PHC Chapter 15: Central nervous system conditions

15.1 STROKE

I61.0-6/I61.8-9/I63.0-6/I63.8-9/I64

DESCRIPTION

Stroke consists of rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting >24 hours or leading to death. Most strokes are ischaemic (embolism or thrombosis) whilst others may be caused by cerebral haemorrhage. A transient ischaemic attack (TIA) is defined as stroke symptoms and signs that resolve within 24 hours.

The diagnosis of stroke depends on the presentation of sudden onset of neurological loss, including:

» Weakness, numbness or paralysis of the face or limb/s.
» Sudden onset of blurred or decreased vision in one or both eyes; or double vision.
» Difficulty speaking or understanding.
» Dizziness, loss of balance or any unexplained fall or unsteady gait.
» Headache (severe, abrupt).

GENERAL MEASURES

Acute management

» Assess airway, breathing, circulation and disability.
» Measure blood glucose and treat hypoglycaemia if present. See Section 21.2.6: Hypoglycaemia and hypoglycaemic coma.
» BP is often elevated in acute stroke. Do not treat elevated BP at PHC, but refer patient urgently.
» Patients should be given nil by mouth until swallowing is formally assessed.

Long term management

» Optimise treatment for existing medical conditions such as hypertension, diabetes mellitus, dyslipidaemia and cardiac conditions.
» Increase regular physical activity: aim for 30 minutes 5 times a week.
» Advise patient regarding appropriate weight loss, if weight exceeds ideal weight.
» Advise patient regarding smoking cessation.
» Refer for rehabilitative therapy including physiotherapy, occupational therapy and / or speech therapy if indicated.
» Initiate a palliative care approach if the patient's condition is deteriorating / in case of a massive stroke (see Chapter 22: Medicines used in palliative care).

LoE:IIb[1]

MEDICINE TREATMENT

Acute treatment

- Aspirin, oral, 300 mg, as a pre-referral dose. *LoE:Ia*[2]

Note: Do not give aspirin if the patient:

» is unconscious;
» cannot swallow;
» is on long-term anticoagulation therapy;
» has signs of a subarachnoid bleed: i.e. neck stiffness, headache;
» or will be transferred and treated with a thrombolytic within 3 hours. *LoE:Ia*[3]

Secondary prevention for adults (i.e. continuation of aftercare treatment initiated at higher level of care).

Antiplatelet therapy

All patients, if not contraindicated (e.g. haemorrhagic stroke, peptic ulcer, patients on anticoagulation therapy, etc.):

- Aspirin, oral, 150 mg daily. *LoE:Ia*[4]

Lipid-lowering therapy

See Section 4.1: Prevention of ischaemic heart disease and atherosclerosis.

Hypertensive therapy

For blood pressure management, see Section 4.7: Hypertension.

Diabetes mellitus and dietary management information

See Chapter 9: Endocrine system.

REFERRAL

Urgent

» Refer all acute stroke cases for further management (preferably within 3 hours).

15.2 DEMENTIA

A52.3/B23.8 + (F02.8)/E03.2-3/E03.8-9/E52/F03

DESCRIPTION

Progressive loss of cognitive function, usually of insidious onset. Initial presentation may be with mild personality or memory changes, before more pronounced deficits become evident.

Common reversible causes of dementia include:

» Metabolic
  - Hypothyroidism
  - Vitamin B12 deficiency

  - Pellagra
» Medications and drugs
  - Long-term alcohol abuse
  - Many medications have CNS side effects
» Infections
  - Neurosyphilis
  - HIV dementia
» Surgical
  - Normal pressure hydrocephalus
» Severe depression (pseudo-dementia)

GENERAL MEASURES

All patients must be seen by a doctor to confirm the diagnosis.
People with dementia are vulnerable to delirium and worsening confusion.
Manage conditions that may worsen symptoms, including:

» Electrolyte disturbances and dehydration.
» Infections, usually originating from the respiratory or urinary tract.
» Medication toxicity.
» For confirmed diagnosis of mild to moderate dementia, the following supportive measure may be taken:
  - Refer patients to occupational therapy, if available, for assessment of functioning and advice to the family on adaptive measures.
  - Disclose the diagnosis to family members/ primary care giver. *LoE:IIb*[5]
  - Explain that the condition is evolving and future planning is necessary.
  - Advise driving cessation for the patient, if relevant.
  - Discuss home safety risks – e.g. potential for patient to leave stove on while cooking or wander if unattended.
  - Ensure that the patient has a caregiver that can supervise medication taking when the patient is unable to do so themselves.
  - Monitor functional problems and manage as they arise e.g. urinary incontinence.
  - Monitor nutritional status and intervene or refer if necessary.
  - Provide ongoing medical care.
» Initiate a palliative care approach as the patient's condition deteriorates. (See Chapter 22: Medicines Used in Palliative Care).

REFERRAL

» Adults < 60 years of age, adolescents, and children, where common reversible causes of dementia could not be identified.
» When behavioural and/or psychological symptoms pose a risk to patient or carer.

15.3 PARKISONISM

G20/G21.0-4/G21.8-9/G22

DESCRIPTION

Parkinsonism is a syndrome that affects the nervous system and the parts of the body controlled by the nerves. It may be characterised by tremor, rigidity, stiffness, slow movements and postural disturbances. It may be primary, i.e. Parkinson's disease, or secondary, i.e. drug-induced, or due to uncommon disorders that may initially resemble Parkinson's disease.

Patients and caregivers may report:

» A tremor, or rhythmic shaking, which usually begins in a limb, often the hand or fingers.
» Slowed movement (bradykinesia), for example steps may become shorter as they walk and it may be difficult to get out of a chair.
» Decreased ability to perform unconscious movements, including blinking, smiling or swinging their arms while walking.
» Speech changes such as slurring or hesitation in speaking.
» Difficulty in writing.

The objective of treatment is to:

» minimise disabling symptoms
» prevent complications and avoid serious drug-induced side effects

GENERAL MEASURES

All patients demonstrating signs and symptoms of parkinsonism should be referred to a medical practitioner for assessment and treatment.

REFERRAL

» Patients suffering from motor difficulties should be referred for general supportive therapy and advice about lifestyle modification, and multidisciplinary rehabilitation to optimise their functioning. *LoE:IIIb*[6]

15.4 EPILEPTIC SEIZURES

G40.6-7; G41.0-2; G41.8-9; R56.8

DESCRIPTION

An epileptic seizure is a change in movement, attention or level of awareness that is sustained or repetitive and occurs because of abnormal and excessive neuronal discharge within the brain.

LoE:IVb[7]

Epileptic seizures should be differentiated from:

» Collapse, e.g. syncope, anoxic seizures, transient ischaemic attack, cardiac arrhythmias;
» Movement disorders, e.g., paroxysmal dyskinesias, tic disorders;
» Mental health conditions, e.g., functional/dissociative seizures (also called psychogenic non-epileptic seizures), rage reactions, panic attacks, daydreaming/ inattention;
» Sleep-related conditions, e.g., parasomnias, narcolepsy;
» Migraine associated disorders, e.g., migraine with visual aura

See https://www.epilepsydiagnosis.org/epilepsy-imitators.html for a full list of conditions which may look like an epileptic seizure.

LoE:IVb[8]

Not all persons who have an epileptic seizure have epilepsy.
Specific criteria must be met to diagnose epilepsy (See Section 15.7: Epilepsy).

DIAGNOSIS

Epileptic seizures are diagnosed clinically, through eye-witness accounts, videos, careful observation by the healthcare professional, and a history from the patient of the symptoms, signs and behaviours experienced prior to and during the seizure. Epileptic seizures are classified by the International League Against Epilepsy (ILAE) into three types: focal, generalised, and unknown (see Figure 1). The evolution of the seizure (how it starts and progresses clinically) directs investigations to determine the cause of the seizure and related management.

LoE:IVb[9]

SEIZURE TYPES

Focal seizures:

The epileptic activity arises from a specific focus, or networks limited to one hemisphere of the brain.

Focal seizures may present with motor signs (e.g., rhythmic jerking of one limb; automatisms such as lip-smacking) or with non-motor signs (e.g., olfactory, tactile, or visual hallucinations, or intense emotions such as fear). This depends on the site of origin, which may be the frontal lobe, temporal lobe, parietal lobe or occipital lobe. A focal brain lesion should always be excluded in new focal seizures.

Focal seizures are classified according to the degree of impaired consciousness and whether there is progression to a tonic-clonic seizure. Consciousness is evaluated by assessing the levels of awareness (of themselves and their

surroundings) and responsiveness (to other people or stimuli) of the person during the seizure. Any impairment in consciousness means that the person's safety and the safety of others must be protected during the seizure.

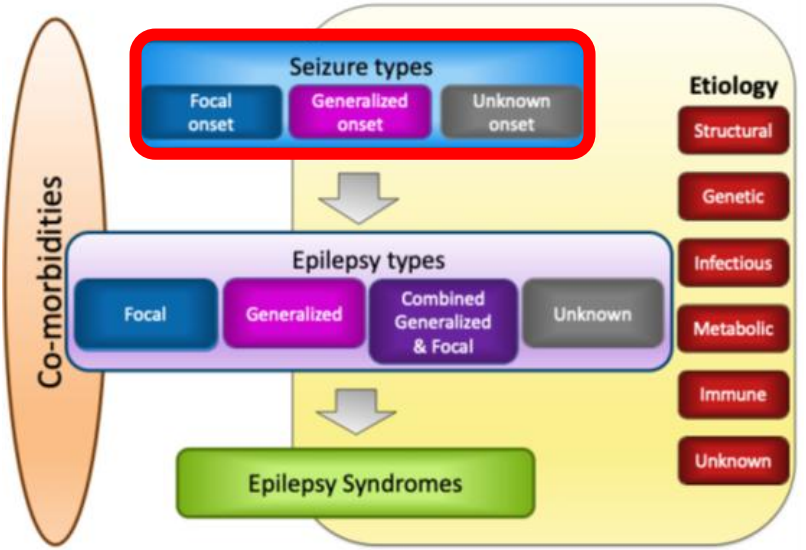


Figure 1. International League Against Epilepsy classification of seizure types *(Taken From: Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L. ILAE classification of epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017, 58 (4): 512-521).*

LoE:IVb[10]

» **Focal preserved consciousness seizures** (previously termed 'simple partial seizures'): the person is fully aware of themselves and their surroundings and fully responsive to others throughout the seizure.
» **Focal impaired consciousness seizures:** (previously termed 'complex partial seizures'), the person has impaired awareness or responsiveness at any time during the seizure.
» **Focal unknown state of consciousness seizures:** used when the state of consciousness is not known (e.g. unclear information).
» **Focal-to-bilateral tonic-clonic seizure:** the epileptic seizure progresses to both brain hemispheres. Bilateral tonic-clonic seizures are differentiated from

generalised tonic-clonic seizures by a history of preceding focal signs (either sensory or motor) occurring before complete loss of consciousness and the development of tonic-clonic movements. The terms 'aura' or 'warning signs' may be used by people for the focal signs of the seizure.

Generalised seizures

The epileptic activity arises within and rapidly spreads to involve networks in both hemispheres of the brain. Generalised seizures are almost always associated with impaired or loss of consciousness.

Generalised seizures are classified as:

» **Generalised motor seizures**, which include:
  – **Generalised tonic-clonic seizures**, with loss of consciousness and bilateral tonic-clonic limb movements.
  – **Generalised seizures other than tonic-clonic**, including seizures with varying degrees of impaired consciousness and bilateral *tonic* movements (stiffening, sometimes with vibratory movements) of limbs or eyes, bilateral *atonic* movements (sudden loss of muscle tone) of head, trunk or limbs, bilateral jerks (brief shock-like muscle contractions), as in *myoclonic* seizures.

» **Absence seizures** (previously termed 'petit-mal seizures'), which usually occur in association with an epilepsy syndrome (See Section 15.7: Epilepsy). Absence seizures may be:
  – **'typical'** with abrupt loss of consciousness lasting 5-30 seconds and clonic movements of face and/or automatisms, or
  – **'atypical'** with a less abrupt onset of impaired consciousness, longer seizure duration and loss of muscle tone of head, trunk and limbs. Atypical absence seizures are rare and can be challenging to differentiate from focal sensory seizures.

LoE:IVb[11]

Unknown:

The category of 'unknown onset' is used when there is not enough information, or the clinical presentation is too unclear, to distinguish between focal or generalised seizures.

For more detail and educational videos on seizure types, see https://www.epilepsydiagnosis.org/seizure/seizure-classification-groupoverview.html

15.5 STATUS EPILEPTICUS

G41.0-2; G41.8-9

DESCRIPTION

In status epilepticus, the seizures do not stop, or they occur repeatedly in close succession with impaired consciousness between seizures. Status epilepticus may be 'convulsive' (associated with prominent motor symptoms) or 'non-convulsive' (i.e., without prominent motor symptoms).

Convulsive status epilepticus:

Convulsive status epilepticus is defined as ≥ 5 minutes of either:

- a continuous generalised or bilateral tonic clonic seizure, or
- two or more discrete generalised, or bilateral tonic clonic seizures with incomplete recovery of consciousness between the seizures.

Convulsive status epilepticus is a **medical emergency**. There are two critical time points:

- Time point 1: **5 minutes** from the onset of the initial epileptic seizure (i.e., at the point of diagnosis). Immediate treatment is needed to prevent ongoing epileptic seizure activity.
- Time point 2: **30 minutes** of epileptic seizure activity, timed from the onset of the seizure. After 30 minutes of seizure activity, irreversible brain damage related to hypoxia, acidosis, depletion of local energy stores, cerebral oedema and structural damage, is likely to occur.

Complications of convulsive status epilepticus include:

- hyperpyrexia
- respiratory depression
- cerebral oedema
- blood pressure disturbances
- inappropriate antidiuretic hormone (ADH) secretion
- hypoxic ischaemic damage to brain, myocardium and muscles.
- disturbances of blood glucose
- renal failure
- acidosis

Non-convulsive status epilepticus:

Non-convulsive status epilepticus refers to abnormally prolonged or rapidly recurring epileptic seizures with impaired consciousness but no major motor symptoms (e.g., focal seizures with autonomic, sensory or perceptual manifestations or absence seizures). The presentation is often subtle, and the seizures may not be recognised. Diagnosis is confirmed on EEG. Treat as for convulsive status epilepticus below; see Sections 15.5.1:Epileptic seizures

and status epilepticus in children <13 years and 15.5.2: Epileptic seizures and status epilepticus in adolescents (13 – 18 years) and adults. Ensure that underlying causes are identified and managed.

Causes of epileptic seizures and status epilepticus

With every epileptic seizure, the underlying cause of the seizure must be determined and treated, including in people with epilepsy.

Important causes of epileptic seizures that must be considered include:

» Infectious conditions e.g., meningitis or encephalitis
» Encephalopathy e.g., hypertensive encephalopathy or cerebral hypoxia
» Metabolic conditions e.g., hypoglycaemia, hypo- or hypernatraemia, hypocalcaemia
» Brain lesions e.g., brain tumours, stroke and post-stroke sequelae, trauma and post-traumatic sequelae
» Substance withdrawal e.g., alcohol or benzodiazepines
» Substance intoxication e.g., cocaine or amphetamines
» Poisoning or toxin ingestion (accidental or intentional as in an overdose) e.g. isoniazid
» Other neurological (e.g., cerebral palsy) or neurodegenerative (e.g., Alzheimer's dementia) conditions
» Epilepsies e.g., breakthrough seizures, treatment non-adherence, recent changes to antiseizure medicine (ASM), antiseizure medication toxicity.

15.5.1 EPILEPTIC SEIZURES AND STATUS EPILEPTICUS IN CHILDREN < 13 YEARS OF AGE

DESCRIPTION

Central nervous system infections are a common cause of epileptic seizures in children < 13 years of age in South Africa. The most common seizures in children are febrile seizures (See Section 15.6: Febrile seizures) but the history, examination and investigations must aim at excluding the following conditions:

Perinatal conditions	Infections	Poisoning
» congenital infection » hypoxic-ischaemic damage » trauma	» meningitis » encephalitis » brain abscess » neurocysticercosis	» medicine toxicity, e.g., isoniazid, antihistamines, antiseizure medicines

» cerebral haemorrhage or thrombosis		» substance abuse, e.g., solvents, amphetamines » environmental and other toxins e.g., pesticides (organophosphates), essential oils » substance withdrawal, e.g. benzodiazepines.
Metabolic abnormalities	**Systemic disorders**	**Primary cerebral causes**
» hypoglycaemia » hypocalcaemia » hypomagnesaemia » hyponatraemia » hypernatraemia » inborn errors of metabolism	» vasculitis » hypertensive encephalopathy » uraemia (renal failure) » hyperammonaemia (liver failure)	» cerebral malformation » genetic/familial (syndromic) » tumour » idiopathic/ unknown

Special considerations by age group

Neonates:

Neonatal seizures are usually provoked, most commonly by hypoxic ischaemic encephalopathy (HIE). They rarely lead to a subsequent diagnosis of epilepsy. For management, refer to Section 19.6.2: Seizures, Neonatal.

Infants and children up to 2 years of age:

» The most frequent cause of epileptic seizures that present in infancy are febrile seizures (See Section 15.6: Febrile seizures).
» Infants under 6 months of age cannot manifest generalised tonic-clonic seizures.
» Most provoked seizures presenting in this age group appear to be focal even when a generalised brain pathology is present.
» Infants and children under 2 years may not have typical signs of meningitis, i.e. neck stiffness or Kernig sign. Meningitis should be excluded in all children with a fever and seizure.
» Infants and children are at risk of metabolic derangement which may be from common triggers (e.g., dehydration) or rare causes (e.g., inborn errors of metabolism).
» Neuroimaging is often very useful, especially to exclude structural aetiologies (e.g., intracranial bleeds).

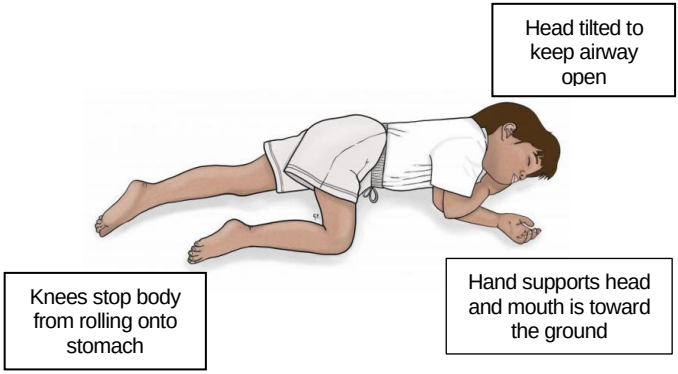
Children 2 to 12 years of age:
Older children are often able to present with clearer descriptions of seizure onset, i.e. a focal onset seizure is more likely to be specifically driven by an underlying focal cause (potentially a structural pathology):

» Ask for focality – point to the side of movement or change
» Change in behaviour before convulsive seizure evident
» Altered consciousness
» Type of seizure is related to the underlying aetiology

GENERAL MEASURES

On arrival/ while fitting:

» Ensure the environment is safe. Remove all sharp objects and hot liquids.
» Place the child in a recovery position to prevent aspiration of secretions or vomitus, on the floor if necessary.
» Do not place anything (spoon or spatula, etc.) in the patient's mouth.
» Ensure the airway is not obstructed.



Adapted from https://www.kidshealth.org.nz/emergencies/emergencies-cpr

LoE:IVb[12]

» Administer oxygen via face mask or nasal cannula to maintain $SaO_2 \geq 95\%$.

- » Obtain eyewitness account of when the seizure started and associated impaired consciousness: **If seizure duration is ≥ 5 minutes, commence urgent medicine treatment for convulsive status epilepticus** (refer to table below on medicine management and supportive care of status epilepticus in children < 13 years).
- » Examine for fever, dehydration, meningism, hypoglycaemia, evidence of toxin or poison ingestion, head, neck or other trauma, obvious focal neurology and other possible causes of the seizure.
- » Establish vascular (IV or IO) access, if possible. See Paediatric Hospital Level STGs and EML Chapter 1: Emergencies and Trauma, Section 1.1.10 Intra-Osseous Infusion in Emergencies.
- » Once threat of falling no longer present, move to bed (with cot sides up), if needed.
- » Monitor vital signs every 15 minutes.
- » Keep nil per mouth.
- » Ensure the family/caregiver/escort is attended to; social worker or auxiliary staff member should obtain all contact details and provide counselling as needed.

MEDICINE TREATMENT

The aim is to control the seizure within 30 minutes of its onset, prevent complications of status epilepticus with supportive care, and identify and correct underlying causes. Follow standard resuscitation protocols, such as the ABCDE approach.

Table 1: MEDICINE MANAGEMENT AND SUPPORTIVE CARE OF STATUS EPILEPTICUS IN CHILDREN < 13 YEARS OF AGE

PHASE	MEDICINE MANAGEMENT	SUPPORTIVE CARE
EARLY STATUS EPILEPTICUS **5-10 minutes after seizure onset**	**LEVEL 1 INTERVENTION:** (benzodiazepines, up to 2 doses). If vascular access is available: » Midazolam, IV, 0.25mg/kg over 60 secs, (max 10mg/dose) (doctor prescribed). **OR** *LoE:IVba*[13] » Diazepam, IV, 0.25mg/kg IV over 60 secs (max 10mg/dose) (doctor prescribed). *LoE:IIVb*[14] If vascular access is not available: » Midazolam, IM 0.1 mg/kg, **OR** buccal* 0.5 mg/kg (doctor prescribed). *LoE:IIIa*[15] **OR** » Diazepam, rectal**, 0.5 mg/kg (max 10mg/dose) (doctor prescribed). *LoE:IIIa*[16] Expect a response within 1–5 minutes. **If the seizure does not resolve within 5 minutes after first dose, give a repeat dose of benzodiazepine.** **CAUTION** Benzodiazepines can cause respiratory depression.	» Aim for seizure control within 30 minutes of onset. » Provide supplemental oxygen, maintain $SaO_2 \geq 95\%$. » Monitor cerebral perfusion pressure (CPP), heart rate, oxygen saturation. » Check glucose. If low, correct and start maintenance IV fluid with dextrose 5% in sodium chloride 0.9%. Do not overhydrate. » Blood gas analysis for electrolytes. Correct as required. Other biochemical disorders: Correct abnormalities, if present, e.g. glucose, calcium and sodium. Take blood for electrolytes, LFTs, FBC. If patient is a known epileptic, check therapeutic levels of ASMs. If meningitis cannot be excluded, give:

PHASE	MEDICINE MANAGEMENT	SUPPORTIVE CARE
	Monitor oxygen saturation and respiratory rate. If respiratory depression occurs, assist ventilation with bag-valve mask (1 breath every 3–5 seconds) and refer urgently/transfer to a high care setting.	» Ceftriaxone, IM or IV, 100 mg/kg/dose stat
ESTABLISHED STATUS **10-30 minutes after seizure onset**	**LEVEL 2 INTERVENTION:** If no vascular access: • Phenobarbital, IM 20mg/kg (doctor prescribed) ○ Slow IM Injection **OR** if no IM formulation available: • Levetiracetam oral, crushed and given by nasogastric tube, 60 mg/kg as a single dose (Maximum dose: 4500 mg). » **OR** *LoE:IIIb*[17] • Phenobarbital, oral, crushed and given by nasogastric tube, 20 mg/kg as a single dose. Note: if no response to phenobarbital IM or oral after 5-20 minutes, levetiracetam oral may be given via NG tube, but avoid repeating oral phenobarbital as it may take over an hour to achieve therapeutic concentrations and repeat doses increases the risk of respiratory depression. **Refer to higher level of care**	» Consult with higher level care, refer urgently. » Prepare for intubation and ventilation.
» Watch For complications of the prolonged seizure. » Check all possible underlining conditions. » Watch for adverse effects of administered ASM.		
Prescribing notes:		

PHASE	MEDICINE MANAGEMENT	SUPPORTIVE CARE
* Midazolam, buccal, 0.5 mg/kg/dose. See Chapter 23: Standard paediatric dosing tables. o Use midazolam for injection 5 mg in 1 mL undiluted. o Draw up the required volume in a 5 mL syringe. o Remove needle then administer midazolam into the buccal cavity (between gum and cheeks). o Note: Buccal midazolam should not be used in infants < 6 months of age. *LoE:IIIa*[18] **Diazepam, rectal, 0.5 mg/kg/dose as a single dose. See Chapter 23: Standard paediatric dosing tables. o Use diazepam for injection 10 mg in 2 mL undiluted. o Draw up the required volume in a 2 mL syringe. o Remove needle then connect syringe to an NGT and gently insert into the rectum (or insert the whole barrel of the lubricated syringe if no NGT available) and inject the contents. o Remove NGT / syringe and hold buttocks together to minimise leakage.		

After The Seizure

Post-ictal phase

» Keep nil per mouth and haemodynamically stable until child has regained consciousness.
» Determine the seizure type (focal or generalised) and cause of the seizure. Further investigations are driven by clinical signs and seizure onset, e.g.:
  – History of toxin exposure
  – Evidence of neuro-infection
  – History of trauma
  – Focal onset (e.g., a warning experience prior to generalised tonic-clonic movements) and/or focal neurology warrants neuroimaging.
» If meningitis cannot be excluded, commence antibiotic therapy within one hour of arrival. See Section 15.8.1: Acute meningitis.

Pre-discharge

» Consider whether the criteria for a diagnosis of epilepsy are met (see Section 15.7: Epilepsy). Initiate appropriate ASM for type of epilepsy and develop an emergency care plan for recurrent seizures.
» If not epilepsy, start weaning any ASMs.
» Counsel the caregiver on the current state of the child, the reason for the seizure, management given and likely sequelae of the seizure. Offer only as much information as the caregiver can receive at that time.
» Set up a follow up appointment to re-evaluate the diagnosis, educational and social needs, and to reinforce educational counselling about the child's condition.

Active follow-up

» Ensure underlying medical conditions are appropriately managed.
» Reduce and stop any residual ASMs if not epilepsy.
» Assess neurodevelopmental conditions, educational and social needs. Refer as necessary
» If epilepsy is the cause of the seizure, check seizure control and if emergency care plan is understood.

Referral

» All children with status epilepticus.
» All children < 2 years.
» Children over ≥ 2 years, except for those with simple febrile seizures (see Section 15.6: Febrile seizures).

Follow up social worker or rehabilitation services required.

15.5.2. EPILEPTIC SEIZURES AND STATUS EPILEPTICUS IN ADOLESCENTS (13 – 18 YEARS) AND ADULTS

Additional causes of epileptic seizures to consider in adolescents and adults are categorised below:

Pregnancy related	Infections	Substances & poisoning
» eclampsia (See Adult Hospital STGs and EML, Section 6.4.2: Eclampsia) » electrolyte abnormalities (e.g. in hyperemesis gravidarum) » stroke » reduced blood levels of antiseizure medication	» meningitis » encephalitis » brain abscess » neurocysticercosis	» substance abuse (e.g. cocaine, amphetamines) » withdrawal syndromes (e.g., benzodiazepine, alcohol) » medicine toxicity and overdose (e.g., antiseizure medications, antidepressants, antipsychotics, isoniazid) » environmental toxins (e.g. pesticides)
Metabolic conditions	**Systemic disorders**	**Primary cerebral causes**
» hypoglycaemia » hypocalcaemia » hypomagnesaemia » hyponatraemia » hypernatraemia	» vasculitis » hypertensive encephalopathy » uraemia (renal failure) » hyperammonaemia (liver failure)	» tumour » trauma » neurodegenerative conditions » idiopathic/unknown

Special considerations

Adolescents and young adults:

» High risk for substance intoxication or withdrawal, and for traumatic brain injuries.

» Mental health conditions are common, and may present as 'epilepsy imitators' (see differentials of epileptic seizures above and https://www.epilepsydiagnosis.org/epilepsy-imitators.html).

» Idiopathic generalised epilepsies (including epilepsy with generalised tonic-clonic seizures, juvenile myoclonic epilepsy, juvenile absence epilepsy) may first present in this age group.

» High risk for poor adherence to ASMs and breakthrough seizures.

» Often require intensive individual and family counselling and support, with appropriate involvement of social welfare and education sectors.

Girls and women in child-bearing age group:

» Exclude pregnancy and pregnancy related complications.
» ASM concentrations may become sub-therapeutic in pregnant women with epilepsy, causing breakthrough seizures. An increase in ASM dose may be required during pregnancy (reduce dose after delivery). Where possible monitor.

CAUTION

Children born to women taking valproate are at significant risk of birth defects (11%) and persistent developmental disorders (40%).
Valproate is contra-indicated and should be avoided in pregnancy and in adolescents and women of child-bearing potential.

