CHAPTER 14

NEUROLOGICAL DISORDERS

14.1 CEREBROVASCULAR DISEASE

14.1.1 STROKE

I61.0-6/I61.8-9/I63.0-6/I63.8-9/I64 + (G46.0-8*)

GENERAL MEASURES

Optimise hydration and nutrition; insert nasogastric tube if patient cannot swallow. Take precautions to ensure an open airway if patient is unconscious. Physiotherapy and good nursing care. Consider rehabilitation for suitable patients and refer if necessary.

Do an ECG to rule out an acute coronary event or atrial fibrillation as precipitants.

Do serology to exclude meningovascular syphilis (in patients <45 years old who do not have risk factors for stroke).

Check lipid profile in ischaemic strokes.

Ischaemic stroke in young adults (< 45 years of age) may be due to atherosclerosis, but also consider:

» Embolic: e.g. rheumatic heart disease, atrial fibrillation, cardiomyopathy, previous myocardial infarction, and, very rarely, patent foramen ovale: history, careful clinical cardiac examination, ECG/CXR, and echocardiography.

» Vessel wall disease: e.g. syphilis, HIV infection, collagen-vascular diseases, TB or bacterial meningitis, and extracranial arterial dissection. Investigate as guided by clinical presentation, but at least perform syphilis and HIV serology, urinalysis (haematuria and/or proteinuria), and ANF/RF. ANCA, and cerebral angiography or carotid Doppler may be indicated. Note that absence of a carotid bruit does not exclude significant carotid stenosis.

» Hypercoagulable states: e.g. antiphospholipid antibody syndrome, thrombotic thrombocytopenic purpura. Useful screening investigations are FBC and, in women, PTT/Anti-phospholipid Ab. Testing and management of thrombophilias should be done in consultation with an expert.

Initiate a palliative care approach if the patient's condition is deteriorating / in case of a massive stroke (See Chapter 24: Medicines Used in Palliative Care).

Ensure adequacy of swallowing ability by dietician or by asking the patient to swallow 10 mL of water.

MEDICINE TREATMENT

Hyper-acute management:

Symptom onset ≤ 3 hours:

» Do not give aspirin.

» Refer immediately to hospital that **can provide thrombolytic therapy:**

- Alteplase, IV, 0.9 mg/kg. Total dose should not exceed 90 mg.

- 10 % of total dose given as a bolus and the remainder continued as an infusion over an hour. *LoE:Ib*[i]

Symptoms >3 hours:

- Aspirin, oral, 300 mg, immediately. *LoE:Ia*[ii]

Followed by:

- Aspirin, oral, 150 mg daily.
  - If patient is unable to swallow, administer through a naso-gastric tube.

Do not administer aspirin if there are symptoms suggestive of a sub-arachnoid bleed, e.g. headache, stiff neck, etc.

AND

For DVT prophylaxis, see section 2.8: Venous thrombo-embolism.
Treat secondary pulmonary and urinary tract infections appropriately.

Secondary prevention:

Measures for secondary prevention may not be appropriate for patients with severe disability.

All patients with a thrombotic stroke, not on anticoagulation and irrespective of the LDL level:

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

AND

- HMGCoA reductase inhibitors (statins), e.g.:
- Simvastatin, oral, 40 mg at night.

LoE:IIb[iv]

Patients on protease inhibitor:

- Atorvastatin, oral, 10 mg at night.

LoE:IIb[v]

Patients on amlodipine (and not on a protease inhibitor):

- Simvastatin, oral, 10 mg at night.

LoE:IVb[vi]

If patient complains of muscle pain:

Reduce dose:

- HMGCoA reductase inhibitors (statins), e.g.:
- Simvastatin, oral, 10 mg at night.

OR

Consult specialist for further management. *LoE:IVb*[vii]

Anticoagulation:

In patients with cardioembolic strokes (e.g. secondary to atrial fibrillation) with no evidence of haemorrhage on CT scan, the optimal time to start anticoagulation therapy is likely to vary among individual patients; this can be from 7 to 14 days and up to 21 days and is dependent on the infarct size (> 1/3 of the hemisphere) and the patient's risk factors for recurrent events.

LoE:IIIb[viii]

Bridging anticoagulation with heparin, or earlier initiation of warfarin, is not recommended because, although it reduces ischaemic stroke recurrence, it increases symptomatic intracranial haemorrhage.

LoE:IVb

Blood pressure management:
A transient increase in BP is common after an acute stroke. Lowering BP during the acute phase of stroke (within 6 hours of onset) may not improve morbidity.

Do not actively lower a systolic BP < 220 mm Hg or diastolic BP < 120 mm Hg in the first few days after stroke as this may be associated with an increased risk of death.
In patients presenting with stroke and BP > 220/120 mmHg, lower BP to about 180/110 mm Hg in the first 24 hours.
Antihypertensive medicines may be withheld until patients have suitable oral or enteral access. Cautious incremental reintroduction of treatment is advised to achieve long-term standard BP control. See section: 3.6.3 Hypertensive crisis, hypertensive emergency.

LoE:IIb[ix]

<u>If BP > 220/120 mm Hg:</u>
- Long-acting calcium channel blocker, e.g.:
- Amlodipine, oral, 5 mg daily.

OR *LoE:IIb*[x]

If adequate fluid intake can be ensured:
- Hydrochlorothiazide, oral, 12.5 mg daily. *LoE:IVb*

Note:
» There is some evidence of harm from BP reduction within 7 days of acute stroke; after 7 days cautious incremental re-introduction of treatment is advised to achieve long term standard BP control.
» Antihypertensive medicines should be stopped in acute stroke unless the BP is > 220/120 mm Hg (see above). *LoE:IIb*[xi]
» Reassess the need for re-initiation of patients' previous antihypertensive medication. See section 3.6: Hypertension.

LoE:IIb[xii]

REFERRAL
Patients with aspirin intolerance
To a facility with a CT scan:
» Patients with atypical clinical presentation.
» Selected patients with suspected ischaemic stroke who may benefit from thrombolysis with tissue plasminogen activator if initiated within 3 hours of onset of symptoms.
» Patients with suspected posterior cerebral fossa haemorrhage who may require surgical decompression.
» If there is a history suggestive of subarachnoid haemorrhage or if there is neck stiffness.

14.1.2 TRANSIENT ISCHAEMIC ATTACK (TIA)

G45.0-4/G45.8-9

DESCRIPTION

A transient ischaemic attack is an episode of brain, spinal cord, or retinal ischaemia causing focal neurological dysfunction usually for less than one hour. Risk of subsequent stroke is highest in the week after a TIA. Consider hypoglycaemia, epilepsy, and migraine as alternative causes for the symptoms.

Feature	Points
Age ≥60 years	1
BP ≥ 140/90 mmHg	1
Clinical features:	
speech disturbance without weakness OR	1
unilateral weakness	2
Diabetes	1
Duration:	
10 to 59 minutes	1
≥ 1 hour	2

Table 14.1: The $ABCD^2$ scoring system

Reference: Johnston SC, Rothwell PM, Nguyen-Huynh MN, Giles MF, Elkins JS, Bernstein AL, Sidney S. Validation and refinement of scores to predict very early stroke risk after transient ischaemic attack. Lancet. 2007 Jan 27;369(9558):283-92. doi: 10.1016/S0140-6736(07)60150-0. PMID: 17258668.

$ABCD^2$ score ≥ 4 is regarded as high risk and warrants urgent investigation and management as the risk of stroke within the next week is ≥ 4%.

MEDICINE TREATMENT

Cardioembolic disease:

- Warfarin, oral, 5 mg daily.
  - Measure INR after 48 hours, then every 1 to 2 days until within the therapeutic range of 2 to 3 (refer to initiation dosing tables in Appendix II).
  - Adjust dose to keep INR within therapeutic range (refer to Maintenance dosing tables in the Appendix II). *LoE:IVb*[xiii]

Other patients:

- Aspirin, oral, 150 mg daily.

LoE:IIIb[xiv]

Lipid control (all patients):

- HMGCoA reductase inhibitors (statins), e.g.:
- Simvastatin, oral, 40 mg at night.

LoE:IIb[xv]

Patients on protease inhibitor:

- Atorvastatin, oral, 10 mg at night.

LoE:IIb[xvi]

Patients on amlodipine (and not on a protease inhibitor):

- Simvastatin, oral, 10 mg at night. *LoE:IVb*[xvii]

<u>If patient complains of muscle pain:</u>
Reduce dose:
- HMGCoA reductase inhibitors (statins), e.g.:
- Simvastatin, oral, 10 mg at night.

OR

Consult specialist for further management. *LoE:IVb*[xviii]

Manage hypertension – see section 3.6: Hypertension.

14.1.3 SUBARACHNOID HAEMORRHAGE

I60.0-9

DESCRIPTION

Bleeding into the subarachnoid space, most commonly due to the rupture of a vascular aneurysm. Patients typically present with an acute onset of severe headache and may have additional neurological symptoms and signs. Diagnosis is confirmed preferably by neurological imaging and, when this is not available, by demonstrating CSF xanthochromia on lumbar puncture.

GENERAL MEASURES

Maintain normal hydration and electrolyte status.
Control blood pressure.

MEDICINE TREATMENT

<u>Analgesia if level of consciousness is not impaired:</u>
Avoid NSAIDs.
- 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.

<u>If no response to paracetamol:</u>
- Morphine, IV, to a total maximum dose of 10 mg (See Appendix II, for individual dosing and monitoring for response and toxicity).

<u>In all patients presenting with aneurysmal subarachnoid haemorrhage while waiting for transfer to neurosurgical facility and in consultation with neurosurgeon</u>:
- Nimodipine, oral, 60 mg 4 hourly for 21 days.

REFERRAL

All patients with minimal impairment of consciousness level for angiography and appropriate neurosurgical management. Patients initially deemed unsuitable for further investigation, may be referred at a later stage, should their condition improve.

14.2 DEMENTIA

E51.2/E52/E63.9/F00.0-2/F00.9/F01.0-3/F01.8-9/F03

DESCRIPTION

Progressive loss of cognitive function, usually of insidious onset. Initial presentation may be with mild personality or memory changes, before more pronounced defects become evident. Investigate patients for potentially reversible causes:

» Metabolic
  - Hypothyroidism
  - Vitamin B_{12} deficiency
  - Pellagra
  - Thiamine deficiency (Wernicke's syndrome)
» Medications and drugs
  - Alcohol abuse
  - Many medicines with CNS side-effects
» Infections
  - Syphilis
  - HIV
» Surgical
  - Chronic subdural haematoma
  - Normal pressure hydrocephalus
» Severe depression (may mimic dementia)

Conditions which may worsen already existing dementia include:

» electrolyte disturbances and dehydration
» infections
» medicine toxicity

GENERAL MEASURES

Appropriate care and support, according to the level of impairment.
Ambulatory care is preferred to hospitalisation, if feasible.
Family counselling and support.
Use a palliative care approach: involve a multidisciplinary care team early and plan for advanced dementia care.

MEDICINE TREATMENT

Management is mainly symptomatic.

<u>To control restless patients:</u>

- Haloperidol, oral, 0.75–1.5 mg 8 hourly with a higher dose at night, if required.

Note:

» There is uncertainty of benefit versus harm of long-term use of antipsychotics in dementia, but antipsychotics may be of benefit in severe behavioural and psychological symptoms.

» Inform the family of a possible elevated risk of mortality with prolonged use of antipsychotics.
» If there is no improvement, stop the antipsychotic.
» Initiate treatment at a low dose and titrate to the lowest effective dose for the shortest possible time. Reassess the person at least every 6 weeks, to check whether they still need medication.

LoE:IIIa[xix]

For pellagra:

- Nicotinamide, oral, 100 mg 8 hourly.

Wernicke's syndrome: E51.2 + (F02.8*)

- Thiamine, IM, 500 mg immediately and daily for 3 to 5 days.
  - Follow with thiamine, oral, 100 mg 8 hourly.

CAUTION
Thiamine should preferably be administered prior to intravenous glucose to prevent permanent neurological damage.
Do not delay the dextrose administration in a hypoglycaemic patient.

Prophylaxis in patients at risk (alcoholism, malnutrition): Z29.2

- Thiamine, IM, 200 mg daily or oral, 100 mg 8 hourly for 14 days.

LoE:IIb[xx]

Treat other commonly associated nutritional deficiencies:

If confirmed Vitamin B_{12} deficiency, manage as section 2.1.2: Anaemia, megaloblastic.

14.3 DELIRIUM

See section 20.8: Delirium with perceptual disturbances.

14.4 EPILEPTIC SEIZURES

G40.6-7; G41; 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[xxi]

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[xxii]

Not all persons who have an epileptic seizure have epilepsy. Specific criteria must be met to diagnose epilepsy (See Section 14.6: 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 (first level in Figure 1). The evolution of the seizure (how it starts and progresses clinically) directs special investigations to determine the cause of the seizure and related management.

LoE:IVb[xxiii]

SEIZURE TYPES

Focal seizures:

The epileptic activity arises from a particular 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.

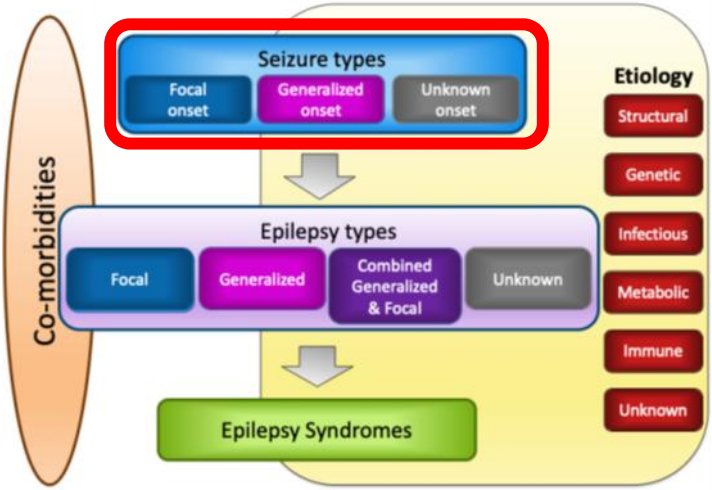

Figure 1. International League Against Epilepsy classification of seizure types *(Source: Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L. ILAE classification of epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017, 58 (4): 512-521)*

LoE:IVb[xxiv]

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.

» **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 14.6: 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[xxv]

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

14.5 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 recognized. Diagnosis is confirmed on EEG. Treat as for convulsive status epilepticus below. See Section 14.5.1: Epileptic seizures and status epilepticus in adolescents (13 – 18 years) and adults. Identify and manage all underlying causes.

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.
» Suboptimal treatment of epilepsies e.g., breakthrough seizures, treatment non-adherence, recent changes to antiseizure medicine (ASM), antiseizure medication toxicity.

14.5.1 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 Section 6.4.2: Eclampsia) » electrolyte abnormalities (e.g., in hyperemesis gravidarum) » stroke » reduced blood concentrations 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 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[xxvi]

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 (see figure 2).
» Do not place anything (spoon or spatula, etc.) in the patient's mouth.

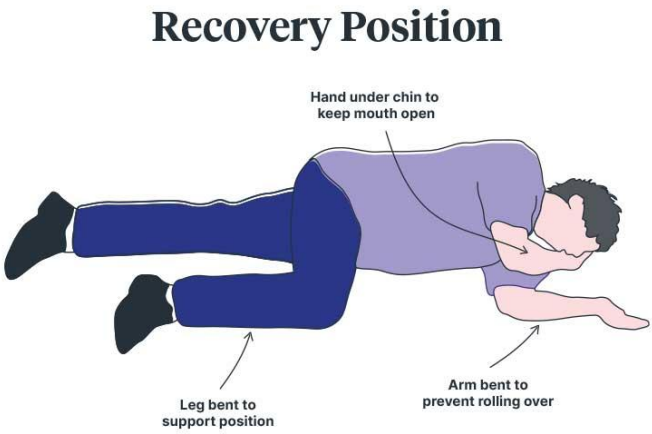

Figure 2: Recovery position for adults experiencing a seizure

Source: Ausmed: Adult Basic Life Support

LoE:IVb[xxvii]

» 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 1 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 by 5 minutes of its onset, commence urgent medicine treatment.

MEDICINE TREATMENT

Aim 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 ADOLESCENTS AND ADULTS

PHASE	MANAGEMENT	SUPPORTIVE CARE
EARLY STATUS EPILEPTICUS (5 – 10 minutes)	**LEVEL 1 INTERVENTION:** (Benzodiazepines) <u>If IV access:</u> • Lorazepam, IV, 4 mg, administered not faster than 2 mg/minute. *LoE:IIb*[xxviii] **OR** • Midazolam, IV, 10 mg. *LoE:IIb*[xxix] **OR** • Diazepam, IV, 10 mg administered over at least 5 minutes (not faster than 2mg/min). **OR** • Clonazepam, IV, 1 mg. *LoE:IIb*[xxx] *LoE:IIIb*[xxxi] <u>If no IV access:</u> • Midazolam, 10 mg, IM or buccal, using the parenteral formulation, while continuing to establish IV access <u>If no IV access and no midazolam is available:</u> • Clonazepam, IM, 1 mg. **OR** • Diazepam, rectal, 0.2 – 0.5 mg/kg as a single dose (maximum 20 mg/dose). *LoE:IVb*[xxxii] *LoE:IVb*[xxxiii] 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/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.

