



**SOUTH AFRICAN SOCIETY
OF ANAESTHESIOLOGISTS (SASA)**

South African Acute Pain Guidelines

**Official publication of The South African Society
of Anaesthesiologists (SASA)**

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1. Acute pain management – Foreword

I prefaced the first edition of the *South African acute pain guidelines* by stating that “acute pain management is not a luxury, it is a human right!” Six years have passed and the statement is still pertinent.

The World Federation of Societies of Anaesthesiologists and the International Association for the Study of Pain have both identified the fact that pain is badly managed in all parts of the world, but that attention needs to be given to pain management in developing countries. It has become evident that acute pain management must be the starting point for educational initiatives. Chronic pain can only be addressed when the management of acute pain is effected.

Anaesthesiologists predominantly treat acute postoperative pain. Records of their success have been documented, but it has been demonstrated in only a few studies that alleviating this form of pain is effective. The classic Apfelbaum study of 2003 revealed that in the period 1995–2003, very little progress was made in managing pain. Approximately 80% of all surgical patients experienced moderate to extreme pain following their surgery. Reports from the recent European PAIN OUT Symposium 2014 were also not encouraging as it was revealed that 40% of patients experienced severe postoperative pain, and almost 50% of patients wished that they had received better pain therapy. Is this acceptable today? I believe not. This fact merely serves to demonstrate that the need identified by the two world bodies exists! We need to focus our attention on the management of acute pain, as the effective treatment of acute pain must become a fundamental component of quality patient care.

Is the relief of acute pain the only outcome that we need to assess when managing postoperative patients? The very simple answer to this question is: “No”. Unrelieved pain has other consequences besides patient satisfaction. Adverse physiological and psychological effects may result from unrelieved severe acute pain. The effective treatment of postoperative pain may reduce the incidence of postoperative morbidity and facilitate earlier discharge from hospital. Furthermore, the successful treatment of postoperative pain reduces the incidence of chronic pain. It can be concluded that there are physiological, psychological and economic reasons to ensure that patients receive effective acute pain therapy.

If acute pain management is a priority, then it follows that educational initiatives must form part of the overall plan. This guideline forms an integral part of the initiative as it serves as a reference to all practitioners who manage acute pain. The guideline not only provides factual medical information, but also deals with non-medical issues, such as patient education. The authors focus on how analgesia, its role in recovery and rehabilitation, and other available nonpharmacological options can improve acute pain management.

As stated in the first edition of the guideline, this document must be considered an aid to any healthcare professional managing acute pain, rather than a “recommended” regimen. The individual practitioner must evaluate the patient and adapt any of the suggestions according to the medical condition or American Society of Anesthesiologists status of that particular patient.

I concluded the first foreword by stating, “It is hoped that by using the information provided in this publication there will be meaningful benefit for both the medical professional and the patient”. Six years later, I can proudly state that the use of this guideline will provide meaningful benefit to both medical practitioners and patients.

Dr Milton Raff

Chairperson: World Federation of Societies of Anaesthesiologists Pain Relief Committee

2. Introduction

Welcome to the second edition of the South African Acute Pain Guidelines. It has been revised, incorporating new drugs and recent advances in acute pain management. These guidelines are recommended for use by all medical practitioners involved in acute pain management of adults and children.

Guidelines should always be viewed as “works in progress”, and the Regulation Business Unit of the South African Society of Anaesthesiologists would appreciate inputs from colleagues from all sectors of medical practice over the next few years. Address your contributions and opinions to the SASA CEO, via email: ceo@sasaweb.com, who shall ensure the contributors and Councillors responsible for Practice Guidelines are informed. A formal review of these guidelines is due in 2021, at the discretion of the South African Society of Anaesthesiologists.

The South African Society of Anaesthesiologists appointed a consensus group of practitioners from varying specialities, with varying areas of expertise and interest, to update these guidelines, which cover a wide range of important clinical topics.

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3. The physiology of acute pain

Pain is a complex interaction of sensory, emotional and behavioral factors. There are no pain pathways, only nociceptive pathways. Nociception is modulated at the level of the spinal cord and interpreted by the cortex, resulting in varying degrees of discomfort and pain.

Pain is defined by the International Association for the Study of Pain as an “unpleasant sensory and emotional experience, associated with actual or potential tissue damage or described in terms of such damage” (Mersky).

Acute pain is defined as pain of short and limited duration. The pain relates to an identifiable cause (trauma, surgery or inflammation).

Acute and chronic pain represent a continuum of a process where inflammatory neuropathic visceral and somatic pain plays a role. The central nervous system (CNS) is not a hard-wired system. It allows for peripheral, central, intracellular and synaptic modifications. Acute pain can result in long-term changes and a subsequently modified response to sensory input (neuroplasticity).

Pain is divided into physiological pain and pathophysiological or clinical pain.

Physiological pain is the activation of nociceptors in response to a noxious stimulus, whereas clinical pain includes tissue and/or nerve injury and the inflammatory response. Physiological pain serves as a protective mechanism, is well localised, is transient and is well differentiated from touch.

Clinical pain outlasts the stimulus and spreads to non-damaged areas, leading to primary hyperalgesia. Peripheral sensitisation occurs as part of the inflammatory response and results in activation of the high threshold A beta fibres. This leads to the sensation of touch not being differentiated from pain. Antidromic impulses result in the release of neurotransmitters from nerve endings of a primary afferent in response to noxious stimulation.

3.1 Understanding nociceptive pathways

3.1.1 Primary afferent fibres and the dorsal horn

Peripheral nociceptors are organs which respond to pressure, temperature and chemical stimuli. The nociceptor cells are located in the dorsal root ganglia, except for the fibres innervating the head and the oral cavity, whose cell bodies are located at the trigeminal ganglion. There are two main categories of nociceptors:

- A δ fibres (10–20%) are thinly myelinated and transmit mechanothermal stimuli.
- C fibres (80–90%) are non-myelinated and are polymodal.

The A δ and C fibres are high threshold fibres. Inflammatory soup chemicals sensitise high threshold nociceptors; common after surgery and trauma.

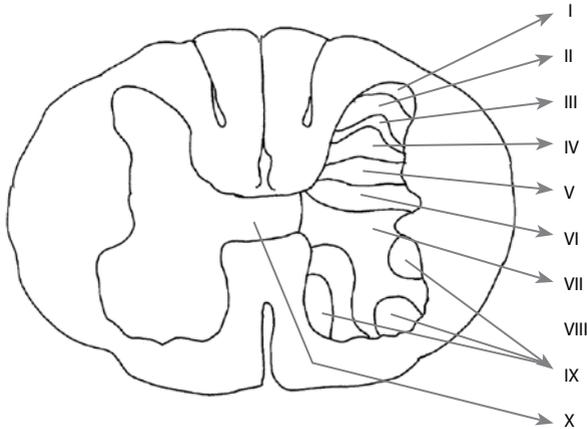


Figure 1: Laminae in the dorsal horn

Silent nociceptors become active in the presence of inflammation and play a part in peripheral sensitisation. The laminae in the dorsal horn are outlined in Figure 1.

The dorsal horn is made out of lamina I–X:

- Lamina I mainly consists of A δ fibres.
- Lamina II is called the substantia gelatinosa, and mainly contains C fibres and interneurons. Ascending tracts do not originate from lamina II.
- Laminae III and IV contain interneurons.
- Lamina V contains wide dynamic range (WDR) neurons (high threshold interneurons).
- Lamina IX mainly represents motor neurons, and lamina X is made of visceral interneurons.

Primary afferents interact extensively with other afferents, as well as with interneurons (second order neurons) and the endings of descending fibres. Second order neurons are divided into high threshold neurons (nociceptive specific) and WDR neurons. When sensitised, the WDR neurons respond and discharge in response to tactile non-noxious stimuli (allodynia).

Central sensitisation results from activation of the N-methyl-D aspartic acid (NMDA) receptors and leads to secondary hyperalgesia, wind-up and long-term potentiation, which represents increased activity in the dorsal horn following repetitive stimulation. Repetitive low threshold stimulation results in the phenomenon of wind-up and temporal sum-

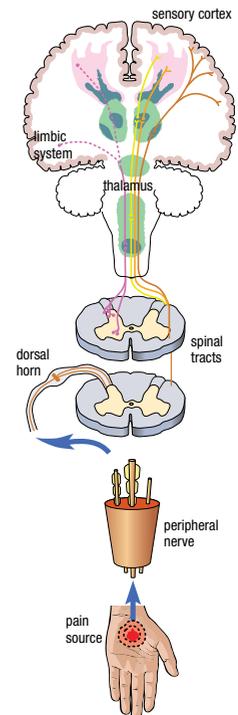


Figure 2: Basic afferent pain pathway

mation. These phenomena represent the decreased threshold and increased intensity which occur in the spinal cord neurons as a result of repetitive stimulation from the primary nociceptors.

A stimulus occurring at a low threshold results in an increased magnitude and longer duration of depolarisation at the postsynaptic neuron.

Ten per cent of the primary afferents terminate in the anterior horn (which explains the possible failure of rhizotomy).

Collateral branches of the small fibres A δ and C may travel in the lateral part of the entry zone for several segments before synapsing in the dorsal horn (Lissauer's tract). The basic afferent pain pathway is outlined in Figure 2.

3.2 Neurotransmitters

3.2.1 At the periphery

Peripheral sensitisation occurs due to substances released by the damaged tissues, blood vessels and sympathetic terminals. This is termed the inflammatory soup and contains hydrogen and potassium ions, bradykinine, histamine, noradrenalin, 5-hydroxytryptamine (5-HT), prostaglandin, substance P, leukotrienes, nerve growth factor and others.

3.2.2 Dorsal horn

Excitatory

Substance P, neurokinine 1 and glutamate activate the low threshold α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and neurokinin 1 (NK-1) receptors, which, in turn, sensitise and activate the high threshold NMDA receptor.

Inhibitory

Noradrenalin, dopamine, serotonin, histamine, oxytocin and vasopressin, acetyl choline, γ -aminobutyric acid (GABA), glycine and opioids predominantly occur at the descending pathways.

3.3 Intracellular events

NMDA activation in the CNS (removal of the Mg plug) leads to Ca influx to the cell, the production of nitric oxide and secondary messengers, as well as prostaglandin production. C-fos gene expression occurs within minutes of a painful stimulus and serves as a marker for noxious stimulation. C-fos is thought to be the link between acute and chronic pain.

3.4 Receptors and ligands

Ligands transduce the specific stimulus into an action potential which is sodium (Na) channel dependent. Tetrodotoxin, which is present in all sensory neurons, rapidly deactivates the Na current. Local anaesthetics

Table 1: Receptors and ligands

Receptor	Subtypes	Ligands
Transient receptor potential receptors (TRPs)	TRPV1	Heat ≥ 42 °C, H+ and capsaicin
	TRPV2	Heat ≥ 54 °C
	TRPA	Cold ≤ 17 °C
Acid sensing	ASIC	Protons
	DRASIC	
Purine	P2X3	ATP
Serotonin	5-HT ₃	5-HT
NMDA receptor	NRI	Glutamate
AMPA	iGlutR1	Glutamate
Kainate	iGlutR5	Glutamate
Prostanoids	EP1-4	PGE ₂
	IP	PGI ₂
Histamine	H1	HA
Serotonine	5-HT _{1A} , 5-HT _{2A} and 5-HT ₄	5-HT
Bradykinine	BK1 and BK2	BK
Cannabinoids	CB1-2	Anandamide
Opioids	Mu, delta and kappa	Enkepalin, dynorphin and beta-endorphin
Thacykinine	NK-1	Substance P and neurokinine A

5-HT: 5-hydroxytryptamine, AMPA: α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, ASIC: acid-sensing ion channel, ATP: adenosine triphosphate, DRASIC: dorsal root acid sensing ion channel, NK-1: neurokinin 1, NMDA: N-methyl-D-aspartic acid, PGE₂: prostaglandin 2, PG1₂: prostacyclin, TRP: transient receptor potential

act at this level, but as Na channels are present in all nerve fibres, blocking of the autonomic motor and sensory fibres can occur. Agents which block subtypes of Na channels (specific to sensory fibres) are not yet available.

Pain modulation can be achieved by decreasing excitation (opioid receptor, Na channel blockers and ketamine) and/or increasing inhibition [increased alpha-2 agonist (clonidine) and glycine (GABA agonists) at the level of the spinal cord].

The most common receptors and ligands are outlined in Table 1.

3.4.1 Ascending pathways

The spinothalamic tract originates in laminae I, II and V, ascends to the thalamus and then the somatosensory cortex, providing information on the type and the site of the painful stimulus.

The spinomesencephalic tract mainly originates in lamina I and mediates the affective and emotional component of the nociceptive stimulus. Autonomic and sensory coordination is provided by this pathway. The cingulate cortex, insula, periaqueductal grey (PAG), reticular formation and prefrontal cortex receive multiple inputs, and help to coordinate autonomic and emotional responses.

3.4.2 Descending inhibition

These pathways modulate the nociception by action on the primary afferents and interneurons at the level of the dorsal horn. They inhibit transmission towards the cortex and other higher centres. Tracts originate in the cortex, PAG and brain stem nuclei. These fibres terminate in the dorsal horn, facilitating inhibition and modulating the nociceptive input. Tricyclic antidepressants, opioids and alpha 2 agonists are important agents for modulating nociception via the descending pathways. Inhibitory neurotransmitters include opioids, 5-HT, norepinephrine (NE) and GABA.

3.4.3 Neuropathic pain

By definition, neuropathic pain is pain which originates in the nervous system. There is no clear distinction between neuropathic and nociceptive pain as they often co-exist. Trauma and surgery cause nociceptive as well as neuropathic pain (cutting nerve endings), while pure nerve destruction results in an inflammatory process.

3.4.4 Receptors

Activation of the nociceptors produces depolarisation and eventually triggers an action potential and release of ligands from the nerve endings.

3.4.5 Opiate receptors

Opiate receptors were first identified in 1973. They are synthesised by the cell body in the dorsal horn and respond to endogenous and exogenous opiates. Note that opiate receptors are also transmitted peripherally along the nerve fibre. This explains the opioid's effect when administered intra-articularly or into the subcutaneous tissue. They are mainly located presynaptically (75%). Activation of the opioid receptors reduces the release of neurotransmitters from the primary afferent neuron. Inflammation and nerve injury result in the loss of opioid receptors presynaptically, and the formation of the metabolite, morphine 3 glucuronide, which antagonises opioid analgesia.

3.4.6 γ -aminobutyric acid and the glycine receptors (central nervous system)

GABA and the glycine receptors in the CNS have an inhibitory function. GABA-A is largely postsynaptic and responds to endogenous GABA ligand and benzodiazepines. GABA-B is a presynaptic receptor which responds to endogenous GABA and baclofen. Barbiturate, anaesthetic drugs and corticosteroids are also thought to activate the GABA receptor.

3.4.7 Adrenoreceptors

Activation of the alpha adrenoreceptors at the dorsal horn has an analgesic effect (endogenous NE and exogenous clonidine). The effect is synergistic with the opioid agonists.

3.4.8 N-methyl-D-aspartic acid receptor

The release of glutamate and substance P from the nociceptive primary afferents activates the low threshold AMPA and NK-1 receptors, which, in turn, activate the NMDA receptor. The removal of the Mg plug is followed by an influx of Ca into the cell and subsequent depolarisation. Ketamine is an NMDA antagonist with the potential to provide analgesia and modulate the development of chronic pain. The NMDA receptor is involved in the development of tolerance to opioids.

3.4.9 Transient receptor potential receptors

Transient receptor potential (TRP) V1 (TRPV1), previously called VR1, is a nonselective ion channel, activated by capsaicin (a vanilloid compound), heat above 43 °C, lipoxygenase, products of arachidonic acid and N-archidonoyl dopamine.

Other members of the TRP family of ion channels have been described and found to be important in nociceptor activation. TRPV2-4, as well as TRPM8 and TRPA1, are all activated by temperature in the noxious and non-noxious range, and together encode the entire temperature spectrum.

3.4.10 The autonomic nervous system

The autonomic nervous system is closely linked to the nociceptive pathways. It is important to remember that the sympathetic system is an efferent system. Biofeedback is maintained at the:

- *Dorsal horn level:* Extensive synapses between the afferent and sympathetic fibres take place at the dorsal horn level.
- *Dorsal respiratory group (DRG) level:* Sympathetic fibres form a "basket" around the DRG, influencing afferent transmission.
- *Peripheral level:* Somatic and visceral nociception causes vasodilatation, tissue damage and the subsequent release of neurotransmitters. Circulating catecholamine and NE released from the sympathetic fibres perpetuate the noxious stimulus.

3.4.11 The gate control theory

In 1965, Melzack and Wall first published the gate control theory. The modulating role of the dorsal horn was conceptualised. Melzack and Wall postulated in the initial theory that the large fibres could be viewed as "closing the gate" to nociception transmission into the higher centres. In 1982, they modified the theory to include the inhibitory descending mechanisms. This theory is still valid today, but the role of the small fibres in modulating nociception is now being examined more closely.

3.4.12 Psychological aspects of acute pain

Pain is an individual biopsychosocial phenomenon (Turk), and is largely influenced by culture, the previous pain experience and the ability to cope. It is a personal and subjective experience. Psychological factors which influence the pain experience are catastrophising and focusing on the pain, secondary gain and environmental factors, fear avoidance and anxiety. Preoperative anxiety has been shown to contribute to increased postoperative pain, while preoperative depression is a predictor of postoperative pain.

Clinical practice points

1. Identifying and attending to fear avoidance and catastrophising, and the presence of possible gain factors can lessen the impact of pain.
2. Anxiety and depression are associated with higher pain intensity.
3. Cognitive behavioural modification can be achieved by patient education.
4. A multidisciplinary approach is key.

3.5 The progression of acute to chronic pain

Chronic pain can develop following an acute pain episode. Postoperative pain, post zoster pain and low back pain are often associated with chronic pain. One and a half per cent of all surgical procedures results in chronic pain development.

Risk factors for the development of chronic pain are:

- Intense and prolonged preoperative and/or postoperative pain.
- Repeated surgery.
- Chemotherapy and/or radiotherapy perioperatively.
- Postoperative complications, i.e. infection.

There is some evidence to suggest that epidural analgesia initiated before thoracotomy, and carried into the postoperative period, reduces the development of chronic pain compared to that with patients who received intravenous patient-controlled analgesia.

Some surgical procedures result in an increased incidence of chronic pain (Table 2).

Central sensitisation and wind-up phenomena are the pathophysiological mechanisms postulated to be involved in chronic pain development.

Table 2: An increased incidence of chronic pain with certain surgical procedures

Procedure	Incidence (%)
Dental surgery	5–13
Vasectomy	0–37
Cholecystectomy	3–56
Mastectomy	11–57
Inguinal hernia repair	0–63
Thoracotomy	5–67
Amputations	30–85

3.6 Adverse effects of pain

Acute pain provokes physiological modification in multiple organ systems. The stress response involves neurohumoral changes with multiple implications. The aim of adequate pain management is to provide pain relief as a humane measure, as well as to minimise the multi-system deleterious effects caused by the stress response.

A catabolic state, sympathetic stimulation and immuno-suppression are hallmarks of the stress response. The psychological effects can create a vicious cycle, maintaining the negative effects. The endocrine system changes result in a catabolic state, increased adrenocorticotrophic hormone, cortisol, antidiuretic hormone, catecholamines, angiotensin II, interleukin (IL)-1 and IL-6, and tumour necrosis factor (Table 3).

Sympathetic stimulation results in an increased heart rate and blood pressure, increasing the risk of myocardial ischaemia. Pain limits coughing and decreases functional residual capacity, which, in turn increases the risk of atelectasis and pulmonary infection. Decreased mobility results in an increased risk of deep vein thrombosis. Anxiety, helplessness, loss of control, an inability to interact and sleep deprivation all contribute to psychological disturbances, which can increase the risk of persistent pain developing.

Clinical practice points

1. Attention to pain control throughout the pre-, intra- and postoperative period might reduce development of chronic pain.
2. Neuroaxial blockade and nerve blocks in the perioperative period might reduce chronic pain development by minimising central sensitisation.
3. N-methyl-D-aspartic acid receptor antagonist drugs demonstrate a preventive analgesic effect.

Table 3: The adverse effects of pain

Endocrine
Increased catabolism
Increased ACTH, ADH, GH, catecholamines, angiotensin II, IL-1 and IL-6, and TNF
Decreased anabolism
Decreased insulin and testosterone
Metabolic
Carbohydrates
Hyperglycaemia, glucose intolerance and insulin resistance
Protein
Increased acute phase protein catabolism
Lipids
Increased lipolysis
Water and electrolytes
Water retention
Potassium loss

ACTH: adrenocorticotrophic hormone, ADH: antidiuretic hormone, GH: growth hormone, IL: interleukin, TNF: tumour necrosis factor

4. Measurement and assessment of acute pain

Key issues to be discussed in this section are:

- Tools for pain measurement.
- Regular assessment and monitoring of pain as the fifth vital sign.
- Adjust the treatment according to the intensity of pain.
- The need for pain services team documentation and an evaluation of the service.

4.1 Pain assessment tools

The patient's personal report is essential, as pain is subjective. An assessment and the rating of the pain provide an objective tool which gives a guideline for management. Always believe the patient. Validated scales for children and adults with impaired cognition are available, but are beyond the scope of this chapter.

It is vital to record the patient's level of consciousness in order to avoid complications and opiate overdose.

Acute pain requires only unidimensional assessment and measurement.

Pain intensity should be measured. It is not practical, nor is it efficient, to employ questionnaires and assess qualitative aspects of pain. Qualitative aspects are only relevant when assessing chronic pain and are employed as part of its management.

Simple-to-administer scales, which are easily understood by the patient, should be employed. A large number of validated scales are listed in the literature. Each has its own strengths and weaknesses. The most widely used scales will now be discussed.