LoE:IIIb[19]

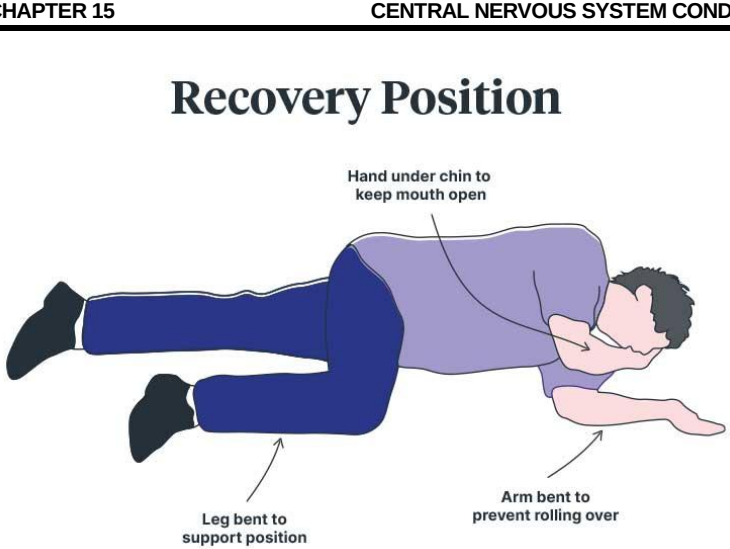
People > 65 years of age:

» Common reversible conditions include metabolic abnormalities, medications, alcohol withdrawal.
» The risk of developing epilepsy increases with age. Epilepsy in this age group is commonly caused by stroke, brain tumours and dementias. Continued ASM may be advisable after a single seizure in these patients.

GENERAL MEASURES

On arrival/ while fitting:

» Ensure the environment is safe. Remove all sharp objects and hot liquids.
» Place the patient in a lateral position to prevent aspiration of secretions or vomitus, on the floor if necessary.
» Do not place anything (spoon or spatula, etc.) in the patient's mouth.



Taken from Ausmed: Adult Basic Life Support

LoE:IVb[20]

» Obtain an eyewitness account of the seizure onset and any associated impaired consciousness. **If seizure duration is ≥ 5 minutes, commence urgent medicine treatment for convulsive status epilepticus** (refer to table below on medicine management and supportive care of status epilepticus in adolescents and adults).
» Ensure the airway is not obstructed and administer oxygen via face mask or nasal cannula to maintain SaO_2 ≥ 95%.
» Intubation should be performed if airway, ventilation, or oxygenation cannot be maintained, or if seizure is prolonged.
» Examine for fever; dehydration; meningism; hypoglycaemia; evidence of toxin or poison ingestion; head, neck or other trauma; obvious focal neurology; and other possible causes of the seizure.
» Secure intravenous access.
» Monitor vital signs every 15 minutes.
» Keep nil per mouth.
» Ensure the family/caregiver/escort is attended to. Social worker or auxiliary staff member should obtain all contact details and provide counselling as needed.

Convulsive status epilepticus:
If the seizure does not resolve within 5 minutes of onset, commence urgent medicine treatment.

MEDICINE TREATMENT

The aim is to control the seizure within 30 minutes of its onset, prevent complications of status epilepticus with supportive care, and identify and correct underlying causes. Follow standard resuscitation protocols, such as the ABCDE approach.

Table 2: MEDICINE MANAGEMENT AND SUPPORTIVE CARE OF STATUS EPILEPTICUS IN ADOLESCENTS AND ADULTS

PHASE	MANAGEMENT	SUPPORTIVE CARE
EARLY STATUS EPILEPTICUS (5 – 10 minutes)	**LEVEL 1 INTERVENTION:** (Benzodiazepines; See Caution below). <u>If IV access is available:</u> » Midazolam, IV, 10mg (doctor prescribed). *LoE:IIb*[21] **OR** » Diazepam, IV, 10mg administered over at least 5 minutes (not faster than 2mg/min) (doctor prescribed). *LoE:IIb*[22] <u>If IV access is not available:</u> • Midazolam, 10mg, IM or buccal, using the parenteral formulation, while continuing to establish IV access (doctor prescribed). **OR** <u>If no midazolam available:</u> • Diazepam, rectal, 0.2–0.5 mg/kg as a single dose (maximum 20 mg/dose) (doctor prescribed). *LoE:IVb*[23] If the seizure does not resolve 5 minutes after first dose of benzodiazepine, repeat the dose of benzodiazepine. If seizure aborts after 1 or 2 doses of benzodiazepines, but patient is at high risk of recurrent seizures (e.g., known with epilepsy and defaulted treatment), load with antiseizure medicine.	» Stabilize and support airway breathing and circulation. » Identify and treat the underlying cause of seizures such as: – Hypoglycaemia – Electrolyte derangements (e.g. calcium, sodium, potassium, magnesium and urea) – Poisoning – Intoxication/overdoses (e.g. isoniazid, theophylline, tricyclic antidepressants, cocaine, methamphetamine) – Withdrawal syndromes (e.g. alcohol, benzodiazepines) » If patient is known with epilepsy and on treatment, take blood for measurement of antiseizure medicine levels.

ESTABLISHED STATUS EPILEPTICUS (10 – 30 minutes)	**LEVEL 2 INTERVENTION:** (Antiseizure medicine) • Levetiracetam oral, crushed and given by nasogastric tube, 60 mg/kg as a single dose (Maximum dose: 4500 mg) *LoE:IIb*[24] **Refer all patients.**	» Prepare for intubation/ventilation. » Arrange referral to higher level of care.
CAUTION: Benzodiazepines can cause respiratory depression. Monitor closely for respiratory depression. If this occurs, assist ventilation with bag-valve mask (1 breath every 3–5 seconds) and refer urgently/transfer to a high-care setting.		

After The Seizure

Post Ictal Phase:

» Keep nil per mouth and haemodynamically stable until patient has regained consciousness and is aware of themself and their surroundings.
» If there is agitation or disturbed behaviour, consider post-ictal delirium and manage as for delirium – see Section 21.2.4: Delirium.
» Clarify the cause of the seizure and manage appropriately. Further investigations (e.g. lumber puncture and neuroimaging) are driven by clinical signs and seizure onset (e.g. focal onset).
  » If meningitis is suspected, commence antibiotic therapy urgently.
  » Counsel the patient and their family regarding the cause of the seizure, management given and likely sequelae of the seizure. Offer only as much information as the family or patient is able to receive at that time.
  » If reversible causes of the epileptic seizure have been addressed, wean and stop ASMs. Consider whether the person meets the criteria for a diagnosis of epilepsy that requires ongoing ASMs (see Section 15.7: Epilepsy).
» On discharge, set up a follow-up appointment to reinforce the counselling messages.

Active follow up:

» Wean any residual ASMs, unless ongoing maintenance treatment is indicated, or epilepsy has been diagnosed.

Referral

» All patients with status epilepticus must be referred to hospital for continued acute management and evaluation of the cause.
» New focal seizures for neuroimaging.
» Suspected meningitis.

Follow up social worker or rehabilitation services required.

15.6 FEBRILE SEIZURES

R56.0

DESCRIPTION

Febrile seizures occur between the ages of 6 months and 6 years of age in association with a significant fever (>38.5°C) in the absence of an intracranial infection and typically associated with viral upper respiratory tract infections. These are the most common type of seizures in children of this age. *LoE:IVb*[25]

However, the diagnosis requires the exclusion of other causes of seizures.
Febrile convulsions can be simple or complex.

Simple febrile seizures (SFS):

» are generalised,

- occur once per illness,
- are less than 15 minutes (typically 1–2 minutes),
- are not associated with any neurological deficit,
- are self-limiting,
- consist of only one seizure during the febrile illness which needs no specific treatment, and
- may be associated with a family history of simple febrile seizures.

Complex febrile seizures have *one or more* of the following characteristics:

- Seizure duration of 15 minutes or more;

OR

- are recurrent within the same febrile illness;

AND/OR

- have a focal onset.

AND/OR

- are associated with post-ictal, focal neurological abnormalities.

Children with febrile seizures have a good prognosis, and very rarely develop epilepsy. The overall risk for recurrence of simple febrile seizures is 30–40%. Factors which increase the risk for recurrent febrile seizures include:

- seizure disorder in a first-degree relative,
- onset before 12 months of age,
- initial complex seizures.

DIAGNOSTIC CRITERIA

Clinical

- Investigate for intracranial, extracranial, and biochemical causes of fever or seizure.
- Signs of meningism are unreliable in children under 18 months of age.
- If raised intracranial pressure or meningitis cannot be excluded, the diagnosis of febrile seizures cannot be made. Treat children empirically for meningitis if suspected.

Investigations

Lumbar puncture

- Lumbar puncture is indicated in:
  - All children with clinical features of meningitis.
- Lumbar puncture may be indicated in:
  - Children where meningitis cannot be excluded, e.g. under 18 months of age or those who have received antibiotics prior to the event.
- In children ≥ 18 months of age, where a focus of extracranial infection is present and intracranial infection such as meningitis has been excluded clinically, no further investigation is required.

Neuroimaging

» Children with complex febrile seizures and/or persistent lethargy may require neuroimaging, followed by a lumbar puncture if raised intracranial pressure can reliably be excluded based on clinical assessment. (see Paediatric Hospital Level STGs and EML, Section 13.2: Lumbar Puncture).

» Based on clinical findings, investigate complex febrile seizures for possible underlying conditions such as meningitis, focal brain lesions and epilepsy.
Note: An EEG is of no value in simple febrile seizures but may be considered in recurrent complex febrile seizures.

GENERAL AND SUPPORTIVE MEASURES

» Reassure parents and caregivers.
» Educate parents and caregivers regarding the first aid management of seizures.
» Counsel against tepid sponging and fans as this increases the core temperature.
» Counsel that recurrent febrile seizures occur in 30-40% of patients.
» Look for a cause of the fever.
» **Always exclude meningitis** (See Section 15.8: Meningitis).

MEDICINE TREATMENT

For fever related symptoms (temperature > 38.5°C):

- Paracetamol, oral, 15 mg/kg/dose 6 hourly.
  - Note: Paracetamol has no effect on seizure prevention.

If convulsing for > 5 minutes:
See Section 15.5: Status epilepticus (convulsive).

Continuous antiseizure medication prophylactic therapy

» Routine daily antiseizure medication prophylaxis is not recommended for patients with simple febrile seizures.
» For children with recurrent complex febrile seizures, discuss the treatment options with a specialist.

REFERRAL

» All febrile seizures, except if:
> Previous episode of simple febrile seizures has been investigated,
AND
– the child regains full consciousness and function immediately after the seizure,
AND
– meningitis has been excluded (See Section 15.8: Meningitis).

» Complex convulsions:
  - All patients with recurrent complex febrile seizures without an obvious cause of the seizure and/or not responding to initial management should be discussed with a specialist.
  - Developmental delay/regression.

15.7 EPILEPSY

G40.0-9

DESCRIPTION

Epilepsy is a disease of the brain defined by any of the following conditions:

» At least two unprovoked (or reflex) seizures occurring >24 hours apart,
» One unprovoked (or reflex) seizure if there is a high risk (60% or more) of having recurrent seizures within the next 10 years (i.e., if the person is vulnerable to having another unprovoked seizure, e.g., because of structural damage such as from a stroke),
» Diagnosis of an epilepsy syndrome.

Note:

» An “unprovoked” epileptic seizure is a seizure which does not have evidence of an identifiable temporary or reversible factor acting on a healthy brain (e.g., hypoglycaemia, alcohol withdrawal, concussion).
» A “reflex” epileptic seizure is a seizure which occurs in response to a stimulus such as flashing lights. Such epileptic seizures indicate the person’s brain is predisposed to having seizures and therefore warrant a diagnosis of epilepsy.
» Epilepsy may be diagnosed after a single unprovoked seizure in people with an increased risk of recurrence for example in people with previous conditions such as TB meningitis, neurocysticercosis, stroke, brain tumour or traumatic brain injury. Note that the single unprovoked seizure is not caused by the immediate insult to the brain but occurs spontaneously (i.e., is unprovoked) because of the long-term sequelae of the initial insult. The damaged brain is thus at high risk of a recurrent unprovoked epileptic seizure.
» Epileptic syndromes confer a diagnosis of epilepsy, even if the risk of recurrent epileptic seizures is low for a particular individual.
» Epilepsy is considered to be resolved and no longer needing maintenance treatment in individuals who either:
  - had an age-dependent epilepsy syndrome, but are now past the applicable age, **OR**
  - have remained seizure-free for the last 10 years and weaned off ASM for at least the last 5 years.
» Epilepsy is associated with many psychological, social and legal problems, and cultural misperceptions which should be explored and addressed at the time of diagnosis and throughout the course of the illness.

Epilepsy types

As shown in Figure 2, epilepsies are classified by the International League Against Epilepsy (ILAE) according to:

» Type of seizures experienced, e.g.: focal, generalised, combined generalised and focal, or unknown.

AND

» Aetiology, which may be:
  – Structural (e.g., cerebral or vascular malformations, stroke, traumatic brain injury, brain tumours).
  – Genetic (the epilepsy is a direct result of chromosomal or gene abnormalities, e.g., Down syndrome, Fragile X syndrome, Dravet syndrome).
  – Infectious (e.g., post-infectious sequelae of TB meningitis).
  – Metabolic (e.g., inborn errors of metabolism).
  – Immune (rare conditions involving neuroreceptor antibodies).
  – Unknown.

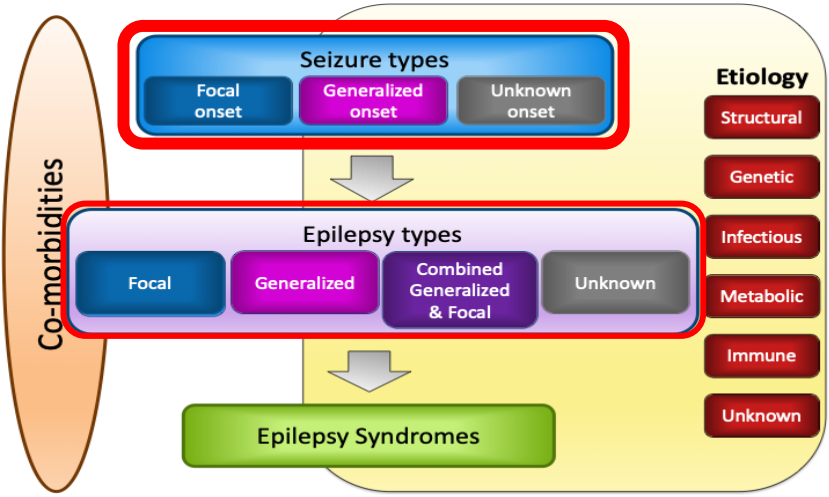


Figure 2. International League Against Epilepsy classification of seizure types *(Source: Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L. ILAE classification of epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017, 58 (4): 512-521).*

LoE:IVb[26]

Focal epilepsy

Characterised by unprovoked focal seizures, which may or may not evolve to bilateral tonic-clonic seizures. The diagnosis is made clinically and requires a

detailed description of how the seizure started. In people presenting with generalised tonic-clonic seizures, it is important to ask about any warning symptoms or 'aura' experienced by the person before losing consciousness. Typical interictal and/or ictal EEG findings may be present, and neuroimaging may reveal a focal brain lesion, supporting the diagnosis, but may also be normal.

Generalised epilepsy
Characterised by unprovoked generalized seizures, including tonic-clonic, tonic, myoclonic, and absence seizures. Typical interictal and/or ictal EEG findings may be present.

Combined generalised and focal epilepsy
Diagnosed in people with more than one type of seizure, e.g., unprovoked focal seizures and unprovoked generalised seizures. This may occur in people with Dravet syndrome or Lennox-Gastaut syndrome.

Unknown epilepsy
This classification is used when it is not possible to determine whether the epilepsy is focal, generalised, or combined generalised and focal epilepsy from the available history, clinical, and investigative findings.

For seizure types, see Section 15.4: Epileptic seizures.
For more information and educational videos on epilepsy types, see https://www.epilepsydiagnosis.org/epilepsy/epilepsy-classification-groupoverview.html.

Investigations:
- Neuroimaging (a CT Brain or MRI if available) should be conducted:
  - in new focal onset seizures to exclude a focal brain lesion,
  - if the epilepsy features change in an individual (i.e., new symptoms appear, noting that most people will experience the same march of symptoms with each seizure),
  - if epileptic seizures recur despite adherence to treatment and the diagnosis is unclear.
- EEG is indicated for recurrent or syndromic seizures where a diagnosis cannot be made on clinical grounds alone. Delay an EEG for at least one week after the convulsive episode.
- EEG is not indicated for simple febrile seizures.
- If the seizure presentation is atypical, a 12-lead ECG should be considered to identify prolonged QT interval syndromes. Syncope with exercise, syncope in response to loud noise, fright, or extreme emotional stress, syncope whilst supine, a family history of sudden

death in a young person e.g., <40 years old, or sensorineural deafness are associated with some types of long QT syndrome.

15.7.1 EPILEPSY IN CHILDREN <13 YEARS OF AGE

A child may be diagnosed with focal, generalised, combined generalised and focal, or unknown epilepsy types.

Special considerations

Seizures in neonates

Seizures in the neonatal period seldom confer a diagnosis of epilepsy. For management of seizures, See Paediatric Hospital Level STGs and EML Chapter 19: Prematurity And Neonatal Conditions, Section 19.6.2: Seizures, Neonatal.

Underlying conditions and co-morbidities

The sequelae of neurocysticercosis and TB meningitis are a common cause of childhood epilepsy in South Africa. See Paediatric Hospital Level STGs and EML Chapter 13: The Nervous System, Section 13.7: Neurocysticercosis and Chapter 10: Tuberculosis, Section 10.4: Meningitis, Tuberculosis in Children.

Common co-morbidities with epilepsy which need to be managed in conjunction with treatment of the epilepsy include:

» Neurodevelopmental disorders, e.g., autism spectrum disorder, intellectual disability, attention deficit hyperactivity disorder, specific learning disorders.
» Behavioural and psychiatric disorders, e.g., anxiety disorder, depression, oppositional defiant disorder, conduct disorder, sleep disorders.
» Cognitive and academic difficulties.
» Developmental delays, particularly with epilepsies that have their onset in early childhood.

Infantile epileptic spasms (see syndromes below)

Infantile epileptic spasms (previously called infantile spasms) are a type of seizure that typically occur in infants between 3 and 12 months of age. They involve brief, repetitive stiffening of the body (for 1-2 seconds), typically recurring in clusters, and usually happen when the infant is waking up or falling asleep.

These spasms are often associated with a severe epilepsy syndrome called West syndrome or Infantile Epileptic Spasms Syndrome, which includes:

» Epileptic spasms
» Developmental delay or regression
» A specific abnormal EEG pattern called hypsarrhythmia

Infantile spasms are a **medical emergency.** Early diagnosis and treatment are crucial to prevent long-term developmental problems. Discuss with a specialist and refer immediately.

Children on ART

Drug interactions between ASM and ARVs can arise from several mechanisms, including liver metabolism (increased or decreased) and competition for protein binding. There is a lack of strong evidence to guide clinicians at present.

The following points are important to remember when treating epilepsy in patients on ART:

» Carbamazepine, phenobarbital and phenytoin induce hepatic enzymes, which may lead to sub-therapeutic ARV plasma concentrations, especially of INSTIs, NNRTIs and PIs.
» If clinically indicated, monitor ASM levels in patients taking concurrent ART and ASM therapy.
» Consider lamotrigine, levetiracetam or valproate, and avoid prescribing carbamazepine, phenytoin or phenobarbital.

Girls likely to need treatment when of child-bearing potential/ after 10 years of age

» The potential for child-bearing must be considered in all girls requiring treatment for epilepsy.
» Choose the ASM with the least potential for harm in pregnancy (see Figure 3).
» Valproate should not be used if the child is likely to need epilepsy treatment as they grow older / develop child-bearing potential, unless other ASMs are not effective or intolerable. Annual acknowledgment of risk must be obtained if valproate is used.
» Girls over the age of 10 years should be counselled regarding sexual activity and contraception needs.
» Refer any girls who may be vulnerable to sexual abuse to a social worker.

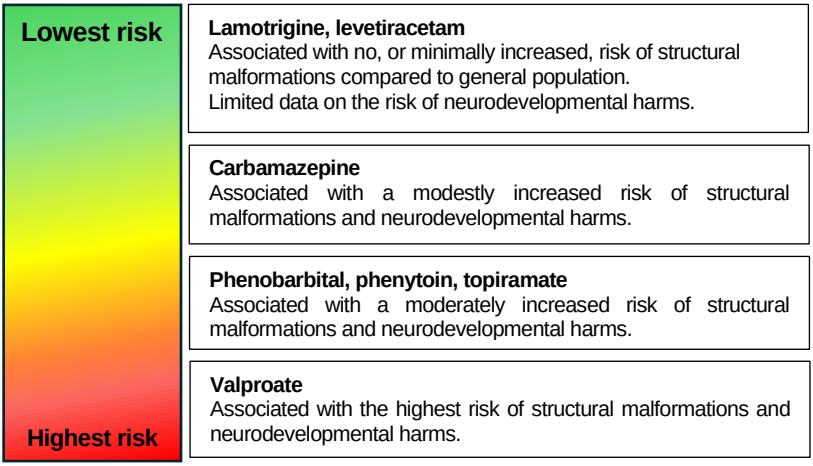


Figure 3. Risk of congenital structural malformations and neurodevelopment harms associated with various antiseizures medicines.
Increasing risk refers to increasing number of pregnancies or children affected. (Adapted from Pennell PB. *Neurotherapeutics*. 2016 and Medicines & Healthcare products Regulatory Agency safety leaflet).

LoE:IVb[27]

GENERAL AND SUPPORTIVE MEASURES

» Offer ongoing counselling to the patient and caregiver about epilepsy, its associated complications and comorbidities e.g. learning difficulties, ADHD, anxiety, and aggression.
» Encourage participation in activities of daily living and ensure that the patient is not precluded from school and lifestyle activities, unless valid safety concerns are evident.

MEDICINE TREATMENT

The goal of medicine treatment is to prevent recurrent seizures and optimise quality of life, balanced against potential adverse effects of ASM. Being seizure-free may not be achievable with all children and may require individualised treatment goals, e.g., severe to profound intellectual disability with intractable seizures that do not interfere with the care of that child. Cautious escalation of treatment should be done with consideration of potential adverse effects. In the settings of apparent drug-resistant epilepsy, revisit the diagnosis, check adherence, consider if the prescribed ASM and dose are correct, and refer to a specialist if treatment goals are not achieved.

Acute therapy

Manage acute seizure and status epilepticus as per seizures/status epilepticus, see Sections 15.4: Epileptic Seizures, and 15.5: Status epilepticus.

Maintenance therapy

Principles of management

» Monotherapy is preferred.
» Combination therapy, if necessary, should be specialist initiated in the form of add-on management.
» As a general rule, start with low doses according to the lower dose per kilogram for the child and titrate upwards slowly until seizures are controlled. This is often at the low-to-mid-therapeutic dose range.
» If seizures continue, titrate to high therapeutic doses, monitoring for unacceptable adverse effects.
» If the patient experiences unacceptable adverse effects, consult a doctor about cross-titrating to another ASM. Verify that the ASM is being given correctly and that the epilepsy type has been correctly identified.
» ASMs can interact with other drugs, affecting their effectiveness and safety. These interactions mainly occur through changes in drug metabolism (enzyme induction or inhibition) and protein binding.
» Monitoring of therapeutic ASM levels is only indicated when there is concern about toxicity or adherence. It is not recommended when titrating to establish the appropriate dose.

Continuation and cross-titration of treatment

» Cross-titration may be required when changing from one ASM to another if there is poor control or adverse effects. Add on the new medication, up-titrate to a therapeutic dose; when seizures are controlled, slowly reduce and stop the initial medication (doses should only be changed at 2 weekly intervals).

In most children, it is appropriate to continue effective ASM therapy as they grow older as indicated by the type of epilepsy. Exceptions are:

» **Valproate in girls approaching puberty and of child-bearing potential**.
Valproate should be deprescribed by cross-titration onto another suitable ASM in girls at approximately 10 years of age. **Lamotrigine and levetiracetam are the safest ASMs in pregnancy** and therefore the first choice in girls and women of child-bearing potential. As carbamazepine and topiramate are both teratogenic, they should be avoided.
» **Phenobarbital** may be initiated in infants under 6 months of age or for children with severe or profound intellectual disability, for whom the adverse effects will not interfere with their care or activities of daily living. In children who are controlled on phenobarbital, cross-titration onto another suitable ASM should be undertaken by 2 years of age.

Table 3: Epilepsy treatment in children 1 month to ≤ 12 years

	Epilepsy type	Population	1st line	2nd line	Comments
Focal	With or without evolution to bilateral tonic-clonic seizures *LoE:IIIb*[28]	All	Lamotrigine	Carbamazepine **OR** Levetiracetam	Avoid carbamazepine in children on ART due to drug-drug interactions Avoid carbamazepine in girls who are likely to require treatment when/ if of child-bearing potential.
Generalised epilepsy	Tonic-clonic, atonic, clonic, or tonic seizures	» Boys » Girls unlikely to need treatment after 10 years of age or develop child-bearing potential	Lamotrigine (low risk*) **OR** Levetiracetam (high-risk*)	Levetiracetam or lamotrigine (whichever not used as first line) **OR** Valproate	Valproate should not be used unless lamotrigine and levetiracetam are poorly tolerated or ineffective. If valproate used in girls 10 years and older - see note below on **acknowledgement of risk form**.
		Girls likely to need treatment after 10 years of age	Lamotrigine (low risk*) **OR** Levetiracetam (high-risk*)	Levetiracetam or lamotrigine (whichever not used as first line) **OR** Consider combination therapy with lamotrigine and levetiracetam	Valproate should not be used unless lamotrigine or levetiracetam, alone or in combination, are ineffective or poorly tolerated. **If valproate is used, see note below on "Acknowledgment of risk form"** and effective family planning.
	Absence	» Boys » Girls unlikely to need treatment after 10 years age of age or to develop child-bearing potential	Valproate	Lamotrigine	**If valproate is used, see note below on "Acknowledgment of risk form"**. Girls aged 10 years or older that are on valproate should be cross-titrated to lamotrigine.

Epilepsy type	Population	1st line	2nd line	Comments
Absence (Continued)	Girls likely to continue treatment after 10 years of age	Lamotrigine	Levetiracetam	**If valproate is used, see note below on "Acknowledgment of risk form"** and effective family planning.
Myoclonic *Confirm diagnosis and discuss management with a specialist in all cases*	» Boys » Girls unlikely to need treatment after 10 years of age or to develop child-bearing potential	Valproate	Levetiracetam	Seizures may be aggravated by phenytoin or carbamazepine. Lamotrigine may be effective but may also exacerbate myoclonic seizures. **If valproate is used in girls, see note below on "Acknowledgment of risk form"** and effective family planning. Girls aged 10 years or older should be cross titrated to levetiracetam or lamotrigine.
	Girls likely to continue treatment after age of 10 years	Levetiracetam	Lamotrigine	These seizures may be aggravated by phenytoin or carbamazepine. Lamotrigine may be effective but may also exacerbate myoclonic seizures. **If valproate is used, see note below on "Acknowledgment of risk form"** and effective family planning.
Combined generalised and focal epilepsy OR Unknown/unclassified Discuss clinical presentation and management with a specialist in all cases.				

NOTE:

» Lamotrigine is the preferred first line treatment for all adult patients, including women of child-bearing potential, pregnant women, and people on ART.

» Lamotrigine requires slow dose up-titration and may not be suitable in people at high-risk of seizures.

» **If valproate is used in girls, an acknowledgment of risk form must be obtained annually, even if not of child-bearing potential. Girls aged 10 years and older should receive effective family planning and consider a long-acting form of contraception.**
https://www.sahpra.org.za/wp-content/uploads/2025/05/GLF-CEM-PV-S01_v2-Valproate-Annual-Risk-Acknowledgement-Form-ARF.pdf
*Assess level of risk (high vs low) based on clinical judgement and discuss with a specialist if unsure. In general, high-risk patients are those with frequent seizures, a previous history of hospitalization for seizures, or previous history of status epilepticus. Low-risk patients are those with infrequent seizures, no previous hospitalization for seizures, and no history of status epilepticus. *LoE:IVb*[29]

- Lamotrigine, oral
  Monotherapy:
  - Starting daily dose: 0.2 mg/kg/dose.
  - Increase slowly at 2 weekly intervals to 1–5 mg/kg/dose 12–24 hourly.
  - Rapid escalation associated with adverse effects (e.g., skin rash).

Table 4: Dosing regimens when lamotrigine is used as add-on therapy:

	Week 1 and 2	Week 3 and 4	Maintenance dose
Add on therapy where regimen **does not include valproate** or other inducers/inhibitors of lamotrigine glucuronidation	0.3 mg/kg in one or two divided doses	0.6 mg/kg in one or two divided doses	0.6 mg/kg increments every 1–2 weeks to achieve a maintenance dose of 1–10 mg/kg (once a day or two divided doses) to a maximum of 200 mg/day.
Add-on therapy where **regimen includes ASMs that induce lamotrigine glucuronidation** *(e.g. phenytoin, carbamazepine, phenobarbital, etc.)*	0.6 mg/kg in two divided doses	1.2 mg/kg in two divided doses	1.2 mg/kg increments every 1–2 weeks to achieve a maintenance dose of 5–15 mg/kg (once a day or two divided doses) to a maximum of 400 mg/day.
Add-on therapy where **regimen includes valproate** *(regardless of other concomitant medication)*	0.15 mg/kg daily	0.3 mg/kg daily	0.3 mg/kg increments every 1–2 weeks to achieve a maintenance dose of 1–5 mg/kg (once a day or two divided doses) to a maximum of 200 mg/day.