	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.	
ESTABLISHED STATUS EPILEPTICUS (10 – 30 minutes)	**LEVEL 2 INTERVENTION:** (Antiseizure medicine) <u>If IV access **and not suspected to be drug- or toxin-induced**:</u> • 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. *LoE:IVb*[xxxiv] **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. <u>If no IV access, consider:</u> » 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

	LoE:IVb[xxxv]	
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). *LoE:IVb*[xxxvi] **OR** • Midazolam, IV, 0.1 – 0.2 mg/kg bolus, followed by 0.05 – 0.5 mg/kg/hour infusion, titrated to effect. *LoE:IVb*[xxxvii] **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.	» Admit to high- or intensive-care unit, if possible. » Employ a neuroprotective ventilation strategy (See Chapter 23: Adult Critical Care) – 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.

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 20.8: 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 (see Section 14.6: Epilepsy) and requires ongoing ASMs.
- 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

- Refractory status.
- Need for more intensive care than can be provided at the facility.

14.6 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, or
- 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) or
- 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[MR1] [JR2] [MR3] 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 3, 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.

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.

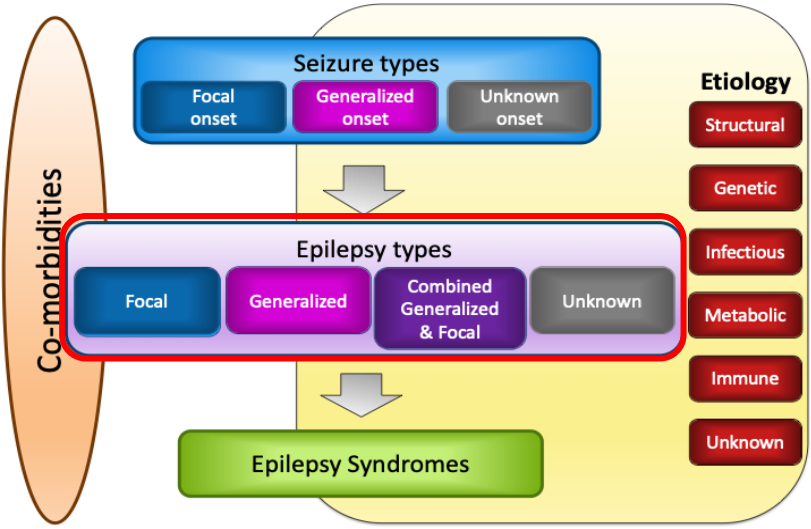

Figure 3. International League Against Epilepsy classification of seizure types *(Source: Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L. ILAE classification of epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017, 58 (4): 512-521)*

LoE:IVb[xxxviii]

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 14.4: 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.

14.6.1 EPILEPSY IN ADOLESCENTS AND ADULTS

G40.0-9

DESCRIPTION

See Section 14.6: 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 (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).

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

» 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 ASMs. See Chapter 7: Family planning.
» In pregnant women, women of child-bearing potential (i.e. women < 55 years of age), and young girls who are likely to need to continue treatment into their child-bearing years, initiate treatment with a lower risk ASM.
  – Lamotrigine and levetiracetam are the safer ASM 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 who have infrequent seizures, and no previous history of seizures requiring hospitalisation or status epilepticus.
  – Levetiracetam may be used if there is a poor response or adverse effects to lamotrigine, or in high-risk patients with frequent seizures, a previous history of hospitalization for seizures or status epilepticus.
» Valproate **must not** be used in pregnant women, women of child-bearing potential and young girls who are likely to need to continue 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 leaning

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 ASM.

» During pregnancy women may experience an increased number of seizures.
- This may be due to sleep deprivation, increased emotional stress and changes in ASM plasma concentrations.
- ASM plasma concentrations may decrease during pregnancy due to decreased absorption from nausea and vomiting, increased volume of distribution and increased clearance.
- There is increased hepatic metabolism of lamotrigine and increased renal clearance of levetiracetam in pregnancy, which return to normal post-partum; increase the dose if necessary, according to clinical response.

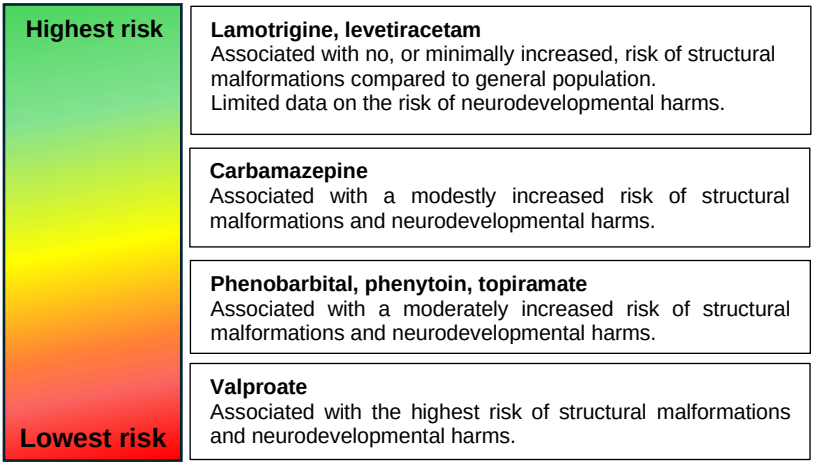

Figure 4. Risk of congenital structural malformations and neurodevelopment harms associated with various antiseizures medicines.
Increasing risk refers to increasing number of pregnancies or children affected.
(Adapted from Pennell PB. *Neurotherapeutics*. 2016 and Medicines & Healthcare products Regulatory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

LoE:IVb[xxxix]

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 of child-bearing potential.

LoE:IIIb[xl]

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 with HIV on ART because of fewer medicine interactions.
» Phenytoin, phenobarbital and carbamazepine are enzyme inducing ASMs. 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.

» Metabolism of lamotrigine is induced by lopinavir/ritonavir and atazanavir/ritonavir. The dose of lamotrigine may need to be increased when patients are switched to, or 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 at least 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 14.4: Epileptic seizures, and 14.5: Status epilepticus).

Maintenance Treatment

» Refer to Table 2 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 officer in consultation with a specialist.

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[xli]

» 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 Table 2, however 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.

Table 2: Epilepsy treatment in adolescents and adults

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*	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. Lamotrigine may be effective but may also exacerbate myoclonic seizures.

	with a specialist				Consider combination therapy.	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 absence epilepsy*	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 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 **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.

LoE:IVb[xlii]

Medicine Treatment

- Lamotrigine, oral (Doctor initiated).
  - Dose-titrate using table below.

Table 3: Dosing table for lamotrigine as monotherapy or add-on therapy:

	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.
Lamotrigine as add on therapy to existing regimen			
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[xliii]

CAUTION - LAMOTRIGINE

Lamotrigine may cause Stevens-Johnson Syndrome.

LoE:IVb[xliv]

- 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[xlv]

- 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 essential at doses > 300 mg daily.

LoE:IVb

Poorly controlled epilepsy

- » Ensure diagnosis of epilepsy and seizure type is confirmed, and exclude imitators of epileptic seizures.
- » 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 abuse 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 therapy unchanged (unless dose adjustment is necessary

because of a drug interaction). Reassess the patient within 2 weeks.

REFERRAL

» People with epilepsy who have not responded to two trials of ASM monotherapy at therapeutic drug concentrations and require consideration of combination therapy.
» Epilepsy with unexplained neurological symptoms or signs.

Information on the seizures 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?

14.7 HEADACHE AND FACIAL PAIN SYNDROMES

14.7.1 MIGRAINE

G43.0-3/G43.8-9

DESCRIPTION

A migraine is an episodic headache, usually located unilaterally and throbbing/ pulsating in nature, which may occur with or without an aura. Migraines are usually accompanied by nausea and/or vomiting, photophobia (sensitivity to light) and phonophobia (sensitivity to noise). There are several variants of migraine.

GENERAL MEASURES

Reassure patient that this is a benign condition.
Attempt to identify any precipitating factors or food triggers from the patient's history.

MEDICINE TREATMENT

Acute treatment

Initiate therapy during the migraine attack or at the onset of the headache.

Analgesia:

- 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.

OR

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

For nausea:

- Metoclopramide, oral/IM, 10 mg 8 hourly, as required.

Prophylaxis (Z29.2)

Regular, daily, prophylactic therapy is advised if:

» attacks are frequent, i.e. more than 2–3 per month, or
» severe, causing a significant amount of disability, or
» attacks are long lasting, or
» patient poorly tolerates therapy for acute attacks.

- Amitriptyline, oral, 10–25 mg at bedtime. *LoE:IIIa*[xlvi]
  - Up-titrate dose to adequate clinical response.
  - Doses greater than 75 mg are seldom required.

OR *LoE:IIb*[xlvii]

Poor response or contraindication to amitriptyline:

- β-blocker, e.g.:
- Propranolol, oral, 40 mg 12 hourly.
  - Titrate dose to adequate response
  - Maximum dose: 120–240 mg daily. *LoE:IIIb*[xlviii]

REFERRAL

Inadequate response to treatment.

14.7.2 CLUSTER HEADACHE

G44.0

DESCRIPTION

Repetitive episodes of excruciating headache typically of short duration (up to 2 hours) in clusters for weeks to months at a time. Typically, the headache is of sudden onset, unilateral during the specific cluster, and quickly reaches a climax. Associated redness of the eye with lacrimation and rhinorrhoea occurs.

MEDICINE TREATMENT

- Oxygen inhalation may abort some episodes.

LoE:IIIb[xlix]

Analgesics are ineffective.

To induce rapid remission in patients with episodic cluster headache:

- Corticosteroids (intermediate-acting) e.g.:

- Prednisone, oral, 40 mg daily for 5–10 days.
  - Tapering is not necessary when the above duration is used.

LoE:IVb[i]

Prophylaxis

- Verapamil, oral, 40–80 mg 12 hourly.

REFERRAL

Inadequate response to treatment.

14.7.3 TRIGEMINAL NEURALGIA

G50.0

See section 26.1.4: Management of neuropathic pain.

14.7.4 TENSION HEADACHE

G44.2

DESCRIPTION

Tension headaches are described as a tight band around the head and are generally worse in the afternoon. Usually occurs over the back of the head, but may extend over the entire head.

GENERAL MEASURES

Consider use of relaxation techniques.
Exclude medication overuse headache (see section 14.5.5: Medication overuse headache).

MEDICINE TREATMENT

- Amitriptyline, oral, 10–75 mg at night.

REFERRAL

» Atypical pain and/or focal neurological signs and symptoms, suggestive of alternate diagnosis.
» Poor response to therapy.

14.7.5 MEDICATION OVERUSE HEADACHE

G44.4

DESCRIPTION

Medication overuse headache generally occurs for ≥ 15 days per month for more than 3 months, and develops as a consequence of regular overuse of analgesics for acute pain-relief. The headache develops or markedly worsens during medication overuse, and usually, but not invariably, resolves after the overuse is stopped. *LoE:IVb[ii]*

GENERAL MEASURES

Stop all analgesics.
Counsel patient regarding the link between overuse of analgesics and the development of and/or worsening of the headache syndrome.
The headache usually resolves after the overuse is stopped, but may transiently worsen.

MEDICINE TREATMENT

- Amitriptyline, oral, 10 mg at night.
  - Increase to a maximum of 75 mg at night. *LoE:IIIb[ii]*
  - May be used during withdrawal of acute or symptomatic headache treatment.

14.7.6 IDIOPATHIC INTRACRANIAL HYPERTENSION (PSEUDOTUMOUR CEREBRI)

G93.2

DESCRIPTION

Patients present with symptoms (chronic headache, visual disturbance or loss due to papilloedema and tinnitus) and signs (papilloedema) of raised intracranial pressure without structural intracranial abnormality and with normal CSF composition.

Diagnosis

All patients should have neuroimaging (CT scan).
» If this is normal, i.e. the absence of structural lesions or hydrocephalus, perform a lumbar puncture and measure intracranial pressure.
» Diagnosis is confirmed by the presence of raised CSF pressure > 20 cm H_20.

GENERAL MEASURES

Stop medicines associated with benign intracranial hypertension (e.g. doxycycline, corticosteroids, combined oral contraceptives).
Regular monitoring of visual fields is crucial.
Weight loss.
Repeated lumbar punctures with measurement of opening pressure (do lumbar puncture with patient in left lateral position).
Consider surgery if there is progression of visual defects, despite medical therapy, visual loss at onset, or severe papilloedema.

MEDICINE TREATMENT

Discuss all cases with a specialist.

For visual involvement, persistent headaches, or severe papilloedema:

- Acetazolamide, oral, 250 mg 12 hourly
  - Increase, as required, by 250 mg daily every week to the maximum tolerated dose (not exceeding 4 g daily).

OR *LoE:IIIb*[iii]

- Furosemide, oral, 40 mg daily.

REFERRAL

» For neuro-imaging, if not available locally.
» Visual symptoms or deterioration of visual fields for opthalmology evaluation.
» Patients not responding to therapy or in need of surgical management.

14.8 INFECTIOUS AND PARASITIC CONDITIONS

14.8.1 MENINGITIS

A32.1† + (G01*)/A39.0† + (G01*)/G00.0-3/G00.8-9/G03.0-2/G03.8-9
**N. meningitidis*, *H. influenzae* Type B and listeriosis are notifiable medical conditions.

DIAGNOSIS

Computed tomography should be done before lumbar puncture in patients with:
» focal neurological signs,
» new seizures,
» papilloedema, or
» reduced level of consciousness.
In cases where lumbar puncture is delayed or cannot be done (e.g. uncontrolled significant bleeding tendency), commence empiric antibiotic therapy after taking samples for blood cultures. Attempt the lumbar puncture later, if possible.

GENERAL MEASURES

Observe patient closely with regular monitoring of vital signs and neurological state.
Pay close attention to hydration status.
Nurse patients in a quiet, semi-dark surrounding.
Repeated lumbar punctures are of no benefit in uncomplicated bacterial meningitis.
Prompt initiation of antibiotic therapy is associated with improved outcomes in patients with bacterial meningitis.

MEDICINE TREATMENT

All patients require sufficient analgesia:

- 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 400 mg.

Antibiotic therapy

Empiric therapy for bacterial meningitis, until sensitivity results are available:

- Ceftriaxone, IV, 2 g 12 hourly for 10 days. *LoE:IIIb[liv]*

Adjunctive corticosteroids are not recommended as trials in low-middle income countries have not demonstrated benefit.

Meningococcal meningitis A39.0† + (G01*)

For confirmed meningococcal disease only:

- Benzylpenicillin (penicillin G), IV, 20–24 MU daily in 4–6 divided doses for one week.

AND

Eradicate nasopharyngeal carriage with a single dose of ciprofloxacin 500 mg after completing course of benzylpenicillin. This is not required if the patient received an initial, pre-referral dose of ceftriaxone.

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

Severe penicillin allergy: (Z88.0)

- Meropenem, IV, 2 g 8 hourly for 7 days. *LoE:IIIb[lv]*

Prophylaxis of contacts:
Only for close household contacts and for healthcare workers who resuscitate patients before they received appropriate treatment.
- Ciprofloxacin, oral, 500 mg immediately as a single dose.

Pneumococcal meningitis G00.1
Conditions causing cerebrospinal fluid (CSF) leaks increase the risk for this type of infection, e.g. skull fractures, congenital defects, neurosurgery.

If sensitive to penicillin:
- Benzylpenicillin (penicillin G), IV, 20–24 MU daily in 4–6 divided doses for 10 days.

If resistant to penicillin:
- Ceftriaxone, IV, 2 g 12 hourly for at least 10 days.

Severe penicillin allergy: (Z88.0)
- Meropenem, IV, 2 g 8 hourly for 10 days.

Note: Consult a microbiologist/infectious diseases specialist.

Haemophilus influenzae G00.0
- Ceftriaxone, IV, 2 g 12 hourly for 10 days.

Severe penicillin allergy: (Z88.0)
- Meropenem, IV, 2 g 8 hourly for 10 days.

Note: Consult a microbiologist/infectious diseases specialist.

***Listeria monocytogenes* meningitis** A32.1†
- Ampicillin, IV, 3 g 6 hourly for 21 days. *LoE:IIIb*[lvi]

AND
- Gentamicin, IV, 5 mg/kg daily for 7 days (may be prolonged if response is poor). See Appendix II for guidance on prescribing.

Severe penicillin allergy: (Z88.0)
Consult a specialist.

REFERRAL
» For neuro-imaging: patients not responding or worsening in condition, i.e. decrease in consciousness and cranial nerve palsies, despite appropriate therapy. This is especially urgent in patients with tuberculous meningitis, who may develop hydrocephalus and require an urgent shunting procedure.
» Patients with shunts.

14.8.1.1 TUBERCULOUS MENINGITIS (TBM)

A17.0† + (G01*)

DIAGNOSIS

CSF findings are extremely variable. Generally, lymphocytes predominate, however, polymorphs predominate initially in about a third of patients.
Protein is usually > 1 g/L and glucose is usually low.

