health
Department:
Health
REPUBLIC OF SOUTH AFRICA

SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 14: NEUROLOGY DISORDERS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2017 -2019)

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the chapter for neurology disorders.

A: NEW SECTIONS(S)/ SUBSECTION(S)

SECTION	CONDITION	MEDICINE MANAGEMENT	MEDICINE ADDED
14.5.5	**Medication overuse headache**	Yes	Amitriptyline, oral

14.5.5 MEDICATION OVERUSE HEADACHE

Guidance for management of medication overuse headache included as the condition is common:

Description
Headache occurring on 15 or more days per month developing as a consequence of regular overuse of acute or symptomatic headache medication. Patients are known with a pre-existing primary headache who, in association with medication overuse, develop a new type of headache or a marked worsening of their pre-existing headache

General measures
Stop ALL acute or symptomatic headache medication.
Council patient regarding the link between medication overuse and the development of and/or worsening of the headache syndrome.
The headache, but not invariably, resolves after the medication is stopped.

Medicine treatment
- Amitriptyline, oral, 10–75 mg at night.
  - Can be used during withdrawal of acute or symptomatic headache treatment.
  - Reassess need for long-term use of long-term amitryptiline once resolved.

Pilot study: Small double blind 9-week RCT (n=17) showed that amitriptyline decreased headache frequency amongst non-depressed patients with chronic drug-induced headache by 45% vs 28%, compared to placebo. Amitriptyline shown also to improve quality of life.

Level of Evidence: III disease oriented RCT of low methodological quality[1]

[1] Descombes S, Brefel-Courbon C, Thalamas C, Albucher JF, Rascol O, Montastruc JL, Senard JM. Amitriptyline treatment in chronic drug-induced headache: a double-blind comparative pilot study. Headache. 2001 Feb;41(2):178-82. https://www.ncbi.nlm.nih.gov/pubmed/11251703

B: AMENDMENTS TO MEDICINE TREATMENT

B: AMENDMENTS TO MEDICINE TREATMENT SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED
14.1.1 Stroke		
- Hyper acute management	Alteplase, IV	Added, and window of therapy retained as <3 hours
	Aspirin, oral	Added
- Secondary prevention	Aspirin, oral	Dose amended
	Simvastatin, oral	Intermediate dose added (40 mg) –secondary prevention
	Simvastatin, oral	Low dose amended (10-20 mg) – myalgia/on amlodipine
	Atorvastatin, oral	Added (10 mg) – myalgia/on protease inhibitor
	Clopidogrel, oral	Not added
- Blood pressure management (If BP > 220/120 mm Hg)	BP management	Additional guidance amended
	Hydrochlorothiazide, oral	Dose amended; note added
14.1.2 Transient ischaemic attack (TIA)	Aspirin, oral	Dose amended
	Simvastatin, oral	Intermediate dose added (40 mg) –secondary prevention
	Simvastatin, oral	Low dose amended (10-20 mg) – myalgia/on amlodipine
	Atorvastatin, oral	Added (10 mg) – myalgia/on protease inhibitor
14.1.3 Acute spinal cord injury	Symptomatic management	Cross-referenced to section 24.1.2: Constipation; section 7.3.6: Overactive bladder
14.2 Dementia *- to control restless patients*	Antipsychotics	Guidance added
	Vitamin B co tablets	Deleted
	Vitamin B 12, parenteral	Added
	Haloperidol, oral	Retained, directions for use expanded, dose amended
	Risperidone, oral	Not added
- Treat other nutritional deficiencies	Vitamin B co tablets	Deleted
	Vitamin B 12, parenteral	Added
14.4 Epilepsy	Management of epilepsy	Delineated according to type of epilepsy
- Focal (partial) seizures:	Carbamazepine, oral	Retained; dosing not amended
	Lamotrigine, oral	Retained; dose titration amended
	Levetiracetam, oral	Not added
- Generalised seizures	Carbamazepine, oral	Retained as immediate release formulation; dosing not amended
	Carbamazepine, oral	Slow release formulation added to therapeutic interchange database
	Lamotrigine, oral	Retained; dose titration table amended
	Phenytoin, oral	Retained; directions for use amended
	Valproic acid, oral	Retained as second line option
	Levetiracetam, oral	Not added
- Other epilepsy types	Valproic acid, oral	Directions for use and dosing added
	Lamotrigine, oral	Directions for use and dosing added
- "Stopgap", whilst lamotrigine is up-titrated	Clobazam, oral	Not added
- Pregnancy	Valproic acid, oral	Caution in pregnancy added
	Folic acid, oral	Added
- Prophylaxis in head trauma (acute management)	Phenytoin, IV	Loading dose retained
	Phenytoin, oral	Loading dose added, if patient awake and able to swallow; NGT administration not added
- Prophylaxis in head trauma (maintenance therapy)	Phenytoin, IV	Amended (duration of maintenance therapy added)
	Phenytoin, oral	Added
14.4.1 Status epilepticus		
- Initial treatment	Lorazepam, IV, IM	Retained as first line option and IM route deleted
	Midazolam, IV/IM	Moved to second line option
	Midazolam, buccal	Moved to third line option
	Clonazepam, IV	Moved to fourth line option
	Diazepam, IV	Moved to fifth line option
	Benzodiazepines, IV/IM	Direction for use amended
	Phenytoin, IV	Retained as add-on therapy
- Seizure*s continuing after 30 minutes*	Thiopental, IV	Dose amended from "4 mg/kg" to "2-4 mg/kg"
	Propofol, IV	Dosing regimen amended
	Midazolam, IV	Added
14.5.1 Migraine *- Prophylaxis*	Migraine prophylaxis	Indications amended
	Amitriptyline, oral	Retained, dosing amended
	Carbamazepine, oral	Deleted

	Beta-blockers, oral	Added as a therapeutic class (propranolol 40 mg 2xd; atenolol 50 mg 2xd)
	Propranolol, oral	Added as an example of class (listed in STG)
	Atenolol, oral	Added as a therapeutic alternative
	Morphine, IM	Deleted
14.5.5 Idiopathic intracranial hypertension (pseudotumour cerebri)	Acetazolamide, oral	Retained as 1st line therapy
- For visual involvement, persistent headaches, or severe papilloedema	Furosemide, oral	Retained as 2nd line therapy
14.6.1 Meningitis		
- Severe penicillin allergy (all bacterial meningitis, except neurolisteriosis)	Vancomycin, IV	Deleted
	Rifampicin, oral	Deleted
	Meropenem, IV	Added
- Listeria monocytogenes meningitis	Ceftriaxone, IV	Not added
	Ampicillin, IV	Added
	Gentamicin, IV	Added
14.6.1.1 Tuberculous meningitis	Corticosteroids, IV	Indication amended for use in HIV-uninfected only
14.6.1.2 Cryptococcal meningitis	Amphotericin B, IV	Duration of therapy amended
	Amphotericin B liposomal, IV	Not added
14.6.2 Viral meningoencephalitis *- Herpes simplex encephalitis*	Aciclovir, IV	Duration of therapy amended
14.6.3 Meningovascular syphilis	Diagnosis	Amended
	Benzathine benzylpenicillin, IM	Not added for latent syphilis
	Ceftriaxone, IV	Added as an alternative (listed on Therapeutic Interchange database)
	Measuring treatment success	Additional guidance provided
- Severe penicillin allergy	Desensitisation protocol	Retained
	Tetracycline, oral	Not added
14.6.6 Neurocysticercosis	Albendazole, oral	Retained
	Praziquantel, oral	Not added as combination therapy with praziquantel
14.7.1 Primary Parkinsonism	Carbidopa/levodopa, oral (high dose 25/250mg)	Deleted
14.7.1.1 Idiopathic parkinsonism	Carbidopa/levodopa, oral (standard dose)	Dosing amended
14.7.2 Secondary parkinsonism	Orphenadrine, oral	Note added
14.7.3 Essential tremor	Primidone, oral	Not added
	Beta-blockers, oral	Not added as a therapeutic class
	Propranolol, oral	Retained
14.7.4 Chorea	Haloperidol, oral	Prescriber level amended to specialist, and dose amended
14.8 Neuropathy	Amitriptyline, oral	Deleted – moved to pain chapter
	Pyridoxine, oral	Deleted – moved to pain chapter
	Carbamazepine, oral	Deleted – moved to pain chapter
	Prednisone, oral	Deleted – moved to pain chapter

14.1.1 STROKE

Hyper acute management

Alteplase, IV: *added; but thrombolytic time window retained as < 3 hours*

The Tertiary and Quaternary (T&Q) EML recommends tissue plasminogen activator (rtPA) for management of acute stroke within 3 hours of presentation. An external motivation was received to consider rtPA for inclusion to the Adult Hospital Level EML (and administration of rtPA within 4.5 hours as opposed to 3 hours of onset of acute stroke.

Refer to the medicine review: Alteplase administered within 4.5 hours for acute ischaemic stroke (January 2018):

AlteplaseTherapeuticWindow-Stroke_A

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on the evidence review, the Adult Hospital Level Committee recommended 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 specialist level.

Level of Evidence: I Meta analyses[2] [3], Cost-effectiveness analyses[4], Expert opinion

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).

Symptoms >3 hours

Aspirin, oral: *added*

Aspirin added for acute management of stroke, if CT scans not available. Aligned with PHC STGs and EML, 2018 recommendation of a pre-referral dose of aspirin 300 mg for acute presumptive ischaemic stroke, if thrombolysis within 3 hours is not achievable.

Rationale: Evidence of a moderate benefit of aspirin outweighing harms of aspirin as in reducing recurrent ischaemic stroke of unknown aetiology.

Level of Evidence: I Meta-analyses[5] [6]

Secondary prevention:

Aspirin, oral: *dose amended*

STG provides the option of evidence-based medicine recommendation of 100 mg or if this is not available on tender, the option of 150 mg daily (1/2 of a 300 mg tablet).

Level of Evidence: I Systematic review[7], Expert opinion

NEMLC MEETING OF 26 SEPTEMBER 2019:

However, further deliberations were made by NEMLC at the meeting of 26 September 2019, noting that the current tender price of "100 mg" is more expensive than the "150 mg"[8].

Recommendation: Aspirin be recommended as a daily dose of 150 mg throughout the STGs, until such time that there is price parity. Doses of 100 mg and 81 mg to be added to the Adult Hospital Level Therapeutic Interchange database.