LoE:IVb[30]

CAUTION - LAMOTRIGINE
Lamotrigine may cause Stevens-Johnson Syndrome.

- Levetiracetam, oral,
  - Infants 1 to < 6 months:
    - Initial dose: 7 mg/kg/dose twice daily.
    - Increase dosage every 2 weeks by 7 mg/kg/dose twice daily based on response and tolerability to the recommended dose of 21 mg/kg/dose twice daily.

  - Infants ≥ 6 months and children < 4 years:
    - Initial dose: 10 mg/kg/dose twice daily
    - Increase dosage every 2 weeks by 10 mg/kg/dose twice daily based on response and tolerability to the recommended dose of 25 mg/kg/dose twice daily.
  - Children ≥ 4 years to 12 years:
    - Initial dose: 10 mg/kg/dose twice daily
    - Increase dosage every 2 weeks by 10 mg/kg/dose twice daily based on response and tolerability to the recommended dose of 30 mg/kg/dose twice daily.

- Carbamazepine, oral, 5 mg/kg/day (starting dose), 8–12 hourly.
  - Increase slowly by 2 mg/kg/day at 2 weekly intervals.
  - Usual maintenance total daily dose: 10–20 mg/kg/day.
  - Maximum total daily dose: 20 mg/kg/day.
  - Dosage intervals: syrup 8 hourly, tablets 12 hourly.
  - Exacerbates myoclonic seizures and absence seizures.

- Valproate, oral, 5 mg/kg/dose (starting dose), 8–12 hourly.
  - Increase by 5 mg/kg weekly to 15–20 mg/kg/day, given 8–12 hourly over 4 weeks.
  - Usual maintenance dose: 20-30 mg/kg/day.
  - Maximum total daily dose: 40 mg/kg/day.
  - Exclude liver dysfunction prior to initiating therapy (at least ALT), in children under 2 years or if clinical suspicion of liver dysfunction or metabolic disease.
  - Consider hepatotoxicity if clinical signs such as nausea, vomiting, malaise, jaundice or abdominal pain develop.

- Phenobarbital, oral, 3–5 mg/kg/dose as single dose at night.
  - May be used in children under six months of age.
  - Not recommended as maintenance therapy for children older than 2 years due to undesirable side-effects such as sedation, behaviour disturbances, hyperkinesia and dependence, except in situations where there is poor adherence to other drugs.
  - Exacerbates absence seizures.

REFERRAL

» Suspected but undiagnosed secondary cause for seizures (e.g., structural, metabolic, infectious, genetic causes).
» All myoclonic seizures and infantile epileptic spasms at presentation.
» Mixed seizure types in one patient.
» Focal seizures requiring neuroimaging (MRI preferred).
» Neuroregression (loss of previously acquired milestones or skills).

» Seizure-free patients on therapy for ≥ 5 years to assess whether treatment discontinuation is appropriate.

Information that should accompany each referral case.

» Number and frequency of seizures per month (or year).
» Date and time of most recent seizures.
» Detailed description of the seizures, including:
  – aura or warning sign
  – what happens during the seizure? (give a step-by-step account)
  – is the person conscious during the seizure?
  – how long do the seizures last on average?
  – what does the patient experience after the seizure e.g., weakness, loss of speech?
  – how long does this experience last?
» Is there a family history of seizures?
» What is the initial date of diagnosis?
» Is there evidence of alcohol use?
» Are there any comorbid conditions, e.g., diabetes, HIV and what medication is used?
» What is the name and dosage of the ASM used to date?
» Does the person return regularly for repeat of medication?

15.7.1.1 EPILEPSY SYNDROMES

G40.3-5

See Paediatric Hospital Level STGs and EML Chapter 13: the Nervous System, Section 13.4.1.1: Epilepsy Syndromes.

15.7.2 EPILEPSY IN ADOLESCENTS AND ADULTS

G40.0-9

DESCRIPTION

See Section 15.7: Epilepsy.

Diagnostic criteria

» The diagnosis of epilepsy is usually made clinically.
» Take an adequate history and get an accurate witness description of the seizures to define the type of epilepsy.
» Juvenile myoclonic epilepsy and absence seizures specifically should be considered and identified, as some first line medicines may be less efficacious or may even worsen seizure frequency or severity.
» Patients with new onset epilepsy should have a CT scan (this is essential in immunocompromised patients), and other investigations as clinically indicated.

Special considerations

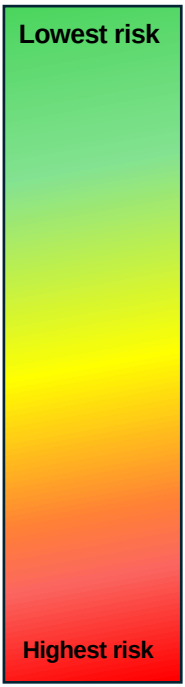
Women and girls of child-bearing potential and pregnancy

» Antiseizure medicines during pregnancy can cause structural or physical malformations and neurodevelopmental harms that may impact learning and education.
» The risk of antiseizure medicine to the unborn child needs to be balanced against the risk of uncontrolled seizures to both the mother and unborn child.
» The risk associated with each antiseizure medicine during pregnancy differs (see Figure 4).
» Women and girls of child-bearing potential with epilepsy should be counselled regarding contraception and the need to plan pregnancy.
  – NOTE: There are important drug-drug interactions between hormonal contraceptives (except DMPA) and several anticonvulsant medicines (e.g. carbamazepine, phenobarbital, phenytoin).
  – Progestin-only injectable contraceptives or IUCDs are the preferred contraceptive methods for women of child-bearing potential on ASM medication. See Chapter 7: Family planning.

It is crucial to treat epilepsy during pregnancy to prevent epileptic seizures, which pose significant risks to both the mother and the foetus/infant.

» In pregnant women, women of child-bearing potential (i.e. women < 55 years), and young girls who are likely to need to continue treatment into their child-bearing years, should initiate treatment with a lower risk antiseizure medication.
  – Lamotrigine and levetiracetam are safer antiseizure medicines to use.
  – Large amounts of data consistently show no increased risk of major congenital malformations associated with the use of lamotrigine or levetiracetam at usual doses.
  – Since lamotrigine requires slow dose titration, initiation of lamotrigine is best suited to low-risk patients.
  – Levetiracetam may be used if there is a poor response or adverse effects to lamotrigine, or in high-risk patients.
  – Seizure risk is based on clinical judgement (discuss with a specialist if unsure). In general, high-risk patients are those with frequent seizures, a previous history of hospitalisation for seizures, or previous history of status epilepticus. Low-risk patients are those with infrequent seizures, no previous hospitalisation for seizures, and no history of status epilepticus.

» Valproate **must not** be used in pregnant women, women of child-bearing potential and young girls who are likely to need continued treatment into their child-bearing years.
  – In women who take valproate while pregnant, around 1 in 9 babies (11%) will have a major birth defect and about 3–4 children in every 10 may have neurodevelopmental problems and these disorders can be seriously debilitating and permanent (e.g. delayed learning to walk and talk, lower intelligence, poor speech and language skills, memory problems, autism or autism spectrum disorders, attention deficit hyperactivity disorder).
  – In situations where valproate is deemed the only option in a female patient after all other treatment options have been ruled out, health professionals (prescribers and dispensers) are required to:
    ▪ Regularly review treatment.
    ▪ Provide counselling on the risks of valproate use in pregnancy.
    ▪ Ensure that the woman has completed and signed an acknowledgment of risk form annually: https://www.sahpra.org.za/wp-content/uploads/2025/05/GLF-CEM-PV-S01_v2-Valproate-Annual-Risk-Acknowledgement-Form-ARF.pdf
    ▪ Provide supplemental folic acid, oral, 5 mg daily.
» Women and girls with epilepsy who discover they are pregnant should not abruptly stop their ASM due to the risk of seizures.
  – Women and girls who become pregnant while on valproate should be transitioned off valproate and onto levetiracetam as early as possible during pregnancy to decrease the risk of neurodevelopmental harms, provided their seizures are not refractory to other antiseizure medications.
» During pregnancy, women may experience an increased number of seizures.
  – This may be due to sleep deprivation, increased emotional stress and changes in antiseizure medicine concentrations.
  – Antiseizure medication concentrations may decrease during pregnancy due to decreased absorption from nausea and vomiting, increased volume of distribution and increased clearance of antiseizure medicines.
  – There is increased hepatic metabolism of lamotrigine and increased renal clearance of levetiracetam in pregnancy, which returns to normal post-partum. Increase the dose if necessary, according to clinical response.



Lamotrigine, levetiracetam

Compared to the general population, lamotrigine and levetiracetam are associated with no increased risk or only a minimally increased risk of structural malformations. There is limited data on the risk of neurodevelopmental harms associated with levetiracetam and lamotrigine.

Carbamazepine

Carbamazepine is associated with a modestly increased risk of structural malformations and neurodevelopmental harms.

Phenobarbital, phenytoin, topiramate

Phenobarbital, phenytoin and topiramate are associated with a moderately increased risk of structural malformations and neurodevelopmental harms.

Valproic acid

Valproate is associated with the highest risk of structural malformations and neurodevelopmental harms.

Figure 4. Risk of congenital structural malformations and neurodevelopment harms associated with various antiseizures medicines. Increasing risk refers to increasing number of pregnancies or children affected. Adapted from Pennell PB. *Neurotherapeutics*. 2016 and Medicines & Healthcare products Regulatory Agency safety leaflet.

LoE:IVb[31]

CAUTION – ASM and pregnancy

Children born to women taking valproate are at significant risk of birth defects (11%) and persistent developmental disorders (40%). Valproate is contra-indicated and should be avoided in pregnancy and women or adolescents of child-bearing potential.

LoE:IIIb[32]

Children and adolescents transitioning to adult care

» Children and adolescents whose seizures are controlled on levetiracetam should be continued on levetiracetam in adulthood.

Adults on ART

» Lamotrigine is the preferred ASM in people on ART because of fewer medicine interactions.
» Phenytoin, phenobarbital and carbamazepine are enzyme inducing ASM. Due to potential drug interactions with ARVs, switch these medicines to lamotrigine.
» Where concurrent use of dolutegravir and carbamazepine, phenytoin, or phenobarbital is unavoidable, double dolutegravir dose to 50 mg 12-hourly.
» The metabolism of lamotrigine is induced by lopinavir/ritonavir and atazanavir/ritonavir. The dose of lamotrigine may need to be increased if patients are switched to/initiated on lopinavir/ritonavir or atazanavir/ritonavir.

GENERAL AND SUPPORTIVE MEASURES

» Patients should record dates and, if possible, times of seizures in a seizure diary. Review seizure diary at each consultation for assessment of therapy.
» Patients with epilepsy should be issued a disease identification bracelet, necklace or card.
» Patients with uncontrolled seizures should avoid driving, swimming, working at heights and operating machinery until they have been seizure free for one year. Refer to an occupational therapist for rehabilitation and a workplace assessment. The patient should sign in the medical notes that they have received workplace and lifestyle advice.
» Provide counselling and advice on:
  – the adverse effect of alcohol on seizures,
  – sleep hygiene,
  – the effect of missing a dose of medication,
  – discontinuing the medication without advice of a doctor.

MEDICINE TREATMENT

Acute treatment

Manage acute seizure and status epilepticus as per seizures/status epilepticus, see Sections 15.4: Epileptic Seizures, and 15.5: Status epilepticus.

Maintenance Treatment

» Refer to the table below for guidance around the choice of medicine by seizure type.
» HIV status, child-bearing potential and pregnancy are important determinants of medicine choice.

- The antiseizure treatment strategy should also be individualised based on use of other medicines, comorbidities, as well as response to medication, and adverse effects.
- The goal of medicine treatment is to prevent recurrent seizures and optimise quality of life.
- As a general rule, a single ASM (monotherapy) is best. Progressively increase the dose of the ASM until the seizures are controlled or clinically important side effects occur.
- Recommended drug doses are general guides and will be effective in most patients. However, some patients may need much higher or lower doses. Doses should be increased at 2-weekly intervals only.
- If the initial ASM fails to achieve satisfactory control (no seizures) at optimal dosages, or causes unacceptable adverse effects, then a trial of a second ASM medicine may be commenced.
- Initiate second medicine, titrate to therapeutic dose, then gradually reduce and stop the first ASM over 6–8 weeks or longer if necessary. (See notes below for individual medicines).
- Failure of second-line monotherapy, after exclusion of alcohol use/misuse and poor adherence, may require add on therapy. Add on therapy may be initiated by a medical practitioner in consultation with a specialist.
- Therapeutic drug monitoring is not necessary in stable patients, but should be performed in the following situations:
  - To confirm ASM toxicity in a symptomatic patient,
  - In patients with poor seizure control,
  - To confirm suspected poor adherence despite self-reported good adherence.
- Phenytoin is not recommended in the table below, however, it may be continued in adults whose seizures are well-controlled on phenytoin. Therapeutic drug monitoring should be conducted in patients receiving higher than usual doses of phenytoin.
- Long term use of phenytoin and carbamazepine are associated with potential risks. Continued use of these ASM requires careful consideration of the balance between benefits and risks in individual patients.

MEDICINE INTERACTIONS

Phenytoin, phenobarbital and carbamazepine are potent enzyme inducing agents and should be used with caution with other medicines metabolised by the liver, especially warfarin, antiretrovirals, progestin subdermal implants and oral contraceptives

LoE:IVb[33]

Table 5: Epilepsy treatment in adolescents and adults

Epilepsy type		Population	1st line	2nd line	Comments
Focal epilepsy	With and without evolution to bilateral tonic-clonic seizures	Adolescent boys, men and women not able to have children	Lamotrigine	Carbamazepine OR Levetiracetam	Avoid carbamazepine in people with HIV on ART due to drug-drug interactions
		Pregnant women and women of child-bearing potential	Lamotrigine	Levetiracetam	Avoid carbamazepine in people with HIV on ART due to drug-drug interactions
Generalised epilepsy	Tonic-clonic, atonic, clonic or tonic seizures	Adolescent boys, men and women not able to have children.	Lamotrigine (low-risk)* **OR** Levetiracetam (high-risk)*	Lamotrigine or levetiracetam (whichever not used as first line) **OR** Valproate	Valproate should not be used unless lamotrigine and levetiracetam are poorly tolerated or ineffective. If valproate used in girls 10 years and older - see note below on acknowledgement of risk form.
		Pregnant women and women of child-bearing potential	Lamotrigine (low risk)* **OR** Levetiracetam (high-risk)*	Levetiracetam or lamotrigine (whichever not used as first line) **OR** Consider combination therapy with lamotrigine and levetiracetam	Valproate should not be used unless lamotrigine or levetiracetam alone or in combination are ineffective or poorly tolerated. **If valproate is used,** see note below on "Acknowledgment of risk form" and effective family planning.
	Myoclonic *Confirm diagnosis and discuss management with a specialist*	Adolescent boys, men and women not able to have children	Valproate	Lamotrigine	These seizures may be aggravated by phenytoin or carbamazepine. Lamotrigine may be effective but may also exacerbate myoclonic seizures.

Epilepsy type	Population	1st line	2nd line	Comments
Myoclonic (continued)				If valproate used in girls 10 years and older - see note below on acknowledgement of risk form.
	Pregnant women and women of child-bearing potential	Lamotrigine	Levetiracetam	These seizures may be aggravated by phenytoin or carbamazepine. Lamotrigine may be effective but may also exacerbate myoclonic seizures.
Absence *e.g. Juvenile absence epilepsy or persistent childhood absence epilepsy*	Adolescent boys, men and women not able to have children	Valproate	Lamotrigine	These seizures may be aggravated by phenytoin or carbamazepine. If valproate used in girls 10 years and older - see note below on acknowledgement of risk form.
	Pregnant women and women of child-bearing potential	Lamotrigine	Levetiracetam	These seizures may be aggravated by phenytoin or carbamazepine. Valproate should not be used unless lamotrigine or levetiracetam, alone or in combination, are ineffective or poorly tolerated. **If valproate is used**, see note below on "Acknowledgment of risk form" and effective family planning.
Combined generalised and focal epilepsy OR Unknown/unclassified Discuss clinical presentation and management with a specialist in all cases.				

Epilepsy type	Population	1st line	2nd line	Comments
NOTE: » Lamotrigine is the preferred first line treatment for all adult patients, including women of child-bearing potential, pregnant women, and people living with HIV. » Lamotrigine requires slow dose up-titration and may not be suitable in people at high-risk of seizures. *High-risk patients are those with frequent seizures, a previous history of hospitalization for seizures, or previous history of status epilepticus. Low-risk patients are those with infrequent seizures, no previous hospitalization for seizures, and no history of status epilepticus. » **If valproate is used in girls, an acknowledgment of risk form must be obtained annually, even if not of child-bearing potential. Girls aged 10 years and older should receive effective family planning and consider a long-acting form of contraception**. https://www.sahpra.org.za/wp-content/uploads/2025/05/GLF-CEM-PV-S01_v2-Valproate-Annual-Risk-Acknowledgement-Form-ARF.pdf. *LoE:IVb*[34] *Assess level of risk (high vs low) based on clinical judgement and discuss with a specialist if unsure. In general, high-risk patients are those with frequent seizures, a previous history of hospitalization for seizures, or previous history of status epilepticus. Low-risk patients are those with infrequent seizures, no previous hospitalization for seizures, and no history of status epilepticus.				

MEDICINE TREATMENT

- Lamotrigine, oral (Doctor initiated).

Table 6: Dosing table for lamotrigine as monotherapy or add-on therapy
Dose-titrate as per table below:

	Week 1 and 2	Week 3 and 4	Maintenance dose
Monotherapy	25 mg daily	50 mg daily	100–200 mg (once a day or two divided doses). To achieve maintenance, doses may be increased by 50–100 mg every 1–2 weeks.
Add on therapy where **regimen does not include** valproate or other inducers/inhibitors of lamotrigine glucuronidation	25 mg daily	50 mg daily	100–200 mg (once a day or two divided doses). To achieve maintenance, doses may be increased by 50–100 mg every 1–2 weeks.
Add-on therapy where **regimen includes ASMs that induce glucuronidation** *(e.g. phenytoin, carbamazepine, phenobarbital, etc.)*	50 mg daily	100 mg in two divided doses	200–400 mg (two divided doses). To achieve maintenance, doses may be increased by 100 mg every 1–2 weeks.
Add-on therapy where **regimen contains valproate** *(regardless of other concomitant medication)*	25 mg on alternate days.	25 mg daily	100–200 mg (once a day or two divided doses). To achieve maintenance, doses may be increased by 25–50 mg every 1–2 weeks.

Note:

» If therapy is interrupted for more than a week, restart the titration protocol.
» Metabolism of lamotrigine is induced by lopinavir/ritonavir and atazanavir/ritonavir. The dose of lamotrigine may need to be increased when people with HIV are switched to or initiate lopinavir/ritonavir or atazanavir/ritonavir.
» Metabolism of lamotrigine is induced during pregnancy. The dose of lamotrigine may need to be increased during pregnancy.

LoE:IVb[35]

CAUTION - LAMOTRIGINE
Lamotrigine may cause Stevens-Johnson Syndrome.

LoE:IVb[36]

- Carbamazepine, oral:
  - Start with 100 mg 12 hourly.
  - Increase by 100–200 mg/day at weekly intervals according to seizure control and adverse events.
  - Usual maximal dose: 600 mg 12 hourly. *LoE:IIIb*[37]

- Levetiracetam, oral Initially 250 mg 12 hourly, increasing to a therapeutic dose of 500 mg 12 hourly.
  - Dose can be adjusted upwards in increments of 500 mg 12 hourly every 2 to 4 weeks to a maximum of 1500 mg 12 hourly (3000 mg per day).

- Valproate, oral:
  - Usual starting dose: 200–300 mg 12 hourly.
  - Increase, as required, every 3 days to 2 weeks (depending on the seizure frequency) to a maximum dose of 1200 mg 12 hourly.

- Phenytoin, oral, 4.5–5 mg/kg (lean body mass) daily, at night.
  - Only consider continuing phenytoin in patients already well controlled on phenytoin, and in whom phenytoin is well tolerated.
  - Usual starting and maintenance dose in adults: 300 mg once daily.
  - Dose increases above 300 mg should be done in no more than 50 mg increments at intervals no shorter than 2 weeks.
  - Doses > 300 mg/day of phenytoin are potentially toxic and could lead to permanent cerebellar damage. Caution and frequent monitoring of drug levels are obligatory at doses > 300 mg daily.

LoE:IVb

Poorly controlled epilepsy

» Ensure diagnosis of epilepsy and seizure type is confirmed, and imitators of epileptic seizures excluded.

» Ask the patient, and if possible, a family member or primary care giver, about the following, as these factors can influence decisions regarding medicine therapy:
  - Has the patient been adherent in taking the medication regularly for at least 2 weeks or more before the seizure? Ask about medicine dosage and frequency.

- If non-adherence has been established, ask for reasons contributing to non-adherence and offer guidance.
- Has the patient recently used some other medicine and/or herbal remedy (i.e. look for drug interactions, substance use or traditional medicine use).
- Is there a chance that alcohol is involved?
- If ≥ 1 of the above are present, address the problem/s but leave ASM unchanged (unless dose adjustment is necessary because of a drug interaction). Reassess the patient within 2 weeks.

REFERRAL

» All patients with new onset epilepsy for further investigations such as neuroimaging.
» Patients with seizures other than generalised tonic-clonic seizures, including absence seizures.
» Patients with an increase in seizure frequency despite attempts to address adherence issues.
» Patients with a change in seizure type.
» Patients who have been seizure free on ASM for 2 years or more, to review medications and to consider cessation of treatment.
» Development of new neurological signs and symptoms.
» Adverse medicine reactions or suspected toxicity in children.
» If uncontrolled on monotherapy, and patient has been shown to be adherent, referral for initiation of a second agent can be made to a medical officer at primary care level and does not require hospital / specialist referral.

Information that should accompany each referral case:

» Number and frequency of seizures per month (or year).
» Date and time of most recent seizures.
» Detailed description of the seizures, including:
  - Presence of an aura or warning signs
  - what happens during the seizure? (give a step-by-step account)
  - is the person conscious during the seizure?
  - how long do the seizures last on average?
  - what does the patient experience after the seizure?
  - how long does this experience last?
» Is there a family history of seizures?
» What is the initial date of diagnosis?
» Is there evidence of alcohol use?
» Is there another medical condition, e.g. diabetes, HIV and what medication is used?
» What is the name and dosage of the ASM used to date?
» Does the person return regularly for repeat of medication?

15.8 MENINGITIS

15.8.1 ACUTE MENINGITIS

A39.0+(G01*)/G00.0-3/G00.8-9/G01/G02.0-1/G02.8/G03.0/G03.8-9

DESCRIPTION

Infection of the membranes of the brain.

Clinical signs and symptoms include:

- » headache
- » neck stiffness
- » vomiting
- » fever
- » impaired level of consciousness
- » photophobia
- » bulging fontanelle in infants

Note:

- » During the early phase of TB meningitis, malaise, low-grade fever, headache and personality change rather than the above-mentioned symptoms may be present.
- » Duration of treatment for TB meningitis is 9 months.

Neck stiffness is rare in young children, especially in neonates, and may be absent in adults, especially debilitated patients and the elderly.

Young children with fever, vomiting and convulsions or an impaired level of consciousness must be assumed to have meningitis. Signs may be even more subtle in newborns.

EMERGENCY MEASURES

- » Stabilise before referral.
- » Treat for shock, if present.
- » If patient's level of consciousness is depressed:
  - maintain airway
  - give oxygen
- » Ensure hydration.
- » If convulsing, see Section 21.2.11: Seizures and status epilepticus.

MEDICINE TREATMENT

Initiate medicine treatment before transfer.

Children

- Ceftriaxone, IM/IV, 100 mg/kg/dose immediately as a single dose before referral. See dosing table, Chapter 23: Standard paediatric dosing tables.
  - For IM administration, do not inject more than 1 g at one injection site.
  - Maximum pre-referral dose: 2 g IM/IV.
  - If referral is delayed, repeat dose after 12 hours.
  - Maximum daily dose of 4 g, given in divided doses 12 hourly.

LoE:IVb[38]

CAUTION: USE OF CEFTRIAXONE IN NEONATES AND CHILDREN

» If *SUSPECTING SERIOUS BACTERIAL INFECTION* in neonate, give ceftriaxone, even if jaundiced.

» Avoid giving calcium-containing IV fluids (e.g. Ringer Lactate) together with ceftriaxone:
- If ≤ 28 days old, avoid calcium-containing IV fluids for 48 hours after ceftriaxone administered.
- If > 28 days old, ceftriaxone and calcium-containing IV fluids may be given sequentially provided the giving set is flushed thoroughly with sodium chloride 0.9% before and after.
- Preferably administer IV fluids without calcium contents

» Always include the dose and route of administration of ceftriaxone in the referral letter.

- Paracetamol, oral, 10–15 mg/kg/dose 6 hourly when required. See dosing table, chapter 23 standard paediatric dosing tables.

AND/OR

- NSAID, e.g.:
- Ibuprofen, oral, 5–10 mg/kg/dose 8 hourly with or after a meal. See dosing table, chapter 23 standard paediatric dosing tables.

Adults

- Ceftriaxone, IM, 2 g immediately before referral.
  - Do not inject more than 1 g at one injection site.
  - If referral is delayed, repeat dose after 12 hours.

LoE:IVb[39]

- Paracetamol, oral, 500 mg–1 g, 4–6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

AND/OR

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg then 8 hourly with meals, if needed.

Severe pain:

- Tramadol, oral, 50–100 mg 4–6 hourly.
  - May be increased to a maximum daily dose of 400mg.

During a listeria outbreak, ADD as a pre-referral dose:

A32.1/A32.7-9

Children

- Ampicillin, IM/IV 75 mg/kg/dose immediately before referral.
  - If referral is delayed by 6 hours or more, administer second dose.

Weight kg	**Dose** mg	**Injection** 500 mg/mL (500 mg diluted in 0.9 mL water for injection (WFI))	**Age** months/years
>3.5–5.5 kg	300 mg	0.6 mL	>1–3 months
>5–7 kg	450 mg	0.9 mL	>3–6 months
>7–9 kg	600 mg	1.2 mL	>6–12 months
>9–11 kg	750 mg	1.5 mL	>12–18 months
>11–17.5 kg	1000 mg	2 mL	>18 months–5 years
>17.5–25 kg	1500 mg	3 mL	>5–7 years
>25–35 kg	2000 mg	4 mL	>7–11 years
>35 kg	3000 mg	6 mL	>11 years

Adults

- Ampicillin, IM/IV, 3 g immediately before referral.
  - If referral is delayed by 6 hours or more, administer second dose.

Severe penicillin allergy:

Z88.0

Children

- Cotrimoxazole, oral, immediately before referral. See dosing table, pg 23.4.
  - If referral delayed by 12 hours or more, administer second dose.

Adults

- Cotrimoxazole, oral, 80/400 mg immediately before referral.
  - If referral delayed by 12 hours or more, administer second dose. *LoE:IVb*[40]

REFERRAL

All patients with meningitis, or suspected meningitis or suspected listeria meningitis.

15.8.2 MENINGOCOCCAL MENINGITIS, PROPHYLAXIS

Z20.8+Z29.2

In cases of meningococcal infection, the following close contacts should receive prophylaxis:

» household members,

» child-care centre contacts, and

» anyone directly exposed to the patient's oral secretions, e.g. kissing, mouth-to-mouth resuscitation, endotracheal intubation, or endotracheal tube management.

Chemoprophylaxis is only effective for the current exposure.

MEDICINE TREATMENT

Prophylaxis

Children < 6 years of age

- Ceftriaxone, IM, 125 mg, as a single dose.

CAUTION: USE OF CEFTRIAXONE IN NEONATES AND CHILDREN

» If *SUSPECTING SERIOUS BACTERIAL INFECTION* in neonate, give ceftriaxone, even if jaundiced.

» Always include the dose and route of administration of ceftriaxone in the referral letter.

Children 6–12 years of age

- Ciprofloxacin, oral, 250 mg, as a single dose.

Children > 12 years of age and adults

- Ciprofloxacin, oral, 500 mg, as a single dose.

LoE:IIIb[41]

Pregnant women

- Ceftriaxone, IM, 250 mg, as a single dose.

15.8.3 CRYPTOCOCCAL MENINGITIS

See Section 11.3.4.2: Cryptococcal Meningitis.

15.9 HEADACHE, MILD, NON-SPECIFIC

R51

DESCRIPTION

Headache can be benign or serious.

Headache can have serious underlying causes including:

» encephalitis
» meningitis
» mastoiditis
» benign intracranial hypertension
» hypertensive emergencies
» venous sinus thrombosis
» stroke
» brain tumour

Headache due to a serious disease will often be associated with neurological symptoms and signs including:

» vomiting
» fever
» mood change
» cranial nerve fall-out
» convulsions
» confusion
» impaired consciousness
» pupillary changes and difference in size
» focal paralysis
» visual disturbances
» neck stiffness

Tension headache due to muscle spasm:
» May be worse in the afternoon, but often present all day.
» Is normally felt in the neck and the back of the head, but may be felt over the entire head.
» Is often associated with dizziness and/or blurring of vision.
» Is often described as a tight band around the head or pressure on the top of the head.
» Does not progress through stages like a migraine (no nausea, no visual symptoms).