In cases where the differential diagnosis between bacterial and tuberculous meningitis is in doubt, lumbar puncture should be repeated 2–3 days later while still on ceftriaxone. If the aetiology is bacterial, considerable improvement in CSF findings may be expected, but with untreated tuberculous meningitis, the cell counts and protein levels will be the same or higher as the original CSF findings; and the glucose level will be the same or lower.

MEDICINE TREATMENT

Treat with standard combination tuberculosis therapy according to National protocol and extend duration of therapy to 9 months (2 months intensive phase, 7 months continuation phase). See section 16.9: Tuberculosis, Pulmonary for details.

In HIV-uninfected individuals:
Corticosteroid use may be of benefit in reducing neurological deficit in patients with grade II to III disease (focal neurological disease, depressed levels of consciousness, or a Glasgow Coma Scale of 14 or less).

- Dexamethasone, IV, dosing as follows:

Weeks	Dosing regimen
Initial dose	0.3-0.4 mg/kg/day for 2 weeks.
Week 3	0.2 mg/kg daily.
Week 4	0.1 mg/kg daily.
Week 5 to 8	4 mg/day, tapering daily dose by 1 mg each week.

OR

- Corticosteroids (intermediate-acting) e.g.: *LoE:IIa*[lvii]
- Prednisone, oral, 60 mg daily for 2 weeks.
  - Then taper gradually over the next 6 weeks (See Appendix II for an example of a dose reduction regimen). *LoE:IVb*[lviii]

LoE:IIa[lix]

In people with HIV:
Note: There is uncertainty whether the use of corticosteroids is beneficial in PLWH with TBM. *LoE:IIa*[lx]

14.8.1.2 CRYPTOCOCCAL MENINGITIS

GENERAL MEASURES

People living with HIV (see section 10.2.4: Cryptococcosis)

» In PWH the aim is to suppress the infection until immune restoration occurs with antiretroviral therapy.

HIV-uninfected patients

» In HIV-uninfected patients the aim is to cure the infection.

14.8.1.2.1 CRYPTOCOCCAL MENINGITIS, HIV-INFECTED

See section 10.2.4: Cryptococcosis.

14.8.1.2.2 CRYPTOCOCCAL MENINGITIS, HIV-UNINFECTED

B45.1 + (G02.1*)

MEDICINE TREATMENT

Initial therapy: *LoE:IIIb*[lxi]

- Amphotericin B, IV, 1 mg/kg daily.
  - Ensure adequate hydration to minimise nephrotoxicity (See Appendix II for preventing, monitoring, and management of toxicity).
  - Duration of initial IV therapy:
    - Treat intravenously for 4 weeks, provided that there are no neurological complications and follow up CSF culture at 2 weeks is negative.
    - In patients with neurological complications or persistent positive culture: increase the initial phase of therapy to 6 weeks in consultation with a specialist.

AND *LoE:IIb*[lxii]

- Fluconazole, oral, 800 mg daily for 2 weeks, followed by 400 mg daily for 2 months.

Maintenance therapy:

- Fluconazole, oral, 200 mg daily for a minimum of 1 year.

Follow all patients closely for relapses. *LoE:IVb*[lxiii]

Therapeutic lumbar puncture:

This should be considered as the intracranial pressure is often elevated with a communicating hydrocephalus. See section 10.2.4: Cryptococcosis.

14.8.2 VIRAL MENINGOENCEPHALITIS

A86/B00.4† + (G05.1*)

DESCRIPTION

Patients present with headache, neck stiffness, and encephalitic symptoms which may include fever, personality or behavioural changes, hallucinations

and seizures. Lumbar puncture typically shows mildly elevated protein, normal glucose and mild pleocytosis (< 500), mainly lymphocytes (early on polymorphs may predominate). Treatment for herpes simplex encephalitis should be commenced in all patients until this has been excluded (see below).

MEDICINE TREATMENT

Analgesia:

- 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 immediately then 8 hourly with meals, if needed.

OR *LoE:IVb*[lxiv]

- Morphine, IV, to a total maximum dose of 10 mg (See Appendix II, for individual dosing and monitoring for response and toxicity).

Herpes simplex encephalitis

Clinical features are fever, change in behaviour and seizures, which may be either focal or generalised.

Evidence of mucocutaneous involvement is usually not present. Lumbar puncture shows the above features of viral meningoencephalitis. Evidence of encephalitis involving medial temporal lobe region on MRI/CT neuro-imaging or on EEG is strongly supportive of the diagnosis and positive HSV PCR test on CSF is diagnostic.

- Aciclovir, IV, 10 mg/kg 8 hourly for 14 days (21 days in immunocompromised patients).
  - Start therapy as early as possible, i.e. before results are available.
  - A negative herpes PCR usually excludes the diagnosis unless the specimen was taken within 72 hours of onset of symptoms, when false negatives have been described.

Treat seizures appropriately, see section 14.6: Epilepsy. *LoE:IIa*[lxv]

All suspected cases of herpes encephalitis should be discussed with a specialist.

REFERRAL

» For neuro-imaging: patients not responding or worsening in condition, i.e. decrease in consciousness and cranial nerve palsies, despite appropriate therapy.

» Patients with shunts.

14.8.3 MENINGOVASCULAR SYPHILIS (NEUROSYPHILIS)

A52.1 + (G01*)

DIAGNOSIS

Lumbar puncture typically shows lymphocytosis with mildly elevated protein and low/normal glucose.

Serum syphilis serology: a negative TPHA or FTA excludes the diagnosis; RPR may be negative in some cases.

CSF syphilis serology: a CSF VDRL positive result is highly specific for neurosyphilis, but may be negative in approximately 50%. A negative CSF FTA-ABS excludes the diagnosis of neurosyphilis.

MEDICINE TREATMENT

- Benzylpenicillin (penicillin G), IV, 20 MU daily in 4–6 divided doses for 10 days.

LoE:IVb

A serum RPR response (4-fold decline in titre) after 6 months is predictive of treatment success for neurosyphilis.

LoE:IIIb[lxvi]

Severe penicillin allergy: (Z88.0)

Refer for consideration of desensitisation and subsequent treatment with benzylpenicillin at a referral centre.

14.8.4 BRAIN ABSCESS

G06.0

DIAGNOSIS

Patient may present with focal neurological signs and signs of infection. Neurological signs may not always be prominent. Neuro-imaging usually confirms diagnosis. Patients may have concomitant infection of ears, paranasal sinuses or lower respiratory tract.

MEDICINE TREATMENT

Empiric antibiotic therapy

- Ceftriaxone, IV, 2 g 12 hourly.

AND

- Metronidazole, oral, 400 mg 8 hourly **or** IV, 500 mg 8 hourly.

Adjust according to antimicrobial sensitivity after surgical drainage.

REFERRAL

All, as patients require urgent neurosurgery opinion and treatment.

14.8.5 ANTIMICROBIAL USE IN PATIENTS WITH HEAD INJURIES

S02.10-11/ /S06.11/S06.21/S06.31/S06.41/S06.51/S06.61/S06.71/S06.81/S06.91/ S09.9

MEDICINE TREATMENT

Basal skull fractures

Antibiotic prophylaxis is not indicated.

Penetrating brain injuries

Antibiotics are given for therapy.

- Ceftriaxone, IV, 2 g 12 hourly for 7 days. *LoE:IVb*

14.8.6 NEUROCYSTICERCOSIS

B69.0 + (G99.8*)

DIAGNOSIS

Patients may present with seizures and/or focal neurological deficit. Typical cystic lesions are seen on neuroimaging. Old, calcified lesions are inactive and do not require treatment.

GENERAL MEASURES

Health education.

Surgery for treatable ventricular blockage or spinal or intraocular cysts.

MEDICINE TREATMENT

For active or viable cysts only:

- Albendazole, oral, 12 hourly for 8 days.
  - ≥ 60 kg: 400 mg.
  - < 60 kg: 7.5 mg/kg to a maximum of 800 mg daily.

Note: Do not use in pregnancy due to teratogenicity.

AND *LoE:IIb*[lxvii]

- Corticosteroids (intermediate-acting) e.g.:
- Prednisone, oral, 60 mg daily for 8 days. *LoE:IVb*[lxviii]

Anticonvulsants, if required. See section 14.6: Epilepsy. *LoE:IIIb*[lxix]

REFERRAL

Uncontrolled seizures despite antiparasitic and anticonvulsant therapy.

14.9 MOVEMENT DISORDERS

DESCRIPTION

Abnormalities of movement/initiation of movement, divided into those with reduction of movement (hypokinesia or bradykinesia), or those with excessive movements (hyperkinesia).

14.9.1 PARKINSONISM, PRIMARY

14.9.1.1 IDIOPATHIC PARKINSON DISEASE

G20

DESCRIPTION

Parkinsonism is a syndrome characterised by tremor, rigidity, bradykinesia, 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.

The objective of treatment is to:

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

GENERAL MEASURES

General supportive therapy and advice about lifestyle modification, physiotherapy and occupational therapy.

MEDICINE TREATMENT

Note: Set therapeutic targets so that the patient is functioning as well as possible.

<u>Bradykinesia, rigidity and postural disturbance:</u>

- Carbidopa/levodopa, 25/100 mg (1 tablet), oral, 8 hourly, increase gradually according to clinical response.
  - Maximum dose of 200/800 mg daily (8 tablets).
  - Increase dose in consultation with a specialist.

REFERRAL

» Alternative diagnosis suspected (e.g. secondary Parkinsonism)
» No improvement or poor control with treatment.
» Increasing on/off phenomenon.
» Dyskinesias.

14.9.2 PARKINSONISM, SECONDARY

G21.0-4/G21.8-9/G24.0

DESCRIPTION

Secondary parkinsonism is caused by certain medicines (typical and atypical antipsychotics, anti-emetics, anticonvulsants (phenytoin, sodium valproate) and SSRIs), nervous system disorders, or other systemic illnesses.

GENERAL MEASURES

Primary approach in drug-induced parkinsonism should be to stop the offending medicine if possible.

Refer to psychiatric services for review of antipsychotic treatment in patients requiring treatment for parkinsonism (see section 15.5.2: Schizophrenia spectrum disorders).

MEDICINE TREATMENT

Anticholinergics have a limited role in this setting and should be used with caution.

- Anticholinergic agent, e.g.:
- Orphenadrine, oral, 50 mg 8 hourly, increase gradually according to clinical response.
  - Usual dose: 150–250 mg daily. *LoE:IVb*[lxx]
  - Maximum dose: 400 mg daily.

Note: Anticholinergic side effects are common and may be exacerbated by antipsychotics.

OR

- Carbidopa/levodopa, 25/100 mg (1 tablet), oral, 8 hourly.

Acute dystonic reaction: G24.0

Usually follows administration of dopamine-antagonistic drug, e.g. metoclopramide and phenothiazines.

- Anticholinergic agent, e.g.:
- Biperiden, IM/IV, 2 mg.
  - Repeat as necessary.

OR

- Promethazine, deep IM, 25–50 mg.
  - Decrease dose in the elderly to 25 mg. *LoE:IVb*

14.9.3 ESSENTIAL TREMOR

G25.0

GENERAL MEASURES

Exclude and manage alternate causes, such as drugs, thyrotoxicosis and hyperadrenergic states. Occasionally a patient may present with essential tremor and an additional neurological condition, which may make the diagnosis difficult.

MEDICINE TREATMENT

If tremor is severe and interfering with normal daily activity:

- Propranolol, oral,
  - Start at 20 mg daily and titrate as needed up to 80 mg 8 hourly.
  - Monitor for symptomatic bradycardia and/or hypotension. *LoE:IIIb*[bxi]

14.9.4 CHOREA

G25.5

DESCRIPTION

Chorea is a hyperkinetic movement disorder characterized by involuntary brief, random, and irregular contractions conveying a feeling of restlessness to the observer. Chorea may be caused by hereditary neurodegenerative diseases; structural damage to deep brain structures; or be associated with autoimmune disorders, metabolic derangement, or certain drugs and hormones.

Aetiology is classified as:

» Rarer primary (idopathic or hereditary) – Huntington's chorea,; or
» More common secondary (acquired) – Sydenham's chorea, hemiballismus secondary to infarction, diabetes (hyperglycemia)

Symptoms include involuntary, random, irregular movements.

GENERAL MEASURES

Exclude potential underlying causes initially.
A careful history should include age of onset, time course (acute or insidious), past medical history, history of recent infection with group A beta-hemolytic streptococcus (GABHS), family history, and drug exposure.
Neuroimaging should be performed for new-onset cases, especially when asymmetric.
A variety of laboratory tests may be useful depending on the clinical context.

MEDICINE TREATMENT

Treat the underlying cause, if relevant.

First-generation antipsychotic agents (typical neuroleptics) may reduce chorea although there is little evidence to support their efficacy, and they are increasingly avoided due to increased risk of side effects.

- Haloperidol, oral, 0.75–5 mg 8–12 hourly (Specialist consultation).

REFERRAL

The need to refer may be based on the underlying cause and diagnostic workup.
Refer primary choreas for genetic counselling.

LoE:IVb

14.10 NEUROPATHY

See section 26.1.4: Management of neuropathic pain

14.11 MYELOPATHY, ACUTE

G95.9

DESCRIPTION

Patients present with a sudden onset of paraparesis, with associated sensory loss, i.e. a sensory level may be found. Incontinence and autonomic instability may be present.

GENERAL MEASURES

Do cervical and thoracic spine films, with chest X-ray to exclude obstructive lesions before performing a lumbar puncture.

REFERRAL

All patients for urgent imaging.

14.12 MULTIPLE SCLEROSIS

G35

DESCRIPTION

A demyelinating disease of the central nervous system, characterised by relapsing and remitting episodes of unifocal or multifocal neurological dysfunction. Diagnosis is confirmed by imaging. The CSF may show oligoclonal bands and raised IgG index.

Recovery between acute flares of illness is common, although a general stepwise deterioration from baseline is usually found.

GENERAL MEASURES

Consult with neurologist for diagnosis and treatment.

REFERRAL

All patients.

14.13 MYASTHENIA GRAVIS

G70.0

DESCRIPTION

Myasthenia gravis is an autoimmune neuromuscular disorder characterised by fluctuating motor weakness involving ocular, bulbar, limb, and/or respiratory muscles.

The weakness is due to an antibody-mediated, immunologic attack directed at proteins in the postsynaptic membrane of the neuromuscular junction (acetylcholine receptors or receptor-associated proteins).

Consider this in patients with new onset weakness and fatiguability, particularly involving muscles of the eyes and those involved in swallowing.

MEDICINE TREATMENT

Discuss both diagnosis and treatment with a specialist.

- Pyridostigmine, oral, 60 mg 5 times daily. *LoE:IVb*[lxxii]

Corticosteroids and azathioprine should only be used in consultation with a specialist.

14.14 OEDEMA, CEREBRAL

DESCRIPTION

Swelling of brain parenchymal tissue, due to vasogenic, cytotoxic and osmotic causes. Only the vasogenic causes, such as brain tumours and inflammation, respond to corticosteroids.

14.14.1 BRAIN OEDEMA DUE TO TUMOURS AND INFLAMMATION

G93.6

GENERAL MEASURES

Supportive management. See section 14.1.1: Stroke.
Treat the underlying cause. This is especially important where brain oedema is associated with systemic conditions, such as electrolyte disturbances and organ failure.
Patients with primary brain tumours or brain metastases should be considered for definitive treatment of the tumour, which includes surgery and/or radiotherapy.

MEDICINE TREATMENT

- Dexamethasone, IV, 4 mg 6 hourly, initially.

OR

- Betamethasone, oral/IV, 4 mg 6 hourly.
  - Discontinue if no response has occurred after 48 hours.
  - Taper dose according to response and duration of therapy.

14.14.2 BRAIN OEDEMA DUE TO TRAUMATIC INJURY

S06.10-11 + External Cause Code (V,W,X,Y)

GENERAL MEASURES

Refer patient for neurosurgical opinion, if indicated.
Supportive management. See section 14.1.1: Stroke.
Note: DVT prophylaxis with heparin may be contraindicated due to increased risk of bleeding.

The following measures should be used in patients with raised intracranial pressure:
» head elevation and position,
» airway and ventilation control,
» sedation and analgesia,
» control of fever,
» control of hypertension, and
» prevention of seizures.

Currently, no evidence supports the use of hyperventilation in this setting.

MEDICINE TREATMENT

For raised intracranial pressure, pending a definitive neurosurgical procedure only:

- Mannitol 15–25%, IV, 0.25–1 g/kg administered over 30–60 minutes.
  - Monitor neurological response and urine output.
  - Beware of hypovolaemia and electrolyte disturbances, especially hypokalaemia.

Note: Corticosteroids should not be used in this setting as they have a harmful effect.

14.15 SPINAL CORD INJURY, ACUTE

T09.3

GENERAL MEASURES

There is insufficient evidence for the use of high dose corticosteroids in this clinical setting.

For symptomatic management of:
» Constipation – see section 24.1.2: Constipation.
» Urinary retention – see section 7.3.6: Overactive bladder.
» High risk of pressure sores – See Primary Health Care STG & EML, section 5.19: Pressure ulcers/ sores.
» Spasticity – refer patients for multi-disciplinary rehabilitation.

REFERRAL

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

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SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 14: NEUROLOGICAL DISORDERS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2020-4)

The Adult Hospital Level Neurological Disorders 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/.