Simvastatin, oral: *Intermediate dose (40 mg) added low dose (10-20 mg) amended*

Atorvastatin, oral: *10 mg added*

Aligned with recently NEMLC approved PHC STG and EML, 2018 recommendations[9], and additional amendments as described below.

Myalgia

The Adult Hospital Level STGs and EML, 2019 recommends that if myalgia develops whilst on a statin, then to reduce the dose to simvastatin 10 mg or equivalent. The Adult Hospital Level Committee recommends that provision be made for 20 mg simvastatin or equivalent and that this be listed on the therapeutic interchange database.

Drug interaction of statins with amlodipine

Simvastatin, oral (or equivalent): *dose amended from "10 mg" to "10-20 mg"*

[2] Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al.; Stroke Thrombolysis Trialists' Collaborative Group. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet. 2014 Nov 29;384(9958):1929-35 https://www.ncbi.nlm.nih.gov/pubmed/25106063

[3] Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev. 2014 Jul 29;(7):CD000213. https://www.ncbi.nlm.nih.gov/pubmed/25072528

[4] Joo H, Wang G, George MG A literature review of cost-effectiveness of intravenous recombinant tissue plasminogen activator for treating acute ischaemic stroke Stroke and Vascular Neurology 2017;2:doi: 10.1136/svn-2016-000063

[5] Sandercock PA, Counsell C, Tseng MC, Cecconi E. Oral antiplatelet therapy for acute ischaemic stroke. Cochrane Database Syst Rev. 2014 Mar 26;(3):CD000029. https://www.ncbi.nlm.nih.gov/pubmed/24668137

[6] Rothwell PM, Algra A, Chen Z, Diener HC, Norrving B, Mehta Z. Effects of aspirin on risk and severity of early recurrent stroke after transient ischaemic attack and ischaemic stroke: time-course analysis of randomised trials. Lancet. 2016 Jul 23;388(10042):365-375. https://www.ncbi.nlm.nih.gov/pubmed/27209146

[7] Sandercock PA, Counsell C, Tseng MC, Cecconi E. Oral antiplatelet therapy for acute ischaemic stroke. Cochrane Database Syst Rev. 2014 Mar 26;3:CD000029.http://www.ncbi.nlm.nih.gov/pubmed/24668137

[8] Contract circular RT289-2019: Aspirin 100 mg single tablet = R 0.502; Weighted average price of aspirin 300 mg tablet = R0.211 [Accessed 8 October 2019]

[9] Minutes of the NEMLC meeting of 12 April 2018.

Background: An external comment was received about the use of a dose higher than simvastatin 10 mg with concomitant amlodipine.

Review: Simvastatin is metabolized by the cytochrome P450 isoenzyme 3A4 (CYP3A4) and is a substrate of CYP3A4. Amlodipine is a weak inhibitor of CYP3A4, with simvastatin being susceptible to the inhibitory effect of amlodipine. Amlodipine leads to an estimated 30% increase in the plasma concentration of simvastatin. [10] Concomitant administration of amlodipine with simvastatin could lead to a greater risk of adverse effects such as myopathy and rhabdomyolysis. A dose of maximum 20 mg simvastatin together with amlodipine 10 mg, has been found to be safe and effective.[11] A dose exceeding 20 mg simvastatin in combination with 10 mg amlodipine is not recommended.
Atorvastatin, a substrate of CYP3A4, is less affected by the inhibitory effect of amlodipine and can safely be administered with amlodipine. The dose of atorvastatin is not to exceed 80 mg with concomitant administration of amlodipine 10 mg.[12]

Recommendation: Reduced dose of simvastatin 10 to 20 mg be recommended for patients on concomitant amlodipine.
Rationale: Drug-drug interaction of simvastatin with amlodipine leads to an estimated 30% increase in the plasma concentration of simvastatin with possible subsequent myopathy and rhabdomyolysis. Pharmacokinetic studies suggests that maximum dose of simvastatin 20 mg is safe when used in combination with amlodipine 10 mg. Atorvastatin, is less affected by the inhibitory effect of amlodipine and can safely be administered with amlodipine and thus, atorvastatin 20 mg is recommended for use with concomitant amlodipine.
Level of Evidence: III Pharmacokinetic studies, Guidelines

Clopidogrel, oral: *not added*
The T& Q EML recommends clopidogrel, oral for long-term therapy where patient has confirmed aspirin intolerance. The Adult Hospital Level Committee was of the opinion that as this would be a very limited patient population, it would best to manage these patients at T&Q level of care.
Level of Evidence: III Expert opinion

In patients with cardio embolic strokes
The text of the STG was editorially amended as follows for clarity purposes:

In patients with cardio embolic strokes (e.g. secondary to atrial fibrillation) with no evidence of haemorrhage on CT scan, the optimal time to start anticoagulation ~~with warfarin 7 days after an index event provided there is no haemorrhage on CT scan~~ 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.

Level of Evidence: III Guidelines[13], Expert opinion

Blood pressure management
If BP > 220/120 mm Hg: Emergency hypertension

BP management: *additional guidance provided*
Authors of a Cochrane review[14] also concluded that "*There is insufficient evidence that lowering blood pressure during the acute phase of stroke improves functional outcome. It is reasonable to withhold blood pressure-lowering drugs until patients are medically and neurologically stable, and have suitable oral or enteral access, after which drugs can than be reintroduced".*

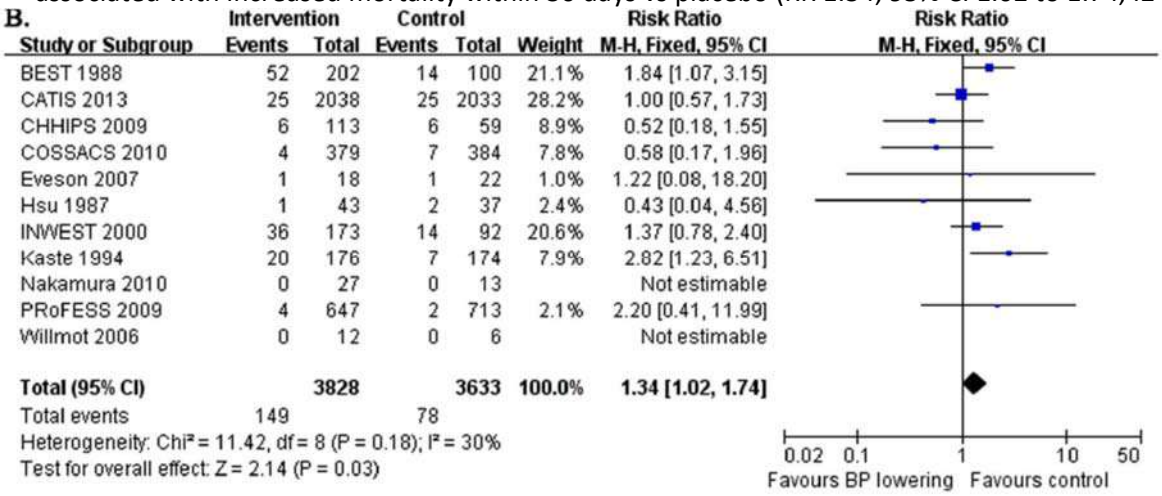
Text of the STG was amended to include this guidance, as follows:

[10] Nishio S, Watanabe H, Kosuge K, Uchida S, Hayashi H, Ohashi K. Interaction between amlodipine and simvastatin in patients with hypercholesterolemia and hypertension. Hypertens Res. 2005;28(3):223–7.
[11] Son H, Lee D, Lim LA, Jang SB, Roh H, Park K. Development of a pharmacokinetic interaction model for co-administration of simvastatin and amlodipine. Drug Metab Pharmacokinet. 2014;29(2):120–8.
[12] SAMF, 2016/2020
[13] Lansberg MG, O'Donnell MJ, Khatri P, Lang ES, Nguyen-Huynh MN, Schwartz NE, Sonnenberg FA, Schulman S, Vandvik PO, Spencer FA, Alonso-Coello P, Guyatt GH, Akl EA; American College of Chest Physicians. Antithrombotic and thrombolytic therapy for ischemic stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice
Guidelines. Chest. 2012 Feb;141(2 Suppl):e601S-36S. http://www.ncbi.nlm.nih.gov/pubmed/22315273
[14] Bath PM, Krishnan K. Interventions for deliberately altering blood pressure in acute stroke. Cochrane Database Syst Rev. 2014 Oct 28;(10):CD000039. https://www.ncbi.nlm.nih.gov/pubmed/25353321

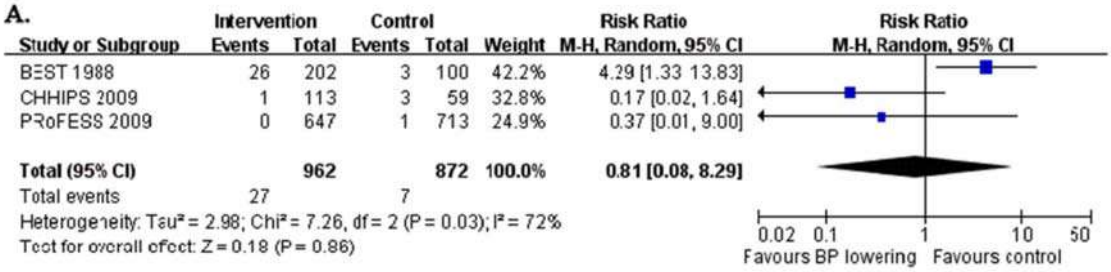
Lowering the blood pressure during the acute phase of stroke (within 6 hours of onset) may not improve morbidity. Blood pressure-lowering medicines may be withheld until patients have suitable oral or enteral access. Cautious incremental reintroduction of treatment is advised to achieve long-term standard BP control.
See section: 3.6.3 Hypertensive crisis, hypertensive emergency.

Evidence review:

- Wang et al meta-analysis[15] showed that early BP lowering (i.e. within 7 days) after acute stroke onset was associated with increased mortality within 30 days vs placebo (RR 1.34; 95% CI 1.02 to 1.74, I2=30%; p = 0.03):



- No significant effect of early death after early BP lowering within 7 days (RR 0.81; 95% CI 0.08 to 8.29, I2=72%; p=0.03):



Level of Evidence: I Meta-analysis and systematic review, III Guidelines[16]

Hydrochlorothiazide, oral: *dose amended and note added*

Dose: No available evidence could be sourced from the published literature for high dose HCTZ (100 mg), in this clinical setting. It was recommended that the HCTZ dose be aligned with the hypertension STG.
Recommendation: HCTZ daily dose be amended from "25-50 mg" to "12.5 mg".
Rationale: Alignment with dose recommendations in the hypertension STG.
Level of Evidence: III Expert opinion

Note: The following note relating to hydrochlorothiazide was added to the text of the STG:

» 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.

