CHAPTER 25
PAIN

25.1 PAIN, CHRONIC

R52.1/R52.2/R52.9

DESCRIPTION

An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage. The relationship between pain (a subjective experience) and tissue damage (which may be assessed directly by others) is moderated by socio-cultural context as well as the nervous system. Acute pain is defined as pain present for less than 4 weeks and usually occurs in response to tissue damage. Chronic pain is pain present for more than 3 months.

LoE:IVb[i]

The goals of pain management include pain reduction and improved function, sleep, and well-being. Family members play an important part in the patient's treatment and should be included where possible.

Measure care outcomes by evaluating pain severity, quality of life, and functionality, e.g. Pain, Enjoyment and General Activity (PEG) scale, https://health.gov/hcq/trainings/pathways/assets/pdfs/PEG_scale.pdf

25.1.1 ANALGESIA FOR CHRONIC NON-CANCER PAIN

Assessment of chronic non-cancer pain

A biopsychosocial assessment is necessary to inform effective pain management.

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

» Nociceptive pain, e.g. rheumatoid arthritis (see section 13.1), osteoarthritis (see section 13.3); 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 25.1.2); endometriosis (see section 5.4).
» Neuropathic pain (see section 25.1.4).
» Fibromyalgia and irritable bowel syndrome – See Primary Health Care (PHC) Standard Treatment Guidelines (STG) and Essential Medicines List (EML), section 2.12: 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 symptoms, and related disorders.

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

Ascertain the patient's beliefs about their pain and hopes of care. Common issues to address are:

» Patients' perception of pain and the idealised nature of reality, e.g. that life must be pain-free.
» That pain means exercise and physical activity must be avoided.
» Catastrophic thinking regarding the pain.
» A need to be unwell to be cared for by others.
» Fear of work and responsibility, for various reasons.
» Stigma, with denial of mental illness or interpersonal conflict.

Social stressors, trauma, interpersonal conflict or violence may predispose to and perpetuate chronic pain.

GENERAL AND SUPPORTIVE MEASURES

Patients with chronic pain should be treated with a biopsychosocial approach, ideally using a multidisciplinary team, according to findings of a comprehensive assessment. Note that those with greater subjective pain complaints may also be at higher risk of an opioid use disorder.

LoE:IIIb[ii]

» Validate the pain experienced and manage with empathy.
» Explore and manage exacerbating factors for pain. See section 25.1: Chronic pain.
» Educate regarding the 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, https://health.gov/hcq/trainings/pathways/assets/pdfs/PEG_scale.pdf
» Treat the 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 disorder, refer to SANCA/ rehabilitative services.
» Encourage physical activity; refer to Physiotherapy and Occupational Therapy (OT).
» Address self-esteem, motivation, daily function, and social skills; refer to OT.
» Address social stressors and interpersonal conflicts; refer to social worker, counselling services, psychologist, social welfare organisations, NGOs (e.g. FAMSA, https://www.famsawc.org.za; or POWA, https://www.powa.co.za, if domestic violence is reported).

LoE:IIIb[iii]

MEDICINE TREATMENT

Paracetamol, ibuprofen and tramadol may be used alone or in combination according to the severity of pain.

Mild/moderate pain:

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

- NSAID, e.g.: *LoE:IIb*[iv]
- Ibuprofen, oral, 400 mg 8 hourly with meals.
  - May be used in combination with paracetamol and/or opioids.

CAUTION - NSAIDs

» Avoid long-term use of NSAIDs (e.g. ibuprofen) as they are associated with increased risk of arterial thrombosis, renal impairment and GI bleeding.
» Concomitant use of more than one NSAID has no additional clinical benefit and only increases toxicity.
» All NSAIDs are associated with increased risks of gastrointestinal bleeding, renal dysfunction, and cardiovascular events (stroke and myocardial infarction).
» Use NSAIDs judiciously at the lowest effective dose and for the shortest duration.
» Do not use NSAIDs in pregnancy or while breastfeeding.

In high-risk patients: i.e. patients >65 years of age, or with a history of peptic ulcer disease, or on concomitant warfarin, aspirin or corticosteroids:

ADD *LoE:IIb*[v]

- PPI, e.g.:
- Lansoprazole, oral, 30 mg daily.

Moderate pain unresponsive to simple analgesia:

- Tramadol, oral, 50–100 mg, 6 hourly; may be increased to a maximum of 400 mg daily.
  - Warn patient of adverse effects and risk of addiction. Advise not to operate machinery/drive initially and after dosage increases.
  - Evaluate response to treatment using a pain rating scale at 2 weeks and every 4 weeks afterwards: **taper and stop tramadol if not reducing pain.** See PHC STG & EML, section 20.1: Pain control for rating scales.
  - In patients with uncontrolled pain, the dose can be increased to a maximum of 100 mg 6 hourly.
  - Improved effect when given with paracetamol. *LoE:IVb*[vi]

CAUTION – TRAMADOL

» Tramadol causes respiratory depression and may be fatal in overdose.
» Avoid concurrent prescribing of opioid pain medication, benzodiazepines or other respiratory depressants.
» After a period of no treatment, re-initiate at 50 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). The Opioid Risk Tool (ORT) is a brief, self-report screening tool used to assess risk for opioid abuse among adults prescribed opioids for treatment of chronic pain. https://nida.nih.gov/sites/default/files/opioidrisktool.pdf

LoE:IVb[vii]

» Tramadol inhibits reuptake of noradrenaline and serotonin – increases risk of seizures, of serotonin syndrome, and mania or hypomania. Use with caution in high-risk patient groups (e.g. epilepsy, severe head injury, if taking antidepressants, bipolar disorder). Educate the patient, optimise treatment of primary condition, avoid polypharmacy, and monitor closely.
» Other adverse effects include constipation, dry mouth, drowsiness, and confusion.