TABLE A: AMENDMENTS

SECTION		MEDICINE/MANAGEMENT			ADDED/DELETED/AMENDED/ NOT ADDED/ RETAINED
14.1.1 STROKE		**General Measures**			Editorial update to specify patient population
		Blood pressure management: Hydrochlorothiazide			Dose aligned to the Hypertension STG in the cardiovascular conditions chapter (Section 3.6: Hypertension)
		Hyper-acute management: Recombinant tissue plasminogen activator (rtPA) time window			Retained
		Direct oral anticoagulants (DOACs)			Not Added
		Medicine Treatment			Editorial update to ensure adequate swallowing ability
14.2 DEMENTIA		**Restless Patients:** Haloperidol, Oral:			Retained with amendment in dosage range
		Wernicke's syndrome: Thiamine, IM			Retained with amendment in dose
		Other commonly associated nutritional deficiencies: Vitamin B12 Testing:			Retained
14.4 EPILEPTIC SEIZURES		Types of seizures			Detail on seizure types added and expanded
14.5 STATUS EPILEPTICUS	**14.5.1 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
				Clonazepam, IM	Added
			If IV access:	Lorazepam, IV	Retained
				Midazolam, IV	Retained
				Clonazepam, IV	Retained
				Diazepam, IV	Retained
		ESTABLISHED STATUS EPILEPTICUS (10 – 30 minutes) **LEVEL 2 INTERVENTION:** Antiseizure medicine	**If no IV access**	Levetiracetam NGT	Added
			If vascular access	Phenytoin, IV	Retained – Moved to level 2 intervention

SECTION		MEDICINE/MANAGEMENT		ADDED/DELETED/AMENDED/ NOT ADDED/ RETAINED
		REFRACTORY STATUS (30 – 60 minutes)	Propofol, IV	Retained
			Midazolam, IV	Retained
			Thiopental, IV	Removed
14.6.1 EPILEPSY IN ADOLESCENTS AND ADULTS		**Focal Epilepsy:** With and without evolution to bilateral tonic-clonic seizures	**First line:** Lamotrigine	Retained, moved to first-line: Adolescent boys, men and women not able to have children
			Second Line: Carbamazepine	Retained, moved to second-line: 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 treatment or add-on topiramate	Added: Adolescent boys, men and women not able to have children
			First line: Lamotrigine	Retained: 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 OR Combination lamotrigine and levetiracetam OR add-on topiramate	Added as third-line option: Pregnant women and women of child-bearing potential
		Generalised Epilepsy: 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	Deleted
			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 Consider: Consider combination therapy OR add-on topiramate	Added: Adolescent boys, men and women not able to have children.

SECTION	MEDICINE/MANAGEMENT		ADDED/DELETED/AMENDED/ NOT ADDED/ RETAINED
		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	Added: Pregnant women and women of child-bearing potential
	Myoclonic Confirm diagnosis and discuss management with a specialist	**First line:** Valproic acid	Retained: 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	Added: Adolescent boys, men and women not able to have children
		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	Added: Pregnant women and women of child-bearing potential
	Absence e.g. Juvenile absence epilepsy or persistent childhood absence epilepsy	**First line:** Valproic acid	Retained: Adolescent boys, men and women not able to have children
		Second Line: Lamotrigine	Retained, moved to second-line: Adolescent boys, men and women not able to have children
		Third Line *(specialist consultation):* Discuss with specialist Consider levetiracetam	Added: Adolescent boys, men and women not able to have children

SECTION	MEDICINE/MANAGEMENT		ADDED/DELETED/AMENDED/ NOT ADDED/ RETAINED
		OR Consider combination therapy.	
		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 sodium valproate	Added: Pregnant women and women of child-bearing potential
	Only consider continuing phenytoin in patients already well controlled on phenytoin, and in whom phenytoin is well tolerated	Phenytoin, oral	Only consider continuing phenytoin in patients already well controlled on phenytoin, and in whom phenytoin is well tolerated
14.7.2 CLUSTER HEADACHE	Oxygen Inhalation		Retained
14.7.6 IDIOPATHIC INTRACRANIAL HYPERTENSION (PSEUDOTUMOUR CEREBRI)	Acetazolamide, oral		Amended (Up Titration for maximum dose added)
14.9.1.1 IDIOPATHIC PARKINSON DISEASE	Dopamine agonists (Pramipexole extended-release tablets)		Not added
14.9.4 CHOREA	Clinical, medicine management & referral criteria		Expanded
	Haloperidol, Oral		Retained with amendment in dosage range
14.13 MYASTHENIA GRAVIS	Clinical description		Expanded to include clinical symptoms
14.14.1 BRAIN OEDEMA DUE TO TUMOR AND INFLAMMATION	Evidence Base for Medicine Management		Not Added
	Dexamethasone, IV		Retained, with no amendment in dosage
14.14.2 BRAIN OEDEMA DUE TO TRAUMATIC INJURY	Evidence Base for Medicine Management		Not Added
OTHER:	Endoscopic Cystoventriculostomy and Ventriculo-Cysternostomy for patients with Hydrocephalus (Adult and Paediatric) Referral to Specialist Neurosurgeon for surgical treatment		Not Added
14.15 (previously 14.1.3) SPINAL CORD INJURY, ACUTE	Management of sequalae of high risk of pressure sores		Added cross reference to PHC STG
	Symptomatic management of spasticity		Added with referral note for multi-disciplinary rehabilitation
	Symptomatic management of management of patients with cervical spinal cord injury		Added with referral note for multi-disciplinary rehabilitation

Paracetamol[1] 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.

14.1.1 STROKE

General Measures

In cases of cryptogenic stroke in young patients, it is important to consider neurosyphilis as a possible cause, given that about 15% of untreated neurosyphilis patients and nearly 3% of all syphilis patients present with a stroke, particularly those under 50 years of age.[2] Therefore, the age for conducting serology to exclude meningovascular syphilis was set at < 45 years also in line with risk factors for ischaemic stroke in young adults mentioned later under general measures.

The following editorial update was made to the STG:

From:
Do serology to exclude meningovascular syphilis

To:
Do serology to exclude meningovascular syphilis, (in patients < 45 years old who do not have risk factors for stroke).

An external comment received to include a cross reference to palliative care chapter was supported by the Committee.

The STG was updated as follows:

GENERAL MEASURES
Optimise hydration and nutrition; insert nasogastric tube if patient cannot swallow. Take precautions to ensure an open airway if patient is unconscious.
Physiotherapy and good nursing care. Consider rehabilitation for suitable patients and refer if necessary.
Do an ECG to rule out an acute coronary event or atrial fibrillation as precipitants.
Do serology to exclude meningovascular syphilis (in patients <45 years old who do not have risk factors for stroke).
Check lipid profile in ischaemic strokes.
Ischaemic stroke in young adults (< 45 years of age) may be due to atherosclerosis, but also consider:

- Embolic: e.g. rheumatic heart disease, atrial fibrillation, cardiomyopathy, previous myocardial infarction, and, very rarely, patent foramen ovale: history, careful clinical cardiac examination, ECG/CXR, and echocardiography.
- Vessel wall disease: e.g. syphilis, HIV infection, collagen-vascular diseases, TB or bacterial meningitis, and extracranial arterial dissection. Investigate as guided by clinical presentation, but at least perform syphilis and HIV serology, urinalysis (haematuria and/or proteinuria), and ANF/RF. ANCA, and cerebral angiography or carotid Doppler may be indicated. Note that absence of a carotid bruit does not exclude significant carotid stenosis.
- Hypercoagulable states: e.g. antiphospholipid antibody syndrome, thrombotic thrombocytopenic purpura. Useful screening investigations are FBC and, in women, PTT/Anti-phospholipid Ab. Testing and management of thrombophilias should be done in consultation with an expert.

Initiate a palliative care approach if the patient's condition is deteriorating / in case of a massive stroke (See Chapter 24: Medicines Used in Palliative Care).
Ensure adequacy of swallowing ability by dietician or by asking the patient to swallow 10 mL of water.

Blood pressure management (if adequate fluid intake can be ensured)
Hydrochlorothiazide, Oral: *Aligned to the hypertension STG*

Alignment of the dose of Hydrochlorothiazide for the management of blood pressure (if adequate fluid intake can be ensured) was confirmed against the cardiovascular conditions chapter (Section 3.6: Hypertension) as follows:

Hydrochlorothiazide, oral, 12.5 mg daily.

Hyper-acute management:
Recombinant tissue plasminogen activator (rtPA) time window: Retained

[1] South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.
[2] Singh AE, Romanowski B. Syphilis: review with emphasis on clinical, epidemiologic, and some biologic features. Clin Microbiol Rev. 1999; 12(2): 187-209.

An external comment to revise recombinant tissue plasminogen activator (rtPA) time window from 3 to 4.5 hours for the treatment of acute ischaemic stroke was not accepted as an evidence review3 for the same comment reviewed by NEMLC in the previous review cycle (2019), concluded reduced cost-benefit beyond 3 hours.

Refer to evidence review:

Alteplase for stroke - therapeutic window_A

Recommendation: Based on this evidence review, the Adult Hospital Level Committee recommends that rtPA time window not be extended from 3 to 4.5 hours for the treatment of acute ischaemic stroke. rtPA is only to be considered for use at facilities where specialised neuro-radiological services and relevant expertise that are available within the prescribed three hours.

Rationale: Cost-benefit beyond 3 hours decreases and rtPA is expensive. rtPA can only be administered where specialised neuro-radiological services are available. Alteplase is currently included on the Tertiary & Quaternary EML and Provincial PTCs have the mandate to authorise use at appropriate levels by relevant specialists.

Level of Evidence: I Meta analysis, Systematic review, Guidelines, Expert opinion

Review indicator:

Evidence of efficacy	Evidence of harm/safety	Price reduction
		x

VEN status: (T&Q EML)

Vital	Essential	Necessary
	x	

NEMLC MEETING OF 6 DECEMBER 2018:

The NEMLC accepted the Adult Hospital Level Committee's recommendation, above and further recommended that a registry be set up to determine actual use of tPA throughout the country. This would also assist in identifying facilities that provide thrombolytic therapy for management of stroke (and training needs as required).

Bridging Anticoagulation

Direct oral anticoagulants (DOACs): *Not Added*

An external comment to include direct oral anticoagulants (DOACs) as bridging anticoagulation was not accepted for adult secondary level of care, but deferred to the Tertiary and Quaternary expert review committee for review.

The maximum dose of Alteplase, IV, was confirmed and set as 90mg in line with the South African Medicines Formulary[4].

Medicine Treatment

The following update was made to the STG

Hyper-acute management:

Symptom onset ≤ 3 hours:

» Do not give aspirin.
» Refer immediately to hospital that **can provide thrombolytic therapy:**

- Alteplase, IV, 0.9 mg/kg. Total dose should not exceed 90 mg.
  - 10 % of total dose given as a bolus and the remainder continued as an infusion over an hour.

3 Tissue plasminogen activator: Alteplase (window period 3 hours versus 4.5 hours): National Department of Health: Affordable Medicines, EDP-Adult Hospital level. Medicine Review: Alteplase – Window period for treating hyper acute ischaemic stroke, February 2018. http://www.health.gov.za/

4 South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.

14.2 DEMENTIA

General Measures

An external comment received to involve a palliative care team or interdisciplinary team early and commence advanced care planning for dementia was supported by the Committee; because this implies focus on quality of life throughout care. It is further recommended to involve a multidisciplinary care team early and plan for advanced dementia care

The STG was updated as follows:

GENERAL MEASURES
Appropriate care and support, according to the level of impairment.
Ambulatory care is preferred to hospitalisation, if feasible.
Family counselling and support.
~~Involve a palliative care team~~ Use a palliative care approach: involve a multidisciplinary care team early and plan for advanced dementia care.

To control restless patients

Haloperidol, Oral: *retained with amendment in dosage range*

Haloperidol IM has been discontinued in South Africa. However, oral haloperidol is available locally. The recommendation for the use of oral haloperidol to control restless patients was retained. As the oral haloperidol formulation available is a 1.5mg scored tablet; the dosage range for oral haloperidol was amended for ease of dosing.

The STG was updated as follows:

From:

MEDICINE TREATMENT
Management is mainly symptomatic.

To control restless patients:
- Haloperidol, oral, 0.5–1 mg 8 hourly with a higher dose at night, if required.

To:

MEDICINE TREATMENT
Management is mainly symptomatic.

To control restless patients:
- Haloperidol, oral, 0.75–1.5 mg 8 hourly with a higher dose at night, if required.

Wernicke's syndrome: E51.2 + (F02.8*)
Thiamine, IM: *Retained with amendment in dose*

Refer to the evidence summary for the optimum dose of thiamine for prevention and treatment of Wernicke's encephalopathy:

Thiamine_PHC-Adults_Review_Final.docx

NEMLC MEETING OF 23 JUNE 2022:
NEMLC accepted the proposal to amend the dose of thiamine from "100mg" to "200mg", aligned with available RCT evidence, for the prevention of Wernicke's encephalopathy. NEMLC also deliberated on the route of administration and recommended that for the prevention of Wernicke's encephalopathy, that thiamine should be administered intramuscularly and not by the intravenous route.

Review of the evidence for the optimum dose of thiamine for prevention and treatment of Wernicke's encephalopathy showed that no good quality evidence could be identified to support a dose of thiamine 500mg three times a day although recommended in most guidelines[5]; and that thiamine 500mg once daily may be sufficient for 3-5 days. In the absence of any evidence updates and no reported harms, the pragmatic solution was to retain thiamine for the treatment of Wernicke's syndrome with an adjustment of dose to 500mg IM immediately and daily for 3 to 5 days.

For prophylaxis in patients at risk (alcoholism, malnutrition) intramuscular (IM) dose was clarified as 200mg daily and route of administration restricted to IM and not extended to intravenous as IM indicated as preferred route of administration in package information leaflet[6].

The STG was updated, with inclusion of a caution box for the administration of thiamine, as follows

FROM:

Wernicke's syndrome: E51.2 + (F02.8*)
- Thiamine, IV, 500 mg 12 hourly for 3 days, followed by 500 mg daily for 3–5 days.
  - Follow with oral thiamine 100 mg 8 hourly.

To:

Wernicke's syndrome: E51.2 + (F02.8*)
- Thiamine, IM, 500 mg immediately and daily for 3 to 5 days.
  - Follow with thiamine, oral, 100 mg 8 hourly

CAUTION
Thiamine should preferably be administered prior to intravenous glucose to prevent permanent neurological damage.
Do not delay the dextrose administration in a hypoglycaemic patient.

Prophylaxis in patients at risk (alcoholism, malnutrition): Z29.2
- Thiamine, IM/~~IV~~ 200mg daily or oral, 100 mg 8 hourly for 14 days.

Level of Evidence: Low to Moderate Certainty Evidence

Treat other commonly associated nutritional deficiencies
Vitamin B_{12} Testing: *Retained*
The availability of Vitamin B_{12} tests was queried with the National Health Laboratory Services (NHLS). The test is freely available at all levels of care without restrictions.

14.4 EPILEPTIC SEIZURES, 14.5 STATUS EPILEPTICUS, AND 14.6 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 sodium valproate as first line treatment for generalised tonic-clonic

5 Latt N, Dore G. Thiamine in the treatment of Wernicke encephalopathy in patients with alcohol use disorders. Intern Med J. 2014;44(9):911-5.10.1111/imj.12522
6 South African Health Product Regulatory Authority. Professional Information for Medicines for Human Use. A-Lennon Vitamin B Complex. Available at: https://pi-pil-repository.sahpra.org.za/

seizures, absence seizures, and children with HIV due to the concerns regarding sodium valproate 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 1: Medicine Amendments outlines the medicine changes to the AHL 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.

14.7.2 CLUSTER HEADACHE

Oxygen inhalation: *Retained*
An external comment, without supporting evidence, was received to add the following statement: '100% oxygen mask for 10 minutes' to the existing STG recommendation for oxygen therapy for cluster headaches.

The American headache society evidence-based guidelines[7] mention two class I randomised controlled trials with a level A recommendation for efficacy of oxygen. The rates and duration of oxygen therapy varied in the studies mentioned in the guidelines. Therefore, oxygen inhalation was retained in the STG without specifying rate or duration of therapy. An AGREE II appraisal was conducted, in duplicate, on the guideline and summarised below.

AGREE II Appraisal Summary

Guideline: Robbins MS, Starling AJ, Pringsheim TM, Becker WJ, Schwedt TJ. Treatment of Cluster Headache: The American Headache Society Evidence-Based Guidelines. Headache. 2016 Jul;56(7):1093-106. doi: 10.1111/head.12866. PMID: 27432623	
Domain 1: Scope and purpose	72%
Domain 2: Stakeholder involvement	6%
Domain 3: Rigour of development	63%
Domain 4: Clarity of presentation	86%
Domain 5: Applicability	42%
Domain 6: Editorial independence	88%

Overall Assessment: 75%
Level of Evidence: Low to Moderate Certainty Evidence

14.7.6 IDIOPATHIC INTRACRANIAL HYPERTENSION (PSEUDOTUMOUR CEREBRI)

Acetazolamide, oral: *Amended* (Up titration for maximum dose added)

Following an external comment highlighting a gap in instruction on reaching the maximum acetazolamide dose; the STG was amended to include an up titration of acetazolamide to the maximum allowable daily dose. Acetazolamide has been used to treat idiopathic intracranial hypertension with doses ranging from 250 to 500 mg twice daily; increasing the dose as tolerated by 250 mg every week to reach a desired clinical effect or a maximum dose of 4 g/day[8].