Refer to the NDOH circular report[17]: Hydrochlorothiazide and the evidence review summary, Hydrochlorothiazide and skin cancer (November 2018), for an evidence overview of the safety signal of non-melanoma skin cancer with high accumulative dose of hydrochlorothiazide.

[15] Wang H, Tang Y, Rong X, Li H, Pan R, Wang Y, Peng Y. Effects of early blood pressure lowering on early and long-term outcomes after acute stroke: an updated meta-analysis. PLoS One. 2014 May 22;9(5):e97917. https://www.ncbi.nlm.nih.gov/pubmed/24853087
[16] Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. American Heart Association Stroke Council. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2018 Mar;49(3):e46-e110. https://www.ncbi.nlm.nih.gov/pubmed/29367334
[17] NDOH circular: Updated notice: Risk of skin cancer associated with hydrochlorothiazide, March 2019 – Ref: EDP032019/02. www.health.gov.za

14.1.2 TRANSIENT ISCHAEMIC ATTACK (TIA)

Aspirin, oral: *dose amended*
STG provides the option of evidence-based medicine recommendation of 100 mg or if this is not available on tender, the option of 150 mg daily (1/2 of a 300 mg tablet).
Level of Evidence: I Systematic review[18], Expert opinion

NEMLC MEETING OF 26 SEPTEMBER 2019:
However, further deliberations were made by NEMLC at the meeting of 26 September 2019, noting that the current tender price of "100 mg" is more expensive than the "150 mg"[19].
Recommendation: Aspirin be recommended as a daily dose of 100 mg throughout the STGs, until such time that there is price parity. Doses of 100 mg and 81 mg to be added to the Adult Hospital Level Therapeutic Interchange database.

Simvastatin, oral: *Intermediate dose (40 mg) added low dose (10 mg) retained*
Atorvastatin, oral: *10 mg added*
Aligned with recently NEMLC approved PHC STG and EML, 2018 recommendations[20]; and additional low dose recommendations as outlined in section 14.1.1: Stroke, above.

14.1.3 ACUTE SPINAL CORD INJURY

Cross-reference included for symptomatic management of constipation (section 24.1.2: Constipation) and for urinary retention (section 7.3.6: Overactive bladder).

14.2 DEMENTIA

To control restless patients
Antipsychotics: *guidance added*
Haloperidol, oral: *retained, directions for use expanded, dose amended*
Risperidone, oral: *not added*

Tampi et al, 2016: Systematic review of meta-analyses[21] showed a modest effect of psychotics (first and second generation) on moderate to severe dementia; but an increased risk of death and cerebrovascular events (specifically with risperidone). Systematic review was mostly of RCTs with publication bias (language restrictions) where trials were too heterogenous for further quantitative analysis. The results of the systematic review is aligned with American Psychiatric Association (APA) practice guideline[22] recommendations on the use of antipsychotics to treat agitation or psychosis in individuals with dementia: assessing potential risks vs benefits of antipsychotics in discussion with patient and patient's family, prior to starting treatment at a low dose and titrating to the minimum effective dose as tolerated; antipsychotics to be tapered and discontinued when there is no clinically significant response after a 4-week trial of an adequate dose or if patient has a clinically significant adverse effect associated with antipsychotic that outweighs benefit.

[18] Thijs V, Lemmens R, Fieuws S. Network meta-analysis: simultaneous meta-analysis of common antiplatelet regimens after transient ischaemic attack or stroke. Eur Heart J. 2008 May;29(9):1086-92. http://www.ncbi.nlm.nih.gov/pubmed/18349026
[19] Contract circular RT289-2019: Aspirin 100 mg single tablet = R 0.502; Weighted average price of aspirin 300 mg tablet = R0.211 [Accessed 8 October 2019]
[20] NEMLC Minutes of the meeting, 12 April 2018.
[21] Tampi RR, Tampi DJ, Balachandran S, Srinivasan S. Antipsychotic use in dementia: a systematic review of benefits and risks from meta-analyses. Ther Adv Chronic Dis. 2016 Sep;7(5):229-45. https://www.ncbi.nlm.nih.gov/pubmed/27583123
[22] Reus VI, Fochtmann LJ, Eyler AE, Hilty DM, Horvitz-Lennon M, Jibson MD, Lopez OL, Mahoney J, Pasic J, Tan ZS, Wills CD, Rhoads R, Yager J. The American Psychiatric Association Practice Guideline on the Use of Antipsychotics to Treat Agitation or Psychosis in Patients With Dementia. Am J Psychiatry. 2016 May 1;173(5):543-6. https://www.ncbi.nlm.nih.gov/pubmed/27133416

Ballard et al, 2009: Long-term follow up of RCT[23] (included in systematic review by Tampi et al, 2016) suggests an increased long-term risk of mortality in patients on long-term antipsychotics. Cumulative probability of survival during the 12 months was 70% (95% CI 58 to 80%) in the continue treatment group vs 77% (95% CI 64 to 85%) in the placebo group for the modified intention to treat population. The survival differences between groups was more evident during periods of follow up longer than 12 months: at 24 months – 46% vs 71%; 36 months survival - 30% vs 59%; and at 42 months - 26% vs 53%.

Nikooie et al, 2019: A recently published meta-analysis of RCTs and observational studies[24] shows that the current evidence does not support the routine use of antipsychotics to treat delirium in adult inpatients. However, of note is that Adult Hospital Level STG provides guidance for haloperidol, administered in the acute setting to control a restless patient with delirium. Emergency services requires management of the agitated patients to enable further emergency treatment.

Recommendation: Following text be added to the STG:

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.

Rationale: Current evidence does not support the routine use of long-term antipsychotics to treat dementia in adult inpatients. Systematic review of metaanalysis of RCTs[25] shows a possible risk for death, cerebrovascular adverse events (specifically in the risperidone group), Parkinsonism, sedation, gait disturbance, cognitive decline and pneumonia and somnolence. The Adult Hospital Level STG, however, provides guidance for haloperidol, administered in the acute setting to control a restless patient with delirium to enable further management, especially in the emergency setting.

Level of Evidence: I RCT, Systematic review, Guidelines

Re**commendations:**

- Haloperidol, oral retained for management of patients with symptoms of severe dementia or who are at risk of harming themselves or others.

Rationale: Limited evidence suggests that antipsychotics have a modest effect on those with a moderate to severe dementia, including symptoms of psychosis, aggression and agitation; but an increased risk of overall mortality death, cerebrovascular adverse events, Parkinsonism, sedation, gait disturbance, cognitive decline and pneumonia and somnolence compared to placebo.

Level of Evidence: II Systematic review and meta-analysis of RCTs of low to moderate quality[26], Guidelines[27]

- Directions for use of antipsychotics in dementia to include use of lowest effective doses for shortest period of time, with reassessment at least every 6 weeks.

Rationale: Aligned with NICE Guideline recommendations.

Level of Evidence: III Guidelines[7]

- Dose amended as sole pharmaceutical supplier has discontinued haloperidol 0.5 mg from the South African market; however the 1.5 mg and 2.5 mg formulations are still currently available. Both tablet strengths are scored.

Dose for haloperidol was amended as follows:

14.2 Dementia

To control restless patients:

- Haloperidol, oral, ~~0.5–1~~ 0.75–1.5 mg 8 hourly with a higher dose at night, if required.

[23] Ballard C, Hanney ML, Theodoulou M, Douglas S, McShane R, Kossakowski K, Gill R, Juszczak E, Yu LM, Jacoby R; DART-AD investigators. The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial. Lancet Neurol. 2009 Feb;8(2):151-7. https://www.ncbi.nlm.nih.gov/pubmed/19138567

[24] Nikooie R, Neufeld KJ, Oh ES, Wilson LM, Zhang A, Robinson KA, Needham DM. Antipsychotics for Treating Delirium in Hospitalized Adults: A Systematic Review. Ann Intern Med. 2019 Sep 3. https://www.ncbi.nlm.nih.gov/pubmed/31476770

[25] Tampi RR, Tampi DJ, Balachandran S, Srinivasan S. Antipsychotic use in dementia: a systematic review of benefits and risks from meta-analyses. Ther Adv Chronic Dis. 2016 Sep;7(5):229-45. https://www.ncbi.nlm.nih.gov/pubmed/27583123

[26] Ma H, Huang Y, Cong Z, Wang Y, Jiang W, Gao S, Zhu G. The efficacy and safety of atypical antipsychotics for the treatment of dementia: a meta-analysis of randomized placebo-controlled trials. J Alzheimers Dis. 2014;42(3):915-37. https://www.ncbi.nlm.nih.gov/pubmed/25024323

[27] NICE. Guideline - Dementia: assessment, management and support for people living with dementia and their carers, 20 June 2018. https://www.nice.org.uk/guidance/ng97

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.

Level of Evidence: III Guidelines[28]

- Risperidone, oral not recommended for management of dementia

Rationale: Metaanalyses evidence shows that cerebrovascular adverse events more common with antipsychotics compared to placebo, with risk most prominent in risperidone group.
Level of Evidence: II Systematic review of low to moderate quality meta-analyses[29]

Treat other commonly associated nutritional deficiencies:
Vitamin B co tablets: *deleted*
Vitamin B 12, parenteral: *added*
Aligned to the SAMF, 2016 edition as follows:

If confirmed Vitamin B_{12} deficiency:
- Vitamin B_{12}, IM, 1 mg daily for 5 days.
  - Followed with 1 mg IM weekly for 4 weeks, then 1 mg, IM monthly
  - Check Vitamin B_{12} blood level at 6 months.