4.1.1 Visual analogue scale

The visual analogue scale (VAS) is a sensitive tool consisting of a 0–100 mm straight line. The one end is marked “no pain”, and the other “worst possible pain”. The patient is asked to mark the point on the scale

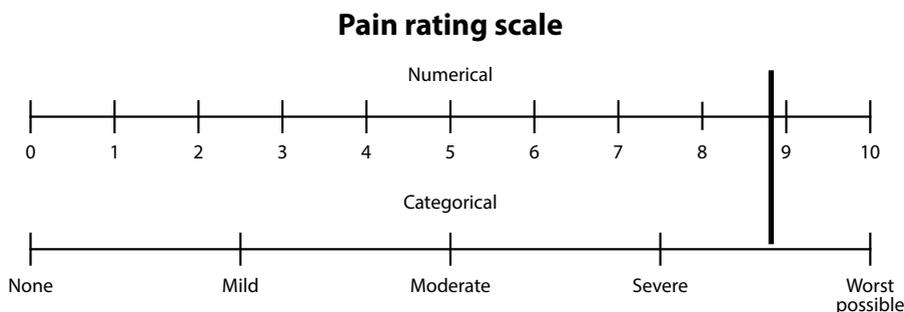


Figure 1: Pain rating scale

Universal Pain Assessment Tool

This pain assessment tool is intended to help patient care providers assess pain according to individual patient needs. Explain and use 0-10 Scale for patient self-assessment. Use the faces or behavioral observations to interpret expressed pain when patient cannot communicate his/her pain intensity.

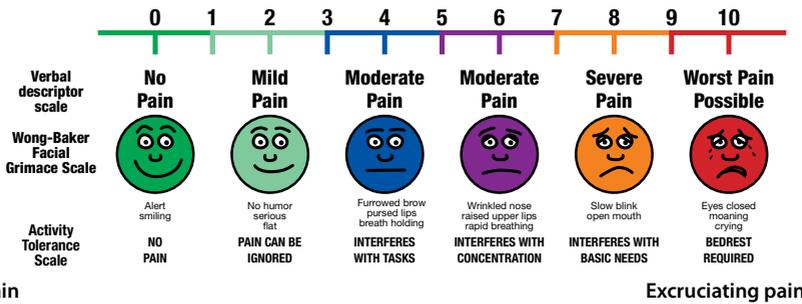


Figure 2: A universal pain assessment tool

that best describes his or her pain. The result is presented as a ratio. VAS measurement is accurate, but the assessing nurse or doctor has to carry the required instrument around. Also, some patients do not understand the tool.

4.1.2 Verbal numeric rating scale

The verbal numeric rating scale (VNRS) is simple and quick, and correlates well with the VAS. This tool consists of a simple 0–10 verbal scale. The patient is asked to rate his or her pain verbally on the scale of 1–10, with 1 being very slight discomfort and 10 being the most severe pain imaginable or experienced. This scale is operator friendly as specific tools do not need to be carried around. It is also patient friendly as a short explanation is all that is required. It is also easily understood. The VNRS is also research friendly as using a numeric scale provides a simple documentation, reporting and comparison tool (Figure 1).

4.1.3 Verbal rating scale or verbal descriptor scale

The patient is required to report his or her pain as “none”, “mild”, “moderate”, “severe” or “very severe” using the verbal rating scale or verbal descriptor scale. This tool’s effectiveness is limited in a multilingual society.

4.1.4 Wong-Baker FACES® (facial expressions) pain rating scale

The Wong-Baker FACES® pain rating scale has been validated for children aged ≥ 5 years. It can also be used for adults with cognitive impairment (Figure 2).

The VAS, VNRS and the Wong-Baker FACES® pain rating scales are available from various pharmaceutical companies and can easily be acquired for ward nursing staff and other health professionals involved in treating postoperative patients.

Table 1: The Pain Assessment in Advanced Dementia scale

Items	0	1	2	Score
Breathing independent of vocalisation	Normal	Occasional laboured breathing. A short period of hyperventilation	Noisy laboured breathing. A long period of hyperventilation Cheyne-Stokes respirations	
Negative vocalisation	None	Occasional moaning or groaning. Low-level speech with a negative or disapproving quality	Repeated troubled calling out. Loud moaning or groaning. Crying	
Facial expression	Smiling or inexpressive	Sad, frightened or frowning	Facial grimacing	
Body language	Relaxed	Tense. Distressed pacing. Fidgeting.	Rigid. Fists clenched. Knees pulled up. Pulling or pushing away. Striking out.	
Consolability	No need to console	Distracted or reassured by voice or touch	Unable to console, distract or reassure	

4.1.5 The Pain Assessment in Advanced Dementia scale

Assessing the pain of patients with advanced dementia presents a unique challenge. A common example of this group is elderly patients who present to theatre with a femur fracture. The Pain Assessment in Advanced Dementia (PAINAD) scale is often used internationally for this group. This is a five-item observational tool which requires observation of the patient for a certain time and can be time consuming. The higher score indicates an increased level of pain (Table 1).

Breathing

“Normal” breathing is characterised by effortless, quiet, rhythmic (smooth) respirations.

“Occasional laboured breathing” is characterised by episodic bursts of harsh, difficult or wearing respirations.

A “short period of hyperventilation” is characterised by intervals of rapid, deep breathing lasting a short period.

“Noisy laboured breathing” is characterised by negative-sounding respirations on inspiration or expiration. They may be loud, gurgling or wheezing. They appear to be strenuous or wearing.

A “long period of hyperventilation” is characterised by an excessive rate and depth of respirations which last a considerable time.

Cheyne-Stokes respirations are characterised by rhythmic waxing and waning of the breathing from very deep to shallow respirations, with periods of apnoea, i.e. the cessation of breathing.

Negative vocalisation

“None” is characterised by speech or vocalisation that has a neutral or pleasant quality.

Occasional moaning or groaning” is characterised by mournful or murmuring sounds, wails or laments.

Groaning is characterised by louder-than-usual inarticulate involuntary sounds, often abruptly beginning and ending.

“Low-level speech with a negative or disapproving quality” is characterised by muttering, mumbling, whining, grumbling, or swearing in a low volume with a complaining, sarcastic or caustic tone.

“Repeated troubled calling out” is characterised by phrases or words being used over and over in a tone which suggests anxiety, uneasiness or distress.

“Loud moaning or groaning” is characterised by mournful or murmuring sounds, or wails or laments much louder than the usual volume. Loud groaning is characterised by louder-than-usual inarticulate involuntary sounds, often abruptly beginning and ending.

“Crying” is characterised by an utterance of emotion accompanied by tears. Sobbing or quiet weeping may take place.

Facial expressions

“Smiling” is characterised by upturned corners of the mouth, brightening of the eyes and a look of pleasure or contentment. Inexpressive refers to a neutral, at ease, relaxed or blank look.

“Sad” is characterised by an unhappy, lonesome, sorrowful or dejected look. The eyes may be filled with tears.

“Frightened” is characterised by a look of fear, alarm or heightened anxiety. The eyes appear to be wide open.

4.2 Recommended tools

The assessment tool needs to be appropriate to the patient’s developmental age, cognitive status and emotional status.

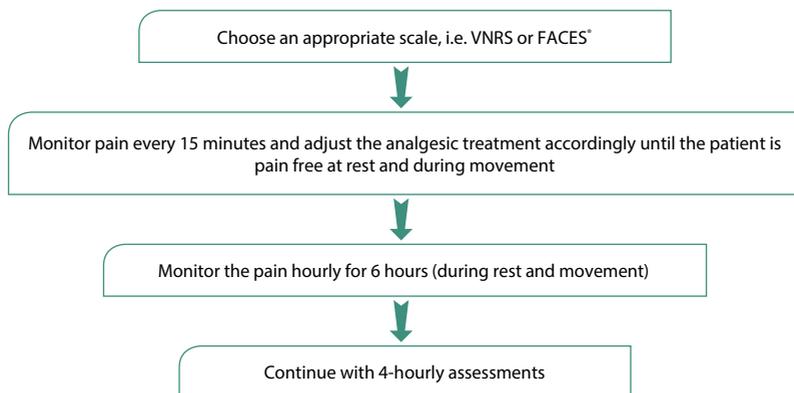
The VNRS is used for adults in the routine clinical setting, and the Wong-Baker FACES[®] pain rating scale for children or adults with impaired cognition, or when there is a language barrier.

A scale should be chosen for a given institution or practice and used consistently. The same scale should be used for patients for pain assessment purposes.

Coordination and collaboration must take place between nurses and medical practitioners in order to avoid confusion and facilitate reliable documentation and management.

4.3 Regular assessment and the fifth vital sign

Regular pain evaluation is as important and as basic as monitoring blood pressure, pulse rate, temperature and respiratory rate in the patient with acute pain. Therefore, pain is considered to be the fifth vital sign. It is important to remember that pain is subjective.



FACES®: Wong-Baker FACES® pain rating scale, VNRS: verbal numeric rating scale

Figure 3: The design of a pain measuring and monitoring protocol

While nociception is a universal concept, pain is subjective and is dependent on personality, culture, previous experiences and expectations. Pain is a biopsychosocial phenomenon and is dynamic. Pain intensity varies with activity and with time.

Pain needs to be measured during rest, as well as with movement, i.e. when moving the legs or coughing. It is in the scope of practice to provide safe and effective pain relief that is relevant to patient expectations and to local South African conditions.

The vital signs monitoring chart should include a column on which pain intensity can be reported at regular intervals. All care providers who deal with surgical postoperative patients need to be educated on an ongoing basis. Awareness should be raised with regard to the importance of monitoring pain intensity. It is vital that the nurse has a clear and immediate line of communication with the doctor responsible for pain control so that rapid adjustment of the pain medication can take place. An outline of how to design a pain measuring and monitoring protocol is provided in Figure 3.

4.4 Recommended strategy

The recommended strategy is as follows:

- The nursing chart must include fifth vital sign monitoring.
- Pain should be assessed at rest and during movement.
- Respond and treat promptly and appropriately.

If the pain intensity increases to $> 5/10$:

- Contact the relevant physician.
- Adjust the pain treatment.
- Revert to a 15-minute, and then an hourly, monitoring schedule.

In the meantime:

- Look for complications which might cause pain, i.e. deep vein thrombosis, compartment syndrome and infection.
- Monitor the medication's side-effects, i.e. excessive sedation, respiratory depression, and nausea and vomiting.

4.5 How to adjust the treatment according to the intensity of pain

A treatment ladder, based on the severity of the pain, available drugs and patient condition, can be utilised. Recommended treatment according to the pain scale is detailed in Table 2. A combination drug of oxycodone and Naloxone has recently been available in South Africa. This combination might offer analgesia while minimising gastrointestinal side effects of opioids.

Table 2: Recommended treatment according to the pain scale

Pain scale	Interpretation	Action
0-2/10	No pain	No treatment, or NSAIDs or paracetamol
3-5/10	Mild pain	Paracetamol and "weak opioids", i.e. codeine, and tramadol
6-8/10	Moderate	Codeine, paracetamol, NSAIDs, morphine, tramadol, and a oxycodone naloxone combination
9-10/10	Severe	PCA epidural and nerve blocks, morphine, paracetamol, NSAIDs and an oxycodone naloxone combination

NSAIDs: nonsteroidal anti-inflammatory drugs, PCA: patient-controlled analgesia

4.6 The pain team and the need to document and evaluate the service

In order to control pain effectively, a pain team is needed to perform the following functions:

- Provide specialised, prompt, efficient, safe and multimodal pain management 24 hours a day.
- Develop protocols and guidelines to assist in the provision of safe and effective treatment designed specifically for particular conditions at the institution.
- Provide an up-to-date, evidence-based and appropriate understanding of postoperative pain management to all health workers involved in caring for postoperative patients, in the form of formal lectures, informal teaching and printed communications.
- Provide links to chronic and palliative care services.
- Provide patient information and preoperative counselling.
- Monitor patient outcomes and document the results in the institution, in order to compare and improve services.
- Promote participation in a national audit of pain services.

4.7 Conclusion

It might not be possible for all hospitals to have access to a pain unit. However, a consultant anaesthetist who is dedicated to acute pain management 24 hours a day is desirable.

5. Drug listings – enteral and parenteral

5.1 Opioids – mainly for severe pain

5.1.1 General information

Classification for opioids:

- Opioid agonists
- Opioid dualists: Both antagonism and agonism. (Theoretically, the side-effects should cancel one another out)
- Opioid antagonists
- Atypical opioids.

Side-effects include:

- Respiratory depression: Opioid patches should not be used for acute pain
- Sedation
- Nausea and vomiting
- Pruritis
- Constipation
- Tolerance

Table 1 details the relevant information on opioid administration (mainly for severe pain) in adults.

Table 1: Relevant information on opioid administration (mainly for severe pain) in adults

OPIOID AGONISTS			
Drug	Route of administration in adults and dosage	Use in porphyria ¹	Relevant information
Morphine <ul style="list-style-type: none"> • SRM-Rhotard® • MST Continus® • Merck Morphine Sulphate® • Micro Morphine injection® • Morphine Sulphate-Fresenius® <p><i>Combination:</i> Morphine + cyclizine = cyclimorph</p>	<p>Oral 10-20 mg q 12 hourly</p> <p>IM 0.1-0.3 mg/kg q 4 hourly</p> <p>IV <i>Bolus:</i> 1-5 mg q 1 hourly* <i>Infusion*:</i> Give a loading dose, then titration, depending on the pain and sedation scale, i.e. 3-5 mg (*: Titration should only be given in the intensive care unit²)</p> <p><i>PCA</i> Bolus 1–2 mg, with 5-10 minutes lockout time</p> <p><i>Neuraxial</i></p>	Use ¹	<ul style="list-style-type: none"> • Oral morphine preparations are usually used in the treatment of chronic pain • Dosage is dependent upon the severity of pain and the patient's previous analgesic history, i.e. opioid naivety • Infusions may readily cause excessive accumulation of the drug with respiratory depression, and if undetected, death • PCA is a safer option³ • IV opioid PCA provides better analgesia than conventional parenteral opioid regimens • Patient preference for IV PCA is higher when compared with conventional regimens • Extreme caution with neuraxial morphine is advised as the onset of respiratory depression only occurs 8–12 hours post administration⁴ • Respiratory depression in the elderly is more prevalent and the neuraxial dose of opioids should be drastically decreased. • Any opioid injected neuraxially should be "preservative-free"⁵ • The side-effects of opioids (see 5.1.1) occur with all opioid-type drugs⁶

OPIOID AGONISTS

Drug	Route of administration in adults and dosage	Use in porphyria ¹	Relevant information
Pethidine • Merck-Pethidine HCl® • Micro-Pethidine® • Pethidine HCl-Fresenius®	IM 1–1.5 mg/kg q 3–4 hourly	Use ¹	<ul style="list-style-type: none"> No one opioid has ever been shown to be superior than another Opioids are no longer considered to be the first-line analgesic The type of opioid depends on the preference and experience of the prescriber Pethidine commonly causes euphoria and dysphoria Pethidine has drug interactions with MAOIs and SSRIs⁶
	PCA 10–20 mg bolus with 5–10 minute lockout		
Papaveratum • Omnopon-Fresenius®	IM 0.15 mg q 4 hourly		<ul style="list-style-type: none"> Not for children aged ≤ 1 year
Dihydrocodeine tartrate • DF-118®	Oral 30 mg q 4–6 hourly	Use ¹	<ul style="list-style-type: none"> Not for children aged ≤ 4 years 30 mg of DF-118® exhibits comparative analgesia to 10 mg morphine May worsen asthma
	IM 25–50 mg q 4–6 hourly		
Dipipanone HCl (10 mg) + cyclizine (30 mg) • Wellconal®	Oral 1 tablet q 6 hourly. May increase by ½ tablet increments to a maximum of 3 tablets		<ul style="list-style-type: none"> For moderate to severe pain
Propoxyphene • Doloxene®	Oral 65 mg (1 capsule) q 4 hourly <i>p.o.</i> to a maximum of 390 mg/day		<ul style="list-style-type: none"> For mild to moderate pain Low-affinity agonist
Codeine • Lennon-Codeine Phosphate	Oral 15–60 mg daily <i>p.o.</i>	Use ¹	<ul style="list-style-type: none"> Mild to moderate pain Low affinity agonist May not have any analgesic activity, but 10% is demethylated to morphine, and this is probably active⁶
Oxycodone • Oxycotin® • Oxynorm®	Oral <i>Oxycotin tablets (sustained release):</i> 5 mg, 10 mg, 20 mg and 40 mg, depending on the severity of the pain Start with 5–10 mg <i>p.o.</i> bd in an opioid-naïve patient <i>Oxynorm:</i> 5 mg, 10 mg, 20 mg for severe postoperative pain Start with 5 mg <i>p.o.</i> q 4–6 hourly	Use ¹	<ul style="list-style-type: none"> Mild to moderate to severe pain Has an identical opioid side-effect and contraindication profile Pharmacology depends on the age of patient. Elderly patients have a 15% higher plasma level It is excreted in the urine. Drastically decrease dose in instances of renal failure⁶

bd: twice daily, PCA: patient-controlled analgesia, *p.o.*: per os, IM: intramuscular, IV: intravenous, MAOIs: monoamine oxidase inhibitors, SSRIs: selective serotonin reuptake inhibitors, Use¹: Safe

This section of Table 1 details the relevant information on opioid dualists.

Table 1: Relevant information on opioid administration (continued)

OPIOID DUALISTS			
Drug	Means of administration and dosage	Use in porphyria ¹	Relevant information
Tilidine • Valeron®	Oral <i>Tablets:</i> 50 mg q 6–8 hourly. May increase to 100 mg for 2 doses only. <i>Drops:</i> 10–20 drops q 6–8 hourly	UWECO ¹	<ul style="list-style-type: none"> • Not for infants aged ≤ 1 year • For moderate to severe pain • 1 drop = 2.5 mg⁷ • It is probably better to calculate the dose on weight, rather than age • Do not exceed a single dose of 1 mg/kg • Drops are useful in adults who have dysphagia
Pentazocine • Pentazocine-Fresenius® • Sosenol®	Injection 30–40 mg q 3–4 hourly intramuscularly, intravenously or subcutaneously (if IV, only 30 mg/dose) To a maximum of 360 mg/24 hours	Avoid ¹	<ul style="list-style-type: none"> • For moderate to severe pain • Not known as a potent analgesic, but proponents claim superior analgesia, especially postoperatively in women undergoing a varicose vein operation • Also increases peripheral vascular resistance which may be detrimental in the elderly • Respiratory depression is prevalent in children⁸
Buprenorphine • Temgesic® • Subutex®	Oral 0.2–0.4 mg q 6–8 hourly SL IM/slow IV infusion 0.3–0.6 mg q 6–8 hourly	Use ¹	<ul style="list-style-type: none"> • Not for children aged ≤ 12 years • For moderate to severe pain • May experience excitation and hallucinations • Contraindications include concomitant MAOI use and acute asthma • The IM injection must be administered deep⁹

Avoid¹: Unsafe, IM: intramuscular, IV: intravenous, MAOI: monoamine oxidase inhibitor, SL: sublingual, UWC¹: Use with caution, UWECO¹: Use with extreme caution; may be unsafe

This section of Table 1 details the relevant information on opioid antagonists.

Table 1: Relevant information on opioid administration (continued)

OPIOID ANTAGONISTS			
Drug	Means of administration and dosage	Use in porphyria ¹	Relevant information
Naloxone • Narcan®	IV 0.006 mg/kg	Use ¹	<ul style="list-style-type: none"> • May cause pulmonary oedema if the entire calculated dose is rapidly administered • The ampoule contains 0.4 mg. This should be diluted in 10 ml prior to administration • Will reverse all effects of opioids. The half-life is 15–60 minutes. Unwanted side-effects of the opioid may reoccur, warranting re-administration of naloxone¹⁰

IV: intravenous, Use¹: Safe

This section of Table 1 details the relevant information on atypical opioids.

Table 1: Relevant information on opioid administration (continued)

ATYPICAL OPIOIDS			
Drug	Means of administration and dosage	Use in porphyria ¹	Relevant information
Tramadol	<p>Oral</p> <ul style="list-style-type: none"> • <i>Tramal</i>[®] • <i>Dolotram</i>[®] • <i>Tramahexal</i>[®] • <i>Capsules</i>: 50-150 mg q 4–6 hourly to a maximum of 400 mg/day • <i>SR tablets</i>: 100-150 mg q 12 hourly • <i>Drops</i>: 100 mg = 1 ml = 40 drops. Start with 20 drops and titrate up, if necessary. Do not exceed 400 mg/24 hours <p>Rectal</p> <p>100 mg/suppository. Do not exceed > 400 mg/24 hours</p> <p>IV/IM</p> <ul style="list-style-type: none"> • 100 mg IM • IV administration must be slow 	Use ¹	<ul style="list-style-type: none"> • Not for children aged ≤ 12 years • Avoid using 5-HT₃ antagonists (antiemetics) with tramadol as it works on the μ-receptors, noradrenaline and serotonin receptors • Caution extends to its use with SSRIs as serotonin syndrome effects, e.g. sweating and anxiety, may occur • Avoid higher doses and rapid IV administration as this leads to an increased incidence of nausea and vomiting • Large dose variation exists owing to reduced active metabolite production in 10% of the Caucasian population • <i>Therapeutic range</i>: Moderate to severe pain⁶

5-HT₃: 5-hydroxytryptamine, IM: intramuscular, IV: intravenous, SR: slow release, SSRIs: selective serotonin reuptake inhibitors, Use¹: Safe

5.2 Paracetamol

5.2.1 General information

The following information is important with regard to paracetamol:⁶

- Caution should be exercised in patients with liver failure.
- An excessive dosage may cause irreversible liver failure.
- Use with caution or decrease the dose if there is:
 - Acute liver disease
 - Alcohol-related liver disease
 - Glucose-6-phosphate dehydrogenase deficiency.

Table 2 details the relevant information on paracetamol.

Table 2: Relevant information on paracetamol

PARACETAMOL			
Drug	Route of administration and dosage	Use in porphyria ¹	Relevant information
Enteral <ul style="list-style-type: none"> Adco-Paracetamol® Antalgic® Fevamol® Go-Pain P® Pacimol® Painomol Be Tabs® Panado® Prolief® Tylenol® 	Oral (500 mg) tablet <ul style="list-style-type: none"> 0.5–1.0 g q 4 hourly to a maximum of 4 g/day 	Use ¹	<ul style="list-style-type: none"> Not recommended for children aged ≤ 3 months Mild to moderate pain only
<ul style="list-style-type: none"> Tylenol® Extended Release 	2 capsules q 8 hourly, to a maximum of 6 capsules/24 hours	Use ¹	<ul style="list-style-type: none"> Do not crush, chew or dissolve the extended-release capsules
<ul style="list-style-type: none"> Varipan® 			
<ul style="list-style-type: none"> Oral (paediatric syrup) Adco-Paracetamol® Antalgic® Calpol GSK® Go-Pain® Napamol® Panamol® Panado® Pyradol® 		Use ¹	
<ul style="list-style-type: none"> Empaped® 	Rectal N/A	Use ¹	<ul style="list-style-type: none"> Rectal absorption is inconsistent Beware of renal and liver disease
<ul style="list-style-type: none"> Parenteral Perfalgan® Paraspen®/Kabimol® 	IV <i>Adults (≥ 50 kg):</i> 1 g q 6 hourly to a maximum dose of 4 g/24 hours		<ul style="list-style-type: none"> Prescribe carefully according to weight, age and co-morbidities Administer as a 15-minute infusion, otherwise drug becomes inactive Registered for use for 24–48 hours Hypotension is known to occur, and may be due to mannitol in some of the formulations¹¹ Do not administer other oral paracetamol concomitantly. Beware of combination analgesics which may contain paracetamol An inadvertent overdose should be urgently treated with N-acetylcysteine.