LoE:IVb[viii]

OR

- Morphine solution (Mist morphine), oral.
  - Starting dose: 5–10 mg (maximum 0.2 mg/kg) 4 hourly.
  - Elderly or frail patients: 2.5–5 mg oral (maximum 0.1 mg/kg) 4 hourly.
  - Increase total daily dose by 30% every 24 hours if pain control is inadequate.
  - Increase the dosing interval in patients with renal or liver impairment.

LoE:Ivb[ix]

When stable on morphine solution, the morphine solution can be changed to an equivalent dose of long-acting, slow-release morphine:

- Morphine, slow-release, oral, 12 hourly.
  - Available in tablets of 10 mg, 30 mg, and 60 mg.
  - Duration of action: 12 hours.
  - Dose according to previous morphine solution requirements, e.g. a patient whose pain is controlled by 6 doses of 10 mg morphine solution per 24 hours (i.e. 60 mg morphine per day) can be converted to receive slow-release morphine tablets, 30 mg 12 hourly, oral.
  - Maximum dose for non-cancer pain is usually 60 mg 12 hourly.

Note:

» When morphine is used for chronic non-cancer pain, discuss potential

side-effects with the patient, the maximum dose of opioids that will be prescribed, and anticipated duration of treatment. Address all fears and concerns with the patient to alleviate fear. Provide support and education for caregivers and family.

» Patients with breakthrough pain should be treated appropriately. See PHC STG & EML, Section 20.5: Breakthrough Pain.
» Avoid in patients with history of alcohol or other drug addiction, where possible.

25.1.2 ANALGESIA FOR CHRONIC CANCER PAIN

DESCRIPTION

The term “cancer pain” also includes pain due to “palliative care needs/ serious illness”.

GENERAL MEASURES

Follow the same steps as provided in section 25.1.1: Analgesia for chronic non-cancer pain, with the following exceptions:

Morphine:

» There is no maximum dose of morphine – Titrate as needed.
» Concerns regarding addiction/dependency should not compromise adequate pain control with opioids when used to treat “palliative care needs/serious illness”.
» For patients on slow-release morphine, it is advisable to still prescribe morphine solution for breakthrough pain or for painful procedures.
» Breakthrough pain is a transient exacerbation of pain which occurs either spontaneously or in relation to a specific trigger despite relatively stable and adequately controlled background pain. It may or may not be at the same location as the background/controlled pain.
» Treat breakthrough pain by giving an extra dose of immediate-release morphine equal to the regular 4-hour dose (i.e. one sixth of the total daily dose).
» The next regular dose of morphine must still be given at the prescribed time, and not be delayed because of the additional dose.

LoE:IVb[x]

The regular 4-hourly dosage should be titrated upward against the effect on pain in the following way:

» Add up the amount of “breakthrough morphine” needed in 24 hours.
» Divide this amount by 6 (the number of 4 hourly doses in 24 hours).
» The next day increase maintenance dose by that amount.

Example:

» Patient receives 10 mg morphine every four hours.

» The patient has 3 episodes of breakthrough pain over 24 hours and is given an additional 10 mg during each episode:
  – Total breakthrough pain dosage: 3 x 10 mg = 30 mg.
  – Dose to add to maintenance dose the following day: 30 mg ÷ 6 = 5 mg.
» The day following the breakthrough pain, the regular 4 hourly dose of 10 mg will be increased by 5 mg, i.e. 10 mg + 5 mg = 15 mg.
» The new morphine dose will be 15 mg 4 hourly.

Note:
» Opioid–induced hyperalgesia is defined as increasing pain sensitivity in patients chronically exposed to opioids without any new causes for pain. Increasing doses of morphine paradoxically result in increased pain, often with features of neuropathic pain such as hyperalgesia or allodynia (consult with a pain clinician/specialist).

Bisphosphonates may be considered for metastatic bone pain – refer to the Tertiary and Quaternary EML (specialist management/consultation).

25.1.3 TREATMENT OF ADVERSE EFFECTS OF CHRONIC OPIOID USE

Y45.0

MEDICINE TREATMENT

Constipation: (K59.0)
Patients on chronic opioids should routinely be prescribed a laxative.
- Sennosides A and B, oral, 13.5 mg, 1–2 tablets at night.
  - Contraindicated in patients with potentially obstructive lesions.

LoE:IVb[xi]

In patients with potentially obstructive lesions:
- Lactulose, oral, 10–20 mL 12–24 hourly.

LoE:IVb[xii]

Nausea and vomiting: (R11)
- Metoclopramide, oral/IM/slow IV, 10 mg 8 hourly (see section 12.6.5.2: treatment of PONV).