Rationale: Doses of components of vitamin B co tablets currently on tender are insufficient to manage specific vitamin B deficiencies.
Level of Evidence: III Guidelines[30], Expert opinion

14.4 EPILEPSY

Management of epilepsy: *delineated according to type of epilepsy*
Management was delineated between i) focal (partial); ii) generalised tonic-clonic and iii) other epilepsy types.

i) Focal (partial) seizures:
Carbamazepine, oral: *retained; dosing not amended*
Lamotrigine, oral: *retained; dose titration table amended*
Levetiracetam, oral: *not added*

ii) Generalised tonic clonic seizures:
Carbamazepine, oral: *retained as immediate release and dosing not amended*
Lamotrigine, oral: *retained; dose titration table amended*
Phenytoin, oral: *retained and indication amended*
Valproic acid, oral: *retained as second line option*
Levetiracetam, oral: *not added*

Cochrane review[31]showed that for the primary outcome '*Time to withdrawal of allocated treatment,*' for individuals with partial seizures; levetiracetam performed significantly better than carbamazepine and lamotrigine; lamotrigine performed better than all other treatments (aside from levetiracetam), and carbamazepine performed significantly better than gabapentin and phenobarbitone (high-quality evidence). For individuals with generalised onset seizures, first-line treatment sodium valproate performed better than carbamazepine, topiramate and phenobarbitone (moderate- to high-quality evidence)".
However, budget impact analyses done in previous review cycles showed that valproic acid is unaffordable and the price of this medicine had not decreased. Therefore, valproic acid was retained as second line option for generalised seizures. However, the safety concern of valproate in pregnancy and women of childbearing potential warranted

[28] SAMF, 2016
[29] Tampi RR, Tampi DJ, Balachandran S, Srinivasan S. Antipsychotic use in dementia: a systematic review of benefits and risks from meta-analyses. Ther Adv Chronic Dis. 2016 Sep;7(5):229-45. https://www.ncbi.nlm.nih.gov/pubmed/27583123
[30] SAMF, 2016
[31] Nevitt SJ, Sudell M, Weston J, Tudur Smith C, Marson AG. Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. Cochrane Database Syst Rev. 2017 Dec 15;12:CD011412. https://www.ncbi.nlm.nih.gov/pubmed/29243813

evidence reviews for levetiracetam.

Carbamazepine, oral – immediate release formulation: *retained in the STG*
Carbamazepine, oral – slow release formulation: *added to the therapeutic interchange database*
Carbamazepine, oral formulations: Cochrane review of poor quality evidence[32] suggests that for stable patients with newly diagnosed epilepsy, carbamazepine immediate-release maintenance therapy may be as effective as controlled-release preparations. Data from the RCTs was not pooled due to heterogeneity, and was insufficient to confirm or refute an advantage of controlled-release over immediate-release formulation in terms of seizure frequency and adverse effects.
Pharmacokinetic study[33] shows that carbamazepine levels are significantly higher with immediate-release formulations vs slow release on day 10; whilst on day 20 (when steady-state is reached) the mean difference in serum carbamazepine levels became insignificant ($p<0.05$). This suggests that immediate release formulations would be preferred for titration purposes in new acute onset epilepsy.
Level of Evidence: III Systematic review of poor quality studies, Pharmacokinetic study

Carbamazepine, oral dosing: Not amended as guidance is aligned to SAMF, 2016.
Level of Evidence: III Guidelines[34]

Focal/partial seizures: External stakeholder comment to delete management for focal (partial) seizures was not considered as the evidence (described above) differentiates between the partial and generalised seizures and thus, guidance has been provided for the various seizure types.

iii) Other epilepsy types
Valproic acid, oral: *directions for use and dosing added*
Lamotrigine, oral: *directions for use and dosing added*
The text of the STG was expanded to provide medicine dosing recommendations, aligned with SAMF 2016.

Manage in consultation with a specialist.
~~Specifically, juvenile myoclonic epilepsy is best controlled with valproate initially, and absence seizures with valproate or lamotrigine.~~
Juvenile myoclonic epilepsy:
Refer all for specialist investigation and initiation of therapy with valproic acid.

Absence seizures:
- Valproic acid, oral (specialist consultation).
  - Usual starting dose: 200–300 mg 12 hourly.
  - Increase, as required, every 2 weeks to a maximum daily dose of 1.2 g 12 hourly.

OR
- Lamotrigine, oral (specialist consultation).
  - Usual starting dose: 25 mg daily for 2 weeks, then 50 mg daily for 2 weeks.
  - Thereafter, increase by 50 mg every 2 weeks according to response.
  - Usual maintenance dose: 100–200 mg daily as a single dose.

Level of Evidence: III Guidelines[35]

Lamotrigine, oral: *dose titration table amended*
Clobazam, oral: *not added*
The following lamotrigine dose titration table was added to the STG, aligned with SAMF 2016 and NICE Guidelines and adapted from the Western Cape protocol – excluding clobazam as a "stopgap" to control seizures whilst lamotrigine is up-titrated to effective doses. No available evidence could be sourced for clobazam for this indication. Although clobazam is generally used as add-on therapy for refractory seizures[36], evidence is insufficient to recommend clobazam monotherapy for focal or generalized seizures in adults and children[37].

32 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:CD007124. https://www.ncbi.nlm.nih.gov/pubmed/27933615
33 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. J Assoc Physicians India. 1998 Feb;46(2):185-8. https://www.ncbi.nlm.nih.gov/pubmed/11273108
34 SAMF, 2016
35 SAMF, 2016
36 SAMF 2016
37 Arya R, Giridharan N, Anand V, Garg SK. Clobazam monotherapy for focal or generalized seizures. Cochrane Database Syst Rev. 2018 Jul 11;7:CD009258. https://www.ncbi.nlm.nih.gov/pubmed/29995989

Dose-titration of lamotrigine:

NOT ON VALPROATE		ON VALPROATE	
Weeks	**Dose**	**Weeks**	**Dose**
1,2	25 mg daily	1,2	25 mg alternate days
3,4	25 mg 12 hourly	3,4	25 mg daily
5	25 mg in the morning; 50 mg at night	5	25 mg 12 hourly
6	50 mg 12 hourly	6	25 mg in the morning; 50 mg at night
		7	50 mg 12 hourly

Level of Evidence: III Guidelines [38] [39]

(Note: NICE Clinical Guideline states: The diagnosis and management of the epilepsies in adults and children in primary and secondary care, 11 January 2012 was appraised using the AGREE II tool and assessed to be of moderate quality).

Phenytoin, oral: *directions for use amended*

External stakeholder comment received regarding therapeutic drug monitoring of very high doses of phenytoin, and the following note was added:

Note: Caution and frequent monitoring of drug levels are obligatory at doses >300 mg daily as the risk for toxicity is high and could lead to permanent cerebellar damage.

Level of Evidence: III Expert opinion

Levetiracetam, oral: *not added*

1. Evidence review:

Refer to the medicine review, levetiracetam, oral for first onset seizures partial or generalized tonic-clonic seizures (January 2019):

Leviteracetam for new-onset epilepsy-

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on this evidence review, the Adult Hospital Level Committee reccomends that levetiracetam may be considered as an alternative to lamotrigine, carbamazepine or phenytoin for partial or focal seizures in adult epileptics. Adverse effects associated with specific AEDs and affordability would further inform recommendations.

Rationale:

- Avaliable evidence suggests that levetiracetam is as efficacious as lamotrigine and better than carbamazepine or phenytoin for time to withdrawal of allocated treatment in partial seizures.
- For generalized seizures levetiracetam was equally efficacious when compared to carbamazepine, lamotrigine and phenytoin.
- An economic evaluation taking cognicance of the relative prevelance of partial and generalised seizures in our population is required to further inform decision-making.
- Better tolerability of levetiracetam when compared to both carbamazepine and lamotrigine.

Level of Evidence: I Meta-analysis[40]

2. Economic analysis

Refer to the economic analysis report for levetiracetam for newly diagnosed epilepsy in adults, June 2019:

Levetiracetam Economic evaluatior

Levetiracetam Economic evaluatior

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Following economic modelling of levetiracetam for newly diagnosed epilepsy, the Adult Hospital Level Committee recommends that this agent not be considered for inclusion to the Adult Hospital Level EML.

Rationale: Levetiracetam found to be not cost-effective.

Level of Evidence: III Cost effectiveness and Budget Impact analyses

[38] SAMF, 2016

[39] National Institute for Health and Clinical Excellence. Clinical Guideline, The diagnosis and management of the epilepsies in adults and children in primary and secondary care, 11 January 2012. http://www.nice.org.uk/guidance/cg137

[40] Nevitt SJ, Sudell M, Weston J, Tudur Smith C, Marson AG. Antiepileptic drug monotherapy for epilepsy: a network meta-analysis of individual participant data. Cochrane Database Syst Rev. 2017 Dec 15;12:CD011412. https://www.ncbi.nlm.nih.gov/pubmed/29243813

Base-case model:

Drug	Expected Cost (ZAR)	Expected Effect (QALYs)	ICER
Lamotrigine	R63 567	4,01	
Levetiracetam	R64 819	3,99	Dominated*
Phenytoin	R66 028	3,97	Dominated
Valproate	R66 588	3,97	Dominated
Carbamazepine	R66 983	3,97	Dominated

Table 9: Summary of the cost-effectiveness results for the treatment of epilepsy using levetiracetam.
***** Dominated strategy is one which costs more but has a lower health effect.

NEMLC Recommendations:

- Levetiracetam not be considered for inclusion to the Adult Hospital Level EML for newly diagnose epilepsy, as this medicine considered to be not-cost effective and unaffordable.
- The final reports be published on the NDoH website and the respective companies be advised of the estimated willingness to pay (93% reduction of model medicine price: 250 mg tablets, 30 = R 2.149; 500 mg tablets, 20 = R4.298; 750 mg tablets, 30 = R 6.447).

PREGNANCY

Valproic acid, oral: *Caution in pregnancy added*

The following caution was added (aligned with the PHC STGs and EML, 2018), following the European Medicine Agency's Pharmacovigilance Risk Assessment Committee (PRAC) assessment and recommendation to strengthen the caution to avoid valproate exposure in pregnancy.

CAUTION
Children born to women taking valproic acid are at significant risk of birth defects (10%) and persistent developmental disorders (40%).
Valproic acid is contra-indicated and should be avoided in pregnancy and women of child-bearing potential.

Level of Evidence: III Registry data[41]

Folic acid, oral: *added*

The text of the STG was further updated as follows:

» Optimal control of epilepsy on a single agent is the best management.
» Patients who fall pregnant on valproic acid, should be risk-assessed in consultation with a specialist to determine if switching is required.
» If alternate treatment cannot be recommended and valproic acid are required:
- Folic acid, oral, 5 mg daily.