IV: intravenous, NA: not applicable, Use¹: Safe

5.3 Nonsteroidal anti-inflammatory drugs (for mild to moderate pain relief)

5.3.1 General information

Nonsteroidal anti-inflammatory drugs (NSAIDs) can be classified into:

- Cyclo-oxygenase (COX-1 and 2) inhibitors
- Selective COX-2 inhibitors
- Specific COX-2 inhibitors.

Side-effects include the following:

- Renal damage, especially if there is prior renal impairment or if the patient is hypovolaemic.
- Platelet impairment.
- Gastric erosions and haemorrhage.

- Possible poor wound healing (a concern of surgeons).
- Asthma, which may be exacerbated in some patients.

Parenteral administration applies to the following:

- Ketorolac
- Tenoxicam
- Parecoxib.

Table 3 details the relevant information on NSAIDs for mild to moderate pain relief.

Table 3: Relevant information on nonsteroidal anti-inflammatory drugs for mild to moderate pain relief

NSAIDS (FOR MILD TO MODERATE PAIN RELIEF)			
Drug	Means of administration and dosage	Use in porphyria ¹	Relevant information
Aspirin <ul style="list-style-type: none"> • Bayer Aspirin[®] • Be Tabs Aspirin[®] • Dispirin[®] • Ecotrin[®] • Myoprin[®] 	Oral 300–900 mg q 4–6 hourly to a maximum of 4 g daily	Use ¹	<ul style="list-style-type: none"> • Associated with Reye's syndrome • Use with caution in the elderly, in cases of poor renal function and when there is gastric bleeding
Diclofenac¹² <ul style="list-style-type: none"> • ACU-Diclofenac[®] inj • Adco-Diclofenac[®] • Austell-Diclofenac[®] Sodium • BE-TABS Diclofenac[®] inj • Cataflam D[®] • Dicloflam[®] • Dichohexal[®] • Dichohexal-KDynak[®] • Fortfen[®] • Infla-Ban[®] • K-Fenak[®] • Merck Diclofenac[®] • Micro Diclofenac[®] • Panamor[®] suppositories and tablets • Rolab-Diclofenac Sodium[®] • Sandoz Diclofenac[®] Sodium[®] • Veltex[®] 	Oral 25–50 mg q 8 hourly, to a maximum of 150 mg/day IM 75 mg q 12 hourly, to a maximum of 150 mg/day for 2 days only	UWECO ¹	<ul style="list-style-type: none"> • Not for children aged ≤ 2 years via all routes • Mild to moderate pain • Available in drops • Good COX-1 to COX-2 ratio • Avoid if there is asthma, gastrointestinal or renal disease and hypovolaemia • <i>IM injections:</i> The intragluteal injection must be administered deeply. It may cause necrotising fasciitis, in which case a switch should be made to oral therapy as soon as possible. An inadvertent injection into the nerve may cause irreversible neural damage • Suppositories can cause proctitis. Avoid using them for ≥ 5 days • The IM injections are for moderate to severe pain • Controversial for post-tonsillectomy use • Swallow the tablet whole with food. Do not chew it • A combination of a NSAID and prostacyclin may decrease the NSAID side-effects

NSAIDS (FOR MILD TO MODERATE PAIN RELIEF)

Drug	Means of administration and dosage	Use in porphyria ¹	Relevant information
• Voltaren®	Oral <i>Drops (only Voltaren®)</i> 15 mg = ml, 1 drop = 0.5 mg 1 ml = 30 drops 100 mg in 2–3 divided doses A daily maximum of 150 mg		
• Voltaren Acti-Go®	Rectal 100 mg suppositories daily The maximum by all routes is 150 mg/day		
• Arthrotec® • (diclofenac 75 mg + misoprostol 200 µg)	Oral 1 tablet q 12 hourly		
Ibuprofen 13 • Advil® • Ibumax® • Ibumed® • Norflam T® • Nurofen® • Adco-Ibuprofen® • Betaprofen® • Brufen® • Iboflam® • Inza® • Ranfen® • Sandoz-Ibuprofen®	Oral 200–400 mg q 4–6 hourly to a maximum of 1 200 mg/day	Use ¹	<ul style="list-style-type: none"> • Beware of gastrointestinal bleeds • Beware of cases of asthma • For moderate pain
Indomethacin • Adco-Indomethacin® • Aflamin® • Arthrexin® • Betacin® • Flamecid® • Indocid® suppositories • Methocaps® • NISAID-25® • Rolab-Indomethacin LA® • Sandoz Indomethacin®	Oral 25–50 mg q 6–8 hourly to a maximum of 200 mg/day	Use ¹	<ul style="list-style-type: none"> • Take with food, an antacid or milk • Beware of gastrointestinal bleeding, asthma and renal insufficiency • Central nervous system disturbances can occur
Ketoprofen • Ketoflam® • Oruvail®	Oral 200 mg daily with food. Do not exceed 300 mg/day	Use ¹	
Ketorolac¹⁴ • Toradol®	IV/IM 10–30 mg IV/IM q 4–6 hourly Do not give for longer than 24 hours Administer the IV injection slowly Oral 10 mg q 4–6 hourly	UWECO ¹	<ul style="list-style-type: none"> • Not for children aged ≤ 16 years • Do not use for ≥ 5 days

NSAIDS (FOR MILD TO MODERATE PAIN RELIEF)

Drug	Means of administration and dosage	Use in porphyria ¹	Relevant information
Mefenamic acid <ul style="list-style-type: none"> Adco-Mefenamic Acid[®] Fenamin[®] Ponac[®] Ponstan[®] Ponstel[®] Sandoz Mefenamic Acid[†] 	Oral 500 mg q 8 hourly		<ul style="list-style-type: none"> Do not administer for ≥ 5 days Not for children aged ≤ 6 months or weighing < 10 kg
Lornoxicam <ul style="list-style-type: none"> Xefo[®] 	Oral 8–16 mg/day, in 2–3 divided doses		<ul style="list-style-type: none"> Not for children aged ≤ 18 years
Naproxen <ul style="list-style-type: none"> Adco-Naproxen[®] Aleve[®] Aspen Naproxen[®] Merck-Naproxen[®] Nafasol[®] Napflam[®] Rolab-Naproxen[®] Synflex[®] 	Oral 500 mg q 12 hourly	Use ¹	<ul style="list-style-type: none"> Not for children aged ≤ 5 years Caution should be taken in patients with a diathesis for gastrointestinal bleeding, with renal compromise and with asthma Has drug interactions with hydantoin, anticoagulants and sulphonylureas For mild to moderate pain¹⁵
Piroxicam <ul style="list-style-type: none"> Adco-Piroxicam[®] Brexecam[®] CPL Alliance Piroxicam[®] Pixicam[®] Pyrocaps[®] Rheugesic[®] Rolab-Piroxicam[®] Sandoz-Piroxicam[®] Xycam[®] 	Oral 20–40 mg daily		<ul style="list-style-type: none"> Not recommended in children The usual concerns with NSAIDs apply Caution must be exercised in cases of hepatic insufficiency The long half-life may be given as a single daily dose For moderate pain
Sulindac <ul style="list-style-type: none"> Adco-Sulindac[®] 	Oral 100–200 mg q 12 hourly, to a maximum of 400 mg/day		<ul style="list-style-type: none"> Caution should be taken in cases of renal and hepatic insufficiency, gastrointestinal bleeds and asthma
Tenoxicam <ul style="list-style-type: none"> Tilcotil[®] 	Oral 20 mg daily IV/IM 20 mg daily for 1–2 days only		<ul style="list-style-type: none"> Parenteral use

COX: cyclo-oxygenase, IM: intramuscular, inj: injection, IV: intravenous, NSAIDs: nonsteroidal anti-inflammatory drugs, Use¹: Safe, UWECO¹: Use with extreme caution; may be unsafe

This section of Table 3 details the relevant information on selective and specific COX-2 inhibitors.

Table 3: Relevant information on nonsteroidal anti-inflammatory drugs for mild to moderate pain relief (continued)

SELECTIVE COX-2 INHIBITORS			
Drug	Means of administration and dosage	Use in porphyria¹	Relevant information
Meloxicam <ul style="list-style-type: none"> • Coxflam[®] • Flexocam[®] • Loxiflam[®] • Melflam[®] • Mobic[®] • Sandoz Meloxicam[®] • Zydus Meloxicam[®] 	Oral 7.5 mg q 12 hourly or 15 mg daily, to a maximum dose of 15 mg/day	Use ¹	<ul style="list-style-type: none"> • Give with food • Selective COX-2 inhibitors in very high doses may result in COX-1 inhibition as well
SPECIFIC COX-2 INHIBITORS (COXIBS)			
Celecoxib <ul style="list-style-type: none"> • Celebrex[®] 	Oral 100–200 mg q 12 hourly, to a maximum of 400 mg/day	Use ¹	<ul style="list-style-type: none"> • Not for children aged ≤ 18 years • Contraindicated if there is a sulphonamide allergy • A specific COX-2 inhibitor, i.e. a coxib, only has COX-2 effects even at very large doses
Parecoxib <ul style="list-style-type: none"> • Rayzon[®] 	IV/IM 40 mg q 6–12 hourly IV/IM, to a maximum of 80 mg/day		<ul style="list-style-type: none"> • Not for children aged ≤ 18 years • Contraindicated if there is a sulphonamide allergy
Etoricoxib <ul style="list-style-type: none"> • Arcoxia[®] 	60mg osteoarthritis daily 90mg Rheumatoid arthritis daily 120mg Acute gouty arthritis daily		<ul style="list-style-type: none"> • Risk factors for cardio- and peripheral vascular disease • Blood pressure may increase and therefore should be monitored • Not for use in inflammatory bowel disease, congestive cardiac failure and renal failure • Not for use in pregnancy and lactation

COX: cyclo-oxygenase, IM: intramuscular, inj: injection, IV: intravenous, Use: Safe

5.4 Approach to oral combination analgesics

Combinations of the oral drugs are used extensively in South Africa. It is not possible to include all combinations in this section. The rationale to combine drugs is to reduce the dose of each drug, therefore improving the side-effect profile.

Table 4 details components in these combination preparations and highlights specific effects or side-effects.

Table 4: Relevant information on the correct approach to oral combination analgesics

Oral combination analgesic	Relevant information
Paracetamol	Usually a lower dose is seen in combinations Caution is required when adding a combination preparation if the patient is receiving paracetamol via another route e.g. intravenously or rectally, as an overdose can occur
Caffeine hydrate	Has a vasodilatory effect and may be good for migraines
Codeine phosphate	Has a mild analgesic effect Has to be metabolised to morphine Excessive sedation is problematic in a subset of patients
Aspirin	Caution should be exercised if the patient has a prior history of dyspepsia or bleeding diathesis
Propoxyphene napsylate	Has a weak analgesic effect, but some sedation
NSAIDs	Caution should be exercised if the patient has a prior history of dyspepsia or bleeding diathesis and renal impairment
Meprobamate	A weak analgesic Probable addiction after 10 days of use. This is a physical, as well as emotional, addiction NB. This is one of the main constituents of Stopayne*
Doxylamine succinate	The rationale is unclear for its inclusion in analgesic drugs
Promethazine	Has an antiemetic and sedatory effect A "black box" warning applies in the USA (↑ QT interval)
Orphenadrine	Has an antimuscurinic effect
Diphenhydramine	Is an antihistamine with a sedatory effect A "black box" warning applies

NSAIDs: nonsteroidal anti-inflammatory drugs

5.5 N-methyl-D-aspartate receptor antagonists (excitatory amino acid antagonists)

Table 5 details the relevant information on N-methyl-D-aspartate receptor antagonists (excitatory amino acid antagonists).¹⁶

Table 5: Relevant information on N-methyl-D-aspartate receptor antagonists (excitatory amino acid antagonists)

NMDA ANTAGONISTS (EXCITATORY AMINO ACID ANTAGONISTS)			
Drug	Means of administration and dosage	Use in porphyria ¹	Relevant information
Ketamine	Oral 0.25 mg/kg PCA May be added to PCA in combination with morphine	Use ¹	<ul style="list-style-type: none"> • <i>Side-effects:</i> Hallucinations and excessive salivation • Synergism with opioids. Supposedly decreases tolerance to the opioid • No decrease in the opioid side-effects • May give some pre-emptive analgesia • May reduce opioid requirements in opioid-tolerant patients
Magnesium	Oral 30 mg/kg at the start of induction and then 25 mg/kg/hour	Use ¹	<ul style="list-style-type: none"> • Concern regarding the potentiation of muscle relaxation • Decrease in the blood pressure, but easy to manage
Nitrous oxide • Entonox®	Oral N ₂ O 50%/O ₂ 50%	Use ¹	<ul style="list-style-type: none"> • Do not store cylinders in temperatures ≤ 7 °C • Used in labour for analgesia • Used in the dental chair • Appropriate monitoring should always be applied • Bone marrow depression occurs with prolonged use
Dextrometorphan • Benlyn Original® • Benlyn Dry Cough® • Benalin®	Oral 45 mg <i>p.o.</i> preoperatively	Use ¹	<ul style="list-style-type: none"> • Use pre-emptively preoperatively • Said to decrease the use of other analgesics post tonsillectomy in adults • Usually only prescribed with the premedication

N₂O: nitrous oxide, NMDA: N-methyl-D-aspartate, O₂: oxygen, PCA: patient-controlled analgesia, *p.o.*: *per os*, Use¹: Safe

5.6 α 2 agonists

Table 6 details the relevant information on α 2 agonists.

Table 6: Relevant information on α 2 agonists

α2 AGONISTS			
Drug	Means of administration and dosage	Use in porphyria¹	Relevant information
Clonidine	Oral 2.5 μ g/kg as premedication		<ul style="list-style-type: none"> • Premedication <ul style="list-style-type: none"> - Sedation - Pre-emptive analgesia • Partial agonist, therefore hyper- or hypotension may manifest • Bradycardia may be problematic
	IV 2.5 μ g/kg slow injection		
	Epidural/caudal 2–10 μ g/kg epidurally in 10 ml saline		
Dexmedetomidine¹⁷	IV <i>LD:</i> 1.0 μ g/kg slowly over 30 minutes <i>MD:</i> 0.2–0.7 μ g/kg/hour		<ul style="list-style-type: none"> • For moderate to severe pain • Expensive • The loading dose should be given slowly over 10–30 minutes • Patients on an infusion should always go to the ICU for their level of sedation and hypotension to be monitored • It is essential to monitor with arterial line if the drug has been given as an infusion • Side-effects include hypotension, sedation and bradycardia

ICU: intensive care unit, IV: intravenous, LD: , MD: stat: immediately

5.7 Local anaesthetics

Local anaesthetics^{18,19} are either short or long acting. Lignocaine is an example of a short-acting anaesthetic, and bupivacaine, ropivacaine and L-bupivacaine are examples of long-acting anaesthetics.

When administering an anaesthetic, it is important to be aware of the following side-effects:

- The effects of a toxic dose
- Cardiotoxicity
- Neurotoxicity.

Table 7 details the relevant information on local anaesthetics.

Table 7: Relevant information on local anaesthetics

LOCAL ANAESTHETICS			
Drug	What constitutes a toxic dose	Use in porphyria ¹	Relevant information
Licnocaine 2%	Toxic dose		
<ul style="list-style-type: none"> Renucaine® 	<ul style="list-style-type: none"> <i>Without adrenaline:</i> 5 mg/kg <i>With adrenaline:</i> 7 mg/kg <i>For mucous membranes:</i> 9 mg/kg 		<ul style="list-style-type: none"> Neurotoxicity occurs before cardiotoxicity Do not use intrathecally as toxicity to the spinal cord and nerves is a concern Continuous perineural infusions of lignocaine result in less effective analgesia and more motor block than a long-acting local anaesthetic
Bupivacaine	Toxic dose		
<ul style="list-style-type: none"> Microbupivacaine® Macaine® 	2 mg/kg		<ul style="list-style-type: none"> Cardiotoxicity occurs before neurotoxicity Intralipid may be used for cardiotoxicity 1.0–1.5 ml/kg intravenously Most potent. Thus, motor block and cardiotoxicity may be more pronounced However, there are no consistent differences between ropivacaine, levobupivacaine and bupivacaine when given in low doses for regional analgesia in terms of quality of analgesia or motor blockade
L-bupivacaine	Toxic dose		
<ul style="list-style-type: none"> Chirocaine® 	2 mg/kg		
Ropivacaine	Toxic dose		
<ul style="list-style-type: none"> Naropin® 	2 mg/kg		

References

- Porphyria Information Services, Welsh Medicines Information Centre. Drugs that are considered to be SAFE for the use in the acute porphyrias Porphyria Information Services, WMIC, 2015.
- Auburn FJ, Mazoit B, Riou B. Post-operative intravenous morphine titration. *Br J Anaesth.* 2012;108(2):193–201.
- Taheri A, et al. Patient controlled analgesia versus conventional analgesia for post-operative pain. *AMHSR.* 2014;12:58–63.
- Sultan P, Gutierrez MC, Carvallo B. Neuraxial morphine and respiratory depression. *Drugs.* 2011;71(14):1807–1819.
- Triredi D, Patel H, Shah P. The evaluation of intrathecal morphine for post-operative analgesia in vaginal hysterectomy. *Journal of Medical Thesis.* 2013;1(1):14–16.
- Shipton E. Analgesic agents for acute pain. *Applied pharmacology in anaesthesiology and critical care.* Milner A, Welsh E, editors. Centurion: Mepharm Publications, 2012, p. 526–571.
- Bauters T, Claus B, Willems E, et al. What's in a drop? Optimizing strategies for administration of drugs in pediatrics. *Int J Clin Pharm.* 2012;34(5):679–681.
- Brogden R, Speight TM, Avery GS. Pentazocine: a review of its pharmacological properties, therapeutic efficacy and dependence liability. *Drugs.* 1973;5(1):6–91.
- Walsh SL, Preston K, Stitzer ML. Clinical pharmacology of buprenorphine: ceiling effects at high doses. *Clin Pharmacol Ther.* 1994;55(5):569–580.
- Andree R. Sudden death following naloxone administration. *Anesth Analg.* 1980;59(10):782–784.
- Chiam E, Weinberg L, Bellomo R. Paracetamol: a review with specific focus on the haemodynamic effects of intravenous administration. *Heart, Lung Vessel.* 2015;7(2):121–132.
- Small R. Diclofenac sodium. *Clin Pharm.* 1989;8(8):545–558.
- Busson M. Update on ibuprofen. *J Int Med Res.* 1986;14(2):53–62.
- De Oliveira GS Jr, Agarwal D, Benzon HT. Single dose of peri-operative ketorolac to prevent post operative pain: a meta-analysis of randomised trials. *Anesth Analg.* 2012;114(2):424–433.
- Rothman K, Lanza L. Adverse pharmacology-epidemiology associated with aminoacetophen, ibuprofen, naproxen sodium used for analgesia. *Drug Saf.* 2013;
- Milner A, Kuhn M. Neuropsychiatric drugs. *Applied pharmacology in anaesthesiology and critical care.* Milner A, Welsh E, editors. Centurion: Mepharm, 2012; p.
- Nienaber L, Biccard B. *Applied pharmacology in anaesthesiology and critical care.* Milner A, Welsh E, editors. Centurion: Mepharm, 2012; p.
- Dippenaar J. Local anaesthetic toxicity. *South Afr J Anaesth Analg.* 2007;13(3):23–28.
- Byrne K, Engelbrecht C. Toxicity of local anaesthetic agents. *Trends in Anaesthesia and Critical Care.* 2013;3(1): 25–30.

6. Paediatric guidelines

Key issues to be discussed in this section are:

- Good pain control is a basic human right.
- Anxiety, fear and pain in children are closely linked.
- A decision must be made on what is required, i.e. analgesia, sedation, amnesia and/or anxiolysis, and the drug choice made accordingly.
- Drug administration should be the right drug for the right patient for the right reasons via the right route at the right time.

6.1 The neurobiology of pain

Even the most premature neonate responds to painful stimuli. More generalised reflex responses occur in early development in response to lower-intensity painful stimuli. Adverse long-term consequences may arise from pain and injury early on in life.

Pain measurement and assessment are prerequisites to optimal pain management. Pain assessment and measurement are important components of paediatric pain management. Pain measurement tools are available for children of all ages, and must be matched to the age and development of the child, be appropriate for the clinical context, and be explained clearly and used consistently.

The consequences of poorly managed pain are outlined in Table 1.

Table 1: The consequences of poorly managed pain

Organ system	Possible clinical manifestations
Cardiovascular	Tachycardia, hypertension, increased systemic vascular resistance and increased cardiac workload
Pulmonary	Tachypnoea, hypoxia, hypercarbia, decreased cough, decreased VC and FRC, atelectasis, pneumonia and mismatching V/Q ratio
Gastrointestinal	Anorexia, nausea, vomiting and ileus
Renal	Oliguria and urinary retention
Neuroendocrine	Increased adrenergic activity, catabolism and increased oxygen consumption and vagal inhibition
Central nervous system	Anxiety, fear, sedation, fatigue and depression
Immunological	Impaired, especially cell-mediated immunity
Musculoskeletal	Reduced mobility, pressure sores and an increased risk of DVT

DVT: deep vein thrombosis, FRC: forced vital capacity, VC: vital capacity, V/Q: ventilation/perfusion

6.2 Types of acute pain

6.2.1 Postoperative pain

The circle described in Figure 1 should not be broken if effective pain control is to be achieved.

The type of surgery is the greatest predictor of increased requirements for analgesia, i.e. thoracic and abdominal surgery are the most painful and thus have the highest analgesic requirement, followed by neurosurgery, then by orthopaedics, and then by minor procedures.

6.2.2 Procedural pain

The aim of procedural pain management is to minimise physical discomfort or pain, and movement and psychological disturbance, without compromising patient safety.

Pharmacological management includes analgesic agents, sedatives or general anaesthesia. Nonpharmacological methods include bubble blowing and distraction techniques.

