health
Department:
Health
REPUBLIC OF SOUTH AFRICA

SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 26: PAIN
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 pain chapter.

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED/RETAINED
26.1 Pain, chronic	*Management*	Amended
26.1.1 Analgesia for chronic non-cancer pain		
- general supportive measures	Non-pharmacological management	Added
- mild/moderate pain	NSAIDs, oral	Caution box added
	PPI, oral	Added for concomitant use with NSAIDs in high-risk patients
- severe pain	Tramadol, oral	Indication, dosing, directions for use and caution box amended
	Tramadol SR, oral	Not added
-severe pain	Morphine, long-acting, oral, 10 mg	Retained
	Morphine, long-acting, oral, 30 mg	Retained
	Morphine, long-acting, oral, 60 mg	Added
26.1.3 treatment of adverse effects of chronic opioid use *- nausea and vomiting*	Metoclopramide oral/IM/slow IV	Directions for use not amended
	Metoclopramide IM/slow IV	Directions for use not amended
	Promethazine, oral	Retained
	Prochlorperazine, oral:	Not added
26.1.4 Management of neuropathic pain	Amitriptyline, oral	Retained as first line option; directions for use amended
	Carbamazepine, oral	Retained as second line-option if poor response to amitryptyline/or is contra-indicated
	Duloxetine, oral	Not added
	Venlafaxine, oral	Not added
	Opioids, oral/parenteral	Not added
	Gabapentin, oral	Not added as first line option in the elderly
	Pregabalin, oral	Not added as first line option in the elderly
26.2.2 Acute pain due to gastrintestinal colic	Hyoscine butylbromide, oral	Retained
	Hyoscine butylbromide, IV	Retained

26.1 PAIN, CHRONIC

The content of this section has been amended to provide guidance that pain management should be holistic and inclusive and not revolve around pharmacotherapy only. The STG further provides guidance on the realistic expectations regarding pain management; general principles for management of chronic pain determined by underlying aetiology; and on measuring pain medicine effectiveness using objective scale measuring quality of life or functionality.

26.1.1 ANALGESIA FOR CHRONIC NON- CANCER PAIN

Assessment of chronic non-cancer pain:

STG text was editorially amended (following NEMLC recommendation to describe condition specific

pain-management to cross-reference to relevant sections) from:

~~**Biological:** Ascertain the aetiology and perpetuating factors and manage accordingly. Note, there may be overlap between different aetiologies.~~

~~» Nociceptive pain, e.g. arthritis (see chapter 13); chronic post-surgical or injury pain; visceral pain, e.g. chronic pancreatitis; chronic cancer pain (see section 25.1.1: Analgesia for chronic cancer pain, and chapter 24: Palliative care).~~

~~» Neuropathic pain (see section 25.1.3)~~

~~» Fibromyalgia; irritable bowel syndrome~~

~~» Mental illness, e.g. mood disorders (depression and bipolar disorder, anxiety, post-traumatic stress disorder (see chapter 15: Mental health conditions), somatic symptom and related disorders.~~

~~Substance use disorders, including over the counter analgesics, opioids, benzodiazepines, and alcohol.~~

To:

Biological: Ascertain the aetiology and perpetuating factors and manage accordingly. Note, there may be overlap between different aetiologies and condition-specific pain management may be required.

» Nociceptive pain, e.g. osteoarthritis (see section 13.3); rheumatoid arthritis (see section 13.1); gout (see section 13.4); spondylarthritis (see section 13.5); chronic post-surgical or injury pain; visceral pain, e.g. chronic pancreatitis; chronic cancer pain (see section 26.1.2); endometriosis (see section 5.4).))

» Neuropathic pain (see section 26.1.4).

» Fibromyalgia; irritable bowel syndrome (see PHC STGs and EML, section 2.12).

» Mental illness, e.g. mood disorders (depression and bipolar disorder, anxiety, post-traumatic stress disorder (see chapter 15: Mental health conditions), somatic symptom and related disorders.

» Substance use disorders, including over the counter analgesics, opioids, benzodiazepines, and alcohol.