Level of Evidence: III Guidelines[42]

PROPHYLAXIS IN HEAD TRAUMA

Acute management:

Phenytoin, IV: *loading dose retained*

Phenytoin, oral: *loading dose added (patient awake and able to swallow)*

Limited evidence[43] is available that shows that oral phenytoin may be used as a loading dose:
Pharmacokinetic study of 51 patients randomised to receive loading dose of oral phenytoin as a capsule or suspension. Phenytoin serum levels were obtained at baseline, 4 and 8 hours after loading (therapeutic range of 10-20ug/mL). No seizures observed in 44/51 patients during an eight-hour observation period with 64% of patients with therapeutic levels at 8 hours. Seizure–free maintained 24 hours after loading and 2 reports of gastrointestinal discomfort.

[41] Valproic acid – caution in pregnancy: European Medicines Agency - Pharmacovigilance Risk Assessment Committee. Assessment report EMA/198940/2018 - valproate exposure in pregnancy, 8 February 2018.
http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Valproate_2017_31/Position_provided_by_CMDh/WC500250221.pdf
Valproic acid – caution in pregnancy: Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res. 2008 Sep;81(1):1-13. https://www.ncbi.nlm.nih.gov/pubmed/18565732
[42] SAMF, 2016
[43] Osborn HH, Zisfein J, Sparano R. Single-dose oral phenytoin loading. Ann Emerg Med. 1987 Apr;16(4):407-12. https://www.ncbi.nlm.nih.gov/pubmed/3826809

Recommendation: Loading dose of oral formulation of phenytoin be recommended as an alternative to intravenous administration at a dose of 1.8 mg/kg.
Rationale: Pharmacokinetic study indicated therapeutic levels reached within 8 hours of phenytoin loading with an oral formulation resulting in seizure-free response that was maintained at 24 hours. Oral loading dose also shown to be relatively safe.
Level of Evidence: III Pharmacokinetic study

Maintenance therapy:
Phenytoin, IV: *amended – duration of maintenance therapy added*
Phenytoin, oral: *amended – duration of maintenance therapy added*

Recommended duration of prophylaxis therapy with phenytoin is 7 days, aligned with pooled meta-analysis[44] of 4 RCTs (moderate to low quality) that showed a significantly lower rate of early seizures (occurring within 7 days of trauma brain injury (TBI)) in the phenytoin prophylaxis group vs control group; RR 0.37 (95% CI 0.18 to 0.74).
Level of Evidence: II Meta-analysis of RCTs of low to moderate quality

Background: Previously the NEMLC accepted the option of phenytoin, oral as a loading dose in patients who can swallow be considered in this clinical setting. NEMLC further recommended that the evidence be reviewed for the option of phenytoin via nasogastric tube (NGT) be considered in patients who cannot swallow.

Phenytoin, oral: *not added for administration via NGT in patients who cannot swallow*
Nasogastric tubes are made of polyvinyl chloride, and phenytoin[45] has been shown to bind to the wall of the tubing. Furthermore, phenytoin binds strongly to serum proteins and serum phenytoin levels has been shown to decrease by an average of 71.6% when administered with enteral feeds[46]. Guidance[47] for management of phenytoin with enteral tube feeding is complex as enteral feeding interferes with bioavailability of phenytoin via NGT. Enteral feeding generally occurs at higher level of care (in ICU/high care).
Level of Evidence: III Pharmacokinetic and in vitro studies

14.4.1 STATUS EPILEPTICUS

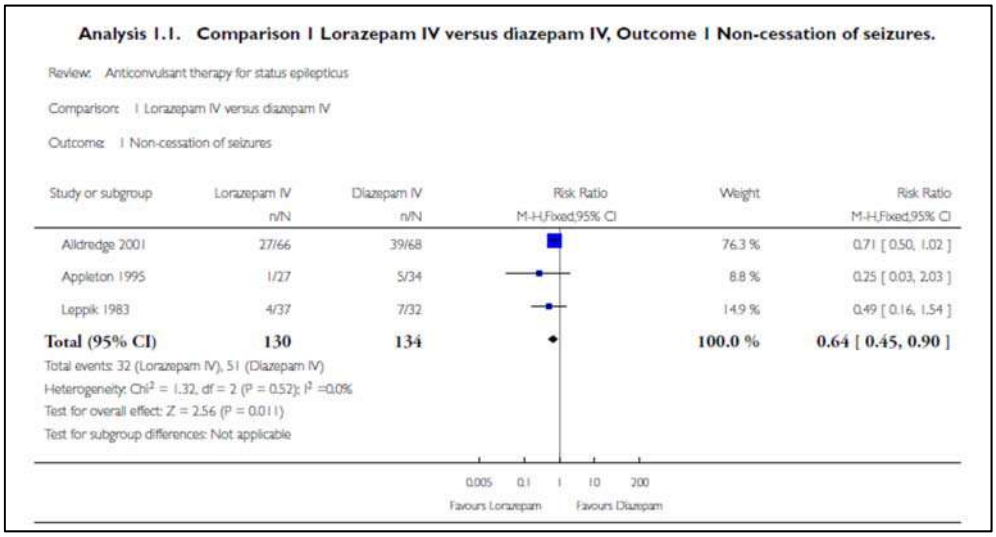
Initial treatment
Lorazepam, IV: *retained as first line option and IM route deleted*
Midazolam, IV/IM: *moved to second line option*
Midazolam, buccal: *moved to third line option*
Clonazepam, IV: *moved to fourth line option*
Diazepam, IV: *moved to fifth line option*

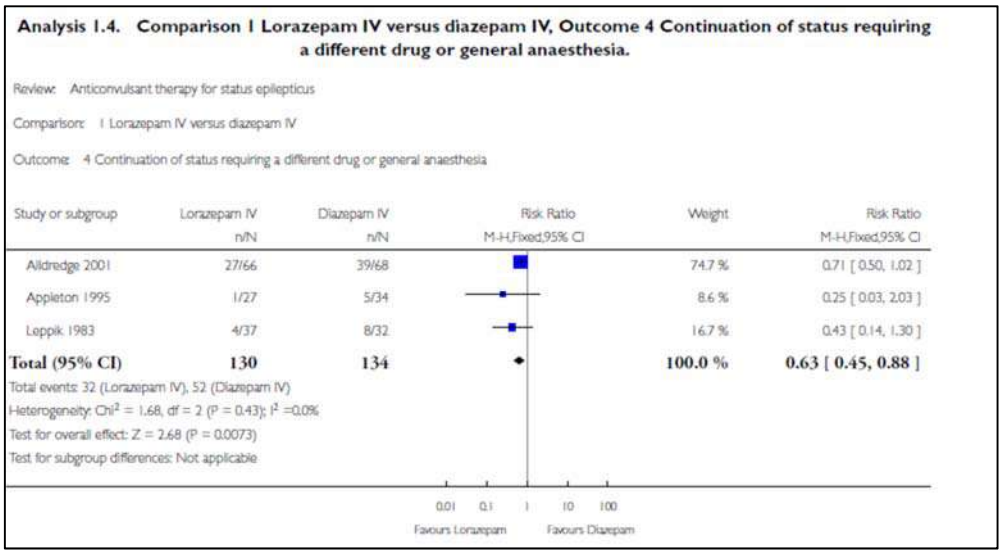
Cochrane review showed that lorazepam, IV is better than diazepam, IV for cessation of seizures and has a lower risk of continuation of status epilepticus requiring a different drug or general anaesthesia compared to diazepam, IV; whilst limited evidence suggests that midazolam, IV may be comparable to lorazepam, IV. For pre-hospital management, midazolam IM seemed more effective than lorazepam IV for cessation of seizures, frequency of hospitalisation and ICU admissions; whilst no RCT data was retrieved for clonazepam (promising agent, but more expensive than diazepam and midazolam). From a pragmatic perspective, midazolam buccal is more convenient than midazolam, IV, delivering medication non-invasively and more rapidly, and a feasible option for use by paramedics.

Evidence review
Lorazepam, IV: Systematic review and meta-analysis of 18 RCTs (n=2755)[48] showed that lorazepam, IV was better than

[44] Chang BS, Lowenstein DH; Quality Standards Subcommittee of the American Academy of Neurology. Practice parameter: antiepileptic drug prophylaxis in severe traumatic brain injury: report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2003 Jan 14;60(1):10-6. https://www.ncbi.nlm.nih.gov/pubmed/12525711
[45] Cacek AT, DeVito JM, Koonce JR. In vitro evaluation of nasogastric administration methods for phenytoin. Am J Hosp Pharm. 1986 Mar;43(3):689-92. https://www.ncbi.nlm.nih.gov/pubmed/3706323
[46] Bauer LA. Interference of oral phenytoin absorption by continuous nasogastric feedings. Neurology. 1982 May;32(5):570-2. https://www.ncbi.nlm.nih.gov/pubmed/6803191
[47] Phelps N. Management of phenytoin with enteral tube feeding. Mental Health Clinician: November 2012;2 (5):108-109. https://doi.org/10.9740/mhc.n126907
[48] Prasad M, Krishnan PR, Sequeira R, Al-Roomi K. Anticonvulsant therapy for status epilepticus. Cochrane Database Syst Rev. 2014 Sep 10;(9):CD003723. https://www.ncbi.nlm.nih.gov/pubmed/25207925

diazepam, IV for reducing the risk of non-cessation of seizures in status epilepticus (32/130 vs 51/134 participants; ARR=13%; NNT=8; RR 0.64, 95%CI 0.45 to 0.90) – see analysis 1.1 below. Lorazepam, IV also had a lower risk for continuation of status epilepticus requiring a different drug or general anaesthesia (32/130 vs 52/134; ARR=14%; NNT=7; RR 0.63, 95% CI 0.45 to 0.88) – see analysis 1.4 below. There was no statistically significant difference between lorazepam, IV and diazepam, IV in terms of respiratory failure/depression, or hypotension. Intramuscular lorazepam is not preferred, as therapeutic lorazepam levels may not be reached as quickly as with IV administration[49].





