populations was stated in the Global Burden of Disease report. Approximately 24% of new-onset epilepsy occurs after age 60. New-onset epilepsy in the elderly is mainly the consequence of accumulated injuries to the brain and other secondary factors. The most common cause of seizures and epilepsy in older people is cerebrovascular disease, which accounts for more than a third to half of the cases. Brain tumors (primary or metastatic) may account for 10-30% of new cases. Neurodegenerative disorders, particularly Alzheimer's disease and amyloid angiopathy, represent another common aetiology, with up to 10-20% of people with AD developing epilepsy. Focal-onset impaired awareness seizures remain the most common semiology, likely driven by the development of new focal lesions. Extratemporal lobe epilepsies are more common than in the younger population.

9.3.1 Diagnosis of Epilepsy

The diagnosis of epilepsy is a clinical decision, but in older people this can be more challenging. Most seizures in this group are focal in origin and often do not conform to a typical presentation. In older people, most seizures are of extratemporal onset, diverse in semiology, and convulsions are relatively rare. Paroxysmal confusion or episodes of behavioural arrest in an older adult should always lead to suspicion of non-convulsive seizures. Multi-comorbidity and polypharmacy are the norm in the older age group and present a further diagnostic challenge. Cardiac arrhythmias can present with seizures in this age group and conversely, seizures could present with autonomic disturbance and cardiac dysrhythmia. Similarly, epilepsia partialis continua might be confused with an involuntary movement disorder, and the rare paroxysmal sensory epilepsy is often labelled as recurrent transient cerebral ischaemia. Postictal paresis (also known as Todd's paresis) can persist for days and is often misinterpreted as a new stroke. Dissociative seizures might also present de novo in later life but non-epileptic attacks are more likely to have a physiological rather than a psychological basis in older people. Reviewing video clips of events can be helpful. Carers, partners, family members, or other people directly involved with the older person should, within the limits of safety, attempt to record the events.

Diagnostic evaluation: EEG remains the cornerstone for diagnosis. The diagnostic yield of a routine EEG maybe lower in the elderly because definite epileptiform activity is less common, and more non-specific EEG abnormalities are frequently seen. Brain imaging is necessary in new-onset epilepsy in the elderly to investigate for both explanatory aetiologies, such as stroke or tumor, and potentially reversible causes, such as a subdural hematoma. MRI is preferred over CT for its ability to visualise subtle changes or abnormalities within the brain tissue.

Management of seizures: The mainstay of management for older people with epilepsy is ASM. In comparison to young adults with epilepsy, older people are more likely to benefit from ASMs in terms of seizure control, although they might also be more prone to potential side-effects. Treatment with ASMs after a single seizure would seem reasonable in some cases, particularly as the potential risk from seizures in older people can be greater (e.g. prone to fractures, bruising and haemorrhage especially if they are also on anticoagulants). In general, in older people the initial dose and rate of titration of ASM is half that used in younger individuals, which aids with tolerability. The treatment dose required might also be half that normally prescribed to those younger than 65 years. The choice of an appropriate ASM in older people is more restricted than for younger people, owing to potential side effects and interactions with concomitantly taken medications. For example, older ASMs such as carbamazepine and phenytoin, should probably be avoided owing to their effects on bone health, lipid metabolism, balance, and their propensity to enzyme induction. Given its favourable pharmacological profile and low potential for drug interactions, levetiracetam can be a beneficial drug for older people.

Candidates for long-term ASM therapy include patients with recurrent seizures, onset of epilepsy presenting as status epilepticus, or a clear structural predisposition for seizures. In general, it is advisable to "start low and go slow" with one ASM. Results from the Veterans

Affairs Cooperative Study on the effects of age on epilepsy and its treatment indicate that compared with younger adults, older adults appear to be more responsive to ASM therapy. However, they are also more likely to experience side effects at lower serum ASM concentrations. Consequently, older adults usually require lower dosages and longer dosing intervals.