General supportive measures

- *WHO pain ladder:* Validated for use as a tool to improve cancer pain management, using a step-wise approach according to patients reported pain intensity. Unlike cancer pain and end-of-life pain, persistent non-cancer pain has an unpredictable course, may continue for lengthy periods of times and substantial reduction in pain intensity is seldom achieved. Various pathophysiologic mechanisms need consideration and other factors such as patient's current distress, previous pain experience, emotions etc needs consideration[1]. Rational approach for chronic non-cancer pain management would be to use a stepped-wise approach starting with non-pharmacological measures (e.g. physiotherapy) regardless of pain intensity; counselling that pain may be resistant to medication and that improve in functionality/quality of life rather than complete relief of symptoms is the goal of pain therapy); regular review and monitoring of pain medication to determine continued efficacy; and periodic dose tapering to evaluate need for on-going treatment[2] [3].
- *High risk groups of opioid addiction:* These include patients with comorbid substance misuse (personal or family history) and/or mental health disorders[4], high levels of subjective pain and age <45 years.

Recommendation: STG text editorially amended and updated to reflect non-pharmacological management of chronic pain management using a stepped-wise approach starting with non-pharmacological measures regardless of pain intensity (includes comprehensive baseline assessment, patient counselling/education, physiotherapy, treatment of underlying and comorbid disorder(s), psychological support as required).

Patients with chronic pain should be treated with a biopsychosocial approach, according to findings of a comprehensive assessment. Note that those with greater subjective pain complaints may also be at higher

[1] Ballantyne JC, Kalso E, Stannard C. WHO analgesic ladder: a good concept gone astray. BMJ. 2016 Jan 6;352:i20. https://www.ncbi.nlm.nih.gov/pubmed/26739664

[2] Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. JAMA. 2016 Apr 19;315(15):1624-45. https://www.ncbi.nlm.nih.gov/pubmed/26977696

[3] The Royal College of Anaesthetists. Opioid Aware Resource, 2019. [Accessed August 2019]. https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware

[4] Kaye AD, Jones MR, Kaye AM, Ripoll JG, Galan V, Beakley BD, Calixto F, Bolden JL, Urman RD, Manchikanti L. Prescription Opioid Abuse in Chronic Pain: An Updated Review of Opioid Abuse Predictors and Strategies to Curb Opioid Abuse: Part 1. Pain Physician. 2017 Feb;20(2S):S93-S109. https://www.ncbi.nlm.nih.gov/pubmed/28226333

risk of an opioid use disorder. Utilise allied professional healthcare providers and non-governmental counselling services (e.g. FAMSA, http://famsa.org.za, or POWA, https://www.powa.co.za)

» Validate the pain experienced and manage with empathy.
» Educate regarding cause of pain, prognosis (including that pain may not be fully relieved) and realistic expectations regarding pain reduction.
» Establish goals of care with the patient and select a measure of effectiveness e.g. Pain, Enjoyment and General Activity (PEG) scale, http://www.med.umich.edu/1info/FHP/practiceguides/pain/PEG.Scale.12.2016.pdf
» Treat underlying physical cause of pain. Refer for specialist care (e.g. rheumatologist, orthopaedic surgeon) where necessary.
» Treat underlying or comorbid mental illness.
» Manage substance use, refer to SANCA/ rehabilitative services.
» Encourage physical activity; refer to Physiotherapy and Occupational Therapy.
» Address self-esteem, motivation, daily function, and social skills; refer to Occupational Therapy.
» Address social stressors and interpersonal conflicts; refer to social worker, counselling services, psychologist, social welfare organisations.

Rationale: Aligned with Guidelines, noting that the WHO pain ladder (management determined by pain intensity) would probably not be appropriate for persistent non-cancer pain.
Level of Evidence: III Guidelines

Mild/moderate pain
NSAIDs, oral: *caution box added*
PPI, oral: *added for concomitant use with NSAIDs in high-risk patients*
Aligned to chapter 13: Musculoskeletal conditions, for consistency.

Severe pain
Tramadol, oral: *indication, dosing, directions for use and caution box amended*
The Adult Hospital Level Committee was of the opinion that the weak opiate, tramadol be recommended for "severe pain", as opposed to "moderate pain" before morphine is considered, due to the irrational prescribing and use of this medicine in clinical practice. It is noted that this is contrary to the WHO pain ladder stepped approach (and the PHC STGs and EML, 2018).
Dosing aligned to SAMF, 2016.