OR
- Promethazine, oral, 25 mg 8 hourly. *LoE:IVb*

OR
- Ondansetron, oral, 8 mg 12 hourly.

25.1.4 NEUROPATHIC PAIN

G62.9

DESCRIPTION

Pain caused by a lesion or disease of the somatosensory nervous system.

LoE:IVb[xiii]

Different patterns are noted, i.e. polyneuropathy, mononeuritis multiplex, and mononeuropathy, each of which may be caused by axonal degeneration or demyelination or a combination of the above. Clinical features may be predominantly of a sensory, sensorimotor, or motor nature.

Important causes of a predominantly sensory neuropathy include:
» alcohol;
» diabetes;
» HIV infection;
» Vitamin deficiency: thiamine, vitamin B12 (although the latter more commonly presents as subacute combined degeneration of the cord);
» medicines (e.g. isoniazid, stavudine, metronidazole, amiodarone, certain chemotherapeutic agents).

Important causes of a predominantly motor neuropathy include:
» Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP – also known as Guillain-Barrè syndrome),
» Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP),
» Acute porphyrias

GENERAL MEASURES

» If there is a history of rapid progression, particularly in patients with features suggestive of AIDP, (e.g. rapid progression with stabilisation within 4 weeks) admit the patient and monitor vital capacity carefully with spirometry, as intubation and ventilatory support may be required.
» Manage the cause where possible.
» Specialised nursing care and dedicated physiotherapy may be indicated. If not managed appropriately, chronic cases may develop contractures, weakness affecting gait, and chronic bedsores, and they may become wheel chair-bound. Encourage activity, with referral to OT and physiotherapy.
» Address psychosocial stressors and enhance perceived social support, and refer to social worker as required.
» Treat comorbid mental illness (see chapter 15: Mental health conditions).
» Assess outcome of treatment with objective measures of function, e.g. Pain, Enjoyment and General Activity (PEG) scale: https://health.gov/hcq/trainings/pathways/assets/pdfs/PEG_scale.pdf

MEDICINE TREATMENT

Most cases respond to management of the underlying disease process or removal of the aetiological agent.

In addition to the analgesics for chronic nociceptive pain (see section 25.1.1: Analgesia for chronic non-cancer pain), anti-neuropathic pain medicines to stabilise affected sensory nerves can be used.

- Amitriptyline, oral, 10 mg, two hours before usual sleep time.
  - Titrate up to 75 mg (to a maximum of 150 mg) at night if needed. *LoE:IIb*[xiv]
  - In the elderly: 10–25 mg daily, increasing gradually up to 50–100 mg daily, if required and tolerated. A single bedtime dose is optimal for most patients. *LoE:Ivb*[xv]
  - Use regularly as it takes 2–6 weeks for maximal effect. *LoE:IIIb*[xvi]

Post-herpetic neuralgia: (G53.0)
Initiate treatment with adjuvant amitriptyline therapy early. *LoE:IIIb*[xvii]

<u>If no response after 2-4 weeks to amitriptyline:</u>

ADD

- Carbamazepine, oral, 100mg 12 hourly for 2 weeks.
  - If response is inadequate, increase the dose every 2 weeks to a maximum dose of 600 mg 12 hourly.
  - Monitor for possible drug interactions in patients on ART. *LoE:Iib*[xviii]

<u>If amitriptyline is contraindicated:</u>

REPLACE WITH

- Carbamazepine, oral, 100mg 12 hourly for 2 weeks.
  - If response is inadequate, increase the dose every 2 weeks to a maximum dose of 600 mg 12 hourly.
  - Monitor for possible drug interactions in patients on ART. *LoE:Iib*[xix]

Note: Aciclovir is not beneficial in treating post-herpes zoster neuropathy.

Isoniazid–induced polyneuropathy: (G62.9 + Y41.1)

- Pyridoxine, oral 75 mg daily for 3 weeks.
  - Follow with 25–50 mg daily.

Trigeminal neuralgia (G50.0)
Sudden, usually unilateral, severe, brief, stabbing, recurrent episodes of pain in the distribution of one or more branches of the trigeminal nerve.

- Carbamazepine, oral 100 mg 12 hourly, initial dose.
  - Increase dose slowly. Doses of up to 1 200 mg daily may be required.
  - After exacerbation, reduce to maintenance dose of 400–800 mg daily. *LoE:Ivb*[xx]

REFERRAL

» Neuropathic pain unresponsive to these medicines, refer patient to an experienced pain clinician.

25.2 ANALGESIA FOR ACUTE NON-SURGICAL PAIN

25.2.1 MEDICAL CONDITIONS ASSOCIATED WITH SEVERE PAIN

R52.0/R52.1/R52.2/R52.9

DESCRIPTION

There are numerous medical conditions associated with severe acute or chronic pain e.g. myocardial infarction, renal colic, sickle-cell crisis and intra-articular haemorrhage due to haemophilia.

GENERAL MEASURES

» The analgesic treatment for these conditions is as for patients with acute post-operative pain (see section 12.4.2: Postoperative pain in the recovery room).

» Patients should be monitored for respiratory and cardiovascular depression when IV opioids are administered.
Patients already on opioids for chronic pain, who experience an acutely painful event, may be opioid tolerant and require higher IV opioid doses to control their pain.