Epilepsy Surgery: Older people with drug-resistant epilepsy are less likely to undergo surgery, which might reflect patient choice, physician choice, or both. Despite a possible bias towards publication of positive results, overall, the studies show that resective epilepsy surgery can be effective and is usually safe in carefully selected older individuals.

9.3.2 Specific Epilepsy Syndromes in Older People

1. Dementia-associated epilepsy:
   Dementia, notably Alzheimer disease, is a common cause of epileptic seizures in older age. In people older than 65 years, those with Alzheimer disease are up to 10 times more likely to suffer from epileptic seizures than those without dementia.

2. Transient epileptic amnesia:
   Transient epileptic amnesia is an episode of amnesia associated with an epileptic seizure, which frequently lasts less than an hour. It is predominantly observed in men older than 65 years. Specific characteristics include seizures being more frequent on awakening, repetitive questioning, and a residual incomplete amnesia of the event itself (being able to remember not being able to remember). About 40% of people with transient epileptic amnesia have olfactory hallucinations. Transient epileptic amnesia is distinguished from transient global amnesia by the recurrent nature of stereotypical events.

3. Antibody-mediated epilepsy:
   The clinical manifestations associated with antibody-mediated disease are becoming progressively more pleomorphic but people with autoimmune epilepsy tend to present with a combination of seizures coupled with cognitive and behavioural changes. Certain well defined phenotypic features have also emerged. Anti-LGI 1 antibodies can be associated with characteristic faciobrachial dystonic seizures. Delayed-onset dyskinesia is observed in anti-NMDAR syndromes and myoclonus in anti-glycine receptor antibody disease.

9.4 Social Issues in Epilepsy

The psychosocial impact of epilepsy is significant and varied among the people with epilepsy (PWE). 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 for PWE. Healthcare professionals have the role in educating the public and their patients, besides medically managing the PWE. On the other side, PWE should be empowered to understand their illness and equip themselves with reliable information.

Education and driving are discussed in chapter 5 of these guidelines.

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. This finding could just reflect the tip of the iceberg, given that this study was carried out in a single tertiary centre. However, despite having uncontrolled seizures, a systematic review reported that 58% were still able to have full-time employment. Although clinical factors have been frequently reported to be associated with unemployment, psychological and social factors also play important roles.

9.4.2 Approach to Employment Issues

Epilepsy and ASMs are major factors leading to unemployment. Seizure freedom, which is the ideal goal for epilepsy treatment, is associated with good quality of life. However, these are only achieved in 60% of PWE treated medically.

Cognitive, behavioural and affective side effects due to ASMs may occur, affecting the individual's ability to work and blend into the society. Hence, a balance between seizure control and minimisation of the side effects of ASM should be the aim.

PWE may also have 'de novo' psychosocial issues, apart from those due to ASM. These include low self-esteem, poor coping style, maladapted health belief and low self-efficacy. Often these are aggravated by poor family support and stigma especially at the workplace. These psychosocial difficulties are non-revealing most of the time, because of the perceived associated stigma and shame. Therefore, healthcare providers should actively look out for this during each encounter with PWE.

It is essential to develop a multifactorial assessment and individualised intervention with the aim of increasing employability in PWE.

9.4.3 Disclosure in Workplace

There is NO law that requires PWE to disclose their diagnosis to their employers, and this needs to be done on a voluntary basis. It is not necessary to disclose the diagnosis if the epilepsy is well controlled and the workplace has a low risk of injury. On the contrary, if the epilepsy control is under-optimised and the risk of injury at the workplace is high, then he or she should be encouraged to disclose the diagnosis.

Unfortunately, it is known that disclosure of the diagnosis of epilepsy may lead to failure in securing a job and unjustifiable work dismissal due to stigma. Unnecessary restriction can be minimised with proper recommendations and engaging in frequent dialogues with the employees' union, employers, and the public.