GENERAL MEASURES
» Teach relaxation techniques where appropriate.
» Reassurance, where applicable.
» Exclude analgesia overuse headache.

MEDICINE TREATMENT
Children
- Paracetamol, oral, 10–15 mg/kg/dose 6 hourly when required. See Chapter 23: Standard paediatric dosing tables.

Adults
- Paracetamol, oral, 500 mg–1 g, 4–6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

REFERRAL
» Refer patients with suspected meningitis immediately after initial treatment. See Section 15.8: Meningitis.
» Headache in children lasting for 3 days.
» Recent headache of increasing severity.
» Headache with neurological manifestations.
» Analgesia overuse headache.
» Newly developed headache persisting for >1 week in an adult.
» Chronic recurrent headaches in an otherwise healthy patient: refer if no improvement after 1 month of treatment.
» Tension headache due to muscle spasm: refer if no improvement after 1 month of treatment.

15.10 NEUROPATHY
DESCRIPTION
Defective functioning of nerves, which may involve peripheral nerves (peripheral neuropathy) and/or cranial nerves.
Clinical features may be predominantly of a sensory, sensorimotor or motor nature.

15.10.1 POST-HERPES ZOSTER NEUROPATHY (POST HERPETIC NEURALGIA)
See Section 10.13: Shingles (Herpes zoster).

15.10.2 BELL'S PALSY

G51.0

DESCRIPTION

Unilateral paralysis of all the muscles of facial expression (the corner of the mouth drops, the forehead is unfurrowed, and the eyelid will not close).

Taste sensation may be lost unilaterally and hyperacusis (painful sensitivity to loud sounds) may be present.

Most patients recover within a few weeks or months.

GENERAL MEASURES

» HIV testing.
» Referral for facial muscle massage and exercises
» Eye patch for protection of the eye during sleep.

MEDICINE TREATMENT

Adults

LoE:IVb[42]

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 60 mg daily for 7 days started within 72 hours, preferably within 48 hours of onset (Doctor prescribed). *LoE:Ia*[43]

Children

- Corticosteroids (intermediate-acting) e.g.: *LoE:IVb*[44]
- Prednisone, oral, 2 mg/kg daily for 7 days within 3 days of onset (Doctor prescribed).

Weight (kg)	Dose (mg)	Tablet (5 mg)	Age (Months/years)
>17.5–25 kg	40 mg	8 tablets	>5–7 years
>25–40 kg	55 mg	11 tablets	>7–12 years

REFERRAL

» If diagnosis uncertain.
» All cases for physiotherapy, if available.
» Eye irritation requiring lubrication.

15.10.3 PERIPHERAL NEUROPATHY

E10.4/E11.4/G60.9/G62.0-1/G62.9

DESCRIPTION

Initially sensory symptoms consisting of tingling, prickling, burning in the balls of the feet or tips of the toes or in a general distribution over the soles. The symptoms are symmetrical and with progression spread proximally.

Later sensory loss over both feet and weakness of dorsiflexion of the toes may be present. Patients may experience difficulty in walking on their heels and foot drop becomes apparent.

Common causes include HIV, diabetes mellitus, isoniazid, antiretrovirals, vitamin B12 deficiency and alcohol.

GENERAL MEASURES

» HIV testing.

» Screen for diabetes mellitus, syphilis and vitamin B12 deficiency
» Avoid alcohol.
» A balanced diet to prevent nutritional deficiency.

MEDICINE TREATMENT

» Stop the offending medicine or give suitable substitute.
» Patients on isoniazid (TB treatment or prophylaxis): increase pyridoxine to 25–50 mg 8 hourly for 3 weeks, followed by 25–50 mg daily.
- Amitriptyline, oral, 25 mg at night (Doctor prescribed).
  - Titrate at two weekly intervals to a maximum of 75 mg at night.

REFERRAL

» All children.
» All patients to rehabilitation to improve postural control and gait as well as education for prevention of complications.
» Difficulty in walking or foot drop.
» Any limb weakness present.
» Unsteady/ataxic gait.
» Severe sensory loss. *LoE:IIIb*[45]

15.11 CEREBRAL PALSY

G80.0-4/G80.8-9

DESCRIPTION

Cerebral palsy (CP) is a neurodevelopmental disorder resulting from an injury to the developing brain.

The most common type of CP is hypertonia/spasticity (85%), followed by dyskinesia (7%), ataxia (4%), and hypotonia (3%). The distribution of motor impairment may be bilateral (as in diplegia, quadriplegia, or triplegia) or unilateral (as in hemiplegia).

The primary impairments associated with CP include reduced muscle strength, impaired sensation, abnormal muscle tone and reduced cardiorespiratory fitness, resulting in difficulties performing selfcare activities and mobility. Some children with CP experience hearing loss, which may affect posture and balance.

Poor communication from speech and language impairment may also occur.

GENERAL MEASURES

» Children with CP require regular screening of their general health and wellbeing e.g. for evidence of neglect or abuse, infections, constipation, and malnutrition.
» Refer to rehabilitation services to optimise function, training on assistive devices, assessment, and management of hearing and communication problems, as well as caregiver training and support.

LoE:IIIb[46]

15.12 SPINAL CORD INJURIES

DESCRIPTION

Multiple symptoms may manifest in these patients, requiring accompanying medications and rehabilitative therapy at different levels of care.
Patients with spinal cord injuries may initially be managed at hospital level before referral to primary care level for long-term management. After referral, patients should be assisted with access of items prescribed at hospital level to ensure continuity of care.

GENERAL MEASURES

LoE:IIb[47]

Refer patients with cervical spinal cord injury for multidisciplinary rehabilitation to optimise cardiorespiratory and functional (including mental health) performance.

MEDICINE TREATMENT

Neurogenic bowel dysfunction

For constipation, see Section 2.8: Constipation.

Neuropathic and nociceptive pain

See Section 20.3: Chronic non-cancer pain.

Depression

See Section 16.4.1: Depressive disorders.

Anxiety

See Section 16.3: Anxiety disorders.

Infections

See Chapter 10: Infections and related conditions.

Pressure sores

See Section 5.19: Pressure ulcers/sores.

REFERRAL

» All patients for initial multidisciplinary assessment and management.
» Patients who require treatment for chronic conditions not covered above, such as spasticity, neurogenic bladder, DVT (prophylaxis or treatment), and osteoporosis.

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SOUTH AFRICAN PRIMARY HEALTHCARE LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 15: CENTRAL NERVOUS SYSTEM CONDITIONS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2020-4)

The Primary Health Care (PHC) Central Nervous System Conditions chapter underwent detailed clinical editing and editorial changes for clarity.

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG) and supporting medicine reviews. All reviews and costing reports may be accessed at: https://www.health.gov.za/nhi-edp-stgs-eml/.

A: NEW STANDARD TREATMENT GUIDELINES

SECTION	CONDITION	MEDICINE MANAGEMENT	MEDICINE ADDED
15.3	PARKINSONISM	No	n/a
15.11	CEREBRAL PALSY	No	n/a
15.12	SPINAL CORD INJURIES	No	Cross references added to other STGs

15.3 PARKINSONISM

A new STG on parkinsonism has been added to the PHC CNS Conditions chapter. At PHC level of care, a definitive diagnosis of Parkinson's disease may not be possible, therefore 'parkinsonism' has been referred to in the chapter. The addition to the chapter includes description of the syndrome and referral for rehabilitation in response to the external comments with supporting evidence[1,2,3] received from RuReSA and Rehabilitation Associations of SA in collaboration with the Department of Health and Rehabilitation Sciences, Stellenbosch University to "Refer patients with Parkinson's disease for multidisciplinary rehabilitation to optimise motor and speech outcomes." Broader outcomes including patients suffering from motor difficulties are addressed in the referral than proposed through the external commentator.

Level of Evidence: Low Certainty Evidence (IIIb)

The following STG was added:

G20/G21.0-4/G21.8-9/G22

DESCRIPTION

Parkinsonism is a syndrome that affects the nervous system and the parts of the body controlled by the nerves. It may be characterised by tremor, rigidity, stiffness, slow movements and postural disturbances. It may be primary, i.e. Parkinson's disease, or secondary, i.e. drug-induced, or due to uncommon disorders that may initially resemble Parkinson's disease.

Patients and caregivers may report:

- A tremor, or rhythmic shaking, which usually begins in a limb, often the hand or fingers.
- Slowed movement (bradykinesia), for example steps may become shorter as they walk and it may be difficult to get out of a chair.
- Decreased ability to perform unconscious movements, including blinking, smiling or swinging their arms while walking.
- Speech changes such as slurring or hesitation in speaking.
- Difficulty in writing.

The objective of treatment is to:

[1] Orgeta V, McDonald KR, Poliakoff E, Hindle JV, Clare L, Leroi I. Cognitive training interventions for dementia and mild cognitive impairment in Parkinson's disease. Cochrane Database of Systematic Reviews 2020, Issue 2. Art. No.: CD011961. https://doi.org/10.1002/14651858.CD011961.pub2.

[2] Tomlinson CL, Patel S, Meek C, Herd CP, Clarke CE, Stowe R, Shah L, Sackley CM, Deane KHO, Wheatley K, Ives N. Physiotherapy versus placebo or no intervention in Parkinson's disease. Cochrane Database of Systematic Reviews 2013, Issue 9. Art. No.: CD002817. https://doi.org/10.1002/14651858.CD002817.pub.

[3] Herd CP, Tomlinson CL, Deane KHO, Brady MC, Smith CH, Sackley CM, Clarke CE. Speech and language therapy versus placebo or no intervention for speech problems in Parkinson's disease. Cochrane Database of Systematic Reviews 2012, Issue 8. Art. No.: CD002812. https://doi.org/10.1002/14651858.CD002812.pub2.

» minimise disabling symptoms
» prevent complications and avoid serious drug-induced side effects

GENERAL MEASURES
All patients demonstrating signs and symptoms of parkinsonism should be referred to a medical practitioner for assessment and treatment.

REFERRAL
Patients suffering from motor difficulties should be referred for general supportive therapy and advice about lifestyle modification, and multidisciplinary rehabilitation to optimise their functioning.

15.11 CEREBRAL PALSY

A new STG on cerebral palsy has been added to the PHC CNS Conditions chapter including a description of the condition and general measures. Referral criteria includes rehabilitation in response to the external comments with supporting evidence[4] received from RuReSA and Rehabilitation Associations of SA in collaboration with the Department of Health and Rehabilitation Sciences, Stellenbosch University. **Level of Evidence: Low Certainty Evidence (IIIb).**

The following STG was added:

G80.0-4/G80.8-9
DESCRIPTION
Cerebral palsy (CP) is a neurodevelopmental disorder resulting from an injury to the developing brain.
The most common type of CP is hypertonia/spasticity (85%), followed by dyskinesia (7%), ataxia (4%), and hypotonia (3%). The distribution of motor impairment may be bilateral (as in diplegia, quadriplegia, or triplegia) or unilateral (as in hemiplegia).
The primary impairments associated with CP include reduced muscle strength, impaired sensation, abnormal muscle tone and reduced cardiorespiratory fitness, resulting in difficulties performing selfcare activities and mobility. Some children with CP experience hearing loss, which may affect posture and balance.
Poor communication from speech and language impairment may also occur.
GENERAL MEASURES
» Children with CP require regular screening of their general health and wellbeing e.g. for evidence of neglect or abuse, infections, constipation, and malnutrition.
» Refer to rehabilitation services to optimise function, training on assistive devices, assessment, and management of hearing and communication problems, as well as caregiver training and support.

15.12 SPINAL CORD INJURIES

A new STG on spinal cord injuries has been added to the PHC CNS Conditions chapter including referral criterion[5] received from RuReSA and Rehabilitation Associations of SA in collaboration with the Department of Health and Rehabilitation Sciences, Stellenbosch University for patients for multidisciplinary rehabilitation to optimise cardiorespiratory and functional (including mental health) performance.

Level of Evidence: Moderate Certainty Evidence (IIb)

An external comment to include various pharmacological management of multiple symptoms which may manifest in spinal cord injury patients was received and considered. Cross references to appropriate medicine management in the PHC STGs were added for: neurogenic bowel dysfunction (for constipation), neuropathic and nociceptive pain (for chronic non-cancer pain), depression, anxiety, infections, and pressure sores. As a cross reference to the PHC STGs was not possible for neurogenic bladder management, spasticity, DVT prophylaxis and treatment of DVT/pulmonary embolism, and osteoporosis, an instruction to refer was added for these conditions.

[4] Chorna O, Hamm E, Cummings C, Fetters A, Maitre NL. Speech and language interventions for infants aged 0 to 2 years at high risk for cerebral palsy: a systematic review. Dev Med Child Neurol. 2017 Apr;59(4):355-360. doi: 10.1111/dmcn.13342. Epub 2016 Nov 29. PMID: 27897320; PMCID: PMC5395422.
[5] Gaspar R, Padula N, Freitas TB, de Oliveira JPJ, Torriani-Pasin C. Physical Exercise for Individuals With Spinal Cord Injury: Systematic Review Based on the International Classification of Functioning, Disability, and Health. J Sport Rehabil. 2019 Jul 1;28(5):505-516. doi: 10.1123/jsr.2017-0185. Epub 2019 Feb 19. PMID: 30300056.

The external comment to consider oral short acting nifedipine, selective beta-blockers, calcium blockers for short-term use if no contra-indication for autonomic dysreflexia, pharmacological management for heterotopic ossification and sexual functioning was deferred for prioritization for review in the next review cycle for the standard treatment guidelines.

The STG outlines that spinal cord injured patients may initially be managed at hospital level, but be more appropriately managed long-term at primary care level. Where this happens, patients should be facilitated in accessing any items prescribed at hospital level at the primary care level to ensure continuity of care.

The STG was added as follows:

DESCRIPTION

Multiple symptoms may manifest in these patients, requiring accompanying medications and rehabilitative therapy at different levels of care.

Patients with spinal cord injuries may initially be managed at hospital level before referral to primary care level for long-term management. After referral, patients should be assisted with access of items prescribed at hospital level to ensure continuity of care.

GENERAL MEASURES

Refer patients with cervical spinal cord injury for multidisciplinary rehabilitation to optimise cardiorespiratory and functional (including mental health) performance.

MEDICINE TREATMENT

Neurogenic bowel dysfunction

For constipation, see Section 2.8: Constipation.

Neuropathic and nociceptive pain

See Section 20.3: Chronic non-cancer pain.

Depression

See Section 16.4.1: Depressive disorders.

Anxiety

See Section 16.3: Anxiety disorders.

Infections

See Chapter 10: Infections and related conditions.

Pressure sores

See Section 5.19: Pressure ulcers/sores.

REFERRAL

All patients for initial multidisciplinary assessment and management.

Patients who require treatment for chronic conditions not covered above, such as spasticity, neurogenic bladder, DVT (prophylaxis or treatment), and osteoporosis.

B: PROPOSED AMENDMENTS

SECTION		MEDICINE/MANAGEMENT		ADDED/DELETED/AMENDED/ NOT ADDED/ RETAINED
15.1 STROKE		Long term management		Expanded to include a wider range of rehabilitative therapies
15.2 DEMENTIA		Referral		Added
15.4 EPILEPTIC SEIZURES AND STATUS EPILEPTICUS		Types of seizures		Detail on seizure types added and expanded
15.5 STATUS EPILEPTICUS	**15.5.1 EPILEPTIC SEIZURES AND STATUS EPILEPTICUS IN CHILDREN ≤**	**EARLY STATUS EPILEPTICUS** **5-10 minutes after seizure onset**	Lorazepam, IM or buccal	Not Added at PHC
			<u>If no vascular access:</u> Diazepam, rectal	Retained

	13 YEARS	**LEVEL 1 INTERVENTION:** (benzodiazepines, up to 2 doses)		Midazolam, IM and buccal	Retained
				Lorazepam , IV	Not added at PHC
				Diazepam, IV	Added
				Midazolam, IV	Added
				Lorazepam/diazepam/midazolam IO	Not added at PHC
		ESTABLISHED STATUS **10-30 minutes after seizure onset** **LEVEL 2 INTERVENTION**	**If no vascular access:**	Phenobarbital, IM	Added
				Levetiracetam oral crushed and given by nasogastric tube	Added if no IM Phenobarbital, formulation available
				Phenobarbital, oral, crushed and given by nasogastric tube	Retained
				Phenytoin, IV or IO	Not Added
				Phenobarbital, IV or IO	Not Added
		REFRACTORY STATUS Seizures persist despite treatment with adequate doses of two or three antiseizure medications **USUALLY by 30-60 minutes after seizure** **Failure of level 1 and level 2 interventions to control seizures** **ICU**		Considerations for Midazolam infusion	Not Added
	15.4.2 Epileptic Seizures and status epilepticus in Adolescents (13 – 18 years) and Adults	**EARLY STATUS EPILEPTICUS (5 – 10 minutes)** **LEVEL 1 INTERVENTION:** Benzodiazepines	**If no IV access:**	Midazolam, IM or buccal	Retained
				Diazepam, rectal	Added if no midazolam available
			If IV access:	Lorazepam, IV	Not Added at PHC
				Midazolam, IV	Added
				Clonazepam, IV	Not Added at PHC
				Diazepam, IV	Retained
		ESTABLISHED STATUS EPILEPTICUS (10 – 30 minutes) **LEVEL 2 INTERVENTION:**	**If no IV access:**	Levetiracetam NGT	Added
			If vascular access:	Phenytoin, IV	Added

		Antiseizure medicine			
		REFRACTORY STATUS (30 – 60 minutes) REFRACTORY STATUS (30 – 60 minutes)	Propofol, IV		Not Added at PHC
			Midazolam, IV		Not Added at PHC
15.6 Febrile Seizures		For fever related symptoms (temperature > 38.5 ˚C):	Paracetamol, oral,		Retained
		Status epilepticus	Midazolam buccal OR diazepam rectal		Cross referenced to status epilepticus
15.7 Epilepsy	**15.7.1 Epilepsy in children <13 years** **(Epilepsy treatment in children 1 month to ≤ 12 years)**	Types of seizures			Detail on seizure types added and expanded
		Focal Seizures: With or without evolution to bilateral tonic-clonic seizures		**First Line:** Lamotrigine	Added for all populations
				Second Line: Carbamazepine	Added for all populations
				Second Line: Levetiracetam	Added for all populations
				Third Line: Consider combination therapy, or add-on topiramate	Not Added at PHC
		Generalised epilepsy Tonic-clonic, atonic, clonic, or tonic seizures		Phenobarbital or carbamazepine	Removed
				First Line: Lamotrigine (low risk*) OR Levetiracetam (high-risk*)	Added for Boys and girls unlikely to need treatment after age 10 years or unlikely to develop child-bearing potential
				Second Line: Levetiracetam or lamotrigine (whichever not used as first line) OR Valproic acid	Added for Boys and girls unlikely to need treatment after age 10 years or unlikely to develop child-bearing potential (Valproic acid should not be used unless lamotrigine and levetiracetam are poorly tolerated or ineffective.)
				Third Line *(specialist consultation):* Combination therapy, with add-on: Lamotrigine, or Levetiracetam, or Valproic acid, or Topiramate	Not added for PHC

			First Line: Lamotrigine (low risk*) **OR** Levetiracetam (high-risk*)	Added for Girls likely to need treatment after age of 10 years
			Second Line: Levetiracetam or lamotrigine (whichever not used as first line) **OR** Consider combination therapy with lamotrigine and levetiracetam	Added for Girls likely to need treatment after age of 10 years
			Third Line *(specialist consultation):* Consider: Valproic acid OR Add-on Topiramate	Not added for PHC
		Absence	**First Line:** Valproic acid	Added for Boys and girls unlikely to need treatment after age 10 years or unlikely to develop child-bearing potential
			Second Line: Lamotrigine	Added for Boys and girls unlikely to need treatment after age 10 years or unlikely to develop child-bearing potential
			Third Line ***(specialist consultation):*** Levetiracetam **OR** Consider combination therapy	Not Added for PHC
			First Line: Lamotrigine	Added for Girls likely to continue treatment after age of 10 years
			Second Line: Levetiracetam	Added for Girls likely to continue treatment after age of 10 years
			Third Line *(specialist consultation):* Consider combination treatment **OR** Valproic acid	Not Added for PHC
		Myoclonic Confirm diagnosis and discuss management	**First Line:** Valproic acid	Added for Boys and girls unlikely to need treatment after age 10 years/ develop child-bearing potential

		with a specialist in all cases	**Second Line:** Levetiracetam	Added for Boys and girls unlikely to need treatment after age 10 years/ develop child-bearing potential
			Third Line *(specialist consultation):* Consider Lamotrigine **OR** Topiramate, **OR** combination therapy	Not Added for PHC
			First Line: Levetiracetam	Added for Girls likely to continue treatment after age of 10 years
			Second Line: Lamotrigine	Added for Girls likely to continue treatment after age of 10 years
			Third Line: *(specialist consultation):* Consider Topiramate **OR** Combination therapy **OR** Valproic acid	Not Added for PHC
		Combined generalised and focal epilepsy OR Unknown/unclassified		No medicine management added *Discuss clinical presentation and management with a specialist in all cases*
		Lamotrigine is the preferred first line treatment - All adult patients, including women of child-bearing potential, pregnant women, and people living with HIV.		
	15.7.1.1 EPILEPSY SYNDROMES	See Paediatric Hospital Level STGs and EML Chapter 13: the Nervous System, Section 13.4.1.1: Epilepsy Syndromes		
	15.7.2 EPILEPSY IN ADOLESCENTS AND ADULTS	**Focal Epilepsy:** With and without evolution to bilateral tonic-clonic seizures	**First line:** Lamotrigine	Added: Adolescent boys, men and women not able to have children
			Second Line: Carbamazepine	Added: Adolescent boys, men and women not able to have children
			Second Line: Levetiracetam	Added: Adolescent boys, men and women not able to have children
			Third Line: *(specialist consultation):* *Consider combination therapy*	Not Added for PHC
			First line: Lamotrigine	Added for focal epilepsy: Pregnant women and women of child-bearing potential
			Second Line: Levetiracetam	Added: Pregnant women and women of child-bearing potential
			Third Line: *(specialist consultation):* Carbamazepine	Not Added for PHC

		Generalised Epilesy: Tonic-clonic, atonic, clonic or tonic seizures	**First line:** Lamotrigine (low-risk)	Retained: Adolescent boys, men and women not able to have children.
			First line: Levetiracetam(high-risk)	Added: Adolescent boys, men and women not able to have children.
			Carbamazepine	Removed
			Second Line: Lamotrigine or levetiracetam (whichever not used as first line) OR Valproic acid	Added: Adolescent boys, men and women not able to have children.
			Third Line: ***(specialist consultation):*** Discuss with specialist Valproic acid Consider combination therapy	Not Added for PHC.
			First Line: Lamotrigine (low risk)	Retained: Pregnant women and women of child-bearing potential
			First Line: Levetiracetam (high-risk)	Added: Pregnant women and women of child-bearing potential
			Second Line: Levetiracetam or lamotrigine (whichever not used as first line) OR Consider combination therapy with lamotrigine and levetiracetam	Added: Pregnant women and women of child-bearing potential
			Third Line ***(specialist consultation):*** Refer for specialist assessment and intervention	Not Added for PHC
		Myoclonic	**First line:** Valproic acid	Added: Adolescent boys, men and women not able to have children

		Confirm diagnosis and discuss management with a specialist	**Second Line:** Lamotrigine	Added: Adolescent boys, men and women not able to have children
			Third Line *(specialist consultation):* Discuss with specialist Consider levetiracetam OR Consider combination therapy	Not Added for PHC
			First line: Lamotrigine	Added: Pregnant women and women of child-bearing potential
			Second Line: Levetiracetam	Added: Pregnant women and women of child-bearing potential
			Third Line *(specialist consultation):* Discuss with specialist Consider combination therapy	Not Added for PHC
		Absence e.g. Juvenile absence epilepsy or persistent childhood absence epilepsy	**First line:** Valproic acid	Added: Adolescent boys, men and women not able to have children
			Second Line: Lamotrigine	Added: Adolescent boys, men and women not able to have children
			Third Line *(specialist consultation):* Discuss with specialist Consider levetiracetam OR Consider combination therapy.	Not Added for PHC
			First line: Lamotrigine	Added: Pregnant women and women of child-bearing potential
			Second Line: Levetiracetam	Added: Pregnant women and women of child-bearing potential
			Third Line *(specialist consultation):* Discuss with specialist Consider combination therapy OR Consider Valproic acid	Not Added for PHC

		Only consider continuing phenytoin in patients already well controlled on phenytoin, and in whom phenytoin is well tolerated	Phenytoin, oral	Retained: Only consider continuing phenytoin in patients already well controlled on phenytoin, and in whom phenytoin is well tolerated
15.8.1 ACUTE MENINGITIS		Ceftriaxone IV		Added Dose and route aligned with Paediatric STG
		Ceftriaxone IM		Retained Dose amended
		Paracetamol, oral		Added
		NSAID (e.g., Ibuprofen), oral		Added
		Tramadol, oral		Added
15.8.2 MENINGOCOCCAL MENINGITIS, PROPHYLAXIS		Ciprofloxacin, oral		Retained
		Ceftriaxone, IM (Children < 6 years of age and Pregnant Women)		Retained Editorial amendment to caution box
15.9 HEADACHE, MILD, NON-SPECIFIC		Description of the various types of headaches		Retained
15.10.3 PERIPHERAL NEUROPATHY		Referral		Added

Paracetamol[6] dosing has been amended in the chapter with dosage range amended and maximum dose reiterated and aligned to AHL Chapter 25: Pain. Additionally, the maximum daily dose for Tramadol has also been aligned to the AHL Chapter 25: Pain.

15.1 STROKE

General Measures

Long term management: *Expanded to include a wider range of rehabilitative therapies*

Long term management of stroke was expanded to include a wider range of rehabilitative therapies on receipt of motivation and evidence[7] from RuReSA and Rehabilitation Associations of SA in collaboration with the Department of Health and Rehabilitation Sciences, Stellenbosch University for various interventions for various sequalae of stroke, depending on the difficulties experienced. These included occupational therapy and / or speech therapy.

An external comment received to include a cross reference to the palliative care chapter if the patient's condition is deteriorating / in case of a massive stroke was supported by the Committee.

The following update was made to the STG:

From:

Long term management

» Optimise treatment for existing medical conditions such as hypertension, diabetes mellitus, dyslipidaemia and cardiac conditions.
» Increase regular physical activity, aim for 30 minutes 5 times a week.
» Advise patient regarding appropriate weight loss, if weight exceeds ideal weight.
» Advise patient regarding smoking cessation.
» Refer for physiotherapy, if indicated

To:

[6] South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.
[7] Pollock A, Baer G, Campbell P, Choo PL, Forster A, Morris J, Pomeroy VM, Langhorne P. Physical rehabilitation approaches for the recovery of function and mobility following stroke. Cochrane Database Syst Rev. 2014 Apr 22;2014(4):CD001920. doi: 10.1002/14651858.CD001920.pub3. PMID: 24756870; PMCID: PMC6465059.

Long term management
Optimise treatment for existing medical conditions such as hypertension, diabetes mellitus, dyslipidaemia and cardiac conditions.
Increase regular physical activity: aim for 30 minutes 5 times a week.
Advise patient regarding appropriate weight loss, if weight exceeds ideal weight.
Advise patient regarding smoking cessation.
Refer for rehabilitative therapy including physiotherapy, occupational therapy and / or speech therapy if indicated.
Initiate a palliative care approach if the patient's condition is deteriorating / in case of a massive stroke (see Chapter 22: Medicines used in palliative care).

Level of Evidence: Moderate Certainty Evidence - IIb

15.2 DEMENTIA

General Measures

Referral: *Added*

Referral criterion was added on receipt of motivation and evidence[8,9,10,11] from RuReSA and Rehabilitation Associations of SA in collaboration with the Department of Health and Rehabilitation Sciences, Stellenbosch University.

The recommendation received was for the following wording "Refer patients with dementia for cognitive or exercise rehabilitation to improve function and QOL" to be added to the STG. However, for feasibility the referral criteria wording was adapted to "Refer patients to occupational therapy, if available, for assessment of functioning and advice to the family on adaptive measures."

Level of Evidence: Low to High Certainty

External comment received to consider a palliative care approach as the patient's condition deteriorates was supported by the Committee. However, an external comment to reconsider wording for nutritional status in dementia with regard to counselling requirements for family of patients who might require interventions such as nasogastric feeds and percutaneous endoscopic gastrostomy following monitoring of nutritional requirements was deliberated but not included for the primary health care level. Instead referral requirements for patients was emphasized in the STGs.