The use of hypnotics increases the risk of side-effects.

6.3 Types of procedures

Analgesic and anxiolytic requirements may be mild, moderate or major.

6.3.1 Venepuncture and intravenous cannulation

Topical local anaesthesia, inhaled nitrous oxide and distraction should be used for venepuncture and intravenous cannulation. Do not apply pressure above venous pressure to the arm. Hard pressure is painful, and will not help fill the vein. At the end of the procedure, do not press on the needle when withdrawing it from the skin. Remove the needle, and then press on the puncture site.

6.3.2 Arterial puncture

Arterial puncture is painful, and should only be used when absolutely essential. If repeated specimens are required, consider the use of an arterial line. After arterial puncture has been carried out, compress the puncture site for a timed five minutes to avoid the development of a haematoma.

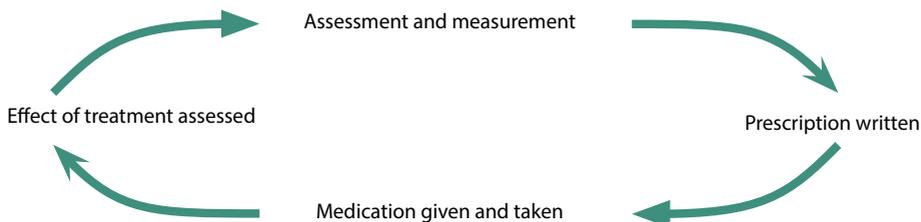


Figure 1: The assessment, decision and treatment cycle

6.3.3 Lumbar punctures

Lumbar punctures require inhaled nitrous oxide, local anaesthesia (topical then infiltrated) and simple analgesics. Avoid hyperflexion of the neck during the procedure as this adds to the discomfort.

6.3.4 Heel pricks

Avoid using the same site each time as bruising aggravates pain. Warm the heel and avoid the apex of the heel where there is less subcutaneous tissue. Two minutes prior to giving a heel prick, offer the infant oral sucrose or breast milk.

6.3.5 Major procedures

The following procedures require the use of a number of analgesic techniques.

Chest drains

Use local analgesia or anaesthesia, an oral or intravenous analgesic and anxiolytic, and inhaled nitrous oxide, for the insertion or removal of a chest drain. General anaesthesia is often preferred.

Marrow punctures or trephines

A local anaesthetic (topical and infiltration), analgesia and anxiolysis with sedation are often required. Ketamine is useful. General anaesthesia may be preferred. Airway and mediastinal chest assessment is critical in oncology patients prior to sedation and analgesia as lymphoid tissue hyperplasia may compromise the upper and/or lower airway.

Endotracheal intubation outside the operating theatre

The techniques chosen will depend upon the experience of the operator, the condition of the child and the available drugs. Options include propofol, ketamine, etomidate, midazolam or fentanyl, with or without the use of muscle relaxation. Paralysis should never be used when airway maintenance cannot be ensured.

6.4 The control of pain and anxiety

6.4.1 Nonpharmacological methods

Nonpharmacological methods to control pain and anxiety include:

- *Psychological preparation:* Giving a preoperative explanation, holding a discussion and educating the child and parents.
- Teaching coping strategies, especially to children and their parents (breathing exercises and blowing bubbles).
- Using relaxation therapies to calm and quieten the mind, and free the patient of anxiety and muscle tension.
- Using distraction techniques and guided imagery (virtual reality).
- Splinting and immobilising wounds.
- Conducting hypnosis.

6.4.2 Pharmacological options

“Multimodal analgesia” describes the use of different types of drugs, not exceeding the recommended dose of any one, used in combination to increase efficacy, but also to decrease the incidence of the side-effects of any one. These include local anaesthetics, simple analgesics, opioids and tramadol, inhalational agents, and anxiolytics, among others.

Local anaesthetics

Local anaesthetics are short- or long-acting, with or without adrenaline. They include infiltration, nerve block and regional or central blockade, with or without catheters. Some of these techniques may require specialist expertise.

Simple analgesics

Simple analgesics include:

- *Paracetamol*: Oral, rectal and intravenous.
- *Nonselective nonsteroidal anti-inflammatory drugs (NSAIDs)*: Oral, rectal, intravenous and transdermal patches.
- *Steroidal anti-inflammatory drugs*: Hydrocortisone, methylprednisolone and dexamethasone, given orally, intravenously and into the joints.

Opioids and tramadol

Examples of opioids are as follows:

- *Short acting*: Remifentanil, alfentanil, fentanyl and sufentanil.
- *Intermediate acting*: Morphine, meperidine (pethidine), tramadol, tilidine hydrochloride (Valoron®) and codeine.
- *Long acting*: Methadone and duragesic (fentanyl) patches in older children.

Inhalational agents

Entonox® is inhaled nitrous oxide. (Scavenging should be available).

Anxiolytics

Anxiolytics include the benzodiazepines, ie midazolam, diazepam and lorazepam, and the alpha₂ agonists, clonidine and dexmedetomidine.

Others

- *Ketamine*: Oral and intravenous, and intramuscular when there is no alternative.
- *Steroidal anti-inflammatory drugs*: Dexamethasone dose 150 µg/kg.
- *Alpha 2-adrenoreceptor agonists*: Clonidine and dexmedetomidine. The latter is a highly selective, intravenously administered α₂ agonist.
- *A combination of drugs*: Numerous options apply.
- *Sucrose (25%) and breast milk*: This is important for use in neonates and infants.

6.5 Doses of commonly used drugs in children

6.5.1 Local anaesthetics

A guideline to local anaesthetic doses is provided in Table 2.

Table 2: Guideline to local anaesthetic doses in children

Local anaesthetic doses in children	
Lignocaine	
Topical	Maximum spray 5 mg/kg/dose (Xylocaine® spray is 10 mg per spray) <ul style="list-style-type: none"> • <i>Gels:</i> 2% • <i>Eutectic mixture of local anaesthetic cream:</i> 2.5% lignocaine + 2.5% prilocaine 1.5 g/10 cm² under occlusive dressing for 1-3 hours, effective after half an hour
Infiltration or nerve block	<i>With adrenaline:</i> 7 mg/kg/dose <i>Without adrenaline:</i> 3-4 mg/kg/dose
Intravenous	1 mg/kg/dose
Bupivacaine	<i>Maximum dose:</i> 2-3 mg/kg/dose (0.4-0.6 ml/kg of 0.5%)
Ropivacaine	<i>Maximum dose:</i> 2-3 mg/kg/dose

6.5.2 Paracetamol

A guideline to paracetamol doses is provided in Table 3.

Table 3: Guideline to paracetamol doses in children

Paracetamol doses in children	
Oral	20 mg/kg stat, then 20 mg/kg 6 hourly to a maximum of 90 mg/kg/day <i>Neonates:</i> 60 mg/kg/day in divided doses 30-40 mg/kg mg/kg stat, then a 30 mg/kg/dose 6-hourly, to a maximum of 5 g/day
Rectal	<i>Neonates:</i> 60 mg/kg/day in divided doses <i>Other infants and children:</i> 90 mg/kg/day
Intravenous	<i>Neonates:</i> 7.5 mg/kg, 6-hourly, to a maximum of 30 mg/kg/day. (Decrease the dose and increase the interval in jaundiced babies) <i>Other infants and children:</i> 15 mg/kg, 6-hourly, to a maximum of 60 mg/kg/day

stat: immediately

6.5.3 Paracetamol antidote

A guideline to paracetamol antidote doses is provided in Table 4.

Table 4: Guideline to paracetamol antidote doses in children

Paracetamol antidote doses in children	
N-acetylcysteine	
	For paracetamol poisoning, regardless of the time delay
	Start with 150 mg/kg in 5% dextrose intravenously over one hour
IV	Then continue at 10 mg/kg/hour for: <ul style="list-style-type: none"> • 20 hours (delay < 10 hours) • 32 hours (delay 10-16 hours) • 72 hours (delay > 16 hours)
	Continue for longer if still encephalopathic
	Monitor potassium
Oral	140 mg/kg stat, then a 70 mg/kg dose 4-hourly for 72 hours
	Monitor potassium

* IV: intravenous, stat: immediately

6.5.4 Non-specific nonsteroidal anti-inflammatory drugs*

A guideline to non-specific NSAID doses is provided in Table 5.

Table 5: Guideline to non-specific nonsteroidal anti-inflammatory drug doses in children

Non-specific NSAID doses in children	
Ibuprofen	5–10 mg/kg/dose, 8 hourly
Diclofenac	1 mg/kg/dose 8–12-hourly <i>p.o.</i> or <i>p.r.</i>
Ketorolac	<ul style="list-style-type: none"> • <i>Oral:</i> 0.2 mg/kg/dose 6-hourly (a maximum of 10 mg, or a maximum of 0.8 mg/kg/day) • <i>IV:</i> 0.3 mg/kg/dose (a maximum of 10 mg)
Mefenamic acid	10 mg/kg/dose <i>p.o.</i> or <i>p.r.</i> 8-hourly

NSAID: nonsteroidal anti-inflammatory drug; *p.o.*: *per os*, *p.r.*: *per rectum*

* Use where contraindications do not exist

6.5.5 Opioids and tramadol

A guideline to opioid and tramadol doses is provided in Table 6.

Table 6: Guideline to opioid and tramadol doses in children

Opioid and tramadol doses in children	
Morphine	
Intravenous	0.1 mg/kg/dose 4–6 hourly
Intramuscular	0.2 mg/kg/dose 4–6 hourly
Oral	0.3–0.4 mg/kg/dose 4–6 hourly <i>Slow-release morphine:</i> 0.6 mg/kg/dose 12-hourly, increasing every 48 hours, if required 5–40 µg/kg/hour
Infusion	Draw up 0.5 mg/kg of morphine sulphate in 50 ml normal saline Run at 0.5–4 ml/hour, which will deliver 5–40 µg/kg/hour (1 ml = 10 µg/kg morphine)
PCA	20 µg/kg bolus with 5-minute lockout time. (Weight in kg = mg of morphine, dilute up to 50 ml volume. This will give 20 µg/kg/ml) If a background infusion is used, the dose for this is 5 µg/kg/hour
Tilidine hydrochloride (Valoron[®])	
Sublingual	1 mg/kg/dose sublingual drops (2.5 mg/drop) Weight in kg divided by 2.5 = the number of drops required <i>Obese older children:</i> 1 drop per year of age <i>Analgesia:</i> 0.5–1 mg/kg/dose 4-hourly <i>p.o.</i> <i>Antitussive:</i> 0.25–0.5 mg/kg/dose 6-hourly
Codeine phosphate	
Dihydrocodeine 0.5–1 mg/kg/dose 4–6-hourly <i>p.o.</i>	
Pethidine 0.5–1 mg/kg/dose intramuscularly or intravenously	
Fentanyl	
Slow bolus	1.0–3.0 µg/kg/dose stat intravenously
Infusion	1.0–5.0 µg/kg/hour in theatre or ICU
Intranasal	1.5–2.0 µg/kg/dose 10 µg/kg/dose
Alfentanil Hcl	
When ventilated, use a 10–50 µg/kg/dose	
Remifentanil	
1 µg /kg slowly intravenously <i>Infusion:</i> 0.05–0.3 µg/kg/minute	
Tramadol 1–2 mg/kg/dose 4- to 6-hourly <i>p.o.</i> or ivy	

ICU: intensive care unit, PCA: patient-controlled analgesia, *p.o.*: *per os*, stat: immediately

6.5.6 Opioid antagonists

A guideline to opioid antagonist doses is provided in Table 7.

Table 7: Guideline to opioid antagonist doses in children

Opioid antagonist doses in children	
Naloxone	<p><i>For opioid overdose:</i> 0.1 mg/kg/dose, to a maximum of 2 mg, intravenously, intramuscularly, subcutaneously and intratracheally</p> <p><i>Infusion:</i> 0.01 mg/kg/hour</p>

6.5.7 Anaesthetic agents

A guideline to anaesthetic agent doses is provided in Table 8.

Table 8: Guideline to anaesthetic agent doses in children

Anaesthetic agent doses in children	
Propofol	Sole agent intubating dose 3–5 mg/kg/dose
Ketamine	
Intravenous	<ul style="list-style-type: none"> • <i>Sedation + analgesia:</i> 0.25–0.5 mg/kg/dose • <i>Anaesthesia:</i> Bolus of 1–2 mg/kg/dose • <i>Infusion:</i> 10–20 µg/kg/minute or 1–4 mg/kg/hour
Intramuscular	<ul style="list-style-type: none"> • <i>Sedation + analgesia:</i> 2–4 mg/kg/dose • <i>Anaesthesia:</i> 7–10 mg/kg/dose
Oral	<ul style="list-style-type: none"> • <i>Sedation + analgesia:</i> 2–5 mg/kg/dose • <i>Anaesthesia:</i> 10 mg/kg/dose

6.5.8 Alpha 2 agonists

A guideline to alpha 2 agonist doses is provided in Table 9.

Table 9: Guideline to alpha 2 agonist doses in children

Alpha 2 agonist doses in children	
Clonidine	<p>1–6 µg/kg/dose <i>p.o.</i> 8- to 12-hourly</p> <p>2–3 µg/kg/dose <i>p.o.</i> for a premedicated single dose one hour before the procedure</p>
Dexmedetomidine	Intravenous (ventilated patients only), load 0.5-1.0 mcg/kg over 10-20 minutes if haemodynamically stable. Follow with infusion 0.5-1.0 mcg/kg/hr

p.o.: per os

6.5.9 Anxiolytics

A guideline to anxiolytic doses is provided in Table 10.

Table 10: Guideline to anxiolytic* doses in children

Anxiolytic doses in children	
Diazepam	0.2–0.4 mg/kg/dose intravenously or via the rectal route Do not give as an infusion as it binds to PVC
Lorazepam	
Oral	0.02–0.06 mg/kg/dose 8- to 24-hourly <i>p.o.</i>
IV	0.05–0.20 mg/kg/dose slowly intravenously
Infusion	0.01–0.10 mg/kg/hour
Midazolam	
Oral sedation	0.25–0.50 mg/kg/dose, to a maximum of 7.5 mg
IV	0.05–0.10 mg/kg/dose
IM	0.10 mg/kg/dose
Intranasal	0.20–1.00 mg/kg/dose
Infusion	0.10–0.20 mg/kg/hour or 1.00–4.00 µg/kg/minute
Anticonvulsant	0.20 mg/kg/dose intravenously

IM: intramuscular, IV: intravenous, *p.o.*: *per os*, PVC: polyvinyl chloride

* Benzodiazepines provide no analgesia

6.5.10 Antidote to benzodiazepines

A guideline to the antidote to benzodiazepines is provided in Table 11.

Table 11: The antidote to benzodiazepines in children

Antidote to benzodiazepines in children	
Flumazenil (anexate)	5 µg/kg intravenously every 60 seconds, to a maximum total of 40 µg/kg (a maximum of 2 mg) <i>Infusion:</i> 2–10 µg/kg/hour

6.5.11 Summary

Important principles of management include the following:

- Allow sufficient time for local anaesthetics and oral drugs to work before starting a planned procedure.
- Keep the environment safe and predictable.
- Only perform what is necessary, when it is necessary.
- Tell the truth in good time, and do not exclude the parents.

- Educating the parents and the child and providing them with an explanation prior to procedures or operations is invaluable, and decreases the need for medication.
- Use appropriate restraint. Restraint should not hurt the child, and should only be sufficient for the procedure to be performed efficiently and quickly.
- Monitor according to the condition of the patient, the drug choice made, the procedure being performed and the experience and expertise of the medical carer or operator.
- Drug choices should be rational, multimodal and safe.

Pain is soul destroying. A patient should not have to endure intense pain unnecessarily. The quality of mercy is essential to the practice of medicine. Here, of all places, it should not be strained. – The Quality of Mercy

6.6 Acute pain control for specific procedures in paediatrics

6.6.1 Medical procedures

Whenever possible, pain management for procedures should include both pharmacological and nonpharmacological strategies.

6.6.2 Procedural pain in the neonate

General recommendations

If feasible, breastfeeding mothers should be encouraged to breastfeed during the procedure. Non-nutritive sucking and/or the use of sucrose or other sweet solutions should be used for brief procedures.

Specific recommendations

- Blood sampling

Sucrose or other sweet solutions should be used. Topical local anaesthetics may be used for venepuncture pain.

- Heel prick (lancing)

Avoid the same site each time as bruising aggravates pain. Warm the heel, while avoiding the apex of the heel where there is less subcutaneous tissue. Give oral sucrose or allow the mother to breastfeed. Because it is less painful, venepuncture is preferred to a heel prick. Topical local anaesthetics alone are insufficient for heel lance pain. Morphine alone is insufficient for heel lance pain. Sensory stimulation, including tactile stimulation, such as holding or stroking, can be used, or combined with sucrose, where feasible, as it may further reduce the pain response.

- Percutaneous central venous catheter insertion

A topical local anaesthetic with tetracaine alone is insufficient to abolish the pain of percutaneous central venous catheter insertion. Tetracaine plus morphine is superior in ventilated infants. General anaesthesia may be the preferred option in difficult cases.

- Ocular examination for retinopathy of prematurity

Infants should receive local anaesthetic eyedrops, and/or be offered a pacifier. Sucrose may contribute to a reduction in the response to pain.

- Lumbar puncture

Topical local anaesthesia is effective in reducing lumbar puncture pain. Topical local anaesthetic and local anaesthetic infiltration are effective for lumbar puncture pain, and do not decrease the success rate. Inhaled Entonox® (50% nitrous oxide in oxygen) should be offered to children who are willing and able to cooperate. Consider adding a simple analgesic. Avoid hyperflexion of the neck during the procedure as this adds to discomfort.

- Urine sampling

Transurethral catheterisation with local anaesthetic gel is preferred as it is less painful than suprapubic aspiration using a topical local anaesthetic.

6.7 Procedural pain in older children

6.7.1 General comments

Children and their parents or carers may benefit from psychological preparation prior to a painful procedure. Pain management for procedures should include both pharmacological and nonpharmacological strategies, where possible. Entonox® should be considered for painful procedures in children who are able to cooperate with self-administration. Sedation or general anaesthesia should be considered, particularly for invasive, multiple and repeated procedures.

6.7.2 Specific recommendations

Blood sampling and intravenous cannulation

Topical local anaesthesia should be used for intravenous cannulation. Psychological strategies, e.g. distraction or hypnosis, to reduce pain and anxiety, should be used. Nitrous oxide is effective for pain reduction in venous cannulation.

Lumbar puncture

Behavioural techniques of pain management should be used to reduce lumbar puncture pain. Topical local anaesthetic and local anaesthetic infiltration are effective for lumbar puncture pain, and do not decrease the success rate. Inhaled Entonox® (50% nitrous oxide in oxygen) should be offered to children who are willing and able to cooperate.

Chest drain (tube) insertion and removal

Consider general anaesthesia or sedation combined with subcutaneous infiltration of buffered lidocaine for chest drain insertion. The selection of an appropriate drain type may reduce the pain by facilitating easy insertion. Consider a combination of two or more strategies for chest drain removal which are known to be effective for painful procedures, such as a psychological intervention, offering sucrose or a pacifier to neonates, and/or the use of opioids, nitrous oxide and NSAIDs.

Urine sampling

Lubricant, containing local anaesthesia, should be applied to the urethral mucosa prior to bladder catheterisation, e.g. Cathigel[®]. Psychological preparation and psychological and behavioural interventions should be used during bladder catheterisation and invasive investigations of the renal tract.

The insertion of nasogastric tubes

Topical local anaesthetics, such as lidocaine-containing lubricant gel, or atomised or nebulised 4–10% lidocaine, applied prior to placement, are likely to reduce the pain and discomfort of nasogastric tube insertion.

6.8 Surgical procedures

6.8.1 Repair of lacerations

Consider sedation or general anaesthesia for extensive wounds or in children who are very anxious.

Recommendations are as follows:

- *Repair of simple low-tension lacerations:* Tissue adhesives should be considered as they are less painful, are quick to use and have a similar cosmetic outcome to sutures or adhesive skin closures, i.e. steri-strips.
- If sutures are needed, topical anaesthetic preparations, e.g. lidocaine-adrenaline-tetracaine (LAT), if available, can be used in preference to injected lidocaine as they are less painful to apply and are equi-analgesic. It is not necessary to use a preparation containing cocaine. Buffering injected lidocaine with sodium bicarbonate should be considered.
- The hair apposition technique should be considered for scalp lacerations. It is less painful than suturing, does not require shaving and produces a similar outcome.
- If injected lidocaine is used, pretreatment of the wound with a topical anaesthetic preparation, e.g. LAT gel, reduces the pain of a subsequent injection.
- 50% nitrous oxide reduces pain and anxiety during laceration repair.

6.8.2 Change of dressings in children with burns

Recommendations are as follows:

- Potent opioid analgesia, given by oral, transmucosal or nasal routes according to patient preference and the availability of suitable preparations, should be considered for dressing changes in burnt children.
- Nonpharmacological therapies, such as distraction, relaxation and massage, should be considered as part of pain management for dressing changes in burnt children.

6.8.3 Circumcision

A dorsal penile nerve block provides similar analgesia to a caudal block, and is more effective than the application of topical local anaesthetic cream [eutectic mixture of local anaesthetic (EMLA)]. A subcutaneous ring block of the penis is less effective than a dorsal penile nerve block, and has a higher failure rate than caudal analgesia, but potentially fewer complications. Topical local anaesthetic cream only partially attenuates the pain response to circumcision in awake neonates, so more effective analgesic techniques, such as a dorsal penile nerve block, are recommended. The toxic effects with EMLA are seen with repeated doses in the postoperative period.

6.8.4 Inguinal hernia repair

Similar levels of efficacy for reducing pain following inguinal hernia repair have been reported following wound infiltration, ilioinguinal or iliohypogastric nerve block or caudal analgesia. Supplementation with paracetamol is recommended.

6.8.5 Ear, nose and throat procedures

Myringotomy

Recommendations are as follows:

- Oral paracetamol, ibuprofen or diclofenac, in suitable doses, and administered 30 minutes preoperatively, can achieve adequate early postoperative analgesia. Alternatively intravenous formulations can be given intraoperatively.
- Ketorolac can provide satisfactory analgesia.
- Opioids are effective, but not recommended, for routine use, because of the increased side-effects of nausea and vomiting, compared with minor analgesics.

Tonsillectomy

As significant levels of pain, behavioural disturbance, sleep disruption and altered activity can persist for 5–8 days following a tonsillectomy, the regular administration of paracetamol and NSAIDs may be necessary during this period. Information for families on pain assessment and medication use following discharge is particularly important.

