health
Department:
Health
REPUBLIC OF SOUTH AFRICA

2030 NDP

SOUTH AFRICAN PRIMARY HEALTHCARE ESSENTIAL MEDICINES LIST
CHAPTER 20: PAIN
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2016 -2018)

Medicine amendment recommendations, following initial review of the chapter, are listed below. Kindly review the medicine amendments in the context of the complete pain chapter.

GENERAL

The PHC Expert Review Committee recommended that the STGs and EML would only differentiate between nurse and doctor prescribing; but that all medicines prescribed should be determined by different disciplines' scope of practice (e.g. paramedics, optometrists, clinical research associates, etc.).
The foreword of the PHC book will include a disclaimer that the scope of practice of healthcare workers will determine the medicines prescribed.
NEMLC accepted this recommendation at the NEMLC meeting of 5 July 2018.[1]

A: NEW SECTIONS(S)

SECTION	CONDITION	MEDICINE MANAGEMENT	MEDICINE ADDED
20.2	**Acute pain**	Yes	Paracetamol, oral NSAIDs, oral Tramadol, oral Morphine solution, oral Morphine, IM Morphine, IV

New STG was developed, separating guidance on management of acute pain from section 20.1: Pain control, to ensure consistency with the rest of the chapter. Recommendations were further aligned with the Adult and Paediatric Hospital Level STGs and EMLs and the SAMF, 2016 edition.

20.2 Acute pain

Description
Pain that has been present for less than 4 weeks and usually occurs in response to tissue damage.

General measures
» Patient counselling.
» Lifestyle adjustment.

Medicine treatment
Mild pain:
Non-opioid treatment.

Non-inflammatory or post trauma:
Children
- Paracetamol, oral, 10–15 mg/kg/dose 6 hourly when required. See dosing table, pg 22.6.

Adults
- Paracetamol, oral, 1 g 4–6 hourly when required to a maximum of 4 doses per 24 hours.
  - Maximum dose: 15 mg/kg/dose.
  - Maximum dose: 4 g in 24 hours.

Pain associated with inflammation:
Adults

[1] Minutes of the NEMLC meeting of 5 July 2018.

- NSAIDs,
- e.g. Ibuprofen, oral, 400 mg 8 hourly with food.

If no relief after 2 or 3 doses, combine paracetamol and ibuprofen at the above dosages.

Moderate pain:
If no relief to paracetamol:
ADD
Children
- NSAIDs, e.g.:
- Ibuprofen, oral, 5–10 mg/kg/dose 8 hourly with food. See dosing table, pg 23.5.
  - Discontinue if not effective after 2–3 days.

If no response to paracetamol and ibuprofen, refer.

Adults
- NSAIDs, e.g.:
  - Ibuprofen, oral, 400 mg 8 hourly.
  - Discontinue if not effective after 2–3 days.

If still no relief to paracetamol and ibuprofen:
ADD
- Tramadol, oral, 50 mg, 4–6 hourly as a starting dose. (Doctor prescribed).
  - May be increased to a maximum of 400 mg daily.

Acute severe pain:
Children
Refer.

Adults
- Tramadol, oral, 50 mg, 4–6 hourly as a starting dose (Doctor prescribed).
  - May be increased to a maximum of 400 mg daily.

and
- Paracetamol, oral, 1 g ~~4~~–6 hourly when required to a maximum of 4 doses per 24 hours.
  - Maximum dose: 15 mg/kg/dose.
  - Maximum dose: 4 g in 24 hours.

OR
- Morphine solution, oral.
  - Starting dose: 10–15 mg (maximum 0.2 mg/kg) 4 hourly.
  - Elderly or frail patients: 2.5–5 mg (maximum 0.1 mg/kg) 4 hourly.

OR
- Morphine, IM, 10mg, 4–6 hourly when required (Doctor prescribed).

OR
- Morphine, IV, to a total maximum dose of 10 mg.
  - Dilute 10 mg up to 10 mL with sodium chloride 0.9%.
  - Morphine, IV, 3–5 mg as a single dose then further boluses of 1–2 mg/minute and monitor closely.
  - Total maximum dose: 10 mg.
  - Repeat after 4 hours if necessary.
  - Monitor response to pain and effects on respiration and BP.

Patients requiring morphine for acute pain of unknown cause or pain not responding with 1 dose must be referred for definitive treatment.

