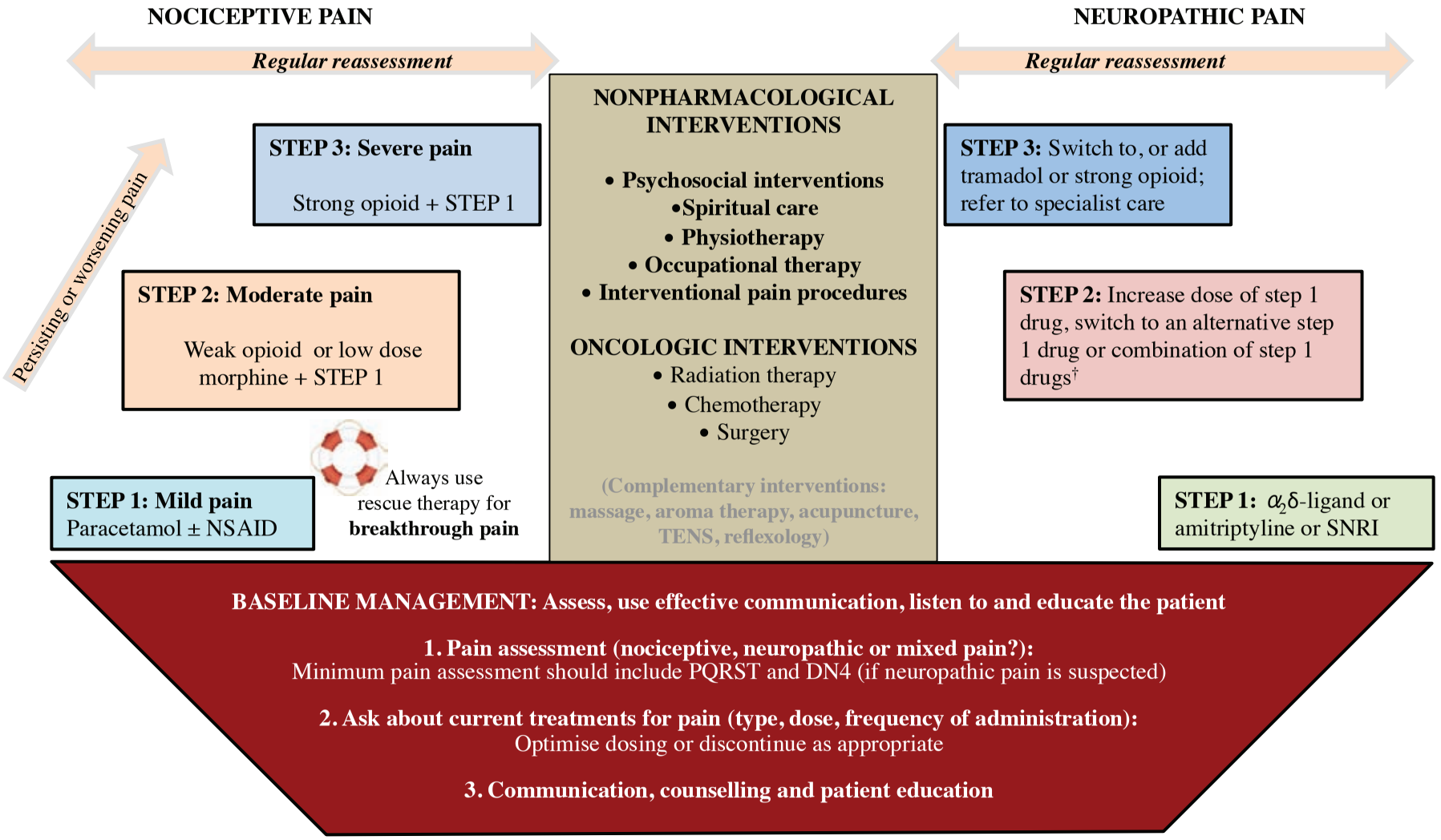
Guide to the Treatment of Cancer Pain in South Africa

2015

South African
Cancer Pain Working Group

Stepwise Healthcare Interventions for Pain (SHIP)



The Stepwise Healthcare Interventions for Pain (SHIP) model for pain management, including an analgesic ladder for nociceptive pain (left) and a stepwise pharmacotherapeutic approach to neuropathic pain (right). Mixed pain may require a combination of treatments from both sides of the diagram. Communication, counselling and patient education should be initiated at the first consultation and continued throughout the duration of management. Other psychosocial interventions (social interaction, spiritual counselling, recreational activities, relaxation therapy, imagery), nonpharmacological approaches to pain management and specific interventions for the cancer should be initiated at any step when they are indicated or where they will improve the patient's quality of life. See text for details.

†Rational combinations for neuropathic pain are amitriptyline + $\alpha_2\delta$-ligands, or SNRI + $\alpha_2\delta$-ligands . NSAID: nonsteroidal anti-inflammatory drug; $\alpha_2\delta$-ligand : gabapentin or pregabalin; SNRI: serotonin noradrenalin reuptake inhibitor (duloxetine or venlafaxine); TENS: transcutaneous electrical nerve stimulation.

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FOREWORD

There is far too much unnecessary suffering experienced by cancer patients at every stage of their condition, from the moment of diagnosis to either cure or death. There is ample evidence for this, and yet, despite the means now available to control pain and suffering, these means are not always adequately employed by the oncologists, medical or surgical specialists, or general practitioners involved in the management cancer patients.

Why is it that in 2015 the suffering of cancer patients is still so prevalent in hospitals, in institutions and in their homes? Why are all doctors and nurses not adequately trained in the scientific methods of relieving pain and symptoms, the art of communicating with their patients and the importance, scientifically as well as good doctoring, of dealing with their emotions?

The answer to these questions lies in the history of Palliative Medicine. Only 60 to 70 years ago doctors had little ability to cure disease. No sophisticated diagnostic aids, no antibiotics and very little in the way of curative measures.

They practised the *"Art of Medicine"*. Their main function was to alleviate symptoms as best they could and to give comfort to the patient and the family. There was often less suffering among dying patients as laudanum was available in those days, the administering of which was all that could be done.

Then in the 1960s came the explosion in the science and technology of medicine; the ability to cure beyond all previous expectations and the heady experience of actually being able to artificially prolong life. But, what is often not realised is that this often means prolonging suffering or even causing it.

The excitement of these dramatic advances in medicine gave birth to a new era, with its own problems. The thrust of teaching, especially in the Western world, shifted towards a disease-focused approach in which the patient as an individual is largely forgotten. Medical schools started to produce scientists, at the expense of teaching patient-centered "good medicine".

In 1998 I founded The Palliative Medicine Institute to teach doctors and nurses an Expanded Approach to Palliative Care, meaning that *"the skills and ethos of palliative care should be available for any patient, with any illness or condition, at any stage, from the moment of first contact with the patient for the duration of the illness or condition"* and not only for those with life-threatening or terminal illnesses.

Then, in 2000 at the request of the then Professor of Medicine, we started the Hospital Palliative Care Team. This has been operating in the CMJAH for 14 years, receiving referrals, not only from the Oncology and HIV/AIDS wards, but from diverse disciplines. In addition to teaching and ensuring the implementation of appropriate pain management protocols, the Team is of indispensable value to overworked and understaffed medical staff, who rarely have sufficient time

to listen and communicate adequately with the patients. The documented results and benefits are undisputable. Not only do the patients benefit in hospital, but they frequently are discharged earlier consequent to relief from their physical and emotional suffering. Shorter hospital stays are cost beneficial, so the hospital administration benefits too.

This guide is an important tool, which can assist any medical practitioner, not only those treating patients with cancer, to manage patients optimally. The message it holds is that this is not difficult to achieve if all doctors and nurses learned the skills and ethos taught in palliative medicine.

This is a guide for doctors who might say to patients, "I'm so sorry, but there is nothing more that I can do." It demonstrates that there is always something that one can do. It is a guide for doctors who do not know that they do not know the comprehensive approach that is necessary for optimum patient care, and have never been taught the important skills and ethos of relief of suffering – not only to the cancer patient, but to every patient.

The management of chronic pain is not a "one-person job". It is far too complex, with too many disciplines that may need to be involved to be managed by only one physician, surgeon or oncologist. Bringing the nurse dealing with the patient into the management team is not practised often enough. She/he should be asked to report on the needs of the patient, whether the pain and/or symptom relief is adequate, and any psychosocial or emotional problems that need referral. When the nurses are given that task, it relieves the doctors and makes the nurses feel that their work is important.

So it is clear that there is no "one size fits all". Care must be individualised and comprehensive, and that demands a team approach. The ideal composition of the appropriate team is well described in the guide.

In conclusion, I would like to say that I feel honored to have been asked to write the foreword to this important document. This excellent guide to cancer pain and suffering is long overdue. It gives me, personally, great hope that at last, after 25 years, the struggle I have experienced to integrate the ethos and principles of palliative care into the main stream of medicine – in other words, patient-centered medicine – is being taken up by younger dedicated and knowledgeable professionals. I believe that if properly used, this guide will make an enormous difference not only to the patient experience, but also to the doctors and nurses involved in patient management.

I encourage readers to approach what follows with an open and curious mind. The words that I have found most important in my long career are these: "I don't know, but I will do my best to find out".

Professor Selma Browde;
MBBCh, MMed RadT

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Section A: General principles and management of cancer pain in adults

1. Introduction

More than half of all cancer patients will experience pain, which may be associated with both the disease and its treatment. Generally, pain is moderate to severe and will significantly impact on emotional wellbeing, disability and quality of life. In long-term cancer survivors, it can become persistent and chronic.[1]

The prevalence of cancer pain increases with disease progression. More than three quarters of patients with advanced disease suffer from pain.[2] A recent study in Uganda and South Africa indicated that pain was the most prevalent presenting symptom among cancer patients referred for palliative care, occurring in almost all.[3]

Palliative care, including effective management of cancer pain, is recognised under international law as a human right. Pain management can and should be delivered from the time of diagnosis. It is inexpensive, safe and effective and can be delivered in a variety of settings including hospitals, outpatient clinics, residential hospices, nursing homes, community health centers and at home.[4,5] However, cancer pain is frequently inadequately treated. In South Africa palliative care has been a low priority among health care educators, policy makers and health administrators. Healthcare providers often feel insufficiently prepared to assess and manage cancer pain.[1,6-8]

Guidelines are necessary to guide a comprehensive multidisciplinary approach to the management of cancer pain and appropriate, effective and safe use of medication and other treatment modalities. Although it is not always fully achievable, the aim is ultimately to allow patients to be pain free.

Therefore the purpose of this guide is to assist members of all healthcare professions in South Africa to optimise patient care within the limitations of their resources, aiming to reduce suffering while maintaining quality of life and dignity.

2. Methods

2.1 Background and process

In December 2012, expert specialists in pain management and palliative care were approached by PAINSA to participate in a working group. This working group convened in March 2013 to review current international guidelines and to adapt them for South Africa. Once a working document had been completed, it was reviewed by members of the working group and other selected pain specialists.

2.2 Adaptation of current pain management guidelines

Current guidelines were identified through internet-based health sciences literature databases and Oncological and Palliative Care Societies in South Africa. Because of their ease of use and practical nature, four guidelines for the management of pain in adults and one for children were chosen as the foundation of this document. They are from the Scottish Intercollegiate Guidelines Network (SIGN)[9]; European Society for Medical Oncology (ESMO)[10]; European Association for Palliative Care (EAPC)[11], National Institute for Health and Clinical Excellence (NICE)[12], and World Health Organisation (WHO)[13]. Additional guidelines and references were consulted where necessary and appropriate. Management approaches from these guidelines were then endorsed or adapted for use in South Africa. Where necessary, readers are referred back to these original publications for key evidence supporting recommendations.

2.3 Objective

The objective of this document is to provide a reference guide to the management of pain for all healthcare providers caring for patients with cancer.

The scope and practice of medicine is always changing and new medicines and treatment modalities are constantly being introduced. As such, we have attempted to document current practice at the time of publication and it is anticipated that this guide will be updated in the future. The document is a guide only and is not intended to constitute inflexible treatment recommendations or to represent the standard of care. The recommendations here may not apply to all patients or all clinical situations, and shared decision making among a multidisciplinary treatment team is encouraged.

2.4 Target users

The guide will be useful to nurses, general practitioners, family physicians and specialists whose work will require them to assess and manage pain in patients with cancer. It will also be of interest to allied health workers, social workers, psychologists and other caregivers of people living with cancer.

3. Definitions of pain

The International Association for the Study of Pain (IASP) defines pain as *"an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"*.[14]

Another proposed definition of pain is *"Pain is what the experiencing person says it is, existing whenever (s)he says it does."*[9,15]

The IASP definition attempts to define pain in clinical terms while acknowledging an emotional component of the experience. The second definition tends to focus on the subjective nature of the pain experience. The concept of 'total pain' first introduced by Dame Cicely Saunders in the 1960s is used to define the interrelationship between the social, emotional, physiological, cultural and spiritual aspects of pain (Figure 1).[15]

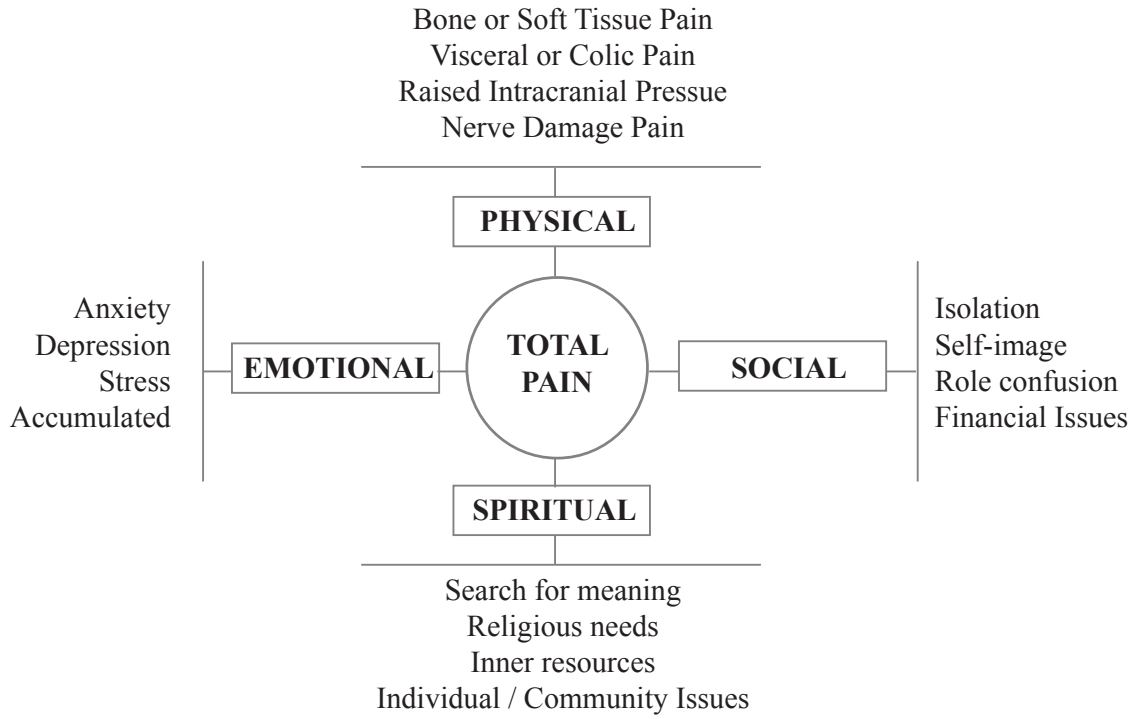


Figure 1. Total Pain: The complex and interrelated dimensions of pain.
Reproduced with permission from Teno JM, et al. Center for Gerontology and Health Care Research, Brown University, USA; 2001.[15]

Pain is feared. In patients with advanced, progressive illness it has physiological and psychological consequences that affect both them and their loved ones. It is isolating, emotionally draining and impacts adversely on social relationships, daily functions, sleep and self-worth. Thus the perception of physical pain is affected by the patient's emotional and psychological well-being, social circumstances and cultural and spiritual beliefs. It is impossible to directly measure pain and individual suffering may be difficult to fully appreciate or understand.

Effective management of pain therefore requires skills in communication and an adequate understanding of assessment and treatment.

Furthermore, there are patients, such as the young, disabled, obtunded and demented who may not be able to describe their individual experience.

There is a wide spectrum of different types of pain that may occur in patients with cancer. Common terms used to describe pain and painful syndromes are listed in Table 3.1.

Table 3.1. Definitions of pain[14, 16-19]	
Acute pain	Sudden, recent onset pain, usually sharp in quality. Serves as a warning of disease or a threat to the body.
Breakthrough pain	Transient exacerbation of pain of moderate or severe intensity arising on a background of controlled pain.
Central pain	Neuropathic pain arising from a lesion in the central nervous system (brain or spinal cord).
Chronic pain	Pain that persists beyond an expected time frame for tissue healing. Chronic pain results from a chronic pathologic process and from poorly treated acute pain. Pain signals remain active in the nervous system for weeks, months or years.
Complex regional pain syndrome (CRPS)	A syndrome of spontaneous burning pain, allodynia and hyperpathia after an injury, often combined with vasomotor and sudomotor dysfunction and later trophic changes. CRPS type I (reflex sympathetic dystrophy) typically follows minor injuries or fracture of a limb. CRPS type II (causalgia) develops after injury to a major peripheral nerve.
End of dose pain	Pain occurring when the blood level of the medicine falls below the minimal effective analgesic level near the end of the dosing interval. End of dose pain indicates that the next analgesic dose is due and should not be confused with breakthrough pain.
Incident pain	Pain that occurs in relationship to a particular posture or motor activity (e.g., standing, sitting up, coughing, sneezing, straining). It may be chronic, but, because it is intermittent, it is better managed with local measures where possible.
Neuropathic pain	Pain caused by a lesion (abnormality or trauma) or disease (e.g., stroke, diabetes, vasculitis) of the somatosensory nervous system. It may involve the central or peripheral nervous system. Central and peripheral sensitisation and ectopic transmission and spontaneous discharge at the level of peripheral nerves means that pain may persist beyond the tumour or disease process.
Nociceptive pain	Pain that is transmitted by an undamaged nervous system consequent to actual or threatened damage to non-neural tissue.
Procedural pain	Pain related to a procedure or intervention. This is especially important in children with chronic illnesses and is an important cause of anxiety that can be prevented.
Definitions of responses to medication	
Addiction	Compulsive drug use associated with drug-seeking behaviour (multiple sources, legal and illegal), noncompliance with suggested changes to drug use, craving and abrupt withdrawal reactions.
Dependence	Physiological adaptations occurring as a consequence of drug administration. Physical dependence is associated with withdrawal syndrome when the dose is reduced.
Pseudoaddiction	Drug seeking behaviours such as drug hoarding, requests for additional prescriptions or increased doses, occurring in patients with inadequate treatment. These behaviours may be mistaken as signs of addiction, but occur in an attempt to obtain better pain relief and cease when pain is controlled.
Tolerance	Reduced analgesic effect for an equivalent dose, or requirement of an increased dose to achieve the same effect.