Recommendations are as follows:

- A combination of individually titrated intraoperative opioids and regularly administered perioperative mild analgesics (a NSAID and/or paracetamol) is required for the management of tonsillectomy pain.
- Local anaesthesia injection in the tonsillar fossa may improve the pain score, reduce the time to the first oral intake, and reduce the incidence of referred ear pain, following a tonsillectomy.
- Tramadol can produce similar analgesia to morphine or pethidine.
- Intraoperative intravenous ketamine does not provide significant postoperative advantage, compared with an opioid.
- The implementation of standardised protocols, including an intraoperative opioid \pm an antiemetic, perioperative NSAID (diclofenac or ibuprofen) and paracetamol, are associated with acceptable pain relief and low rates of postoperative nausea and vomiting (PONV).

Mastoid and middle ear surgery

Compared with morphine, a greater auricular nerve block can provide similar analgesia and reduced PONV. Especially if a vasoconstrictor agent is used, local anaesthetic infiltration is a valuable option. Pre-incision timing of the block confers no additional benefit. Compared with middle-ear surgery, mastoid surgery is associated with increased pain. Therefore, patients are more likely to require an opioid, treatment for PONV and hospital admission.

6.8.6 Ophthalmology

Strabismus surgery

Intraoperative local anaesthetic blocks (subtenon or peribulbar) reduce PONV, and may improve perioperative analgesia in comparison with an intravenous opioid. Topical NSAIDs do not improve the pain score or postoperative analgesic requirements, when compared with a topical local anaesthetic or placebo. An intraoperative opioid and NSAID provide similar postoperative analgesia, but opioid use is associated with increased PONV.

Vitreoretinal surgery

NSAIDs provide similar analgesia, but a lower rate of PONV, than opioids. Compared with an opioid, a peribulbar block improves analgesia and reduces PONV.

Clinical practice points

1. Intermittent intramuscular injections are distressing to children and are less effective in achieving pain control than intravenous infusions.
2. Intravenous opioids can be used safely and effectively in children of all ages.
3. The initial doses of an opioid should be based on the age and weight of the child, and then titrated against the individual's response.
4. Unwanted side-effects should be anticipated and treated.
5. Effective patient-controlled analgesia prescription in children incorporates a bolus that is adequate for the control of movement-related pain, and may include a low-dose background infusion to improve efficacy and sleep.
6. Caudal local anaesthesia provides prolonged analgesia after surgery for lower abdominal, perineal and lower limb surgery, and has a low incidence of complications.
7. Clonidine prolongs analgesia when added to a caudal local anaesthetic block, and prolongs analgesia when added to a local anaesthetic epidural infusion.
8. Continuous epidural infusions provide effective postoperative analgesia in children of all ages, and are safe if appropriate doses and equipment are used by experienced practitioners, and accompanied by adequate monitoring and management of any complications.
9. When compared with systemic opioids, an epidural infusion of a local anaesthetic provides a similar level of analgesia.
10. A topical local anaesthetic does not provide adequate pain control for circumcisions in awake neonates.
11. Wound infiltration, peripheral nerve blocks and a caudal local anaesthetic provide effective analgesia after day case inguinal surgery.
12. NSAIDs do not increase the risk of re-operation for bleeding after a tonsillectomy. Ketorolac has been associated with increased bleeding and should be avoided.
13. Dexamethasone reduces post-tonsillectomy pain, nausea and vomiting, but high doses may increase the risk of bleeding. The recommended dose is 150-200 µg/kg.
14. Paracetamol and nonselective NSAIDs are effective for moderate to severe pain, and decrease opioid requirements after major surgery.
15. The efficacy of oral codeine is variable, and individual differences in the ability to generate the active metabolite may reduce the efficacy or increase the side-effects, including respiratory depression.
16. Consideration of the age and body weight of the child, and the duration of therapy, are required for the safe dosing of paracetamol.
17. Aspirin should be avoided in children.
18. Serious adverse events after NSAIDs are rare in children aged ≥ 6 months of age.
19. NSAIDs may cause pulmonary hypertension and alterations in cerebral, gastrointestinal and renal blood flow in infants aged ≤ 3 months.

NSAIDs: nonsteroidal anti-inflammatory drugs

7. Acute pain management in the elderly patient

As a greater proportion of the population falls into the “elderly” (aged ≥ 65 years) category, more and more elderly patients are presenting for treatment of their acute pain. Conditions which may cause acute pain include:

- Acute exacerbations of arthritis.
- Osteoporotic fractures.
- Cancer.
- Acute medical conditions, such as ischaemic heart disease, vascular disease and herpes zoster.
- Surgery.

7.1 Factors affecting pain control in the elderly

Factors that make effective pain control more difficult in the elderly patient include age-related alterations in pharmacokinetics and pharmacodynamics, an altered perception of pain and potential difficulties in assessment, diminished physiological reserve and concurrent diseases, and polypharmacy, which leads to an increased risk of drug interactions.

7.1.1 Age-related alterations in pharmacokinetics and pharmacodynamics

Age-related alterations in pharmacokinetics and pharmacodynamics occur as a result of the progressive physiological decline which occurs with increasing age, and the increasing likelihood of concurrent disease. The rate of decline can be highly variable between individuals, and is very difficult to predict. A 50% increase in sensitivity of the brain to opioids in the elderly is a pharmacodynamic change which must be noted. The most significant pharmacokinetic changes of which to be aware are a 20% drop in cardiac output, a 30–50% decrease in renal function, a 25% decrease in liver function, and reduced protein binding due to reduced plasma protein levels.

7.1.2 Altered perception of pain and potential difficulties in assessment

The assessment of pain, and an evaluation of the efficacy of treating this pain, is often more difficult in the elderly. This may be due to differences in pain perception and the reporting of pain, cognitive impairment, and difficulties with measuring pain. Thresholds to pain are often increased in the elderly, making diagnosis more difficult in conditions such as acute myocardial infarction and peritonitis, where pain is usually the presenting symptom. However, importantly, pain tolerance can be reduced in the elderly, thus necessitating its immediate treatment. Often, elderly patients under-report pain for a number of reasons, including fear, anxiety, depression and cognitive impairment. The latter may make the measurement of pain very difficult, especially in the case of noncommunicative elderly patients. Behaviour, such as restlessness, grunting and grimacing, needs to be assessed in these circumstances.

7.1.3 Diminished physiological reserve and concurrent diseases

Diminished physiological reserve and concurrent diseases can affect many analgesic drugs, as well as the techniques employed. Thus, the dose and duration of effect of anticoagulant drugs may be altered. This is relevant if regional techniques are used.

7.1.4 Polypharmacy, leading to an increased risk of drug interactions

Polypharmacy is particularly relevant when an elderly patient receives patient-controlled analgesia (PCA). The concomitant administration of long-acting central nervous system depressants, e.g. benzodiazepines, should be avoided.

7.2 Analgesic techniques in the elderly

As with younger patients, multimodal drugs and techniques should be used, with drugs titrated in a “start low, go slow” manner.

7.2.1 Patient-controlled analgesia

PCA should not be withheld from elderly patients simply because of their age. The basic requirements are that the patient must fully understand the technique, that breakthrough pain must be reported, and that there are no contraindications to its use. It is suggested that the size of the bolus dose should be reduced, and a continuous background infusion avoided.

7.2.2 Epidural analgesia

Elderly patients can be safely managed with an epidural, providing there is appropriate monitoring and staff education. There are three important guidelines, namely that:

- Epidural opioid requirements decrease with increasing patient age.
- The spread of a given volume of local anaesthetic drug in the epidural space is greater in the elderly.
- The elderly may be more prone to side-effects (hypotension). Spinal stenosis may predispose to neurological complications.

Be aware that many elderly patients may be taking anticoagulants as chronic medication. It is advised that lower doses and infusion rates should be used.

Analgesic drugs in the elderly are outlined in Table 1.

Clinical practice points

1. Pain thresholds increase in the elderly, but pain tolerance decreases.
2. PCA and epidural analgesia are more effective in elderly patients.
3. Acute pain may be under-reported.
4. Self-reported measures of pain can be used in the elderly, as opposed to other measures.
5. There is an age-related decrease in opioid requirements in the elderly.
6. Extreme caution is required with the use of NSAIDs and COX-2 inhibitors in this age group.
7. Paracetamol is the preferred non-opioid analgesia, except in frail patients.

COX: cyclo-oxygenase, NSAIDs: nonsteroidal anti-inflammatory drugs, PCA: patient-controlled analgesia

Table 1: Analgesic drugs in the elderly

Opioids	<p>Pure agonists are good, but the dose should be decreased in the event of renal dysfunction</p> <p>The effective duration of a single dose can be increased, if desired</p> <p>Pruritis, nausea and vomiting decrease with opioid use. Thus, the routine administration of antiemetics is not recommended owing to their side-effects</p> <p>Agonist-antagonists are not recommended because of the increased incidence of delirium</p>
Pethidine	<p>Pethidine is best avoided because a significant accumulation of the metabolite norpethidine might occur</p> <p>It can also cause cognitive dysfunction</p>
Fentanyl	<p>Fentanyl is a good drug in elderly patients, particularly in renal impairment</p> <p>It also causes less confusion than other analgesic drugs</p>
Propoxyphene	The accumulation of norexpropoxyphene may lead to confusion or cardiac toxicity
Tramadol	The elimination half-life is prolonged with tramadol. Thus, elderly patients require lower daily doses
Local anaesthetic drugs	Clearance may be decreased with local anaesthetic drugs, so lower doses should be used
NSAIDs and COX-2 inhibitors	<p>There is an increased risk of complications, i.e. renal impairment, cardiac failure and hypovolaemia</p> <p>There is an increased risk of gastrointestinal side-effects and an increase in cognitive dysfunction in frail elderly patients who take NSAIDs</p>
Paracetamol	Paracetamol is a safe drug in the elderly. There is no need to reduce the dosage unless the patient is very frail
Nitrous oxide	Ideally, nitrous oxide should not be used in the elderly because of the likelihood of vitamin B ₁₂ deficiency occurring

COX: cyclo-oxygenase, NSAIDs: nonsteroidal anti-inflammatory drugs

8. Analgesia during pregnancy, childbirth, the puerperium and lactation

Pregnant women and new mothers are at high risk of experiencing pain. Antenatally, the changing anatomy can result in back pain and an altered centre of gravity, predisposing women to falls and other injuries. The physiological changes of pregnancy can also result in increased headaches. Giving birth is painful, and the puerperium takes time to recover, regardless of how the infant was delivered. Breastfeeding is associated with new changes which can also be painful.

Thus, these women require analgesia frequently. However, pain control in this group is often poorly managed. Parturients (and inexperienced healthcare providers) fear the effects of drugs on the developing foetus and the breastfeeding infant. The coding of drugs in terms of safety during pregnancy is complicated, and the use of many drugs is restricted owing to lack of conclusive data, resulting in many healthcare providers incorrectly labelling them all as unsafe.

In addition to the usual adverse effects of pain, poorly managed pain in this group can interfere with the experience of pregnancy, and issues may develop around maternal-infant bonding. Postnatal depression is increased in mothers with a poor experience of pregnancy. Mothers may terminate breastfeeding prematurely because of the pain. Poorly managed acute pain can also result in the development of chronic pain.

8.1 Pregnancy

8.1.1 First trimester

The first trimester is the highest risk period for the development of foetal abnormalities, as this is the period during which organogenesis occurs. However, it also carries the highest risk for miscarriage during times of stress, and this can occur following an injury.

Analgesia following the termination of pregnancy should include nonsteroidal anti-inflammatory drugs (NSAIDs) and paracetamol. Short-acting opiates can be used for the procedure.

8.1.2 Second trimester

There is a lower risk of foetal abnormalities occurring during the second trimester, as well as a lower risk of miscarriage following stress. This is considered the safest period in which to perform an emergency procedure if a delay (until six months postpartum) is not a feasible option.

8.1.3 Third trimester

There is minimal risk of developmental abnormalities occurring during the third trimester as this is the period during which growth occurs. However, all drugs given to the mother may cross into the foetus, so the side-effects of drugs must be taken into account. The same organ systems which are affected by drugs in the mother are affected by drugs in the foetus. There is a high risk of the onset of premature labour during this period, and the well-being of the foetus should be considered after all stressful experiences.

Analgesia throughout pregnancy is outlined in Table 1.

Table 1: Analgesia throughout pregnancy

Analgesia throughout pregnancy
Paracetamol (1 g 6-hourly <i>p.o.</i>)
Short-course opiates, i.e. codeine 15–40 mg 4- to 6-hourly, or short-acting oxycodone up to 5 mg 4- to 6-hourly for up to five days. Codeine should be prescribed, together with symptomatic relief for constipation. The prescription of any opiate should be undertaken with due caution. An opiate should not be prescribed on a PRN basis
If pain is not controlled with paracetamol and opiates, a short-course, low-dose NSAID, e.g. ibuprofen 200 mg <i>p.o.</i> 8-hourly, or indomethacin 100 mg suppositories daily for up to five days, may be prescribed up to 30 weeks' gestation. All NSAIDs are to be avoided after 30 weeks' gestation to avoid the risk of premature ductal closure in the infant. The use of NSAIDs in pregnancy is off label

NSAID: nonsteroidal anti-inflammatory drug, *p.o.*: *per os*, PRN: *pro re nata* ("as the thing is needed")

8.2 Childbirth

All women should be offered methods of managing pain regularly throughout the time during which they give birth. Appropriate analgesia options should be available in all institutions with birthing facilities.

8.2.1 Analgesia for vaginal delivery

Non-pharmacological methods

Mothers should be allowed to choose methods of pain control that will improve their experience. This is subjective. Distraction techniques, e.g. breathing exercises and white noise, may be effective. Labouring in a bath is often helpful, as is the presence of a birthing partner, e.g. mother, sister, friend or partner.

Systemic analgesia

There are two ways of administering systemic analgesia:

- *Opiates*: Traditionally pethidine is offered. However, the analgesia it provides is relatively ineffective, and the perceived benefit is obtained from the resultant sedation and euphoria. It causes respiratory depression in both the mother and infant. It is not recommended for use during labour or delivery. Morphine provides good analgesia during labour. However, it should not be given within four hours of delivery. Naloxone must be available for the infant immediately after delivery, if required.
- *Patient-controlled analgesia (PCA) pump*: Usually, morphine is used in a PCA pump. The analgesia quality is slightly better, although the side-effects are similar to those of pethidine. The use of short-acting opiates in PCA pumps is well described. However, the risk of respiratory depression and respiratory arrest is also a reported feature, and use should be limited to specialised practitioners only.

Regional analgesia

An epidural provides high-quality analgesia, and the use of low doses allows minimal motor block, rendering the mother more mobile. Hypotension may occur, especially during initiation of the block, and the mother should be regularly monitored, i.e. every five minutes for 30 minutes after initiation or top-up, and thereafter every 30 minutes. Mothers should be encouraged to sit or lie in a position that is comfortable for them, although care should be taken to avoid aortocaval compression (in other words not fully supine unless a wedge is used to raise the right side at least 15 degrees). Walking should not be allowed unaided, as there may be some motor block, and proprioception (position sense) is lost. Mothers can walk if supported on both sides.

Combined spinal and epidural anaesthesia, an intrathecal injection of opiate, is given before the epidural is sited and used. This allows the faster onset of analgesia, but offers no other benefits, requiring special sets and added skill.

Analgesia during vaginal delivery is outlined in Table 2.

Table 2: Analgesia during vaginal delivery

Analgesia during vaginal delivery

Non-pharmacological methods

Morphine: 5–10 mg intramuscularly 4-hourly

PCA pump: Morphine 1 mg bolus, 6-minute lockout

Epidural: 0.1% bupivacaine + fentanyl 2 µg/ml, at 8–10 ml/hour

- Top up with 5–10 ml 0.25% bupivacaine
- If for a Caesarean section, top up with 5–15 ml 0.5% bupivacaine, or 5–15 ml 1% lignocaine
- CSE: Intrathecal injection 20–25 µg fentanyl, as well as the epidural mix, as described

Nitrous oxide in oxygen (1:1): Self-administered via a face mask

CSE: combined spinal and epidural anaesthesia, PCA: patient-controlled analgesia

Inhalational analgesia

Nitrous oxide is useful during labour in areas close to sea level. It does not completely eliminate the pain of contractions, and should be administered from the very beginning of the contraction, until the very end of it. It should be provided in a 1:1 ratio with oxygen, preferably premixed as Entonox[®]. It should only be administered by the parturient herself in order to avoid overdose and excessive sedation. It should be avoided in parturients with respiratory compromise, neurological injury (acute or chronic) and pulmonary hypertension.

8.2.2 Analgesia for Caesarean section

Neuraxial block

Neuraxial block is recommended in all mothers, unless there are contraindications, such as severe hypotension, coagulopathy, raised intracranial pressure and local sepsis. This provides analgesia for the operation itself, and for approximately 2–3 hours postoperatively.

The addition of fentanyl improves and prolongs the quality of the block, and allows less bupivacaine to be used, hence less haemodynamic compromise.

General anaesthesia

Analgesia is often forgotten in the rush of an emergency. The same level of analgesia should be given to mothers as that given to any patient undergoing abdominal surgery.

If it is required that the intubation response should be blunted (e.g. in pre-eclampsia), long-acting opiates should be avoided, if possible. Magnesium sulphate is recommended (this is not necessary if the patient has recently been loaded with magnesium), as is alfentanil.

From incision until delivery, the infant is exposed to all the drugs given to the mother. The mother should be kept deeply sedated, and short-acting opiates used, if necessary. The person receiving the infant must be informed as to whether or not opiates were used. He or she must have naloxone ready.

Once the infant has been delivered, the mother should be given multimodal analgesia, as with all abdominal surgery. The local anaesthetic can be infiltrated into the wound at the end of the procedure, or a bilateral transversus abdominis plane (TAP) block given, expertise permitting.

Analgesia for a Caesarean section is outlined in Table 3.

Table 3: Analgesia for a Caesarean section

Analgesia for a Caesarean section

Neuraxial block

Recommended intrathecal injections are as follows:

- 2.0–2.5 ml 0.5% heavy bupivacaine, i.e. bupivacaine with dextrose
- 1.8–2.0 ml 0.5% heavy bupivacaine, i.e. with 12.5–20.0 µg fentanyl added

General anaesthesia

If it is required that the intubation response is blunted, the following applies:

- *Magnesium sulphate:* A 40 mg/kg IV infusion over 10 minutes preinduction
- *Alfentanil:* 0.5–1.0 mg intravenously, or remifentanil 0.5–1.0 mg intravenously

Intraoperative analgesia following delivery of the infant is as follows:

- *Fentanyl:* 50–200 µg intravenously
- *Morphine:* 5–10 mg intravenously
- *NSAID:* Diclofenac 50–100 mg PR, or indomethacin 100 mg PR
- *Paracetamol:* 1 g intravenously
- *Local anaesthetic (infiltration into the wound or TAP block):* 0.25–0.5% bupivacaine, not exceeding a total dose of 2.5 mg/kg, i.e. approximately 50–100 ml

IV: intravenous, NSAID: nonsteroidal anti-inflammatory drug, PR: per rectum, TAP: transversus abdominis plane

8.3 The puerperium

Accurately managing pain during this period has added benefits, as previously described, and the use of multimodal analgesia allows for decreased doses of the individual component drugs in the treatment regimen. This benefits the breastfeeding infant as less drug is available to cross into the breast milk.

8.3.1 Analgesia following vaginal delivery

Mothers experience pain from ongoing contractions, vaginal tears and episiotomies. They also have headaches (from prolonged labour, their emotions, prolonged pushing, or even from accidental dural puncture during insertion of an epidural), as well as breast pain.

Perineal pain is acute, and may be severe. Sitting in iced water, or the use of ice packs, may alleviate it, in combination with multimodal analgesia.

Other forms of pain can be managed by using a combination of paracetamol and a NSAID (this combination is very effective), and adding a short-course opiate, but only if necessary. The breastfeeding infant should be monitored for sedation if high doses of opiates are used.

8.3.2 Analgesia following Caesarean section

As with all abdominal surgery, the pain postoperatively is considerable. Again, multimodal analgesia is the most effective way of alleviating this. Patients should be discharged with an oral medication and/or suppositories.

Analgesia during the puerperium is outlined in Table 4.

Table 4: Analgesia during the puerperium

Analgesia during the puerperium

Following normal vaginal delivery

- A NSAID, e.g. ibuprofen 200 mg 8-hourly, or diclofenac 50–100 mg, 8- to 12-hourly
- Paracetamol, 1 g 6 hourly
- Short-course opiates, e.g. codeine, 15–40 mg, 4- to 6-hourly
- Combination tablets are available. Check the relative doses of each component, and supplement with individual components, rather than increasing the doses of all of them

Following Caesarean section

- Paracetamol, 1 g 6-hourly
- A NSAID, e.g. ibuprofen 200 mg 8-hourly, or diclofenac 50–100 mg 8- to 12-hourly
- *Short-course opiates:* Short-course opiates should be nurse administered, e.g. morphine 10 mg 4-hourly/PRN; or short-acting oxycodone 5 mg 4- to 6-hourly; or PCA, i.e. PCA morphine 1 mg bolus with 6-minute lockout, while in hospital, then an oral short-course opiate, e.g. codeine 15–40 mg 4- to 6-hourly. Codeine should be prescribed, together with symptomatic relief for constipation. The prescription of any opiate should be undertaken with due caution, and an opiate should not be prescribed on a PRN basis. The use of oxycodone in lactating mothers is off label
- Tramadol, e.g. 50–100 mg 6- to 8-hourly, can be added to augment analgesia and limit opiate doses

NSAID: nonsteroidal anti-inflammatory drug, PCA: patient-controlled analgesia, PRN: *pro re nata* ("as the thing is needed")

8.4 Lactation

Mothers can experience pain for a variety of reasons while they are breastfeeding. Breast pain is common, especially after the first few days, and results from engorgement and cracked nipples. Headaches are also commonly experienced. Abdominal and perineal pain can continue for several days.

While most drugs cross into the breast milk, the concentrations are usually far too small to be of concern with regard to the well-being of the infant if the dose of each drug is carefully chosen.

Multimodal analgesia is recommended. The choice of the combination should be appropriate to the level of pain experienced.

Analgesia for lactating mothers is outlined in Table 5.