Amended from:

~~**Mild/moderate pain:**~~
- ~~Tramadol, oral, 50–100 mg, 6 hourly.~~
  - ~~Avoid in head injury, epilepsy and people at high risk of addiction.~~

~~**Note:**~~
» ~~Do not use tramadol with other opioids.~~
» ~~Tramadol blocks neuronal reuptake of noradrenaline and serotonin. Do not use tramadol with other medicines that also block serotonin reuptake (e.g. pethidine, fentanyl, antidepressants) the serotonergic syndrome can result (altered mental status, neuromuscular hyperactivity, autonomic hyperactivity).~~
» ~~Avoid long-term use of NSAIDs as they are associated with an increased risk of arterial thrombosis, renal impairment and gastrointestinal bleeding.~~

To:

Severe pain:

- Tramadol, oral, 50-100 mg **4**-6 hourly.
  - Warn patient of adverse effects and addiction potential. Advise not to operate machinery/drive initially and after dosage increases.
  - Evaluate response to treatment using a rating scale at 2 weeks, and every following 4 weeks: **taper and stop tramadol if not reducing pain.**
  - In patients with uncontrolled pain the dose can be increased to a maximum of 100 mg (2 x 50 mg) 6 hourly.
  - Improved effect when given with paracetamol.

CAUTION

» Tramadol causes respiratory depression, may be fatal in overdose. Do not use with other opioids, benzodiazepines or other respiratory depressants. After a period of no treatment, re-initiate at 25 mg. Treat overdose as in section 19.5.3. Opioid poisoning.
» Avoid use in those at high risk of opioid addiction (a personal or family history of any substance use disorder, comorbid mental illness, high levels of subjective pain and age <45 years).
» Increases seizure risk: avoid in head injury and epilepsy.
» Blocks noradrenaline and serotonin reuptake: avoid use with antidepressants and fentanyl.
» Other adverse effects include constipation, dry mouth, drowsiness, confusion.

Rationale: Aligned with Guidelines[5] [6] [7] [8], recommending that:

- Opioids should be used only when benefits for pain and function are expected to outweigh risks, as evidence of efficacy of long-term opioids in chronic pain is limited, whilst opioid use is associated with harms (opioid use disorder and overdose).
- Before starting opioids, treatment goals should be established and treatment plan to discontinue opioids of harms outweigh benefit.
- Assess for high risk of opioid addiction (comorbid substance misuse and/or mental health disorders, high levels of subjective pain and age <45 years) and manage appropriately.
- Initiating opioids at lowest effective dosage, reassessing benefits vs risks when daily dose ≥ 50 morphine mg.
- Opioids should not be used concomitantly with benzodiazepines due to associated respiratory depression.
- Clinicians should regularly evaluate benefits and harms of continued opioid therapy and review other medicines used to monitor for high-risk combinations or dosages.
- Regular review and monitoring of pain medication to determine continued efficacy; and periodic dose tapering to evaluate need for on-going treatment, if required.

Level of Evidence: III Guidelines

Caution box: Following receipt of external comments, the caution box was further amended as follows:

[5] Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. JAMA. 2016 Apr 19;315(15):1624-45. https://www.ncbi.nlm.nih.gov/pubmed/26977696
[6] The Royal College of Anaesthetists. Opioid Aware Resource, 2019. [Accessed August 2019]. https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware
[7] Kaye AD, Jones MR, Kaye AM, Ripoll JG, Galan V, Beakley BD, Calixto F, Bolden JL, Urman RD, Manchikanti L. Prescription Opioid Abuse in Chronic Pain: An Updated Review of Opioid Abuse Predictors and Strategies to Curb Opioid Abuse: Part 1. Pain Physician. 2017 Feb;20(2S):S93-S109. https://www.ncbi.nlm.nih.gov/pubmed/28226333
[8] SAMF, 2016

CAUTION

» Tramadol causes respiratory depression, may be fatal in overdose.
» ~~Do not use with other opioids, benzodiazepines or other respiratory depressants.~~ Avoid concurrent prescribing of opioid pain medication, benzodiazepines or other respiratory depressants, whenever possible.
» After a period of no treatment, re-initiate at 25 mg. Treat overdose as in section 19.5.3. Opioid poisoning.
» Avoid use in those at high risk of opioid addiction (a personal or family history of any substance use disorder, comorbid mental illness, high levels of subjective pain and younger people).
~~» Increases seizure risk: avoid in head injury and epilepsy.~~
~~» Blocks noradrenaline and serotonin reuptake: avoid use with antidepressants and fentanyl.~~
» Inhibits reuptake of noradrenaline and serotonin – increases risk of seizures, of serotonin syndrome, and mania or hypomania. Avoid use in at-risk groups (e.g. epilepsy, head injury, if taking antidepressants, bipolar disorder). Educate the patient, optimise treatment of primary condition, avoid polypharmacy, monitor closely.
» Other adverse effects include constipation, dry mouth, drowsiness, confusion.