9.4.4 Occupational Hazard and Recommendations

The magnitude of the occupational hazard among PWE will depend on both individual factors and the nature of the work. Absolute rules in employment for PWE are not available in our local setting. Similar rules in driving (Chapter 5) can also be applied to employment. Patients in seizure remission or have only nocturnal seizures should be treated as normal individuals. High-risk jobs such as working with machinery, chemicals and heights should be avoided for PWE with impaired awareness seizures. Patients with preserved awareness during their seizures should be counselled on the nature of their work on a case-by-case basis. Jobs that require shift work, e.g. security guard, are not recommended due to sleep disruption that may cause breakthrough seizures. Work modification, like changing to a lower occupational hazard setting and working during 'office hours' can be negotiated, but prior consent by the PWE is required.

Besides seizure control and types of seizure, medication side effects and intellectual ability should always be taken into consideration when choosing a suitable job. The most appropriate choice of job is essential to avoid frustration and stress among PWE.

9.4.5 Stigma and Discrimination

People with epilepsy are burdened multiple social, psychological and economic consequences of stigmatisation, which lead to poor quality of life. Social stigma in epilepsy is a universal issue, and it is profound especially in lower- and middle-income countries, like Malaysia.

Recently, the International Bureau for Epilepsy (IBE) and International League Against Epilepsy (ILAE) have intensified the fight against the stigma attached to epilepsy through international collaboration in increasing public awareness about this stigma.

Three types of stigmas have been identified by the IBE/ILAE:

1. Internalised stigma- arising from within PWE

2. Interpersonal stigma- arising from relatives, healthcare providers, employers, and colleagues of PWE

3. Institutional stigma – unfair laws restricting the freedom of PWE in common areas such as transportation and employment

Tackling stigma in epilepsy warrants collective efforts from every stakeholder; and does not end with PWE and their social circles. All nations, of different income status should cooperate and figure out a common ground in tackling these psychosocial problems plaguing PWE.

9.4.6 Lifestyle and Leisure

PWE should maintain a healthy lifestyle as well as active social life including sports and leisure. Any deviation from the norms should be identified and dealt with proactively. Recreational drugs, alcohol and sleep deprivation might aggravate seizures and should be avoided.

9.4.7 Sports

Many PWE do not participate in sports, and caregivers often discourage epilepsy patients from participating in sports, due to excessive, often unfounded fear. Steinhoff *et al*. reported that among PWE, 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.

9.4.8 Sexual Life in Epilepsy

Sexual dysfunction can be a significant but often hidden issue in up to 20% of PWE. The problem is multifactorial, and is related to poor seizure control, temporal lobe epilepsy, interaction between enzyme inducing ASMs 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.

9.4.9 Malaysian Epilepsy Society & Epilepsy Resources for PWE (The Lay Person)

Interaction among PWE will enable the sharing of experiences and emotions and promote patient-initiated support. PWE may find it more comfortable to disclose and share their problem with their peers who are in a similar situation.

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 their Facebook - “Malaysian Society of Epilepsy (Persatuan Epilepsi Malaysia)”.

Some reliable resources for PWE- the lay person, include the following:

- The International League Against Epilepsy (ILAE) official website
- International Bureau for Epilepsy (IBE) official website
- The Epilepsy Foundation official website

9.5 Special Medical Conditions

Many PWE may have a comorbid medical condition at some point during their life time. This includes general medical, surgical and or psychiatric conditions.

The following is a brief list of a few of the medical conditions that are seen quite often in PWE:

- Stroke
- Migraine
- Diabetes
- Infections
- Neoplasia
- Musculoskeletal system disorders
- Gastrointestinal and digestive disorders
- Respiratory disorders
- Chronic pain disorders
- Arthritis/rheumatism
- Obesity
- Fractures
- Allergies
- Alcoholism
- Drug abuse
- Trauma

Multiple causal models have been envisaged to explain the co-occurrence of epilepsy with other medical conditions. The three most common are: first, epilepsy itself (or its treatment) causes the comorbid condition(s); second, the comorbid condition (or its treatment) leads to epilepsy; or third, a shared underlying mechanism (biological and/or environmental factors) mediates the occurrence of both epilepsy and the comorbid condition(s).