Table 5: Analgesia for lactating mothers

Analgesia for lactating mothers

- *Mild pain:* Paracetamol 1 g 6-hourly, with the possible addition of a short course of low-dose NSAID, e.g. ibuprofen 200 mg, 8-hourly
- *Moderate pain:* Paracetamol + NSAID at regular intervals
- *Severe pain:* Paracetamol + NSAID + a short-course opiate, i.e. codeine. (Large doses of an opiate may cause the infant to become drowsy)

NSAID: nonsteroidal anti-inflammatory drug

Bibliography

1. Butwick A. What's new in obstetric anesthesia in 2011? Reducing maternal adverse outcomes and improving obstetric anesthesia quality of care. *Anaesth Analg.* 2012;115(5):1137–1145.
2. International Association for the Study of Pain. Guide to pain management in low-resource settings. IASP [homepage on the Internet]. c2015. Available from: http://www.iasp-pain.org/files/Content/ContentFolders/Publications2/FreeBooks/Guide_to_Pain_Management_in_Low-Resource_Settings.pdf
3. Babb M, Koren G, Einarson A. Treating pain during pregnancy. *Can Fam Physician.* 2010;56(1):25–27.
4. Seaton S, Reeves M, McLean S. Oxycodone as a component of multimodal analgesia for lactating mothers after Caesarean section: relationships between maternal plasma, breast milk and neonatal plasma levels. *Aust N Z J Obstet Gynaecol.* 2007;47(3):181–185.
5. Park BY, Jeong CW, Jang EA, et al. Dose-related attenuation of cardiovascular responses to tracheal intubation by intravenous remifentanyl bolus in severe pre-eclamptic patients undergoing Caesarean delivery. *Br J Anaesth.* 2011;106(1):82–87.

9. Routes of systemic drug administration

Treating acute pain orally (enterally) is the most common and cheapest route for the administration of medication. Alternative routes of administration may be required in special circumstances, particularly in the perioperative management of patients, or during medical and/or surgical emergencies. Alternative routes allow for more rapid onset, as well as titration of the dose, and avoidance of the gastrointestinal tract, should it be inaccessible.

Therapeutic interventions for pain relief should be individualised on the basis of actual or expected pain severity, patient characteristics and the resources available to monitor both the effectiveness of the analgesia and the adverse effects.

Drugs for pain relief should be prescribed regularly, rather than on a *pro re nata* ("as the thing is needed") basis. Frequent monitoring of the degree of pain and the presence of the drug's side-effects is required so that drug doses, dosing intervals and routes of administration can be adjusted.

The routes of administration of drugs used in pain relief can be classified according to enteral or parenteral administration.

9.1 Enteral administration

9.1.1 Oral route

The oral route is the most cost-effective and accepted method of administering drugs for pain relief. The efficacy of oral drugs is determined by the following factors:

- *Gastrointestinal motility:* Delayed gastric emptying may result in inadequate analgesia, especially when vomiting occurs. Conversely, drugs can accumulate in the stomach with multiple doses which enter the proximal gastrointestinal tract as a bolus with the return of gastric motility, resulting in high systemic levels (dumping).
- *Drug formulation:* Liquids are absorbed faster than capsules, while tablets are absorbed the slowest. Enteric coating delays dissolution until entry into the proximal gastrointestinal tract. Enterically coated tablets should never be split or broken. Slow-release preparations allow for delivery of a larger dose of medication, with slower onset, longer duration and reduced peak levels, and hence reduced side-effects. A number of slow-release pain medications are marketed as having a 12-hour duration of action. However, most require eight-hourly administration to maintain adequate pain relief. These drugs are most useful for the provision of baseline analgesia for acute pain, and for the long-term therapy of chronic and cancer pain.
- *Hepatic first-pass metabolism:* Hepatic first-pass metabolism occurs when the drugs are absorbed from the gastric, intestinal or rectal mucosa; not from the sublingual mucosa. This has two consequences, i.e. the amount of drug reaching the systemic circulation is reduced by 20-50%, thus reducing both peak levels and duration of action, when compared with parenteral administration; and secondly, the liver is exposed to higher levels of the administered drug than the other organs.

Specific drug classes that are administered orally

Anti-hyperalgesic drugs include the following:

Paracetamol

Paracetamol is safe to administer preoperatively. The loading dose is 40 mg/kg. The maintenance dose is 20 mg/kg (to a maximum of 1 g) six-hourly (to a maximum of 4 g/day up to age 65 years, and to a maximum of 3.5 g/day to age \geq 65 years).

Nonselective nonsteroidal anti-inflammatory drugs

Nonselective nonsteroidal anti-inflammatory drugs (nsNSAIDs) have potential renal, gastrointestinal and antiplatelet effects, which makes them less suitable for preoperative administration after a period of fasting, or in bleeding and/or hypovolaemic emergency patients. Parenteral administration should be considered after fluid repletion in patients, provided that they have no contraindications to the administration of these drugs.

Cyclo-oxygenase-2 inhibitors

Compared with the nonselective NSAIDs, Cyclo-oxygenase-2 inhibitors (coxibs) have a lower propensity to cause gastrointestinal side effects, no antiplatelet effects, but similar renal effects to the nsNSAIDs. Thus, coxibs may also precipitate renal dysfunction in hypovolaemic patients. Therefore, initially the administration may need to be parenteral after adequate fluid repletion.

Primary analgesics

Codeine

Codeine may be given orally in doses of 0.5-1 mg/kg. A number of genetic variants of the cytochrome that metabolise codeine to morphine to provide analgesia exist:

- *Ultra-rapid metabolisers:* Ultra-rapid metabolisers achieve rapid high morphine levels, with the potential for respiratory depression, coma and death.
- *Slow metabolisers:* Slow metabolisers result in the slow or absent metabolism of codeine to morphine, and thus provide inadequate analgesia, but still result in the development of constipation, a codeine-mediated side-effect.

Thus, codeine is not recommended for preoperative administration. If a patient has not taken codeine before, he or she should receive 0.5 mg/kg, and be observed at 10- to 15-minute intervals for the first 90 minutes after its administration. Codeine is most effective in the acute pain setting when combined with paracetamol and/or a NSAID (coxib or nonselective).

Tramadol

Tramadol is rapidly absorbed, with a minimal risk of respiratory depression, making it a useful drug for premedication. The slow-release preparation not only provides a longer duration of action, but limits the peak level. High peak levels are responsible for the main side-effects of nausea and dysphoria.

Morphine

Oral morphine is available as a liquid (most commonly formulated as 20 mg/5 ml), immediate-release tablets and as a slow-release formulation. Oral morphine is effective in acute pain relief at a dose of 20 mg every 30 minutes. The main concern with this therapy, particularly with poorly staffed wards, is diversion of the oral morphine to visitors for illicit use.

With longer-term use, daily oral morphine use should be quantified, and 60% of the requirement administered as an eight-hourly, slow-release formulation, with 40% used, as needed, for breakthrough pain.

Oxycodone

Oxycodone has a similar onset and duration of action to morphine, and is available as an immediate (Oxynorm[®]) and slow-release (Oxycontin[®]) preparation. Differences from morphine include reduced first-pass metabolism and improved bioavailability. With longer-term use, daily oral oxycodone use should be quantified, and 60% of the requirement administered as an 8-12 hourly, slow-release formulation, with 40% used, as needed, for breakthrough pain. The newest formulation of oxycodone is Targinact[™] combining oxycodone and naloxone in a 2:1 ratio. Naloxone has 97% hepatic first pass metabolism so does not inhibit oxycodone analgesia but naloxone in the GI tract reduces GI side effects, excluding nausea, by up to 60%.

Hydromorphone (Jurnista[®])

Hydromorphone (Jurnista[®]) is a slow-release preparation used for the management of chronic opioid responsive pain. This formulation is not suitable for acute pain management. Hydromorphone has five times the potency of morphine, and also contains an active metabolite which is renally excreted and is neuro-excitatory like nor-pethidine.

Procedural sedation

The intravenous (IV) formulations of ketamine 5 mg/kg and midazolam 0.2 mg/kg may be combined and added to 20-40 mg/kg paracetamol syrup as a useful oral preparation for procedural sedation in children. (In other words, the child drinks fluid from ampoules usually intended for IV use mixed with a suitable syrup). Onset is within 20-30 minutes, and duration is 30-45 minutes.

Secondary analgesics

Amitriptyline and dothiepin

Amitriptyline or dothiepin are well absorbed orally, and provide analgesia and light sedation superior to the benzodiazepines, as well as relief from muscle spasm.

Clonidine

The available oral formulation (Dixarit[®]) contains 25 µg clonidine. Effective dosing is 1.5–3.0 µg/kg twice daily. Hence, the number of tablets required may be as many as 12 per dose.

9.1.2 Rectal route

The rectal administration of medication, particularly NSAIDs and paracetamol, is commonly practised in South Africa.

Rectal administration allows drugs to be given where the upper gastrointestinal tract is inaccessible or inactive (gastroparesis). Absorption from the rectum is slow, and may be erratic, especially if the patient is hypovolaemic, and splanchnic blood flow is reduced. Hepatic first-pass metabolism also occurs with rectally administered medications absorbed through the superior rectal veins. Absorption from the inferior veins is directly into the systemic circulation. Local irritation and diarrhoea have been reported after suppository use, and this route is contraindicated if significant lesions (inflammatory and/or neoplastic) of the anorectal area are present.

The division of suppositories to titrate the dose is not recommended as the active drug may be unevenly distributed within the suppository.

Consent to the administration of rectal medication cannot be presumed. It should be obtained prior to administration, especially if the administration is to be carried out while a patient is anaesthetised, and/or the surgical procedure does not require exposure of the perineum.

Paracetamol can usually be given orally prior to surgery. However, suppositories are substantially cheaper than the IV formulation for use in acute pain emergency scenarios. Rectal paracetamol still undergoes hepatic first-pass metabolism, hence absorption may be slow in hypovolaemic patients with reduced splanchnic blood flow.

NSAIDs were originally recommended in suppository formulation to avoid direct exposure of the gastric mucosa to the nsNSAIDs. However, gastric side-effects are dependent upon the systemic level of the NSAID, rather than the level in the gastric lumen. Similarly, the renal and antiplatelet effects are independent of the route of administration.

The rectal administration of NSAIDs allows administration after adequate hydration, which is preferable to preoperative oral administration owing to the inevitable dehydration which occurs with preoperative fasting. Tramadol is the only opioid available for rectal administration. Dosage adjustment is not necessary.

Suppositories may also be administered via intestinal stomas, especially an end colostomy after abdominoperineal resection.

9.1.3 Sublingual route

Sublingual drug administration is different from oral administration as the drug is absorbed directly into the systemic circulation. This results in a faster onset and a higher peak level because of direct absorption into the systemic circulation, with no hepatic first-pass metabolism.

Drugs in an IV formulation may be given sublingually prior to the establishment of IV access. Sublingual administration appears to provide equivalent onset of action, without the need for an infusion pump, in the case of a drug which requires a loading dose over a period of 20-30 minutes, such as dexmedetomidine.

The sublingual administration of drugs, such as morphine or fentanyl, in the prehospital setting or emergency department, provides more reliable onset of analgesia than intramuscular (IM) or subcutaneous (SC) administration, as peripheral blood flow is reduced in situations of sympathetic activation and/or hypovolaemia. Once IV access is established, further titration of pain relief can occur via the IV route.

Oral transmucosal systems for analgesic administration include fentanyl, formulated as a lollipop and as a rapidly dispersible wafer. Both are associated with intense facial pruritis. Concerns over dependence and addiction issues have been raised with the lollipop. Neither is available in South Africa. The anti-emetic ondansetron, is available as a rapidly dissolving sublingual lyophilisate wafer (Zofran Zydis™).

9.1.4 Feeding tubes (orogastric, nasogastric, post-pyloric, gastrostomic and enterostomic)

All drugs given orally, except those in a slow-release formulation, may be given via a feeding tube. Liquids or suspensions should be used for the administration via feeding tubes, if possible. The contents of capsules may be removed from the capsule and directly administered down the tube. Crushing is required should a particular medication only be available in a tablet. The powdered medication should be well flushed through the tube to prevent tube occlusion. Slow-release preparations cannot be crushed, and are unsuitable for administration via a feeding tube.

9.2 Parenteral administration

9.2.1 Noninvasive systemic drug administration

Intranasal droplets

The IV formulation of analgesics, such as morphine and fentanyl, as well as sedatives, such as midazolam, dexmedetomidine and ketamine, may be given via the nose. This route remains accessible in uncooperative patients who refuse to open their mouths.

The aim is for systemic absorption of the nasally administered drug via the nasal mucosa, with fast onset and high peak levels of the drug, providing efficacy similar to IV administration.

In reality, more than 70% of the medication administered by this route passes through the nasal passage and into the nasopharynx, to be swallowed. The swallowed medication is then absorbed via the gastrointestinal tract, with a slow onset and low peak due to hepatic first-pass metabolism, as with any orally administered drug.

Another disadvantage of nasal droplet administration is that most IV formulations are bitter. Medication passing from the nasopharynx to the oropharynx comes into contact with the posterior tongue, the site of the bitter taste receptors, making the experience extremely unpleasant for the patient.

The administration of an opioid via the nasal route is associated with intense pruritis because of the large numbers of histamine-releasing immune cells in the nasal mucosa which are degranulated after exposure to the opioid, particularly the synthetic fentanyl derivatives.

Nasal transmucosal administration

A device known as the LMA MAD (mucosal atomisation device) Nasal[®] (Teleflex medical, USA), produces a fine mist (droplet size < 0.2 micron) when the medication is injected from a standard syringe via the MAD. More than 90% of the medication in the droplets from the MAD is absorbed by the nasal mucosa. Less than 10% is swallowed. The result is that MAD-administered drugs, such as morphine, midazolam and dexmedetomidine, achieve fast onset and a high peak levels equivalent to that achieved with IV administration. There is extensive experience with this method of drug administration in the prehospital environment and for paediatric premedication. Efficacy is equivalent to that of IV administration.

Less than 10% of the drug administered by MAD reaches the oropharynx, so bitter receptors on the posterior tongue are minimally activated. Nasal pruritis remains a significant side-effect.

Passive transdermal drug delivery

Fat-soluble drugs may be delivered from a matrix reservoir into the stratum corneum of the skin, and from there into the SC veins. The onset of action of transdermally delivered drugs is slow. Maximum plasma levels are achieved 6-8 hours after the application of the transdermal patch. The effect of the drug will persist for 6-8 hours after patch removal as a reservoir of drug remains in the *stratum corneum*. Compliance is improved by using transdermal patches as the patch only needs to be changed (with application at a new site) every three days for fentanyl (Durogesic[®] and generics) and every seven days for buprenorphine (Sovenor[®]).

The technology of transdermal drug delivery has been widely used for the delivery of capsaicin, hormone replacement and nicotine.

Fentanyl and buprenorphine are available in transdermal delivery systems in South Africa. A transdermal delivery system is available in Europe for the delivery of high-dose capsaicin for the treatment of localised areas of neuropathic pain.

Transdermal is not suitable for acute pain management, particularly in opioid-naïve patients. Not only is the onset of action too slow for acute pain relief, but the sustained blood level may induce respiratory depression, coma and death in particularly opioid-sensitive patients.

There have been reports of clinicians cutting transdermal patches to reduce the rate of drug delivery in the acute pain setting. This is a negligent practice which is impossible to justify, and carries significant medico-legal consequences in the event of an adverse outcome.

Transdermal fentanyl or buprenorphine are best suited to the maintenance of opioid analgesia in patients with chronic pain or cancer pain. Transdermal fentanyl or buprenorphine do not have a role for in acute pain management.

9.2.2 Invasive systemic drug delivery

Subcutaneous drug delivery

Drugs that are formulated for IV use may also be safely administered subcutaneously. Conversely, drugs that are formulated for IM administration are not suitable for SC administration as the volume is excessive, and the solution is irritant, e.g. diclofenac.

The rate of administration of SC drugs should not exceed 1 ml in a single bolus, or a 3 ml/hour total dose. At least 30 minutes should be allowed to elapse between 1 ml boluses to allow for drug dispersion and absorption. Smaller boluses may be given more frequently, e.g. every 5-6 minutes in disposable patient-controlled analgesia (PCA) systems.

A SC butterfly, or 22-G IV cannula, under a clear, semi-permeable dressing, e.g. OpSite™ or Tegaderm™, is the route of choice for administration of SC drugs. The SC device should be capped with a needle-free injection port. The subclavian or anterior upper arm areas are the most comfortable sites for butterfly or cannula insertion, with optimal consistency in drug absorption. The cannula or butterfly is best inserted in the operating theatre, during or after the operation, in patients undergoing surgery where systemic opioids and/or NSAIDs are likely to be required for postoperative pain relief. The butterfly or cannula device simplifies the administration of analgesic drugs in wards. Staff have less exposure to needles, and thus there is a reduced risk of needle-stick injury. Patients are spared the pain and inconvenience of multiple injections. Sites need to be changed every 48-72 hours.

PCA may also be delivered subcutaneously. The SC route may be less comfortable, with minor localised burning on injection (sometimes interpreted by patients as an indicator of efficacy), and localised swelling and redness after 24-48 hours, which resolves rapidly on butterfly or cannula removal and replacement at an alternative site. There are a number of advantages to SC PCA administration:

- PCA may be continued when IV access is no longer required.
- Misconnection of the PCA device to the IV line is not possible.
- The efficacy of PCA is independent of the presence of a flowing IV infusion.
- The danger of dead space in IV infusion tubing (which may become filled with PCA solution if the IV infusion is stopped) is obviated.

Intramuscular drug delivery

The IM route of drug delivery remains the most common route of opioid delivery in postoperative patients.

This popularity persists, despite well-recognised complications, including drug toxicity from intra- and perivascular injection, inadequate analgesia, nerve damage and injection abscesses.

Examples of inadequate analgesia include:

- *Inappropriate dosing:* Morphine is commonly dosed at 10–15 mg, and pethidine at 50–100 mg, both 4- to 6-hourly. These prescriptions provide adequate post-surgical analgesia in < 50% of post-surgical patients following optimal IM injection, but will cause significant respiratory depression in up to 2%.

- *Reduced blood muscle and skin flow:* This occurs particularly after surgery and in emergency situations.
- Injection into fat or subcutaneously.

Injection abscess complications are increased with the following risk factors: a high injection volume, increasingly irritant injectate and immunocompromised patients.

The following principles apply for the appropriate management of postoperative pain by IM injection:

- IM injections should be given at two-hourly rather than four-hourly intervals.
- Medication for adult patients weighing ≥ 50 kg should be morphine 5-10 mg and tramadol 50-100 mg. Pethidine should be avoided, but prescribed at 50 mg, if used.
- Consideration should be given to hourly SC bolus analgesic injections and subcutaneous PCA after three IM injections, with persistent pain.

There is no place for IM drug administration in the emergency management of acute pain.

Intravenous drug delivery

IV drug delivery provides the most rapid onset of action through direct access to the systemic circulation. However, side-effects, as well as overdose, are also more common.

Monitoring is often required for the IV administration of drugs for pain relief.

Paracetamol and NSAIDs do not cause acute, life-threatening complications, but monitoring (every 4-6 hours) is required for longer-term complications, particularly for reduced urine output, and gastric bleeding in the case of the NSAIDs.

Opioids given intravenously have the potential to cause fatal respiratory depression. Patients should be constantly monitored, with a clinical assessment made of the respiratory rate and level of consciousness, preferably using pulse oximetry.

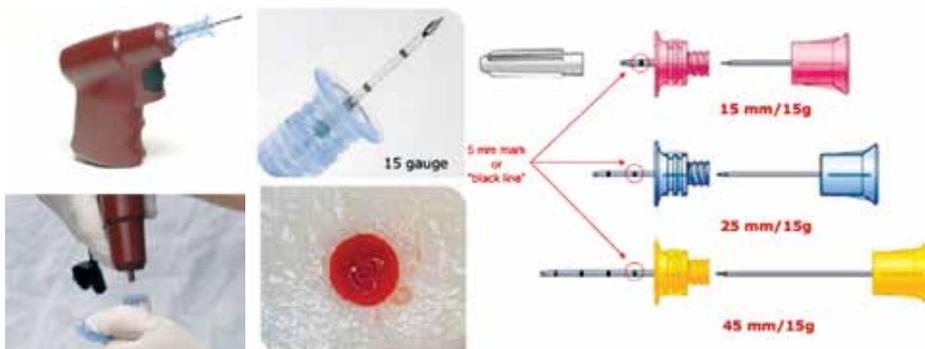


Figure 1: The Arrow EZ-IO[®] Intraosseous Vascular Access System

The limitations and dangers of IV PCA have been discussed in this chapter, as well as in the relevant section on PCA elsewhere in these guidelines.

Intraosseous drug delivery

Intraosseous drug delivery occurs in rare situations, particularly in paediatric burns, where an intraosseous line may be the only route of access for the administration of drugs for pain relief. A reliable device for intraosseous access, the Arrow® EZ-IO® Intraosseous Vascular Access System (Teleflex, USA), is now available in South Africa (Figure 1).

Morphine, in weight-appropriate doses, may be administered via an intraosseous line, until the establishment of IV access.

The following topics are discussed in detail in relevant sections of the guidelines:

- *Regional (plexus) anaesthesia*: Single-shot/catheter – local anaesthetic ± vasoconstrictor.
- *Neuraxial anaesthesia*: Intrathecal and epidural anaesthesia, and single-shot/catheter anaesthesia.

10. Locally and regionally administered analgesic drugs

10.1 Drugs used for local and regional analgesia

10.1.1 Local anaesthetics

Local anaesthetics exert their effect as analgesics by the blockade of sodium channels, and hence impede neuronal excitation and/or conduction.

Short-duration local anaesthetics

Lignocaine is the most widely used short-duration local anaesthetic in acute pain management. Although the plasma half-life is approximately 90 minutes, the duration of the local anaesthetic effect depends upon the site of administration, dose administered and the presence or absence of vasoconstrictors. Although lignocaine is hydrophilic, it is delivered in high concentrations. Therefore, it usually diffuses well into nerve bundles, resulting in little separation of sensory and motor blocking actions.

Long-duration local anaesthetics

The three most commonly used long-duration local anaesthetic agents; bupivacaine, levobupivacaine and ropivacaine, are structurally related. Whereas bupivacaine is a racemic mixture of the S- and R-enantiomers, levobupivacaine is the S-(or levo) enantiomer of bupivacaine. Ropivacaine is an S-enantiomer formulation as well.