25.2.2 ACUTE PAIN DUE TO GASTROINTESTINAL COLIC

R10.0-4

MEDICINE TREATMENT

- Hyoscine butylbromide, IV/oral, 10 mg 8 hourly.

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SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 25: PAIN
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2020-4)

The Adult Hospital Level (AHL) Pain chapter underwent detailed clinical editing and editorial changes for clarity. Previously the AHL Pain chapter appeared as chapter 26 in the AHL STGs. In the 2020-4 review cycle the chapter has been renumbered as chapter 25.

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

A: PROPOSED AMENDMENTS

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED/ NOT ADDED/ RETAINED
25.1 PAIN, CHRONIC	Definition: Pain	Editorial update providing a definition for acute and chronic pain
25.1.1 ANALGESIA FOR CHRONIC NON-CANCER PAIN	**Mild/moderate pain:** Paracetamol	Retained with amendment to dosage range and reiteration of maximum daily dose
	Moderate pain unresponsive to simple analgesia: Tramadol	Retained with amendment to dosage range
	Morphine solution (Mist morphine), oral	Amended
	Breakthrough pain	Added cross reference to PHC STG
25.1.2 ANALGESIA FOR CHRONIC CANCER PAIN	Breakthrough pain	Expanded breakthrough pain
		Guidance on fear alleviation and support for caregivers and family added
		Editorial amendment – "terminal illness" revised to "palliative care needs/serious illness"
25.1.3 TREATMENT OF ADVERSE EFFECTS OF CHRONIC OPIOID USE	**Constipation:** Lactulose, oral	Retained and aligned to Adult Hospital Level Chapter 24: Medicine Used in Palliative Care
25.1.4 NEUROPATHIC PAIN	Amitriptyline, oral	*Maximum dose[1] amended; initiation dose retained*
	Post-herpetic neuralgia: Carbamazepine	Retained with adjustment in dose range

For consistency with the primary health care Pain chapter, "morphine syrup" was revised to "morphine solution".

25.1 PAIN, CHRONIC

As per external comment received, the description of pain was updated and aligned to the current International Association for the Study of Pain (IASP) definition of pain. Pain is now described as an "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage"[2].

Level of Evidence: Guidelines: IVb

[1] Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for neuropathic pain in adults. Cochrane Database Syst Rev. 2015 Jul 6;7:CD008242. http://www.ncbi.nlm.nih.gov/pubmed/26146793

Amitriptyline: Charlesworth, S. (Ed.). (2020). Palliative Care Formulary (7th ed.). Pharmaceutical Press

[2] International Association for the Study of Pain. IASP Announces Revised Definition of Pain. 2020. https://www.iasp-pain.org/resources/terminology/

An external comment to expand the definition of pain to include the addition of all six key notes and the etymology of the word pain for further context was not accepted as the Committee considered the expanded detail (point 2 to 6) outlined below outside the scope of the STGs:

1. Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors.
2. Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons.
3. Through their life experiences, individuals learn the concept of pain.
4. A person's report of an experience as pain should be respected.
5. Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being.
6. Verbal description is only one of several behaviours to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain.

Point 1 is included in section 25.1.1 Analgesia For Chronic Non-Cancer Pain (see below).

A proposal to differentiate between acute and chronic pain was accepted.

The following editorial update was made to the STG:

An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage. ~~Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage.~~ The relationship between pain (a subjective experience) and tissue damage (which may be assessed directly by others) is moderated by socio-cultural context as well as the nervous system. Acute pain is defined as pain present for less than 4 weeks and usually occurs in response to tissue damage. **Chronic pain is pain present for more than 3 months.**

The goals of pain management include pain reduction and improved function, sleep, and well-being. Family members play an important part in the patient's treatment and should be included where possible.

Measure care outcomes by evaluating pain severity, quality of life, and functionality, e.g. Pain, Enjoyment and General Activity (PEG) scale, https://health.gov/hcq/trainings/pathways/assets/pdfs/PEG_scale.pdf

25.1.1 ANALGESIA FOR CHRONIC NON-CANCER PAIN

An external commentator queried the context of the definition of "biopsychosocial" in the assessment of pain to inform effective pain management and suggested that the statement be amended to include "biopsychosocial spiritual" assessment. This suggestion was not supported by the Committee as this STG is for non-cancer pain and not for palliative treatment. The committee retained the statement "*biopsychosocial assessment is necessary to inform effective pain management*" noting that as per the IASP[3] "pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors."

The Committee accepted an external comment to explore the patient's perceptions of pain as a way to ascertain the patient's beliefs about their pain.

An external comment to caution that "exercise means pain" was not included; as movement should always be encouraged in patients.

[3] International Association for the Study of Pain. IASP Announces Revised Definition of Pain. 2020. https://www.iasp-pain.org/resources/terminology/

The STG was updated as follows:

General and Supportive Measures

ASSESSMENT OF CHRONIC NON-CANCER PAIN
A biopsychosocial assessment is necessary to inform effective pain management.