A few of the co-morbidities needing special attention while treating the seizure are discussed below:

9.5.1 Stroke

Seizure after stroke or post-stroke seizure (PSS) is a common complication of stroke. It can be divided into early seizures (< 2 weeks) or late seizures (> 2 weeks) depending on the time to seizure onset after the stroke. Post-stroke epilepsy (PSE) is diagnosed by the occurrence of two or more seizures with a greater than 60% risk of a subsequent seizure occurring in the next decade after a stroke. It has been reported that ischaemic and haemorrhagic stroke accounts for about 11% and 45% of all PSE. Risk factors for PSE include age less than 65 years, stroke severity measured by the National Institutes of Health Stroke Scale (NIHSS), cortical involvement, and genetic factors such as TRPM6 polymorphism.

In the early phase following an ischaemic or haemorrhagic stroke, EEG is an essential diagnostic tool that aims to detect electrographic seizure activity which can serve to predict the occurrence of overt epilepsy later.

Patients with their EEG showing periodic lateralized and bilateral independent periodic lateralized epileptiform discharges are prone to a higher risk of developing post-stroke seizures. Continuous EEG for at least 24-48 hours should be undertaken when non-convulsive seizures are suspected.

ASM, however, is not recommended routinely after stroke for the prevention of seizures. It is generally accepted that ASM should be started after the second early epileptic seizure and the first late epileptic seizure to prevent recurrence. Either the earlier classic ASMs (carbamazepine, valproate, phenytoin, and phenobarbitone), or the newer ASMs (lamotrigine, topiramate, levetiracetam, and oxcarbazepine) can be used for patients with post-stroke epilepsy.

9.5.2 Migraine

Epilepsy and migraine often tend to co-occur. The underlying pathogenesis for both conditions is common with a high degree of neuronal excitement coupled with ion channel abnormalities. Similarly, in terms of treatment many ASM are helpful in controlling/ preventing migraine attacks. Shared genetic susceptibility has also been identified in both these conditions. Specific subtypes of epilepsy (childhood epilepsy with occipital seizures) and SeLECTS and migraine (familial hemiplegic migraine) have been linked to genetic mutations in CACNA1A, ATP1A2 and SCN1A on chromosome 17.

9.5.3 Trauma

An epileptic seizure that occurs as a direct sequel to traumatic brain injury (TBI) is referred to as post-traumatic seizure (PTS). Depending on when the first seizure occurs, they are classified as immediate (soon after TBI), early (within 7 days post-TBI) or late (after 7 days). Post traumatic epilepsy (PTE) on the other hand refers to the much later occurrence of unprovoked seizures, usually about one to three months following the TBI, and in some cases may be delayed up to 2 years or even more. If such unprovoked seizures do not occur within 3 to 5 years following the TBI, the chances of remaining seizure-free thereafter is given as 95 %.

The rationale behind seizure prophylaxis with an ASM during the acute phase of moderate–severe TBI is that the incidence of early PTS is as high as 14%. Phenytoin or levetiracetam significantly reduces the incidence of early PTS and is recommend for the first 7 days after severe TBI. Levetiracetam has demonstrated comparable efficacy to phenytoin and is associated with fewer adverse effects. Prolonged prophylactic ASM following TBI does not help in preventing PTE occurring later on. For those TBI patients who develop PTE at a later date, long term ASM becomes necessary as in any other case of epilepsy.

9.5.4 Interaction of ASM with Common Metabolic Disorders

9.5.4.1 Liver Disease

Effective ASM in hepatic diseases requires special attention to drug pharmacokinetics. In hepatic dysfunction, the impaired cytochrome P450 metabolism and the low albumin binding affinity from hypo-albuminaemia can increase the free ASM 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, 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 ASMs in liver diseased states.