Precautions and special comments on the use of morphine
» Morphine may cause respiratory depression. This can be reversed with naloxone. See Section 21.8: Exposure to poisonous substances.
» **Do not administer** morphine in:
– severe head injury
– acute asthma
– uncontrolled hypothyroidism
» Morphine can be used for acute abdominal pain without leading to surgical misdiagnosis.
» **Use** morphine **with extreme care** if there is:
– recent or concurrent alcohol intake or other CNS depressants
– hypovolaemia or shock
– in the elderly

In these circumstances use:

Adults

OR

- Morphine, IV, to a total maximum dose of 10 mg.
  - Dilute 10 mg up to 10 mL with sodium chloride 0.9%.
  - Morphine, IV, 3–5 mg as a single dose then further boluses of 1–2 mg/minute and monitor closely.
  - Total maximum dose: 10 mg.
  - Repeat after 4 hours if necessary.
  - Monitor response to pain and effects on respiration and BP.

If morphine has been administered, the time and dose should be clearly documented on the referral letter as this may alter some of the clinical features of acute abdomen or head injury.

Referral

» All children with acute severe pain.
» No response to oral pain control and unable to initiate opioid therapy.
» Uncertain diagnosis.
» Management of serious underlying conditions.

B: MEDICINE AMENDMENTS

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED/NOT ADDED
20.1 Acute pain		
- *Moderate pain relief: Children*	Diclofenac, oral	Not added
	Ibuprofen, oral	Retained
20.3 Chronic non-cancer pain		
- *Mild pain: children*	Paracetamol, oral	Added
	NSAIDs, oral	Not added
	Antidepressants, oral	Not added
	Anti-epileptic medicines, oral	Not added
	Opioids, oral	Not added
- *Chronic neuropathic pain: Adults*	Amitriptyline, oral	Retained
	Tramadol, oral	Not added
	Morphine, oral	Not added
	Pregabalin, oral	Not added
20.4 Chronic cancer pain		
- *Adults*	WHO pain ladder	Not amended
	Pain management	Amended
	Paracetamol, oral	Retained in step 1 of WHO pain ladder
	NSAIDs, oral	Retained in step 1 of WHO pain ladder
	Tramadol, oral	Retained in step 2 of WHO pain ladder
	Morphine controlled-release formulations, oral	STG amended to provide for all strengths (i.e. 10,20 and 30 mg) and dosing amended from '12 hourly' to '8-12 hourly'
	Oxycodone slow release, oral	Not added
- *Children*	WHO pain step ladder	Not amended
	Paracetamol, oral	Retained
	NSAIDs, oral	Retained
	Tilidine, oral	Not added
- *Adjuvant therapy: adults*	Amitriptyline, oral	Retained as adjuvant therapy
	Corticosteroid, oral	Not added as adjuvant therapy
	Gabapentin, oral	Not added as adjuvant therapy
- *Significant nausea & vomiting: children*	Metoclopramide, oral	Not added
- *Breakthrough pain*	Morphine solution, oral:	Directions for use amended

20.1 ACUTE PAIN

Moderate pain relief: Children

Diclofenac, oral: *not added for use in children*

Ibuprofen, oral: *retained for use in children*

An external comment was received to consider diclofenac rather than ibuprofen for use in children, based on anecdotal experience of safety concerns. However, no evidence was submitted and no evidence could be retrieved from the published literature of greater harms associated with ibuprofen compared to diclofenac in children.

20.3 CHRONIC NON-CANCER PAIN

CHILDREN

Mild chronic pain

Management of mild chronic non-cancer pain such as genetic conditions, nerve damage pain, chronic musculoskeletal pain, and chronic abdominal pain was added to this STG.

Paracetamol, oral: *added*

Aligned with the Paediatric Hospital Level STGs and EML, 2017.

Cochrane review[2]*:* No studies were eligible for inclusion in this review. The quality of the evidence was downgraded by three levels to very low due to the lack of data reported for any outcome. No conclusions could be made about efficacy or harm in the use of paracetamol.

Level of Evidence: II Systematic reviews of low quality studies, Guidelines

NSAIDs, oral: *not added*

Despite the availability of very low quality RCT evidence for NSAIDs[3], a pragmatic decision was made not to include ibuprofen, oral, as children with chronic pain should be managed at higher levels and down-referred accordingly.

Level of Evidence: III Expert opinion

Antidepressants, oral: *not added*

Cochrane review[4]*:*No studies reported on chronic non-cancer pain relief of 30% or greater or 50% or greater, and the quality of studies was low.