The maximum allowable dose was revised from 2 grams daily to 4 grams daily. Two RCTs were also reviewed regarding tolerated doses. Wall[9] et al stopped dose escalation if there was a measurable improvement in papilledema and visual

[7] Robbins MS, Starling AJ, Pringsheim TM, Becker WJ, Schwedt TJ. Treatment of Cluster Headache: The American Headache Society Evidence-Based Guidelines. Headache. 2016 Jul;56(7):1093-106. doi: 10.1111/head.12866. PMID: 27432623.
[8] Up to Date. Idiopathic intracranial hypertension (pseudotumor cerebri): Prognosis and treatment. 2021. Available at: https://www.uptodate.com/contents/idiopathic-intracranial-hypertension-pseudotumor-cerebri-prognosis-and-treatment?search=acetazolamide%20and%20dosing%20&source=search_result&selectedTitle=2%7E94&usage_type=default&display_rank=2.
[9] NORDIC Idiopathic Intracranial Hypertension Study Group Writing Committee; Wall M, McDermott MP, Kieburtz KD, Corbett JJ, Feldon SE, Friedman DI, Katz DM, Keltner JL, Schron EB, Kupersmith MJ. Effect of acetazolamide on visual function in patients with idiopathic intracranial hypertension and mild visual loss: the idiopathic intracranial hypertension treatment trial. JAMA. 2014 Apr 23-30;311(16):1641-51. doi: 10.1001/jama.2014.3312. PMID: 24756514; PMCID: PMC4362615.

field (according to prespecified criteria). ten Hove[10] et al only stopped dose escalation if participants reported symptoms interfering with activities of daily living. Both RCTs showed that acetazolamide appears to have an acceptable safety profile at dosages up to 4 g daily in the treatment of idiopathic intracranial hypertension.

Therefore, maximum dose was set at 4 grams daily but wording included for maximum tolerated dose, not exceeding 4 grams.

Level of Evidence: RCT: IIIb

The STG was updated as follows:

MEDICINE TREATMENT
Discuss all cases with a specialist.

For visual involvement, persistent headaches, or severe papilloedema:

- Acetazolamide, oral, 250 mg 12 hourly~~maximum dose 2 g daily~~
    - Increase, as required, by 250mg daily every week to the maximum tolerated dose (not exceeding 4g daily)

OR

Furosemide, oral, 40 mg daily.

14.9.1.1 IDIOPATHIC PARKINSON DISEASE

Dopamine agonists (Pramipexole extended-release tablets): *Not added*

An external recommendation was received for the inclusion of dopamine agonists specifically pramipexole extended-release tablets for ease of use (once daily dosing), substantial clinical effect, generally well tolerated, delay in dyskinesias and prolonged monotherapy which possibly improves depression. Dopamine agonists were not added as as they are approved for use as management at T&Q level of care[11].

14.9.4 CHOREA

Clinical, medicine management and referral criteria: *Expanded*

The STG was expanded including clinical, medicine management and referral criteria as follows:

From:
G25.5

DESCRIPTION
Involuntary random, irregular movements.
Aetiology is classified as:
» primary – Huntington's chorea,; or
» secondary – Sydenham's chorea, hemiballismus secondary to infarction, diabetes (hyperglycemia)

MEDICINE TREATMENT
Treat the underlying cause, if relevant.

- Haloperidol, oral, 0.5–5 mg 8–12 hourly (Specialist consultation).

To:
G25.5

DESCRIPTION

[10] ten Hove MW, Friedman DI, Patel AD, Irrcher I, Wall M, McDermott MP; NORDIC Idiopathic Intracranial Hypertension Study Group. Safety and Tolerability of Acetazolamide in the Idiopathic Intracranial Hypertension Treatment Trial. J Neuroophthalmol. 2016 Mar;36(1):13-9. doi: 10.1097/WNO.0000000000000322. PMID: 26587993.
[11] National Essential Medicines List Committee (NEMLC). TERTIARY AND QUATERNARY LEVEL. ESSENTIAL MEDICINES LIST. Reviewed Items. June 2022.

Chorea is a hyperkinetic movement disorder characterized by involuntary brief, random, and irregular contractions conveying a feeling of restlessness to the observer. Chorea may be caused by hereditary neurodegenerative diseases; structural damage to deep brain structures; or be associated with autoimmune disorders, metabolic derangement, or certain drugs and hormones.

Aetiology is classified as:
Rarer primary (idopathic or hereditary) – Huntington's chorea,; or
More common secondary (acquired) – Sydenham's chorea, hemiballismus secondary to infarction, diabetes (hyperglycemia)

Symptoms include involuntary, random, irregular movements.

GENERAL MEASURES
Exclude potential underlying causes initially.
A careful history should include age of onset, time course (acute or insidious), past medical history, history of recent infection with group A beta-hemolytic streptococcus (GABHS), family history, and drug exposure.
Neuroimaging should be performed for new-onset cases, especially when asymmetric.
A variety of laboratory tests may be useful depending on the clinical context.

MEDICINE TREATMENT
Treat the underlying cause, if relevant.

First-generation antipsychotic agents (typical neuroleptics) may reduce chorea although there is little evidence to support their efficacy, and they are increasingly avoided due to increased risk of side effects.
- Haloperidol, oral, 0.75–5 mg 8–12 hourly (Specialist consultation).

REFERRAL
The need to refer may be based on the underlying cause and diagnostic workup.
Refer primary choreas for genetic counselling.

Haloperidol, Oral: *retained with amendment in dosage range*

As the oral haloperidol formulation available is a 1.5mg scored tablet; the dosage range (lower end) for oral haloperidol was amended for ease of dosing.
Level of Evidence: LOW Certainty Evidence: Expert Opinion for the use of Haloperidol for the Management of Chorea

14.13 MYASTHENIA GRAVIS

Clinical description: *Expanded to include clinical symptoms*

The STG was expanded as follows:

From:

DESCRIPTION
Consider this in patients with new onset weakness and fatiguability. particularly involving the eyes and the swallowing muscles.

MEDICINE TREATMENT
Discuss both diagnosis and treatment with a specialist.
- Pyridostigmine, oral, 60 mg 5 times daily.

Corticosteroids and azathioprine should only be used in consultation with a specialist.

To:

G70.0

DESCRIPTION

Myasthenia gravis is an autoimmune neuromuscular disorder characterised by fluctuating motor weakness involving ocular, bulbar, limb, and/or respiratory muscles.
The weakness is due to an antibody-mediated, immunologic attack directed at proteins in the postsynaptic membrane of the neuromuscular junction (acetylcholine receptors or receptor-associated proteins).
Consider this in patients with new onset weakness and fatiguability, particularly involving muscles of the eyes and those involved in swallowing.

MEDICINE TREATMENT
Discuss both diagnosis and treatment with a specialist.
- Pyridostigmine, oral, 60 mg 5 times daily.

Corticosteroids and azathioprine should only be used in consultation with a specialist.

14.14.1 BRAIN OEDEMA DUE TO TUMORS AND INFLAMMATION

Dexamethasone, IV: *retained, with no amendment in dosage*

The STG recommends Dexamethasone, IV, 4 mg 6 hourly, initially. External comment was received to consider twice daily dosing instead, due to the risk of corticosteroid-induced adrenal suppression and insomnia. It was noted that treatment with dexamethasone for this indication was not intended as a palliative care approach and that short term IV therapy in hospital was unlikely to result in adrenal suppression and insomnia. The proposed amendment was therefore not supported by the Committee.

Evidence Base for Medicine Management: *Not Added*

In response to an external comment, the evidence base for medicine management for STGs 14.14.1 brain oedema due to tumors and inflammation was considered. However, it was noted that evidence citations for historic recommendations are generally not included in the current STGs, due to space constraints and therefore the evidence base was not included.

14.14.2 BRAIN OEDEMA DUE TO TRAUMATIC INJURY

Evidence Base for Medicine Management: *Not Added*

The evidence base for medicine management for STG 14.12.2 brain oedema due to traumatic injury was considered. However, it was noted that evidence citations for historic recommendations are generally not included in the current STGs, due to space constraints and therefore the evidence base was not included.

OTHER

The following addition suggested by an external commentator was not accepted for inclusion as it likely falls into tertiary management or outside the scope of the EML.

Chapter 14: Neurological Disorders:
Endoscopic Cystoventriculostomy and Ventriculo-Cysternostomy for patients with Hydrocephalus (Adult and Paediatric)
Referral to Specialist Neurosurgeon for surgical treatment.
Surgical Treatment:
- Hydrocephalus is a chronic medical condition that occurs in individuals who are unable to reabsorb cerebrospinal fluid (CSF) created within the ventricles of the brain. Treatment requires excess CSF to be cleared and the clearance of occlusions;

Choice of treatment procedure:
Recent advancements in both fiber laser and endoscope technologies may enable minimally invasive recanalization of ccluded ventricular catheters.
Hydrocephalus procedure options (different equipment used for each option) :
- Surgical insertion of drainage system – Shunt;
- Endoscopic Third ventriculostomy (ETV);

- Endoscopic Third ventriculostomy (ETV) with Choroid Plexus Cauterization (ETV/CPC);

Cost saving/Value adding to the Public Health Sector:
The Thulium Yag laser provides a rapid, safe, and effective means of clearing obstructed catheters in patients suffering from hydrocephalus, potentially reducing the need for surgical revision.

- Safe technique for laser endoscopic third ventriculostomy;
- Good vaporization and haemostasis for Choroid Plexus Cauterization;
- The Thulium Yag laser offers precise surgery with:
  - No deep penetration
  - Safe operation
  - Excellent hemostasis

14.15 SPINAL CORD INJURY, ACUTE

Spinal Cord Injury, Acute STG was moved from section 14.1.3 to 14.15 because section 14.1 relates to cerebrovascular disease. This editorial update is also in keeping with the PHC chapters were 15.12 Spinal Cord Injuries appears as the last STG in the chapter.

Management of sequalae of high risk of pressure sores: *Added cross reference to PHC STG*

Symptomatic management of spasticity: *Added with referral note for multi-disciplinary rehabilitation*

Symptomatic management of patients with cervical spinal cord injury: *Added with referral note for multi-disciplinary rehabilitation*

Only acute spinal cord injury is included in the STG. For the symptomatic management of sequalae of high-risk pressure sores a cross reference to the PHC STG: Skin and dermatology chapter (Section 5.19 Pressure Ulcers/ Sores) was added. Additionally, a referral note for multi-disciplinary rehabilitation was added for the symptomatic management of spasticity and management of patients with cervical spinal cord injury. The referral criterion added on receipt of motivation from RuReSA and Rehabilitation Associations of SA in collaboration with the Department of Health and Rehabilitation Sciences, Stellenbosch University[12] for pressure ulcers/sores and for prevention of pressure sores e.g., wheelchair users should be referred to rehabilitation for wheelchair and transfers training.[13,14]

The STG was updated as follows:

From:

For symptomatic management of:

» Constipation – see section 24.1.2: Constipation.
» Urinary retention – see section 7.3.6: Overactive bladder.

To:

For symptomatic management of:

» Constipation – see section 24.1.2: Constipation.
» Urinary retention – see section 7.3.6: Overactive bladder.
» High risk of pressure sores – See Primary Health Care STG & EML, section 5.19: Pressure ulcers/ sores.
» Spasticity – refer patients for multi-disciplinary rehabilitation.

REFERRAL

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

[12] Arora M, Harvey LA, Glinsky JV, Nier L, Lavrencic L, Kifley A, Cameron ID. Electrical stimulation for treating pressure ulcers. Cochrane Database Syst Rev. 2020 Jan 22;1(1):CD012196. https://pubmed.ncbi.nlm.nih.gov/35244315/.

[13] Harvey LA, Glinsky JV, Bowden JL. The effectiveness of 22 commonly administered physiotherapy interventions for people with spinal cord injury: a systematic review. Spinal Cord. 2016 Nov;54(11):914-923. https://pubmed.ncbi.nlm.nih.gov/27349607/.

[14] Wang J, Ren D, Liu Y, Wang Y, Zhang B, Xiao Q. Effects of early mobilization on the prognosis of critically ill patients: A systematic review and meta-analysis. Int J Nurs Stud. 2020 Oct;110:103708. https://pubmed.ncbi.nlm.nih.gov/32736250/.

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.
- Use midazolam for injection 5 mg in 1 mL undiluted.
- Draw up the required volume in a 5 mL syringe.
- Remove needle then administer midazolam into the buccal cavity (between gum and cheeks).
- 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.
- Use diazepam for injection 10 mg in 2 mL undiluted.
- Draw up the required volume in a 2 mL syringe.
- 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.
- 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:

Access to Schedule 5 medicines

- 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).

Children < 13 years of age

[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

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[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.

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[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)

$$\frac{\text{Maximum possible score = 7 (highest score) x no. of items x no. of appraisers}}{\text{Minimum possible score = 1 (lowest score) x no. of items x no. of appraisers}}$$

Score for each domain

$$\frac{\text{Obtained score - minimum possible score}}{\text{Maximum possible score - minimum possible score}} \times 100$$

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

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

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**	**Adolescent**	**1**
Male	2	Male	1
Adult	**53**	**Adult**	**17**
Female	35	Female	10
Male	17	Male	7
Unknown	1	**Elderly**	**12**
Child	**5**	Female	4
Female	2	Male	8
Male	2	**Unknown**	**26**
Unknown	1	Female	6
Elderly	**21**	Male	19
Female	13	Unknown	1

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

Concomitant medications

Acetazolamide			Acetylsalicylic acid
Acetylsalicylic acid			Allopurinol
Allopurinol			Amitriptyline
Alprazolam			Amlodipine besilate
Amitriptyline hydrochloride			Atorvastatin calcium
Amlodipine			Baclofen
Amoxicillin sodium			Bromazepam
Clavulanate potassium			Budesonide
Atenolol			Formoterol fumarate
Beclometasone			Clobazam
Benzydamine hydrochloride			Clotiapine
Chlorhexidine gluconate			Codeine phosphate
Bisoprolol fumarate			Meprobamate
Bromazepam			Paracetamol
Chloramphenicol			Codeine phosphate
Chlorpromazine			Paracetamol
Citalopram hydrochloride			Promethazine hydrochloride
Clobazam			Estradiol
Clonazepam			Norethisterone acetate
Diazepam			Fluoxetine hydrochloride
Dolutegravir sodium			Furosemide
Dosulepin hydrochloride			Hydrochlorothiazide
Enalapril			Lisinopril
Esomeprazole magnesium trihydrate			Hydrochlorothiazide
Fluoxetine hydrochloride			Valsartan
Flupentixol decanoate			Indapamide
Folic acid			Perindopril
Gabapentin			Insulin aspart
Gentiana lutea root			Insulin degludec
Primula spp. flower			Lacidipine
Rumex spp. herb			Lamotrigine
Sambucus nigra flower			Levetiracetam
Verbena officinalis herb			Lithium
Gliclazide			Olanzapine
Haloperidol			Potassium chloride
Hydrochlorothiazide			Prednisolone
Hydrochlorothiazide			Sertraline hydrochloride
Valsartan			Valproic acid sodium
Indapamide			
Indometacin			
Insulin bovine			
Insulin porcine			
Insulin glargine			
Lamotrigine			
Levetiracetam			
Levothyroxine sodium			
Lorazepam			
Metformin			
Methylephedrine			
Metoclopramide hydrochloride			
Morniflumate			
Nystatin			
Orphenadrine			

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.

health
Department:
Health
REPUBLIC OF SOUTH AFRICA

South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Neurological Disorders

TITLE: Ketamine for the management of refractory status epilepticus

Date: 17 February 2022

Research question: Is Ketamine, (by any route of administration) an appropriate alternative to thiopental for refractory status epilepticus?

Key findings

- Refractory status epilepticus (RSE) is considered as status epilepticus that persists despite treatment with an initial IV benzodiazepine and a second, longer-acting IV anti-seizure agent.
- Thiopental was standard of care in RSE but is no longer available globally.
- Ketamine is a newer or less standard treatment that may be considered.
- No available RCTs of ketamine in treatment of RSE could be retrieved.
- One systematic review of eight retrospective case series and 16 case reports was identified (Rosati et al., 2018).
- ***Efficacy:*** RSE controlled with ketamine in 70.3% (n=156/222) of RSE episodes, ranging from 11% in one retrospective case series (n=9 patients) to 100% in another (n=11 patients), *very low certainty evidence*. A burst-suppression pattern on EEG was noted in 3/7 patients in one case series and in three individual case reports; in two case reports (n=2 patients) it was postulated that ketamine use avoided endotracheal intubation. No person-centred, functional, or long-term outcomes were reported.
- ***Safety:*** In one case series (n=58), shock, sepsis, renal failure, pneumonia & acidosis were reported (number of patients affected unknown); cerebellar atrophy reported in one case report (n=1 patient) and cardiac arrest in another (n=1 patient). Confounding factors were not explored. No adverse effects were reported in other case series or reports.
- There is very limited data and much uncertainty for ketamine in RSE, despite the appropriate risk/benefit profile pressure and cardiac function. Ketamine also has less need of the use of vasopressors often needed with alternative agents such as propofol and benzodiazepines while maintaining respiratory reflexes, with a potentially neuroprotective effect (Rosati et al., 2018).