Midazolam, IV: Systematic review describes a small study[50] (n=27) that reported a statistically non-significant trend favouring midazolam, IV vs lorazepam, IV regarding the following outcomes: non-cessation of seizures (1/15 vs 4/12; RR 0.20, 95% CI 0.03 to 1.56); requirement for ventilatory support (1/15 vs 2/12; RR 0.40, 95% CI 0.04 to 3.90) and adverse effects (1/15 vs 2/12; RR 0.40, 95% CI 0.04 to 3.90) and continuation of status epilepticus requiring a different drug or general anaesthesia (1/15 vs 4/12; RR 0.20, 95% CI 0.03 to 1.56).
Level of Evidence: II Systematic review - single small RCT

Midazolam, IM: Systematic review describes a RCT[51] (n=893) that reported a statistically significant difference favouring midazolam, IM vs lorazepam, IV, in the pre-hospital phase: for cessation of seizures (329/448 vs 282/445; ARR=10%; NNT=10; RR 1.16, 95%CI 1.06 to 1.27), for requirement for intensive care unit (ICU) admission (128/448 vs 161/445; RR 0.79, 95% CI 0.65 to 0.96), and for requirement for hospitalisation (258/448 vs 292/445; RR 0.88, 95% CI 0.79 to 0.97).
Level of Evidence: I Systematic review, RCT

[49] FDA approved package insert: Ativan injection. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/018140s028lbl.pdf
[50] McCormick EM, Lieh-lai M, Knazik S, Nigro M. A prospective comparison of midazolam and lorazepam in the initial treatment of status epilepticus in the pediatric patient. Epilepsia 1999;40(Suppl 7):160, Abstract no: G.07.
[51] Silbergleit R, Durkalski V, Lowenstein D, Conwit R, Pancioli A, Palesch Y, et al. Intramuscular versus intravenous therapy for pre hospital status epilepticus. New England Journal of Medicine 2012;366(7):591–600. https://www.ncbi.nlm.nih.gov/pubmed/25207925

Midazolam, buccal: More convenient than IV administration, delivering medication non-invasively and more rapidly than by the IV route, and may be used also by paramedics. Evidence extrapolated from a RCT where buccal midazolam found to be more effective than rectal diazepam in children with convulsive febrile seizures[52].
Level of Evidence: III Extrapolated from RCT done in paediatrics, Expert opinion

Clonazepam, IV: There is limited evidence to support the use of clonazepam, IV in status epilepticus[53]. No RCTs were retrieved in the Cochrane review by Prasad et al, 2014[54]. Pharmacologically it is a promising agent for status epilepticus with a long half-life (18 to 50 hours) and rapid onset of action[55] – more research is required. However, clonazepam is currently more expensive than diazepam and midazolam.[56]
Level of Evidence: III Observational study, Expert opinion

Benzodiazepines, IV/IM: *direction for use amended*
Guidance updated recommending that the dose of benzodiazepines (lorazepam IV/IM, diazepam IV, clonazepam IV, midazolam IM/IV/buccal) only be repeated once for initial treatment of status epilepticus.
Rationale: Aligned with NICE Guidelines.[57]
Level of Evidence: III Guidelines

Phenytoin, IV: *retained as add-on therapy*
Level of Evidence: III Standard of care

Seizures continuing after 30 minutes
Thiopental, IV: *dose amended from "4 mg/kg" to "2-4 mg/kg"*
Propofol, IV: *dosing regimen amended*
Midazolam, IV: added
Aligned with Guidelines.[58] [59]
Level of Evidence: III Guidelines

Propofol dosing regimen was amended from:

Propofol, IV, 3mg/kg/dose as a bolus o Maintenance dose: 30–100 mcg/kg/minute.

To:

Propofol, IV, 3mg/kg/dose as an immediate dose. o Followed by 2-10mg/kg infusion, titrated to effect. o Maintenance dose: 3-5mg.kg/hour

14.5.1 MIGRAINE

Migraine prophylaxis: *indications amended*
Updated as follows to align with guidelines:

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.

[52] McIntyre J, Robertson S, Norris E, Appleton R, Whitehouse WP, Phillips B, Martland T, Berry K, Collier J, Smith S, Choonara I. Safety and efficacy of buccal midazolam versus rectal diazepam for emergency treatment of seizures in children: a randomised controlled trial. Lancet. 2005;366(9481):205–210. https://www.ncbi.nlm.nih.gov/pubmed/16023510
[53] Alvarez V, Lee JW, Drislane FW, Westover MB, Novy J, Dworetzky BA, Rossetti AO. Practice variability and efficacy of clonazepam, lorazepam, and midazolam in status epilepticus: A multicenter comparison. Epilepsia. 2015 Aug;56(8):1275-85. https://www.ncbi.nlm.nih.gov/pubmed/26140660
[54] Prasad M, Krishnan PR, Sequeira R, Al-Roomi K. Anticonvulsant therapy for status epilepticus. Cochrane Database Syst Rev. 2014 Sep 10;(9):CD003723. https://www.ncbi.nlm.nih.gov/pubmed/25207925
[55] SAMF, 2016
[56] Contract circular RT297-2019:
- Lorazepam, 4 mg injection, 1 mL = R 67.96; Midazolam 10mg inj (weighted average price) =R13.91; Diazepam 10mhg inj = R3.30; Clonazepam 2mg inj = R39.18
[57] NICE. Clinical Guideline - Epilepsies: diagnosis and management, 11 January 2012. http://nice.org.uk/guidance/cg137
[58] SAMF, 2016
[59] NICE Clinical Guideline 137. The epilepsies: the diagnosis and management of the epilepsies in adults and children in primary and secondary care. Issued Jan2012; modified Jan 2015. http://guidance.nice.org.uk/cg137

Level of Evidence: III Guidelines[60]

Amitriptyline, oral: *retained and dosing amended*
Carbamazepine, oral: *deleted*
Beta-blockers, oral: *added as a therapeutic class (propranolol 40 mg 2xd; atenolol 50 mg 2xd)*
Propranolol, oral: *added as an example of class*
Atenolol, oral: *added as a therapeutic alternative*

Refer to medicine review for migraine prophylaxis (June 2018):

Migraine prophylaxis_Adults I

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on this evidence review, the Adult Hospital Level Committee recommends retaining amitriptyline and replacing carbamazepine with a beta-blocker atenolol or propranolol for the prophylactic treatment of episodic migraine. Consider beta-blockers when amitryptiline is not tolerated or contra-indicated. Although carbamazepine was twice as likely to reduce headache frequency as compared to placebo, the study was small (n=48)[61] and information limited; the recommendation for its use cannot be applied uniformly and it is recommended that the current recommendation for carbamazepine in the EML be removed.
Rationale: The evidence for carbamazepine is limited to a single small study of low quality. For the medicines reviewed, no evidence was found to demonstrate consistent superior efficacy of one medicine over the other for the prophylactic treatment of migraine. While side effect profiles differed, no medicine was found to have less side effects than the other medicines. In view of the teratogenic effects of valproic acid and possibly topiramate and given the relatively high costs of these medicines, beta-blockers recommended as an alternative to the amitriptyline.
Level of Evidence: I Meta-analysis[62], Systematic Review[63], Expert opinion

NEMLC MEETING OF 6 DECEMBER 2018 AND 21 FEBRUARY 2019:
The NEMLC accepted the Adult Hospital Level Committee's proposal, recommending a beta-blocker therapeutic group (i.e. atenolol and propranolol) for migraine prophylaxis where there is a poor response or where the use of amitriptyline is contraindicated.

Amitriptyline, oral dosing:
Dosing amended from '75-150 mg' to '25-50 mg' aligned with guidelines[64] and as per study protocol in a RCT[65].
Level of Evidence: I RCT, Guidelines

If severe and not responding to therapy above:
Morphine, IM: *deleted (as not standard practice).*
Level of Evidence: III Standard of care

No evidence could be sourced for the following statement that has historically been mentioned in the Adult Hospital Level STGs and EML: "*Note: Only about half of patients will respond to one of these agents and this response may take 1– 2 months to occur".* The text was therefore, deleted.

[60] Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2000 Sep 26;55(6):754-62. Erratum in: Neurology 2000 Jan 9;56(1):142. https://www.ncbi.nlm.nih.gov/pubmed/10993991
[61] Rompel H, Bauermeister PW. Aetiology of migraine and prevention withcarbamazepine (Tegretol): results of a double-blind, cross-over study. S Afr Med J. 1970 Jan 24;44(4):75-80. https://www.ncbi.nlm.nih.gov/pubmed/4905910
[62] Jackson JL, Cogbill E, Santana-Davila R, Eldredge C, Collier W, Gradall A, et al. A Comparative Effectiveness Meta-Analysis of Drugs for the Prophylaxis of Migraine Headache. PLoS ONE 2015;10(7):1-60.
[63] Mulleners WM, McCrory DC, Linde M. Antiepileptics in migraine prophylaxis: An updated Cochrane review. Cephalalgia 2014; 35(1):51–62.
[64] Loder E, Burch R, Rizzoli P. The 2012 AHS/AAN guidelines for prevention of episodic migraine: a summary and comparison with other recent clinical practice guidelines. Headache. 2012 Jun;52(6):930-45. https://www.ncbi.nlm.nih.gov/pubmed/22671714
[65] Couch JR; Amitriptyline Versus Placebo Study Group. Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. Headache. 2011 Jan;51(1):33-51. https://www.ncbi.nlm.nih.gov/pubmed/21070231

14.5.5 IDIOPATHIC INTRACRANIAL HYPERTENSION (PSEUDOTUMOUR CEREBRI)

For visual involvement, persistent headaches, or severe papilloedema:
Acetazolamide, oral: *retained as 1st line therapy*
Furosemide, oral: *retained as 2nd line therapy*
Aligned with guideline recommendations.
Guidelines recommends acetazolamide as first line option, and furosemide if poor response or intolerance to acetazolamide is not tolerated.[66]
Cochrane review[67] showed that available RCT evidence showed modest benefits for acetazolamide for treatment of idiopathic intracranial hypertension (IIH).
Recommendation: Acetazolamide be retained as 1st line option for IIH; and furosemide recommended where there is poor response of intolerance to acetazolamide.
Rationale: Evidence of efficacy (modest benefit) of acetazolamide for IIH and aligned with guidelines.
Level of Evidence: II Systematic review, Guidelines

14.6.1 MENINGITIS

Severe penicillin allergy:
Vancomycin, IV: *deleted*
Rifampicin, oral: *deleted*
Meropenem, IV: *added*
Management in severe penicillin allergic patients was updated to meropenem, IV, 2 g 8 hourly; noting that an observational study showed no cross-reactivity of carbapenems in patients with documented IgE-mediated hypersensitivity to penicillins.[68]
Level of Evidence: III Observational study