Level of Evidence: III Systematic reviews of very ow quality studies

Anti-epileptic medicines, oral: *not added*

Cochrane review[5]*:*The evidence was downgraded by three levels to very low for one of two reasons: due to the fact that there was no evidence to support or refute the use of anti-epileptic drugs for management of chronic non-cancer pain in children and adolescents, or that there were too few data and the number of events was too small to be meaningful.

Level of Evidence: III Systematic reviews of very low quality studies

Opioids, oral: *not added*

Cochrane review[6]*:* No studies were eligible for inclusion in this review. The quality of the evidence was therefore rated as very low.

Level of Evidence: III Systematic reviews of very low quality studies

[2]Cooper TE, Fisher E, Anderson B, Wilkinson NM, Williams DG, Eccleston C. Paracetamol (acetaminophen) for chronic non-cancer pain in children and adolescents. Cochrane Database Syst Rev. 2017 Aug 2;8:CD012539.

[3] Eccleston C, Cooper TE, Fisher E, Anderson B, Wilkinson NM. Non-steroidal anti-inflammatory drugs (NSAIDs) for chronic non-cancer pain in children and adolescents. Cochrane Database Syst Rev. 2017 Aug 2;8:CD012537. https://www.ncbi.nlm.nih.gov/pubmed/28770976

[4] Cooper TE, Heathcote LC, Clinch J, Gold JI, Howard R, Lord SM, Schechter N, Wood C, Wiffen PJ. Antidepressants for chronic non-cancer pain in children and adolescents. Cochrane Database Syst Rev. 2017 Aug 5;8:CD012535.

[5]Cooper TE, Wiffen PJ, Heathcote LC, Clinch J, Howard R, Krane E, Lord SM, Sethna N, Schechter N, Wood C. Antiepileptic drugs for chronic non-cancer pain in children and adolescents. Cochrane Database Syst Rev. 2017 Aug 5;8:CD012536.

[6]Cooper TE, Fisher E, Gray AL, Krane E, Sethna N, van Tilburg MA, Zernikow B, Wiffen PJ. Opioids for chronic non-cancer pain in children and adolescents. Cochrane Database Syst Rev. 2017 Jul 26;7:CD012538.

ADULTS
Chronic neuropathic pain
Amitriptyline, oral: *retained*
Tramadol, oral*: not added*
Morphine, oral*: not added*
Pregabalin, oral: *not added*

Tramadol: The evidence reviewed in recent Cochrane[7] review was mostly of low or very low quality. More robust RCT data required to confidently recommend tramadol for neuropathic pain.
Morphine: The evidence reviewed in recent Cochrane review[8] was downgraded 3 levels due to small number of studies, participants, and events, and several source of potential bias. More robust RCT data required to confidently recommend morphine for neuropathic pain.
Level of Evidence: III Systematic reviews of very low quality studies

Pregabalin, oral: An external comment was received to consider pregabalin for inclusion to the PHC EML. However, this medicine is currently under review by the Tertiary & Quaternary (T&Q) Committee for consideration for the T&Q EML.

20.4 CHRONIC CANCER PAIN

Recommended steps in management of cancer pain

ADULTS:
WHO pain ladder: *not amended*
In the absence of RCT evidence, it was considered reasonable to initiate treatment with paracetamol. However, no response to paracetamol warrants progression to step 2 of the WHO pain ladder. Most chronic cancer pain is probably categorised as moderate to severe pain.
Recommendation: Paracetamol and NSAIDs were retained for initial management of chronic cancer pain. In addition, the following guidance was added in the STG, "Pain should be controlled as rapidly as possible. If pain is not adequately controlled within 2-3 days, proceed to the next step".
Rationale: Systematic review[9] showed that there is no evidence to show that paracetamol is useful in treating people with cancer pain, either alone or combined with a morphine-like drug. Nor is there evidence to disprove that it is useful. There are currently no good quality RCTs evaluating paracetamol for management of cancer pain. Authors of a Cochrane review[10] likewise concluded that "there is no high-quality evidence to support or refute the use of NSAIDs alone or in combination with opioids for the three steps of the three-step WHO cancer pain ladder. There is very low-quality evidence that some people with moderate or severe cancer pain can obtain substantial levels of benefit within one or two weeks".
Level of Evidence: II Systematic reviews of low quality studies.