PHC/ADULT HOSPITAL LEVEL RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option or to use the alternative **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
		X			

Recommendation: The PHC/Adult Hospital Level Committee proposes that ketamine not be recommended for refractory status epilepticus (RSE).
Rationale: Currently, there is limited RCT data of efficacy and safety for ketamine use for RSE (conditional recommendation).
Level of Evidence: Very low certainty
Review indicator: New data of efficacy and safety

NEMLC RECOMMENDATION: 8 DECEMBER 2022
Due to the limited RCT data of efficacy and safety; NEMLC did not recommend ketamine for refractory status epilepticus (RSE).

Research priorities:
Monitoring and evaluation:

(Refer to appendix 4 for the evidence to decision framework)

1. **Executive Summary**

Date: 24 January 2022
Medicine (INN): Ketamine
Medicine (ATC): N01AX03
Indication (ICD10 code): G41.0-2
Patient population: Adult Patients (≥ 18 years) with refractory status epilepticus (RSE)
Incidence/Prevalence of condition: Population studies from the US, Europe and Asia indicate that the incidence of status epilepticus (SE) ranges from 5 to 40 per 100,000 general population. RSE is reported as occurring in up to 40% of SE. [1] A 2-year prospective observational study found 23% of 128 SE episodes were refractory to treatment. [2]
Level of Care: Hospital
Prescriber Level: Doctor
Current standard of Care: Thiopental
Efficacy estimates: (preferably NNT): Reported in a systematic review (of case series studies): 70.3% (n= 156/222) of RSE episodes were controlled with ketamine administration – but data is uncertain with no adjustment for confounding.
Motivator/reviewer name(s): M Reddy, G Thom, S McGee, L Robertson, T Leong
PTC affiliation: G Thom (KZN PTC Member)

BACKGROUND

Status epilepticus (SE) is defined as either:[3] a) two or more sequential seizures, lasting more than 5 minutes without full recovery of consciousness between seizures, or b) continuous seizure activity for longer than 5 minutes. Refractory status epilepticus (RSE) is persistent SE that fails to respond to first- and second-line longer-acting IV anti-seizure agent.[4] Medicine management of SE should be administered promptly and in adequate doses.[Error! Bookmark not defined.] If seizures continue for 60 to 90 minutes after the initiation of therapy the stage of refractory status is reached.[5]

The incidence of SE does not vary between countries or gender. Population studies from the US, Europe and Asia indicate that the incidence of SE ranges from 5 to 40 per 100,000. The incidence is however higher (about four times higher) in older patients versus younger individuals (annual incidence in elderly of 27.1 per 100,000). RSE is estimated to occur in 29 to 43% of SE cases.[Error! Bookmark not defined.] Rai & Drislane (2018)[6] report a relative prevalence of RSE of 10% to > 30% of all SE, while in a prospective observational study 23% of SE patients became refractory.[Error! Bookmark not defined.]

RSE is a life-threatening condition associated with high morbidity. Midazolam, propofol (IV anaesthetic) and barbiturates such as thiopental and its metabolite pentobarbital are highly sedating anti-seizure agents used in the management of RSE. All present the concern of respiratory depression and hypotension. Pentobarbital has also been associated with hepatoxicity and prolonged sedation.

Ketamine, an anaesthetic agent and glutamate antagonist acting at the N-methyl-D-aspartate (NMDA) receptor, is a newer or less standard treatment that may be considered especially as patients become resistant to benzodiazepines and barbiturates that act at the GABA receptor. Possible advantages of ketamine are that it has a rapid onset of action, is short-acting, and is thought to be rarely associated with respiratory depression and negative cardiovascular outcomes; however, there is uncertainty regarding possible long-term side effects. [6]

As thiopental is no longer available in South Africa, an evidence review for ketamine for the indication of RSE has been undertaken.

Eligibility criteria for review

Population: Adult Patients (≥ 18 years) with refractory status epilepticus

Interventions: Ketamine (by any route of administration)/ ketamine + midazolam IV

Comparators: Thiopentone/ pentobarbital IV, propofol IV, midazolam IV

Outcomes:

- Occurrence of Seizures/Treatment Failure:
  - *Immediate treatment failure* - clinical or electrographic (EEG) seizures occurring between 1 hour and 6 hours after receiving the initial loading dose,
  - *Breakthrough seizures* - clinical or EEG seizure occurring after the first 6 hours of the initial seizure.
  - *Withdrawal seizures* - any seizures occurring within 48 hours after initially discontinuing or tapering treatment.
- Intensive care unit (ICU) stay
  - *Need for ventilation/prolonged Ventilation*
  - *ICU related complications (e.g., infections)*
- Safety/ Side Effects:
  - *Hypotension/refractory hypotension,*
  - *Respiratory depression defined as the occurrence of apnea or need for intubation and*
  - *Cardiac arrest*
- Mortality

Study designs: Randomised control trials (RCTs), systematic reviews, meta-analyses of RCTs, systematic reviews of case reports and case series. Non-randomised controlled trials were included as scoping indicated the limited availability of RCT evidence for ketamine for refractory status epilepticus.

METHODS

We conducted a review by systematically searching PubMed and the Cochrane database on 26th May 2021. We restricted the search to RCTs, systematic reviews and meta-analyses and English language as feasibility of translations was limited. Screening of records was conducted independently and in duplicate (MR & GT), with disagreement resolved through discussion (TL, SM, MR LR, GT). We compared studies between systematic reviews to ensure that there was no duplication and included relevant studies reviewed in systematic reviews independently, as required. The search strategy is shown in Appendix 1. An AMSTAR review was conducted in duplicate (MR & GT) for systematic reviews with support from SD to ensure that the AMSTAR tool (https://www.bmj.com/content/358/bmj.j4008) for review of non-RCTs was conducted appropriately.

A search for national and international guidelines for ketamine in guidelines using google scholar (search terms: "guideline AND treatment AND refractory AND status AND epilepticus"), and relevant guidelines were assessed by two reviewers (SM & GT) using the AGREE II instrument (Bouwer 2010).

RESULTS

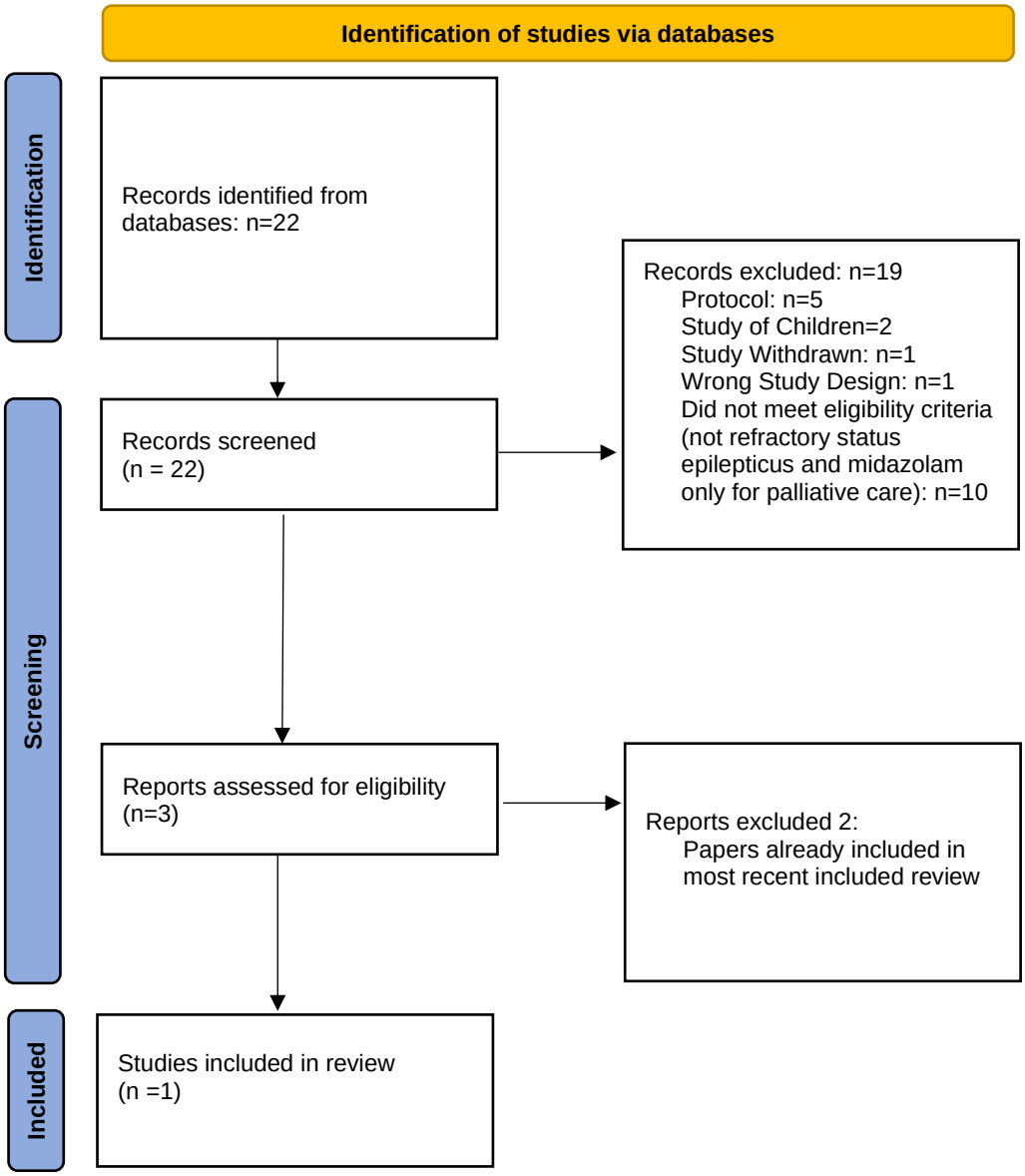
Results of search

The search identified 22 studies. Nineteen records were excluded because the records were a protocol, study of children, study which reviewed midazolam only with an indication for palliative care, was the wrong study design or did not meet eligibility criteria. Three full text records were reviewed. No RCTs were identified. The three publications identified were systematic reviews of case reports, observational and retrospective studies. Two of the reviews were excluded because all but 2 case reports were papers already included in the most recent systematic review. Additionally, one of the 2 reviews excluded was of poor quality. One systematic review was summarised (Table 1), and AMSTAR assessment was conducted (Appendix 2).

The search for guidelines identified five international epilepsy guidelines which either a) did not mention ketamine but were not updated recently (n=3), b) indicated there was no data available to support the use of ketamine (n=1), or c) recommended ketamine as an option for RSE when other conventional treatments fail (n=1).

Table 1 summarises characteristics of included papers. **Table 2** outlines the list of excluded studies with reason for exclusion. **Table 3** summarises a list of international guidelines and content related to Ketamine and the results of the AGREE II assessment.

Figure 1: PRISMA flow diagram for the review



Description of the studies

Three systematic reviews (Zeiler et al., 2014[7]; Golub et al., 2018 [8]; Rosati et al., 2018[9]) were identified but only one (Rosati et al., 2018) was summarised for the review as it contained all but 2 studies[10,11] included in the earlier systematic reviews. One of the two studies not included in the Rosati et al., 2018 paper, Kofke et al., 1997 was of a single case study which did not add any additional information. After several attempts the reviewers were unable to obtain a full text copy of the second study, Svonoros et al., 2011. There were methodological concerns regarding the Golub et al., 2018 systematic review because it included Zeiler et al 2014 and individual papers that were already included in Zeiler et al 2014.

Rosati et al. (2018) reviewed data from eight retrospective case series and 16 case reports. The sample sizes of the case series ranged from 7 - 67 individuals, with a total of n=219 adults and a median age 54.5 years (24–67 years). The 16 case reports were of 19 individuals (20 RSE episodes treated with ketamine). In total, 222 RSE episodes were

documented among the case series and reports. The duration of SE prior to ketamine administration ranged from 24 hours to 26.5 days in the case series and from 12 hours to 5 months in the case reports. Dosage and duration of Ketamine infusion ranged from 0.07 to 15 mg/kg/h and 6 hours to 29 days, respectively.

Overall, the evidence was of very low quality because of selection and attrition bias (no RCTs available but only retrospective case series, and case reports). Studies had small patient numbers and outcome data was poorly documented. Timing of the ketamine response after administration was reported as poorly documented. Additionally, heterogeneity of prior treatments, time to ketamine administration, ketamine dosage and duration made the data on seizure responsiveness difficult to interpret for the reviewers. Polypharmacy was also a concern, and Rosati et al note that ketamine was always administered after conventional anaesthetics, except for 1 case report. Generally, observational studies are subject to confounding and risk of bias – the studies in the review were not adjusted for confounding (e.g. effect of other anti-epileptic agents or aetiologies).

Efficacy:

Clinical resolution of RSE Episodes

- Resolution of RSE on clinical judgement ranged from 11% (n=9) to 100% (n=11) in case series
- A total of 156/222 (70.3%) RSE episodes were eventually controlled by KE administration

EEG and other findings

- EEG features were not specified in majority of case series. A burst-suppression pattern was observed in 3/7 patients in one case series and in three individual cases. Diffuse beta activity was observed in RSE episodes in which KE was effective (in 4/11 participants of one case series and in four individual case reports). The clinical implications of these EEG features are unclear and whether they equate to recovery of the person is not known.
- Endotracheal intubation was believed to have been avoided in two individuals where KE was effective
- No person-centred, functional, or long-term outcomes were reported by Rosati et al.

Safety: Adverse events:

- Shock, sepsis, renal failure, pneumonia & acidosis were noted in one case series (n=58); actual number of people who experienced adverse events is not documented, nor are confounding factors excluded
- Cerebellar atrophy reported in one case report (n=1)
- Cardiac arrest reported in one case report (n=1)

Table 3 provides the details of the international guidelines which were considered. Combined AGREE II scores for the guidelines are provided (SM, GT). Some guidelines did not consider ketamine as a treatment option. The Hong Kong Guideline made a recommendation, but this guideline lacked methodological rigour and conceded that evidence was limited.

CONCLUSION

The lack of RCTs for the use of ketamine in the management of RSE is challenging. Only case reports, case series, observational and retrospective study designs have been reviewed in systematic analyses. These systematic reviews are limited in assessing bias and conducting meta-analyses. The data of efficacy is uncertain and is of very low quality, but has been considered as an option in an international guideline (however lowest AGREE II score) when conventional agents have failed. The reason for conducting this review is that thiopental has been discontinued from the South African market. Ketamine is not a cardiac or respiratory depressant, but the quality of the data is inadequate to prove safety.

Reviewer(s): M Reddy, G Thom, L Robertson, S McGee, T Leong

Declaration of interests: MR (Better Health Programme, South Africa), GT (Amajuba District Clinical Specialist Team), LR (Sedibeng District Specialist Mental Health Team) and T Leong (Essential Drugs Programme, National Department of Health) have no interests to declare. SM is employed by the Ophthalmological Society of South Africa.

Acknowledgements:
Solange Durao (Medical Research Council, South Africa) provided input and support for the AMSTAR Review.