***Listeria monocytogenes* meningitis**
Ceftriaxone, IV: *not added*
Ampicillin, IV: *added*
Gentamicin, IV: *added*
The initial 2017 National Institute of Communicable Diseases (NICD) Guidelines[69] recommends ceftriaxone with ampicillin. However, subsequent communication with NICD ensued - *Listeria monocytogenes* has been shown to be intrinsically resistant to cephalosporins, with resistance mediated by multiple factors (including altered penicillin binding proteins)[70]. An observational study suggested that empiric antibiotic treatment with an aminoglycoside had a lower 30-day mortality, though statistically not significant[71]. However, a larger prospective observational cohort study done in France showed the benefit of beta-lactam with gentamicin for invasive listeriosis and the deleterious effect of adjunctive dexamethasone in neurolisteriosis[72]. Although, clinical trial RCT data is not available for management of *Listeria monocytogenes* meningitis, available observational data was considered sufficient for combination of ampicillin with gentamicin as standard of care.
Level of Evidence: II Patient-oriented observational studies

***Listeria monocytogenes* meningitis – severe penicillin allergy**
For management of severe penicillin allergic patients with neurolisteriosis, the STG recommends that an infectious

[66] Medscape: https://emedicine.medscape.com/article/1214410-treatment#d8
[67] Piper RJ, Kalyvas AV, Young AM, Hughes MA, Jamjoom AA, Fouyas IP. Interventions for idiopathic intracranial hypertension. Cochrane Database Syst Rev. 2015 Aug 7;(8):CD003434. https://www.ncbi.nlm.nih.gov/pubmed/26250102
[68] Gaeta F, Valluzzi RL, Alonzi C, Maggioletti M, Caruso C, Romano A. Tolerability of aztreonam and carbapenems in patients with IgE-mediated hypersensitivity to penicillins. J Allergy Clin Immunol. 2015 Apr;135(4):972-6. https://www.ncbi.nlm.nih.gov/pubmed/25457154
[69] National Institute of Communicable Diseases. Listeriosis: Clinical recommendations for diagnosis and treatment, 5 December 2017. http://www.nicd.ac.za/
[70] Krawczyk-Balska A, Markiewicz Z. The intrinsic cephalosporin resistome of Listeria monocytogenes in the context of stress response, gene regulation, pathogenesis and therapeutics. J Appl Microbiol. 2016 Feb;120(2):251-65. https://www.ncbi.nlm.nih.gov/pubmed/26509460
[71] Thønnings S, Knudsen JD, Schønheyder HC, Søgaard M, Arpi M, Gradel KO, Østergaard C; Danish Collaborative Bacteraemia Network (DACOBAN). Antibiotic treatment and mortality in patients with Listeria monocytogenes meningitis or bacteraemia. Clin Microbiol Infect. 2016 Aug;22(8):725-30. https://www.ncbi.nlm.nih.gov/pubmed/27345176
[72] Charlier C, Perrodeau É, Leclercq A, Cazenave B, Pilmis B, Henry B, Lopes A, Maury MM, Moura A, Goffinet F, Dieye HB, Thouvenot P, Ungeheuer MN, Tourdjman M, Goulet V, de Valk H, Lortholary O, Ravaud P, Lecuit M; MONALISA study group. Clinical features and prognostic factors of listeriosis: the MONALISA national prospective cohort study. Lancet Infect Dis. 2017 May;17(5):510-519. https://www.ncbi.nlm.nih.gov/pubmed/28139432

disease specialist be consulted.

14.6.1.1 TUBERCULOUS MENINGITIS

Corticosteroids, IV: *indication amended for use in HIV-uninfected only*

Cochrane review[73] suggests that corticosteroids reduces TBM mortality, but this benefit is uncertain in the HIV-infected

Results:

- At follow-up from three to 18 months, steroids reduce deaths in the first 2 years (RR 0.75, 95% CI 0.65 to 0.87; nine trials, 1337 participants, high quality evidence).
- Disabling neurological deficit is not common in survivors, and steroids may have little or no effect on this outcome (RR 0.92, 95% CI 0.71 to 1.20; eight trials, 1314 participants, low quality evidence).
- Incidence of adverse events comparable across groups, (i.e. gastrointestinal bleeding, invasive bacterial infections, hyperglycaemia, and liver dysfunction).

Recommendation: Corticosteroids be recommended for TBM in HIV-uninfected, with a note that the role of corticosteroids in HIV-infected patients in TBM is uncertain.

Rationale: Evidence suggests that corticosteroids reduce mortality from TBM, at least in the short term. However, authors of a Cochrane review concluded that 'The number of HIV-positive people included in the review is small, so we are not sure if the benefits in terms of reduced mortality are preserved in this group of patients'.

Level of Evidence: I Systematic review

14.6.1.2.2 CRYPTOCOCCAL MENINGITIS, HIV-UNINFECTED

Amphotericin B, IV: *duration of therapy amended*

Duration of amphotericin B therapy in HIV-uninfected patients was amended as follows, aligned with 2010 Update by the Infectious Diseases Society of America (IDSA)[74]:

Treat intravenously for ~~6~~ 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: Consider lengthening the initial phase of therapy to 6 ~~8~~ weeks in consultation with a specialist.

The IDSA recommendation was based on an old RCT[75] investigated treatment of 4-6 weeks in HIV-uninfected patients, but the treatment regimen was different (Amphotericin B + flucytosine; whilst standard of care is amphotericin B + fluconazole); noting that HIV-uninfected population is mostly transplant patients.

Level of Evidence: III Guidelines

Amphotericin B, liposomal: *not added*

Price in comparison to amphotericin B makes this agent cost-prohibitive. Refer to the medicine review, liposomal amphotericin B for cryptococcal meningitis (November 2018):

Liposomal Amphotericin B for c

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: The current evidence, although limited and of moderate risk of bias, shows that liposomal amphotericin B is as efficacious as amphoteracin B deoxycholate in the management of cryptococcal meningitis. Safety outcomes reflect the superiority of liposomal amphotericin B regarding infusion related reactions, nephrotoxicity, hypokalaemia, and anaemia versus amphoteracin B deoxycholate. However, liposomal amphotericin

[73] Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. CochraneDatabase Syst Rev. 2008 Jan 23;(1):CD002244. http://www.ncbi.nlm.nih.gov/pubmed/18254003

[74] Perfect JR, Dismukes WE, Dromer F, Goldman DL, Graybill JR, Hamill RJ, Harrison TS, Larsen RA, Lortholary O, Nguyen MH, Pappas PG, Powderly WG, Singh N, Sobel JD, Sorrell TC. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. Clin Infect Dis. 2010 Feb 1;50(3):291-322. https://www.ncbi.nlm.nih.gov/pubmed/20047480

[75] Dismukes WE, Cloud G, Gallis HA, Kerkering TM, Medoff G, Craven PC, Kaplowitz LG, Fisher JF, Gregg CR, Bowles CA, Shadomy S, Stamm AM, Diasio RB, Kaufman L, Soong S, Blackwelder WC; National Institute of Allergy and Infectious Diseases Mycoses Study Group. Treatment of cryptococcal meningitis with combination amphotericin B and flucytosine for four as compared with six weeks. N Engl J Med. 1987 Aug 6;317(6):334-41. https://www.ncbi.nlm.nih.gov/pubmed/3299095

B is not currently considered affordable for inclusion on the Adult Hospital Level EML. As there may be a need for consideration of liposomal amphotericin B in mucormycosis, the National Essential Medicines List Committee (NEMLC) recommends that this be investigated for tertiary level of care.

Level of Evidence: II Systematic review and meta-analysis of low to moderate quality RCTs
Review indicator: Price

14.6.2 VIRAL MENINGOENCEPHALITIS

Herpes simplex encephalitis
Aciclovir, IV: *duration of therapy amended*

Twenty one days treatment course based on 2 small RCTs done in the 1980's[76] [77] that compared aciclovir to vidarabone. The protocol was 10 days administration of aciclovir, but duration was increased to 21 days following reports of relapses. However, current clinical guidelines recommends 14-day treatment course of aciclovir. Thus, a 14 to 21 day treatment course of aciclovir is recommended: 14 days for immunocompetent patients and 21 days for immunocompromised patients aligned with Guidelines.[78]
Level of Evidence: III Guidelines

14.6.3 MENINGOVASCULAR SYPHILIS (NEUROSYPHILIS)

Diagnosis
STG text amended for correctness, from:

……~~Serum syphilis serology: a negative TPHA excludes the diagnosis; RPR may be negative.~~
~~CSF syphilis serology: VDRL in CSF is often of low titre, and may be negative; a negative CSFFTA-abs excludes the diagnosis of neurosyphilis.~~

To:

……..Serum syphilis serology: a negative TPHA or TPAb 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.

Benzathine benzylpenicillin, IM: *not added for latent syphilis*
External comment was received to add benzathine benzylpenicillin to treat the latent syphilis. However, neurosyphilis requires management as active syphilis and not latent syphilis. Of note is that the Centers for Disease Control and Prevention (CDC) Guidelines[79] suggests treatment of latent syphilis, but this is not a strong recommendation and may be considered by some clinicians but this is not routinely recommended. Given the limited evidence to include extended treatment and in view of limited supply of benzathine benzylpenicillin, this has not been included in the Adult Hospital Level STGs and EML.