Ascertain the aetiology and perpetuating factors and manage accordingly. Note that there may be overlap between different aetiologies, and condition-specific pain management may be required.
» Nociceptive pain, e.g. rheumatoid arthritis (see section 13.1); osteoarthritis (see section 13.3); 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 25.1.2); endometriosis (see section 5.4).
» Neuropathic pain (see section 25.1.4).
» Fibromyalgia and irritable bowel syndrome – See Primary Health Care (PHC) Standard Treatment Guidelines (STG) and Essential Medicines List (EML), section 2.12: 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 symptoms, and related disorders.
» Substance use disorders, including over the counter analgesics, opioids, benzodiazepines, and alcohol.

Ascertain the patient's beliefs about their pain and hopes of care. Common issues to address are:
» **Patients' perception of pain and the** idealised nature of reality, e.g. that life must be pain-free.
» That pain means exercise and physical activity must be avoided.
» Catastrophic thinking regarding the pain.
» A need to be unwell to be cared for by others.
» Fear of work and responsibility, for various reasons.
» Stigma, with denial of mental illness or interpersonal conflict.

Social stressors, trauma, interpersonal conflict or violence may predispose to and perpetuate chronic pain.

An external comment to replace the heading "General and Supportive Measures" with "Non-Pharmacological" was not accepted as "General and Supportive Measures" is standard wording used throughout the STGs.

An external comment to include "ideally using a multidisciplinary team" with supporting evidence[4] was accepted.

An external comment to add the word "disorder "after "substance use" was supported.

An external comment to specify yoga and Pilates as types of exercises was not accepted as physical activity covers all types of exercise.

The STG was updated as follows:

Patients with chronic pain should be treated with a biopsychosocial approach, ideally using a multidisciplinary team, according to findings of a comprehensive assessment. Note that those with greater subjective pain complaints may also be at higher risk of an opioid use disorder.

» Validate the pain experienced and manage with empathy.
» Explore and manage exacerbating factors for pain. See section 25.1: Chronic pain.
» Educate regarding the 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, https://health.gov/hcq/trainings/pathways/assets/pdfs/PEG_scale.pdf
» Treat the 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 **disorder**, refer to SANCA/ rehabilitative services.
» Encourage physical activity; refer to Physiotherapy and Occupational Therapy (OT).
» Address self-esteem, motivation, daily function, and social skills; refer to OT.
» Address social stressors and interpersonal conflicts; refer to social worker, counselling services, psychologist, social welfare organisations, NGOs (e.g. FAMSA, https://www.famsawc.org.za; or POWA, https://www.powa.co.za, if domestic violence is reported).

[4] Management of chronic pain: Scascighini L, Toma V, Dober-Spielmann S, Sprott H. Multidisciplinary treatment for chronic pain: a systematic review of interventions and outcomes. Rheumatology (Oxford). 2008 May;47(5):670-8. doi: 10.1093/rheumatology/ken021. Epub 2008 Mar 27. PMID: 18375406.

Medicine Treatment

Mild/moderate pain

Paracetamol, oral: *Amended (Dose range amended and maximum dose reiterated)*

The committee reviewed the interpretation of the dosage range for paracetamol as written in the STG (1 gram 4–6 hourly). By implication, if 1 gram is taken 4 hourly the total daily dose would equate to 6 grams which is higher than the maximum allowable daily dose (4 grams in 24 hours) which is stated in the STG. The Committee recommended for the paracetamol oral dose to be amended to include a lower starting dose of 500 mg and to retain the 4 hourly dosing in those with breakthrough pain as needed within the 24-hour dosing period. It was recommended for this dosage to be revised and applied to all applicable sections of the primary health care and adult STGs to ensure uniformity.

Level of Evidence: IVb - Clinical Practice Guidelines[5]

The word "and" was added to provide an option for the combination treatment of ibuprofen, paracetamol and opioids in the stepwise approach offered in the STG.

The STG was updated as follows:

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

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals.
  - May be used in combination with paracetamol **and/**or opioids.

In alignment with the PHC level of care and South African Medicines Formulary[6] "severe pain" was revised to "moderate pain unresponsive to simple analgesia" for the indication of tramadol.

Moderate pain unresponsive to simple analgesia

Tramadol, oral: *Amended* (*Dosage range added)*

An external comment was received to clarify the frequency of tramadol dosing if the maximum dose in the STG is recommended as 400 mg per day. Therefore, for adult's with moderate pain, a dosage range for tramadol is now provided to ensure dosing clarity and to accommodate for breakthrough pain in a 24-hour dosing period. Due to 100 mg now being recommended in a 50 to 100 mg dosing range the frequency of 4 to 6 hourly dosing was revised to 6 hourly[7] as a 100 mg dose given 4 hourly could potentially result in therapy going over the allowable maximum daily dose if the range is read without the maximum dose. It was recommended for the tramadol dosage to be revised and applied to all applicable sections of the primary health care and adult STGs to ensure uniformity.

The STG was updated as follows:

~~**Severe pain:**~~ **Moderate pain unresponsive to simple analgesia**

- Tramadol, oral, 50~~–~~**–100 mg, 6** hourly; may be increased to a maximum of 400 mg daily.
  - Warn patient of adverse effects and risk of addiction ~~potential~~. Advise not to operate machinery/drive initially and after dosage increases.
  - Evaluate response to treatment using a pain rating scale at 2 weeks~~,~~ and every ~~following~~ 4 weeks afterwards: **taper and stop tramadol if not reducing pain.** See PHC STG & EML, section 20.1: Pain control for rating scales.
  - 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.