Summary of evidence based efficacy and safety features of local anaesthetic agents

1. A continuous perineural infusion of lignocaine provides less effective analgesia, and results in denser motor block, than ropivacaine, levobupivacaine and bupivacaine.
2. There are no differences in terms of the quality of analgesia or motor blockade between ropivacaine, levobupivacaine and bupivacaine when given in low doses for regional analgesia.
3. Ropivacaine and levobupivacaine cause less severe cardiovascular and central nervous system toxic effects than racemic bupivacaine.
4. A lipid emulsion may be effective in the resuscitation of circulatory collapse due to local anaesthetic toxicity, but must be used in conjunction with advanced cardiac life support.
5. Resuscitation following accidental overdose with ropivacaine is more likely to be successful than that for a bupivacaine overdose.

10.1.2 Opioids

Although peripheral opioid receptors have been identified, there is very little clinical evidence to support the use of opioids for possible peripheral or local effects. When compared with placebo, intra-articular morphine following knee arthroscopy does not improve analgesia. Furthermore, there is no conclusive evidence that opioids have a peripheral effect at perineural level.

10.1.3 Adjuvant drugs

Alpha-2 agonists and magnesium have been shown to have peripheral analgesic effects. Clonidine prolongs the duration of analgesia and anaesthesia when added to local anaesthetics for axillary and peribulbar blocks, but evidence is inconclusive when clonidine is added to supraclavicular brachial plexus blocks or continuous catheter techniques.

It has also been established that adding clonidine to lignocaine intravenous (IV) regional anaesthesia delays tourniquet pain, while the addition of dexmedetomidine to lignocaine IV regional anaesthesia increases the duration and quality of analgesia.

As the long-term effects of perineural magnesium are unknown, adding magnesium to local anaesthetics when performing nerve blocks is not advised.

Magnesium sulphate improves intra- and postoperative analgesia and tourniquet tolerance when added to lignocaine IV regional analgesia.

Ketamine has been shown to have peripheral analgesic qualities as it reduces pain when applied topically in oral mucositis.

10.1.4 Anti-inflammatory drugs

Corticosteroids

There is evidence to support the use of corticosteroids for their peripheral analgesic action in a number of clinical settings. Subacromial injections of corticosteroids are more effective than oral nonsteroidal anti-inflammatory drugs (NSAIDs) when treating rotator cuff tendonitis.

Intra-articular steroids, in combination with either a local anaesthetic or opioid, reduce pain, analgesic consumption and the duration of immobilisation after knee arthroscopy. There is, however, an increased risk of septic arthritis following intra-articular corticosteroids.

Combining dexamethasone with lignocaine for IV regional anaesthesia improves analgesia for up to 24 hours.

Nonsteroidal anti-inflammatory drugs

Administering nonsteroidal anti-inflammatory drugs at the site of pain is an attractive alternative to oral or parenteral routes, potentially minimising systemic side-effects of the drug. This practice is supported in a number of clinical scenarios. It has been shown that topical NSAIDs cause fewer gastrointestinal side-effects than oral NSAIDs, and are of limited efficacy in lateral elbow pain, providing short-term functional improvement.

Furthermore, topical diclofenac and ketoprofen are comparable to oral naproxen in reducing pain and inflammation associated with musculoskeletal injuries and other inflammatory conditions. Indomethacin, however, is ineffective when applied topically.

Topical NSAIDs also provide effective analgesia for traumatic corneal abrasions.

Finally, adding a non-selective NSAID to a local anaesthetic solution for IV regional anaesthesia improves postoperative analgesia.

10.2 Regional and local analgesic techniques

Various techniques exist for administering analgesic drugs at peripheral sites. Peripheral nerve blocks may be performed either as a single shot or via an indwelling perineural catheter. Wound infusions, and the intraperitoneal and intra-articular administration of analgesics are well documented, and transdermal analgesics are used in various formulations.

Transversus abdominus plane blocks and rectus sheath blocks have emerged as effective treatment modalities for postoperative pain following abdominal and hernia surgery, providing excellent analgesia and decreasing opioid requirements. Patients are able to breathe and cough more comfortably, and early mobilisation and discharge are facilitated.

Single-dose, large-volume, intraoperative local anaesthetic infiltration is effective in reducing short-term pain and hospital stay in patients undergoing total knee replacement. Continuous infusion postoperatively and use in hip replacement is unconfirmed.

10.2.1 Peripheral nerve blocks and the infusion of local anaesthetics

The advantages and disadvantages of peripheral nerve block are outlined in Table 1.

Table 1: The advantages and disadvantages of peripheral nerve blocks

Advantages	Disadvantages
<ul style="list-style-type: none"> • Excellent analgesia • Avoids the complications of systemic analgesics • Promotes early mobilisation and physiotherapy 	<ul style="list-style-type: none"> • Small risk of bleeding with anticoagulation • Continual monitoring of analgesia, together with an adjustment of the dose or infusion rate, is mandatory • Potential local anaesthetic toxicity with prolonged infusion (a rare complication) • Catheter migration with resulting ineffective analgesia • Infection risk with indwelling catheter

Local anaesthetic doses and infusion rates for peripheral nerve blocks in adults are covered in Table 2.

Table 2: Local anaesthetic doses and infusion rates for peripheral nerve blocks in adults

Technique	Drugs	Adult dose	Considerations
Plexus block	Bupivacaine	LD: 0.25-0.50%, 20-40 ml CI: 0.12-0.25%, 5-10 ml/hour	Maximum 2 mg/kg or 6 mg/kg/ 24 hours Maximum 150 mg or 1 ml/kg bolus
	Levobupivacaine	As for bupivacaine	As for bupivacaine
	Ropivacaine	LD: 0.50-0.75%, 10-40 ml CI: 0.20%, 0.10 ml/kg/hour	Maximum 800 mg/24 hours or 28 mg/hour Maximum 1 ml/kg bolus
Minor nerve blocks or infiltration	Bupivacaine	0.25-0.50%, 5-10 ml/nerve	Maximum 2.5 mg/kg or 150 mg
	Levobupivacaine	0.25-0.50%, 1-60 ml	Maximum 2.5 mg/kg or 150 mg
	Ropivacaine	0.20%, 1-100 ml	Maximum dose of 200 mg

CI: continuous infusion, LD: loading dose

10.2.2 Intravenous regional analgesia

Intravenous regional analgesia is a second technique of administering peripherally acting analgesics. IV regional analgesia doses are outlined in Table 3.

Table 3: Intravenous regional analgesia doses

Drug	Dose	Comments
Lignocaine	Maximum dose of 200 mg or 2 mg/kg	Dilute to 40 ml total volume Adding dexamethasone prolongs analgesia

10.2.3 Intra-articular analgesia

Intra-articular administering of peripherally acting analgesics is widely employed in arthroscopic surgery. The doses for intra-articular analgesia are provided in Table 4.

Table 4: Doses for intra-articular analgesia

Drug	Dose	Comments
Bupivacaine, ropivacaine and levobupivacaine	10-20 ml, 0.5-1.0% solution	Limited postoperative analgesia only

10.2.4 Topical analgesia

Topical application of locally acting analgesics is potentially associated with a favourable drug side-effect profile. Evidence based topical use of a number of drugs is summarised in Table 5.

Table 5: Clinical use of topically applied analgesic agents

Drug	Application	Comments
EMLA	Venous ulcer debridement	
Amethocaine	IV cannulation in children	Superior to EMLA
Local anaesthetic on swab	Direct application to tonsil bed with tonsillectomy	Similar analgesia to local anaesthetic infiltration
Ketamine	Mouthwash	Reduced pain from oral mucositis
NSAID eyedrops	Traumatic corneal abrasions	

EMLA: eutectic mixture of local anaesthetics (lignocaine and prilocaine), IV: intravenous, NSAID: nonsteroidal anti-inflammatory drug

A summary of the evidence based clinical use of regional and local analgesic techniques:

Topical techniques

1. Topical EMLA cream (lignocaine and prilocaine) reduces the pain associated with venous ulcer debridement.

Intra-articular techniques

1. When compared with placebo, intra-articular morphine alone following knee arthroscopy does not improve analgesia.
2. Postoperative pain is reduced to a limited degree by intra-articular local anaesthetics.
3. Intra-articular NSAIDs, such as ketorolac, result in improved pain relief after surgery. However, long-term follow-up has not been undertaken during which the effect on bone healing has been examined

4. Following knee joint arthroscopy, intra-articular steroids, in combination with either a local anaesthetic or opioid, reduce pain, analgesic consumption and the duration of immobilisation.
5. Intra-articular bupivacaine infusions have been associated with chondrolysis, and caution should be exercised regarding their use.

Local infiltration and continuous wound infusions

1. Continuous local anaesthetic wound infusions lead to a reduction in pain at rest and during movement.
2. Decreased opioid consumption, postoperative nausea and vomiting, and length of hospital stay are reported, while there is no difference in the incidence of wound infections.
3. The infiltration of the wound with local anaesthetic agents provides good and long-lasting analgesia after ambulatory surgery.
4. Following laparoscopic cholecystectomy, intraperitoneal local anaesthetics reduce early postoperative pain scores.
5. The efficacy of large-volume dilute local anaesthetic periarticular infiltration after total knee replacement and total hip replacement has been shown. Reduced opioid consumption, earlier mobilisation and a lower incidence of vomiting have been confirmed.
6. TAP block reduces the need for postoperative opioid use, increases the time to the first request for further analgesia, provides more effective pain relief than an opioid alone, and reduces opioid-associated side-effects.
7. Peritonsillar infiltration or the topical application of a local anaesthetic produces a modest reduction in acute post-tonsillectomy pain, with topical application and infiltration being equally effective.

Peripheral nerve blocks

1. Continuous peripheral nerve blockade, regardless of catheter location, provides better postoperative analgesia than systemic opioids, and leads to a reduction in opioid use and side-effects, i.e. nausea, vomiting, pruritus and sedation.
2. Continuous peripheral nerve blocks have been shown to be safe if used at home if adequate resources and patient education are provided.
3. Single-shot infraclavicular blocks provide effective analgesia and less nausea following hand and wrist surgery and earlier ambulation and hospital discharge compared with general anaesthesia.
4. When compared with nerve localisation using a peripheral nerve stimulator, ultrasound-guided blocks are faster to perform, have a more rapid onset and longer duration of action, and are more often successful.
5. Continuous thoracic paravertebral catheters results in comparable analgesia to thoracic epidurals with less urinary retention, hypotension, nausea and vomiting, and a lower incidence of postoperative pulmonary complications.
6. Following open shoulder surgery, single-shot or continuous interscalene analgesia provides better analgesia and improved patient satisfaction, with reduced opioid-related side-effects compared with opioid-based, intravenous patient-controlled analgesia.
7. A femoral nerve block provides better analgesia than parenteral opioid-based techniques after total knee arthroplasty.
8. Adductor canal femoral nerve block, with quadriceps muscle function sparing, may facilitate earlier mobilisation.
9. Continuous femoral nerve blockade is equianalgesic to epidural analgesia, but with fewer side-effects following total knee arthroplasty.
10. Continuous posterior lumbar plexus analgesia and continuous femoral analgesia are equally effective following total knee arthroplasty.

EMLA: eutectic mixture of local anaesthetics, NSAIDs: nonsteroidal anti-inflammatory drugs, TAP: transversus abdominus plane

10.3 Safety considerations for regional and local analgesic techniques

10.3.1 Anticoagulation

Caution is advised in patients with impaired coagulation when performing blocks where direct pressure in the event of a traumatised blood vessel is not possible, e.g. during a lumbar plexus block, psoas compartment block and infraclavicular brachial plexus block, as a plexopathy may follow haematoma-induced pressure. Guidelines for the removal of peripheral catheters from non-compressible sites are similar to those for the removal of epidural catheters.

10.3.2 Nerve injury

Most nerve injuries following nerve blocks present as a transient neuropathy with paraesthesia, and rarely as a permanent neurological injury, i.e. persisting for more than 6–12 months. The incidence of transient neuropathy (radiculopathy) varies for different block sites, i.e. 2 (84%) for an interscalene brachial plexus block, 1 (48%) for an axillary brachial plexus block and 0 (34%) for a femoral nerve block. The incidence of a late neurological deficit is approximately 0.04%.

Permanent neurological injury was reported following the injection of a local anaesthetic directly into the cervical spinal cord when an interscalene block was performed under general anaesthesia.

While ultrasound guidance has been shown to reduce the incidence of intravascular injection, the effect on neurological injury has not been elucidated.

10.3.3 Toxicity

Accidental intravascular injection or the rapid absorption of a local anaesthetic can lead to toxicity. The incidence of cardiac arrest was 1.4 per 10 000 in a prospective study involving more than 21 000 cases, while that for seizures was 7.5 per 10 000. A higher rate of seizures (0.2%) was reported following surveys in which brachial plexus blocks were specifically investigated.

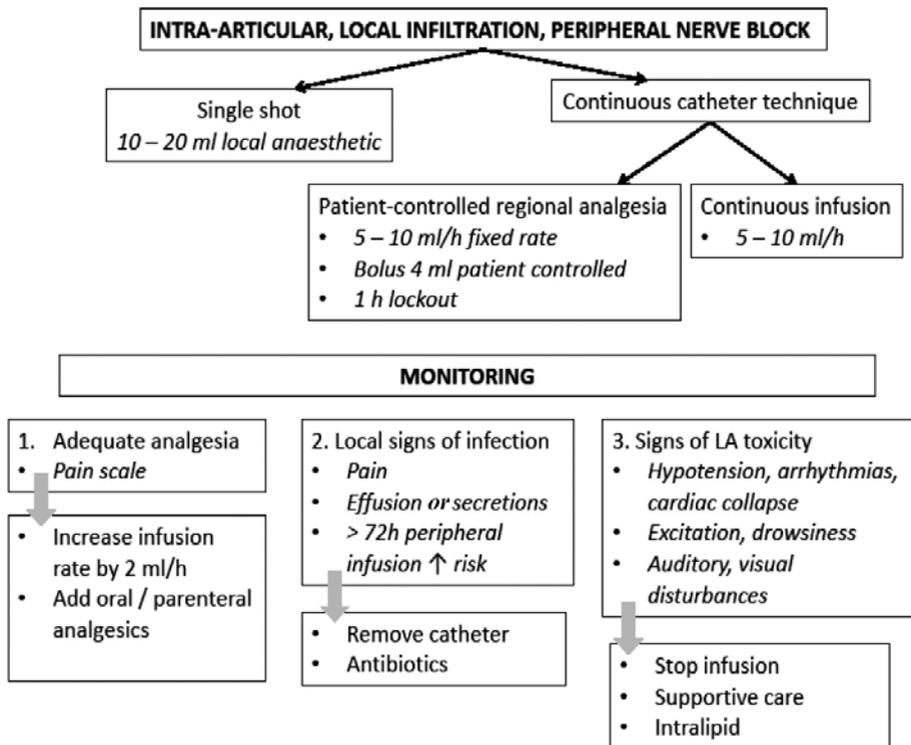
10.3.4 Infection

Although the bacterial colonisation of indwelling continuous peripheral nerve catheters is high (16–57%), serious infections and abscess formation are rare. Groin and axilla catheters, catheter placement \geq 48 hours, and repeated dressing changes are risk factors for colonisation. Catheter tunnelling significantly reduces bacterial colonisation to 6%.

The strongest recommendations for preventing infection are hand hygiene and effective skin preparation, preferably with an alcohol-based chlorhexidine solution. If continuous catheters are used, the full surgical aseptic technique (cap, mask, sterile gown and gloves and large drapes) is recommended.

The clinical approach to peripheral regional analgesia is depicted in Figure 1.

10.4 Clinical approach to peripheral regional analgesia



LA: local anaesthetic

Figure 1: The clinical approach to peripheral regional analgesia

11. Techniques of drug administration

Patient controlled analgesic techniques and neuraxial analgesic techniques offer alternative non-conventional methods for the doctor to provide analgesia for patients after surgery.

11.1 Clinical guidelines on the use of patient-controlled analgesia

11.1.1 Rationale for use

Patient-controlled analgesia (PCA) is a conceptual framework that refers to a method of pain control whereby a patient self-administers small doses of an analgesic agent, and usually implies the use of opioid medications delivered by a programmable infusion pump.

The following guidelines are adapted from: Acute pain management: scientific evidence (Third Edition), published by the Australian and New Zealand College of Anaesthetists and the Faculty of Pain Medicine. With permission. Please consult this document for complete reference to the scientific evidence at www.anzca.edu.au.

Efficacy

The proposed benefits of PCA or self-administered analgesia, compared to conventional parenteral opioid regimens, include the following:

- Improved pain control.
- Patient preference for intravenous (IV) PCA.
- Decreased risk of overdose, but the risk remains.
- Less labour intensive from a nursing perspective.

On the other hand, IV PCA with opioids may lead to higher opioid consumption and pruritis, when compared to intermittent parenteral opioid administration. There may be no difference in efficacy in settings with a high nurse to patient ratio.

The decision to provide PCA is taken after discussion with the patient, where possible. Ongoing communication regarding, for example, the adjustment of demand dosing, may influence the success of PCA management.

Pain control with PCA is only effective after initial rapid pain control under supervision of the prescribing physician, for example, in the theatre recovery room postoperatively. Initial doses should be individually adjusted, and take into account patient factors such as prior opioid use and age.

These guidelines do not apply to patients who are opioid tolerant or with chronic pain.

The concept of PCA continues to be developed in children. Patient-controlled epidural analgesia, subcutaneous (SC) PCA and intranasal PCA are recent extensions of the method. There may also be a role for patient-controlled sedation. PCA, when used with adequate monitoring, is a well-tolerated technique with high patient and staff acceptance. It can now be regarded as a standard for the delivery of postoperative analgesia in children aged ≥ 5 years.

Cost

Comment cannot be made on the economic implications of PCA in South Africa because of the lack of data. Although equipment costs are higher, the possible benefits of reduced adverse effects and nursing time must be considered.

11.1.2 Standards of care

The safety of PCA can be improved by adopting standardised forms and processes. Operator errors may be reduced with the use of “smart pump” technology. Although technical device errors may be more common than operator errors, very few technical errors seem to be associated with patient harm.

Chart 1: Proposed prescription chart

Prescription chart

Instructions

- Nursing staff are not allowed to change settings on the pump
- PCA boluses must only be administered by the patient, not the nursing staff

Prescription

Prescription date & time: _____

Opioid name: _____ Opioid concentration (mg/ml): _____

Additive 1 name: _____ Additive 1 dose or amount: _____

Additive 2 name: _____ Additive 2 dose or amount: _____

	Treatment changes		
	Start	Change 1	Change 2
Continuous infusion (ml/hr)			
Loading dose opioid (mg)			
PCA bolus opioid (mg)			
Lockout time (minutes)			
4-hour maximum opioid (mg)			
Total amount opioid (mg)			

PCA: patient-controlled analgesia

Bag change?	Yes		No	
Prescription for repetition of bag:				
Opioid	Additive 1		Additive 2	
Amount (mg)	Amount (mg)		Amount (mg)	
Type of solution				
Bag size (ml)				

Doctor: _____ Signature: _____ Contact no: _____

Monitoring (hourly)	Findings	Action
Pain (use VAS)	Moderate to severe	Contact doctor
Sedation	Difficult to wake	Administer Narcan® 0.2 mg stat IV
		Contact doctor
Respiratory rate	≤ 10/minute	Administer Narcan® 0.2 mg stat IV
		Contact doctor
Pupil size	≤ 2 mm	Contact doctor
Blood pressure	SBP < 90 mmHg	Contact doctor
Heart rate	≤ 50/minute or ≥ 100/minute	Contact doctor

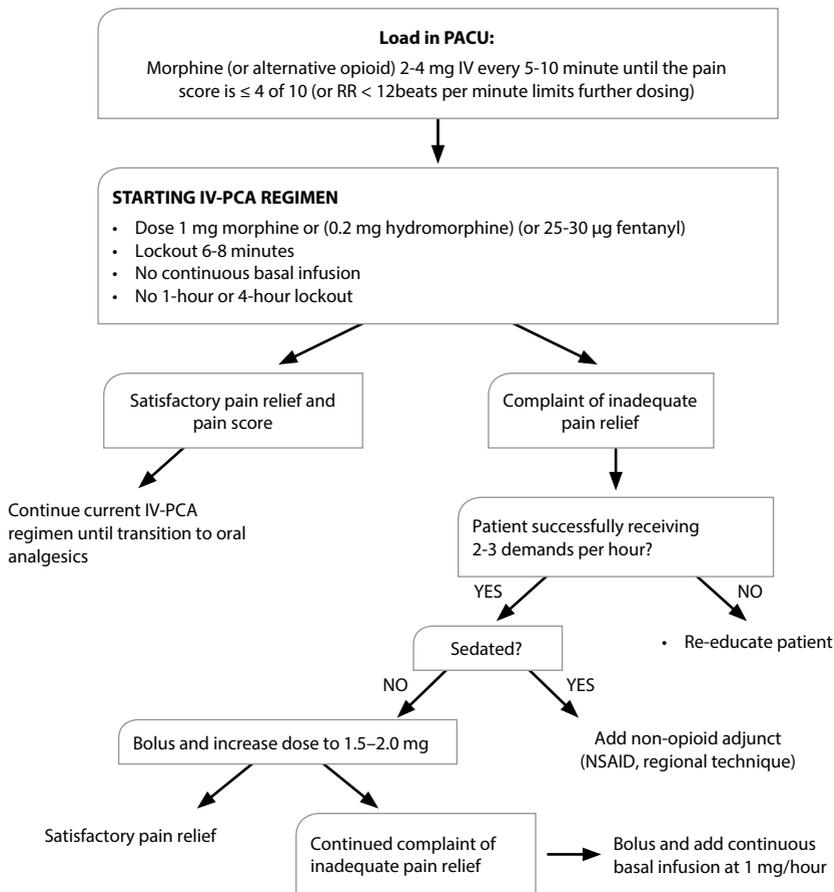
IV: intravenously, stat: immediately, SBP: systolic blood pressure, VAS: visual analogue scale

Attending nurse signature	
Day 1, Shift 1	Day 1, Shift 2
Day 2, Shift 1	Day 2, Shift 2
Day 3, Shift 1	Day 3, Shift 2

Additional instructions:

Clinical practice points

1. The changing pain score and the presence of side-effects should be detected through appropriate routine monitoring of patients, in order to prevent complications such as an inadvertent overdose or inappropriate use, e.g. nurse or doctor administration of the intended PCA bolus. The masking of pain from new problems, such as compartment syndrome of the limbs, urinary retention, pulmonary embolism or myocardial infarction, should also be uncovered.
2. Monitoring addresses the prevention of complications, and also assures that repeated assessment is conducted with regard to the adequacy of pain management.
3. Intensive and frequent monitoring is essential in patients at risk of developing respiratory depression and other side-effects. If peripheral oxygen saturation cannot be continuously monitored, administering oxygen by nasal cannula or face mask for the duration of intravenous opioid administration may be indicated.
4. Standardised prescriptions within institutions also prevent complications arising from the use of supplemental medication, such as opioids by other routes, or sedatives. Table 1.
5. A standardised treatment algorithm may improve pain management by integrating pain assessment and side-effects for the established of a clear reaction pathway. A treatment algorithm for PCA management is detailed in Figure 1.