The STG was updated as follows:

From:

GENERAL MEASURES
All patients must be seen by a doctor to confirm the diagnosis.
People with dementia are vulnerable to delirium and worsening confusion.
Manage conditions that may worsen symptoms, including:
» Electrolyte disturbances and dehydration.
» Infections, usually originating from the respiratory or urinary tract.
» Medication toxicity.
» For confirmed diagnosis of mild to moderate dementia the following supportive measure may be taken:
- Disclose the diagnosis to family members /primary care giver.
- Explain that the condition is evolving and future planning is necessary
- Advise driving cessation for the patient, if relevant.
- Discuss home safety risks – e.g. potential for patient to leave stove on while cooking or wander if not watched.
- Ensure that the patient has a caregiver that can supervise medication taking when the patient is unable to do so themselves.

[8] Bahar-Fuchs A, Clare L, Woods B. Cognitive training and cognitive rehabilitation for mild to moderate Alzheimer's disease and vascular dementia. Cochrane Database of Systematic Reviews 2013, Issue 6. Art. No.: CD003260. https://doi.org/10.1002/14651858.CD003260.pub2.
[9] Woods B, Aguirre E, Spector AE, Orrell M. Cognitive stimulation to improve cognitive functioning in people with dementia. Cochrane Database of Systematic Reviews 2012, Issue 2. Art. No.: CD005562. https://doi.org/10.1002/14651858.CD005562.pub2.
[10] Forbes D, Forbes SC, Blake CM, Thiessen EJ, Forbes S. Exercise programs for people with dementia. Cochrane Database of Systematic Reviews 2015, Issue 4. Art. No.: CD006489. https://doi.org/10.1002/14651858.CD006489.pub4.
[11] Smith TO, Gilbert AW, Sreekanta A, Sahota O, Griffin XL, Cross JL, Fox C, Lamb SE. Enhanced rehabilitation and care models for adults with dementia following hip fracture surgery. Cochrane Database of Systematic Reviews 2020, Issue 2. Art. No.: CD010569. https://doi.org/10.1002/14651858.CD010569.pub3.

- Monitor functional problems and manage as they arise e.g. urinary incontinence.
- Monitor nutritional status and intervene if necessary.
- Provide ongoing medical care.

To:

GENERAL MEASURES

All patients must be seen by a doctor to confirm the diagnosis.
People with dementia are vulnerable to delirium and worsening confusion.
Manage conditions that may worsen symptoms, including:
Electrolyte disturbances and dehydration.
Infections, usually originating from the respiratory or urinary tract.
Medication toxicity.
For confirmed diagnosis of mild to moderate dementia, the following supportive measure may be taken:

- Refer patients to occupational therapy, if available, for assessment of functioning and advice to the family on adaptive measures
- Disclose the diagnosis to family members/ primary care giver.
- Explain that the condition is evolving and future planning is necessary.
- Advise driving cessation for the patient, if relevant.
- Discuss home safety risks – e.g. potential for patient to leave stove on while cooking or wander if unattended.
- Ensure that the patient has a caregiver that can supervise medication taking when the patient is unable to do so themselves.
- Monitor functional problems and manage as they arise e.g. urinary incontinence.
- Monitor nutritional status and intervene or refer if necessary.
- Provide ongoing medical care.

» Initiate a palliative care approach as the patient's condition deteriorates. (See Chapter 22: Medicines Used in Palliative Care).

15.4 EPILEPTIC SEIZURES, 15.5 STATUS EPILEPTICUS, 15.6 FEBRILE SEIZURES AND 15.7 EPILEPSY

The Epilepsy Subcommittee was constituted in October 2024 following the receipt of numerous external comments on the draft epilepsy sections of the Primary Healthcare (PHC) and Adult Hospital level (AHL) Standard Treatment Guidelines (STGs) and Essential Medicines List (EML). Additionally, and as an overarching issue, NEMLC was concerned with the Paediatric Hospital recommendation of valproic acid as first line treatment for generalised tonic-clonic seizures, absence seizures, and children with HIV due to the concerns regarding valproic acid use in pregnancy and women and men of child-bearing potential.

The purpose of the Epilepsy Subcommittee was to align the STGs on epilepsy across all levels of care (i.e. primary, secondary, and tertiary/quaternary care) and age groups (i.e. children, adolescents and adults) to ensure a continuum of care, using the medicines currently on the EML, and to identify gaps in EML treatment.

Table B: Medicine Amendments (above) outlines the epileptic seizures, status epilepticus, febrile seizures and epilepsy antiseizure medicine changes to the PHC STGs and EML.

This is to be read in conjunction with the Epilepsy Subcommittee Report and updated STGs; which summarises the process of updating the STGs and EMLs and highlight rationale for changes.

15.8.1 ACUTE MENINGITIS

Ceftriaxone, IV: *added, dose and route of administration aligned to Paediatric Hospital Standard Treatment Guidelines*
Ceftriaxone IM*: retained with dose amendment*

The STG historically recommended ceftriaxone for IM administration which was aligned to the Integrated Management of Childhood Illness (IMCI) guideline[12]. There was a recommendation from NEMLC to include either IM or IV administration of ceftriaxone. IV administration is ideally the preferred route for meningitis due to the severity of the condition, however any limitations with obtaining IV access should not delay initiating antibiotic treatment. The Committee supported that the STG be updated to include IM or IV administration. IM administration is listed first in line with the IMCI guidance and for pragmatic reasons (i.e., inserting an IV line in children may be challenging for

[12] IMCI guideline march 2014. last accessed 30 May 2023 Child Health and Development (who.int).

nursing staff at PHC level of care). The recommended dose for meningitis (i.e., 100mg/kg) was aligned to the Paediatric Hospital Level STG[13]. It was noted that administration of higher doses should be done as a slow IV injection/infusion. The SAMF advises against IM administration of doses over 50mg/kg[14] and the IMCI guidance advises that doses over 1 gram should not be administered at a single site[12]. Additional guidance on the administration of IM and IV ceftriaxone as a single pre-referral dose of 2 grams has been included, together with the maximum allowable daily dose (4 g, given in divided doses 12 hourly), with reference to the British National Formulary for Children[15].

The repeat dose after 12 hours, if referral is delayed, and maximum daily dose of 4 g to be given in divided doses 12 hourly is now also included for adults[16].

Level of Evidence: IVb: Guidelines

Initiation of analgesia prior to referral

Children & Adults:
Paracetamol, oral: *Added*
NSAID (e.g., Ibuprofen), oral: *Added*

Adults:
Tramadol, oral*:* *Added*

For acute meningitis initiation of analgesia, prior to referral, was added for both adults and children; aligned with Hospital Level STGs. Paracetamol AND/OR NSAIDS as a therapeutic class with ibuprofen as an example were included for adults and children. Tramadol was added for severe pain in adults. Doses for paracetamol and ibuprofen were aligned to the standard dose regimen for children included throughout the PHC STG and cross referenced to the standard paediatric dosing tables included in Chapter 23 of the STG.

The STG was revised as follows:

FROM:

MEDICINE TREATMENT
Initiate medicine treatment before transfer.

Children

- Ceftriaxone, IM, 80 mg/kg/dose immediately as a single dose before referral. See dosing table, pg 23.3.
  Do not inject more than 1 g at one injection site.

CAUTION: USE OF CEFTRIAXONE IN NEONATES AND CHILDREN

» If *SUSPECTING SERIOUS BACTERIAL INFECTION* in neonate, give ceftriaxone, even if jaundiced.
» Avoid giving calcium-containing IV fluids (e.g. Ringer Lactate) together with ceftriaxone:
  - If ≤ 28 days old, avoid calcium-containing IV fluids for 48 hours after ceftriaxone administered.
  - If > 28 days old, ceftriaxone and calcium-containing IV fluids may be given sequentially provided the giving set is flushed thoroughly with sodium chloride 0.9% before and after.
  - Preferably administer IV fluids without calcium contents
» Always include the dose and route of administration of ceftriaxone in the referral letter.

Adults

- Ceftriaxone, IM, 2 g immediately before referral.

Do not inject more than 1 g at one injection site

To:

MEDICINE TREATMENT
Initiate medicine treatment before transfer.

[13] NDOH. Paediatric Hospital Level Standard Treatment Guidelines and Essential Medicines List. Chapter 8. Infective/Infectious Diseases. 2022.
[14] South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.
[15] BNF for children (BNFc). 2020-21 Ed.
[16] South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

Children

- Ceftriaxone, IM/IV, 100 mg/kg/dose immediately as a single dose before referral. See dosing table, chapter 23 standard paediatric dosing tables.
- Maximum pre-referral dose: 2g IM/IV.
- If referral is delayed, repeat dose after 12 hours.
- Maximum daily dose of 4 g, given in divided doses 12 hourly

CAUTION: USE OF CEFTRIAXONE IN NEONATES AND CHILDREN

If *SUSPECTING SERIOUS BACTERIAL INFECTION* in neonate, give ceftriaxone, even if jaundiced.

Avoid giving calcium-containing IV fluids (e.g. Ringer Lactate) together with ceftriaxone:

- If ≤ 28 days old, avoid calcium-containing IV fluids for 48 hours after ceftriaxone administered.
- If > 28 days old, ceftriaxone and calcium-containing IV fluids may be given sequentially provided the giving set is flushed thoroughly with sodium chloride 0.9% before and after.
- Preferably administer IV fluids without calcium contents

Always include the dose and route of administration of ceftriaxone in the referral letter.

Paracetamol, oral, 10–15 mg/kg/dose 6 hourly when required. See dosing table,

AND/OR

- NSAID, e.g.:
- Ibuprofen, oral, 5–10 mg/kg/dose 8 hourly with or after a meal. See dosing table, chapter 23 standard paediatric dosing tables.

Adults

- Ceftriaxone, IM, 2 g immediately before referral.
  - Do not inject more than 1 g at one injection site.
  - If referral is delayed, repeat dose after 12 hours.
  - Maximum daily dose of 4 g, given in divided doses 12 hourly

- Paracetamol, oral, 500 mg–1 g, 4–6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

AND/OR

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg then 8 hourly with meals, if needed.

Severe pain:

- Tramadol, oral, 50–100 mg 4–6 hourly.

15.8.2 MENINGOCOCCAL MENINGITIS, PROPHYLAXIS

Prophylaxis

Ciprofloxacin, oral: *Retained*

Ceftriaxone, IM: *Retained (Children < 6 years of age and Pregnant Women)*

Due to reports of fluoroquinolone resistant strains of *Neisseria meningitidis* circulating widely, the PHC expert review committee recommended that the resistance patterns for *N meningitidis* be reviewed. Good local evidence[17] (National Health Laboratory Services) was identified; showing that local strains of meningococcus that cause invasive disease are nearly universally susceptible to ciprofloxacin. In this study, Meiring et al., 2018[18] identified invasive meningococcal disease cases through a national, laboratory-based surveillance program, GERMS-SA, from 2003–2016 including clinical data on outcomes and human immunodeficiency virus (HIV) statuses from 26 sentinel hospital sites. Isolate susceptibility was 99.9% to ciprofloxacin. Therefore, ciprofloxacin was retained for prophylaxis of meningococcal meningitis.

[17] Meiring S, Cohen C, de Gouveia L, du Plessis M, Kularatne R, Hoosen A, Lekalakala R, Lengana S, Seetharam S, Naicker P, Quan V, Reubenson G, Tempia S, von Mollendorf C, von Gottberg A; GERMS-SA. Declining Incidence of Invasive Meningococcal Disease in South Africa: 2003-2016. Clin Infect Dis. 2019 Jul 18;69(3):495-504. doi: 10.1093/cid/ciy914. PMID: 30351372; PMCID: PMC7848805.

[18] Meiring S, Cohen C, de Gouveia L, du Plessis M, Kularatne R, Hoosen A, Lekalakala R, Lengana S, Seetharam S, Naicker P, Quan V, Reubenson G, Tempia S, von Mollendorf C, von Gottberg A; GERMS-SA. Declining Incidence of Invasive Meningococcal Disease in South Africa: 2003-2016. Clin Infect Dis. 2019 Jul 18;69(3):495-504. doi: 10.1093/cid/ciy914. PMID: 30351372; PMCID: PMC7848805.

Level of Evidence: Low (IIb) to Moderate (IIIb) Certainty Evidence

Caution – ceftriaxone: *Editorial amendment*
The interaction between calcium-containing IV fluids and ceftriaxone when administered via the same IV line is not relevant to the management of meningococcal meningitis, prophylaxis at PHC level of care. In alignment with other published STG chapters the caution box in the STG was revised as follows:

CAUTION: USE OF CEFTRIAXONE IN NEONATES AND CHILDREN
If *SUSPECTING SERIOUS BACTERIAL INFECTION* in neonate, give ceftriaxone, even if jaundiced.
~~Avoid giving calcium-containing IV fluids (e.g. Ringer Lactate) together with ceftriaxone:~~
~~– If ≤ 28 days old, avoid calcium-containing IV fluids for 48 hours after ceftriaxone administered.~~
~~– If > 28 days old, ceftriaxone and calcium-containing IV fluids may be given sequentially provided the giving set is flushed thoroughly with sodium chloride 0.9% before and after.~~
~~– Preferably administer IV fluids without calcium contents.~~
Always include the dose and route of administration of ceftriaxone in the referral letter

15.9 HEADACHE, MILD, NON-SPECIFIC

Description of the various types of headaches: *Retained*

The PHC Adult Expert review committee considered expanding the description of the various headache types in the STG. The original table was retained as detailed description was not considered necessary for PHC level of care.

15.10.3 PERIPHERAL NEUROPATHY

Referral: *Added*
The referral section of the STG was expanded to include: "All patients to rehabilitation to improve postural control and gait as well as education for prevention of complications," following submission of comment and evidence from RuReSA and Rehabilitation Associations of SA in collaboration with the Department of Health and Rehabilitation Sciences, Stellenbosch University. The evidence[19,20,21] related largely to diabetic neuropathy but also included critical illness and a systematic review in various neuropathies.[22]

The STG was revised as follows:

FROM:

REFERRAL
» All children.
» Difficulty in walking or foot drop.
» Any limb weakness present.
» Unsteady/ataxic gait.
» Severe sensory loss.

To:

REFERRAL
» All children.
» All patients to rehabilitation to improve postural control and gait as well as education for prevention of complications.
» Difficulty in walking or foot drop.
» Any limb weakness present.
» Unsteady/ataxic gait.
» Severe sensory loss.

Level of Evidence: Low Certainty Evidence (IIIb)

[19] Mustapa A, Justine M, Mohd Mustafah N, Jamil N, Manaf H. Postural Control and Gait Performance in the Diabetic Peripheral Neuropathy: A Systematic Review. Biomed Res Int. 2016;2016:9305025. doi: 10.1155/2016/9305025. Epub 2016 Jul 20. PMID: 27525281; PMCID: PMC4971307.
[20] Dixit S, Gular K, Asiri F. Effect of diverse physical rehabilitative interventions on static postural control in diabetic peripheral neuropathy: a systematic review. Physiother Theory Pract. 2020 Jun;36(6):679-690. doi: 10.1080/09593985.2018.1491078. Epub 2018 Jul 6. PMID: 29979897.
[21] Streckmann, F., Zopf, E.M., Lehmann, H.C. et al. Exercise Intervention Studies in Patients with Peripheral Neuropathy: A Systematic Review. Sports Med 44, 1289–1304 (2014). https://doiorg.ez.sun.ac.za/10.1007/s40279-014-0207-5.
[22] Hermans G, De Jonghe B, Bruyninckx F, Van den Berghe G. Interventions for preventing critical illness polyneuropathy and critical illness myopathy. Cochrane Database Syst Rev. 2014 Jan 30;2014(1):CD006832. doi: 10.1002/14651858.CD006832.pub3. PMID: 24477672; PMCID: PMC7390458.

Epilepsy Subcommittee Report

November 2024 – March 2025

Background

The Epilepsy Subcommittee was constituted following the receipt of numerous external comments on the draft epilepsy sections of the Primary Healthcare (PHC) and Adult Hospital level (AHL) Standard Treatment Guidelines (STGs) and Essential Medicines List (EML). Comments were received regarding the terminology and classification of epilepsy; specific pharmacological agents; management according to seizure type; special population groups; status epilepticus, and rehabilitation

Additionally, due to the concerns regarding valproate use in pregnancy and women and men of child-bearing potential, NEMLC was concerned with the Paediatric Hospital recommendation of valproate as first line treatment for generalised tonic-clonic seizures, absence seizures, and children with HIV.

Key issues arising from external comments and NEMLC discussion included:

- Alignment between levels of care regarding terminology and classification as well as treatment choices was necessary.
- Sentence level changes related to description, general measures, medicine treatment and referral criteria were required.
- Treatment algorithms were not broadly acceptable. While editing and formatting was necessary, medicine recommendations were queried and the need for and/or treatment options was raised.
- Valproate use in children would very likely be continued in girls and women of child-bearing potential and making it a first-line recommendation encourages its use. Experience reported from the Western Cape was that active engagement with PTCs and family physicians did not reduce valproate prescriptions or strengthen use of acknowledgement of risk forms.
- The long titration period required for lamotrigine makes it unacceptable to some stakeholders as first-line treatment in all paediatric and adult epilepsies.
- There is a demand for increased access to levetiracetam, including at PHC level.

The purpose, functions and decision-making process of the Epilepsy Subcommittee detailed in the Epilepsy Subcommittee terms of reference are as follows:

1. The purpose of the Epilepsy Subcommittee was to align the STGs on epilepsy across all levels of care (i.e. primary, secondary, and tertiary/quaternary care) and age groups (i.e. children, adolescents and adults) to ensure a continuum of care, using the medicines currently on the EML, and to identify gaps in EML treatment.

2. The functions of the Epilepsy Subcommittee included, but were not limited to, the following:
    - Assessing the current epilepsy STGs across all levels of care including EML items indicated for paediatric and adult male and female patients, classification of seizures, and guidance for acute versus maintenance treatment.
    - Preparing recommendations for updating of epilepsy chapters of the STGs, across all levels of care by end of March 2025; and
    - Assisting with the review of bid specifications for national tenders as needed.

Aim of this report

The aim of this report is to summarise the work conducted to date by the Epilepsy Subcommittee. Key changes to the STGs and the rationale for those changes are presented. Gaps in treatment requiring further consideration are discussed with suggested ways forward.

Methods

Members were appointed to the Subcommittee by the Chief Director: Sector Wide Procurement in the Affordable Medicines Directorate of the National Department of Health. The Subcommittee was comprised of NEMLC members, experts who had served on either the PHC and Adult Hospital or the Paediatric Hospital Expert Review Committees, external clinical experts, and a secretariat. For the external clinical experts, invitations to serve on the Subcommittee were first sent to those who had submitted comments on the epilepsy STGs. Thereafter, individual experts were invited upon recommendation by a member of the Subcommittee and according to their discipline to ensure adequate representation of relevant expertise. The Subcommittee members were as follows:

Epilepsy Subcommittee:

Adj. Prof L Robertson (Chairperson)	Psychiatrist: Sedibeng District Health Services & Department of Psychiatry, University of the Witwatersrand
Dr A Gray (Vice-Chair)	Pharmacist: Division of Pharmacology, Discipline of Pharmaceutical Sciences, University of KwaZulu-Natal.
A/Prof K Cohen	Pharmacologist: Division of Clinical Pharmacology, Department of Medicine, University of Cape Town
A/Prof T Crowley	Professional Nurse: School of Nursing, University of Western Cape
Dr MV Gule	Neurologist, Groote Schuur Hospital & University of Cape Town
Ms S McGee	Insight Actuaries and Consultants
A/Prof U Mehta	Pharmacist and Pharmacovigilance Consultant: University of Cape Town
Dr J Mohale	Family Physician: Chris Hani Health District & Walter Sisulu University
Dr G Reubenson	Paediatrician: Rahima Moosa Mother and Child Hospital & Department of Paediatrics, University of the Witwatersrand
Dr S Rossouw (resigned)	Neurologist: Livingstone Hospital, Eastern Cape
Dr T Ruder	Paediatrician: Division of Community Paediatrics, School of Public Health, University of Witwatersrand
Dr J Taylor	Pharmacology Registrar: Division of Clinical Pharmacology, Department of Medicine, University of Cape Town
Prof J Wilmshurst	Paediatric Neurologist: Head of Paediatric Neurology, Red Cross War Memorial Children's Hospital

Secretariate

Dr J Riddin	National Department of Health, Essential Drugs Programme
Ms K MacQuilkan	Health System Research Unit, SAMRC
Dr M Reddy	Health System Research Unit, SAMRC

Revision of the STGs

In revising the STGs, consensus-based decision making was used. Matters where the Subcommittee were unable to reach consensus were discussed with NEMLC on 27 February 2025.

The International League Against Epilepsy (ILAE) classification system,[1] which has been incorporated into the WHO ICD-11 nomenclature,[2] was used to reorganise the guidance. The STGs for each level of care were collapsed into one document so that guidance could be written for a continuum of care according to diagnosis.

The NICE 2022 Guideline (updated in January 2025) *Epilepsies in children, young people and adults*[3] and its evidence reviews were used to inform changes to the indications and hierarchy of choice of the antiseizure medicines (ASMs) already on the EML. An AGREE II (Appraisal of Guidelines, for Research, and Evaluation) assessment of the NICE Guideline was conducted in duplicate to evaluate the process of guideline development and quality of reporting using the AGREE II assessment tool. The NICE Guideline was rated as a high-quality clinical practice guideline with AGREE II scores of 97% overall and 98% for rigour of development (as presented in Appendix A). As the NICE evidence reviews are of high quality, alternative guidelines were not sourced. Additionally, although NEMLC acknowledged the difference in resource settings between counties NEMLC did not recommend a GRADE-ADOLOPMENT of the NICE 2022 guideline at this time.

In addition to redrafting of the guidance, a tender-related query arose regarding carbamazepine immediate versus controlled release. The question was whether to continue to tender for both preparations or only for the immediate or the controlled release preparation. A rapid review of evidence was therefore conducted (Appendix B) and discussed below.

Results

After collating and comparing the STGs for each level of care, acute management of epileptic seizures and management of febrile seizures were separated from maintenance treatment of epilepsy, so that the range of conditions were spread across four sections:

1. Epileptic Seizures; (PHC, AHL and Paediatric Hospital Level)
2. Status Epilepticus; (PHC, AHL and Paediatric Hospital Level)
3. Febrile Seizures; (PHC and Paediatric Hospital Level)
4. Epilepsy; (PHC, AHL and Paediatric Hospital Level)

Epileptic Seizures and Status Epilepticus

Previous STGs

The 2019 AHL, 2020 PHC level and 2023 Paediatric Hospital Level STGs differed as follows:
PHC: Differential diagnosis and important causes of seizures that must be excluded listed in the description. Seizure types described briefly under epilepsy section of CNS chapter. Medicine treatment for convulsive status epilepticus (i.e., status epilepticus with generalised tonic-clonic (GTC) seizures) was located separately in Chapter 21 Emergencies and Injuries. No timing of status and no supportive interventions were provided and there was no second level intervention for adults. Post-seizure recommendations in CNS chapter included the need to investigate the cause and evaluate for possible epilepsy.
Paediatric Hospital: Seizures, febrile seizures, and status epilepticus presented in separate sections prior to section on epilepsy. Aetiological and clinical classification of seizures were

[1] International League Against Epilepsy. EpilepsyDiagnosis.org. 30 June 2024. Available at https://www.epilepsydiagnosis.org/
[2] World Health Organization. ICD-11 for Mortality and Morbidity Statistics. Available at: https://icd.who.int/browse/2025-01/mms/en#1397288146
[3] NICE. Epilepsies in children, young people and adults. April 2022 (Updated 2025) Available at https://www.nice.org.uk/guidance/ng217

described using ILAE terminology.[4] Emphasis was placed on identifying cause of seizure. Guidance on laboratory and neuro-imaging investigations provided. For convulsive status epilepticus, medicine treatment and supportive interventions were provided using ILAE approach of early, established and refractory status, although timing was not 100% accurate.

Adult Hospital: Acute management of seizures was briefly noted in the epilepsy section. No differential diagnosis, or description of differing seizure types or aetiologies. Convulsive status epilepticus followed the section on epilepsy, with exclusion of some possible causes of status epilepticus noted under general measures and a post-seizure recommendation to commence phenytoin. Implication from the section was that seizures and convulsive status epilepticus are always part of epilepsy.

Table 1. Medicine treatment for status epilepticus at each level of care – previous guidance

PHC – Children	Paediatric Hospital (2023)	PHC – Adults (2019)	Adult Hospital (2020)
Initial treatment Midazolam, buccal or IM, or Diazepam, rectal Repeat benzodiazepine if no response after 10 minutes	0-5 mins Lorazepam, IV or IM or Diazepam, rectal or Midazolam, buccal	Initial treatment Midazolam, IM or buccal Or Diazepam, IV Repeat once after 5 – 10 mins if still fitting	Initial treatment Lorazepam, IV or Midazolam, IV, IM or buccal, or Clonazepam, IV or Diazepam, IV Repeat once after 5 – 10 mins if necessary Simultaneously, administer Phenytoin, IV infusion
No response to two doses benzodiazepines and convulsions lasting > 20 mins: Phenobarbital tablets, crushed via NGT	5 – 30 mins Repeat benzodiazepine, add Phenytoin, IV or Phenobarbital, IV If no response after 15 - 20 mins, repeat dose of phenytoin or phenobarbital (use alternative to what was used above)	No guidance	If further/continued seizures Repeat phenytoin infusion at half the dose.
No guidance - refer	30-60 mins Refer ICU Consider midazolam infusion, intubation and ventilation	No guidance - refer	Seizures continuing >30mins Propofol infusion or Midazolam infusion

Blue = PHC level; Orange = Paediatric Hospital level; Green = Adult Hospital

The revised STGs**,** took into consideration guidance from all three levels of care and the ILAE. Of note, the revised STG:

- provides a generic description of epileptic seizures, differential diagnoses, and important causes to exclude.
- briefly describes different seizure types with link to ILAE website
- separates management into a) children < 13 years of age and b) adolescents and adults. The rationale for this separation is that acute causes of epileptic seizures and medicine doses in adolescents are like those of adults and inpatient care of adolescents is in adult wards. Special considerations for each age group are listed under the respective section.
- separates treatment of convulsive status epilepticus using ILAE time points of 5 minutes (t_1 abnormally prolonged seizure) and 30 minutes (t_2 when a seizure may cause long-term consequences) and level 1, 2 and 3 interventions. The existing Paediatric Hospital table has been expanded to include simultaneous supportive interventions.
- post-seizure guidance is provided to include the post-ictal phase and active follow-up period.

[4] International League Against Epilepsy. Epilepsy Classification. 30 June 2024. Available at: https://www.epilepsydiagnosis.org/epilepsy/epilepsy-classification-groupoverview.html

- has refined the medicine treatments from the previous STGs only to clarify dosing and to expand vascular access in children to include the intraosseous route.

Updated medicine treatments for children < 13 years and for adolescents and adults are presented in tables 2 and 3.

Table 2. MEDICINE MANAGEMENT AND SUPPORTIVE CARE OF STATUS EPILEPTICUS IN CHILDREN < 13 YEARS (Extracted from Paediatric Hospital Standard Treatment Guidelines)

PHASE	MEDICINE MANAGEMENT	SUPPORTIVE CARE
EARLY STATUS EPILEPTICUS **5-10 minutes after seizure onset**	**LEVEL 1 INTERVENTION:** (benzodiazepines, up to 2 doses) If vascular access is available: ▪ Lorazepam, IV or IO, 0.1 mg/kg over 60 seconds (max 4 mg/dose). **OR** ▪ Midazolam, IV or IO, 0.25 mg/kg over 60 seconds, (max 10 mg/dose). **OR** ▪ Diazepam, IV or IO, 0.25 mg/kg IV over 60 seconds (max 10 mg/dose). If vascular access is not available: ▪ Lorazepam, IM or buccal, 0.1 mg/kg (max 4 mg/dose). **OR** ▪ Midazolam, IM, 0.1 mg/kg, or buccal*, 0.5 mg/kg. **OR** ▪ Diazepam, rectal**, 0.5 mg/kg (max 10 mg/dose). Expect a response within 1–5 minutes. **If the seizure does not resolve within 5 minutes after first dose, give a repeat dose of benzodiazepine.** **CAUTION** Benzodiazepines can cause respiratory depression. Monitor oxygen saturation and respiratory rate. If respiratory depression occurs, assist ventilation with bag-valve mask (1 breath every 3–5 seconds) and refer urgently/transfer to a high care setting.	» Aim for seizure control within 30 minutes of onset. » Provide supplemental oxygen, maintain $SaO_2 \geq 95\%$. » Monitor cerebral perfusion pressure (CPP), heart rate, oxygen saturation. » Check glucose. If low, correct and start maintenance IV fluid with dextrose 5% in sodium chloride 0.9%. Do not overhydrate. » Blood gas analysis for electrolytes. Correct as required. Other biochemical disorders: Correct abnormalities, if present, e.g. glucose, calcium and sodium. Take blood for electrolytes, LFTs, FBC. If patient is a known epileptic, check therapeutic levels of antiseizure medications (ASM). If meningitis cannot be excluded, give: ▪ Ceftriaxone, IM or IV, 100mg/kg/dose stat
ESTABLISHED STATUS **10-30 minutes after seizure onset**	**LEVEL 2 INTERVENTION:** If vascular access is not available: ▪ Phenobarbital, IM 20 mg/kg. ○ Slow IM injection **OR** if no IM formulation available: ▪ Levetiracetam oral, crushed and given by nasogastric tube, 60 mg/kg as a single dose (Maximum dose: 4500 mg). **OR** ▪ Phenobarbital, oral, crushed and given by nasogastric tube, 20 mg/kg as a single dose. Note: Avoid repeating oral phenobarbital as it may take over an hour to achieve therapeutic concentrations, and repeat doses increase the risk of respiratory depression. If no response to phenobarbital IM or oral after 5-20 minutes, levetiracetam oral may be given via nasogastric tube. If vascular access is available: ▪ Phenytoin, IV or IO, 20 mg/kg *(diluted in sodium chloride 0.9% and infused over 20 minutes, not exceeding 3 mg/kg/min with cardiac monitoring)*. **OR** ▪ Phenobarbital, IV or IO, 20 mg/kg over 5 mins (max 600 mg/dose). **CAUTION** Do not use phenytoin to manage drug- or toxin-induced seizures. Cardiac monitoring is mandatory to ensure safe use. If phenytoin given and no response after 15–20 mins of infusion: ▪ Phenobarbital, IV or IO, 20 mg/kg over 5 mins (max 600 mg per dose).	» Consult with higher level care and refer urgently. » Prepare for intubation and ventilation. » Ensure that phenytoin is administered independently of other IV fluid, i.e. use a separate IV line, or stop maintenance fluids, flush the line with saline and commence the phenytoin infusion. » Seizures due to poisoning should **NOT** be treated with phenytoin.