Table 1: Characteristics of reviewed studies

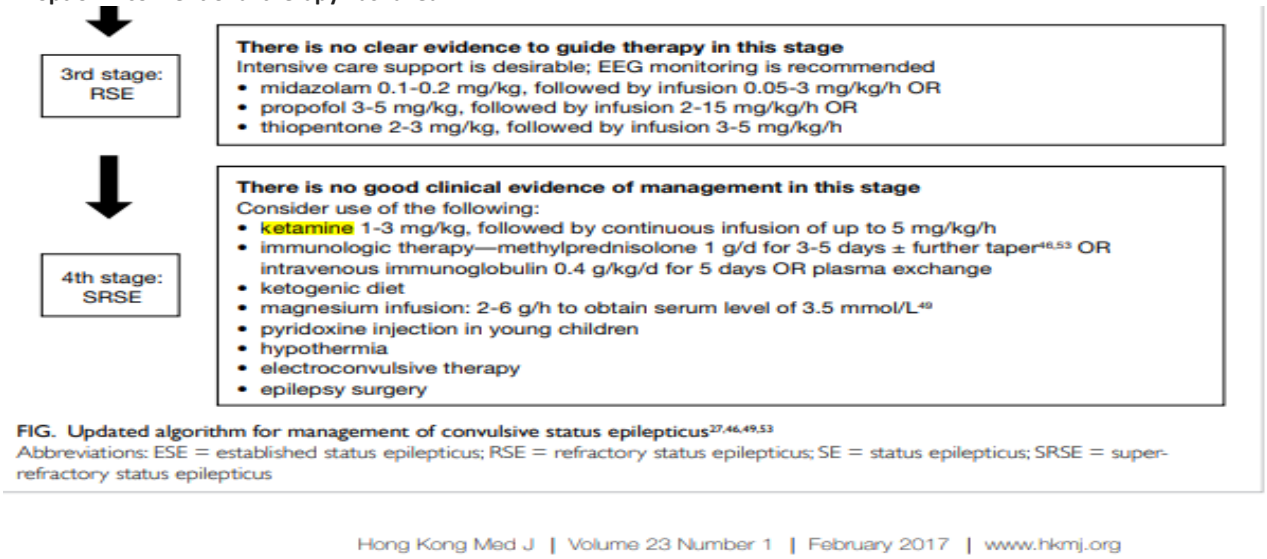
i) Systematic review of observational data

Citation	Study Design	Population	Treatment	Main findings	Risk of Bias assessment
Rosati et al. 2018 Ketamine for Refractory Status Epilepticus: A Systematic Review CNS Drugs (2018) 32:997–1009[9] https://doi.org/10.1007/s40263-018-0569-6	Systematic review of 27 case reports, 14 case series (n=8 were for adults; n=6 were for children) 0 RCTS reported Most were retrospective	n= 219 adults in 8 retrospective case series (sample sizes ranged from 7-67 individuals) n=19 adults in 16 case reports Median age 54.5 years (24–67 years)	Ketamine	**Overall treatment** • n=222 RSE episodes treated with KE **Frequent Aetiologies** • Infections & anoxia were reported • n=60 aetiology remained unknown **Type of RSE** • n=4/8 case series RSE was not specified • Non-convulsive SE (NCSE) most common SE treated with KE, both in case series & in case reports **Mean Duration of SE** • 24 h 26.5 days in case series • 12 h - 5 months in case reports • Highly heterogenous regardless of SE type **Administration of KE & Add-ons** • Both case series & case reports reported that KE always given after conventional anesthetics, except for 1 case report • Propofol was the most common third-line treatment • Add-ons: Benzodiazepines, especially midazolam **Doses & Duration of KE** • Doses ranged from 0.07 to 15 mg/kg/h • Duration ranged from 6 h - 29 days **Effectiveness of KE** • Resolution of RSE: KE effective in 156/ 222 (70.3%) RSE episodes, ranging from 11% in one case series (n=9) to 100% in another (n=11) • EEG changes: (EEG) features were not specified in majority of case series. Burst-suppression patterns observed in 3/7 patients in one case series and in three individual case reports. Diffuse slowing & diffuse beta activity were EEG patterns observed in RSE episodes in which KE was effective. Clinical implications of EEG changes unknown. • Avoidance of endotracheal intubation: KE administration thought to prevent intubation in two cases. **Adverse Events** - shock, sepsis, renal failure, pneumonia & acidosis were reported in one case series (n=58) - cerebellar atrophy reported in one case report (n=1) and cardiac arrest in another (n=1)	Available information on the efficacy of KE is biased by the design of the available studies - observational, mostly retrospective Quality of Evidence: **Low to very Low** **Overall:** **Selection Bias:** NO RCTs. Retrospective Case Series and CASE Reports and prospective cohort studies. Small numbers – **high risk** **Attrition Bias:** Outcome data was poorly documented to obtain a definitive conclusion – The timing of ketamine response after administration was poorly documented within the majority of the adult studies – **high risk** Heterogeneity of prior treatments, time to ketamine administration, & ketamine dosage & duration make the data on seizure responsiveness difficult to interpret Some studies reported /met GRADE D level of evidence i.e., **Non-analytic studies, such as case reports and case series** **High Risk:** • Low sample sizes • 90% case reports & case series • No meta-analyses • Heterogeneity • Polypharmacy Studies sometimes did not differentiate adults & paediatrics - data was included for both groups – skewing results **Favourable considerations for ketamine:** • Less pronounced hypotensive & respiratory depressive effects • Potentially favourable risk/benefit profile vs conventional anesthetics, • Neuroprotective effect AMSTAR assessment presented in Appendix 2

Table 2: List of Excluded Studies

No	Citation	Reason for Exclusion
Ineligible Studies: Studies Excluded During Screening Before Full Text Review		
1	Rosati A, et al. Efficacy of ketamine in refractory convulsive status epilepticus in children: a protocol for a sequential design, multicentre, randomised, controlled, open-label, non-profit trial (KETASER01). BMJ Open. 2016 Jun 15;6(6):e011565. doi: 10.1136/bmjopen-2016-011565.	Protocol. Children
2	Zaporowska-Stachowiak I, et al. Midazolam: Safety of use in palliative care: A systematic critical review. Biomed Pharmacother. 2019 Jun;114:108838. doi: 10.1016/j.biopha.2019.108838.	Midazolam only and indication is palliative care
3	Ketamine in Refractory Convulsive Status EpilepticusNCT02431663. https://clinicaltrials.gov/show/NCT02431663, 2015 | added to CENTRAL: 31 January 2020 |	Protocol (Study terminated - futility)
4	Efficacy of Ketamine Infusion Compared With Traditional Anti-epileptic Agents in Refractory Status Epilepticus NCT03115489. https://clinicaltrials.gov/show/NCT03115489, 2017 | added to CENTRAL: 31 May 2018 | 2018 Issue 5 CT.gov	Protocol (withdrawn- no participants enrolled)
5	Levetiracetam, Lacosamide and Ketamine as Adjunctive Treatment of Refractory Status Epilepticus NCT02726867 https://clinicaltrials.gov/show/NCT02726867, 2016 | added to CENTRAL: 31 May 2018 | 2018 Issue 5 CT.gov	No Study Results (withdrawn- no participants enrolled)
6	Pharmacotherapy for Refractory and Super-Refractory Status Epilepticus in Adults M Holtkamp Drugs, 2018, 1-20 | added to CENTRAL: 31 March 2018 | 2018 Issue 3 Embase	Review (Wrong Study Design)
7	Efficacy of ketamine in refractory convulsive status epilepticus in children: a multicenter, randomized, controlled, open-label, no-profit, with sequential design study. EUCTR2013-004396-12-IT	Children
8	Efficacy of ketamine in refractory convulsive status epilepticus in children: a protocol for a sequential design, multicentre, randomised, controlled, open-label, non-profit trial (KETASER01) A Rosati, BMJ open, 2016, 6(6) (no pagination) | added to CENTRAL: 30 September 2016 | 2016 Issue 9 Embase	Protocol
9	Efficacy of ketamine in refractory convulsive status epilepticus in children: a protocol for a sequential design, multicentre, randomised, controlled, open-label, non-profit trial (KETASER01) A Rosati, L Ilvento, M L'Erario, S De Masi, A Biggeri, G Fabbro, R Bianchi, F Stoppa, L Fusco, S Pulitanò, D Battaglia, A Pettenazzo, S Sartori, P Biban, E Fontana, E Cesaroni, D Mora, P Costa, R Meleleo, R Vittorini, A Conio, A Wolfler, M Mastrangelo, MC Mondardini, E Franzoni, KS McGreevy, L Di Simone, A Pugi, L Mirabile, F Vigevano, R Guerrini BMJ open, 2016, 6(6), e011565 | added to CENTRAL: 31 January 2018 | 2018 Issue 1 PubMed	Protocol & duplicate
10	A cautionary tale of synthetic marijuana use L Zhang, P Patel, D Dani. Neurology, 2018, 90(15) | added to CENTRAL: 30 June 2018 | 2018 Issue . Embase	Does not meet PICO
11	Colquhoun H, et al. Phase 1/2 open-label data suggest that heterogeneity of presentation and high burden of comorbid illness do not impact the activity of SAGE-547 in patients with super-refractory status epilepticus. Conference: 14th annual meeting of the neurocritical care society. United states, 2016, 25(1 Supplement 1), S207	Does not meet PICO
12	Legros B et al. Intravenous lacosamide in refractory seizure clusters and status epilepticus: comparison of 200 and 400 mg loading doses. Neurocritical care, 2014, 20(3), 484-488	Does not meet PICO
13	Nomayo HO. Intravenous levetiracetam in the management of refractory complex-partial status epilepticus Epilepsia, 2009, 50, 32	Does not meet PICO
14	Kanes SJ et al. SAGE-547 for the treatment of super-refractory status epilepticus: response and relationship to underlying patient characteristics.. Neurocritical care, 2016, 25(1), S205	Does not meet PICO
15	Prasad et al. Anticonvulsant therapy for status epilepticus.	Not Refractory
16	Propofol versus thiopental sodium for the treatment of refractory status epilepticu. Hemanshu Prabhakar, Mani Kalaivani	Does not meet PICO
17	Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. Amy McTague, Timothy Martland, Richard Appleton	Children
18	Early versus late antiepileptic drug withdrawal for people with epilepsy in remission. Isabella Strozzi, Sarah J Nolan, Michael R Sperling, Dean M Wingerchuk, Joseph Sirven	Does not meet PICO
19	Rapid versus slow withdrawal of antiepileptic drugs. Fernando Ayuga Loro, Enrique Gisbert Tijeras, Francesco Brigo	Does not meet PICO
Studies Excluded After Full Text Review		
20	Zeiler et al. 2014. NMDA antagonists for refractory seizures. Neurocrit Care. 2014 Jun;20(3):502-13. doi: 10.1007/s12028-013-9939-6. PMID: 24519081	Papers already included in Rosati et al 2018
21	Golub et al. 2018. Potential consequences of high-dose infusion of ketamine for refractory status epilepticus: case reports and systematic literature review. Anaesth Intensive Care. 2018 Sep;46(5):516-528. doi: 10.1177/0310057X1804600514. PMID: 30189827.	Papers already included in Rosati et al 2018

Table 3: List of International Guidelines

Guideline	Recommendations	AGREE II overall rating and recommendation to use
NICE (2004)	**No mention of ketamine but not updated recently**	Score: 5/7 Use: Yes
American Epilepsy Society (2016)	**No mention of ketamine**	Score: 4/7 Use: Yes, with modifications
American Epilepsy Society (2020)	Convulsive Refractory Status Epilepticus (CRSE) "For children and adults with CRSE, insufficient evidence exists on the effectiveness of ketamine (level U; 25 class IV studies)" Conclusions: "Mostly insufficient evidence exists on the efficacy of stopping clinical CRSE using brivaracetam, lacosamide, LEV, valproate, ketamine, MDZ, PTB, and PRO either as the last ASM or compared to others of these drugs. Adrenocorticotropic hormone, IVIg, corticosteroids, magnesium sulfate, and pyridoxine have been used in special situations but have not been studied for CRSE. For the treatment of established convulsive SE (ie, not RSE), LEV, VPA, and fosphenytoin are likely equally effective, but whether this is also true for CRSE is unknown. Triple-masked, randomized controlled trials are needed to compare the effectiveness of parenteral anesthetizing and nonanesthetizing ASMs in the treatment of CRSE."	Not a guideline – rather a review of the possible treatments
European Federation of Neurological Societies Published (2010)	"Ketamine has been described in some case reports and patient series to terminate SE after failure of GABAergic anticonvulsants [55–57] (Class IV)" **Mentioned but not included in the guideline**	Score: 4/7 Use: Yes, with some modifications
Hong Kong Epilepsy Society Published (2017)	**An option if conventional therapy has failed**  **FIG. Updated algorithm for management of convulsive status epilepticus**[27,46,49,53] Abbreviations: ESE = established status epilepticus; RSE = refractory status epilepticus; SE = status epilepticus; SRSE = super-refractory status epilepticus Hong Kong Med J | Volume 23 Number 1 | February 2017 | www.hkmj.org	Score: 2/7 Use: No

Appendix 1: Search strategy

Database: **PUBMED**
Date: **26 May 2021**

Search Strategy:
ketamine and refractory status epilepticus
ketamine plus midazolam and refractory status epilepticus
ketamine and thiopentone and refractory status epilepticus
ketamine and pentobarbital and refractory status epilepticus
ketamine and propofol and refractory status epilepticus
ketamine and midazolam and refractory status epilepticus
ketamine and status epilepticus
ketamine plus midazolam and status epilepticus
ketamine and thiopentone and status epilepticus
ketamine and pentobarbital and status epilepticus
ketamine and propofol and status epilepticus
ketamine and midazolam and status epilepticus

Number of studies: **5 Records**

Database: **Cochrane Database**
https://www.cochranelibrary.com/
Date: **26 May 2021**

Search Strategy:
ketamine and refractory status epilepticus
midazolam and refractory status epilepticus
anticonvulsants and refractory status epilepticus
anticonvulsants and status epilepticus
ketamine and status epilepticus

Number of studies reviews: **17 records**

Restricted Search to: Meta-Analysis, Systematic Reviews, Randomized Controlled Trials

Appendix 2: Evaluating the methodological quality of the Rosati et al (2018) systematic review and meta-analysis – AMSTAR 2 tool (Shea 2017[1])

No.	Criteria	Yes/ Partial Yes/ No
1	Research questions and inclusion criteria for the review included the components of PICO	No
2*	Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol	No
3	Review authors explained selection of the study designs for inclusion in the review	No
4*	Review authors used a comprehensive literature search strategy	No
5	Review authors perform study selection in duplicate	No
6	Review authors perform data extraction in duplicate	No
7*	Review authors provided a list of excluded studies and justify the exclusions	No
8	Review authors described the included studies in adequate detail	Partial Yes
9*	Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review	No
10	Review authors reported on the sources of funding for the studies included in the review?	No meta-analysis conducted
11*	For meta-analyses, review authors used appropriate methods for statistical combination of results	No meta-analysis conducted
12	For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis	No
13*	Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review	Yes
14	Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review	Yes
15*	For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review	No meta-analysis conducted
16	Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review	Yes

** Critical domains = 2, 4, 7, 9, 11, 13, 15*

Rating overall confidence in the results of the review

- *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
- *Moderate:* More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review
- *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest
- *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

(*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence).

OVERALL ASSESMENT: Critically low

Rationale: Flaws in critical domains 2, 4, 7 and 9

Conclusion: The AMSTAR assessment suggests that the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

[1] Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008.

Appendix 3: AGREE II Score Sheets

1. NICE Guidelines: Epilepsies: diagnosis and management: Clinical guideline [CG137], 12 May 2021

Domain	Item	AGREE II Rating						
		1 *Strongly Disagree*	**2**	**3**	**4**	**5**	**6**	**7 *Strongly Agree***
Scope and purpose	1. The overall objective(s) of the guideline is (are) specifically described.			X				
	2. The health question(s) covered by the guideline is (are) specifically described.			X				
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.						X	
Stakeholder involvement	4. The guideline development group includes individuals from all the relevant professional groups.							X
	5. The views and preferences of the target population (patients, public, etc.) have been sought.						X	
	6. The target users of the guideline are clearly defined.						X	
Rigor of development	7. Systematic methods were used to search for evidence.							X
	8. The criteria for selecting the evidence are clearly described.					X		
	9. The strengths and limitations of the body of evidence are clearly described.						X	
	10. The methods for formulating the recommendations are clearly described.						X	
	11. The health benefits, side effects and risks have been considered in formulating the recommendations.							X
	12. There is an explicit link between the recommendations and the supporting evidence.							X
	13. The guideline has been externally reviewed by experts prior to its publication.						X	
	14. A procedure for updating the guideline is provided.						X	
Clarity of presentation	15. The recommendations are specific and unambiguous.							X
	16. The different options for management of the condition or health issue are clearly presented.						X	
	17. Key recommendations are easily identifiable.						X	
Applicability	18. The guideline describes facilitators and barriers to its application.				X			
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.				X			
	20. The potential resource implications of applying the recommendations have been considered.						X	
	21. The guideline presents monitoring and/ or auditing criteria.	X						
Editorial independence	22. The views of the funding body have not influenced the content of the guideline.				X			
	23. Competing interests of guideline development group members have been recorded and addressed.	X						
Overall Guideline Assessment	• Rate the overall quality of this guideline.	1 *Lowest possible quality*	2	3	4	**5**	6	7 *Highest possible quality*
Overall Guideline Assessment	• I would recommend this guideline for use.	***Yes***	*Yes, with modifications*					*No*
		X						

2. Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society - 2016

Domain	Item	AGREE II Rating						
		1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree
Scope and purpose	1. The overall objective(s) of the guideline is (are) specifically described.						X	
	2. The health question(s) covered by the guideline is (are) specifically described.						x	
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.				X			
Stakeholder involvement	4. The guideline development group includes individuals from all the relevant professional groups.				X			
	5. The views and preferences of the target population (patients, public, etc.) have been sought.		X					
	6. The target users of the guideline are clearly defined.		X					
Rigor of development	7. Systematic methods were used to search for evidence.							X
	8. The criteria for selecting the evidence are clearly described.						X	
	9. The strengths and limitations of the body of evidence are clearly described.						X	
	10. The methods for formulating the recommendations are clearly described.						X	
	11. The health benefits, side effects and risks have been considered in formulating the recommendations.					X		
	12. There is an explicit link between the recommendations and the supporting evidence.							X
	13. The guideline has been externally reviewed by experts prior to its publication.						X	
	14. A procedure for updating the guideline is provided.	X						
Clarity of presentation	15. The recommendations are specific and unambiguous.							X
	16. The different options for management of the condition or health issue are clearly presented.						X	
	17. Key recommendations are easily identifiable.							X
Applicability	18. The guideline describes facilitators and barriers to its application.		X					
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.		X					
	20. The potential resource implications of applying the recommendations have been considered.	X						
	21. The guideline presents monitoring and/ or auditing criteria.	X						
Editorial independence	22. The views of the funding body have not influenced the content of the guideline.	X						
	23. Competing interests of guideline development group members have been recorded and addressed.				X			
Overall Guideline Assessment	• Rate the overall quality of this guideline.	1 Lowest possible quality	2	3	**4**	5	6	7 Highest possible quality
Overall Guideline Assessment	• I would recommend this guideline for use.	Yes	**Yes, with modifications**					No
			X					