4. Communication

Clear communication, both between provider and patient and among healthcare professionals, is a vital component of good patient care. It builds trust and confidence, helps to dispel fears and concerns, establishes realistic and achievable expectations, avoids misunderstandings, facilitates adherence to therapy, helps to ensure timeous delivery of necessary healthcare interventions and optimises co-operation between providers of healthcare, patients and their families.

Good communication between physician and patient requires the establishment of rapport and time should be set aside for this. Listening is as important as talking and patients' beliefs, fears and concerns need to be heard, understood and addressed. Where language differences present a barrier, a competent translator, preferably one who is a healthcare worker sharing the same first language, should be employed. It should be borne in mind that communication using a shared second language or even different dialects of the same language, and between individuals from different cultural backgrounds, may not be clear. In the same way, the sensitivity of pain rating scales may be influenced by cultural and language differences.[20]

It is important to invite the patient to tell their own story in their own words. The clinician then summarises what is heard and asks the patient to correct any misunderstandings. This helps to improve the rapport between patient and physician and ensure correct assessment and clinical decisions. Wherever possible, explanations should be delivered in the patient's home language and should be free of jargon. To confirm that the explanation has been clear, patients should be asked to repeat what they have understood and misunderstandings need to be corrected.

Although the degree to which patients, caregivers or their proxies want to be involved in decision-making with their practitioner is variable, patient participation is vital to get the most out of treatment. A 'partnership' or 'concordant' approach with open and clear discussion between patients and their doctor leads to decisions that respect the beliefs and wishes of the patient in determining whether, when and how treatment is administered. In this way, it is more likely that agreement on treatment strategies that are acceptable to the patient/proxy will be reached, with the aim of improving patient adherence.

Five prerequisites have been proposed for a concordant consultation:[21]

1. A willingness to share power and a commitment to giving appropriate weight to the patient's values and goals.
2. Open discussion of the options with explicit enquiry as to patients' views without making assumptions.
3. Adequate sharing of information, including uncertainties, to arrive at a decision.

4. Listening as much as talking.
5. Time.

Table 4.1 lists some practical considerations for open discussion with patients and their families.

Table 4.1. How to have open discussions about treatment options[21]

- Explain the disease, treatment options and benefits, side effects and risks associated with treatment.
- Determine the patient's views and concerns and expectations from treatment. Proactively ask and listen to the patient. Acknowledge and summarise to ensure that their position has been correctly understood.
- Involve the patient (and, where appropriate, relevant family members) in treatment decisions as far as they want to be involved.
- Offer your opinion and check any assumptions that you are making.
- Invite response from the patient.
- Be open to disagreement and check that you understand the basis for that.
  Clarify misunderstandings where they exist.
- Try to achieve a shared decision and confirm that you have understood the patient's decision correctly. Allow time for the patient to consider their options before making a decision and schedule a future appointment to discuss this if necessary.
- Arrange follow-up and support as appropriate.
- Anticipate non-adherence rather than adherence and ask about it at every follow-up visit in a non-judgmental way.
- Ask the patient for their thoughts on what might help them to be compliant with treatment and hospital appointments.

Communication between healthcare professionals at all levels is also crucial. Because much of patient care may occur at home, the primary care practitioner and community nursing staff must be included.

5. Assessment of pain

5.1 Causes of pain and barriers to pain relief

In addition to the disease itself, there are multiple additional causes of pain in patients with cancer (Table 5.1). Pain tolerance may be reduced by various emotional or situational factors, including discomfort, insomnia, fatigue, anxiety, fear, anger, boredom, sadness, depression, social abandonment and mental isolation.[9]

Each of these will need to be considered when assessing and managing pain.

Table 5.1. Causes of pain in cancer patients[10,22]

Pain associated with the cancer itself	Acute pain associated with patient handling, diagnostic or prognostic procedures	Iatrogenic pain	Pain related to comorbidity	Pain in cancer survivors
• Extension into soft tissues • Visceral involvement • Bone involvement • Nerve compression • Nerve injury • Raised intracranial pressure	• Blood sampling • Injections • Insertion and position of central line • Arterial line • Wound care • Moving the patient • Tissue biopsy • Lumbar puncture ± headache • Endoscopy ± visceral dilatation • Bone marrow aspiration/biopsy • Management of skin ulcers • Myelography and lumbar puncture • Thoracocentesis • Pleurodesis • Tumour embolization • Suprapubic catheterization	• Surgery • Chemotherapy • Hormonal therapy • Radiation therapy • Targeted therapy for osteonecrosis of the jaw • Steroids can cause pain due to skin lesions, peripheral neuropathy, mucositis, aseptic necrosis of the femoral head, infection • Cryosurgery • Radiothermoablation-high intensity focused ultrasound • Transarterial chemoembolization • Nephrostomy insertion	• Cardiovascular • Pulmonary • Diabetic neuropathy • Vasomotor headache • Fibromyalgia • Postherpetic neuralgia • Acute thrombosis pain *Comorbidity-related pain may be worsened by anticancer treatments and /or worsen cancer-related pain*	• Follow up procedures • Persisting postsurgical pain • Persisting anticancer drug-related pain • Persisting radiation therapy-related pain • Postherpetic neuralgia

5.2 Evaluation of pain

A thorough evaluation of pain requires attention to all of the aspects of 'total pain', including physical, psychological, social and spiritual components.[10,16,17,22,23] This is best achieved by a multidisciplinary team approach and should include the following steps:

1. Acknowledge and understand the patient's report of pain.
2. Initiate discussions about the pain.
3. Evaluate the aetiology, nature and severity of the pain.

4. Evaluate psychosocial factors.
5. Evaluate spiritual factors.
6. Determine the occurrence and severity of breakthrough pain.
7. Ongoing assessment and reassessment of pain.
8. Be aware of patient groups who may be at risk of underassessment of pain.
9. Consider a pain diary to monitor pain levels, medication requirements, analgesic efficacy and side effects of medication.

Each pain assessment and subsequent re-assessments must be adequately documented to ensure ongoing quality of care by all members of the team.

5.2.1 Acknowledge and understand the patient's report of pain

The perception of pain is subjective and influenced by many aspects that may lower or raise pain tolerance. Cancer pain is complex and new pains may arise or previously controlled pain may escalate. Breakthrough pain may occur even in a patient with seemingly well controlled pain. It is important to listen to the patient's account of their pain and understand the influence it is having on their quality of life.

5.2.2 Initiate discussions about the pain

Clinicians should proactively ask about pain. Some patients may be reluctant to spontaneously report pain. They may believe it to be part of having a cancer diagnosis. Fears of treatment and hospitalisation, or personal or cultural beliefs (e.g., 'admitting pain is a weakness'; 'I don't want to be a burden') may prevent them from expressing their pain. Speaking to caregivers, looking for signs of discomfort (vocalizations, facial expression, changes in physiological responses such as blood pressure) and gauging responses to analgesic medications are important means by which to determine the presence of pain. However, remember that adaptation can occur, especially with chronic pain, and the absence of physiological and even behavioural signs may not mean absence of pain.

Fears and expectations of pain treatment should be discussed with both family members/carers and the patient. Misconceptions regarding pain treatment, such as fears of addiction or reaching a ceiling dose, or the belief that prescription of an opioid means the end of life must be addressed if treatment and compliance are to be optimised.

5.2.3 Evaluate the aetiology, nature, severity of the pain and impact on functional activities

A history and examination should be performed with relevant special investigations to determine the likely cause of pain and its functional and psychosocial impact.

PQRST is a simple mnemonic that can be adapted to an individual patient to form a basis for history taking (Table 5.2). Typical descriptions of pain quality are summarised

in Table 5.3. Most patients with advanced cancer have more than one type of cancer-related pain arising from different aetiologies.

If neuropathic pain is suspected, the DN4 questionnaire is a brief and easily applied validated tool used to support the diagnosis. A score of 4 or higher suggests the presence of neuropathic pain (Figure 2).[24]

Table 5.2. PQRST mnemonic for assessment of pain

P	**Provoking/Relieving**	What brings the pain on; what makes it better; what makes it worse? What medications are you using at the moment? How often are you taking them? Do they help? Do they cause any side effects? Have you taken anything else in the past for this pain? What was the effect of that?
Q	**Quality**	Describe the pain. What does it feel like (e.g., stabbing, burning, sharp, aching)?
R	**Region and radiation**	Where is the pain? Does it spread anywhere else?
S	**Severity**	How severe is the pain? Now? At its worst? At its least? Most of the time? How does the pain affect your daily activities?
T	**Time**	When did the pain start? Is it constant or intermittent? How often does it occur? How long does it last?

Table 5.3. Typical qualitative descriptions of pain[10,25,16]

	Nociceptive pain	**Neuropathic pain**	**CRPS**	**Psychogenic pain**
Description	• Superficial arising from skin, subcutaneous structures or mucous membranes: sharp, well localised. • Deep arising from muscles, tendons, joints: diffuse and dull. • Visceral pain (organs): dull, poorly localised; aching, cramping, gnawing, sharp (may be associated with autonomic responses; e.g., sweating, nausea).	• Hot/burning, prickling, tingling, pins and needles, electric shocks, shooting.	• Burning with hyperaesthesia. • Localised vasomotor instability (erythema, pallor, oedema). • Trophic changes.	• Physical pain that is caused, increased, or prolonged by mental, emotional, or behavioral factors. Organic causes must be excluded. • Examples include headache, muscle spasms, back pain, abdominal pain.
Response to treatment	Opioids and non-opioid analgesics.	Responds to α2δ-ligands, SNRI or TCA. Unlikely to respond to NSAIDs or paracetamol; less responsive to opioids.	Responds to regional sympathetic block. Less responsive to opioid and non-opioid analgesics.	May respond to psychotherapy, antidepressants or non-narcotic analgesics.

CRPS: Complex regional pain syndrome; SNRI: serotonin noradrenaline re-uptake inhibitor; TCA: tricyclic antidepressant

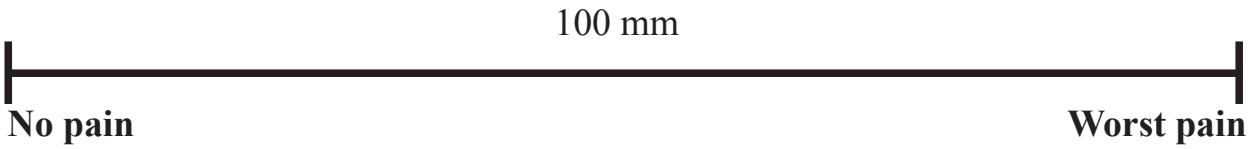
There are various tools to document pain severity and which can be compared from one visit to the next to monitor efficacy and continued response to treatment. The most commonly used tools in adults are the visual analogue scale (VAS), numeric rating scale (NRS) and verbal rating scale (VRS) (Figure 3). The Brief Pain Inventory (Figure 4) more thoroughly documents pain location and radiation, severity, the effect of treatment and the impact of pain on daily function, mood and relationships. Assessment of pain in children requires specialised tools described in Section B. A comprehensive checklist for pain assessment is listed in Figure 5.

DN4 Questionnaire YES = 1 point NO = 0 points	
Patient interview	
1.	Does the pain have any of the following characteristics? ❑ Burning ❑ Painful sensation of cold ❑ Electric shocks
2.	Is the pain associated with any of the following symptoms in the same area? ❑ Tingling ❑ Pins and needles ❑ Numbness ❑ Itching
Patient examination	
3.	Is the pain located in an area where the physical examination may reveal one or more of the following characteristics? ❑ Hypoaesthesia to touch ❑ Hypoaesthesia to prick
4.	In the painful area, can the pain be caused or increased by: ❑ Brushing
Patient's score:	(Score ≥4 suggests neuropathic pain)

Figure 2. DN4 (Douleur Neuropathique en 4 questions) Questionnaire to confirm neuropathic pain. If the patient's score is ≥4, the test is positive (sensitivity 82.9%; specificity 89.9%).

This questionnaire has been reproduced with permission of the International Association for the Study of Pain® (IASP).[24] The questionnaire may not be reproduced for any other purpose without permission.

Visual analogue scale (VAS)



Verbal rating scale (VRS)

•	No pain	1
•	Very mild pain	2
•	Mild pain	3
•	Moderate pain	4
•	Severe pain	5
•	Very severe pain	6

Numeric rating scale (NRS)

No pain	0
Mild pain	1-3
Moderate pain	4-6
Severe pain	7-10

0 1 2 3 4 5 6 7 8 9 10

No pain **Worst pain**

Figure 3. Validated pain rating scales.

Brief Pain Inventory

Name: _____

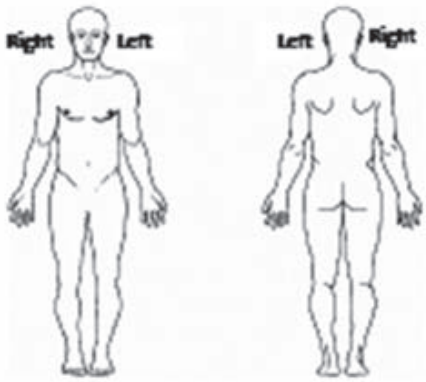
Date: _____

Time: _____

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains and toothaches). Have you had pain other than these everyday kinds of pain today?

   1. YES 2. NO

2. On the diagram, shade the area where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the past 24 hours.

1 2 3 4 5 6 7 8 9 10

No pain Pain as bad as you can imagine

4. Please rate your pain by circling the one number that best describes your pain at its least in the past 24 hours.

1 2 3 4 5 6 7 8 9 10

No pain Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on average.

1 2 3 4 5 6 7 8 9 10

No pain Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

1 2 3 4 5 6 7 8 9 10

No pain Pain as bad as you can imagine

7. What treatments or medications are you receiving for your pain?

8. In the past 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that shows how much relief you have received.

10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

No relief Complete relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General activity

1 2 3 4 5 6 7 8 9 10

Does not interfere Completely interferes

B. Mood

1 2 3 4 5 6 7 8 9 10

Does not interfere Completely interferes

C. Walking ability

1 2 3 4 5 6 7 8 9 10

Does not interfere Completely interferes

D. Normal work (includes both work outside the home and housework)

1 2 3 4 5 6 7 8 9 10

Does not interfere Completely interferes

E. Relations with other people

1 2 3 4 5 6 7 8 9 10

Does not interfere Completely interferes

F. Sleep

1 2 3 4 5 6 7 8 9 10

Does not interfere Completely interferes

G. Enjoyment of life

1 2 3 4 5 6 7 8 9 10

Does not interfere Completely interferes

Figure 4. Brief Pain Inventory (BPI). Reproduced with permission from Dr Charles S. Cleeland (1991).

Comprehensive Pain Assessment

Patient's self-report of pain is the standard of care.

If the patient is unable to verbally report pain, an alternative method to obtain pain rating and response should be utilized.

1. Pain experience
   - Location, referral pattern, and radiation of pain(s)
   - Intensity
     - Last 24 h and current pain
     - At rest and with movement
   - Interference with activities
     - General activity, mood, relationship with others, sleep, and appetite
   - Timing: onset, duration, course, persistent, or intermittent
   - Description or quality
     - Aching, stabbing, throbbing, pressure often associated with somatic pain in skin, muscle and bone
     - Gnawing, cramping, aching, sharp pain often associated with visceral pain in organs or viscera
     - Burning, tingling, shooting, or electric/ shocking pain often associated with neuropathic pain caused by nerve damage
   - Aggravating and alleviating factors
   - Other current symptoms
   - Current pain management plan, both pharmacologic and nonpharmacologic.

If medications are used, determine:

   - What medication(s), prescription, and/or over the counter?
   - How much?
   - How often?
   - Current prescriber?
   - Response to current therapy
     - Pain relief
     - Patient adherence to medication plan
     - Medication side effects such as constipation, sedation, cognitive slowing, nausea, and others
     - Breakthrough pain
   - Prior pain therapies
     - Reason for use, length of use, response, and reasons for discontinuing and adverse effects encountered
   - Special issues relating to pain
     - Meaning and consequences of pain for patient and family
     - Patient and family knowledge and beliefs surrounding pain and pain medications
     - Cultural beliefs toward pain, pain expression and treatment
     - Spiritual, religious considerations, and existential suffering
     - Patient goals and expectations regarding pain management
     - Assess for use of alternative or complimentary therapies and screen for potential adverse interactions or effects

2. Psychosocial
   - Patient distress
   - Family and other support
   - Psychiatric history including current or prior history of substance abuse
   - Risk factors for aberrant use or diversion of pain medication
     - Patient, environmental, and social factors
   - Risk factors for undertreatment of pain
     - Pediatric, geriatric, minorities, female, communication barriers, history of substance abuse, neuropathic pain, and cultural factors
3. Medical history
   - Oncologic treatment including current and prior chemotherapy, radiation therapy and surgery
   - Other significant illnesses and conditions
   - Pre-existing chronic pain
4. Physical examination
5. Relevant laboratory and imaging studies to evaluate for disease progression
6. The endpoint of the assessment is to establish the ''pain diagnosis'' and individualised pain treatment plan based on mutually developed goals

The ''pain diagnosis'' includes the aetiology and pathophysiology of pain:

   - Aetiology of pain
     - Direct involvement of the cancer itself
     - Cancer therapy (radiotherapy, chemotherapy, or surgery) or procedures
     - Coincidental or noncancer pain (e.g., arthritis)
   - Pathophysiology of pain
     - Nociceptive
     - Neuropathic
     - Visceral
     - Affective
     - Behavioural
     - Cognitive components

Figure 5. Comprehensive pain assessment.

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In terms of the clinical examination, pain is often associated with physiological, verbal, postural and behavioural responses that provide clues to its presence and severity (Table 5.4). These may be especially important in patients who are unable to communicate verbally.

Table 5.4. Examples of physiological, behavioural and verbal responses to pain

Physiological	Facial	Verbal	Body movement
• Increased blood pressure • Increased heart rate • Increased respiratory rate • Dilated pupils • Perspiration • Flushing/pallor	• Grimace • Frowning • Wincing • Teeth clenching	• Moaning • Screaming • Whimpering • Crying	• Rigidity, splinting, tension • Slow, cautious movement • Arching • Clenched fists • Restlessness • Repetitive movements • Guarding

The patient should undergo a full physical examination, paying particular attention to the factors listed in Table 5.5.