PHASE	MEDICINE MANAGEMENT	SUPPORTIVE CARE
	<u>If phenobarbital given and no response 5 mins after administration:</u> ▪ Phenytoin, IV or IO, 20 mg/kg *(diluted in sodium chloride 0.9% and infused over 20 minutes, not exceeding 3 mg/kg/min with cardiac monitoring)*. **OR** Repeat phenobarbital, IV in half doses: ▪ Phenobarbital, IV or IO, 10 mg/kg over 5 mins (max 600 mg/dose). <u>If still no response:</u> ▪ Phenobarbital, IV or IO, 10 mg/kg over 5 mins (max 600 mg/dose). Prepare for intubation if sufficiently skilled in the procedure and relevant rescue devices are available. **Refer to ICU**	
REFRACTORY STATUS Seizures persist despite treatment with adequate doses of two or three antiseizure medications **USUALLY by 30- 60 minutes after seizure onset**	**Failure of level 1 and level 2 interventions to control seizures** **Refer to ICU** Consider: » Midazolam infusion. » Maintain SaO2 ≥ 95%: Oxygen, by facemask or nasal cannulae while convulsing. » Endotracheal intubation with neuroprotective ventilation strategy (See Section 23.1: Rapid sequence intubation). » If it is necessary to ventilate, maintain PaCO2 in the low-normal range, i.e. 4.0–4.5 kPa. » Measure antiseizure medication blood concentrations if there are breakthrough seizures on medication, signs of toxicity, drug interactions or concerns about adherence.	» Stop seizure. » Support haemodynamic status. » Admit to high- or intensive-care, if possible. » Monitor: > heart rate, respiratory rate, > blood pressure, SaO2; > blood gas analysis, acid-base status; > electrolytes, blood glucose, neurological status; > fluid balance, osmolality; > Blood levels of ASM. » Cardiovascular and/or respiratory support if the patient is unable to maintain blood gases and blood pressure within the normal physiological range. **Cerebral oedema** Treat when clinically proven. See Section 13.12: Raised intracranial pressure.

<u>Note:</u>
» Watch for complications of the prolonged seizure.
» Check all possible underlining conditions.
» Watch for adverse effects of administered ASM.

* Midazolam, buccal, 0.5 mg/kg/dose. See Primary Health Care STGs and EML, Chapter 23: Standard paediatric dosing tables.
o Use midazolam for injection 5 mg in 1 mL undiluted.
o Draw up the required volume in a 5 mL syringe.
o Remove needle then administer midazolam into the buccal cavity (between gum and cheeks).
o Note: Buccal midazolam should not be used in infants < 6 months of age.

**Diazepam, rectal, 0.5 mg/kg/dose as a single dose. See Primary Health Care STGs and EML, Chapter 23: Standard paediatric dosing tables.
o Use diazepam for injection 10 mg in 2 mL undiluted.
o Draw up the required volume in a 2 mL syringe.
o Remove needle then connect syringe to an NGT and gently insert into the rectum (or insert the whole barrel of the lubricated syringe if no NGT available) and inject the contents.
o Remove NGT / syringe and hold buttocks together to minimise leakage.

Table 3: MEDICINE MANAGEMENT AND SUPPORTIVE CARE OF STATUS EPILEPTICUS IN ADOLESCENTS AND ADULTS (Extracted from Adult Hospital Standard Treatment Guidelines)

PHASE	MANAGEMENT	SUPPORTIVE CARE
EARLY STATUS EPILEPTICUS (5 – 10 minutes)	**LEVEL 1 INTERVENTION:** (Benzodiazepines) If IV access: ▪ Lorazepam, IV, 4 mg, administered not faster than 2 mg/minute. **OR** ▪ Midazolam, IV, 10 mg. **OR** ▪ Diazepam, IV, 10 mg administered over at least 5 minutes (not faster than 2mg/min). **OR** ▪ Clonazepam, IV, 1 mg. If no IV access: ▪ Midazolam, 10 mg, IM or buccal, using the parenteral formulation, while continuing to establish IV access If no IV access and no midazolam is available: ▪ Clonazepam, IM, 1 mg. **OR** ▪ Diazepam, rectal, 0.2 – 0.5 mg/kg as a single dose (maximum 20 mg/dose). If the seizure does not resolve 5 minutes after first dose of benzodiazepine, repeat the dose of benzodiazepine. If seizure aborts after 1 or 2 doses of benzodiazepines, but patient is at high risk of recurrent seizures (e.g., known with epilepsy and defaulted treatment), load with antiseizure medicine. **CAUTION** Benzodiazepines can cause respiratory depression. Monitor closely for respiratory depression. If this occurs, assist ventilation with bag-valve mask (1 breath every 3–5 seconds) and refer urgently/transfer to a high-care setting.	» Stabilize and support airway breathing and circulation » Identify and treat the underlying cause of seizures such as: – Hypoglycaemia – Electrolyte derangements (e.g. calcium, sodium, potassium, magnesium and urea) – Poisoning – Intoxication/overdose (e.g. isoniazid, theophylline, tricyclic antidepressants, cocaine, methamphetamine) – Withdrawal syndromes (e.g. alcohol, benzodiazepines) » If patient is known with epilepsy and on treatment take blood for measurement of ASM levels.
ESTABLISHED STATUS EPILEPTICUS (10 – 30 minutes)	**LEVEL 2 INTERVENTION:** (Antiseizure medicine) If IV access **and not suspected to be drug- or toxin-induced**: • Phenytoin, IV, 20 mg/kg diluted in 200 ml sodium chloride 0.9% **(not dextrose containing fluid)** administered not faster than 50mg/minute (usually 20–30 minutes) with cardiac monitoring. ○ If arrhythmias/hypotension occur, interrupt infusion temporarily and reintroduce at a slower rate. **CAUTION** Do not use phenytoin to manage suspected drug- or toxin-induced seizures. Cardiac monitoring is mandatory to ensure safe use. **Note:** » **Do not use phenytoin if seizures are suspected to be drug- or toxin-induced.** To manage, proceed to level 3 intervention, refractory status epilepticus, and address the acute poisoning (See Chapter 19: Poisoning). » If phenytoin toxicity is suspected (e.g. in a patient on chronic phenytoin treatment), proceed to level 3 intervention, refractory status epilepticus. If no IV access, consider: » Levetiracetam oral, crushed and given by nasogastric tube, 60 mg/kg as a single dose. (Maximum dose: 4500 mg).	» Prepare for intubation/ventilation » Arrange referral to higher level of care
REFRACTORY STATUS (30 – 60 minutes)	▪ Propofol, IV, 1–2 mg/kg/dose as a bolus, followed by a continuous infusion at 1.2 mg/kg/hour. If necessary, titrate to effect by increasing infusion rate by 0.3 to 0.6 mg/kg/hour every 5 minutes (maximum rate of 12 mg/kg/hour or maximum total dose of 4 mg/kg/hour over 48 hours). **OR**	» Admit to high- or intensive-care unit, if possible. » Employ a neuroprotective ventilation strategy (See Chapter 23: Adult Critical Care)

	▪ Midazolam, IV, 0.1 – 0.2 mg/kg bolus, followed by 0.05 – 0.5 mg/kg/hour infusion, titrated to effect. **Note:** » To prevent recurrent seizures if epilepsy is diagnosed or suspected, continue treatment with the most appropriate antiseizure medication during the infusion and weaning of propofol or midazolam. » Continue propofol or midazolam infusion for 12−24 hours after the last clinical or electrographic seizure, then wean the infusion.	– If it is necessary to ventilate, maintain PaCO2 in the low-normal range, i.e. 4.0–4.5 kPa. » Monitor: – heart rate, acid-base status, – respiratory rate, blood gas analysis, – blood pressure, SaO2, – electrolytes, neurological status, – blood glucose, fluid balance, – antiseizure medication blood concentrations, osmolality.

Key changes to the medicine treatment guidance are:

- Removal of a repeat dose of phenytoin IV for all age groups. The safety of a second dose of phenytoin had previously been questioned by NEMLC but not appraised. While its safety was also raised by the subcommittee, a second dose of phenytoin (which is infused over 20 minutes) is not possible before reaching t_2 (30 minutes).
- Repeat doses of phenobarbital IV in children < 13 years to be administered in two half doses, to prevent administering too high a dose and causing respiratory depression.
- Recommendation to give ASM (phenytoin, IV) simultaneously with benzodiazepines as 1st line intervention in the Adult STGs changed to a recommendation to sequential administration.
- Replacement of recommendation to initiate phenytoin 300mg (oral) per day in adults once the seizure has resolved with a more general statement of "To prevent recurrent seizures if epilepsy is diagnosed or suspected, continue treatment with the most appropriate antiseizure medication during the infusion and weaning of propofol or midazolam." Post-seizure guidance then emphasises the need to wean ASMs unless a diagnosis of epilepsy is confirmed.
- Addition of levetiracetam administration via NGT (See appendix C).
- Addition of phenobarbital IM at PHC level (if product is available).

Identified gaps

Serious gaps in the treatment of status epilepticus exist for both children < 13 years of age and people ≥13 years, especially at PHC level of care, as follows:

<u>Access to Schedule 5 medicines</u>

- PHC Nurses and Clinical Associates are currently not authorised to prescribe schedule 5 medicines for epileptic seizures and therefore may not prescribe benzodiazepines or the required doses of phenobarbital.[5,6] Medical practitioners giving verbal instructions to a pharmacist must provide a written prescription within 7 days of the instruction. There is no legislated provision for verbal instruction to a nursing sister.
- Most Emergency Medicine Services (EMS) staff only have Basic Life Support training and are not authorised to administer Schedule 5 medicines (anecdotal information).

<u>Children < 13 years of age</u>

[5] Medicines and Related Substances Act 101 of 1965

[6] Consolidated Schedules (6 September 2024) available from https://www.sahpra.org.za

- Phenobarbital, tablets crushed via nasogastric tube (NGT) 20mg/kg does not permit a repeat dose due to the time taken to reach therapeutic levels and therefore the risk of overdosing and causing respiratory depression. However, levetiracetam, oral via NGT has been included and may be administered after phenobarbital has been given if necessary.
- At PHC level, there is no intravenous second level treatment (IM/IV phenobarbital formulation only available on section 21). Phenytoin IV requires cardiac monitoring, which is not always available at PHC level.
- At hospital level, phenytoin, IV is the only intravenous second level treatment, with no alternative when phenytoin is not recommended, i.e., if there is suspected poisoning with cardio-toxic agents (phenobarbital, IV is not on tender and not registered in South Africa and is only available through SAHPRA section 21 bulk import application).

Adolescents and adults

- At PHC level, no second- level intravenous intervention.
- At hospital level, no intravenous alternative to phenytoin, IV.

Proposals for a way forward

Access to Schedule 5 medicines

- Engagement with the Directorate for Noncommunicable Diseases in the NDOH with respect to:
    - Training of PHC Nurses in management of status epilepticus in children, adolescents and adults.
    - Engagement with EMS regarding training of public health sector paramedics.
- Engagement with Nursing Council regarding extending Section 56(6) authorisation to include Schedule 5 medicines in status epilepticus, which can be done by updating the 1984 regulations.

Intravenous second level treatment other than phenytoin

- Revisit previous reviews of the evidence and costs for intravenous valproate for consideration for use at PHC and Hospital levels as an alternative to phenytoin, IV.
- Review safety and efficacy of levetiracetam, IV, although not registered with SAHPRA

Epilepsy

Previous STGs

The 2019 AHL, 2020 PHC level and 2023 Paediatric Hospital Level STGs differed as follows:

PHC: Comprehensive general guidance provided (general measures, assessment of poorly controlled epilepsy, information to accompany referrals). However, little to no information on epilepsy types. For children, medication guidance only provided for epilepsy with generalised tonic-clonic seizures and for children with HIV on ART. Recommendation for absence seizures is to refer. For adults, no differentiation is made between epilepsy types in treatment approach. Instead, medication guidance focussed on special population groups including women of child-bearing potential (WOCBP), pregnant women, and women with HIV.

Paediatric Hospital: Epilepsy types and specific syndromes are described, but little general guidance for overall clinical care. Medication guidance provided according to epilepsy type, with cautionary statement for valproate use in girls of child-bearing potential. Description and diagnostic (including EEG) features provided. Furthermore, the paediatric hospital STGs recommended valproate for children as a first line agent for generalised tonic and or clonic seizures; and concerns were raised about the use of valproate in these children as they transition

to child-bearing potential. A misalignment existed between the PHC, AHL and Paediatric Hospital STGs.

Adult Hospital: Same as for PHC guidance for adults, with treatment approach being according to special population groups rather than epilepsy type.
Medicine choices for epilepsy at each level of care in the previous STGs are presented in Table 4. All medicines on the EML for epilepsy are available at PHC level for at least one population group, except for levetiracetam syrup and topiramate which are only at Paediatric Hospital level and tertiary and quaternary levels (for treatment resistant epilepsy).

Table 4. Medicine treatment for epilepsy at each level of care – previous guidance

PHC – Children	Paeds Hospital	PHC – Adults and Adult Hospital
Focal seizures No specific guidance	**Focal seizures** 1st line • Carbamazepine 2nd line • Levetiracetam syrup, or • Lamotrigine, or • Topiramate	**All seizure types** 1st line • Lamotrigine 2nd line Not of child-bearing potential: • Valproate Pregnant women with HIV: • Levetiracetam Pregnant women without HIV: • Carbamazepine Stable on phenytoin: • Phenytoin Stable on levetiracetam initiated as a child/ adolescent: • Levetiracetam
Generalised Tonic Clonic (GTC) seizures 1st line • Phenobarbital (children < 6 months), OR • Carbamazepine Children with HIV on ART: • Valproate, to be switched to lamotrigine when girls reach child-bearing age	**GTC and/or clonic seizures** 1st line • Valproate OR • Phenobarbital (children < 6 months) 2nd line • Levetiracetam syrup, or • Lamotrigine tablets	
Other seizure types including absence seizures • Refer	**Absence seizures** 1st line • Valproate 2nd line • Lamotrigine tablets	
	Myoclonic seizures • Valproate	

Blue=available at PHC level for the specific indication; Orange=Paediatric Hospital level only

Revised STGs

As attached, the revised STGs for PHC, AHL and Paediatric hospital focus the treatment on epilepsy types according to the ILAE classification system, rather than special population groups. The medicine choices for each epilepsy type are presented in Table 5 (children < 13 years of age) and Table 6 (adolescents and adults). While the NICE 2022 Guideline[7] does not provide separate guidance for the two age groups, the Subcommittee separated them for pragmatic reasons, to accommodate dosing advice for children and levels of care. Medicine choices for 1st, 2nd and 3rd line treatment were decided upon using the NICE 2022 Guideline recommendations with consideration of practical implications in the South African public health sector.

The table of epilepsy syndromes in the Paediatric Hospital STG was also expanded to include recommended medicines and caution regarding medications that may cause exacerbations. Dosing was not included as all syndromes are to be managed with specialist advice.

[7] NICE. Epilepsies in children, young people and adults. April 2022 (Updated 2025) Available at https://www.nice.org.uk/guidance/ng217

Table 5. Epilepsy treatment in children 1 month to ≤ 12 years (Extracted from Paediatric Hospital Standard Treatment Guidelines)

Epilepsy type		Population	1st line	2nd line	3rd line *(specialist consultation)*	Comments
Focal epilepsy	With or without evolution to bilateral tonic-clonic seizures	All	Lamotrigine	Carbamazepine **OR** Levetiracetam	Consider combination therapy, or add-on topiramate	Avoid carbamazepine in children with HIV on ART due to drug-drug interactions Avoid carbamazepine and topiramate in girls who may require treatment when/ if of child-bearing potential.
Generalised epilepsy	Tonic-clonic, atonic, clonic, or tonic seizures	» Boys » Girls unlikely to need treatment after age 10 years or to develop child-bearing potential	Lamotrigine (low risk*) **OR** Levetiracetam (high-risk*)	Levetiracetam or lamotrigine (whichever not used as 1st line) **OR** Valproate	Consider combination therapy with add-on Lamotrigine, **OR** Levetiracetam, **OR** Valproate, **OR** Topiramate	Valproate should not be used unless lamotrigine and levetiracetam are poorly tolerated or ineffective. Avoid topiramate in girls who are likely to require treatment when/ if of child-bearing potential. If valproate used in girls 10 years and older - see note below on **acknowledgement of risk form**.
		Girls likely to need treatment after age of 10 years	Lamotrigine (low risk*) **OR** Levetiracetam (high-risk*)	Levetiracetam **OR** lamotrigine (whichever not used as 1st line) **OR** Consider combination therapy with lamotrigine and levetiracetam.	Consider: Valproate **OR** Add-on Topiramate	Valproate should not be used unless lamotrigine or levetiracetam, alone or in combination, are ineffective or poorly tolerated. **If valproate is used, see note below on "Acknowledgement of risk form"** and effective family planning.
	Absence	» Boys » Girls unlikely to need treatment after age 10 years or to develop child-bearing potential	Valproate	Lamotrigine	Levetiracetam **OR** Consider combination therapy	If valproate used in girls 10 years and older - see note below on **acknowledgement of risk form**.
		Girls likely to continue treatment after age of 10 years	Lamotrigine	Levetiracetam	Consider combination treatment **OR** Valproate	**If valproate is used, see note below on "Acknowledgement of risk form"** and effective family planning.

Epilepsy type		Population	1st line	2nd line	3rd line *(specialist consultation)*	Comments
	Myoclonic *Confirm diagnosis and discuss management with a specialist in all cases*	» Boys » Girls unlikely to need treatment after age 10 years or to develop child-bearing potential	Valproate	Levetiracetam	Consider Lamotrigine **OR** Topiramate, **OR** combination therapy	These seizures may be aggravated by phenytoin or carbamazepine. Lamotrigine may be effective but may also exacerbate myoclonic seizures. If valproate used in girls 10 years and older - see note below on **acknowledgement of risk form**.
	Myoclonic (Continued)	Girls likely to continue treatment after age of 10 years	Levetiracetam	Lamotrigine	Consider Topiramate **OR** Combination therapy **OR** Valproate	These seizures may be aggravated by phenytoin or carbamazepine. Lamotrigine may be effective but may also exacerbate myoclonic seizures. **If valproate is used, see note below on "Acknowledgement of risk form"** and effective family planning.
Combined generalised and focal epilepsy OR Unknown/unclassified *Discuss clinical presentation and management with a specialist in all cases*						
	NOTE: » Lamotrigine is the preferred first line treatment for all adult patients, including women of child-bearing potential, pregnant women, and people living with HIV. » Lamotrigine requires slow dose up-titration and may not be suitable in people at high-risk of seizures. » *Assess level of risk (high vs low) based on clinical judgement and discuss with a specialist if unsure. In general, high-risk patients are those with frequent seizures, a previous history of hospitalization for seizures, or previous history of status epilepticus. Low-risk patients are those with infrequent seizures, no previous hospitalization for seizures, and no history of status epilepticus. » **If valproate is used, acknowledgment of risk must be obtained annually, even if not of child-bearing potential.** https://www.sahpra.org.za/wp-content/uploads/2025/05/GLF-CEM-PV-S01_v2-Valproate-Annual-Risk-Acknowledgement-Form-ARF.pdf » **Girls aged 10 years and older should receive effective family planning and consider a long-acting form of contraception.**					

Table 6. Epilepsy treatment in adolescents and adults (Extracted from Adult Hospital Level Standard Treatment Guidelines)

Epilepsy type		Population	1st line	2nd line	3rd line *(specialist consultation)*	Comments
Focal epilepsy	With and without evolution to bilateral tonic-clonic seizures	Adolescent boys, men and women not able to have children	Lamotrigine	Carbamazepine **OR** Levetiracetam	Consider combination treatment or add-on topiramate	Avoid carbamazepine in people with HIV on ART due to drug-drug interactions
		Pregnant women and women of child-bearing potential	Lamotrigine	Levetiracetam	Consider Carbamazepine **OR** Combination of lamotrigine and levetiracetam **OR** add-on topiramate	Avoid carbamazepine in people with HIV on ART due to drug-drug interactions
Generalised epilepsy	Tonic-clonic, atonic, clonic or tonic seizures	Adolescent boys, men and women not able to have children.	Lamotrigine (low-risk) **OR** Levetiracetam (high-risk)	Lamotrigine or levetiracetam (whichever not used as first line) **OR** Valproate	Discuss with specialist Consider: Combination therapy **OR** Add-on topiramate	Valproate should not be used unless lamotrigine and levetiracetam are poorly tolerated or ineffective. If valproate used in girls 10 years and older - see note below on acknowledgement of risk form.
		Pregnant women and women of child-bearing potential	Lamotrigine (low risk) **OR** Levetiracetam (high-risk)	Levetiracetam or lamotrigine (whichever not used as first line) **OR** Consider combination therapy with lamotrigine and levetiracetam	Refer for specialist assessment and intervention	Valproate should not be used unless lamotrigine or levetiracetam alone or in combination are ineffective or poorly tolerated.
	Myoclonic *Confirm diagnosis and discuss management with a specialist*	Adolescent boys, men and women not able to have children	Valproate	Lamotrigine	Discuss with specialist Consider levetiracetam **OR** Consider combination therapy.	These seizures may be aggravated by phenytoin or carbamazepine. Lamotrigine may be effective but may also exacerbate myoclonic seizures. If valproate used in girls 10 years and older - see note below on acknowledgement of risk form.
		Pregnant women and women of child-bearing potential	Lamotrigine	Levetiracetam	Discuss with specialist Consider combination therapy	These seizures may be aggravated by phenytoin or carbamazepine. Lamotrigine may be effective but may also exacerbate myoclonic seizures.
	Absence *e.g. Juvenile absence epilepsy or persistent childhood*	Adolescent boys, men and women not able to have children	Valproate	Lamotrigine	Discuss with specialist Consider levetiracetam **OR**	These seizures may be aggravated by phenytoin or carbamazepine If valproate used in girls 10 years and older - see note below on acknowledgement of risk form.

	absence epilepsy				Consider combination therapy.	
		Pregnant women and women of child-bearing potential	Lamotrigine	Levetiracetam	Discuss with specialist Consider combination therapy **OR** Consider valproate	Valproate should not be used unless lamotrigine or levetiracetam alone or in combination are ineffective or poorly tolerated. f valproate is used, see note below on "Acknowledgement of risk form" and effective family planning. . These seizures may be aggravated by phenytoin or carbamazepine

Combined generalised and focal epilepsy
OR
Unknown/unclassified

Discuss clinical presentation and management with a specialist in all cases.

NOTE:

- Lamotrigine is the preferred first line treatment for all adult patients, including women of child-bearing potential, pregnant women, and people living with HIV.
- Lamotrigine requires slow dose up-titration and may not be suitable in people at high-risk of seizures. High-risk patients are those with frequent seizures, a previous history of hospitalization for seizures, or previous history of status epilepticus. Low-risk patients are those with infrequent seizures, no previous hospitalization for seizures, and no history of status epilepticus.
- **If valproate is used, acknowledgment of risk must be obtained annually, even if not of child-bearing potential. Girls aged 10 years and older should receive effective family planning and consider a long-acting form of contraception.** https://www.sahpra.org.za/wp-content/uploads/2025/05/GLF-CEM-PV-S01_v2-Valproate-Annual-Risk-Acknowledgement-Form-ARF.pdf

*Assess level of risk (high vs low) based on clinical judgement and discuss with a specialist if unsure. In general, high-risk patients are those with frequent seizures, a previous history of hospitalization for seizures, or previous history of status epilepticus. Low-risk patients are those with infrequent seizures, no previous hospitalization for seizures, and no history of status epilepticus.

Key changes

Key changes to the medicine treatment guidance and related concerns are as follows:

- Focal epilepsy:
    - Lamotrigine is now recommended as 1st line in all age groups. ***LoE I*** – high quality systematic review and meta-analysis (Nevitt et al., 2022),[8] with high certainty findings indicating superiority of lamotrigine compared to carbamazepine, valproate, and topiramate for treatment failure for any reason and adverse effects. There are concerns of the long initiation period placing people with ongoing seizures at risk.
    - Carbamazepine is now 2nd line in those with no child-bearing potential and/or no HIV infection even though it is inferior to levetiracetam for treatment failure for any reason and for adverse effects because of its lower cost compared to levetiracetam.
    - Levetiracetam is a 2nd line option in those where child-bearing potential is or will become a concern (as evidence suggests it has lower risk of teratogenicity than carbamazepine) and those with HIV on ART. ***LoE I*** – levetiracetam is equivalent to lamotrigine in primary outcomes of treatment failure for any reason, efficacy, and adverse effects. Rationale for proposing levetiracetam as a 2nd and not 1st line option was that lamotrigine is more affordable and does not have the neuropsychiatric side effects associated with levetiracetam (although no statistically significant difference in adverse effects found by Nevitt et al.[8])
    - Topiramate was in the Paediatric Hospital STG as a 2nd line option in focal seizures. However, no difference was found between topiramate and carbamazepine by Nevitt et al.[8] and topiramate was not considered as a monotherapy option by NICE. There are also concerns around use in WOCBP. Therefore, topiramate, was removed as a 2nd line option but add-on topiramate may be considered as a 3rd line option with specialist consultation in children, adolescents and adults (as per NICE guideline[9] recommendation, AGREE II assessment conducted by the subcommittee).
    - Valproate was not an option for focal epilepsy in our existing STGs and is only listed as a 2nd line add-on option by NICE. It therefore appears reasonable to continue without it, given the safety concerns in pregnant women and people of child-bearing potential.

- Generalised epilepsy with tonic-clonic seizures
    - No difference between levetiracetam and valproate was found by Nevitt et al. 2022 in terms of treatment failure for any reason (moderate certainty evidence). Costs of levetiracetam and valproate are similar. In addition, rapid control of seizures may be achieved, therefore is a suitable replacement of valproate as 1st line option.
    - Lamotrigine retained as a 1st line option and encouraged in patients where the long-titration period is feasible ("low-risk" patients) as there is no difference to valproate in treatment failure for any reason or adverse effects, has a favourable side effect profile and is low cost. However, Nevitt et al. found less efficacy vs valproate on network meta-analysis (no difference in efficacy on direct evidence) and long titration period mean it cannot be a stand-alone 1st option.[8]
    - Valproate is a 2nd line option in those with no child-bearing potential. Although the NICE 2022 Guideline lists valproate as a 1st line option, the supporting evidence is of moderate certainty and there is evidence of effectiveness for other ASMs (lamotrigine and levetiracetam). Additionally, the NICE 2022 Guideline provides for two specialists

[8] Nevitt et al. (2022). Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. *Cochrane Database of Systematic Reviews*. DOI: 10.1002/14651858.CD011412.pub4.
[9] NICE. Epilepsies in children, young people and adults. April 2022 (Updated 2025) Available at https://www.nice.org.uk/guidance/ng217

to concur regarding the need for valproate in individual patients, a process which is not accessible in South Africa.
    - Add-on topiramate included as a 3rd line option with specialist consultation (insufficient evidence to support topiramate in monotherapy).

- Generalised epilepsy with myoclonic seizures
    - Evidence base is weak, and the subcommittee has not been able to examine the evidence fully. Decision-making influenced by NICE guidance[10] (which is based largely on extrapolation of results for generalised tonic-clonic seizures which recommend valproate as 1st line option) and expert opinion on the subcommittee.
    - Valproate replaced by levetiracetam as 1st line recommendation for girls likely to need treatment when of child-bearing potential, because of safety considerations rather than efficacy.
    - Myoclonic seizures usually occur in epilepsy syndromes, often associated with severe to profound intellectual disability, where child-bearing potential is not a concern.[11] Therefore, it does not seem reasonable to withhold valproate in these patients.