Ceftriaxone, IV: *added as an alternative (listed on Therapeutic Interchange database)*
Case reports[80] [81] and small studies[82] [83] suggest that ceftriaxone, IV 2g daily for 10-14 days[84] may be effective as

[76] Sköldenberg B, Forsgren M, Alestig K, Bergström T, Burman L, Dahlqvist E, Forkman A, Frydén A, Lövgren K, Norlin K, et al. Acyclovir versus vidarabine in herpes simplex encephalitis. Randomised multicentre study in consecutive Swedish patients. Lancet. 1984 Sep 29;2(8405):707-11. https://www.ncbi.nlm.nih.gov/pubmed/6148470
[77] Whitley RJ, Alford CA, Hirsch MS, Schooley RT, Luby JP, Aoki FY, Hanley D, Nahmias AJ, Soong SJ. Vidarabine versus acyclovir therapy in herpes simplex encephalitis. N Engl J Med. 1986 Jan 16;314(3):144-9. https://www.ncbi.nlm.nih.gov/pubmed/3001520
[78] Solomon T, Michael BD, Smith PE, Sanderson F, Davies NW, Hart IJ, Holland M, Easton A, Buckley C, Kneen R, Beeching NJ; National Encephalitis Guidelines Development and Stakeholder Groups. Management of suspected viral encephalitis in adults--Association of British Neurologists and British Infection Association National Guidelines. J Infect. 2012 Apr;64(4):347-73. https://www.ncbi.nlm.nih.gov/pubmed/22120595
[79] Workowski KA, Bolan GA; Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep. 2015 Jun 5;64(RR-03):1-137. Erratum in: MMWR Recomm Rep. 2015 Aug 28;64(33):924. https://www.ncbi.nlm.nih.gov/pubmed/26042815
[80] Shann S, Wilson J. Treatment of neurosyphilis with ceftriaxone. Sex Transm Infect. 2003 Oct;79(5):415-6. https://www.ncbi.nlm.nih.gov/pubmed/14573840
[81] Chen TC, Wang JH, Tsai TC. Repeated episodes of acute stroke as manifestation of neurosyphilis in a well-controlled human immunodeficiency virus-infected patient-Successful treatment with ceftriaxone. J Formos Med Assoc. 2017 Sep;116(9):725-726. https://www.ncbi.nlm.nih.gov/pubmed/28190667
[82] Marra CM, Boutin P, McArthur JC, Hurwitz S, Simpson PA, Haslett JA, van der Horst C, Nevin T, Hook EW 3rd. A pilot study evaluating ceftriaxone and penicillin G as treatment agents for neurosyphilis in human immunodeficiency virus-infected individuals. Clin Infect Dis. 2000 Mar;30(3):540-4. https://www.ncbi.nlm.nih.gov/pubmed/10722441
[83] Smith NH, Musher DM, Huang DB, Rodriguez PS, Dowell ME, Ace W, White AC Jr. Response of HIV-infected patients with asymptomatic syphilis to intensive intramuscular therapy with ceftriaxone or procaine penicillin. Int J STD AIDS. 2004 May;15(5):328-32. https://www.ncbi.nlm.nih.gov/pubmed/15117503
[84] Marra CM. Neurosyphilis. Continuum (Minneap Minn). 2015 Dec;21(6 Neuroinfectious Disease):1714-28. https://www.ncbi.nlm.nih.gov/pubmed/26633785

treatment for neurosyphilis, particularly in the setting of early syphilis. However, intravenous penicillin G remains the treatment of choice for all forms of neurosyphilis.

Level of Evidence: III Disease-oriented RCTs, Case reports

Measuring treatment success: *additional guidance provided*

The following guidance was added to the STG, as a longitudinal observational study[85] showed that normalisation of serum RPR titre predicts success of treatment of neurosyphilis, and follow-up lumbar puncture may be avoided:

A serum RPR response (4-fold decline in titre) in 6-12 months is predictive of treatment success for neurosyphilis.

Results of the study:

- Serum RPR titre normalised in 63 patients (57%) by 4 months after treatment, in 94 (85%) by 7 months, and in 97 (88%) by 13 months.
- Except for CSF protein concentration, normalisation of serum RPR titre predicted normalisation of other CSF and clinical abnormalities in >80% of patients at 4 months, >85% at 7 months, and >90% at 13 months.
- Odds of normalisation of CSF and clinical abnormalities were 28 to 57-fold higher when serum RPR titre had normalised, compared with when it had not.
- Normalisation of serum RPR titre was consistently less accurate in predicting treatment success in HIV–infected patients who were not receiving ART, vs those on ART.

Level of Evidence: III Observational study

Severe penicillin allergy:

Desensitisation protocol: *retained*

Tetracycline, oral: *not added*

External comment to provide another alternative option in severe penicillin allergy (e.g. tetracycline) as doctors at secondary level of care lack the skills for desensitisation was not accepted, as penicillin is the treatment of choice and this is essentially a training concern.

14.6.6 NEUROCYSTICERCOSIS

Albendazole , oral: *retained*

Praziquantel, oral: *not added as combination therapy with albendazole*

Underpowered RCTs[86] [87] showed that treatment course of praziquantel combined with albendazole was more efficacious than albendazole monotherapy in resolving brain cysts on 6 month MRI. However, studies were underpowered to justify combination therapy at all secondary level facilities.

Recommendation: Combination therapy of praziquantel with albendazole not be recommended for patients with more than two active cysts. Current recommendation of albendazole for neurocysticercosis be recommended. However, cases not responding to albendazole requires referral for further management.

Rationale: Evidence is insufficient for broad use of combination therapy (praziquantel_and albendazole) for neurocysticercosis at district level hospitals. Resistant cases requires referral and MRI scans to detect active cysts.

Level of Evidence: II Low quality RCTs, Expert opinion

14.7 PARKINSONISM

Carbidopa/levodopa, oral (high dose 25/250mg): *deleted*

Following text was deleted, as not considered appropriate for secondary level of care, the referral criteria considered to be adequate:

~~If optimal control has not been achieved, consider an alternative diagnosis or changing to a medicine containing a higher dose of levodopa:~~

[85] Marra CM, Maxwell CL, Tantalo LC, Sahi SK, Lukehart SA. Normalization of serum rapid plasma reagin titer predicts normalization of cerebrospinal fluid and clinical abnormalities after treatment of neurosyphilis. Clin Infect Dis. 2008 Oct 1;47(7):893-9. https://www.ncbi.nlm.nih.gov/pubmed/18715154

[86] Garcia HH, Gonzales I, Lescano AG, Bustos JA, Zimic M, Escalante D, Saavedra H, Gavidia M, Rodriguez L, Najar E, Umeres H, Pretell EJ; Cysticercosis Working Group in Peru. Efficacy of combined antiparasitic therapy with praziquantel and albendazole for neurocysticercosis: a double-blind, randomised controlled trial. Lancet Infect Dis. 2014 Aug;14(8):687-695. https://www.ncbi.nlm.nih.gov/pubmed/24999157

[87] Garcia HH, Lescano AG, Gonzales I, Bustos JA, Pretell EJ, Horton J, Saavedra H, Gonzalez AE, Gilman RH; Cysticercosis Working Group in Peru. Cysticidal Efficacy of Combined Treatment With Praziquantel and Albendazole for Parenchymal Brain Cysticercosis. Clin Infect Dis. 2016 Jun 1;62(11):1375-9. https://www.ncbi.nlm.nih.gov/pubmed/26984901

~~Carbidopa/levodopa 25/250 mg. Specialist initiated.~~

14.7.1 PRIMARY PARKINSONISM

Carbidopa/levodopa, oral (standard dose): *dosing amended*
Aligned with SAMF, 2016.
Level of Evidence: III Guidelines[88]

14.7.2 SECONDARY PARKINSONISM

Orphenadrine, oral: *note added*
The following was added to the text of the STG:

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

Level of Evidence: III Expert opinion

14.7.3 ESSENTIAL TREMOR

Primidone, oral: *not added*
External comment submitted without supporting evidence to recommend primidone, oral for essential tremor. However, a technical medicine review is required and time constraints precludes this review during the current review cycle.

Beta-blockers, oral: *not added as a therapeutic class*
Propranolol, oral: *retained*
Propranolol is the preferred beta-blocker for treating essential tremor[89]. There is insufficient evidence of efficacy for other beta-blockers[90] (RCTs are very small[91 92 93 94] and of very low quality[95]).
Level of Evidence: III Guidelines

14.7.4 CHOREA

Haloperidol, oral: *prescriber level amended to specialist and dose amended*
Sole pharmaceutical supplier has discontinued haloperidol 0.5 mg from the South African market; however the 1.5 mg and 2.5 mg formulations are still currently available. Both tablet strengths are scored.
Dose for haloperidol was amended as follows:

14.7.4 Chorea
Treat the underlying cause, if relevant.
- Haloperidol, oral, ~~0.5~~0.75–5 mg 8–12 hourly (Specialist consultation).

Level of Evidence: III Guidelines[96], Expert opinion

14.8 NEUROPATHY

Amitriptyline, oral: *deleted – moved to pain chapter*
Pyridoxine, oral: *deleted – moved to pain chapter*

[88] SAMF, 2016
[89] Zesiewicz TA, Elble RJ, Louis ED, Gronseth GS, Ondo WG, Dewey RB Jr, Okun MS, Sullivan KL, Weiner WJ. Evidence-based guideline update: treatment of essential tremor: report of the Quality Standards subcommittee of the American Academy of Neurology. Neurology. 2011 Nov 8;77(19):1752-5. https://www.ncbi.nlm.nih.gov/pubmed/26678329
[90] Zesiewicz TA, Kuo SH. Essential tremor. BMJ Clin Evid. 2015 Dec 15;2015. pii: 1206. https://www.ncbi.nlm.nih.gov/pubmed/26678329
[91] Calzetti S, Findley LJ, Perucca E, Richens A. Controlled study of metoprolol and propranolol during prolonged administration in patients with essential tremor. J Neurol Neurosurg Psychiatry. 1982 Oct;45(10):893-7. https://www.ncbi.nlm.nih.gov/pubmed/815306
[92] Jefferson D, Jenner P, Marsden CD. Beta-adrenoreceptor antagonists in essential tremor. J Neurol Neurosurg Psychiatry 1979;42:904–909. https://www.ncbi.nlm.nih.gov/pubmed/512665
[93] Larsen TA, Teravainen H, Calne DB. Atenolol vs. propranolol in essential tremor. A controlled, quantitative study. Acta Neurol Scand 1982;66:547–554. https://www.ncbi.nlm.nih.gov/pubmed/7148397
[94] Koller WC, Biary N. Metoprolol compared with propranolol in the treatment of essential tremor. Arch Neurol 1984;41:171–172.
[95] Lee KS, Kim JS, Kim JW, Lee WY, Jeon BS, Kim D. A multicenter randomized crossover multiple-dose comparison study of arotinolol and propranolol in essential tremor. Parkinsonism Relat Disord. 2003 Aug;9(6):341-7. https://www.ncbi.nlm.nih.gov/pubmed/12853233
[96] SAMF, 2016

Carbamazepine, oral: *deleted – moved to pain chapter*
Prednisone, oral: *deleted – moved to pain chapter*
Guidance for management for neuropathic pain was moved to the pain chapter.

Report prepared by TD Leong: Secretariat to the Adult Hospital Level Committee (2017-2020)
- ***Note**: Information was sourced from NEMLC ratified minutes and NEMLC-approved documents.*