Table 5.5. Physical examination of a patient with pain[28]

General	• General appearance and vital signs, including subjective indications of pain (see Table 5.4.) • Overt abnormalities (e.g., weight loss, muscle atrophy, deformities, trophic changes)
Site of pain	• Appearance, colour, abnormalities of overlying skin • Muscle spasm • Tenderness • Brush, pin prick tests to evaluate for allodynia, hyperalgesia or hyperesthesia • Mass lesion • Evidence of incident pain (e.g., worse on movement or inhalation)
Neurological	• Sensory or motor deficits • Abnormalities of coordination • Orientation, memory, mood
Musculoskeletal	• Posture and symmetry • Deformities • Abnormal movements and/or gait • Muscle strength and joint range of motion

5.2.4 Evaluate psychosocial factors

Both emotional and social influences can determine a patient's experience of pain and response to treatment. Patients should be encouraged to express their emotions, thoughts, fears and expectations and more detailed examination and assessment is required in patients exhibiting features suggestive of emotional distress and/or depression. Examples of psychological and social issues that may need to be addressed include:[17]

Psychological issues

- The patient's understanding of their condition
- What the pain means to them and their family
- The impact of pain on relationships within the family
- The influence of pain on the patient's mood
- Investigation for the presence of anxiety, depression, suicidal thoughts and other psychiatric syndromes
- Fatigue and sleep

Social issues

- Functional capacity and coping strategies
- Social isolation
- Stigma of the diagnosis
- Transport difficulties
- Living circumstances
- Family and social support
- Economic impact

Various multidimensional tools are available to reliably assess psychosocial distress. These include the African Palliative Care Association's (APCA) African Palliative Outcome Scale (POS), which is validated for use in Africa (Figure 6).[29]

The APCA African POS					
Patient No:	**Possible responses**	**Visit 1 DATE:**	**Visit 2 DATE:**	**Visit 3 DATE:**	**Visit 4 DATE:**
ASK THE PATIENT					
Q1. Please rate your pain (from 0 = no pain to 5 = worst/ overwhelming pain) during the last 3 days[a]	0 (no pain) to 5 (worst/ overwhelming pain)				
Q2. Have any other symptoms (e.g., nausea, coughing or constipation) been affecting how you feel in the last 3 days?[a]	0 (not at all) to 5 (overwhelmingly)				
Q3. Have you been feeling worried about your illness in the past 3 days?[a]	0 (not at all) to 5 (overwhelming worry)				
Q4. Over the past 3 days, have you been able to share how you are feeling with your family or friends?[a]	0 (not at all) to 5 (yes, I've talked freely)				
Q5. Over the past 3 days have you felt that life was worthwhile?[a]	0 (no, not at all) to 5 (Yes, all the time)				
Q6. Over the past 3 days, have you felt at peace?[a]	0 (no, not at all) to 5 (Yes, all the time)				
Q7. Have you had enough help and advice for your family to plan for the future?	0 (not at all) to 5 (as much as wanted)				
ASK THE FAMILY CARER					
Q8. How much information have you and your family been given?	0 (none) to 5 (as much as wanted) N/A				
Q9. How confident does the family feel caring for ____?	0 (not at all) to 5 (very confident) N/A				
Q10. Has the family been feeling worried about the patient over the last 3 days?[a]	0 (not at all) to 5 (severe worry) N/A				

a. A different time frame instead of the past 3 days could be used if appropriate (e.g., if only visited once a week).

Figure 6. APCA Palliative Outcome Scale (POS).

Reprinted with permission from Powell RA, Downing J, Harding R, *et al,* on behalf of the APCA M&E Group. Development of the APCA African Palliative Outcome Scale. *Journal of Pain and Symptom Management* 2007; 33: 229-232.[29]

5.2.5 Evaluate spiritual factors

Beliefs including, but not limited to, religious beliefs, emotions, self-awareness, ideas and attitudes influence attitudes towards health and sense of well-being. In addition to medical intervention, nonjudgmental, understanding and supportive care is required to address these needs for each patient as an individual.

Patients find it comforting that they can speak of spiritual issues in a clinical consultation. The clinician may need to specifically ask about these so that patients know that it is acceptable to talk about them. A useful guide to this discussion is the FICA tool (Table 5.6).

The value of proactively addressing spirituality is that the patient is offered a safe space to discuss these issues and the doctor or nurse can involve a spiritual counsellor in the patient's care if necessary or if desired by the patient. It does not require that the clinician is of the same faith as the patient to offer this support.

Table 5.6. FICA tool to aid discussion of spirituality[30]

Ask the patient:

- Do you have a **F**aith or belief?
- How **I**mportant is this to you, especially in your illness?
- Is there a faith **C**ommunity that supports you?
- How can I, as your doctor, **A**ssist you in spiritual care?

5.2.6 Determine the occurrence and severity of breakthrough pain

The occurrence of breakthrough pain needs to be identified. An assessment of breakthrough pain includes the documentation of frequency, duration, intensity, nature, precipitating factors, relieving factors and effect of analgesia.

5.2.7 Ongoing assessment and reassessment of pain

Regular ongoing pain assessment using a consistent instrument, such as PQRST or the Brief Pain Inventory, is required to monitor the efficacy of pain management strategies, to identify breakthrough pain and to review, add or change treatments when necessary. Furthermore, new reports of pain, which may indicate a change in the underlying pathological process, require urgent medical attention and must be appropriately investigated. When reassessing pain, in addition to pain features and impact on daily functioning, psychological status and quality of life, consider and document the following factors that may influence pain and the future management thereof:

- Progression of the disease
- Current pain management strategies, medications, doses and timing of administration
- Recent exposure to painful procedures that may influence pain tolerance
- Drug tolerance, withdrawal, side effects or oversedation
- Presence of a caregiver or family members
- New or pre-existing comorbidities
- New or changed attitudes towards the illness and/or management strategies

The frequency of review depends on pain severity and distress, but initially should be carried out every 24 hours until the patent is stable. In outpatients, review may be weekly or monthly and, where suitable, may be done telephonically by an appropriately skilled healthcare worker.

5.2.8 Consider a pain diary to monitor pain levels, medication requirements, analgesic efficacy and side effects of medication

A pain diary should be completed at least daily and should include the following information: [31]

1. Date and time of pain experience
2. Description and location of the pain
3. What the patient was doing when they experienced the pain
4. Medicine taken, dose and whether it helped to relieve the pain
5. Other relieving factors
6. Repeat pain rating an hour after taking the medicine
7. Other effects of the pain; e.g., on sleep, mood, ability to be active
8. Medication side effects

5.2.9 Be aware of patient groups who may be at risk of underassessment of pain

Patients who may be at risk of underassessment of pain include:

- Elderly and very young
- Cognitively impaired
- Communication difficulties
- Known or suspected substance abusers
- Patients at the end of life
- Patients at risk of painful syndromes consequent to cancer treatments
- Psychiatric patients

- Patients with a depressed level of consciousness
- Other marginalised groups (e.g., patients in prison; HIV and AIDS)

Special assessment tools are available for some of these patient groups (e.g., Pain Assessment in Advanced Dementia, PAINAD; Pain Assessment Checklist for Seniors with Limited Ability to Communicate, PACSLAC; Hand Scale).[16,32,33]

6. WHO recommendations for the use of analgesics

The World Health Organisation (WHO) recommends a five point method for the use of analgesics that is inexpensive and effective for relieving pain in 70%-90% of patients with cancer:[22]

6.1 By mouth

As far as possible, analgesics should be administered by mouth. In patients where oral administration is unsuitable or not possible, alternative routes include rectal suppositories, continuous subcutaneous infusion and, in the hospital setting, intravenous administration.

6.2 By the clock

In order to achieve continuous pain control, analgesic medications must be administered regularly and at the appropriate fixed time interval (e.g., 4 hourly). The dose should be up-titrated until an adequate level of analgesia is achieved and the next dose should be given before the effect of the previous one has fully worn off. Rescue doses at 50% to 100% of the regular dose may be necessary for incident or breakthrough pain.

6.3 By the ladder

Analgesia should be appropriate for the type and severity of pain, stepping up for persisting or worsening pain and stepping down as pain improves, if it can be contained with lower doses or less potent analgesics.

In patients with mild nociceptive pain, step 1 is a non-opioid analgesic (paracetamol) or a nonsteroidal anti-inflammatory drug (NSAID).

For moderate to severe nociceptive pain, steps 2 and 3 include the use of opioids, which may be co-prescribed with non-opioids (paracetamol and/or NSAID) as necessary. Because of its lower cost and predictable efficacy and tolerability, low dose

morphine is a preferred option at step 2. This applies to adults and especially to pain management for children.[11] Codeine should not be used in paediatric patients.

The combination of a weak opioid and a strong opioid is to be avoided. When a patient requires escalation of analgesia with a stronger opioid the weak opioid must be discontinued.

Unlike nociceptive pain, treatment for neuropathic pain is not escalated according to pain intensity, but according to response to step 1 agents, which may be an α2δ-ligand (pregabalin or gabapentin), amitriptyline or a serotonin noradrenaline reuptake inhibitor (SNRI; duloxetine or venlafaxine). Analgesic escalation may be achieved by increasing the dose of the step 1 treatment, switching to an alternative step 1 treatment, combining step 1 treatments and, at step 3, adding a strong opioid. Referral to specialist care should be considered in difficult cases, where, despite escalation of pain management, pain is not adequately controlled.

The Stepwise Healthcare Interventions for Pain (SHIP), is an inclusive progressive approach to pain management (Figure 7). As an initial work-up, all patients require a systematic assessment of their pain with open communication and education about their condition and available management options (see section 4). Special attention should be paid to previously tried and current analgesic use, the dose and how frequently it is being taken, adjusting or discontinuing as appropriate. Identifying the presence of nociceptive pain, neuropathic pain or mixed pain will determine the type of pain medication that is appropriate.

Stepwise management of pain does not need to begin at step 1. Depending on the experience and expertise of the attending physician, it may be appropriate to begin at step 2 or 3 in a patient with moderate to severe pain and to step down as pain control is achieved and maintained. Breakthrough pain should always be treated.

A stepwise algorithm for the use of opioids in patients with cancer pain is illustrated in Figure 8.

Communication, counselling and patient education should be continued throughout the duration of management. Nonpharmacological approaches to pain management and specific interventions for the cancer should be initiated at any step when they are indicated or where they will improve the patient's quality of life. Psychosocial and complementary interventions (e.g., social interaction, spiritual counselling, recreational activities, relaxation therapy, imagery) should also be considered.

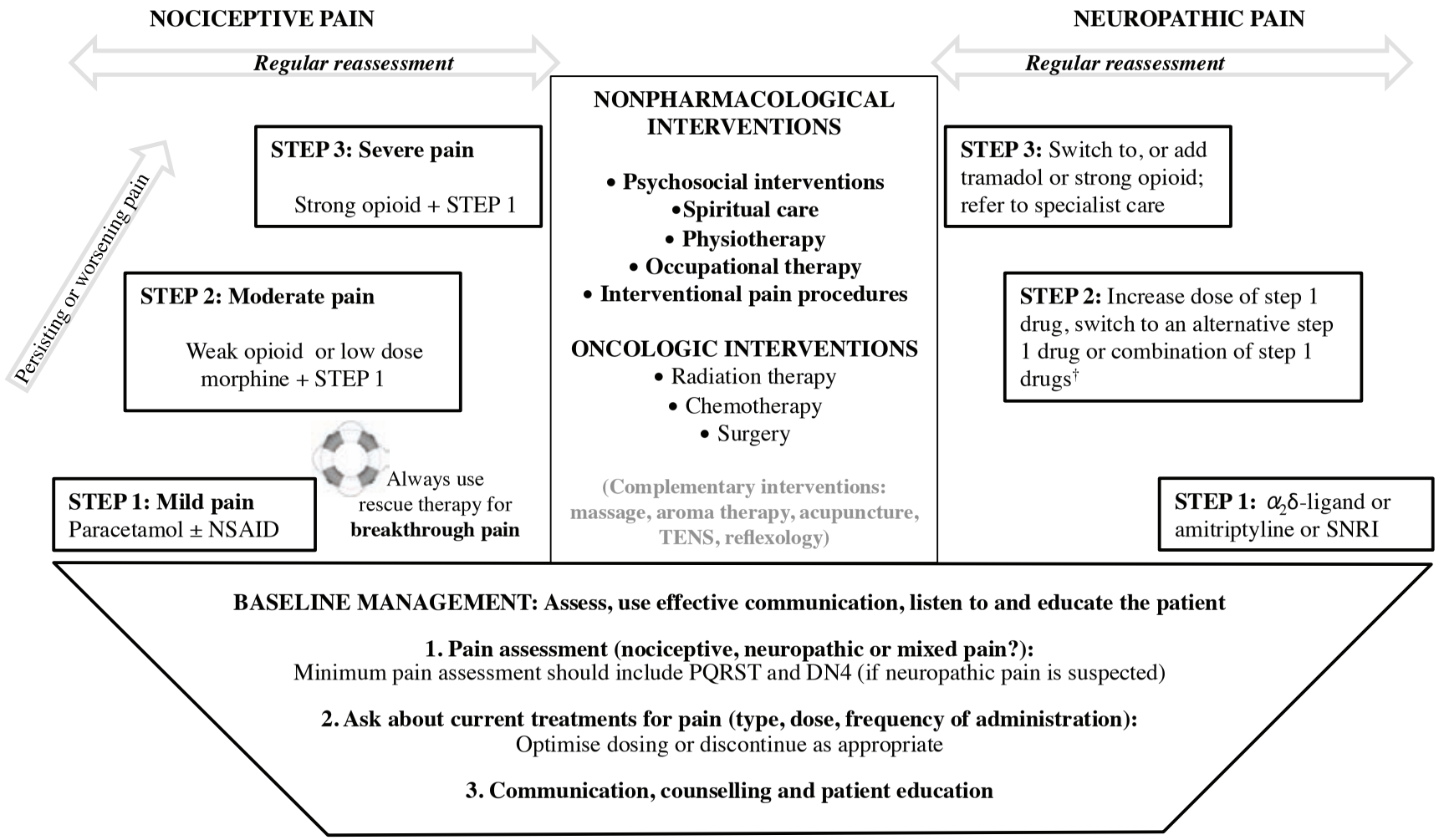


Figure 7. The Stepwise Healthcare Interventions for Pain (SHIP) model for pain management, including an analgesic ladder for nociceptive pain (left) and a stepwise pharmacotherapeutic approach to neuropathic pain (right). Mixed pain may require a combination of treatments from both sides of the diagram. Communication, counselling and patient education should be initiated at the first consultation and continued throughout the duration of management. Other psychosocial interventions (social interaction, spiritual counselling, recreational activities, relaxation therapy, imagery), nonpharmacological approaches to pain management and specific interventions for the cancer should be initiated at any step when they are indicated or where they will improve the patient's quality of life. See text for details.
†Rational combinations for neuropathic pain are amitriptyline + $\alpha_2\delta$-ligands, or SNRI + $\alpha_2\delta$-ligands . NSAID: nonsteroidal anti-inflammatory drug; $\alpha_2\delta$-ligand : gabapentin or pregabalin; SNRI: serotonin noradrenalin reuptake inhibitor (duloxetine or venlafaxine); TENS: transcutaneous electrical nerve stimulation.

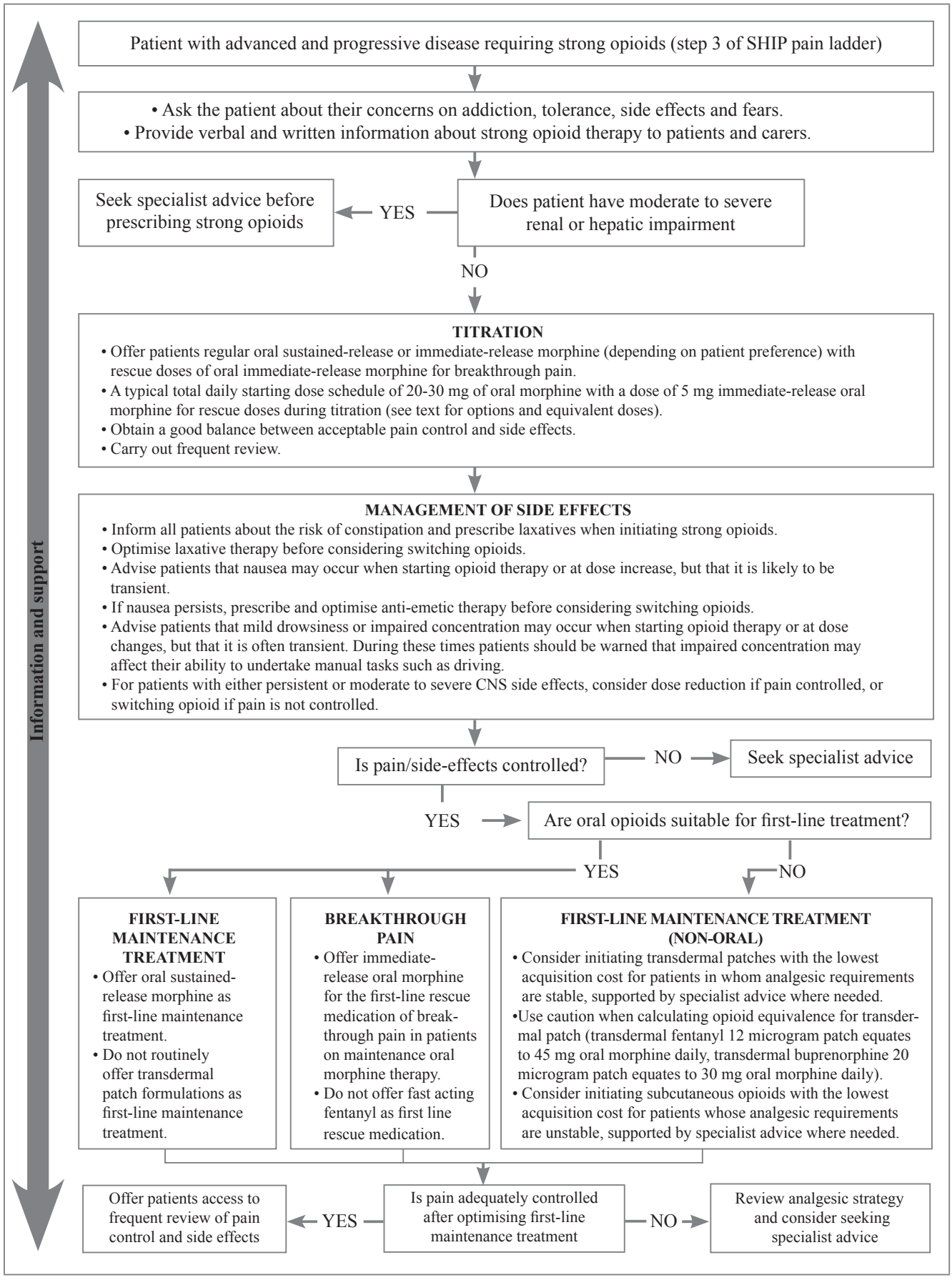


Figure 8. Algorithm for the prescription of opioids in patients with cancer pain.