- Generalised epilepsy with absence seizures
    - Valproate recommended as 1st line in those with no child-bearing potential. Based on results for treatment of childhood absence epilepsy (CAE) by Glauser et al. 2013[12], a high quality RCT which dominates the findings of the NICE 2022 evidence review. Comparing ethosuximide, valproate and lamotrigine, Glauser et al. found:
        - Efficacy at:
          16 or 20 weeks - Eth 53% (81/154) vs Valp 58% (85/146) vs Lam 30% (43/146)
          12 months - Eth 47% (70/150) vs Valp 44% (64/146) vs Lam 21% (31/146)
        - Intolerable adverse effects at:
          16 or 20 weeks - Eth 24% (37/154) vs Valp 24% (35/146) vs Lam 17% (25/146);
          at 12 months - Eth 25% (38/154) vs Valp 33% (48/146) vs Lam 20% (29/146)
        - Inattention at:
          16 or 20 weeks - Eth 33% (35/106) vs Valp 49% (52/106) vs Lam 24% (25/104)
          12 months Eth 29% (20/70) vs Valp 56% (34/61) vs Lam 27% (8/30)

      As ethosuximide is not available in the public sector and is too expensive for it to be made available, valproate is the next best choice.
    - Lamotrigine recommended for girls who may need treatment over the age of 10 years. Based on results from Glauser et al.[12] indicating at least some efficacy in CAE and to prevent continued use once of child-bearing potential. However, lamotrigine as 1st line for CAE is not acceptable to paediatric neurologists in girls or boys as it is less effective than valproate, and the time taken to establish response to treatment is too long (3 – 6 months). Evidence for efficacy of lamotrigine in juvenile absence epilepsy has been deferred by the subcommittee to the next review cycle.
    - Levetiracetam included as a 3rd line option (2nd line if child-bearing potential) based on weak evidence of efficacy vs placebo in one small RCT assessed by NICE guideline[13].

- Epilepsy Syndromes

[10] NICE. Epilepsies in children, young people and adults. April 2022 (Updated 2025) Available at https://www.nice.org.uk/guidance/ng217

[11] International League Against Epilepsy. EpilepsyDiagnosis.org. 30 June 2024. Available at https://www.epilepsydiagnosis.org/

[12] Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Guerreiro C, Kälviäinen R, Mattson R, French JA, Perucca E, Tomson T; ILAE Subcommission on AED Guidelines. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. Epilepsia. 2013 Mar;54(3):551-63. doi: 10.1111/epi.12074. Epub 2013 Jan 25. PMID: 23350722.

[13] NICE. Epilepsies in children, young people and adults. April 2022 (Updated 2025) Available at https://www.nice.org.uk/guidance/ng217

- Description of the syndromes simplified to be more relevant to non-specialists.
- Medicine treatment now included, to facilitate access to care close to home and enable discussion between PHC/ district hospital medical practitioners and specialists, which may occur remotely.

Subcommittee deliberations

Valproate risk/benefit

The overall risk/benefit of valproate was reviewed using the following guidance/criteria**:**

- Level of care and limited indications it will be made available for. (Ensuring there is some enforcement of adherence to guidelines and how to avoid indication creep).
- Onerous dispensing – with risk/safety acknowledgement forms.
- Caution Messaging especially at PHC level of care.
- How to position recommendation (ensure access when required).
- SAHPRA regulations and requirements.
- Pharmacy at the coalface.

Valproate in girls and women of childbearing potential

There was a push for valproate to be removed from the STGs, or at the very least to not be a 1st line option for any conditions due to the concerns regarding use of valproate in pregnancy and child-bearing potential. This recommendation arose from evidence of no change in prescribing patterns despite efforts to warn clinicians, as indicated by:

- almost no response in the Western Cape to 2016 DOH warnings regarding valproate use in WOCBP the following year (Mehta et al., 2021).[14] Valproate was prescribed to 0.94% and 0.91% of all WOCBP, and 0.21% and 0.22% of pregnancies were exposed to valproate in 2016 and 2017, respectively. Over the two years, 459 pregnancies in the Western Cape were exposed to valproate. This means that, at 10% risk, 46 children would have had birth defects and, at 30% to 40% risk, between 138 and 184 children would have one or more neurodevelopmental conditions due to valproate exposure. In both years, valproate was the most used ASM among WOCBP (45.4% in 2016 and 44.4% in 2017), followed by carbamazepine and phenytoin. Lamotrigine and levetiracetam, the safest ASMs in pregnancy, were only prescribed in 8.1% and 8.9%, and 0.3% and 0.4% for 2016 and 2017, respectively.
- another Western Cape experience in which efforts to change prescribing behaviour through education and training in 2019 and 2020[15] failed to change valproate prescribing habits as assessed in 2022. Repeat awareness raising, and education on the SAHPRA risk acknowledgement form had no impact on valproate prescribing among WOCBP, as assessed in 2024, with evidence of poor compliance with the risk acknowledgement form and little justification for valproate use in clinical records.

The sentiment was that having valproate in the STGs makes it very difficult to reduce its use, even if alternative medicines are recommended as 1st line treatment. Making it a 1st line option for selected conditions would compound the effect as it creates the impression that valproate is safe to use. Cautionary statements appear to have no impact, and the SAHPRA form is not being used.

Counter arguments to this strategy for reducing valproate use were:

- There is no good alternative to valproate for certain epilepsies, including CAE, epilepsy with myoclonic seizures, and Lennox Gastaut, Dravet, and myoclonic-atonic epilepsy syndromes.

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[14] Mehta et al. (2021). Understanding and Responding to Prescribing Patterns of Valproic acid-Containing Medicines in Pregnant Women and Women of Childbearing Age in Western Cape, South Africa. *Drug Safety* 44:41–51 DOI: 10.1007/s40264-020-00987-4

[1515] Johnson Y et.al. Department of Health Pharmacy Division in collaboration with the University of Western Cape.

- While safety in pregnancy is a priority, the epilepsy must be treated optimally to reduce mortality as well as improve quality of life.
- Reasons for no reduction in valproate prescribing in the Western Cape and increased use in KZN need interrogation. Possible causes to consider include:
    - the need for a rapid treatment response among acute inpatients, for the patient's health, and to shorten the length of hospital stay and reduce bed occupancy rates, coupled with not having an alternative, rapidly acting ASM which is effective in generalised epilepsies.
    - In addition to acute treatment of generalised seizures, valproate use may be high in psychiatric patients for the same reason, especially those presenting with marked aggression such as with substance induced mood and psychotic disorders. Anecdotally, valproate is often commenced with an antipsychotic in the hope of rapidly containing aggression and disruptive behaviour.
    - Inadequate maintenance treatment of epilepsy and bipolar disorder at PHC level, resulting in repeated acute admissions requiring rapid control of symptoms.
    - A lack of confidence in using lamotrigine among prescribers, possibly related to inadequate training and experience. As well as concern of capacity to supervise incremental dosages which in children could require 2 weekly visits for 3 months, then another 3 months to confirm if agent effective or not.
    - Difficulty in implementing the long-titration period. Pharmacy instructions written on packets of different strength tablets may be confusing to patients. Effective up-titration often requires repeated clinic visits, preferably with the same practitioner at each visit. The case load and turnover of doctors at both PHC and hospital outpatient departments may preclude consistent up-titration/ cross-titration from valproate.
    - Fear that seizures will recur if valproate is changed to an alternative ASM in people who have been stabilised on valproate. Patients stabilised on valproate, including WOCBP, may also not wish to change their treatment. An analysis in Italy[16] found that valproate use remained unchanged in 70% of the cohort of WOCBP (n=528/750) who were on valproate for at least 1 year between 2014 and 2019. Intellectual disability, higher seizure frequency, and higher valproate doses were linked to valproate continuation. Valproate withdrawal from ASM polytherapy was associated with an increased risk of tonic-clonic seizure worsening (OR 2.91, 95% CI 1.09–7.77) compared to valproate continuation.
    - Many of the childhood epilepsies for which valproate is recommended will either outgrow the epilepsy before reaching child-bearing age (e.g., CAE) or will never be of child-bearing potential, mainly due to comorbid severe developmental delay (e.g., Lennox Gastaut syndrome). However, treatment of epilepsy with absence or myoclonic seizures persisting or beginning in adolescence remains a serious concern.
    - Of note epilepsy is a potentially life-threatening disease and clinicians need to be enabled to offer optimal care for their patients.

Valproate use in boys and men

- The reproductive risks of valproate use in men and associated precautionary measures needed in South Africa were deliberated briefly, noting that the UK Medicines and Healthcare Products Regulatory Agency (MHRA) has issued precautionary contraceptive advice regarding valproate use in men[17] and has included men in its recommendation that "valproate must not be started in new patients (male or female) younger than 55 years,

[16] Esposto et al. (2025). Valproic acid discontinuation in girls and women of childbearing age with epilepsy: An Italian multicenter retrospective study on prescribing patterns and outcomes. *Epilepsia.* 00:1–11 DOI: 10.1111/epi.18281
[17] NICE. Valproic acid use in men: as a precaution, men and their partners should use effective contraception. 5 September 2024. Available at: https://www.gov.uk/drug-safety-update/valproic acid-use-in-men-as-a-precaution-men-and-their-partners-should-use-effective-contraception

unless two specialists independently consider and document that there is no other effective or tolerated treatment, or there are compelling reasons that the reproductive risks do not apply."[18]

The following evidence of possible harm was discussed:

- A retrospective observational study, combining data from multiple registry databases in Norway, Denmark and Sweden.[19] Cumulative risk of neurodevelopmental disorders ranged from 4.0% to 5.6% in the valproate treated group versus 2.3% to 3.2% in the composite lamotrigine/levetiracetam monotherapy treated group (pooled adjusted hazard ratio 1.50, 95% CI 1.09 to 2.07). Of note:
    - this potential risk is much lower than the up to 30-40% risk of neurodevelopmental disorders in children born to mothers taking valproate during pregnancy and therefore may not warrant the same level of urgency.
    - the study did not include an untreated group and background risk in this patient population is therefore unknown
    - while an increased risk of neurodevelopmental disorders in children of fathers treated with valproate in the 3 months prior to conception is possible, the causal role of valproate is not confirmed.
    - the European Medicines Agency is currently reviewing data regarding the risk to offspring of men taking valproate,[20] and has issued the following statement "Male patients being treated with valproate should not stop taking their medicine without talking to their doctor, as their epilepsy or bipolar disorder could become worse. Sudden discontinuation of treatment for epilepsy could trigger seizures. Patients who have any questions about their treatment should speak to their healthcare professional."
- A registry linked "nationwide cohort study in Denmark comprising 1 235 353 children [born between 1997 and 2017], including 1336 children born to fathers who filled prescriptions for valproate during spermatogenesis, found no association between paternal valproate use and risk of major congenital malformations or neurodevelopmental disorders, including autism spectrum disorder."[21]
- An observational prospective study reviewed 17 infertile men with epilepsy who were switched from valproate to levetiracetam or lamotrigine.[22] Switching was associated with improved sperm counts (p=.06), total motility (p=.02), non-progressive motility (p=.03) and reduced sperm head defects (p=.03). Spontaneous pregnancies occurred in three of the 17 couples during the follow-up period.
- A meta-analysis of preclinical and clinical data concerning the impact of valproate on male fertility:[23]
    - Preclinical studies (n=112 animals): decreased sperm count and sperm motility, and increased percentage of abnormal sperm found in treated vs control groups.
    - Clinical studies (n=274 men): significant reduction in sperm motility (SMD = -1.62, 95% CI: -2.81 to -0.43, P = 0.033) but non-significant decreased sperm count and increased percentage of abnormal sperm in intervention vs control groups.

[18] NICE. Valproic acid (Belvo, Convulex, Depakote, Dyzantil, Epilim, Epilim Chrono or Chronosphere, Episenta, Epival, and Syonell▼): new safety and educational materials to support regulatory measures in men and women under 55 years of age**. 22 January 2024.**Available at: https://www.gov.uk/drug-safety-update/valproic acid-belvo-convulex-depakote-dyzantil-epilim-epilim-chrono-or-chronosphere-episenta-epival-and-syonellv-new-safety-and-educational-materials-to-support-regulatory-measures-in-men-and-women-under-55-years-of-age#advice-for-healthcare-professionals https://www.ema.europa.eu/en/news/potential-risk-neurodevelopmental-disorders-children-born-men-treated-valproic acid-medicines-prac-recommends-precautionary-measures.

[19] Potential risk of neurodevelopmental disorders in children born to men treated with valproic acid medicines: PRAC recommends precautionary measures. 12 January 2024. Available at: https://www.ema.europa.eu/en/news/potential-risk-neurodevelopmental-disorders-children-born-men-treated-valproic acid-medicines-prac-recommends-precautionary-measures

[20] European Medicines Agency (EMA). EMA review of data on paternal exposure to valproic acid. 16 August 2023. Available at: https://www.ema.europa.eu/en/news/ema-review-data-paternal-exposure-valproic acid

[21] Christensen et al. 2024. Valproic acid Use During Spermatogenesis and Risk to Offspring. *JAMA Network Open.* 7(6): e2414709. DOI:10.1001/jamanetworkopen.2024.14709

[22] Markoula et al. 2020. An open study of valproic acid in subfertile men with epilepsy. *Acta Neurol Scand*. 142:317–322. DOI: 10.1111/ane.13311

[23] Asghar et al. 2024. Understanding the impact of valproic acid on male fertility: insights from preclinical and clinical meta-analysis. BMC Pharmacology an d Toxicology 25:69 DOI:10.1186/s40360-024-00791-1

The subcommittee's conclusion was that the evidence of harm to children from valproate use in men was very weak and did not warrant prescribing limitations such as those recommended for WOCBP. While valproate use may negatively affect fertility, this could be managed with a recommendation to advise the patient, and to use lamotrigine or levetiracetam if needed.
Therefore, medicine treatment guidance has been separated for boys and men vs girls and WOCBP in the STGs (see Tables 5 and 6 above).

Ensuring compliance with SAHPRA recommendations for valproate

Discussion focussed on ways to ensure that completion of the SAHPRA acknowledgement of risk form if valproate is used in girls and WOCBP. Possibilities included simplifying the form (discussions are underway between the EDP and SAHPRA), restricting valproate use to hospital level services and specialist prescription, or training pharmacists at hospital and district level to not dispense if no signed form is attached to the prescription and to discuss with the prescriber in such cases.

If it is a way forward, a simplified form should be coordinated by the regulator. It is unclear whether the simplified form in the Western Cape has reduced valproate prescribing where alternative medicines may be used, improved counselling of the patient and/or caregiver, and appropriate contraception use.

Restricting to hospital level and specialist initiation in this population group may be an option (waiting lists are long and travel is not always available or convenient). Most of the epilepsies for which valproate is recommended 1st line should all be managed in consultation with a specialist, and Part B of the SAHPRA acknowledgement of risk form[24] must be signed by a specialist. The problem is that to prevent breaks in maintenance treatment, valproate should ideally be available at PHC level, as the most accessible point of care. Additionally, typical CAE should be diagnosed and managed by PHC level medical doctors (where they are available), as the condition is not complex and improved coverage is needed.

Valproate will be available at PHC level for epilepsies in boys and men and for bipolar disorder. Therefore, another strategy is that pharmacists at all levels of care would not dispense valproate for girls and WOCBP without a signed motivation or a copy of the risk acknowledgement form attached to the prescription. What is then required is that hard copies of the form should be available at all levels of care, in all relevant clinics.

Cost considerations

Using 2024 tender prices and defined daily dosing (DDD), the cost of levetiracetam is similar to valproate (Table 7). Therefore, expanding use of levetiracetam as a replacement for valproate is unlikely to affect overall expenditure. However, lamotrigine is the cheapest option.

[24] https://www.sahpra.org.za/document/valproic acid-annual-risk-acknowledgement-form/

Table 7. Antiseizure medicine costs per Defined Daily Dose (DDD) at December 2024 tender prices

Medicine	Strength		Formulation	Pack size	Price 2024	Cost/tablet or ml	DDD (in mg)	Tablets /mls in a DDD	Cost of 1 DDD	Cost for 28 days
Carbamazepine	20	mg/ml	Suspension	250	R 126,79	R 0,51	1000	50	R 25,36	R 710,02
Carbamazepine	200	mg	Tablet	28	R 15,64	R 0,56	1000	5	R 2,79	R 78,20
Carbamazepine	200	mg	Tablet	56	R 35,75	R 0,64	1000	5	R 3,19	R 89,38
Carbamazepine	200	mg	Tablet	56	R 31,96	R 0,57	1000	5	R 2,85	R 79,90
Carbamazepine	200	mg	Tablet	84	R 49,81	R 0,59	1000	5	R 2,96	R 83,02
Carbamazepine	200	mg	Tablet	84	R 51,72	R 0,62	1000	5	R 3,08	R 86,20
Carbamazepine	400	mg	Tablet	28	R 52,50	R 1,88	1000	3	R 4,69	R 131,25
Lamotrigine	25	mg	Tablet	56	R 18,20	R 0,33	300	12	R 3,90	R 109,20
Lamotrigine	50	mg	Tablet	56	R 18,20	R 0,33	300	6	R 1,95	R 54,60
Lamotrigine	100	mg	Tablet	56	R 36,68	R 0,66	300	3	R 1,97	R 55,02
Lamotrigine	200	mg	Tablet	56	R 71,18	R 1,27	300	2	R 1,91	R 53,39
Levetiracetam	250	mg	Tablet	30	R 23,46	R 0,78	1500	6	R 4,69	R 131,38
Levetiracetam	500	mg	Tablet	30	R 43,24	R 1,44	1500	3	R 4,32	R 121,07
Levetiracetam	750	mg	Tablet	30	R 64,40	R 2,15	1500	2	R 4,29	R 120,21
Phenobarbital	30	mg	Tablet	28	R 5,42	R 0,19	100	3	R 0,65	R 18,07
Phenobarbital	30	mg	Tablet	56	R 9,91	R 0,18	100	3	R 0,59	R 16,52
Phenobarbital	30	mg	Tablet	84	R 15,54	R 0,19	100	3	R 0,62	R 17,27
Phenytoin	100	mg	Capsule	100	R 66,19	R 0,66	300	3	R 1,99	R 55,60
Phenytoin	100	mg	Tablet	84	R 54,73	R 0,65	300	3	R 1,95	R 54,73
Topiramate	25	mg	Tablet	60	R 25,46	R 0,42	300	12	R 5,09	R 142,58
Topiramate	50	mg	Tablet	60	R 30,98	R 0,52	300	6	R 3,10	R 86,74
Topiramate	100	mg	Tablet	60	R 49,72	R 0,83	300	3	R 2,49	R 69,61
Valproic acid	40	mg/ml	Syrup	300	R 133,11	R 0,44	1500	38	R 16,64	R 465,89
Valproic acid	100	mg	Dispersible tab	100	R 155,95	R 1,56	1500	15	R 23,39	R 654,99
Valproic acid/Valproic acid	200	mg	Tablet	100	R 69,82	R 0,70	1500	8	R 5,24	R 146,62
Valproic acid/Valproic acid	200	mg	Tablet	56	R 44,53	R 0,80	1500	8	R 5,96	R 166,99
Valproic acid/Valproic acid	300	mg	Tablet	100	R 90,56	R 0,91	1500	5	R 4,53	R 126,78
Valproic acid/Valproic acid	300	mg	Tablet	56	R 56,72	R 1,01	1500	5	R 5,06	R 141,80
Valproic acid/Valproic acid	500	mg	Tablet	100	R 136,77	R 1,37	1500	3	R 4,10	R 114,89
Valproic acid/Valproic acid	500	mg	Tablet	56	R 85,30	R 1,52	1500	3	R 4,57	R 127,95

Education and training

Lack of expertise among general medical practitioners in diagnosing and managing epilepsy is concerning, especially at PHC level. The BPNA (British Paediatric Neurology Association) has developed a Paediatric Epilepsy Training (PET)[25] course which has been facilitated and endorsed by ILAE for international roll-out. In addition, ILAE has piloted an Epilepsy Training in Adult Medicine (ETAM) course which should also be widely available in Africa. While the NDOH knowledge hub webinars may be used to disseminate the STGs, there is a need to explore other options for more widespread training.

Medicine treatment recommendations

No new medicines have been added to treatment recommendations. However, there are changes in indications and hierarchy of medicine choices. Points considered:

- Valproate recommended as 1st line recommendation for absence seizures in girls ≤10 years, Lennox Gastaut and Dravet syndromes. NICE guidance has retained valproate as a 1st line option for various epilepsies based on evidence of efficacy. NICE has not used hierarchy of choice as a mechanism for discouraging valproate use but has emphasized the need to trial other 1st line options in girls and WOCBP. Our guidelines differ in that we do not tend to provide alternative options in each category unless they are equivalent, and choice is influenced by availability.
- Affordability of expanding levetiracetam vs lamotrigine use.
- Expansion of topiramate indications to other epilepsies and age groups (is Paediatric Hospital at present for focal epilepsy and indicated for refractory epilepsy at tertiary level). It is always as a 3rd line treatment with specialist consultation, to facilitate care of treatment resistant epilepsy. Evidence for use is not strong, and inappropriate prescribing should be prevented.

Monitoring and evaluation

Medicine utilisation monitoring should be coupled with some form of treatment outcome monitoring (e.g., epilepsy rehospitalisation). This may require expansion of national indicators to include epilepsy. The Affordable Medicines directorate is in the process of approaching relevant NDOH stakeholders to discuss the issue.
Included in stakeholder consultation, is the need to expand education and training programs.

Recommendations for review in the next review cycle

- Consider a full GRADE Adolopment process of NICE guidelines.
- Future review cycles, continue review of generalised epilepsy with tonic-clonic seizures as low-risk and high-risk groups.
- Review motivation and evidence for IV levetiracetam, however not yet registered in South Africa.
- Re-evaluation of previous reviews on use of IV valproate in status epilepticus.
- Evidence for efficacy of lamotrigine in juvenile absence epilepsy.
- Affordability of expanding levetiracetam vs lamotrigine use.
- Need for rescue therapy in specific high-risk cases where the diagnosis of epilepsy is not confirmed is still to be discussed by the subcommittee.

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[25]British Paediatric Neurology Society. Paediatric Epilepsy Training (PET). Available at: https://courses.bpna.org.uk/index.php?page=paediatric-epilepsy-training#:~:text=Paediatric%20Epilepsy%20Training%20(PET)%20is,is%20now%20being%20established%20worldwide.

- Review occupational therapy for the epilepsy STGs in the next review cycle.
- Epilepsy has functional implications that require screening and intervention from a rehabilitation multidisciplinary team to prevent a disability. NEMLC advised that a thorough review regarding occupational therapy and epilepsy be conducted in the next review cycle.

Appendix A: AGREE II assessment on NICE guidelines:

AGREE II assessment scores

Epilepsies in children, young people and adults (April 2022 - Updated 2025)

Scoring the guidelines

	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	7	7	7	7	7	7	7	7	7	7	7	7	6	6	7	7	7	7	7	7	7	7	7	159
Appraiser 2	7	7	6	6	6	7	7	7	7	7	7	7	7	7	7	7	7	5	7	7	6	6	7	154
Item Total	14	14	13	13	13	14	14	14	14	14	14	14	13	13	14	14	14	12	14	14	13	13	14	313
Domain Total	41			40			110								42			53				27		313
Minimum possible score	6			6			16								6			8				4		46
Maximum possible score	42			42			112								42			56				28		322
Domain score	**97%**			**94%**			**98%**								**100%**			**94%**				**96%**		**97%**

Overall assessment: The Guideline is recommened for use in this context

Score: (e.g. domain 1)

Maximum possible score = 7 (highest score) x no. of items x no. of appraisers
Minimum possible score = 1 (lowest score) x no. of items x no. of appraisers

Score for each domain

Obtained score - minimum possible score / Maximum possible score - minimum possible score X 100

NICE. Epilepsies in children, young people and adults. April 2022 (Updated 2025) Available at https://www.nice.org.uk/guidance/ng217

South African National Essential Medicine List
Primary Health Care (PHC), Adult Hospital Level (AHL), Paediatric Hospital Level Medication Review Process
Component:
CARBAMAZEPINE IMMEDIATE VERSUS CONTROLLED RELEASE

EVIDENCE SUMMARY

Date: February 2025

Query: Guidance and approval are required from NEMLC as to whether the NDoH should tender for carbamazepine immediate release and controlled release/modified release:

- separately and awarded separately (as separate specification items)

OR

- as an either-or option and if the least expensive option should be awarded (noting the need for some immediate release formulation for titration etc).

Background

The Affordable Medicines Directorate (AMD) of the National Department of Health is currently preparing for the next tender for solid dosage forms. A query arose during the bid specification process as to how carbamazepine immediate release and modified/controlled release preparations should be tendered for i.e. both provided on tender, or an either-or option as summarised above. This is a historic query raised by the provinces.

Carbamazepine modified release history

- Carbamazepine 400mg tablet, 28 tablets:
  - tender specification was first added in 2015 (note only 400mg specification; not specified as modified release). At the time the item was not awarded on contract.
- Carbamazepine; 400mg; Tablet, MR; 28 tablets:
  - awarded on contract in 2019 – RT89-2019 (*1 May 2019 – 30 April 2021*
  - Not awarded on next tender: HP09-2021 (no bids received for this specification) – item canceled.
  - Awarded on current tender HP09-2023 (ending in April 2026).
  - Note specification always advertised as just 400mg tablet, but only modified release tablets offered.

Historically the carbamazepine immediate release (IR) and modified/controlled release (CR) preparations were tendered for as an either-or option based on previous NEMLC guidance that there is no preference for either product, or the cheaper product should be made available. The Bid Specification Committee however indicated that there is still usage of the modified/controlled release preparation across some of the provinces accessed through the named patient motivation process. In preparation for the next solid dosage form tender, the Essential Drugs Programme is requesting confirmation from NEMLC, that the carbamazepine immediate release and modified/controlled release preparations still be tendered for as an either-or option. Availability of medicines on a national contract facilitates easier access in terms of procurement for all provinces. It was noted that the next Bid Specification meeting is scheduled for 11 February 2025 and the NEMLC meeting will be held on 27 February 2025. Feedback can be provided to the Bid Specification Committee following the February 2025 NEMLC meeting.
Currently there is varied use across the country (see procurement summary below), but feedback during the tender meetings indicate that the provinces prefer the modified release.

The matter was also tabled at the 20 December 2024 epilepsy SC meeting where members indicated preference for tendering separately as there might be instances where the controlled release/modified release is preferred to the immediate release e.g. (1) in young children where adverse effects of drowsiness occurring in the school day could

impact adherence and (2) where patients have already been initiated on a on formulation and switching might not be desired. It was also noted that the issue of offering two different formulations raises concerns around equity as some provinces are purchasing the controlled release preparation while others do not, and some provinces offer the immediate release preparation mainly while the controlled release preparation is maintained through good governance on a named patient basis only.

Purpose of this document

To outline:

- The Query (as above)
- Background (as above)
- Indications of Carbamazepine in the STGs
- Tabulate the pharmacokinetic differences of both options
- External comments related to carbamazepine that might relate to type of formulation **(**PHC CNS conditions and AHL Neurological Disorders)
- National surveillance data for carbamazepine
- Adverse events of carbamazepine
- Outline current medicine health product list (MHPL) prices for carbamazepine

Current indications for Carbamazepine in the Standard Treatment Guidelines

Medicine	Children and adolescents		Adults	
	PHC	Hospital	PHC	Hospital
Carbamazepine, oral (suspension and tablets)	**Central Nervous System Conditions Chapter:** Epilepsy in children (generalised tonic-clonic seizures) Children ≤12 years of age:	**The Nervous System Chapter** Focal (*partial*) seizures - 1st line	**Central Nervous System Conditions Chapter:** Focal (partial) seizures - 2nd line - acute and chronic Mx - HIV negative people only	**Neurological Disorders Chapter:** Focal (partial) seizures - 2nd line - acute and chronic Mx - HIV negative people only
	Pain Chapter Neuropathic Pain - Post-herpetic neuralgia - Trigeminal neuralgia		**Central Nervous System Conditions Chapter:** Generalised tonic clonic seizures - 2nd line - acute and chronic Mx - HIV negative people only	**Neurological Disorders Chapter:** Generalised tonic clonic seizures - 2nd line - acute and chronic Mx - HIV negative people only
			Central Nervous System Conditions Chapter: - Women of child-bearing potential and pregnant women- HIV-uninfected women	**Neurological Disorders Chapter:** - Women of child-bearing potential and pregnant women- HIV-uninfected women

Immediate release vs-controlled release/modified release carbamazepine

Summary of a Cochrane review: Taken from (Powell et al., 2017)[1]

- Objective:
    - To determine the efficacy of immediate-release (IR) carbamazepine versus controlled-release (CR) carbamazepine in patients diagnosed with epilepsy.
- Review questions:
    1. For newly diagnosed patients commencing carbamazepine, how do IR and CR formulations compare for efficacy and tolerability?
    2. For patients on established treatment with IR carbamazepine but experiencing unacceptable adverse events, what is the effect on seizure control and the tolerability of a switch to a CR formulation versus remaining on the immediate release formulation?
- Ten trials (296 participants) fulfilled the criteria for inclusion in this review.
- Only one study had a low risk of bias.
- Two studies had a high risk of bias while 7 studies were rated as unclear risk of bias.
- One trial included patients with newly diagnosed epilepsy and nine included patients on treatment with immediate release carbamazepine
- Eight trials reported heterogeneous measures of seizure frequency with conflicting results.
- A statistically significant difference was observed in only one trial, with patients prescribed controlled release carbamazepine experiencing fewer seizures than patients prescribed immediate release carbamazepine
- Nine trials reported measures of adverse events. (see section below – Adverse events of Carbamazepine: for more detailed information from these trials)
- Data from trials do not confirm or refute an advantage for CR carbamazepine over IR carbamazepine for seizure frequency or adverse events in patients with newly diagnosed epilepsy.
- For trials involving epilepsy patients already prescribed IR carbamazepine, no conclusions can be drawn concerning the superiority of CR carbamazepine with respect to seizure frequency.
- ***There is a trend for CR carbamazepine to be associated with fewer adverse events when compared to IR carbamazepine.***
- ***A change to CR carbamazepine may therefore be a worthwhile strategy in patients with acceptable seizure control on IR carbamazepine but experiencing unacceptable adverse events.***
- The included trials were of small size and of poor methodological quality limiting the validity of this conclusion.
- Randomised controlled trials comparing CR carbamazepine to IR carbamazepine and using clinically relevant outcomes are required to inform the choice of CR carbamazepine preparation for patients with newly diagnosed epilepsy.