Additional amendments made were informed by Guidelines[9] [10]and case reports[11] [12] [13].
Level of Evidence: III Guidelines, Case reports

Tramadol SR, oral: *not added*

NEMLC MEETING OF 26 SEPTEMBER 2019:
Recommendation: Due to the large contract price differential between tramadol slow release 100 mg formulation (R115.48 for 60 tabs) and tramadol 50 mg capsules (50mg, 100 capsules = R27.62; 50mg 6 hourly =120 capsules = R33.14), NEMLC recommended that the slow release formulation not be recommended for inclusion on the EML.
Reference: Contract circular RT289-2019

An external comment was received stipulating that chronic pain therapy should be individualised and there may be a place for the slow release formulation. The Adult Hospital Level Committee acknowledges this, but these exceptional cases would probably not be catered for by the National EML, and individual motivations can be submitted to the relevant Pharmaceutical and Therapeutics Committees for consideration.

Morphine, long-acting, oral: *60 mg dose added*
Morphine, long-acting, oral: *10 mg dose retained*
Morphine, long-acting, oral: *30 mg dose retained*
60 mg dose long-acting oral formulation available on the South African market.

26.1. 26.1.2 ANALGESIA FOR CHRONIC CANCER PAIN

Cross reference to the Tertiary and Quaternary included in the STG, for management of metastatic bone pain with bisphosphonates.

[9] Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. JAMA. 2016 Apr 19;315(15):1624-45. https://www.ncbi.nlm.nih.gov/pubmed/26977696
[10] Hassamal S, Miotto K, Dale W, Danovitch I. Tramadol: Understanding the Risk of Serotonin Syndrome and Seizures. Am J Med. 2018 Nov;131(11):1382.e1-1382.e6. https://www.ncbi.nlm.nih.gov/pubmed/29752906
[11] Beakley BD, Kaye AM, Kaye AD. Tramadol, Pharmacology, Side Effects, and Serotonin Syndrome: A Review. Pain Physician. 2015 Jul-Aug;18(4):395-400. https://www.ncbi.nlm.nih.gov/pubmed/26218943
[12] Sharma V. Tramadol-Induced Hypomania and Serotonin Syndrome. Prim Care Companion CNS Disord. 2016 Dec 15;18(6). https://www.ncbi.nlm.nih.gov/pubmed/28002658
[13] Nimah J, Chen A, Gable KN, Felthous AR. Tramadol-associated mania: A case report. J Opioid Manag. 2017 May/Jun;13(3):197-200. https://www.ncbi.nlm.nih.gov/pubmed/28829520

26.1.3 TREATMENT OF ADVERSE EFFECTS OF CHRONIC OPIOID USE

Nausea and vomiting

Metoclopramide oral/IM/slow IV: *directions for use not amended*

External comment was received to provide renal-adjusted dosing for renal impairment; but the nephrology chapter does contain the following narrative: "*The doses of many medicines need to be adjusted in renal impairment. Recommendations for medicines that require dose adjustment in renal impairment can be found in the SAMF, package insert, and from many online resources e.g.: http://www.globalrph.com/index_renal.htm"*

Promethazine, oral: *retained*

Prochlorperazine, oral: *not added*

External comment without supporting evidence was received for prochlorperazine.

26.1.4 MANAGEMENT OF NEUROPATHIC PAIN

Layout

STG provides guidance on all neuropathic conditions including diabetic neuropathy, isoniazid-induced polyneuropathy, trigeminal neuralgia and herpetic neuralgia (with cross-referencing between the relevant chapters).

Medicine treatment

AGREE II assessment of the NICE Guidelines[14] for neuropathic pain was done and there was general agreement between assessors with a note that the guidelines require to be adapted to local context with consideration of local epidemiology, costs and drug-drug interactions.

Amitriptyline, oral: *retained as first line option; directions for use amended*

Directions for use for amitriptyline updated to include dosing for the elderly and guidance to use regularly, as takes 4-6 weeks for maximal effect.

Level of Evidence: III Guidelines[15], Meta-analysis of disease-oriented studies[16]

Carbamazepine, oral: *retained as 2nd line-option if poor response to amitryptyline/or contra-indicated*

Guidelines: Aligned with the NICE Guidelines for neuropathic pain[17].