Reproduced from National Institute for Health and Clinical Excellence (NICE) clinical guideline 140; 2012.[12]

6.4 For the individual

All pain management strategies must be individualised. Doses of analgesics and frequency of administration will vary depending on the individual patient and their current level of pain.

6.5 Attention to detail

Pain medication must be administered regularly. In patients with normal renal and hepatic function oral morphine is administered every 4 hours. The first and last doses of the day should be linked to the patient's waking and bedtime. A double dose at bedtime may be permissible so that the patient can skip the dose scheduled for the early hours of the morning. For example, if dosing is at 6 am, 10 am, 2 pm, 6 pm, 10 pm and 2 am, taking a double dose at 10 pm means that the patient does not have to wake for the 2 am dose.

Dosing instructions for the patient or their family should be written out in full, including the drug name, reason for use, dose (number of tablets if appropriate) and number of times a day that the medication should be taken. Patients should be warned about possible side effects and cautioned about using other medications that have not been prescribed for them. Combination analgesic preparations (two or more pharmacologically active ingredients combined in a single tablet, capsule or liquid preparation) may pose a risk of overdose or adverse effects when used in conjunction with prescribed or over-the-counter medications containing the same or similarly acting ingredients, and should be avoided.

Thus, in summary, the steps to be considered in the management of cancer pain are as follows:[16]

1. Appropriate assessment to identify cause and severity of symptoms
2. Explanation to patient and family at all stages
3. Correct reversible factors
4. Consider disease-specific palliative therapy
5. Institute non-pharmacological interventions
6. Prescribe appropriate first-line treatment
7. Consider adjuvant/second-line treatment
8. Review assessment and management

At all stages of management consider:

9. Involvement of interdisciplinary team
10. Referral to appropriate service/more experienced clinician

7. Nonopioid analgesics and co-analgesics

7.1 Nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol

NSAIDs and paracetamol are indicated for mild to moderate pain.

NSAIDs are more effective than placebo for reducing cancer pain, although there is no evidence to support the superiority of one NSAID over another.[34] They offer the potential advantage of causing minimal nausea, constipation, sedation or adverse effects on mental functioning and therefore may be useful for control of mild to moderate pain and in conjunction with opioids. Adding a NSAID to opioid analgesia may allow reduction of opioid dose when sedation, confusion, dizziness or other central nervous system effects of opioid analgesia alone have become problematic.[2] However, there is conflicting evidence as to whether combining a NSAID with an opioid regimen provides better pain relief than using either of these drugs alone.[9]

Adverse effects of NSAIDs include dyspepsia and gastrointestinal (GI) ulceration, renal dysfunction and impairment of platelet aggregation. Renal dysfunction and liver failure are relative contraindications to their use. NSAIDs are contraindicated with platelet dysfunction or other potential bleeding disorders, which commonly occur in cancer patients due to either the disease itself or its treatment. Cyclo-oxygenase-2 (COX-2) selective inhibitors (COXIBs) may be associated with a lower risk of GI complications, but this advantage appears to diminish after 6 months of use.[2] Co-prescription of misoprostol, standard dose proton pump inhibitors or double dose histamine-2 receptor antagonists, equivalent to ranitidine 300 mg twice daily, may be effective for prevention of gastric and duodenal ulcers associated with chronic use of NSAIDs.[9]

At prescription doses, ibuprofen has a low risk for gastrointestinal adverse events and with long-term use, in comparison with COXIBs, was no more likely to be associated with withdrawal from clinical studies due to adverse events.[35]

Current recommendations are to use the lowest effective dose of NSAID or COXIB for the shortest period required to control symptoms and to periodically reassess the need for ongoing long-term treatment (Table 7.1).[9]

In contrast, there is little or no evidence of benefit of paracetamol at recommended clinical doses (≤4 g/day) in cancer patients, although a trial of therapy may allow individual patients to decide for themself. [36-39] If the patient experiences no analgesic benefit after 2 days, paracetamol should be discontinued. When an opioid is added to paracetamol in patients with increasing pain despite a definite past benefit of paracetamol, the need for continuing paracetamol should be reviewed after 3-4 days of adequate pain control. If pain returns after discontinuing paracetamol, it should be restarted.[40]

Therefore, treatment recommendations are that, unless contraindicated, NSAIDs and/or paracetamol may be prescribed at all stages of the analgesic ladder, with ongoing

evaluation and regular re-assessment in patients who have a favourable response that may justify prolonged use.[9,11,17,23,36,40]

NSAIDs and paracetamol have a limited role in the treatment of neuropathic pain. However, nociceptive and neuropathic pain are often mixed and some patients report relief, so a trial of these agents may be indicated.[41]

7.2 Management of neuropathic pain

Both cancer and/or its treatment may give rise to neuropathic pain. In a large survey of 8615 oncology patients in Europe, 30% were suffering from pain and, of those, 33% were diagnosed with neuropathic pain (half of whom were confirmed using DN4).[42] Sixty-nine percent of neuropathic pain cases were tumour related and up to 43% were treatment related, primarily due to chemotherapy or biologic therapy.

When prescribing for neuropathic pain, it is important to note that an analgesic response does not occur immediately and patients should receive an adequate trial of medication before treatment failure is considered.

7.2.1 Anticonvulsants (α2δ-ligands)

The α2δ-ligands, pregabalin and gabapentin, are recommended as first-line therapy for neuropathic pain. Both drugs may also be useful for patients with comorbid sleep disorders, and pregabalin in patients with anxiety disorder associated with pain. The analgesic efficacy of the two drugs is similar. For gabapentin the initial dose is 100 mg three times daily, gradually increased based on clinical response and tolerability, to a maximum daily dose of 1800 mg. Pregabalin should be started at 25 mg at night, increased slowly to 150-225 mg twice daily (Table 7.1).[19]

The dose of both drugs needs to be reduced in patients with impaired renal function.

Clonazepam is a reasonable alternative to gabapentin and pregabalin starting at a dose of 0.5 mg twice daily and escalating to 4 mg twice daily. Clonazepam is particularly useful for patients with concomitant insomnia and anxiety, but may result in excessive sedation and/or dissociation when administered in combination with tricyclic antidepressants (TCAs).

7.2.2 Antidepressants

SNRIs (duloxetine and venlafaxine) are recommended as a first-line option for the treatment of neuropathic pain and are also the treatment of choice for patients with comorbid anxiety or depressive disorders.[19] To improve tolerability, doses should

start low and be titrated according to therapeutic response. Duloxetine should be initiated at 30 mg once daily, increased to 60 mg after 1 week. In patients with painful diabetic neuropathy, 60 mg twice daily was not more effective than 60 mg once daily.[43] Venlafaxine should be initiated at 37.5 mg once or twice daily and increased by 75 mg weekly to a maximum daily dose of 225 mg.[19] Because abrupt discontinuation of venlafaxine may be associated with withdrawal, the dose should be tapered when stopping. Dose adjustments of SNRIs are required in patients with renal or hepatic impairment.

Because of a risk of serotonin syndrome and seizures, concomitant use of tramadol and antidepressants should be undertaken with caution and patients must be closely monitored. Monoamine oxidase inhibitors (MOAI) should not be used within 14 days of discontinuing tramadol.

Selective serotonin re-uptake inhibitors (SSRIs) are not recommended for the treatment of neuropathic pain.

Tricyclic antidepressants (amitriptyline, imipramine and nortriptyline) are inexpensive and are dosed once daily. Analgesia occurs at lower doses than the antidepressant effect. Amitriptyline should be started at 10-25 mg/day at bedtime and titrated slowly (10-25 mg/day weekly) according to therapeutic effect and tolerability, to a maximum daily dose of 50-150 mg.

TCAs should be used with caution in patients with glaucoma, cardiovascular disease, hyperthyroidism, impaired liver function, epilepsy, urinary retention, prostatic hypertrophy and constipation, and their use should be avoided in the elderly. They may be associated with cardiotoxicity and are contraindicated with antihypertensives and in patients with myocardial infarction and/or heart block (Table 7.1).

All of the antidepressants have potential for clinically significant drug interactions and these should be considered before prescribing.

A detailed South African guideline for the management of neuropathic pain has been published.[19] It is available for download at: http://www.samj.org.za/index.php/samj/article/view/5472.

Doses of commonly used non-opioid analgesics and precautions for use are listed in Table 7.1.

Table 7.1. Starting and usual maintenance doses of non-opioid analgesics and co-analgesics in adults[9,16,19,35,40,44,45]

	Starting dose	Usual maintenance dose	Maximum daily dose	Precautions
Paracetamol		500-1000 mg po q6h	4000 mg	Generally well tolerated at doses ≤4 g/day; liver toxicity: risk increased in overdose, use of combination products containing paracetamol, alcohol or substance abuse, liver disease, elderly, depression, renal toxicity.
NSAIDs				
Ibuprofen		400 mg po q6-8h	1200 mg	Risk of adverse gastrointestinal events is increased under the following circumstances: • Older age (>65 years). • Previous peptic ulcer disease. • Comorbid medical illness. • Smoking. • Increasing NSAID dose. • Use of multiple NSAIDs. • Combined use of NSAID with other drugs that could increase the risk of ulceration or bleeding, including corticosteroids, anticoagulants (e.g., warfarin), SSRIs, antiplatelet agents (e.g., aspirin). • Renal, cardiac or hepatic impairment.
Diclofenac		50 mg po q8h	150 mg	
Indomethacin		75 mg q8-12h	200 mg	
Naproxen		500 mg q12h	1000 mg	
COX-2 inhibitors				
Celecoxib		200 mg q12h	400 mg	
Rofecoxib		12.5 mg q24h	50 mg	
Anticonvulsants				
Gabapentin	100 mg q8h or 300 mg po nocte	Increase by 300 mg/24 hours every 2-3 days as tolerated to a maximum daily dose of 1800 mg.		Reduce dose in renal insufficiency. Lower starting dose and slower titration in elderly/frail patients.
Pregabalin	25 mg nocte	Increase in 25 mg increments every 2-3 days as tolerated until the patient is taking 75 mg q12h. The dose can then be increased by 75 mg/day every 3-7 days if necessary to a maximum daily dose of 150-225 mg q12h.		
Antidepressants				
Duloxetine	30 mg once daily	60 mg once daily		Dose reduction in renal or liver insufficiency; caution and monitor patients with tramadol; caution in patients with history of mania, seizures, acute narrow-angle glaucoma; glucose monitoring may be required in diabetic subjects.

Venlafaxine	37.5 mg once or twice daily	Increase by 75 mg weekly to a maximum daily dose of 225 mg.	Dose reduction in renal or liver insufficiency; caution and monitor patients with tramadol; caution in patients with cardiac disease, monitor BP in patients with hypertension; caution in patients with history of mania or seizures.
Amitriptyline	10-25 mg	Titrated by 10-25 mg/day weekly to a maximum daily dose of 50-150 mg.	Contraindicated with MAOI use, antihypertensives, patients with myocardial infarction/heart block, untreated narrow-angle glaucoma. Use with caution in patients with glaucoma, cardiovascular disease, especially in elderly patients, hyperthyroidism, impaired liver function, epilepsy, urinary retention, prostatic hypertrophy, constipation, mania.
COX: cyclo-oxygenase; MOAI: monoamine oxidase inhibitor			

7.3 Corticosteroids

Corticosteroids may be useful to help relieve pain associated with nerve compression, spinal cord compression, liver capsule stretch, metastatic arthralgia, bone metastases and headache due to raised intracranial pressure. The dose depends on the clinical situation (Table 7.2). Start by giving a 5-7 day trial of therapy and if there is a benefit, wean to the lowest effective dose. If there is no benefit, stop. Corticosteroids should be administered in conjunction with other relevant treatment modalities (e.g., radiotherapy) and for the shortest duration possible. Because high doses may be associated with insomnia, avoid administering corticosteroids in the evening.

Adverse effects of corticosteroids include oedema, dyspeptic symptoms, gastrointestinal bleeding, proximal myopathy, agitation, hypomania and opportunistic infections. Adverse gastrointestinal effects may be increased when corticosteroids are co-prescribed with NSAIDs.

Table 7.2. Dose of corticosteroids for pain management in cancer patients[22]			
Indication:	**Nerve compression pain**	**Spinal cord compression**	**Raised intracranial pressure**
Initial dose	20-40 mg/ day prednisone/ prednisolone, or 4-6 mg/day dexamethasone or betamethasone. Reduce step by step to maintenance dose after 1 week.	Up to 100 mg/day dexamethasone or betamethasone, reducing to 16 mg during radiation therapy.	8-16 mg dexamethasone or betamethasone. Reduce the dose after 1 week.
Maintenance dose	May be as low as 15 mg prednisone/prednisolone or 2 mg dexamethasone or betamethasone.		
Prednisone and prednisolone can be used for children, 1-2 mg/kg daily[8]			

7.4 Bone pain and role of bisphosphonates

Pain is a common symptom of bone metastases. It occurs in approximately 30% of cancer patients, increasing to 90% in the later stages. Although the pain is mainly nociceptive in origin, neuropathic pain may also occur when the tumour invades or compresses a nerve, neural plexus or the spinal cord, or where it causes periosteal stretch or involves the Haversian canals.[46] In combination with antineoplastic treatment, bisphosphonates (zoledronate, ibandronate, pamidronate and clodronate) have been shown to reduce the incidence of first and subsequent skeletal-related events in some types of cancer and to reduce bone pain due to metastases from solid tumours (breast, lung and prostate) and multiple myeloma.[47-53] However, they may be associated with renal toxicity and osteonecrosis of the jaw (ONJ). Patients who have undergone recent tooth extraction or another form of dentoalveolar trauma are especially at risk of ONJ and bisphosphonates should only be prescribed after preventative dental measures, with regular dental evaluations and with ongoing meticulous attention to oral hygiene.[54] Nevertheless, prescription of bisphosphonates should not be regarded first-line therapy for bone pain or as an alternative to analgesic treatment (NSAIDs and opioids) or the use of other multimodal pain management strategies (e.g., radiotherapy). Suggested management strategies for pain due to bone metastases are listed in Table 7.3.

Table 7.3. Management of pain associated with bone metastases[10]	
Condition	**Management considerations**
Uncomplicated bone pain	• Analgesics • Bisphosphonate • Antalgic radiotherapy
Complicated bone metastases: spinal cord compression or impending fracture	• Urgent radiotherapy and/or surgery • Analgesics • Bisphosphonate
Previous skeletal-related event (e.g., pathologic fractures, spinal cord compression, the need for orthopaedic surgery and palliative radiotherapy to bone, hypercalcaemia of malignancy)	• Bisphosphonate

7.5 Anxiolytic drugs

Although they may be useful for other indications, the use of benzodiazepines to treat cancer pain is not recommended.

7.6 Antispasmodics: baclofen and hyoscine

Baclofen is a GABA-B agonist. It is a centrally acting muscle relaxant with antispasmodic properties. Although evidence is limited, it has been shown to be an effective adjunct for pain relief in patients with cancer-related neuropathic pain.[41,55] The effective dose range is wide (20 mg/day to >200 mg/day) and baclofen should be initiated at a low dose and titrated according to clinical response. Because of the possibility of serious withdrawal syndrome, the dose should be gradually tapered when discontinuing.[56]

Hyoscine butylbromide is an anticholinergic drug that may be useful to relieve pain and reduce gastrointestinal secretions in terminal cancer patients with inoperable bowel obstruction.[57,58]

7.7 Ketamine

Ketamine may be useful in neuropathic pain, ischaemic limb pain and refractory cancer pain, where it may reduce or prevent the development of hyperalgesia and restore opioid sensitivity in opioid-tolerant patients. However, the routine use of ketamine is limited by cognitive and other adverse effects. Furthermore, dosing can be complicated and ketamine should be used only by experienced pain management specialists.[2,9,59]

7.8 Alpha-2 agonists

Clonidine may be given at a dose of 1-2 mcg/kg twice daily (oral 25 mcg tablets are available).

Dexmedetomidine is available as a parenteral preparation that may be given sublingually at a dose of 1 mcg/kg twice daily or added to parenteral morphine or fentanyl.

7.9 Topical lignocaine and capsaicin

Although there is evidence of limited efficacy for topical lignocaine (5% lignocaine patch) and capsaicin in addition to standard analgesia in patients with neuropathic pain syndromes, these agents are not available in South Africa and there is no evidence supporting their use in cancer pain. Therefore they are not recommended for this indication.[9]

7.10 Cannabinoids

Medicinal cannabinoids (nabilone and delta-9-tetrahydrocannabinol, THC) are available in some parts of the world and there is ongoing research into their utility for cancer pain. There is evidence that they may be effective in the treatment of both nociceptive and neuropathic pain syndromes. However, especially at higher doses, THC is highly sedating and adverse effects are common, dose-related and may be severe.[9] The use of cannabinoids is not recommended in South Africa for the treatment of cancer pain.

8. Opioid analgesics

8.1 Step II opioids: tramadol, codeine or low-dose morphine

Patients with moderate pain whose pain is not adequately controlled with regular doses of NSAIDs or paracetamol may experience good pain relief with the addition of a weak opioid (tramadol or codeine).[11]

Side effects of tramadol include nausea/vomiting, constipation, drowsiness, dizziness and seizures.[19] Because it lowers the seizure threshold, tramadol should be used with caution in patients with epilepsy. When tramadol is used in combination with antidepressants there is an increased risk of seizures and serotonin syndrome. Therefore this combination should be used with caution and the patient must be closely monitored.

Codeine is not usually available on its own, but is often contained in combination products with other analgesics, such as paracetamol. The codeine dose in these

preparations is often low and subtherapeutic (e.g., 8-10 mg), where the recommended adult dose sufficient for analgesia is 30-60 mg 4 hourly (Table 8.1). The analgesic effect of codeine is due to metabolism to morphine. A small proportion of patients (<10%) is unable to convert codeine to morphine and analgesia will be inadequate in these individuals.[9] Young children have inadequate amounts of the enzyme required for the conversion and use of codeine is not recommended in this population, where low dose morphine is effective with fewer side effects.[16]
Usual starting doses are listed in Table 8.1. An alternative to codeine or tramadol at step II is to start with a low dose of a more potent opioid (morphine or oxycodone).[11]

8.2 Step III opioids: morphine and other strong opioids

Potent opioids include morphine, oxycodone, hydromorphone and fentanyl, which, at equipotent doses are similar in efficacy, tolerability and safety.[11] Morphine is recommended as a first choice, because it is inexpensive and is often the only strong opioid available for pain management. It is available in oral immediate and slow-release forms and as an injectable. An oral liquid is easily prepared from morphine sulphate powder into different strengths and proportions as required. Immediate-release morphine has a rapid onset of effect (within 20 minutes), but its half-life of 2-4 hours means that it must be administered 4 hourly for effective continuous pain relief. It is metabolised by the liver.