[5] South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022.
[6] South African Medicines Formulary, 14th Edition. Division of Clinical Pharmacology. University of Cape Town, 2022
[7] Charlesworth, S. (Ed.). (2020). Palliative Care Formulary (7th ed.). Pharmaceutical Press

Level of Evidence: Guidelines: IVb

Under the caution box for tramadol, an external commentator raised that a dose of 25 mg is not practical, as most tramadol formulations in the public sector are only available as capsules. In line with the SAMF dosage guidance, confirming there are no safety concerns and tender availability, the re-initiation dose of tramadol 25mg was amended to 50mg.

The Committee supported an external comment received to include the Opioid Risk Tool (ORT) to assess risk for opioid abuse. A link (https://nida.nih.gov/sites/default/files/opioidrisktool.pdf) is provided to the tool.

The STG was updated as follows:

CAUTION – TRAMADOL

» Tramadol causes respiratory depression and may be fatal in overdose.
» Avoid concurrent prescribing of opioid pain medication, benzodiazepines or other respiratory depressants.
» After a period of no treatment, re-initiate at ~~**25**~~ **50** 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). **The Opioid Risk Tool (ORT) is a brief, self-report screening tool used to assess risk for opioid abuse among adults prescribed opioids for treatment of chronic pain. https://nida.nih.gov/sites/default/files/opioidrisktool.pdf**

» Tramadol ~~i~~nhibits reuptake of noradrenaline and serotonin – increases risk of seizures, of serotonin syndrome, and mania or hypomania. ~~Avoid~~ ~~u~~Use with caution in ~~at~~ high-risk patient groups (e.g. epilepsy, head injury, if taking antidepressants, bipolar disorder). Educate the patient, optimise treatment of primary condition, avoid polypharmacy and monitor closely.
» Other adverse effects include constipation, dry mouth, drowsiness, and confusion.

Morphine solution (Mist morphine), oral: *Amended*

The starting dose and dosing range of morphine solution (mist morphine) was conservatively reduced from 10–15 mg to 5–10 mg. Additionally, incremental dose increases by 30% as opposed to 50% were affected as per the palliative care formulary.[8]

Level of Evidence: IVb - Clinical Practice Guidelines

An external comment to add the word "total daily" in order to clarify the dosage for morphine solution to be used was accepted. The dose was confirmed as aligned to the recommended dose as per the PHC Pain Chapter 20 an SAMF guidance[9].

A recommendation to include guidance on fear alleviation and support for caregivers and family was accepted.

An external comment to consider urine drug testing before starting strong opioids and continue urine drug testing at least annually was not supported due to feasibility in the PHC setting.

The STG was updated as follows:

[8] Charlesworth, S. (Ed.). (2020). Palliative Care Formulary (7th ed.). Pharmaceutical Press

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

Morphine ~~syrup~~ solution (Mist morphine), oral.

- Starting dose: ~~**10–15 mg**~~ **5–10 mg** (maximum 0.2 mg/kg) 4 hourly.
- Elderly or frail patients: 2.5–5 mg oral (maximum 0.1 mg/kg) 4 hourly.
- Increase **total daily** dose by ~~**50%**~~ **30%** every 24 hours if pain control is inadequate.
- Increase the dosing interval in patients with renal or liver impairment.

When stable on morphine ~~syrup~~ solution, the morphine ~~syrup~~ solution can be changed to an equivalent dose of long- acting, slow-release morphine:

- Morphine, slow-release, ~~long acting,~~ oral, 12 hourly.
  - Available in tablets of 10 mg, 30 mg, and 60 mg.
  - Duration of action: 12 hours.
  - Dose according to previous morphine ~~syrup~~ solution requirements, e.g. a patient whose pain is controlled by 6 doses of 10 mg morphine ~~syrup~~ solution per 24 hours (i.e. 60 mg morphine per day) can be converted to receive slow-release morphine tablets, 30 mg 12 hourly, oral.
  - Maximum dose for non-cancer pain is usually 60 mg 12 hourly.

see PHC Pain Section 20.5:Breakthrough Pain

Note:

» When morphine is used for chronic non-cancer pain, discuss potential side-effects with the patient, the maximum dose of opioids that will be prescribed, and anticipated duration of treatment. **Address all fears and concerns with the patient to alleviate fear. Provide support and education for caregivers and family.**

» Patients with breakthrough pain should be treated appropriately. See PHC STG & EML, Section 20.5: Breakthrough Pain.

» Avoid in patients with history of alcohol or other drug addiction, where possible.

25.1.2 ANALGESIA FOR CHRONIC CANCER PAIN

A suggestion for amendment of the term “terminal illness” to “palliative care needs/serious illness” was accepted. Furthermore, the PHC expert review committee expanded the section on breakthrough pain; including a definition and dosing approach for immediate release morphine.[10]

An external comment to include “palliative pain therapy” as an umbrella term in the STG to encompass cancer pain and pain due to other conditions was not accepted. The Committee did not support this addition as cancer pain does not always require palliative treatment.