9.5.4.2 Renal Disease

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

9.5.4.3 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 atrio-ventricular block. Valproate, levetiracetam and benzodiazepine appear safer and are good alternative drugs. In long-term ASM treatment, carbamazepine, oxcarbazepine, and phenytoin should be used with caution in patients with heart disease and should be avoided in the event of atrio-ventricular conduction dysfunction. The newer ASM are preferred in patients with concomitant heart disease because interaction with drugs that are commonly used in heart disease (anti-platelets, anti-arrhythmics, anti-hypertensives, oral anticoagulants, diuretics, digoxin and lipid lowering agents) is less likely.

9.5.4.4 Thyroid Disease

Enzyme-inducing ASMs such as carbamazepine, phenytoin, barbiturates, and oxcarbazepine, influence thyroid hormone metabolism and may reduce the levels of free and total thyroxine. This has to be borne in mind while treating patients with hypothyroidism who are on replacement therapy. Valproate can also cause a subclinical, reversible increase in TSH. However, clinically relevant thyroid dysfunction due to ASMs is rare.

9.5.4.5 Organ Transplant

The possible presence of hepatic and renal dysfunction as well as pharmacological interactions between enzyme-inducing ASMs (carbamazepine, phenobarbitone, phenytoin) and immunosuppressive drugs need to be addressed. Enzyme-inducing ASMs can lower plasma levels of cyclosporin, tacrolimus, sirolimus and corticosteroids. Cyclosporin binds largely to plasma proteins and hence can increase the free fraction of ASMs with high protein binding affinity. Azathioprine, mycophenolate and muromonab-CD3 are not significantly affected by ASMs. 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 seem suitable for liver transplantation patients; whereas benzodiazepine, lamotrigine, valproate are appropriate for kidney transplantation patients and gabapentin, levetiracetam and topiramate are more appropriate in bone marrow transplantation.

9.5.4.6 HIV/AIDS

ASM and antiretroviral (ARV) co-administration may be necessary in people with HIV/ AIDS taking ARVs. It is presently unclear whether ASM dosage adjustment is necessary when ASM and ARVs are both being taken by these patients. Pharmacokinetic interactions leading to lowering of ARV may result in virologic failure and this has clinical implications for disease progression and development of ARV resistance. Non-enzyme inducing ASMs that are not metabolised in the liver and newer ASMs such as levetiracetam, pregabalin, gabapentin and topiramate are therefore preferred.

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 aetiogenesis of epileptic seizures and epilepsy syndromes. New ASMs have been developed and new surgical procedures introduced, including implantable devices. The choice of ASM must be tailored to the individual patient. Other than age, gender, child-bearing potential, the epilepsy syndrome and psychosocial factors of the patient, and pharmacogenetics may also influence the choice of ASM. Although the differential diagnosis of epilepsy remains broad, we are now more confident in diagnosing non-epileptic attack disorders (psychogenic non-epileptic seizures). Correct diagnosis of the epilepsy syndrome will guide the physician in selecting the necessary 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 ASMs is not fully understood, but these drugs have proven efficacy in large randomised trials, albeit as add-on therapy in DRE. It is now clear that greater efficacy in comparison with the older ASMs is unlikely to be the reason for the change in clinical practice, but rather the improved safety and tolerability profile of the newer ASMs. 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 ASMs 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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APPENDIX

EPILEPSY CLERKING CHECKLIST

Patient Demographics

Age:
Age at onset of current seizure(s):
Gender:

Chief Complaint (Obtain a detailed description of what the patient and/or witnesses observe during the seizures / video recording from patient/ witnesses)

History of Present Illness

1. Type of Seizure or Seizures (if more than one type are present):
   It is important to ask about other seizure types because if not asked, the patient may not volunteer this information)

   Focal:
   - Aware or Impaired Awareness:
   - Motor onset (tonic/clonic/myoclonic/dystonic)
   - Non motor onset (sensory / cognitive /emotional/ autonomic / behavioural arrest)

   Generalized seizures:

   Ictal Phase (describe in detail):

   Postictal Phase (describe in detail):

   Aura: Ask if the patient experiences any warning signs before the seizure.