Table 8.1. Starting and usual maintenance oral doses of opioid analgesics in adults[9,16,22,40,60]

	Starting dose	Maximum daily dose
Codeine	30-60 mg q4-6h	240 mg
Dihydrocodeine	30 mg q6h	240 mg
Tramadol	50-100 mg q6h	400 mg
Morphine	2.5-10 mg q4h (IR) Patients switching from a regular step II opioid should start on 5-10 mg q4h Frail/elderly patients should start at 2.5 mg q6-8h due to the likelihood of impaired renal function 20-30 mg q12h (CR)	There is no ceiling or maximum dose, but the dose should be increased gradually
Hydromorphone (extended-release tabs)*	4-8 mg once daily	
Oxycodone	5 mg q4-6h (IR) 10 mg q12h (CR)	

IR: immediate-release; CR: continuous-release; *Manufacturer's recommendation.
Opioids should be initiated at lower doses in patients with severe renal impairment.
Patients with HIV may require lower doses of opioids.

Titration of immediate-release morphine should always be used initially to establish control of pain, usually with dose adjustments every 24 hours, unless the pain is more severe, requiring earlier titration. Only thereafter may a slow-release preparation or another opioid (e.g., fentanyl) be used for maintenance of analgesia. Breakthrough pain should be managed with immediate-release morphine as required.

The systemic bioavailability of oral morphine is poor with wide variation between individuals. Therefore dosing should be individualised. There is no ceiling or maximum dose of morphine and the dose should be increased gradually to an appropriate level that controls the patient's pain.[9,12,16]

Usual starting and maintenance doses of commonly used opioids are listed in Table 8.1. Undesirable effects of opioids and potential intolerable effects of morphine are listed in Tables 8.2 and 8.3, respectively.

Table 8.2. Undesirable effects of opioids when used for analgesia[40]

Common initial • Nausea and vomiting • Drowsiness • Light-headedness / unsteadiness • Delirium (acute confusional state) **Common ongoing** • Constipation • Dry mouth **Possible ongoing** • Suppression of hypothalamic-pituitary axis	**Less common** • Neurotoxicity – Hyperalgesia – Allodynia – Myoclonus – Cognitive failure / delirium – Hallucinations • Sweating • Urinary retention • Postural hypotension • Pruritus **Rare** • Respiratory depression • Psychological dependence

8.3 Myths about morphine that may limit its use[16,17]

When initiating opioids, it is necessary to discuss treatment with the patient and their family and address misguided concerns, including:

- *Physical dependence*

Physical dependence, resulting in withdrawal symptoms when a drug is abruptly discontinued, is a normal physiological response to chronic opioid therapy as well as long-term use of various other medications. It does not prevent withdrawal of medication as long as the patient is weaned from the drug slowly. Dependence differs from addiction in that the patient remains compliant with changes in opioid prescription.

Psychological dependence on analgesia may result from fear of pain recurrence or incomplete pain relief and may be associated with requests for increased use of opioids.

Although psychological dependence may also be confused with addiction, it differs in that requests for medication decrease with the establishment of adequate analgesia.

- *Sedation and respiratory depression*

Because pain causes sleep deprivation, effective analgesia may initially be associated with sleep. However, thereafter, if dose is titrated against pain, with an appropriate drug given at the appropriate time by the appropriate route, opioid therapy is not associated with either profound sedation or respiratory depression. In palliative care, low doses of morphine may be used in patients with end-stage chronic obstructive airways disease, lung cancer or severe dyspnoea and makes breathing more comfortable. Nevertheless, sedation is a side effect of opioids that occurs especially when starting treatment and tolerance to the sedating effects develops within a few days.

Pain is a physiological antagonist to the respiratory depressant effects of opioids and respiratory depression is rare if dose is titrated upwards against pain.

- *Tolerance*

Tolerance is defined as a reduced effect for the equivalent analgesic dose, or requirement of increased dose to attain the same effects. It may occur to both analgesia and unwanted side effects, such as nausea, vomiting, sedation and respiratory depression. In palliative care, tolerance to analgesia is uncommon and requirement for increasing doses of morphine is usually related to disease progression. There is no maximum dose of opioid analgesia and dose should be titrated according to the level of pain relief required. Because of the phenomenon of 'incomplete cross-tolerance', switching to another opioid may provide adequate analgesic efficacy when tolerance to current therapy has occurred. Furthermore, non-opioid co-analgesics may also be prescribed to limit the dose of opioid required to achieve the same level of analgesia.

- *Addiction*

Addiction is rare in palliative care when opioids are prescribed at appropriate doses to relieve pain. Drug seeking behaviours such as drug hoarding, requests for additional prescriptions or increased doses occurring in patients with a poor response to certain opioids or low-dose opioids is termed 'pseudoaddiction'. These behaviours may be mistaken as signs of addiction, but occur in an attempt to obtain better pain relief and cease when pain is controlled.

- *The perception that opioids are only used at end of life and hasten death*

Opioids are frequently used for many different conditions associated with severe pain. In some patients they may safely be used for months or years for prolonged analgesia and they significantly improve quality of life.

Table 8.3. Potential intolerable effects of morphine[40]

Type	Effects	Initial action	Comment
Gastric stasis	Epigastric fullness, flatulence, anorexia, hiccup, persistent nausea.	Prescribe prokinetic; e.g., metoclopramide 10-20 mg q6-8h.	If the problem persists, change to an alternative opioid with less impact on the GI tract.
Sedation	Intolerable persistent sedation.	Reduce dose of morphine, consider a psychostimulant, e.g., methylphenidate 5 mg q12h.	Sedation may be caused by other factors; stimulant is rarely appropriate.
Cognitive failure	Agitated delirium with hallucinations.	Prescribe an antipsychotic; e.g., haloperidol 1 mg stat and q2h prn; reduce dose of morphine and, if no improvement, switch to an alternative opioid.	Some patients develop intractable delirium with one opioid, but not with an alternative opioid.
Myoclonus	Multifocal twitching +/- jerking of limbs.	Prescribe a benzodiazepine; e.g., diazepam / midazolam 5 mg or lorazepam 500 mcg stat and q1h prn; reduce dose of morphine, but increase again if pain recurs.	Uncommon with typical doses of oral morphine; more common with high dose IV and spinal morphine.
Neurotoxicity	Abdominal muscle spasms, symmetrical jerking of legs; whole body allodynia, hyperalgesia (manifests as excruciating pain).	Prescribe a benzodiazepine; e.g., diazepam / midazolam 5 mg or lorazepam 500 mcg stat and q1h prn; reduce dose of morphine; consider changing to an alternative opioid.	An uncommon syndrome in patients receiving intrathecal or high dose IV morphine; occasionally seen with typical oral and SC doses.
Vestibular stimulation	Movement-induced nausea and vomiting.	Prescribe an antihistaminic antimuscarinic anti-emetic; e.g., cyclizine 25-50 mg q6-8h.	If intractable, switch to an alternative opioid.
Pruritus	Whole body itch with systemic morphine; localised to upper body or face/nose with spinal morphine.	With systemic opioids, prescribe oral H1-antihistamine (e.g., chlorphenamine 4-8 mg stat; if beneficial continue with 4 mg q8h or prn for 2-3 days). Possibly switch opioids; e.g., morphine to oxycodone. Most patients receiving spinal analgesia are not opioid-naive, so the probability of pruritus is reduced. If it does occur, possibly switch opioids.	Pruritus after systemic opioids is uncommon. Sometimes caused by cutaneous histamine release and self-limiting, but most are chronic and antihistamine-resistant. Centrally-acting opioid antagonists relieve the pruritus, but also antagonise analgesia.
Histamine release	Bronchoconstriction and breathlessness.	Treat as for anaphylaxis; change to a chemically distinct opioid immediately. Seek specialist advice.	Uncommon.

8.4 Methadone

Methadone is a potent opioid with complicated pharmacokinetics and considerable inter-individual variation. It requires careful monitoring and is not recommended for routine use in the management of cancer pain. It should only be used by experienced pain management specialists.[9,11]

8.5 Opioid titration

The usual starting dose of oral immediate-release morphine is 5-10 mg four hourly in young and middle-aged people and 2.5-5 mg in elderly patients. Starting therapy with an immediate-release preparation allows more rapid analgesia. The dose may be adjusted according to pain control, degree of side effects and total amount of opioid required, including breakthrough doses. For example, a patient receiving oral morphine 10 mg four hourly and requiring rescue doses for breakthrough pain (10 mg) three times daily, will be converted to a new daily dose as follows:

(maintenance: 10 mg x 6) + (breakthrough: 10 mg x 3) = 90 mg daily

Once pain control is stable, this dose may be administered as:

- immediate-release oral morphine 15 mg every 4 hours, or
- an equivalent dose of 12 hourly modified-release morphine twice daily plus appropriate doses of immediate-release morphine for breakthrough pain (see section 8.10).

Alternatively, an empiric increase of 30-50% of the previous daily dose is a useful rule of thumb in settings where breakthrough pain is not well monitored or treated.

Once analgesia is stabilised, there is no significant difference between pain control with 4 hourly immediate-release, 12 hourly modified-release, or once daily modified-release opioid preparations administered as appropriate. Modified-release preparations have a slow onset and time to reach peak concentrations, so they do not allow rapid titration for patients who are in severe pain. They are most appropriate for maintenance of analgesia once pain control is stabilised and have been shown to improve compliance and reduce sleep disturbance. Therefore, the following is recommended:

- Patients with stable pain on oral morphine should be prescribed a once or twice daily modified-release preparation.[9]
- Patients with stable pain on oral oxycodone should be prescribed a twice daily modified-release preparation.[9]

The following intervals should be observed before increasing the maintenance dose of opioid:

- Allow 24 hours of regular and breakthrough dosing before increasing the dose of immediate-release opioid.
- Allow 48 hours of regular and rescue dosing before increasing the dose of sustained-release morphine, hydromorphone and oxycodone preparations.
- Allow 72 hours before considering increasing the strength of a transdermal fentanyl or buprenorphine patch.[23]

Care should be taken when calculating a new opioid dose for patients who are pain free at rest, but who have pain on movement. If incident pain is confused with breakthrough pain when calculating the new dose, patients may experience opioid-related adverse effects, including excessive nausea, sedation and confusion.[9] Alternative methods for limiting pain on movement should be considered. Activities that may be associated with pain (e.g., bathing, dressing wounds) should be scheduled for one hour after the last dose of morphine or a breakthrough dose should be administered 1 hour before the event.

8.6 Alternative systemic routes of opioid administration

Because it is effective and simple, the oral route is preferred in the majority of patients receiving opioids.[9] However, alternative routes of administration (intravenous, transdermal, subcutaneous or rectal) may be necessary in patients with nausea or vomiting, those who cannot swallow and patients near the end of life who are weak or debilitated. Once they reach steady state, intravenous (IV) and subcutaneous (SC) continuous infusions of morphine are equianalgesic with similar side effect profiles.

The following recommendations apply:[9,11]

- Opioids should be administered orally as far as practical and feasible.
- Transdermal patches (e.g., fentanyl, buprenorphine) have a long duration of action and are useful alternatives to oral morphine. However, because of their slow onset of action and long time to reach steady state, they should only be initiated in patients whose pain has already been stabilised with oral morphine. The initial patch strength is calculated from the average 24 hour oral morphine dose required to control pain. Breakthrough doses of oral morphine may still be administered and patch strength should be titrated if necessary based on the average opioid requirement during the previous 72 hours.
- In patients unable to achieve adequate analgesia with oral and transdermal administration, continuous SC administration of morphine is simple and effective and the next preferable choice.

- SC opioids may be administered by patient controlled analgesia (PCA) pump, syringe driver, or disposable PCA device.
- Care should be taken when administering SC drugs with a syringe driver as the small volumes used means that the drugs delivered are often very concentrated, increasing the danger of drug incompatibilities and irritation of the SC site. Drug solutions for SC administration should be diluted to the maximum allowed by the administration device.
- Consider IV infusion when subcutaneous administration is contraindicated (e.g., peripheral oedema, coagulation disorders, poor peripheral circulation, need for high doses and volumes).
- When switching from oral to IV or SC opioids, the relative analgesic potency is the same for both routes and is between 3:1 and 2:1 (see section 8.8).
- IV administration should be used for opioid titration when rapid pain control is required. However, patients must be closely monitored for respiratory depression.
- PCA may be used with IV or SC opioid infusions for patients who are willing and able to be in control of doses for breakthrough pain.
- Rectal administration is not acceptable to many patients and is not a preferred route of administration. However, it may be preferable to IV administration when SC is not available.
- Diamorphine, oxycodone and hydromorphone are not available for parenteral administration in South Africa.

8.7 Changing from one opioid to another

A minority of patients may experience inadequate pain relief or persistent unacceptable side effects at step III of the analgesic ladder. In such cases, switching to another opioid to optimise the balance between pain control and side effects may be appropriate after consideration of the following:[9,11]

- Other pain control strategies must be optimised.
- Presumed adverse effects must be carefully differentiated from similar symptoms related to the patient's illness or adverse effects of other co-administered medications.
- Opioid-related side effects may be addressed with temporary reduction of opioid dose followed by slower titration.
- Additional medication may be used to control predictable side effects.
- Symptoms such as nausea or drowsiness may occur after switching to a potent opioid or increasing the dose. These side effects usually resolve within days and do not necessitate changing to another opioid.

8.8 Dose conversion ratios

Equivalent doses of opioids need to be calculated when

- stepping up from a weak opioid to morphine, or
- the need arises to switch to an alternative potent opioid.

Equianalgesic doses and dose ratios are listed in Table 8.4. These dose conversions are specific for patients with a satisfactory response to the first opioid. Therefore, in patients with inadequate analgesia and/or unacceptable side effects from the first opioid, the starting dose should be lower than that listed. In all cases, the dose must be titrated according to clinical response.[9]

It should be noted that there is a wide range of equianalgesic dose ratios listed in the literature and care should be taken with individual patients.

Table 8.4. Suggested dose conversion ratios[9,11]

Current opioid (converting from:)	**New opioid or new route of administration (converting to:)**	**Divide 24 hour dose of current opioid (column 1) by relevant figure below to calculate initial 24 hour dose of new opioid and/or new route (column 2) (the same units for both drugs must be used; e.g., mg)**
Example: 120 mg oral morphine in 24 hours	SC morphine	Divide by 3 (120 mg / 3) = 40 mg SC morphine in 24 hours
Oral to oral route conversions		
Oral codeine	Oral morphine	Divide by 10
Oral tramadol	Oral morphine	Divide by 5
Oral morphine	Oral oxycodone	Divide by 2
Oral morphine	Oral hydromorphone	Divide by 7.5
Oral oxycodone	Oral hydromorphone	Divide by 4
Oral to subcutaneous route conversions		
Oral morphine	SC morphine	Divide by 2-3
Oral oxycodone	SC morphine	No change
Oral oxycodone	SC oxycodone	Divide by 2
Oral to transdermal route conversions (see section 8.9)		
Oral morphine	Transdermal fentanyl	See Table 8.5
Oral morphine	Transdermal buprenorphine	Seek specialist palliative care advice (Table 8.6)

Other route conversions (rarely used in palliative medicine)		
SC or IM morphine	IV morphine	No change
Oral morphine	IV morphine	Divide by 2-3
IV morphine	Oral morphine	Multiply by 2
Oral morphine	IM morphine	Divide by 2

SC: subcutaneous; IM: intramuscular; IV: intravenous. Note: These dose conversions are specific for patients with a satisfactory response to the first opioid. Therefore, in patients with inadequate analgesia and/or unacceptable side effects from the first opioid, the starting dose should be lower than that listed. In all cases, the dose must be titrated according to clinical response. Active metabolites are not usually considered in studies and because of the role of metabolites that take longer to reach steady state, the applicability of these ratios to chronic opioid administration is questionable. Bioavailability may differ between individuals for the same and for different opioids.[9]

8.9 Transdermal opioids

Due to costs and dosing complications, it may be appropriate to seek specialist advice before starting therapy with transdermal opioids.

8.9.1 Transdermal fentanyl

Fentanyl patches may be appropriate for patients with stabilised severe pain (step III) who cannot tolerate oral therapy, or who express a preference for the patch. The transdermal system enables slow increase of drug plasma concentrations with a long half-life and provides continuous delivery of fentanyl for 72 hours.

- After initiating therapy or changing the dose there is a long latent period before steady state and analgesia are achieved, so dose titration is slow. Therefore, dose titration intervals should be at least 3 days.
- Starting a patch or titrating the dose must be accompanied by frequent reassessment and an appropriate immediate-release opioid for breakthrough pain.
- If dose titration is required to achieve pain control, the strength (opioid dose) of the patch may be increased, or a combination of lower strength patches may be applied at different places to achieve pain control.
- After patch removal, a subcutaneous depot of fentanyl remains and up to 24 hours may be required for fentanyl to clear from the system. Consequently caution must be applied when converting from the patch to another opioid.

Table 8.5 lists dose conversion ratios for switching from a strong opioid to a fentanyl patch.

Table 8.5. Conversion ratios from oral morphine to fentanyl patch[9]	
Oral 24-hour morphine (mg/day)	**Transdermal fentanyl patch (mcg/h)***
<90	25
90-134	37 (if available, otherwise 25)
135-189	50
190-224	62 (if available, otherwise 50)
225-314	75
315-404	100
405-494	125
495-584	150
585-674	175
675-764	200
765-854	225
855-944	250
945-1034	275
1035-1124	300
*Patches are available in the following strengths (mcg/h): 12, 25, 50, 75, 100. The doses listed are conservative for conversion from oral morphine to transdermal fentanyl. When converting from transdermal fentanyl to oral morphine, reduce the dose by one third. Particular attention to monitoring and dose titration up or down is required when switching between high-dose opioids, or after a recent rapid escalation of the dose of the first opioid.	
Frequency of oral opioid before switch:	**After initiating patch:**
4 hourly	Continue oral opioid for 12 hours
12 hourly	Give last dose when first transdermal patch is applied
24 hourly	Apply transdermal patch 12 hours after last dose

Because they contain an equal distribution of drug, some matrix fentanyl patches may be cut, meaning that it is possible to administer 37.5 mcg/h by using one full and one half 25 mcg patch. However, clinicians should confirm that it is appropriate to cut a particular patch before doing so.