External comments (PHC CNS and AHL Neurological Disorders)

The following external comment which could be related to formulation was raised about carbamazepine during the most recent (October 2024) call for comment on the PHC CNS conditions and AHL Neurological disorders chapters.

Pharmacological Agents: Carbamazepine

- The carbamazepine we have available is very toxic and very seldom do patients tolerate a total dose of 400mg per day. Hence compliance is very poor. Carbamazepine CR or oxcarbazepine are better alternatives to CBZ.

National surveillance data for carbamazepine

Table 1 summarises national procurement for the period January 2019 to December 2024 (6 years).

Table 1: National procurement for the period January 2019 to December 2024 (6 years)

Medicine Pack Short Description	Units Procured from January 2019 to December 2024	Average monthly units over 6-year period	% Total National Carbamazepine Procurement
Carbamazepine; 200mg; Tablet; 56 Tablets	7405276	102851	37.18%
Carbamazepine; 200mg; Tablet; 84 Tablets	8981036	124737	45.10%
Carbamazepine; 200mg; Tablet; 28 Tablets	2617380	36353	13.14%
Carbamazepine; 400mg; tablet, CR; 28 Tablets	607049	8431	3.05%

Carbamazepine; 100mg/5ml; Suspension; 250 ml	304439	4228	1.53%

According to the data provided from the national surveillance centre, three provinces (NC, EC and MP) contributed to the total national usage of carbamazepine 400mg controlled release (28 tablets) for the 6-year period - January 2019 to December 2024.

Table 2: Provincial Procurement Breakdown of Carbamazepine 400mg controlled release (28 tablets) for the period January 2019 to December 2024

Province	Total Units Procured from January 2019 to December 2024	% of Total
Northern Cape	10	0.002%
Eastern Cape	22774	3.752%
Mpumalanga	584265	96.247%
Total National Usage	607049	

Adverse events of carbamazepine

Although the current data as reported by Powell et.al. is unable to confirm or refute an advantage of CR carbamazepine over IR carbamazepine, there was a trend for CR carbamazepine to be associated with fewer adverse events. See individual studies adverse event findings below.

Newly diagnosed patients:	Established epilepsy
Nag et.al. 1998[26] Unblinded parallel trial (20 adult patients with newly diagnosed epilepsy) – 20-day study period: • Four adverse events were reported in patients prescribed immediate release carbamazepine: diplopia, rash, and two reports of sedation. • Two adverse events were reported in patients prescribed controlled release carbamazepine, sedation and diplopia.	Studies using scale scores to assess adverse events: • McKee 1991[27]: (N=25 participants, 21 completed study) ▪ Cognitive adverse event scores at one hour were significantly lower with controlled release carbamazepine as compared to immediate release. ▪ Reaction times were significantly shorter at one and four hours with controlled release carbamazepine as compared to immediate release. • Aldenkamp 1987[28] (N=11 participants) ▪ Reported increased performance in various tests of cognitive function in patients taking controlled release carbamazepine. *(The statistical significance of this result was not reported)* • Persson 1990[29] (N=21 participants, 20 completed study) ▪ Reported lower scores on a combined systemic toxicity and neurotoxicity scale in patients taking controlled release carbamazepine as compared to immediate release. (*The difference was statistically significant)* Studies reporting individual numbers of adverse events • Anonymous 1995[30] (N=101 participants, 87 completed study) ▪ No statistically significant differences between adverse events in immediate release and controlled release groups: ▪ 6 adverse events were reported by 4 patients with prescribed controlled release carbamazepine (dizziness (2 patients), diplopia, headache, nausea, vomiting).

26 Nag D, Garg RK, Agarwal A. A comparative evaluation of pharmacokinetics of conventional and slow-release carbamazepine formulation in newly treated patients of epilepsy: a random evaluation. Journal of the Association of Physicians of India 1998;46(2):185-8.

27 McKee PJW, Blacklaw J, Butler E, Gillham RA, Brodie MJ. Monotherapy with conventional and controlled release carbamazepine: a double blind, double dummy comparison in epileptic patients. British Journal of Clinical Pharmacology 1991;32(1):99-104.

28 Aldenkamp AP, Alpherts WC, Moerland MC, Ottevanger N, Van_Parys JA. Controlled release carbamazepine: cognitive side effects in patients with epilepsy. Epilepsia 1987;28(5):507-14.

29 Persson LI, Ben-Menachem E, Bengtsson E, Heinonen_E. Differences in side effects between a conventional carbamazepine preparation and a slow-release preparation of carbamazepine. Epilepsy Research 1990;6(2):134-40.

30 Anonymous. Double-blind crossover comparison of Tegretol-XR and Tegretol in patients with epilepsy. The Tegretol OROS Osmotic Release Delivery System Study Group. Neurology 1995;45(9):1703-7.

	▪ 5 adverse events were reported by 5 patients with immediate release carbamazepine (dizziness, drowsiness, hand-tremor, stomach cramps and vomiting). • Reunanen 1990[31] (N=21 participants, 18 completed study) ▪ 19 adverse events with immediate release carbamazepine therapy compared to 12 with controlled release carbamazepine. The differences were statistically different for dizziness (7 times in immediate release group compared to 1 time in controlled release group). Studies reporting only number of adverse events (no details on event type) • Sivenius 1988[32] (N=24 participants, 22 completed study) ▪ 4 patients in each treatment group (IR and CR carbamazepine) experienced adverse events. • Canger 1990[33] (N=48 participants) ▪ 26 patients reported adverse events with IR carbamazepine and 6 reported adverse events with CR carbamazepine. This difference was reported as statistically significant.

A request was made to South African Health Products Regulatory Authority (SAHPRA) for information around reports on adverse events associated with either CR or IR carbamazepine.

The SAHPRA VigiFlow Safety database showed that there had been 238 adverse reactions in 118 cases with IR carbamazepine (154 serious), and 42 adverse reactions in 23 cases with CR carbamazepine (35 serious).
See annexure 1 for full information provided.

Cost considerations

December 2024 tender prices,[2] are outlined in the table 3 below. Where the award is split weighted averages were calculated.

[31] Reunanen_M, Heinonen_E, Antila_M, Jarvensivu_P, Lehto_H, Hokkanen_E. Multiple dose pharmacokinetic study with a slow-release carbamazepine preparation. Epilepsy Research 1990;6(2):126-33.
[32] Sivenius_J, Heinonen_E, Lehto_H, Jarvensivu_P, Anttila_M, Ylinen_A, et al. Reduction of dosing frequency of carbamazepine with a slow-release preparation. Epilepsy Research 1988;2(1):32-6.
[33] Canger_R, Altamura_AC, Belvedere_O, Monaco_F, Monza_GC, Muscas_GC, et al. Conventional vs controlled release carbamazepine: a multicentre, double blind, crossover study. Acta Neurologica Scandinavica 1990;82(1):9-13.

Table 3: Medicine Health Product List Prices for Carbamazepine (December 2024)

**Usual maintenance dose: 600 – 1200mg/day[3] (800mg/day used for comparison purposes)*

Medicine pack short description	Quantity Awarded	Pack size	Price (Rand)	Split %	Price Per Tablet/mL (Rand)*	Usual Maintenance dose	Cost per day (Rand)*	Cost per month (28 days) (Rand)*	Comments
Carbamazepine; 200mg; Tablet; 28 Tablets	1 583 492	28	R15,18	100	0,54	800mg daily	R2.16	R60,48	Least Expensive Per Month
Carbamazepine; 200mg; Tablet; 56 Tablets	805 366	56	R34,69	25	0.58**	800mg daily	R2.32	R64,96	Weighted Average calculated based on supplier split
Carbamazepine; 200mg; Tablet; 56 Tablets	2 416 097	56	R31,39	75		800mg daily			
Carbamazepine; 200mg; Tablet; 84 Tablets	1 145 004	84	R48,41	40	0.59**	800mg daily	R2.36	R66.08	Weighted Average calculated based on supplier split
Carbamazepine; 200mg; Tablet; 84 Tablets	1 717 505	84	R50,20	60		800mg daily			
Carbamazepine; 400mg; tablet, cr; 28 Tablets	692 969	28	R52,5	100	1,88	800mg daily	R3.76	R105.28	Controlled release tablet 1g dose on 400mg would not be advised as should not break tablet
Carbamazepine; 100mg/5ml; Suspension; 250 ml	179 463	250	R126,79	100	0,51	800mg daily	R20.40	R571.20	Liquid Option

*Rounded to 2 decimal places

**Weighted Average:

Weighted Average: Carbamazepine; 200mg; Tablet; 56 Tablets = R32.22

Weighted Average: Carbamazepine; 200mg; Tablet; 84 Tablets = R49.48

Price of 2 x 200mg (28s) = R1.08 (80 cents less than 1 x 400mg CR carbamazepine tablet on tender
Price of 2 x 200mg (56s) = R1.16 (72 cents less than 1 x 400mg CR carbamazepine tablet on tender
Price of 2 x 200mg (84s) = 1.18 (70 cents less than 1 x 400mg CR carbamazepine tablet on tender
Price of 1 x 400mg CR = R1.88

Conclusion

- There is a trend to better tolerance and less adverse events with CR carbamazepine, particularly in the area of drowsiness and dizziness.
- Adherence with CR carbamazepine is considered better, however there are limited studies to support this, and it is no longer being investigated as a question of interest or relevance internationally.
- Convenience benefits of less frequent daily dosing may be applicable to school going children or the adults needing to focus at work (where drowsiness hinders this), particularly those operating machinery etc.
- The current pricing indicates that CR carbamazepine is still approximately 30% more than comparative IR carbamazepine, however no assessment of cost-effectiveness, have been undertaken to assess the potential benefits of less adverse events, better adherence and compliance.

Proposal

- The Epilepsy Subcommittee recommends that both IR and CR carbamazepine be made available on National Tender. It is proposed that CR carbamazepine be specifically utilised for patients experiencing adverse events to the IR carbamazepine, as well as those of school going age, and those operating machinery.

NEMLC Recommendation: 27 February 2025

NEMLC recommended that both immediate release (IR) and controlled release (CR) carbamazepine be tendered for and that both IR and CR carbamazepine be tendered for and the least expensive option be selected for use.

[1] Powell G, Saunders M, Rigby A, Marson AG. Immediate-release versus controlled-release carbamazepine in the treatment of epilepsy. Cochrane Database Syst Rev. 2016 Dec 8;12(12):CD007124. doi: 10.1002/14651858.CD007124.pub5. PMID: 27933615; PMCID: PMC6463840.

[2] NDoH. Medicine Health Product List. December 2024

[3] University of Cape Town, Faculty of Health Sciences, Division of Clinical Pharmacology. (2024). South African Medicines Formulary (SAMF). SAMF website. https://samf-app.com

Annexure A:

Adverse Event reports from the South African Health Products Regulatory Authority (SAHPRA) (report accessed: 17 February 2025).

The SAHPRA VigiFlow Safety database showed the following:

Immediate release Carbamazepine	Controlled Release Carbamazepine
• 238 adverse reactions reported in 118 cases where carbamazepine immediate release was a suspect or co-suspect drug. • 154 adverse reactions were reported as serious.	• 42 adverse reactions reported in 23 cases wherein carbamazepine controlled release was reported as a suspect medicine. • 35 adverse event terms were reported as serious. • Tegretol CR was the reported trade name in all cases.

Adverse reaction system organ class with number reported	
Blood and lymphatic system disorders (SOC)	**2**
Lymphadenopathy	1
Neutropenia	1
Cardiac disorders (SOC)	**6**
Cardiac disorder	2
Cardiac failure	1
Myocardial infarction	2
Sinus arrhythmia	1
Endocrine disorders (SOC)	**1**
Inappropriate antidiuretic hormone secretion	1
Eye disorders (SOC)	**6**
Eye pain	1
Eye swelling	1
Photopsia	1
Vision blurred	3
Gastrointestinal disorders (SOC)	**15**
Abdominal distension	1
Abdominal pain upper	1
Constipation	1
Dysphagia	3
Food poisoning	1
Gingival swelling	1
Lip swelling	2
Mouth haemorrhage	1
Nausea	1
Oral mucosal blistering	1
Swollen tongue	1
Vomiting	1
General disorders and administration site conditions (SOC)	**38**
Chills	1
Condition aggravated	1
Death NOS	8
Drug ineffective	3
Drug interaction	1
Drug resistance	1
Fatigue	1
Feeling abnormal	1
Feeling cold	1
Feeling drunk	1
Foaming at mouth	1
Gait disturbance	1
General physical health deterioration	1

Cardiac disorders (SOC)	
Cardiac disorder (PT)	
Myocardial infarction (PT)	
Gastrointestinal disorders (SOC)	
Abdominal distension (PT)	
Abdominal pain upper (PT)	
Gastrointestinal disorder (PT)	
Mouth swelling (PT)	
General disorders and administration site conditions (SOC)	
Condition aggravated (PT)	
Death NOS (PT)	
Drug ineffective (PT)	
Enanthema (PT)	
Malaise (PT)	
Pain (PT)	
Peripheral swelling (PT)	
Hepatobiliary disorders (SOC)	
Hepatic function abnormal (PT)	
Immune system disorders (SOC)	
Hypersensitivity (PT)	
Infections and infestations (SOC)	
Lower respiratory tract infection (PT)	
Pneumonia (PT)	
Tooth abscess (PT)	
Injury, poisoning and procedural complications (SOC)	
Product use in unapproved indication (PT)	
Investigations (SOC)	
Blood alkaline phosphatase increased (PT)	
Blood glucose abnormal (PT)	
Blood testosterone increased (PT)	
Gamma-glutamyltransferase increased (PT)	
Lipids increased (PT)	
Metabolism and nutrition disorders (SOC)	
Feeding disorder (PT)	
Musculoskeletal and connective tissue disorders (SOC)	
Systemic lupus erythematosus (PT)	
Nervous system disorders (SOC)	
Cerebrovascular accident (PT)	
Dizziness (PT)	
Epilepsy (PT)	
Seizure (PT)	
Speech disorder (PT)	

Hangover	1
Hernia	1
Malaise	2
Pain	5
Peripheral swelling	1
Pyrexia	1
Swelling	1
Swelling face	2
Therapeutic response unexpected	1
Ulcer	1
Infections and infestations (SOC)	**4**
Cystitis	1
Lower respiratory tract infection	1
Pustule	1
Tooth abscess	1
Injury, poisoning and procedural complications (SOC)	**21**
Accidental exposure to product by child	2
Contraindicated product administered	1
Contusion	2
Fall	1
Hip fracture	1
Maternal exposure before pregnancy	1
Maternal exposure during breast feeding	1
Maternal exposure during pregnancy	2
Medication error	1
Overdose	1
Product prescribing issue	1
Spinal fracture	1
Toxicity to various agents	1
Upper limb fracture	2
Wrong technique in product usage process	3
Investigations (SOC)	**12**
Blood potassium decreased	1
Blood pressure abnormal	1
Blood sodium decreased	1
C-reactive protein increased	1
Drug level above therapeutic	1
Haemoglobin decreased	1
Heart rate decreased	1
Heart rate increased	1
Hepatic enzyme increased	2
Viral load increased	1
White blood cell count decreased	1
Metabolism and nutrition disorders (SOC)	**3**

Trigeminal neuralgia (PT)	1
Product issues (SOC)	**1**
Product availability issue (PT)	1
Reproductive system and breast disorders (SOC)	**1**
Priapism (PT)	1
Skin and subcutaneous tissue disorders (SOC)	**4**
Pruritus (PT)	1
Rash (PT)	1
Skin disorder (PT)	1
Skin irritation (PT)	1
Vascular disorders (SOC)	**1**
Venous occlusion	1

Feeding disorder	1
Hypokalaemia	1
Hyponatraemia	1
Musculoskeletal and connective tissue disorders (SOC)	**5**
Arthralgia	1
Arthropathy	1
Back pain	1
Muscle twitching	1
Rheumatoid arthritis	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	**2**
Lung neoplasm malignant	1
Neoplasm malignant	1
Nervous system disorders (SOC)	**52**
Aphasia	1
Ataxia	2
Balance disorder	1
Burning sensation	1
Cerebrovascular accident	1
Coma	1
Dizziness	13
Dysarthria	1
Epilepsy	3
Headache	2
Hypersomnia	2
Hypoaesthesia	2
Loss of consciousness	2
Memory impairment	1
Migraine	1
Multiple sclerosis relapse	1
Sedation	1
Seizure	12
Somnolence	2
Syncope	1
Tremor	1
Pregnancy, puerperium and perinatal conditions (SOC)	**2**
Abortion spontaneous	2
Product issues (SOC)	**1**
Product packaging issue	1
Psychiatric disorders (SOC)	**9**
Completed suicide	1
Depressed mood	1
Depression	1
Disorientation	1

Enuresis	1
Insomnia	3
Stress	1
Renal and urinary disorders (SOC)	**2**
Pollakiuria	1
Renal failure	1
Respiratory, thoracic and mediastinal disorders (SOC)	**5**
Cough	2
Lung disorder	1
Oropharyngeal pain	1
Pulmonary fibrosis	1
Skin and subcutaneous tissue disorders (SOC)	**48**
Angioedema	1
Blister	2
Drug reaction with eosinophilia and systemic symptoms	2
Erythema	1
Hyperhidrosis	1
Pruritus	1
Rash	13
Rash erythematous	1
Rash maculo-papular	3
Rash pruritic	3
Skin erosion	2
Stevens-Johnson syndrome	14
Toxic epidermal necrolysis	2
Urticaria	1
Yellow skin	1
Vascular disorders (SOC)	**4**
Ischaemia	1
Peripheral coldness	1
Thrombosis	2

Patient demographics

Adolescent	**2**
Male	2
Adult	**53**
Female	35
Male	17
Unknown	1
Child	**5**
Female	2
Male	2
Unknown	1
Elderly	**21**
Female	13

Adolescent	**1**
Male	1
Adult	**17**
Female	10
Male	7
Elderly	**12**
Female	4
Male	8
Unknown	**26**
Female	6
Male	19
Unknown	1

Male	8
Infant	**1**
Female	1
No age group	**36**
Female	20
Male	14
Unknown	2

Concomitant medications

Acetazolamide	
Acetylsalicylic acid	
Allopurinol	
Alprazolam	
Amitriptyline hydrochloride	
Amlodipine	
Amoxicillin sodium	
Clavulanate potassium	
Atenolol	
Beclometasone	
Benzydamine hydrochloride	
Chlorhexidine gluconate	
Bisoprolol fumarate	
Bromazepam	
Chloramphenicol	
Chlorpromazine	
Citalopram hydrochloride	
Clobazam	
Clonazepam	
Diazepam	
Dolutegravir sodium	
Dosulepin hydrochloride	
Enalapril	
Esomeprazole magnesium trihydrate	
Fluoxetine hydrochloride	
Flupentixol decanoate	
Folic acid	
Gabapentin	
Gentiana lutea root	
Primula spp. flower	
Rumex spp. herb	
Sambucus nigra flower	
Verbena officinalis herb	
Gliclazide	
Haloperidol	
Hydrochlorothiazide	
Hydrochlorothiazide	
Valsartan	
Indapamide	
Indometacin	
Insulin bovine	
Insulin porcine	
Insulin glargine	
Lamotrigine	
Levetiracetam	
Levothyroxine sodium	
Lorazepam	
Metformin	
Methylephedrine	
Metoclopramide hydrochloride	
Morniflumate	
Nystatin	
Orphenadrine	

Acetylsalicylic acid
Allopurinol
Amitriptyline
Amlodipine besilate
Atorvastatin calcium
Baclofen
Bromazepam
Budesonide
Formoterol fumarate
Clobazam
Clotiapine
Codeine phosphate
Meprobamate
Paracetamol
Codeine phosphate
Paracetamol
Promethazine hydrochloride
Estradiol
Norethisterone acetate
Fluoxetine hydrochloride
Furosemide
Hydrochlorothiazide
Lisinopril
Hydrochlorothiazide
Valsartan
Indapamide
Perindopril
Insulin aspart
Insulin degludec
Lacidipine
Lamotrigine
Levetiracetam
Lithium
Olanzapine
Potassium chloride
Prednisolone
Sertraline hydrochloride
Valproic acid sodium

Oxcarbazepine		
Pantoprazole sodium sesquihydrate		
Paracetamol		
Perindopril erbumine		
Phenytoin		
Potassium chloride		
Riboflavin sodium phosphate		
Prednisone		
Quetiapine fumarate		
Risperidone		
Salbutamol		
Sertraline hydrochloride		
Simvastatin		
Tenofovir		
Theophylline		
Thiamine		
Trazodone		
Valproic acid sodium		
Venlafaxine		
Vitamin b complex		
Zuclopenthixol decanoate		

South African National Essential Medicine List
Primary Health Care (PHC), Adult Hospital Level (AHL), Paediatric Hospital Level Medication Review Process
Component:
PHC: Central Nervous System Conditions, AHL: Neurological Disorders, AHL: Paediatric Hospital Level: The Nervous System

SUMMARY

Date: February 2025

Administration of antiseizure medications via nasogastric tube (NGT)

Background

This document provides a summary of the administration of antiepileptic medicines via NGT from the Handbook of Drug Administration via Enteral Feeding Tubes (written on behalf of the British Pharmaceutical Nutrition Group)[3]. Information is also provided from additional literature identified through a non-structured literature search. Summaries are provided for carbamazepine, lamotrigine, levetiracetam, phenytoin and valproate.

Summary

Carbamazepine

- ***Tablets:*** No specific data on enteral tube administration available for tablets.[Error! Bookmark not defined.] Modified release tablets should not be crushed.
- ***Liquid preparations*** *(Interaction of drug and delivery device):* An invitro study[3] found a loss of drug with use of carbamazepine undiluted suspension administered via a polyvinyl nasogastric tube; however, a 50% diluted suspension resulted in no drug loss. [1]
- ***Peak plasma concentration*** occurs up to 12 hours post oral dose with the tablet formulation; the liquid formulation produces higher and earlier peak plasma concentrations which may be associated with an increase in side-effects[1]

Lamotrigine

- ***Tablets:*** No specific data on enteral tube administration.
- ***Dispersible tablets:*** Tablets disintegrate rapidly when placed in 10 mL of water; the resulting dispersion flushes down an 8Fr NG tube without blockage.
- ***Peak plasma concentration:*** Occurs 2.5 hours after oral dosing. [1]

Levetiracetam

- ***Tablets:*** May be crushed and given via enteral feeding tube.
  - Water-soluble (Brand: Keppra®): 1.04g/mL at room temperature.

- 500 mg tablets (only strength tested) disperse in 10 mL of water if shaken for 5 minutes. This forms a milky, even dispersion that flushes down an 8Fr NG tube without blockage.[1]

- ***Oral solution:*** dilute with twice volume of water. [1]
- ***Peak plasma concentration:*** Oral bioavailability is nearly 100%. Peak plasma concentration occurs at 1.3 hours post dose.

- Birbeck et.al: Conducted a clinical trial of enteral levetiracetam for acute seizures in pediatric cerebral malaria[3].
    - » Study evaluated the pharmacokinetic safety and efficacy of enteral levetiracetam versus phenobarbital.
    - » N = 30 comatose children with cerebral malaria patients (all those allocated to levetiracetam received the treatment, only 15 of the 21 patients assigned to phenobarbital received phenobarbital)
        - o Enteral levetiracetam was rapidly absorbed and well tolerated.
        - o The clearance of enteral levetiracetam was lower in patients with higher serum creatinine.
        - o n = 23 enteral levetiracetam vs n = 15/21 phenobarbital patients:
            - No differences for minutes with seizure (Mean (SD): 165 (266) vs 465 (639); p = 0.54).
            - No difference in seizure freedom (19 (83%) vs 16 (76%), p=0.72).
            - No difference in coma duration (mean hours, SD) (35.4 (29.0), n=22 vs 34.6 (27.8), n=16, p=0.91).
            - No difference in neurologic sequelae or death (3 vs 2).
            - No difference in death (1 vs 5).
            - Enteral levetiracetam was considered safer than phenobarbital (p = 0.019).
            - Phenobarbital was discontinued in 3/15 (20%) due to respiratory side effects.
- Shibata et.al.: Early enteral levetiracetam in diazepam-resistant convulsive status epilepticus (SE)[3]
    - » Single center prospective study to evaluate the efficacy and safety of levetiracetam administration through NGT in acute convulsive SE resistant to intravenous diazepam:
    - » 8/9 diazepam-resistant patients (88.9%) vs 11/12 (91.7%) diazepam-responders, the seizures were controlled within 30 minutes after diazepam (P = 1.00).
    - » 3-day seizure freedom rate was equivalent in the two groups (88.9 vs 83.3%, P = 1.00).
    - » Less than 10% of the overall patients had levetiracetam-related mild side-effects (no differences between the two groups).

Phenytoin

- ***Capsules:*** Some can be opened and powder mixed with 10 mL of water (does not initially mix, but if left for 5 minutes and stirred, if forms a fine dispersion that can be flushed down an 8Fr NGT without blockage.
- ***Tablets:*** Difficult to crush due to film coating and do not disperse readily.
- ***Suspension:*** Viscous, thixotropic (less viscous when agitated, and then return to their original state over time) suspension. Recommended to dilute with equal parts water.
- ***Site of absorption:*** Phenytoin is absorbed from the small intestine after oral administration. Peak plasma concentration occurs 2–4 hours and 10–12 hours post oral dosing. [1]

Valproate

- ***Tablets:***
  - Crushable valproate tablets can flush easily down an 8Fr NGT.
  - Enteric coated or modified release tablets cannot be crushed.
- ***Liquid:*** resistant to flushing via 8Fr NGT but mixes with water which reduces resistance. (note: liquid formulation might contain sorbitol).
- Peak plasma concentration occurs 1–2 hours after administration of liquid and immediate-release preparations, and 2–8 hours after enteric coated or modified-release preparations. [1]

Summary Table

Antiepileptic Medicine	Formulation	Notes	Administer via NG Tube
Carbamazepine	Tablets	No specific data. Modified release tablets should not be crushed.	?
	Liquid	(Interaction of drug and delivery device): Loss of drug with use of carbamazepine undiluted suspension, a 50% diluted suspension resulted in no drug loss.	Yes only if diluted
Lamotrigine	Tablets	No specific data on enteral tube administration.	?
	Dispersible tablets	Tablets disintegrate rapidly when placed in 10 mL of water; the resulting dispersion flushes down an 8Fr NG tube without blockage.	Yes
Levetiracetam	Tablets	May be crushed and given via enteral feeding tube.	Yes
	Oral solution	dilute with twice volume of water.	Yes
Phenytoin	Capsules	Some can be opened and powder mixed with 10 mL of water (does not initially mix, but if left for 5 minutes and stirred, if forms a fine dispersion that can be flushed down an 8Fr NGT without blockage.	Yes
	Tablets	Difficult to crush due to film coating. Do not disperse readily.	No
	Suspension	Viscous, thixotropic (less viscous when agitated, and then return to their original state over time) suspension. Recommended to dilute with equal parts water.	Yes
Valproate	Tablets (Crushable)	Crushable valproate tablets can flush easily down an 8Fr NGT.	Yes
	Tablets (Enteric Coated)	Enteric coated or modified release tablets cannot be crushed.	No
	Liquid	Resistant to flushing via 8Fr NGT but mixes with water which reduces resistance.	Yes only if flushed with water

Taken from: White R, Bradnam V. Handbook of Drug Administration via Enteral Feeding Tubes. Pharmaceutical Press. 2007

NEMLC Recommendation: 27 February 2025

NEMLC accepted the proposal to offer levetiracetam via nasogastric tube.