   Seizure Duration: Note how long the seizures last.

   Postictal State: Inquire about confusion, fatigue, or other symptoms after the seizure.

   Current seizure control (frequency per month) according to seizure type:
   - Date of last attack
   - Longest seizure free interval since onset of epilepsy:

   Attacks during sleep:

2. Triggers: Yes/No/Unknown

   - Sleep Deprivation
   - Stress
   - Alcohol or Drug Use
   - Flashing Lights (photosensitivity)

- Menstrual Cycle
- Missed antiseizure medication

3. Previous Seizures
   Onset: Age at onset of first ever seizure.
   Evolution: Any changes in seizure type, frequency, or severity over time

Past Medical History

Head Trauma:
History of CNS infections (e.g., meningitis, encephalitis).
Neurological Disorders:
Febrile Seizures:
Developmental History:
Perinatal injury/Kernicterus:
History of status epilepticus or non-convulsive status? ___Yes ___No
- Explain approximately how many times
- triggers
- previous treatment

Family History

Family history of epilepsy or other neurological disorders.
Family history of genetic conditions

Social History

Academic achievement:
If still a student: school, university, postgraduate
Occupation: Impact of epilepsy on work.
Driving: History of driving and any accidents related to seizures.
Lifestyle: Alcohol and drug use, sleep patterns, and stress levels.
Sports and other leisure activities.
Support System: Family and social support.

Medications

Current Medications: List all current medications, including antiseizure medications (ASM), date started, dosages, and compliance.
Previous Medications: History of previous ASM, maximal dose and reasons for discontinuation.
Side Effects: Any side effects experienced from medications.

Other medications/supplements used regularly:
- Stimulants:
- Psychotropic drugs:

- Melatonin, formulation/s and doses:
- Calcium/vitamin D
- Folic acid
- Contraception (type)
- Others:

Review of Systems

Neurological: Headaches, focal neurological deficits, cognitive changes.
Cardiovascular: History of syncope or other cardiac issues.
Psychiatric: Anxiety, depression, Psychosis/behavioural, Autism spectrum disorder or other psychiatric conditions.
Other significant medical conditions/comorbidities

Physical Examination

General Physical Examination: Look for signs of systemic illness.
Neurological Examination: Comprehensive neurological examination to assess for focal neurological signs, cognition and associated physical (e.g. neurocutaneous) signs.

Investigations

EEG:
MRI/CT:
Video EEG:
SPECT:
PET:
Blood Tests: To rule out metabolic causes
ASM levels
Genetic tests (*HLA-B*15:02*)

Summary

Diagnosis:
Epilepsy aetiology:
Epilepsy syndrome

Management Plan:
Medication
Patient Education:
- Educate the patient and family about epilepsy, medication adherence, and emergency measures.
- Lifestyle modifications
- Safety precautions

Other treatment

Epilepsy Surgery: Not done ___Done___
- Date of surgery/Hospital:
- Type of surgery:
- Pathology:
- Seizure control 1 year after surgery:

Neuromodulation: Not done_____ Done _____
- VNS/DBS: date implanted (age):
- VNS/DBS model/serial number:
- Date battery replaced (age):
- Seizure control after VNS implantation:

Ketogenic or other diet for epilepsy (specify):
- Never done
- Tried between the ages of _____ and _____
- Results
- Reasons for discontinuation:
- Plans to continue the diet. ___Yes ___No

Miscellaneous treatment received or self-initiated:

Referrals sent to other specialties (tick as appropriate):
___Psychiatry (including for stimulant prescriptions)
___Rehabilitation (for wheelchair or other mobility aids used)
___ Social worker
___ Dietician
___Other services

Completed by: _____ Date: _____

EPILEPSY COUNCIL

Malaysian Society of Neurosciences (Persatuan Neurosain Malaysia)