8.9.2 Transdermal buprenorphine

Transdermal buprenorphine is available in three dosage forms from 5 to 20 mcg/hour. Patches are applied weekly and a second patch may be added after 3-5 days if pain relief is inadequate.

Table 8.6 lists dose conversion ratios for switching from a strong opioid to a buprenorphine patch.

Table 8.6. Conversion ratios from oral morphine to buprenorphine patch[61]

Oral 24-hour morphine (mg/day)	Transdermal buprenorphine patch (mcg/h)*
10	5
15	10
30	20
60	35
90	52.5
120	70
180	105
240	140

*Patches are available in the following strengths (mcg/h): 5, 10, 20.
Seek specialist advice before converting from an oral opioid to transdermal buprenorphine.

8.10 Breakthrough pain

Breakthrough pain (BTP) is common in patients with cancer pain. It is a transient exacerbation of pain occurring in a patient receiving chronic opioid therapy and with otherwise stable pain.[18] Characteristically, BTP has a rapid onset (peaks within 1-3 minutes) and may last from minutes to hours (median 30 minutes; range 1-240 minutes). It may be spontaneous (sudden and unexpected) or incident, related to an action, such as movement, cough, micturition, respiration or swallowing, in which case it may be anticipated.

BTP must be distinguished from 'end of dose failure' of regular analgesia, which has a gradual onset and longer duration than incident or spontaneous BTP.

Recommendations of management of BTP are as follows:[9,11,12,18]

- BTP should be treated with an orally administered immediate-release opioid.
- Oxycodone and morphine have similar analgesic and side effect profiles, but because morphine is less expensive than oxycodone, morphine is recommended as first-line choice for BTP.
- An appropriate dose of immediate-release oral opioid for BTP is equivalent to one sixth the total 24 hour dose of the around-the-clock opioid (i.e., one four-hourly dose).
- Use of BTP doses will dictate adjustment of the maintenance (around-the-clock) opioid dose: the 24 hour maintenance opioid dose should be up-titrated by adding the total BTP doses used in the preceding 24 hours to the current

maintenance dose, which will indicate the new 24-hour maintenance dose to be administered.

- BTP doses should be increased in proportion (1:6) as the maintenance dose is increased.
- Predictable episodes of BTP may be pre-emptively treated with an immediate-release, short-acting opioid 20-30 minutes prior to the provoking activity.

For example, a patient receiving oral morphine 10 mg four hourly and requiring breakthrough doses (10 mg) three times daily, will be converted to a new daily dose as follows:

(maintenance: 10 mg x 6) + (breakthrough: 10 mg x 3) = 90 mg daily

New daily dosage = 15 mg q4h plus 15 mg for breakthrough pain

8.11 Treatment of opioid-related side effects

8.11.1 Nausea and vomiting[11,12,40]

Up to 40% of patients receiving opioids will experience treatment-related nausea and vomiting. Because this side effect may be dose-limiting, effective management is essential.

- Patients should be advised that nausea and/or vomiting may occur when starting or increasing the dose of an opioid, but that it is likely to be transient and improve after 5-7 days.
- General recommendations that may assist to reduce nausea include not administering medication close to meals and avoiding fatty or spicy foods.
- Exclude other causes of nausea and vomiting.
- If nausea persists, consider prescribing and optimising antiemetic therapy (e.g., haloperidol, metoclopramide) before switching to a more potent opioid or increasing the dose.
- Other management strategies include discontinuing or reducing the dose of opioid (including using non-opioid analgesia for opioid-sparing effects), switching to another opioid or to another route of administration.

8.11.2 Constipation[11,12]

Complications of constipation include pain, overflow diarrhoea, bowel obstruction and urinary retention.

- Patients should be advised that constipation is common with all opioids.
- Laxatives should routinely be prescribed for prophylaxis of opioid-associated constipation, to be taken regularly at an effective dose.

- There is no evidence to recommend one laxative in preference to another.
- A combination of laxatives with different modes of action (e.g., stool softener and bowel stimulant) is more effective than a single agent.
- Patients should be advised that laxatives take time to work and adherence is important.
- Manual removal should never be attempted without sedation and pain control.

8.11.3 Drowsiness and other CNS symptoms[11,12]

Drowsiness is defined as 'decreased level of consciousness characterised by sleepiness and difficulty in remaining alert, but with easy arousal by stimuli'.

Opioids may be associated with sedative effects ranging from mild sleepiness to severe drowsiness or coma. Sedation may be accompanied by hallucinations, cognitive impairment, agitation, myoclonus, respiratory depression and delirium.

- Patients should be advised that drowsiness may occur when starting or increasing the dose of an opioid, but that it is likely to be transient, and that it may impair their ability to perform manual tasks (including driving).
- In patients with persistent or moderate-severe central nervous system side effects, if pain is controlled, consider dose reduction. If pain is uncontrolled, switch to another opioid.
- IV morphine should be used with caution in patients who are at risk of respiratory depression.

8.12 Use of opioids in renal failure[10,11,62]

- Accumulation of opioids and their metabolites may occur in patients with severe renal impairment. Therefore, in patients with severe renal impairment (glomerular filtration rate <30 ml/min), opioids should be used with caution.
- Where they are available, the opioids of first choice are fentanyl or buprenorphine administered at a low starting dose, followed by careful titration.
- Dose reduction of buprenorphine is not necessary in patients with renal impairment or undergoing haemodialysis treatment.
- An alternative short-term strategy is to reduce the dose or frequency of administration of morphine.
- Tramadol is recommended with caution.

8.13 Use of opioids in hepatic failure[62]

- Hepatic dysfunction may be associated with accumulation of opioids and their metabolites. Therefore, opioids should be used and titrated with care in patients with liver disease.
- Opioids that may be appropriate in these patients include fentanyl (recommended), or alternatively morphine, hydromorphone, oxycodone or codeine (recommended with caution).

8.14 Use of opioids in patients with HIV and AIDS[16,63]

- In addition to cancers, patients with HIV and AIDS may experience various conditions associated with both nociceptive and neuropathic pain.
- Pain management should follow the SHIP stepwise approach (Figure 7).
- Some antiretroviral medications have important drug interactions and contra-indications that necessitate caution, dose changes or selection of an alternative medication when considering co-prescription. Particular care should be taken with anticonvulsants, corticosteroids and antidepressants.
- There is anecdotal evidence that HIV/AIDS patients may respond to lower doses of opioids and starting doses may need to be reduced.

8.15 Patients with porphyria

Caution is needed when prescribing medication for patients with porphyria and specialist advice should be sought where necessary. Some medications that may be used are listed in table 8.7. For a complete list of drugs that may be used safely, or which should be avoided in patients with porphyria, refer to Porphyria South Africa; Universities of Cape Town and KwaZulu Natal: http://www.porphyria.uct.ac.za/professional/prof-home.htm.

Table 8.7 Use of medications in patients with porphyria[64]		
Use	**Use, but with caution**	**Use only with extreme caution, and only if no other alternative is available**
Ibuprofen	Clonidine	Diclofenac
Indomethacin	Tramadol	Venlafaxine
Naproxen	Metoclopramide	Amitriptyline
Gabapentin		Tilidine
Dexamethasone		
Prednisone		
Prednisolone		
Zoledronic acid		
Buprenorphine		
Codeine		
Dihydrocodeine		
Fentanyl		
Morphine		

9. Medications to be avoided

Pethidine, meprobamate and caffeine are sometimes used for analgesia, either alone or in combination with other analgesics. They are not recommended for use in patients with cancer.

9.1 Pethidine (meperidine)

Pethidine is not suitable for the management of chronic pain. It has a faster onset of action and shorter duration of action than morphine, necessitating dosing every 2-3 hours. It is metabolised to norpethidine, which may have serious side effects, including mood changes, tremors, myoclonus and convulsions.[16]

9.2 Meprobamate

Meprobamate is a central nervous system depressant with anxiolytic, sedative and muscle relaxant properties. Side effects include confusion and loss of consciousness. It has a narrow therapeutic index with a steep dose-response curve, resulting in an increased risk of accidental overdose associated with serious and potentially fatal

adverse events, including coma, profound hypotension, hypothermia, respiratory arrest and cardiogenic shock. When used for prolonged periods meprobamate carries a high risk of addiction, physical and psychological dependence. When discontinued abruptly, it is associated with severe, potentially fatal withdrawal symptoms. Consequently, the adverse effects associated with meprobamate outweigh its benefits and it should not be used.[65]

9.3 Caffeine

Caffeine is included in many combination analgesic products. When combined with non-opioid analgesics for the treatment of acute mild pain, it may be associated with a small increase in analgesic effect that is of questionable clinical relevance. Side effects, which include nervousness and dizziness, are common.[66]

Caffeine has no role in the management of cancer pain.

10. Management of procedural pain

Medical procedures are frequently associated with psychological distress and/or pain that must be anticipated and managed proactively. Painful and distressing procedures include, but are not limited to, moving the patient, changing dressings, venipuncture and venous catheterisation, arterial puncture, lumbar puncture, urinary and suprapubic catheterisation, heel pricks (in paediatric patients), chest drains, bone marrow aspiration and trephines, tissue biopsy and endotracheal intubation.

Certain patient populations, such as children and patients with HIV/AIDS may be especially vulnerable to procedure-related anxiety and pain.

Recommendations for management of procedural pain include:

- Anticipate, prevent and manage pain proactively.
- Keep procedures to a minimum, performing them only if they are really necessary.
- Patients should be reassured with discussion about the procedure and expectations before intervention.
- Where it is possible, patient discomfort may be reduced by consolidating patient interactions rather than spreading out interventional procedures during the day (e.g., washing the patient and changing dressings at the same time; taking all blood samples together with one venipuncture port).
- Maintenance analgesia should be optimised.
- Appropriate analgesia should be administered at an appropriate time before predictable incident pain (e.g., immediate-release oral morphine 20-30 minutes prior to the procedure).

For more information about acute pain management during interventional procedures, refer to the South African Acute Pain Guidelines, available at: http://www.sasaweb.com.

11. Anti-cancer treatments

Radiotherapy and chemotherapy may be effective for relieving pain and other symptoms (e.g., dyspnoea) associated with cancer. Treatment decisions should take into consideration the patient's goals, performance status, sensitivity of the tumour and potential toxicities. The goals of therapy and expectations from treatment need to be clearly explained and discussed with patients and their families.[2]

11.1 Radiotherapy

Patients with pain caused by bone metastases or metastatic spinal cord compression should be referred to a clinical oncologist for consideration for external beam radiotherapy or radioisotope treatment.[9,10]

Pain associated with metastatic spinal cord compression may be radicular and/or localised to the back or neck. Prognosis is poor in patients with neurologic deficits, and early clinical and radiological diagnosis and referral for radiotherapy are essential. Corticosteroids (e.g., dexamethasone) should be administered immediately on diagnosis.[10]

Indications for radiotherapy are listed in Table 11.1.

Table 11.1. Indications for radiotherapy in management of cancer pain[17]

Pain	Cause
Bone pain	Metastases; pathological fracture (nonsurgical; e.g., rib / pelvis)
Headache	Primary cerebral tumour; brain metastases
Abdominal pain	Hepatomegaly
Pelvic pain	Local tumour infiltration
Chest pain	Primary lung cancer; mesothelioma
Soft tissue pain	Local tumour infiltration

11.2 Chemotherapy

Chemotherapy may provide pain relief for patients with widespread metastatic disease and some chemosensitive tumours associated with widespread severe metastatic bone pain (e.g., multiple myeloma and small cell lung cancer). Indications for palliative chemotherapy are listed in Table 11.2. Chemosensitivity of primary tumours commonly metastasising to bone is listed in Table 11.3.[17]

Table 11.2. Indications for chemotherapy in the management of cancer pain[17]		
Pain	**Causes**	**Primary tumour types**
Bone pain	Bone metastases	• Myeloma • Breast cancer • Lung cancer (small cell and non-small cell)
Headache	Brain metastases	• Germ cell tumours • Lymphoma and leukaemias • [Breast cancer] • [Small cell lung cancer]
Abdominal pain	Ascites Subacute obstruction	• Ovary • Colorectal • Stomach
	Pancreatic pain	• Pancreas
Pelvic pain	Local tumour infiltration	• Colorectal • Ovary • Cervix
Chest pain	Local tumour infiltration	• Lung cancer (small cell and non-small cell) • Metastases from chemosensitive sites, e.g., breast, colorectal, [mesothelioma]
[] indicates tumours with only modest (<50%) response rates when other modalities, such as radiotherapy may be preferred.		

Table 11.3. Chemosensitivity of primary tumours commonly metastasising to bone[17]		
High (>50% response rate)	**Mid (25-50% response rate)**	**Low (<25% response rate)**
Myeloma Bronchus Breast	Rectum Oesophagus* *Mid/low	Oesophagus* Prostate Thyroid Kidney

11.3 Painful adverse effects of radiotherapy and chemotherapy

It is important to note that anticancer treatments themselves may be associated with painful syndromes, sometimes leading to chronic pain in cancer survivors. These include peripheral neuropathy due to chemotherapy, radiation-induced plexopathy, chronic pelvic pain secondary to radiation, and postsurgical pain. Pain may interfere with function and quality of life. Management should include patient education and psychological support.

A multidisciplinary approach including physiotherapy and occupational therapy is necessary and patients require early referral to specialist care.[10,67]

Treatment-related side effects associated with radiation therapy are directly related to the region that has received treatment. By definition, acute side effects are those occurring within 90 days from the start of treatment, whereas late effects occur after 90 days. Table 11.4 lists potential side effects and advice for management.

Table 11.4. Side effects of radiation therapy

Treated region	*Acute side effects*	*Management*
Head and neck	Oral mucositis Grade 3-4	Analgesics, mouth gargles, intraoral applications such as triamcinolone acetonide (Kenalog® in Orabase®) cream, oral corticosteroids.
Oesophagus	Oesophagitis	Mucaine® gel (oxethazaine, aluminium hydroxide, magnesium hydroxide) 10 ml 5 minutes before meals, analgesics (paracetamol).
Pelvic region	Cystitis, proctitis	Oral fluids, urinary antiseptics, local application (lignocaine jelly).
Skin	Wet desquamation, bleeding	Hydrocolloid dressings, antibiotic cream if infection is present.

Late effects can occur due to radiation fibrosis of the brachial plexus and lumbar plexus, radiation myelopathy, radiation necrosis of bones and soft tissue, and radiation-induced second primary cancers.

Other late effects include mucosal ulceration of the oesophagus and rectum with associated pain and bleeding. These should be treated using sucralfate, either orally or as an enema, as well as with corticosteroids and analgesics.

12. Invasive techniques for cancer pain

In approximately 10%-20% of patients with cancer pain, the response to oral and other systemic analgesics will be inadequate. Interventional pain procedures may be of value in a select group and patients should be referred to an appropriate center with the expertise to perform them. Prior to the procedure careful consideration should be given to likely benefits, risks, aftercare and possible complications, disease prognosis and expectations of the patient and family. Patients who are most likely to benefit include those with significant locally advanced disease, neuropathic pain or marked movement-related pain.[9,10,67]

12.1 Neuraxial drug delivery

Opioids may be delivered epidurally or intrathecally via percutaneous catheters, tunnelled catheters or implantable programmable pumps (Table 12).

Fully implanted systems offer less risk of infection and need less maintenance than percutaneous routes of administration, but their positioning is more complex. These routes of analgesic administration are associated with better analgesia, lower doses and less drug-related side effects than systemic administration, but are they not suitable in patients with infection, coagulopathy or a very short life expectancy. A trial of spinal analgesia using a temporary epidural or spinal catheter may be appropriate to help find the appropriate dose range before implanting a pump.

Because doses are much lower when opioids are administered by the spinal route, laxatives should be stopped and re-titrated. If peripheral withdrawal symptoms occur, the pre-spinal opioid should be given as necessary at a dose of approximately 25% that previously administered for breakthrough pain (i.e., prn dose).[40]

Table 12. Intrathecal infusion for refractory cancer pain[10]
1. Life expectancy <3 months Epidural or spinal catheter (tunnelled or with implantable system)
2. Life expectancy >3 months Trial of intrathecal catheter • If pain intensity decrease >50% is maintained, consider intrathecal implantable pump • If pain intensity is not reduced by 50%, remove catheter and reassess pain management

12.2 Peripheral nerve blocks

Pain occurring in the field of one or more peripheral nerves or due to complications such as perioperative pain, pathological fracture or vascular occlusion may respond well to a peripheral nerve block or plexus block used in conjunction with systemic analgesia. Pain relief lasts for a few weeks.

12.3 Autonomic neurolytic blockade

The sympathetic nervous system carries pain afferents from the viscera. Neurolytic blockade of these afferents lasts for 3-6 months and is suitable for patients with short life expectancy. Examples of autonomic neurolytic blocks are listed in Table 12.1.

Table 12.1. Autonomic neurolytic blocks/ablation		
Block/ablation	**Anatomy**	**Analgesic applications**
Coeliac plexus	Afferents from abdominal organs including pancreas, liver biliary tract, renal pelvis ureter, spleen, bowel to first part of transverse colon.	Pancreatic cancer, other upper gastrointestinal malignancies, including gastric cancer, oesophageal cancer, colorectal cancer, liver metastases, gallbladder cancer, cholangiocarcinoma.
Superior hypogastric plexus	Afferents from bladder, uterus, vagina, prostate, testes, urethra, descending colon, rectum.	Pelvic pain associated with pelvic malignancy.
Ganglion impar	Most inferior sympathetic ganglion lying anterior to sacrococcygeal junction.	Advanced cancer of the pelvis and perineum, after abdominoperineal resection for rectal cancer, following radiation proctitis.

13. Physiotherapy, occupational therapy and complementary health interventions

13.1 Physical therapies

Physiotherapy and occupational therapy are essential components of cancer rehabilitation. The main aims are to improve or maintain function; foster independence and autonomy; restore participation in occupational and social activities; improve vitality, mobility and quality of life; and to help relieve pain (where that is possible).