Regarding prescribed dosing times for morphine the STG stipulates that the next regular dose of morphine must still be given at the prescribed time. An external comment was received that this only applies to patients who are awake and not acceptable to wake patients in order to dose patients. The STG was not amended as pain control should be individualised according to patient needs.

Methadone is not recommended on the essential medicines list for analgesia. The Committee removed methadone from the note in the STG; with the possibility for a review in a future review cycle, if required, for this indication. Therefore, an external comment received for dose reduction or methadone (opioid rotation) to be considered best practice for opioid-induced hyperalgesia was not accepted.

A note to consult, if available, with a pain clinician/specialist was added to the end of the STG.

The STG was updated as follows:

DESCRIPTION

The term “cancer pain” also includes pain due to ~~terminal illness~~ **“palliative care needs/serious illness”**.

GENERAL MEASURES

Follow t~~T~~he same steps as ~~given~~ **provided** in section 25.1.1: Analgesia for chronic non-cancer pain, ~~should be followed~~ with the following exceptions:

- Morphine:

» There is no maximum dose of morphine ~~that may be needed –~~ Titrate as needed.

10 Charlesworth, S. (Ed.). (2020). Palliative Care Formulary (7th ed.). Pharmaceutical Press

» Concerns regarding addiction**/ dependency** should not compromise adequate pain control with opioids when used to treat ~~**terminal illnesses**~~ **"palliative care needs/serious illness".**
» For patients on slow-release morphine, it is advisable to still prescribe morphine ~~syrup~~ solution for breakthrough pain or for painful procedures.
» **Breakthrough pain is a transient exacerbation of pain which occurs either spontaneously or in relation to a specific trigger despite relatively stable and adequately controlled background pain. It may or may not be at the same location as the background/controlled pain.**
» **Treat breakthrough pain by giving an extra dose of immediate-release morphine equal to the regular 4-hour dose (i.e. one sixth of the total daily dose).**
» **The next regular dose of morphine must still be given at the prescribed time, and not be delayed because of the additional dose**

The regular 4-hourly dosage should be titrated upward against the effect on pain in the following way:
» Add up the amount of "breakthrough morphine" needed in 24 hours.
» Divide this amount by 6 (the number of 4 hourly doses in 24 hours).
» The next day increase maintenance dose by that amount.

Example:
» **Patient receives 10 mg morphine every four hours.**
» **The patient has 3 episodes of breakthrough pain over 24 hours and is given an additional 10 mg during each episode:**
  – **Total breakthrough pain dosage: 3 x 10 mg = 30 mg.**
  – **Dose to add to maintenance dose the following day: 30 mg ÷ 6 = 5 mg.**
» **The day following the breakthrough pain, the regular 4 hourly dose of 10 mg will be increased by 5 mg, i.e. 10 mg + 5 mg = 15 mg.**
» **The new morphine dose will be 15 mg 4 hourly.**

Note:
» Opioid–induced hyperalgesia is defined as increasing pain sensitivity in patients chronically exposed to opioids without any new causes for pain. Increasing doses of morphine paradoxically result in increased pain, often with features of neuropathic pain such as hyperalgesia or allodynia **(consult with a pain clinician/specialist)**
~~» It can be managed by switching to methadone, in consultation with a specialist familiar with the use of this agent.~~
Bisphosphonates may be considered for metastatic bone pain – refer to the Tertiary and Quaternary EML (specialist management/consultation).

25.1.3 TREATMENT OF ADVERSE EFFECTS OF CHRONIC OPIOID USE

Constipation:
Lactulose: *Retained and aligned to Adult Hospital Level Chapter 24: Medicine Used in Palliative Care*

For lactulose use for constipation; for consistency and uniformity in the STGs the Committee recommended alignment in dosing to the AH Ch 24: medicines for palliative care chapter, which includes 24 hourly dosing.

The STG historically recommended promethazine, oral, 10 mg 8 hourly for nausea and vomiting. Promethazine 25mg is available on tender. The Committee therefore supported a dose amendment to promethazine 25mg 8 hourly.

The STG was updated as follows:

Y45.0

MEDICINE TREATMENT
Constipation: **(K59.0)**
Patients on chronic opioids should routinely be prescribed a laxative.
- Sennosides A and B, oral, 13.5 mg, 1–2 tablets at night.
  - Contraindicated in patients with potentially obstructive lesions.

In patients with potentially obstructive lesions:
- Lactulose, oral, 10–20 mL 12**–24** hourly.

Nausea and vomiting: **(R11)**
- Metoclopramide, oral/IM/slow IV, 10 mg 8 hourly (see section 12.6.5.2 treatment of PONV).

» OR
» Promethazine, oral, ~~10~~ **25** mg 8 hourly.
» OR
Ondansetron, oral, 8 mg 12 hourly

25.1.4 NEUROPATHIC PAIN

Description

As per external comment received, the definition of neuropathic pain was updated in line with the IASP[11] definition.

Level of Evidence: Guidelines: IVb

The STG was updated as follows:

G62.9~~/G50.0~~

DESCRIPTION

~~Defective functioning of nerves, which may involve both peripheral nerves (peripheral neuropathy) and cranial nerves~~.
Pain caused by a lesion or disease of the somatosensory nervous system.