Pain management: *amended*
Text of the STG was amended from:
"If pain is not adequately controlled within 2–3 days, proceed to the next step"
to
*"If pain is not adequately controlled within **1-2 days**, proceed to the next step".*
Level of Evidence: III Expert opinion

STEP 1

[7]Duehmke RM, Derry S, Wiffen PJ, Bell RF, Aldington D, Moore RA.Tramadol for neuropathic pain in adults. Cochrane Database Syst Rev. 2017 Jun 15;6:CD003726.
[8] Cooper TE, Chen J, Wiffen PJ, Derry S, Carr DB, Aldington D, Cole P, Moore RA. Morphine for chronic neuropathic pain in adults. Cochrane Database Syst Rev. 2017 May 22;5:CD011669.
[9] Wiffen PJ, Derry S, Moore RA, McNicol ED, Bell RF, Carr DB, McIntyre M, Wee B. Oral paracetamol (acetaminophen) for cancer pain. Cochrane Database Syst Rev. 2017 Jul 12;7:CD012637. https://www.ncbi.nlm.nih.gov/pubmed/28700092
[10] Derry S, Wiffen PJ, Moore RA, McNicol ED, Bell RF, Carr DB, McIntyre M, Wee B. Oral nonsteroidal anti-inflammatory drugs (NSAIDs) for cancer pain in adults. Cochrane Database Syst Rev. 2017 Jul 12;7:CD012638.

Paracetamol, oral: *retained*
NSAIDs, oral: *retained*
Cochrane review[11]*:* There is no evidence to show that paracetamol is useful in treating people with cancer pain, either alone or combined with a morphine-like drug. Nor is there evidence to disprove that it is useful.
Level of Evidence: II Systematic reviews of low quality studies.

Step 2
Tramadol, oral: *retained and caution added*
Following caution of concomitant administration of tramadol with antidepressants was included in the STG:

CAUTION
Use with caution when administered with antidepressants e.g. amitryptyline to avoid over sedation.

Cochrane review[12]*:*Authors concluded that evidence is limited and of low quality and indicated that *"around 19 out of 20 people with moderate or severe pain who are given opioids and can tolerate them should have that pain reduced to mild or no pain within 14 day".* However, this *"overstates to some extent the effectiveness found for the WHO pain ladder".* Adverse effects associated with opioids are common (constipation and nausea) that may lead to a change in treatment. Opioids are recommended for cancer pain and STG recommends pharmacological interventions for opioid-induced adverse drug reactions.
Level of Evidence: II Systematic reviews of low quality studies, Guidelines[13]

Step 3
Morphine controlled-release formulations, oral: *STG amended to provide for all strengths (i.e. 10,20 and 30 mg) and dosing amended from '12 hourly' to '8-12 hourly'*
At the NEMLC meeting of 1 February 2018[14], the NEMLC had recommended that other dosages of morphine controlled release formulation (i.e. 30 mg) be considered.
The text of the STG was amended to make provision for the 10, 20 and 30 mg slow release formulations.

If dosage is established and patient is able to swallow:
- Morphine, long-acting, oral, 8–12 hourly (Doctor prescribed).
  - Start with 10–20 mg/ dose.
  - Titrate the dose and dose frequency against the effect on pain.

Dosing was aligned with SAMF, 2016.
Level of Evidence: III Guidelines[15]

Oxycodone slow release, oral: *not added*
The NEMLC recommended that the PHC Committee review the evidence for oxycodone and develop a medicine review, accordingly.

Refer to the medicine review: Oxycodone for chronic cancer pain in adults, June 2018.

Oxycodone for chronic pain_PHC R

Recommendation: Based on this evidence review, the PHC Committee was of the opinion that it was reasonable to recommend oral slow release oxycodone formulations as an alternative only when there are supply constraints with oral slow release morphine formulations. However, for purposes of the PHC STGs and EML, slow release oxycodone should not be recommended due to concerns of addiction.
Rationale: Limited evidence suggests that oxycodone offers similar levels of pain relief and overall adverse events to morphine. However, it is not justified to include oxycodone in the PHC EML due to concerns of

[11]Wiffen PJ, Derry S, Moore RA, McNicol ED, Bell RF, Carr DB, McIntyre M, Wee B. Oral paracetamol (acetaminophen) for cancer pain. Cochrane Database Syst Rev. 2017 Jul 12;7:CD012637. https://www.ncbi.nlm.nih.gov/pubmed/28700092
[12]Wiffen PJ, Wee B, Derry S, Bell RF, Moore RA. Opioids for cancer pain - an overview of Cochrane reviews. Cochrane Database Syst Rev. 2017 Jul 6;7:CD012592. https://www.ncbi.nlm.nih.gov/pubmed/28683172
[13] SAMF, 2016.
[14] Minutes of the NEMLC meeting of the 22 February 2018 meeting.
[15] SAMF, 2016.

addiction associated with oxycodone and given that supply challenges with morphine has historically not been of a consistent and long-term nature.