In order to prevent chronicity, anticipate future problems and facilitate early discharge from hospital, it is important that patients are referred for physical therapy as early as possible after diagnosis or when beginning cancer treatment. Physical activity interventions are useful to reduce the severity and impact of cancer-associated symptoms, including pain, nausea and fatigue, and may also be effective in rehabilitation and restoring function to parts of the body affected by deconditioning or surgery. Furthermore, there is some evidence that exercise may help to reduce the rate of tumour recurrence.[68-73]

Types of physical interventions and goals of therapy are listed in Table 13.1. These interventions require commitment from the patient and cooperation from the family, so therapy needs to be patient-centred and well planned with clearly defined, achievable goals.[67]

Table 13.1. Physical interventions for patients with cancer	
Intervention	**Goals of therapy**
Graded exercise therapy	• Improve physical function and reduce deconditioning problems associated with inactivity and immobility: muscle wasting and weakness, joint stiffness, reduced motor control and cardiovascular deconditioning. • Reduce severity and impact of symptoms of pain, nausea and fatigue. • Relieve pain-related fear of movement or repeated injury. • Improve self-efficacy. • Improve quality of life.
Transcutaneous electrical nerve stimulation (TENS)	• Pain relief.
Graded and purposeful activity; e.g., scheduling of daily activities, recreation and participation, including work	• Increase activity tolerance, autonomy, social integration, self-esteem and competency. • Restore function and independence for participation in daily activities and work.
Teach activity pacing skills	• Minimise painful episodes. • Increase self-efficacy and pain coping skills.
Educate patients in neurophysiology of pain	• Reduce fear of movement and improve coping self-efficacy.
Physical treatment modalities, including massage and soft tissue mobilisation, heat and cold where appropriate (heat should not be applied directly to an active tumour), posture re-education[74,75]	• Relieve pain where possible. • Restore range of motion and function of the affected regions of the musculoskeletal system.
Environmental adaptation Orthotics	• Restore function and independence for participation in daily activities and tasks. • Minimise painful episodes.

13.2 Complementary therapies for cancer pain

Although there is little or no evidence for effectiveness of complementary therapies in improving cancer pain, they are commonly used by patients who have faith in them or who are disillusioned with the efficacy of conventional medicine. In these terms they have the potential to improve well-being and may be useful in conjunction with conventional treatments and palliative care. Examples include aromatherapy, music therapy, homeopathy, hypnotherapy, massage, reflexology, reiki and relaxation.

Although there is no evidence of a direct effect on cancer pain, acupuncture may assist in alleviating chemotherapy-associated nausea and vomiting.

14. Pain in the terminal phase

When nearing death, pain is often accompanied by other symptoms such as dyspnoea, agitation, delirium and anxiety. To manage total suffering, each of these elements needs to be assessed and managed. This requires a multidisciplinary team including psychological and pastoral care personnel.

Pain assessment may be challenging in patients who are unable to self-report symptoms, especially those in ICU who are ventilated and/or sedated. In these patients, the Behavioural Pain Scale (Table 14.1) is a useful validated assessment tool, but pain assessment from close family members has been shown to accurately gauge the presence or absence of significant pain and should also be considered.[76,77] Behaviours that correlate with patients' self-report of pain include grimacing, rigidity, wincing, shutting of eyes, clenching of fist, verbalization and moaning.

The aim of end of life care is to make the patient as comfortable as possible, and treatments that are not contributing to this may be withdrawn at this time. Communication with both the patient (if possible) and the family to help them understand that is essential. Ethical and legal concerns about palliative methods, such as increasing opioids to achieve patient comfort should not impede appropriate care. Aggressive pain control, including increasing the administration of opioids, has not been shown to hasten death. On the contrary, it may prolong life by reducing the systemic effects of uncontrolled pain that can compromise vital organ functions.[76] Some patients may be unable to take medication orally and consideration of alternative routes of administration (e.g., rectal, sublingual or buccal, transdermal, subcutaneous, nasogastric or gastrostomy tube, IV) will become important.[16]

All changes in medication should be accurately documented.

Additional items that need to be noted in the patient's records include details of discussions with members of the healthcare team, family and patient, and use of advance directives, such as a living will and mandated consent documents.

Where pain is considered to be intractable, sedation may be the only option to relieve suffering, but should be regarded as a last resort for palliative care. In practice this is rarely required. Criteria for palliative sedation are listed in Table 14.2.

Table 14.1. Behavioural Pain Scale[78]

Item	Description	Score
Facial expression	Relaxed	1
	Partially tightened (e.g., brow lowering)	2
	Fully tightened (e.g., eyelid closing)	3
	Grimacing	4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with ventilation	Tolerating movement	1
	Coughing, but tolerating ventilation most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4

Table 14.2. Criteria for palliative sedation[77]

1. Confirmation of a terminal illness, the symptoms of which are refractory to all available treatments:
i. Aggressive efforts fail to provide relief.
ii. Additional invasive/noninvasive treatments are incapable of providing relief.
iii. Additional therapies are associated with excessive or unacceptable morbidity unlikely to provide relief in a reasonable time frame.
2. Psychological and spiritual assessments have been completed by a skilled clinician, clergy, or skilled palliative care team member.
3. Nutrition and hydration issues have been addressed and documented. For example, discussion with clinical staff and family regarding whether to continue or to withdraw parenteral fluids and/or nutrition. Recommendations are that this decision is individualised according to the patient's circumstances, advance directive (if present) and family preferences.

Section B: Management of cancer pain in children

15. Introduction

In general, the principles of pain management in children are similar to those in adults and readers are referred back to the main body of this guide for more detailed information. However, children are not small adults and the practitioner needs to modify his/her approach depending on the developmental level and maturity of the child's physiological systems. Pain assessment tools and drug doses, which are based on body weight, need to be age-appropriate.

Many of the pain treatments that are used for adults have not been adequately studied in paediatric patients and there is insufficient evidence on which to base all treatment and dosing recommendations. However, the evidence base is growing and current guidelines (based mostly on expert opinion) are sufficient to manage most pain in children and, if followed correctly, are safe. In fact, especially with opioids, and if the drugs are used correctly, children experience fewer side effects than adults. Nevertheless, under-assessment and under-treatment of paediatric pain is common and fear of dosing in children often prohibits good pain control. Some medications are unsuitable and need to be avoided in children.

As for adults, involvement of a multidisciplinary team and effective communication is fundamental to providing adequate pain management in children. Furthermore, the role of parents and caregivers should not be forgotten. They should be involved from the outset, to facilitate communication between clinician and patient, to provide comfort and support to the child and to participate in treatment decisions.

The following is a guide to the management of cancer pain in children. It is based on two paediatric guideline documents, namely those from the Hospice and Palliative Care Association of South Africa (http://www.hpca.co.za/resources) and from the World Health Organisation (http://apps.who.int/medicinedocs/en/m/abstract/Js19116en/).[13,25] While the main aim is to guide the management of pain in neonates, infants and children aged 0-10 years, these recommendations may also be applied to adolescents as much of the information on which they were based refer to studies including patients aged from 0 to 18 years.[13]

16. Assessment of pain in children (See Section 5)

Pain in children is often underestimated. Even though non-verbal children may not be able to report their pain, they do respond to pain in ways that are generally recognisable and many validated paediatric pain assessment tools are based on these behavioural and physiological responses.

Remember also that any illness or procedure that would cause pain in an adult will be painful to the child.

16.1 QUESTT principle to assess paediatric pain[25]

Question the parent/caregiver
Use an age-appropriate pain rating scale
Evaluate behaviour, physical findings, and physiologic changes
Secure the parent's or caregiver's involvement
Take the cause of pain into account
Take action and evaluate results

16.2 Summary of questions for the assessment of pain in children[13]

1. What words do the child and family use for pain?
2. What verbal and behavioural cues does the child use to express pain?
3. What do the parents and/or caregivers do when the child has pain?
4. What do the parents and/or caregivers not do when the child has pain?
5. What works best in relieving the pain?
6. Where is the pain and what are the characteristics (site, severity, character of pain as described by the child/parent, e.g., sharp, burning, aching, stabbing, shooting, throbbing)?
7. How did the present pain start (was it sudden/gradual)?
8. How long has the pain been present (duration since onset)?
9. Where is the pain (single/multiple sites)?
10. Is the pain disturbing the child's sleep/emotional state?
11. Is the pain restricting the child's ability to perform normal physical activities (sit, stand, walk, run)?
12. Is the pain restricting the child's ability/willingness to interact with others, and ability to play?

The PQRST (section 5.2.3) approach used in adults is a useful reminder for pain assessment in children (Table 5.2).

Children between the ages of 2-4 years will start to be able to express pain verbally. By the age of 5 they will be able to describe pain and its intensity, and by the age of 6, will be able to differentiate levels of pain intensity. Children older than 7 years will be able to explain why it hurts.

Children may be reluctant to report their pain if they are afraid of consequences, such as injections. Nonverbal cues that indicate the presence of pain and parental behaviours used to console the child (e.g., rocking, touch, verbal reassurance) must also be taken into account when assessing pain. Ask the parents or caregiver about the child's pain. They often know best about how the child expresses pain and what will comfort the child and they should be included in making decisions about symptoms and management.

16.3 Nonverbal expression of pain in children[13]

Main indicators of acute pain	Behaviours in chronic pain
• Facial expression • Body movement and body posture • Inability to be consoled • Crying • Groaning	• Abnormal posturing • Fear of being moved • Lack of facial expression • Lack of interest in surroundings • Undue quietness • Increased irritability • Low mood • Sleep disruption • Anger • Changes in appetite • Poor school performance

Reprinted with permission from the publisher from World Health Organisation. WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses. World Health Organisation; Geneva, Switzerland; 2012. Available at: http://apps.who.int/medicinedocs/en/m/abstract/Js19116en/.

16.4 Age-appropriate pain assessment tools

1.	Neonate:	Neonatal pain rating scale
2.	Nonverbal children or <3 years:	FLACC Score
3.	Children >4 years:	Revised Faces Pain Scale
4.	Children >7 years:	Numeric/word pain scale

16.5 Neonatal Infant Pain Rating Scale (NIPS)

Assess	Examination	Score	Description	Score
Facial expression	Relaxed muscles	0	Restful face, neutral expression	
	Grimace	1	Tight facial muscles, furrowed brow, quivering chin, tight jaw	
Cry	No cry	0	Quiet, not crying	
	Whimper	1	Mild moaning, intermittent	
	Vigorous cry	2	Loud scream, rising, shrill, continuous (Silent cry may be scored if baby is intubated and ventilated as evidenced by obvious mouth and facial movements)	
Breathing pattern	Relaxed	0	Usual pattern for infant	
	Change in breathing	1	Laboured, irregular, faster than usual, gagging, breath holding	
Arms	Relaxed	0	No muscle rigidity, occasional random movement of arms	
	Flexed, extended	1	Tense, straight arms; rigid and/or rapid extension/ flexion of arms	
Legs	Relaxed	0	No muscle rigidity, occasional random movement of legs	
	Flexed, extended	1	Tense, straight arms; rigid and/or rapid extension/ flexion of legs	
State of arousal	Sleeping/awake	0	Quiet, peaceful or alert, random leg movement	
	Fussy	1	Alert/restless and thrashing	

Reprinted from Hospice Palliative Care Association of South Africa.[25]

16.6 FLACC Score for nonverbal children or children <3 years

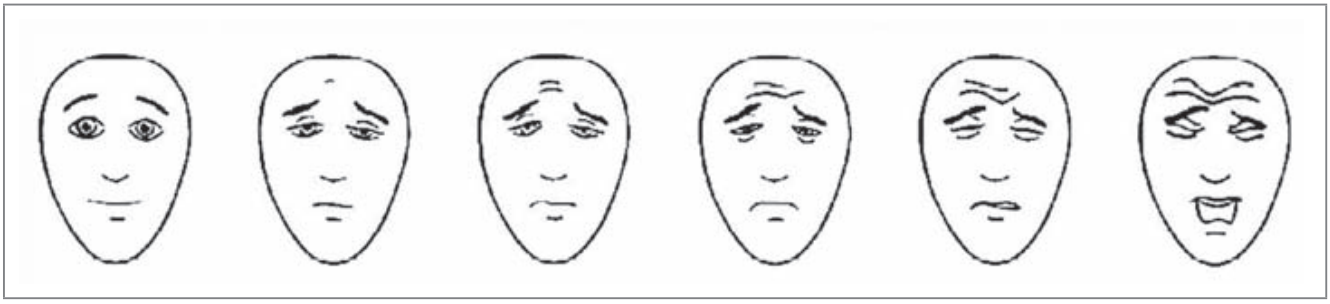
Item	Score		
	0	1	2
Face	No particular expression or smile	Occasional grimace or frown, withdrawn, disinterested	Frequent to constant frown, clenched jaw, quivering chin
Legs	Normal position or relaxed	Uneasy, restless, tense	Kicking, or legs drawn up
Activity	Lying quietly, normal position, moves easily	Squirming, shifting back and forth, tense	Arched, rigid or jerking
Cry	No cry (awake or asleep)	Moans or whimpers, occasional complaint	Crying steadily, screams or sobs, frequent complaints
Consolability	Content, relaxed, no need to console	Reassured by occasional touching, hugging or "talking to", distractible	Difficult to console or comfort

Reprinted from Hospice Palliative Care Association of South Africa.[25]

16.7 Revised Faces Pain Scale for children >4 years

Tell the child: "These pictures show how much something can hurt. No pain (on left); very much pain (on right). Point to the picture that shows how much you hurt."

0 2 4 6 8 10



(No Pain) (Worse pain)

- Do not use words like 'happy' and 'sad'
- The pictures represent how the child is feeling inside and not how their face looks

This Faces Pain Scale-revised has been reproduced with permission of the International Association for the Study of Pain® (IASP).[79] The figure may not be reproduced for any other purpose without permission.

16.8 Numeric/word pain scale for children >7 years

"Choose the number and word that best describes your pain"

0	1	2	3	4	5	6	7	8	9	10
No pain		Little pain			Medium pain			Large pain		Worst pain

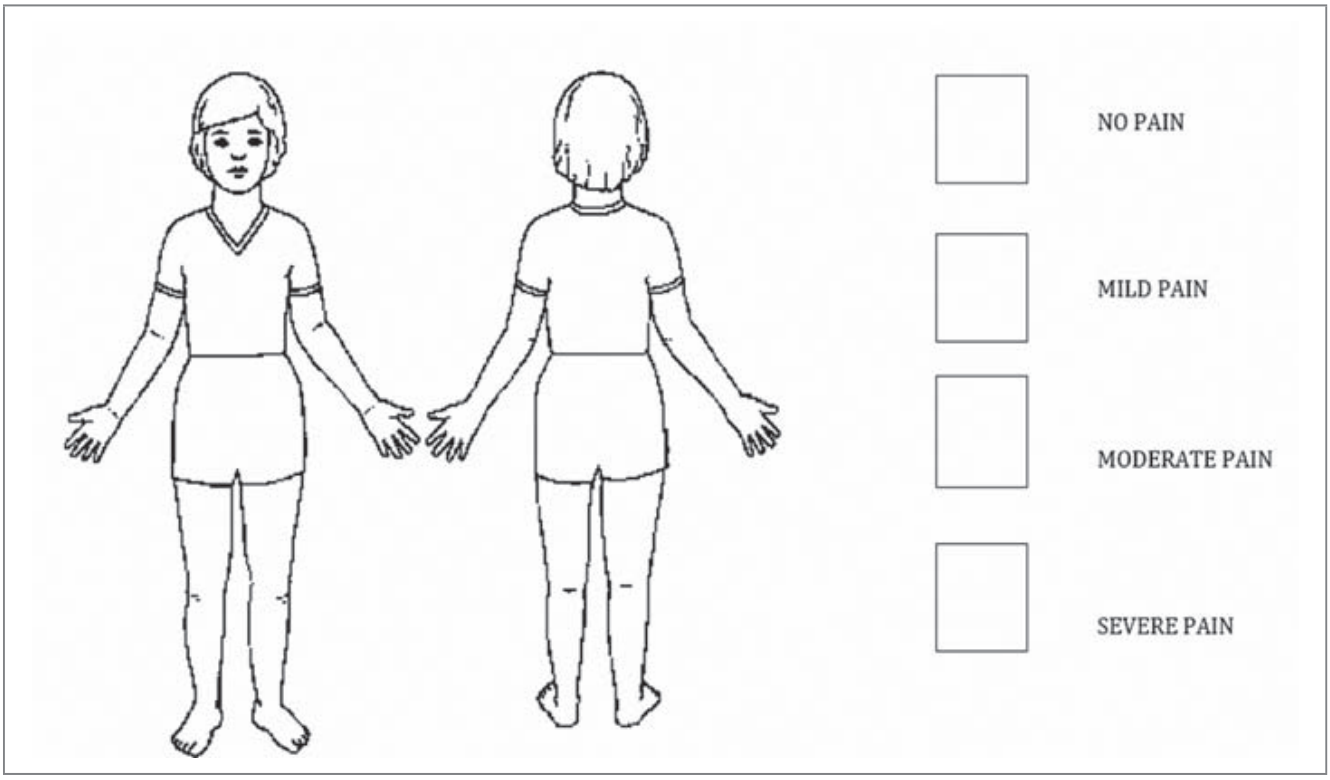
Mild pain: 0-3
Moderate pain: 4-6
Severe pain: 7-10

Reprinted from Hospice Palliative Care Association of South Africa.[25]

16.9 Eland body tool

Ask child to colour the picture of the body using colour to represent the level of pain in that area; e.g.,

Green: no pain Yellow: little pain
Orange: moderate pain Red: severe pain



Reprinted from Hospice Palliative Care Association of South Africa.[25]

17. Analgesic medication for children with cancer pain

17.1 Stepwise treatment of paediatric pain

As for adults, the WHO approach to pain management applies to children (Section 6).

However, there are some differences in the step-wise approach to pain management that apply to paediatric patients.

STEP 1

- Paracetamol alone or with ibuprofen are the drugs of choice at step 1 for children older than 3 months.
- Paracetamol is the only choice for children younger than 3 months.
- In children not able to take orally (e.g., vomiting, postoperative), paracetamol suppositories or IV paracetamol (especially in the postoperative paediatric patient) provide valuable alternatives.
- Other NSAIDs and COXIBs are not recommended for use in children.
- Aspirin should not be used in children or teenagers, because of the risk of Reye's syndrome.[80]
- Children may be at an increased risk of paracetamol-induced liver damage if they are malnourished, obese, suffering from a febrile illness, taking a prolonged course of treatment, have poor oral intake (nutrition and hydration), or are taking liver enzyme-inducing drugs.
- Inadvertent paracetamol poisoning may occur with the concomitant use of combination drugs (prescription or over-the-counter), most of which contain paracetamol.
- Acetylcysteine is the antidote in the case of paracetamol overdose.
- Age-appropriate doses of ibuprofen and paracetamol are listed in Table 17.1.

STEP 2

- Low-dose morphine is the opioid of choice at step 2.
- Tilidine drops are also used at step 2 in South Africa and provide the convenience of being concentrated and easy to administer even in children who cannot swallow.
- Codeine and tramadol are not recommended for use in children, but tramadol may be used in adolescent patients.
- There is anecdotal evidence that tricyclic antidepressants may be useful, especially in pain associated with HIV infection. Ideally, administration of tricyclic antidepressants in children should be preceded by ECG testing (contraindicated if QT is prolonged).