3. European Federation of Neurological Societies (EFNS) guideline on the management of status epilepticus in adults (2010)

Domain	Item	AGREE II Rating						
		1 Strongly Disagree	2	3	4	5	6	7 Strongly Agree
Scope and purpose	1. The overall objective(s) of the guideline is (are) specifically described.					X		
	2. The health question(s) covered by the guideline is (are) specifically described.			X				
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.			X				
Stakeholder involvement	4. The guideline development group includes individuals from all the relevant professional groups.			X				
	5. The views and preferences of the target population (patients, public, etc.) have been sought.	X						
	6. The target users of the guideline are clearly defined.	X						
Rigor of development	7. Systematic methods were used to search for evidence.						X	
	8. The criteria for selecting the evidence are clearly described.					X		
	9. The strengths and limitations of the body of evidence are clearly described.				X			
	10. The methods for formulating the recommendations are clearly described.						X	
	11. The health benefits, side effects and risks have been considered in formulating the recommendations.				X			
	12. There is an explicit link between the recommendations and the supporting evidence.				X			
	13. The guideline has been externally reviewed by experts prior to its publication.				X			
	14. A procedure for updating the guideline is provided.	X						
Clarity of presentation	15. The recommendations are specific and unambiguous.					X		
	16. The different options for management of the condition or health issue are clearly presented.					X		
	17. Key recommendations are easily identifiable.					X		
Applicability	18. The guideline describes facilitators and barriers to its application.	x						
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	X						
	20. The potential resource implications of applying the recommendations have been considered.	X						
	21. The guideline presents monitoring and/ or auditing criteria.	X						
Editorial independence	22. The views of the funding body have not influenced the content of the guideline.	X		X				
	23. Competing interests of guideline development group members have been recorded and addressed.				X			
Overall Guideline Assessment	• Rate the overall quality of this guideline.	1 Lowest possible quality	2	3	**4**	5	6	7 Highest possible quality
Overall Guideline Assessment	• I would recommend this guideline for use.	Yes	**Yes, with modifications**					No
			X					

4. Review and update of the Hong Kong Epilepsy Guidelines for status Epilepticus (2017)

Domain	Item	AGREE II Rating						
		1 *Strongly Disagree*	2	3	4	5	6	7 *Strongly Agree*
Scope and purpose	1. The overall objective(s) of the guideline is (are) specifically described.		X					
	2. The health question(s) covered by the guideline is (are) specifically described.	X						
	3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.		X					
Stakeholder involvement	4. The guideline development group includes individuals from all the relevant professional groups.	X						
	5. The views and preferences of the target population (patients, public, etc.) have been sought.	X						
	6. The target users of the guideline are clearly defined.	X						
Rigor of development	7. Systematic methods were used to search for evidence.	X						
	8. The criteria for selecting the evidence are clearly described.	X						
	9. The strengths and limitations of the body of evidence are clearly described.	X						
	10. The methods for formulating the recommendations are clearly described.	X						
	11. The health benefits, side effects and risks have been considered in formulating the recommendations.		X					
	12. There is an explicit link between the recommendations and the supporting evidence.	X			X			
	13. The guideline has been externally reviewed by experts prior to its publication.	X						
	14. A procedure for updating the guideline is provided.	X						
Clarity of presentation	15. The recommendations are specific and unambiguous.						X	
	16. The different options for management of the condition or health issue are clearly presented.						X	
	17. Key recommendations are easily identifiable.						X	
Applicability	18. The guideline describes facilitators and barriers to its application.	x						
	19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	X						
	20. The potential resource implications of applying the recommendations have been considered.	X						
	21. The guideline presents monitoring and/ or auditing criteria.	X						
Editorial independence	22. The views of the funding body have not influenced the content of the guideline.			X				
	23. Competing interests of guideline development group members have been recorded and addressed.	X						
Overall Guideline Assessment	• Rate the overall quality of this guideline.	1 *Lowest possible quality*	**2**	3	4	5	6	7 *Highest possible quality*
Overall Guideline Assessment	• I would recommend this guideline for use.	*Yes*	*Yes, with modifications*					***No***
								X

Appendix 4: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High [ ] Moderate [ ] Low [ ] Very low [X] *High quality:* confident in the evidence *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Systematic reviews of case studies and retrospective case reports. AMSTAR 2 assessment of the systematic review: critically low. • Low sample sizes • High risk of bias and confounding • Heterogeneity • Polypharmacy • Confounding factors not addressed
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [ ] Moderate [ ] Small [ ] None [ ] Uncertain [X]	**Effectiveness of KE & Resolution of RSE Episodes** • 11% (n=9) to 100% (n=11) reported effectiveness of KE • n= 156/222 (70.3%) were controlled by KE administration • n=2 patients avoided endotracheal intubation where KE was effective
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High [ ] Moderate [ ] Low [ ] Very low [X] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Systematic reviews of case studies and retrospective case reports.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large [ ] Moderate [ ] Small [ ] None [ ] Uncertain [X]	**Adverse Events** 1 case report of shock, sepsis, renal failure, pneumonia & acidosis 1 case report of cerebellar atrophy 1 case report of cardiac arrest Confounding factors not addressed.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention [ ] Favours control [ ] Intervention = Control *or* Uncertain [X]	Ease of use – cardiac and respiratory depression believed to be rare.
FEASABILITY	**Is implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	Ketamine already included on the EML, as an anaesthetic agent.
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [ ] Uncertain [X]	There is no standardised dosing of ketamine, IV for RSE. Dose range extracted from systematic review by Rosati et al (2018). **Direct medicine price:** **Upper** / **Lower** **Dosage Range** *(mg/kg/hr)*: 0.07 / 7.5 **Duration of therapy**: 1 hour / 19 days **Requirement for 70kg patient** *(mg)*: 4.9 / 9975 **Requirement for 70kg patient** *(ml)*: 1 / 200 **Medicine price range**: R 4.92 / R984.00 Contract circular HP06-2021SVP [Accessed 1 January 2022]: Ketamine; 500mg/10ml = R49.20 Medicine price modelled on 70 kg patient.

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [ ] No [ ] Uncertain [X]	There is no survey evidence, but expert opinion reported that ketamine is acceptable amongst clinical practitioners as the agent is likely haemodynamically stable.
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [X] Uncertain [ ]	

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South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Neurological Disorders

EVIDENCE SUMMARY

Date: 27 October 2022 (Initial Review Date: 3 February 2021)

Reviewers: Dr H Dawood and L Robertson*

Affiliation: Infectious diseases , Greys hospital and Caprisa, University of Kwazulu Natal
*Sedibeng District Health Services and Department of Psychiatry, University of the Witwatersrand

QUESTION: The optimum dose of thiamine for prevention and treatment of Wernicke's encephalopathy and chronic alcohol misuse in the acute setting.

Background

In September 2020, a concern was raised by the Western Cape regarding IV administration of thiamine as supplier provides a caution of anaphylaxis in IV use – therefore only recommended for IM use.

The management of suspected alcohol withdrawal/ Wernicke's encephalopathy under 21.2.4 Delirium in the PHC STGs was discussed at an ad hoc NEMLC meeting on 30 September. It was agreed to change the thiamine dose from Thiamine IV/IM 500mg immediately to Thiamine IM 100mg immediately. The decrease in dose was pragmatic, related to poor quality evidence for 500mg, variations in global practice, and thiamine available in 100mg/ml vials and 5ml IM injection unlikely to be tolerable.

At the Adult ERC meeting of 28 October 2020, a query was raised regarding the initial rationale for the 500mg dose with the concern that this was not discussed thoroughly when reducing the dose to 100mg.

High dose IV thiamine is still recommended in the Hospital Adult STGs in Chapter 14 Neurological Disorders: 14.2 DEMENTIA

Wernicke's syndrome: E51.2 + (F02.8*)

- Thiamine, IV, 500 mg 12 hourly for 3 days, followed by 500 mg daily for 3–5 days.
  - Follow with oral thiamine 100 mg 8 hourly.

IV thiamine is also recommended for ethanol poisoning in Chapter 19 (Thiamine, IV, 100 mg in 1 L dextrose 5%) only the dosing of thiamine in prevention and treatment of Wernicke's encephalopathy is considered here.

Introduction

Wernicke's encephalopathy (WE) is an acute neuropsychiatric condition due to overwhelming metabolic demands on cells that have depleted intracellular thiamine (vitamin B_1) resulting in a reversible biochemical brain lesion. It is commonly seen in chronic alcohol misusers, and if treated sub-optimally with thiamine (given by the incorrect route, inadequate dose or too late), leads to irreversible structural changes producing loss of short-term memory and an impaired ability to acquire new information. Failure to treat WE leads to Korsakoff psychosis (KP), a chronic disease characterized by severe memory loss.

In a Royal College of Physicians report,[1] Thomson et al. (2002) note observational evidence suggesting that treatment of WE with low parenteral doses of 50–100 mg of thiamine daily resulted in 16% full recovery, 17–20% died, and 84%

developed KP. Of those with KP, only 21% showed complete recovery; 26% showed no improvement, 28% only slight improvement and 25% showed significant recovery from the amnesic state (can take between 2 months to 10 years). It is therefore essential that thiamine be given as soon as possible in adequate amounts to all patients with suspected or incipient WE. The route of administration must provide sufficient supply of thiamine especially to the dependent enzymes in brain cells. In addition, all hypoglycaemic patients whether or not attributable to chronic alcohol misuse treated with IVI glucose must be given IVI thiamine at the same time to avoid the risk of precipitating WE.

Previous treatment of 500mg IV immediately in the PHC STGs for suspected alcohol withdrawal/ WE and current treatment of WE in Hospital Adult STGs based on empirical clinical practice and uncontrolled trials.[1-3]

Clinical guidelines are vary in recommendations but generally use high doses for treatment (Table 1).[4] NICE recommends thiamine is offered to people at risk of WE 'in doses toward the upper end of the 'British national formulary' (BNF) range' (https://www.nice.org.uk/guidance/qs11/chapter/quality-statement-10-wernickes-encephalopathy)

Summary of the evidence

i) Prevention of WE

Cochrane Systematic Review by Day et al (2013)[5] - one RCT (Ambrose et al., 2001) on prevention of cognitive dysfunction in alcohol withdrawal. 169 patients with alcohol dependence recruited from an inpatient detoxification unit were randomized to receive thiamine doses of 5mg, 50mg, 100mg, or 200mg IM once a day for 2 days. None had signs of WE. 107 patients included in analysis (43 did not complete treatment and data removed for 19 to equate groups for age, sex, and alcohol use). Only 200mg differed significantly from 5mg on cognitive testing post-treatment (mean difference (MD) -17.90, 95% confidence interval (CI) -35.4 to -0.40, P = 0.04).

No further RCTs for prevention or treatment of WE were identified in two recent systematic reviews, one investigating effect of nutritional interventions (McClean et al., 2020)[6] and the other investigating treatment effects on alcohol related cognitive impairment (Caballeria et al, 2020)[7]

ii) Treatment of WE – prevention of Korsakoff's psychosis

The uncontrolled trials noted by Thomson et al. (2002)[1] are not referenced. A citation search of a 2007 Lancet review[8] for trials recommending a minimum dose of 500mg IV three times a day for 3-5 days found reviews but no actual studies or data.

Case-series:

- Nshimoto et al. (2017)[9] – retrospectively reviewed records of 11 patients with suspected or diagnosed WE and who had received high dose thiamine therapy, defined as ≥500mg parenteral thiamine per day. Doses of thiamine varied, including 500mg IV once off, daily, twice a day, and three times a day and duration from 1 to 7 days. Median time to treatment from symptom onset was 92hours. Symptoms resolved in 7 out of 11 patients. No differences observed in those whose symptoms resolved vs those whose symptoms did not in terms of timing of thiamine initiation from symptom onset, patient variables, adverse effects. Conclusion: High-dose thiamine (≥500 mg) appears safe and efficacious for use in patients with suspected WE.
- Soler-González et al. (2014)[10] – describe 10 cases in whom WE had been misdiagnosed and mistreated (time to diagnosis ranged from 2 – 44 days, average 22 days). Three received thiamine at low doses (100mg IM; 300mg oral). All showed at least some degree of improvement with IV thiamine 500 mg/8 h x 3 days, then 500 mg/day x 5 more days with at least 300 mg/day p.o.; some of them suffered severe consequences, mainly Korsakoff's syndrome.

Conclusion

- *Prevention* of WE in alcohol withdrawal/ suspected alcohol withdrawal including hypoglycaemia – 200mg IM/IV should possibly be the minimum dose.

- *Treatment* of WE/ prevention of Korsakoff's – there is no good quality evidence to support 500mg three times a day (recommended in most guidelines – see table 1, below); 500mg once a day IM for 3-5 days, though, may be a pragmatic option.

NEMLC MEETING OF 23 JUNE 2022: NEMLC accepted the proposal to amend the dose of thiamine from "100mg" to "200mg", aligned with available RCT evidence, for the prevention of Wernicke's encephalopathy. NEMLC also deliberated on the route of administration and recommended that for the prevention of Wernicke's encephalopathy, that thiamine should be administered intramuscularly and not by the intravenous route.
NEMLC MEETING OF 8 DECEMBER 2022: • NEMLC accepted the proposal as recommended by the Adult Hospital Level Expert Review Committee (see above)

Table 1. Guideline comparison for prevention and treatment of WE (Latt and Dore, 2014)[4]

Table 2 Some guidelines for thiamine replacement dosage regimen in alcohol-dependent patients with Wernicke encephalopathy/Wernicke Korsakoff syndrome (WE/WKS)

Prophylaxis for patients with suspected WE/WKS or at high risk of WE/WKS	Treatment of patients with a definitive diagnosis of WE/WKS	Reference
(a) 100 mg I/M t.d.s for 3–5 days (b) (UK)250 mg I/M daily for 3–5 days	(a) At least 100 mg I/V for 5 days (b) 500 mg t.d.s for 2 days; if no response, discontinue; if there is response continue with 250 mg I/M or I/V for 5 days	Royal College of Physicians (UK)[3] NB: In the UK , 250 mg thiamine is present in an ampoule of high potency B complex vitamins (Pabrinex)
(a) At least 100 mg I/M for 3–5 days (b) 500 mg I/M daily for 3–5 days (UK) Follow with oral thiamine as an outpatient	(a) At least 100 mg t.d.s I/V for 5 days (b) 500 mg I/V t.d.s. for 2 days; if no response discontinue; if there is response, continue with 250 mg I/m or I/V daily for 5 days, or longer if improvement continues (UK)	*Oxford Specialist Handbooks: Addiction Medicine* (Latt *et al.*, 2009).[15]
	200 mg I/M or I/V t.d.s (preferably I/V)	European Federation of Neurological Sciences (EFNS) guidelines (Galvin *et al.*, 2010)[5]
(a) For healthy, low-risk patients: >300 mg orally daily (during detoxification) (b) For malnourished/unwell high-risk patients: 250 mg I/M or I/V once daily for 3–5 days, or until no further improvement is seen	>500 mg I/M or I/V for 3–5 days, followed by 250 mg once daily for a further 3–5 days depending on response	British Association for Psychopharmacology (BAP) guidelines (Lingford-Hughes *et al.*, 2012)[16]
(a) Low-risk patients: 100 mg orally daily (b) Patients who drink excess alcohol:100–200 mg I/M or I/V daily for 3 days and then 100 mg orally daily	500 mg I/V infusion over 30 min t.d.s for 2–3 days, and then 250 mg I/M or I/V for 3–5 days, or until clinical improvement is seen	Etg Therapeutics Guidelines (http://etg.hcn.com.au/tgc/gig/5209.htn)[17]

Prophylaxis	Treatment of	Reference
	250–500 mg in 100 mL saline over 30 min intravenous infusion t.d.s for 3 days (recommended) or if, less preferred 100 mg I/V once daily 500 mg thiamine I/V infused over 30 min t.d.s. for 2 days and 500 mg I/V or I/M once daily for an additional 5 days in combination with other B vitamins	Wernicke encephalopathy, Best Practice, BMJ Evidence Centre[18] http://bestpractice.bmj.com.acs.hnc.com.au Charness *et al.*[8,9] www.UpToDate.com
(a) For healthy patients with good dietary intake: 100 mg t.d.s orally (b) For chronic drinkers with poor diet: 300 mg I/M or I/V for 3–5 days, followed by 300 mg orally for several weeks	500 mg I/M or I/V for 3–5 days, followed by oral or parenteral thiamine 300 mg for 1–2 weeks	Guidelines for the treatment of alcohol problems Australian Department of Health and Ageing. Commonwealth of Australia (Haber *et al.*, 2009)[19]
100 mg IV or I/M on Day 1, and then 100 mg orally daily	100 mg I/V or I/M daily for 3 days and then orally	NSW Drug and Alcohol Withdrawal Clinical Practice Guidelines. Mental health and Drug & Alcohol, NSW Department of Health 2007[20]

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