Cochrane review: Cochrane review[18] of low quality RCTs (4 RCTs; n=188) (heterogeneous indications - trigeminal neuralgia, painful diabetic neuropathy, chronic post stroke pain - and heterogeneous doses, small studies of short duration of ≤ 4 weeks, imputation not reported) suggests that compared to placebo, carbamazepine may be more effective in reducing substantial neuropathic pain:

- *Results:*
  - At least 50% reduction of pain: 94/1000 vs 608/1000; RR 6.5 (95% CI 3.4 to 12); NNT 1.9 (95% CI 1.6 to 2.5).
  - Adverse events reported: RR 2.4 (95% CI 1.9 to 3.2), NNH 2.6 (95% CI 2.1 to 3.5) in 4 crossover studies (n=346).

Recommendation: Carbamazepine be retained as second line option or add-on therapy to amitriptyline for neuropathy.

Level of Evidence: II Systematic review of low quality RCTs

[14] NICE. Neuropathic pain – pharmacological management, February 2017. NICE clinical guideline 173. http://guidance.nice.org.uk/CG173
[15] SAMF, 2016
[16] Onghena P, Van Houdenhove B. Antidepressant-induced analgesia in chronic non-malignant pain: a meta-analysis of 39 placebo-controlled studies. Pain. 1992 May;49(2):205-19. https://www.ncbi.nlm.nih.gov/pubmed/1535121
[17] NICE. Neuropathic pain – pharmacological management, February 2017. NICE clinical guideline 173. http://guidance.nice.org.uk/CG173
[18] Wiffen PJ, Derry S, Moore RA, Kalso EA. Carbamazepine for chronic neuropathic pain and fibromyalgia in adults. Cochrane Database Syst Rev. 2014 Apr 10;(4):CD005451. https://www.ncbi.nlm.nih.gov/pubmed/24719027

External comment was received that amitriptyline should not be used in the elderly, and gabapentin, pregabalin and carbamazepine should be considered as first line option. STG now provides for dosing of amitriptyline in the elderly, carbamazepine is currently recommended if amitryptiline is contraindicated; and gabapentin and pregabalin is under review by the Tertiary & Quaternary Expert Review Committee.

Duloxetine, oral: *not added*
Venlafaxine, oral*: not added*
Refer to the medicine review: SNRIs for diabetic neuropathy in adults, May 2018:

SNRIs for DiabeticNeuropathy

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

Recommendation: The Adult Hospital Level Committee acknowledges that duloxetine 30 – 60mg once daily may be considered as second line agent for diabetic neuropathy. However, this agent is currently cost-prohibitive. There is little compelling evidence to support the use of venlafaxine for neuropathic pain due to diabetic neuropathy or neuropathic pain related to etiology other than diabetes.
Level of Evidence: II Systematic review with disease oriented outcomes
(*Note:* The SNRI medicine review only answered the PICO question relating to diabetic neuropathic pain, triggered by external stakeholder comments that were received. As this agent is expensive and thus not recommended for inclusion to the Adult Hospital Level EML; and as the same management approach is used for all types of neuropathies, it was recommended that the review not be developed any further - but could be expanded going forward when more time and resources are available).

Opioids, oral/parenteral: *not added*
Refer to the medicine review: Opioids for neuropathy in adults, April 2019:

Opioids for Neuropathy_AdultsF

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

Recommendation: Based on the appraisal of the evidence presented in this technical review, the Adult Hospital Level Committee does not recommend the use of opioid analgesia for the treatment of long-term neuropathic pain.
Rationale: Limited evidence of clinical efficacy (defined as 50% pain reduction).
Level of Evidence: II Systematic review of low quality RCTs

Gabapentin, oral*: not added as first line option in the elderly*
Pregabalin, oral: *not added as first line option in the elderly*
These agents are currently being reviewed by the Tertiary & Quaternary Committee[19].

26.2.2 ACUTE PAIN DUE TO GASTRINTESTINAL COLIC

Hyoscine butylbromide, IV/oral: *retained*
Previously NEMLC had recommended that criteria for hyoscine for GIT colic be included in the STG. However, due to time constraints, an evidence review was not possible and the Adult Hospital Level

[19] Communication from Secretariat to T& Q ERC, May 2019.

Committee proposes that an evidence review for management of gastrointestinal colic be deferred to the next review cycle in collaboration with the South African Gastroenterology Society.

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.*