STEP 3

- Morphine is the opioid of choice at step 3.
- Persistent pain may be managed with prolonged-release oral morphine formulations administered every 8 to 12 hours. Unfortunately available tablet strength and inability of the young child to swallow tablets preclude their use in very young children. MST must not be crushed. The smallest prolonged-release tablet is a 10 mg tablet, which when given twice daily is equivalent to 3.3 mg of morphine given 4 hourly (the starting dose for a 16 kg child).

17.1.1 By the clock administration of analgesia

- Children should receive regular analgesia with supplemental doses for breakthrough pain (taking care not to exceed the maximal daily dose of paracetamol).

17.1.2 Analgesia should be administered by the appropriate route

- Medication should be administered by the simplest, most effective and least painful route.
- The oral route of analgesic administration is preferred (liquid or, when the child is old enough, solid forms).
- IM injections should not be used.
- Alternative routes of administration should be chosen based on clinical judgement and patient preference and include IV, SC, rectal and transdermal. Rectal administration results in unreliable blood concentrations and is not a preferred route of administration.

17.1.3 Individualised treatment

- There is no maximum dose of opioid analgesic for progressive malignant pain and dose should be titrated according to the child's level of pain and tolerability.
- Age-appropriate starting doses of opioids are listed in Tables 17.2 to 17.4.

17.2 Opioid switching

- Switching to an alternative opioid or route of administration is recommended when adequate titration of the initial choice fails to achieve adequate analgesia and side effects are intolerable.
- In children with persistent pain, alternatives to morphine include fentanyl and oxycodone.
- When switching opioids, dose conversions must be age-appropriate and consideration should be given to the bioavailability of the formulation, potential interactions with other medicines, renal and hepatic clearance,

and the opioid analgesics that have previously been used to relieve the child's pain.

- Dose equivalents for opioid switching are listed in Table 17.5.

17.3 Breakthrough pain

- Breakthrough pain must be distinguished from end of dose pain and incident pain related to movement or another precipitating factor.
- Immediate-release and IV morphine are recommended for breakthrough pain in children at a dose of 5% to 10% of the total daily dose of morphine (50%-100% of the regular 4 hourly dose).
- When converting from oral to IV morphine, care must be taken to observe correct dose conversions.
- Morphine takes up to 30 minutes to become fully effective, so another breakthrough dose should not be administered before 30 minutes.
- If breakthrough doses are required, the regular morphine doses should be adjusted (see below).

Increasing the dose of morphine

If pain is not controlled by regular morphine, the dose may be increased in one of two ways:

1. Increase the regular dose by 30%-50% (e.g., increase 5 mg q4h to 6.5-7.5 mg q4h).
2. Add up all the breakthrough doses and divide by 6, then add this total to the current daily maintenance dose; e.g., in a child with maintenance dose 5 mg q4h requiring 4 breakthrough doses of 2.5 mg each in a 24 hour period:
   - Total breakthrough dose = 4 x 2.5 mg = 10 mg
   - 10 mg ÷ 6 = 1.67 mg
   - 5 mg + 1.67 mg = 6.67 mg; round up to 7 mg
   - New dose = 7 mg po q4h with 3.5-7 mg for breakthrough pain

17.4 Discontinuing opioids in children and opioid-withdrawal syndrome

In children who have received significant doses of an opioid, sudden discontinuation of opioids may be associated with symptoms, including:

- Irritability
- Anxiety
- Insomnia
- Agitation
- Increased muscle tone
- Abnormal tremors
- Nausea
- Vomiting
- Abdominal cramps
- Diarrhoea
- Poor appetite
- Tachypnea
- Tachycardia
- Fever
- Sweating
- Hypertension

If the opioid needs to be discontinued, it should be withdrawn slowly, tapering the dose as follows:

- For short-term therapy (7-14 days): the original dose can be decreased by 10-20% of the original dose every 8 hours, gradually increasing the time interval.
- For long-term therapy: the dose should be reduced not more than 10-20% per week.
- These pharmacological approaches should be accompanied by measurement of withdrawal symptoms using a scoring system.

17.5 Opioid overdose

- Opioid overdose may be associated with respiratory depression, pinpoint pupils and coma.
- Naloxone is a specific antidote, starting at doses of 1 mcg/kg titrated over time (e.g., every 3 minutes) until the necessary dose is found. If necessary, this may be followed by a low dose infusion to maintain wakefulness until symptoms of opioid overdose resolve.
- Assisted ventilation should be provided where necessary and the child should be carefully monitored.
- Naloxone should be used with extreme caution so as not to precipitate acute pain or withdrawal symptoms.
- Where necessary, the opioid should be restarted at a lower dose.

17.6 Starting doses of analgesics in children

Starting doses of analgesics for children are listed in Tables 17.1 to 17.4.

Table 17.1. Nonopioid and weak opioid analgesic doses (oral route)[13]

Nonopioid analgesics				
	Neonates (age 0-29 days)	**Infants (age 30 days to 3 months)**	**Infants (age 3-12 months) and Children 1-12 years**	**Maximum daily dose**
Paracetamol	5-10 mg/kg q6-8h[a]	10 mg/kg q4-6h[a]	10-15 mg/kg q4-6h[a,b]	4 doses/day
Ibuprofen	Not indicated		5-10 mg/kg q6-8h	40 mg/kg/day
Weak opioids				
	Children			
Tilidine	1 mg/kg/dose q6h (approximately equivalent to 1 drop per 2.5 kg/dose q6h) Do not exceed a single dose of 1 mg/kg 3-4 times daily (q6h)			
	Adolescents (age >12 years)			
Tramadol	< 50kg: 1-2 mg/kg/dose 3-6 hourly (max 8 mg/kg/day) >50kg: 50-100 mg 3-6 hourly (max 400 mg/day)			

[a] Children who are malnourished or in a poor nutritional state are more likely to be susceptible to toxicity at standard dose regimens due to reduced natural detoxifying glutathione enzyme.
[b] Maximum 1 gram at a time.

Table 17.2. Starting doses for opioid analgesics for opioid-naive neonates[13]

Medicine	Route of administration	Starting dose
Morphine	IV injection[a]	25-50 mcg/kg every 6 hrs
	SC injection	
	IV infusion	Initial IV dose[a] 25-50 mcg/kg, then 5-10 mcg/kg/hr 100 mcg/kg every 6 or 4 hrs
Fentanyl	IV injection[b]	1-2 mcg/kg every 2-4 hrs[c]
	IV infusion[b]	Initial IV dose[c] 1-2 mcg/kg, then 0.5-1 mcg/kg/hr

IV: intravenous; SC: subcutaneous
[a] Administer IV morphine slowly over at least 5 minutes.
[b] The intravenous doses for neonates are based on acute pain management and sedation dosing information. Lower doses are required for non-ventilated neonates.
[c] Administer IV fentanyl slowly over 3-5 minutes.

Table 17.3. Starting doses for opioid analgesics in opioid-naive infants (age 1 month to 1 year)[13]		
Medicine	**Route of administration**	**Starting dose**
Morphine	Oral (immediate-release)	80-200 mcg/kg every 4 hrs
	IV injection[a]	1-6 months: 100 mcg/kg every 6 hrs 6-12 months: 100 mcg/kg every 4 hrs (max 2.5 mg/dose)
	SC injection	
	IV infusion[a]	1-6 months: Initial IV dose: 50 mcg/kg, then: 10-30 mcg/kg/hr 6-12 months: Initial IV dose: 100-200 mcg/kg, then: 20-30 mcg/kg/hr
	SC infusion	1-3 months: 10 mcg/kg/hr 3-12 months: 20 mcg/kg/hr
Fentanyl[b]	IV injection	1-2 mcg/kg every 2-4 hrs[c]
	IV infusion	Initial IV dose 1-2 mcg/kg[c], then 0.5-1 mcg/kg/hr
Oxycodone	Oral (immediate-release)	50-125 mcg/kg every 4 hours

[a] Administer IV morphine slowly over at least 5 minutes.
[b] The intravenous doses of fentanyl for infants are based on acute pain management and sedation dosing information.
[c] Administer IV fentanyl slowly over 3-5 minutes.

Table 17.4. Starting doses for opioid analgesics in opioid-naive children (age 1-12 years)[13]		
Medicine	**Route of administration**	**Starting dose**
Morphine	Oral (immediate-release)	1-2 years: 200-400 mcg/kg every 4 hrs 2-12 years: 200-500 mcg/kg every 4 hrs (max 5 mg)
	Oral (prolonged-release)	200-800 mcg/kg every 12 hrs
	IV injection[a]	1-2 years: 100 mcg/kg every 4 hrs 2-12 years: 100-200 mcg/kg every 4 hrs (max 2.5 mg)
	SC injection	
	IV Infusion	Initial IV dose : 100-200 mcg/kg[a], then 20-30 mcg/kg/hr
	SC infusion	20 mcg/kg/hr
Fentanyl	IV injection	1-2 mcg/kg[b], repeated every 30-60 minutes
	IV infusion	Initial IV dose 1-2 mcg/kg[b], then 1 mcg/kg/hr
Oxycodone	Oral (immediate-release)	125-200 mcg/kg every 4 hours (max 5 mg/dose)
	Oral (prolonged-release)	5 mg every 12 hours

[a] Administer IV morphine slowly over at least 5 minutes.
[b] Administer IV fentanyl slowly over 3-5 minutes.

Tables 17.2, 17.3 and 17.4 reprinted with permission from the publisher from World Health Organisation. WHO guidelines on the pharmacological treatment of persisting pain in children with medical illnesses. World Health Organisation; Geneva, Switzerland; 2012. Available at: http://apps.who.int/medicinedocs/en/m/abstract/Js19116en/.

Table 17.5. Dose conversions for opioid switching		
Dose ratio (parenteral : oral)[13]		
Morphine	1:2-1:3	
Equivalent dose[81]		
Morphine oral	10 mg	
Morphine subcutaneous	5 mg	
Oxycodone oral	5 mg	
Oral morphine to fentanyl patch[13]		
Morphine salt daily dose	***Fentanyl patch***	This table represents a conservative conversion to fentanyl transdermal patch and should NOT be used to convert from transdermal fentanyl to other analgesic therapies; overestimation of the dose of the new agent and possibly overdose with the new analgesic agent may result. The dosing conversion from oral morphine to transdermal fentanyl is conservative to minimize the potential for overdosing patients with the first dose, and therefore approximately 50% of patients are likely to require a higher dose following the initial application.
45 mg daily	12.5 mcg	
90 mg daily	25 mcg	
180 mg daily	50 mcg	
270 mg daily	75 mcg	
360 mg daily	100 mcg	

Note: As with adults, a 12 hour overlap period is required when switching from oral morphine to a fentanyl patch. Patch changes in children, however, may need to be made sooner than adults because of more rapid metabolism of fentanyl. In some instances patches may need to be changed every 48 hours rather than 72 hours. As with adults, provision needs to be made for breakthrough pain relief in patients on fentanyl patches.

One of the limitations with fentanyl patches in young children is their strength size and, where available, buprenorphine patches provide a good alternative for use in the smaller child or infant. See table 8.6.

17.7 Analgesic doses in renal and hepatic impairment

Recommendations for dose adjustment in children with renal or hepatic impairment are described in Table 17.6.

Table 17.6. Dose adjustment in children with hepatic or renal impairment

Drug	Renal impairment†			Hepatic impairment
	Mild	*Moderate*	*Severe*	
Paracetamol		10-15 mg/kg/dose; may administer q8h	10 mg/kg/dose; may administer q8h	Dose-related toxicity; do not exceed daily recommended dose.
Ibuprofen	Use lowest effective dose and monitor renal function. Sodium and water retention may occur, possibly leading to renal failure.	Avoid.		Use with caution – there is increased risk of gastrointestinal bleeding; can cause fluid retention; avoid in severe liver disease.
Morphine	Reduce dose by 25%. Increase dose interval to 6-8 hourly (titrate against pain).		Reduce dose by 50% or consider switching to an alternative opioid with less renal elimination, e.g., fentanyl. Increased and prolonged effect; increased risk of neurotoxicity.	Reduce dose. May precipitate coma.
Naloxone	Opioids may accumulate in renal impairment so extended treatment with naloxone may be required to reverse the opioid effect.			No dose adjustment necessary.
Oxycodone	Dose reduction may be required. Start with lowest dose and titrate according to response.			In moderate to severe hepatic dysfunction, avoid or reduce dose by 50%.

†Mild renal impairment: GFR 20-50 ml/min/1.73 m^2 or serum creatinine 150-300 micromol/L
Moderate renal impairment: GFR 10-20 ml/min/1.73 m^2 or serum creatinine 300-700 micromol/L
Severe renal impairment: GFR <10 ml/min/1.73 m^2 or serum creatinine >700 micromol/L

17.8 Bisphosphonates are not recommended for the management of cancer pain in children

17.9 Other analgesics

There is insufficient evidence to make specific recommendations about the use of antidepressants and anti-epileptic drugs for the treatment of cancer pain.

Typical paediatric doses of drugs that have not been discussed in the previous sections are listed in Table 17.7.

Table 17.7. Typical doses of other analgesics and drugs[25]		
Drug	**Dose**	**Comments**
Amitriptyline	**2- 12 years:** 0.1-0.2 mg/kg at night. Increase to max 1-2 mg/kg at night over 1-2 weeks. **12-18 years:** 10-25 mg po at night, increase to 75 mg maximum.	Do ECG before using. Contraindicated in patients with prolonged QT interval. Pain dose is lower than for depression. Takes up to 3 weeks for effect. No longer considered first line if other adjuvants are available.
Carbamazepine	5-20 mg/kg/day in 2 or 3 divided doses, increase gradually to avoid side effects.	Induces cytochrome P450. Drug interactions with antiretroviral drugs. Can cause pancytopenia.
Gabapentin	**2-12 years:** 3-5 mg/kg/dose. Start nocte, then q12h then q8h. Increase to 10-20 mg/kg/dose. **12-18 years:** 300 mg on day 1; 300 mg q12h on day 2; 300 mg q8h on day 3. Max 1200 mg q8h.	Avoid sudden withdrawal Do not use in patients with history of psychiatric illness.
Corticosteroids	Prednisone 1-2 mg/kg/day Dexamethasone: 0.1-1.5 mg/kg (max 10 mg) increased to 0.1-0.25 mg/kg/dose q12h for 14 days.	Useful for neuropathic pain, bone pain, IRIS.
Clonidine	1-4 mcg/kg/dose q6-12h.	Caution in renal failure, vascular disease, depression.
Diazepam	**1-6 years:** 1 mg/day in divided doses (2-3). **6-14 years:** 2-10 mg/day in divided doses (2-3).	Used for associated anxiety.
Hyoscine butylbromide	**1 month-2 years:** 0.5 mg/kg/dose PO q8h. **2-5 years:** 5 mg po q8h. **6-12 years:** 10 mg po q8h.	For colicky abdominal pain. Can cause nausea, dry mouth and constipation.

IRIS: Immune Reconstitution Inflammatory Syndrome

18. Conclusion

Pain is a significant cause of morbidity and reduced quality of life in patients with cancer and at the end of life. A standardised and co-ordinated multidisciplinary team approach to pain assessment and management is crucial to alleviate suffering for both patients and their families while pursuing healing or a comfortable end of life period.

The South African Cancer Pain Working Group hopes that this guide will be useful to healthcare providers caring for patients with cancer pain. We encourage units to develop their own protocols based on this document to help standardise and afford the best possible care for these challenging patients.

Appendix 1: Essential Drug List (EDL)

EDL Adult Hospital (2012)

- Paracetamol
- Ibuprofen
- Codeine phosphate
- Tramadol
- Morphine syrup
- MST (Morphine long acting/ slow release)
- Amitriptyline
- Carbamazepine
- Metoclopramide
- Sennasides
- Lactulose
- Promethazine
- Diazepam
- Hyoscine butylbromide

Department of Health. Standard Treatment Guidelines And Essential Medicines List For South Africa Hospital Level Adults; 2012 Edition. Copies may be obtained from: The Directorate: Affordable Medicines, Private Bag X828, Pretoria, 0001 OR Department of Health Website: www.doh.gov.za.

EDL Paediatric Hospital (2013)

- Paracetamol
- Ibuprofen
- Codeine phosphate syrup
- Tramadol
- Morphine syrup
- MST (Morphine long acting/ slow release)
- Tilidine
- Prednisone
- Betamethasone
- Carbamazepine
- Cyclizine
- Metoclopramide
- Lactulose
- Promethazine
- Hydroxyzine
- Lorazepam
- Hyoscine butylbromide
- Zinc in castor oil topical lip care or perineal mucositis/nappy rash
- Thymol glycerine compound

- Chlorhexidine/benzydamine oral rinse
- Lignocaine/prilocaine topical cream
- Short acting sedatives
- Benzodiazepine (diazepam)
- Ondansetron
- Midazolam*
- Ketamine*

* The intravenous formulations of ketamine and midazolam can be given orally

Department of Health. Standard Treatment Guidelines And Essential Medicines List For South Africa Hospital Level Paediatrics; 2013 Edition**.** Copies may be obtained from: The Directorate: Affordable Medicines, Private Bag X828, Pretoria, 0001 or Department of Health Website: www.doh.gov.za.

EDL PRIMARY HEALTH CARE (2008)

- Paracetamol
- Ibuprofen (max 1200 mg to be prescribed by a nurse)
- Codeine phosphate
- Tramadol (doctor initiated)
- Morphine syrup (doctor initiated)
- MST (Morphine long acting/ slow release) (doctor initiated)
- Amitriptyline for neuropathic pain (doctor initiated)
- Metoclopramide
- Lactulose
- Chlorpheniramine
- Diazepam
- Hyoscine butylbromide

Department of Health. Standard Treatment Guidelines And Essential Medicines List For Primary Health Care Level; 2008 Edition. Copies may be obtained from: The Directorate: Affordable Medicines, Private Bag X828, Pretoria, 0001 or Department of Health Website: www.doh.gov.za.

Conflicts of interest

Dr Blanchard has received sponsorship from Janssen Pharmaceuticals; Dr Chetty has received honoraria from Janssen Pharmaceticals, Mundipharma, Pfizer Laboratories, Adcock Ingram, Nycomed, Aspen Pharmaceuticals and Reckitt Benckiser; Dr Hodgson has received honoraria from Abbvie/Abbott Laboratories, Bayer, Baxter, Fresenius-Kabi, MSD, Mundipharma, Pfizer, Roche and Sanofi and he is a paid member of advisory boards for Fresenius Kabi and Mundipharma; Dr Webb is a professional medical writer and has provided services to Abbvie/Abbott Laboratories, Adcock Ingram, Alcon Laboratories, AstraZeneca, Eli Lilly, Janssen Pharmaceutica, Mundipharma, Novartis, and Reckitt Beckiser Pharmaceuticals. Drs Gwyther, Kamerman, Meiring, Professor Sharma and Ms Ganca declare no conflict of interests.

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