Different patterns are noted, i.e. polyneuropathy, mononeuritis multiplex, and mononeuropathy, each of which may be caused by axonal degeneration or demyelination or a combination of the above. Clinical features may be predominantly of a sensory, sensorimotor or, motor nature.
Important causes of a predominantly sensory neuropathy include:

» alcohol;
» diabetes;
» HIV infection;
» **Vitamin deficiency:** thiamine ~~deficiency~~, vitamin B12 ~~deficiency~~, (although the latter more commonly presents as subacute combined degeneration of the cord);
» medicines (e.g. isoniazid, stavudine, metronidazole, amiodarone) , certain chemotherapeutic agents).

Important causes of a predominantly motor neuropathy include:

» Acute Inflammatory Demyelinating Polyradiculoneuropathy (AIDP – also known as Guillain-Barrè syndrome),
» Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP),
» Acute porphyrias

For the "General Measures" headings an external comment received to consider revising the heading to "Pharmacological Treatment" was not accepted as general measures is standard wording used throughout all the STGs at all levels of care.

Medicine Treatment

Amitriptyline, oral: *Maximum dose[12] amended; initiation dose retained[13]*
Amitriptyline may be poorly tolerated due to anticholinergic side effects. A proposal to amend the maximum dose of amitriptyline in the treatment of neuropathic pain was accepted as per clinical practice guidelines[14] for management of neuropathic pain in a palliative care setting and the palliative care formulary[15] which suggested a dose of up to 150mg but mentions that high doses are seldom required. Following external comment, a comment to revise the starting dose of amitriptyline from 10mg to 5mg was not accepted. Evidence for starting amitriptyline at 5mg was considered as low certainty evidence. The 10mg dose was suggested as a minimum starting dose as per SAMF[16] guidance.

Level of Evidence: IIb Moderate – Systematic Review & IVb - Clinical Practice Guidelines

[11] International Association for the Study of Pain. 2020.https://www.iasp-pain.org/resources/terminology/

[12] Moore RA, Derry S, Aldington D, Cole P, Wiffen PJ. Amitriptyline for neuropathic pain in adults. Cochrane Database Syst Rev. 2015 Jul 6;7:CD008242. http://www.ncbi.nlm.nih.gov/pubmed/26146793

Amitriptyline: Charlesworth, S. (Ed.). (2020). Palliative Care Formulary (7th ed.). Pharmaceutical Press

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

[14] Chetty S, Baalbergen E, Bhigjee AI, Kamerman P, Ouma J, Raath R, Raff M, Salduker S; South African Expert Panel. Clinical practice guidelines for management of neuropathic pain: expert panel recommendations for South Africa. S Afr Med J. 2012 Mar 8;102(5):312-25. http://www.ncbi.nlm.nih.gov/pubmed/22554341

[15] Charlesworth, S. (Ed.). (2020). Palliative Care Formulary (7th ed.). Pharmaceutical Press.

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

Post-herpetic neuralgia

Carbamazepine: *Retained with adjustment in dose range*
An external comment for the dose of carbamazepine to be listed as three times daily for immediate release tablet and twice daily dosing for long-acting preparations was not accepted. The dosing schedule of twice daily was retained as aligned to the SAMF[17] listed dose. The Committee amended the starting dose from 100–200 mg to 100mg to ensure a definitive starting dose is provided and not a range.

For post-herpetic neuralgia, an editorial suggestion to clarify the STG wording for the addition or replacement of amitriptyline with carbamazepine was accepted. The STG was revised to clearly indicate that carbamazepine should be added when amitriptyline is ineffective and separate guidance provided for carbamazepine to replace amitriptyline when amitriptyline is contraindicated.

The STG was updated as follows:

MEDICINE TREATMENT
Most cases respond to management of the underlying disease process or removal of the aetiological agent.
In addition to the analgesics for chronic nociceptive pain (see section 12.13.1 Analgesia for chronic non-cancer pain), anti-neuropathic pain medicines to stabilise affected sensory nerves can be used.

- Amitriptyline, oral, 10 mg, two hours before usual sleep time.
  - Titrate up to 75 mg (to a maximum of ~~**200**~~ **150 mg**) at night if needed.
  - In the elderly: 10–25 mg daily, increasing gradually up to 50–100 mg daily, if required and tolerated. A single bedtime dose is optimal for most patients.
  - Use regularly~~,~~ as takes 2–6 weeks for maximal effect.

Post-herpetic neuralgia: (G53.0)
Initiate treatment with adjuvant amitriptyline therapy early.
If no response after 2-4 weeks to amitriptyline:
ADD
- Carbamazepine, oral, **100mg** ~~200mg~~ 12 hourly for 2 weeks.
  - If response is inadequate, increase the dose every 2 weeks to a maximum dose of 600 mg 12 hourly.
  - Monitor for possible drug interactions in patients on ART.

If amitriptyline is contraindicated:
REPLACE WITH
- Carbamazepine, oral, 100mg 12 hourly for 2 weeks.
  - If response is inadequate, increase the dose every 2 weeks to a maximum dose of 600 mg 12 hourly.
  - Monitor for possible drug interactions in patients on ART.

Note: Aciclovir is not beneficial in treating post-herpes zoster neuropathy.

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