Level of Evidence: I Systematic review and meta-anaysis[16], Expert opinion

NEMLC accepted the PHC Committee's recommendation at the NEMLC meeting of 5 July 2018.[17]

CHILDREN

WHO pain step ladder: *not amended*

Paracetamol, oral: *retained*

NSAIDs, oral: *retained*

Children with chronic cancer pain are managed at secondary level of care and down-referred with care plan. Furthermore, authors of recent Cochrane reviews concluded that there is no RCT evidence to support or refute use of NSAIDs[18] or opioids[19] for cancer-pain in children.

Level of Evidence: II Systematic reviews of low quality studies, Expert opinion

Tilidine, oral: *not added*

Access determined by down-referral processes and child's care plan that is managed and initiated at secondary level of care. There is a currently a sole supplier of tilidine 100mg/ml, 10 ml oral drops that is currently available on contract RT300-2017 at a unit price of R84.25.

*Cochrane review [20]:*No studies were identified that were eligible for inclusion in this review (very low quality evidence).

Level of Evidence: III Expert opinion

Adjuvant therapy: Adults

Amitryptiline, oral: *retained as adjuvant therapy*

Corticosteroid, oral: *not added as an adjuvant*

Gabapentin, oral: *not added as an adjuvant*

External comment was received to add the above-mentioned medicines as adjuvant therapy in step 1. However, amitriptyline is already recommended in the STG as adjuvant therapy and gabapentin is currently being reviewed by the Adult Hospital Level Expert Review Committee for secondary level of care.

Significant nausea and vomiting: Children

Metoclopramide, oral: *not added*

Metoclopramide, oral for children not to be recommended for general nausea and vomiting, as it has many side-effects in children, including extrapyramidal side-effects.

However, the text of the STG was updated to include the following:

Children For treatment of nausea and vomiting in the palliative care setting (end-of-life care), see Section: 22.1.3 Nausea and vomiting.

Level of Evidence: III Expert opinion

Breakthrough pain:

Morphine solution, oral*: directions for use amended*

Text of the STG was amended as follows for clarity purposes, from:

~~It is recommended that the full dose equivalent to a 4-hourly dose of morphine be administered for breakthrough pain, but it is important that the next dose of morphine be given at the prescribed time, and not be delayed because of the intervening dose.~~

[16] Schmidt-Hansen M, Bennett MI, Arnold S, Bromham N, Hilgart JS. Oxycodone for cancer-related pain. Cochrane Database Syst Rev. 2017 Aug 22;8:CD003870. https://www.ncbi.nlm.nih.gov/pubmed/28829910

[17] Minutes of the NEMLC meeting of 5 July 2018.

[18] Cooper TE, Heathcote LC, Anderson B, Grégoire MC, Ljungman G, Eccleston C. Non-steroidal anti-inflammatory drugs (NSAIDs) for cancer-related pain in children and adolescents. Cochrane Database Syst Rev. 2017 Jul 24;7:CD012563. https://www.ncbi.nlm.nih.gov/pubmed/28737843

[19] Wiffen PJ, Cooper TE, Anderson AK, Gray AL, Grégoire MC, Ljungman G, Zernikow B. Opioids for cancer-related pain in children and adolescents. Cochrane Database Syst Rev. 2017 Jul 19;7:CD012564. https://www.ncbi.nlm.nih.gov/pubmed/28722116

[20]Wiffen PJ, Cooper TE, Anderson AK, Gray AL, Grégoire MC, Ljungman G, Zernikow B. Opioids for cancer-related pain in children and adolescents. Cochrane Database Syst Rev. 2017 Jul 19;7:CD012564.

To:

It is recommended that an additional dose of morphine (up to the same dose as the regular 4-hourly dose) be administered for breakthrough pain. The next regular dose of morphine must still be given at the prescribed time, and not be delayed because of the additional dose.