IV: intravenous, PCA: patient-controlled analgesia, RR: resting rate, PACU: postanesthesia care unit

Source: Grass JA. Patient-controlled analgesia. *Anaesth Analg.* 2005;101(5 Suppl):S44-S61. With permission

Figure 1: Proposed treatment algorithm for patient-controlled analgesic management (adapted, not revised)

11.1.3 Medication

Opioid analgesics

Generally, there are no major differences in the efficacy of various opioid drugs for PCA. On an individual basis, one opioid may be better tolerated than another, and it may be beneficial to change to an alternative agent if a patient is experiencing intolerable side-effects.

The following opioid analgesics are available for PCA use in South Africa:

- *IV morphine:* IV morphine sulphate is included in the adult hospital level Essential Medicines List. A background induction increases the risk of respiratory depression with no additional benefit.

- *IV tramadol*: IV tramadol has been recommended for inclusion in the adult hospital level Essential Medicines List, for regional hospitals only. It provides effective analgesia comparable to morphine
- *IV pethidine*: IV pethidine may cause neurotoxicity owing to the accumulation of norpethidine.
- *IV remifentanyl*: IV remifentanyl offers equivalent analgesia to morphine, and may be associated with less nausea and vomiting.
- *IV fentanyl*: There is limited evidence to indicate that there is a difference between IV fentanyl and morphine.
- *IV oxycodone*: IV oxycodone has similar effects to morphine.

Adjuvant medicines

The opioid dose-sparing effects of concurrent nonsteroidal anti-inflammatory drugs, ketamine, pregabalin, IV lignocaine, clonidine and dexmedetomidine may contribute to a reduction of opioid adverse effects. The following adjuvant medicines may be added to the opioid solution.

Antiemetics

The routine addition of antiemetics to a PCA infusion is not advocated as it provides no benefit over selective administration on indication.

Droperidol is an effective antiemetic, but may cause unacceptable sedation at the dose necessary to prevent nausea and vomiting.

Evidence on the benefit of adding 5-hydroxytryptamine-3 antagonists, e.g. ondansetron, to PCA, is unclear.

Ketamine

The addition of ketamine may benefit patients after thoracic surgery with regard to analgesia and adverse effects.

Naloxone

The incidence of nausea and pruritis may be decreased with the addition of naloxone to IV morphine PCA, but there is no analgesic benefit.

Other

- *Magnesium*: Magnesium is opioid sparing, with better pain relief, when added to morphine. The improved analgesia is short lived, i.e. two hours, when added to tramadol.
- *Dexmedetomidine*: There is some evidence that the use of dexmedetomidine, when added to IV morphine PCA, may improve analgesia, and reduce morphine-related side-effects without increasing sedation or the haemodynamic side-effects.
- *Hydroxyzine*: There is no evidence to support the addition of hydroxyzine to PCA.

11.1.4 Equipment and programme parameters

Several PCA equipment variations are available in South Africa. Systems can be broadly categorised into two groups:

- Those which use durable (often bulky) pumps with disposable cartridges, which usually have multiple programmable options.
- Those which utilise completely disposable components with built-in mechanisms for bolus administration, but do not allow background infusion administration or provide programmable options.

The effectiveness of the latter systems may be compromised by the fact that dose adjustments cannot be made, but they may provide a cost benefit. All PCA infusion systems must incorporate anti-syphon valves, and anti-reflux valves in non-dedicated lines.

Other (than IV) systemic routes of administration

Subcutaneous (SC)

SC administration can be as effective as IV PCA, but the data are inconsistent in this regard.

Oral

Oral administration, using modified IV PCA systems, is as effective as IV PCA.

Intranasal

Intranasal administration can be as effective as IV PCA, but higher doses are needed.

Transdermal

Non-invasive systems for the transdermal delivery of ionisable drugs, such as fentanyl hydrochloride, by the application of an external electrical field, may not be as effective as IV PCA.

Pump settings

Bolus dose

The optimal bolus dose should provide adequate pain relief with minimal side-effects. Age and a history of prior opioid use can influence the efficacy of the bolus dose. The initial dose should be adjusted according to response. The optimal initial dose of IV morphine is 1 mg.

Lockout time

The lockout interval should be long enough for the analgesic to reach its full effect. The optimal lockout for morphine is 7–11 minutes.

Dose limits

An overdose with PCA is usually due to the effect of large doses accumulating after hours or days. Limiting the maximum dose over several hours may be the most effective way of preventing an overdose. However, sound evidence of a benefit which can be attributed to these limits does not exist.

Background infusions

The risk of respiratory depression is higher when a background infusion is used, and it does not improve pain control. It may be useful in opioid-tolerant patients.

Total amount and concentration

Drug concentrations should be standardised within institutions to reduce the occurrence of programming errors.

Examples of PCA management regimens are provided in Table 1.

Table 1: Examples of patient-controlled analgesia management regimens

Opioid	Opioid dilution	Additive	Additive dilution	Pump settings
IV morphine	1 mg/ml	Dexmedetomidine or ketamine	2–5 µg/ml 2 mg/ml	<ul style="list-style-type: none"> • Bolus of 1 mg (1 ml) • Lockout of 7 minutes
		Droperidol or ondansetron	15–100 µg/1 mg morphine, or 5 mg/100 ml 16 mg/100 ml	
IV tramadol	5 mg/ml	Dexmedetomidine	1–2 µg/ml	<ul style="list-style-type: none"> • Bolus of 10–20 mg • Lockout of 5–10 minutes
IV remifentanyl	50 µg/ml			<ul style="list-style-type: none"> • Bolus of 50 µg over 5 minutes (background 0.075–0.15 µg/kg/minute) • Lockout of 5 minutes
IV sufentanil	1 µg/ml			<ul style="list-style-type: none"> • Bolus of 4–6 µg (background of 1.15 µg/hour) • Lockout of 1 minute
IV fentanyl	1 µg/ml			<ul style="list-style-type: none"> • Bolus of 30–40 µg • Lockout of 6–8 minutes

IV: intravenous

11.2 Neuraxial Techniques

11.2.1 Epidural analgesia

Epidural analgesia, i.e. the provision of pain relief by the continuous administration of pharmacological agents into the epidural space via an indwelling catheter, has become a widely used technique for the management of acute pain in adults and children, particularly after surgery, trauma and in the parturient.

Clinical practice points

1. The decision to perform an epidural, and the technique selected, should be appropriate to the intensity of pain anticipated and congruent to the level of tissue damage.
2. All techniques of epidural analgesia, except for epidural using a lipophilic opioid only, for all types of surgery provide better postoperative pain relief than parenteral opioids (including PCA) administration.
3. The complete absence of pain is seldom achievable, and not realistic, even with neuraxial techniques. The objective should be a balance between analgesia, patient satisfaction, safety and available resources.
4. Combinations of low concentrations of local anaesthetics and opioids provide better analgesia than either component alone, and reduce the dose requirements of both drugs.
5. Epidural analgesia at the correct level for an appropriate duration may decrease pulmonary complications, ventilatory requirements or myocardial infarction, and may improve bowel recovery. However, data on improved outcomes are controversial, and the focus should be on pain relief and patient satisfaction.
6. Permanent neurological damage with epidural techniques is rare, but devastating, and efforts should be made to prevent, diagnose and treat these in time. Immediate decompression of a haematoma or abscess increases the likelihood of neurological recovery. Because of these complications, the advantages and risks should be discussed with the patient and informed consent obtained.
7. The insertion of the epidural catheter at spinal level matching the dermatome of the surgery, i.e. catheter incision-congruent analgesia, results in optimal postoperative epidural analgesia by infusing analgesic agents to the appropriate incisional level, providing superior analgesia and minimising side-effects.
8. Infusions of epidural local anaesthetic plus opioid combinations in a general ward have been advocated to be safe, but the precondition is supervision by an anaesthesia-based pain or similar service, with 24-hour medical staff cover, and monitoring by well trained nursing staff. This may not be available in many hospital wards.

PCA: patient-controlled analgesia

Local anaesthetics

Local anaesthetics available for epidural use in South Africa are outlined in Table 2.

Table 2: Local anaesthetics available in South Africa for epidural use

Duration of action	Formulations	Dosage
Short acting	Lignocaine in various formulations	
	Bupivacaine	Macaine [®] 5 mg/ml, with or without adrenaline
Long acting		Macaine [®] 0.1% polybag
	Levobupivacaine	Chirocaine [®] 5.0–7.5 mg/ml
	Ropivacaine	Naropin [®] 5.0, 7.5 and 10 mg/ml, and 2 mg/ml as the 100/200 ml polybag

There are no consistent differences between ropivacaine, levobupivacaine and bupivacaine when given in low doses for regional analgesia in terms of quality of analgesia or motor blockade.

Epidural opioids

The behaviour of epidural opioids is governed largely by their lipid solubility. Morphine is the least lipid soluble of opioids administered epidurally. As it has a prolonged analgesic effect, it can be given by intermittent bolus dose or infusion. The risk of respiratory depression may be higher and analgesia less effective with bolus dose regimens. Lipophilic opioids, e.g. fentanyl, sufentanyl and alfentanyl, have a faster onset, but shorter duration, of action, compared with hydrophilic drugs.

The insertion of an epidural catheter

Epidural catheters are inserted under sterile conditions for obvious reasons. Theatre gowns, masks and caps must be worn for this procedure. It is prudent to use a chlorhexidine solution to prepare the skin, maximise sterility at insertion, maintain sterility at the puncture and infusion ports, and to remove the catheter before or on day five. Chlorhexidine-impregnated dressings of epidural catheters reduce the incidence of catheter bacterial colonisation.

The level of the epidural

The benefits of postoperative epidural analgesia are optimised when the epidural catheter is inserted in a location which corresponds to the dermatomes covered by the surgical incision, i.e. catheter incision-congruent analgesia, resulting in a lower dose of the drug being administered and a decreased incidence of drug-induced side-effects, such as pruritus, nausea, vomiting, urinary retention, motor block and hypotension.

The level of the epidural is outlined in Table 3.

Table 3: Level of the epidural

Surgery	Level of the epidural
Thoracotomy	T 4–T8
Upper abdominal	T 6–T8
Middle abdomen	T 8–T10
Lower abdominal	T 8–T12
Lower extremity	L1–L4

Test doses

This procedure is standard when the epidural is commenced, but should be repeated before top-up doses for analgesic purposes. Although migration of the catheter to the intravascular or intrathecal space from the epidural space is uncommon, aspiration and the administration of a test dose of adrenalin and local anaesthetic before bolus dosing for pain may prevent complications, e.g. high or total spinal anaesthesia, seizures and neurotoxicity, associated with the accidental administration of local anaesthetics into these

spaces. After negative aspiration, 3 ml of a short-acting local anaesthetic or the highest concentration of the local anaesthetic to be used, e.g. 0.5% levobupivacaine, plus 15 µg of adrenalin, can be administered as a test dose. If, after two minutes, there is no evidence of intravascular or subarachnoid injection [tachycardia \geq 100 beats per minute, or hypotension (systolic blood pressure \leq 90 mmHg)], it can be considered safe to proceed.

Patient-controlled epidural analgesia

The use of patient-controlled epidural analgesia is based on the individualisation of therapy, similar to other patient-controlled techniques, but data on reduced epidural analgesic requirements, superior analgesia and greater patient satisfaction are not consistent.

Systemic analgesia in combination with epidural analgesia

The use of epidural analgesia does not preclude the use of systemic analgesia. Patients with epidural analgesia should have concomitant paracetamol prescribed to treat other aches and pains and facilitate the withdrawal of epidural analgesia.

Complications, side-effects and treatment

The concentrations at the lower end of the effective dose ranges are used for continuous infusion epidural techniques in order to:

- Limit side-effects and motor block.
- Facilitate a clinical evaluation for neurological complications.

In the event of complications or side-effects (Table 4), the first reaction should not be to stop the epidural and switch to intramuscular injections. This may leave the patient with rebound pain, and actually be detrimental in the risk to benefit analysis.

Respiratory depression

A strategy to detect and treat this complication should be in place. The incidence is between 1% (decreased respiratory rate) and 15% (desaturation) depending on the criteria used, but clinically significant in less than 1% of patients. High-risk patients for this should be identified preoperatively, e.g. sleep apnoea and obesity. Patients receiving neuraxial opioids should be monitored clinically for adequacy of ventilation, oxygenation and level of consciousness 1–2 hourly for the first 24 hours after the injection with morphine, or during the entire time that an infusion is in use. The absence of a decreased respiratory rate is not a reliable warning sign of respiratory depression, but it is almost always preceded by sedation.

Treatment of this complication is a graded response appropriate to the level of hypoventilation. Supplemental oxygen should be available to patients receiving neuraxial opioids, and administered to those with an altered level of consciousness, respiratory depression or hypoxaemia.

The reason for the respiratory depression should be assessed and the dose of the neuraxial infusion decreased if this is the cause. If an infusion of epidural drugs is stopped, alternative pain treatment should

Table 4: Complications of the epidural technique

Complications	Incidence	Treatment	Remarks
Nausea and vomiting	Common	Odansetron or class equivalent, droperidol or prochlorperazine	Dose dependent
Pruritis	Common	Antihistamine, naloxone or droperidol	Dose dependent
Urinary retention	Common	Catheterise	
Postdural puncture headache	Uncommon, unless dura is perforated	Bed rest, intravenous fluids, caffeine and analgesics. If no improvement of symptoms within 48 hours, consider an epidural blood patch	A blood patch is controversial
Hypotension	Uncommon	IV volume Decrease the dose and rate of the epidural	Prevent hypovolaemia
Motor block	Common with higher concentrations	Decrease the dose if significant	May be more frequent with bupivacaine
Treatment failure	Variable	Rectify the cause or treat the side-effects	Consider another technique
Respiratory depression	Uncommon	Supportive measures (see text below for specific interventions)	Sedation is an early warning sign
Toxicity	Uncommon	Prevent CPR	Bupivacaine > Levobupivacaine ≥ Ropivacaine
Epidural haematoma or abscess	Rare	Surgical decompression within 8 hours	Perform an early scan if epidural haematoma or abscess are suspected
Permanent neurological damage	Rare	Prevent	Warn patient of risk before performing the procedure

CPR: cardiopulmonary resuscitation, IV: intravenous

be prescribed. Indiscriminately stopping the epidural may lead to severe pain and concurrent medications, e.g. parenteral opioids may precipitate severe respiratory depression.

Intravenous access should be maintained if respiratory depression is suspected, or when it occurs. Ensure that naloxone is readily available.

Transferring the patient to a higher level of nursing care and monitoring should be considered if the existing one is not appropriate to the risk. When available, pulse oximetry and end-tidal CO₂ can be considered, but they have not been proven to be better than clinical monitoring.

Naloxone should be administered if preliminary measures fail to rectify the problem. It is administered intravenously in small increments sufficient to improve ventilation, but without reversing the analgesic effect.

Noninvasive positive-pressure ventilation may be considered to improve ventilatory status. The airway should be maintained, and the patient ventilated with a bag and mask pending naloxone administration, in the infrequent event of life-threatening apnoea.

Duration of epidural analgesia

The catheter is commonly left in place for 2–4 days, but it is impossible to scientifically determine what the maximum safe time would be to persist with a percutaneous catheter owing to the rarity of epidural infections.

In summary, the risk versus benefit for every patient should be determined. Note that:

- Epidural analgesia is probably the best type of analgesia that can be offered for acute severe pain.
- A combination of local anaesthetic and opioids can be used through an indwelling catheter.
- The administration should be targeted to the appropriate dermatome.
- The smallest dose and concentration required to produce the desired result should be administered.
- The rapid injection of a large volume of local anaesthetic solution should be avoided and incremental doses always used.
- Dilutions of local anaesthetic solutions should be made with preservative-free 0.9% saline, according to standard hospital procedures for sterility.

Drugs and doses used in epidural analgesia are outlined in Table 5.

Table 5: Drugs and doses used in epidural analgesia*

Drug	Dose	Onset	Duration	Remarks
Lipophilic opioids				
Fentanyl	Dilute the single dose in 10 ml normal saline: • Bolus dose = 50-100 µg • Infusion dose = 25-100 µg/hour	5-10 minutes	2-4 hours	• Limited spread in CSF • Early respiratory depression is most likely • Opioids alone via the epidural route seem to be of limited benefit
Sufentanil	• Bolus dose = 10-50 µg • Infusion dose = 10-20 µg/hour			
Hydrophilic opioids				
Morphine	• Bolus dose = 1-5 mg • Infusion dose = 0.1-1.0 mg/hour	30-60 minutes	6-24 hours	• Extensive spread in CSF • Early and delayed respiratory depression is possible
Local anaesthetics				
Bupivacaine**	5-8 ml/hour of 1.25-2.50 mg/ml solution or Incremental doses of 3-5 ml of 1.25-2.50 mg/ml solution	10-20 minutes 30 minutes for optimal effect	3-4 hours	• Establish the block with a 0.5% bolus of 15-30 ml • <i>Recommendation:</i> Limit to 2 mg/kg in 4 hours and 400 mg/24 hours
L-bupivacaine	10-15 ml/hour of 1.25 mg/ml, or 5.0-7.5 ml/hour of 2.5 mg/ml		150 (-240) minutes	• Minimal to moderate motor block • Dilution stable for up to 7 days at 20 °C • Maximum dose over 24 hours of 400 mg
Ropivacaine	2 mg/ml Bolus:10-20 ml 6-14 ml/hour	15-20 minutes	140 (-200) minutes	• Establish the block for surgery with 15-25 ml of 7.5 mg/ml for a lumbar epidural, or 5-15 ml for a thoracic epidural

Combinations

Ropivacaine 2 mg/ml
+ fentanyl 4 µg/ml 6-14 ml/hour

This combination is marketed as a polybag in some countries (NOT IN SOUTH AFRICA)

Bupivacaine 1 mg/ml
+ fentanyl 4 µg/ml Bolus 1-2 mg/kg bupivacaine,
then infuse 0.5-2 mg/kg/hour

Prepare by adding 20 ml of 0.5% bupivacaine to 40µg (4x100µg ampules) and 72 ml normal saline (Total vol = 100ml)

Patient-controlled epidural analgesia

Continuous infusion in ml/hour

Demand dose in ml

Lockout in minutes

Levobupivacaine
1.25 mg/ml + fentanyl
4 µg/ml

Initial rate of
4 ml/hour

2

10

Stability proven for up to 40 hours at 20 °C

1 mg/ml bupivacaine
+ 5 µg/ml fentanyl

6(3-4 ml/hour for thoracic)

2

10-15

1-2 mg/ml
ropivacaine
+ 2-5 µg/ml fentanyl

3-5

2

10-20

CSF: cerebrospinal fluid

*These are recommendations only. Scientific evidence is not available

**Not commonly used alone in an analgesic infusion

11.2.2 Spinal (intrathecal) analgesia

A single injection of intrathecal local anaesthetic plus an opioid is an acknowledged part of a postoperative analgesia strategy. It is as effective as, or even better than, other established techniques, although the duration of the relief is limited to the first 24 hours and side-effects are common.

Drugs used for intrathecal analgesia

Local anaesthetics are often combined with opioids to provide a smooth transition from the anaesthetic technique to the analgesic plan.

Drugs for intrathecal analgesia are detailed in Table 6.

Table 6: Drugs for intrathecal analgesia

Drug (preservative free)	Intrathecal single dose	Onset	Duration
Fentanyl	5–25 µg	5–10 minutes	1–4 hours
Sufentanil	2–10 µg	5–10 minutes	2–6 hours
Morphine	0.05 to 0.3mg	45–75 minutes	18–24 hours

The longer duration of morphine has established it as the drug of choice, but this advantage is gained at the increased risk of respiratory depression. At doses of 100–800 µg, intrathecal morphine for pain relief, following a range of surgical procedures, produces a high degree of patient satisfaction and effective analgesia in the first 24 hours after the procedure. In particular, the lower dose of 100–200 µg offers effective

analgesia, with a low risk of adverse effects, e.g. for hip replacement in the elderly. However, higher doses are required for thoracotomy and abdominal surgery. In general, there is a ceiling analgesic effect above doses of 200 µg. Significant side effects are:

- Respiratory depression of 3% (partial pressure of carbon dioxide \geq 50 mmHg, and/or a respiratory rate \leq 8/minutes).
- Pruritus (itching), up to 30%.
- Nausea and vomiting of 25%.
- Urinary retention of 35% (with morphine).

When intrathecal morphine has been administered, the patient should be nursed in an area where there is a high level of awareness of the risk of respiratory depression. The monitoring and treatment of these complications is similar to that employed with epidural opioids. The analgesic effect rivals that of PCA, but does not last for longer than a day. A multimodal plan of alternatives should be in place to prevent (preferably) or treat rebound pain. Lipophilic opioids may be suitable for outpatient surgery, but morphine is not.

Indwelling spinal catheters are not established as a routine technique for the treatment of short-term pain.

Clinical practice points

1. Intrathecal morphine offers improved analgesia and opioid sparing for up to 24 hours.
2. Intrathecal morphine doses of \geq 300 µg increase the risk of respiratory depression.
3. The incidence of respiratory depression and pruritus after major surgery is higher with intrathecal morphine than with IV PCA opioids, but there is no difference in the incidence of nausea and vomiting.
4. The lowest effective dose should be used in all circumstances.

IV: intravenous, PCA: patient-controlled analgesia

11.2.3 Neuraxial techniques and concurrent anticoagulant medication

Neurological compromise due to haemorrhagic complications is rare, but devastating, and it can be difficult to decide whether it is worth the risk to carry out spinal or epidural anaesthesia. The risk of haematoma is almost impossible to determine, but has been calculated at 1:150 000 for epidural anaesthesia and 1:220 000 for spinal anaesthesia. Due to the paucity of scientific evidence, the clinician has to rely on clinical judgement, consensus expert opinion, and knowledge of pharmacology, to decide if it is worth the risk to perform the spinal or epidural for anaesthesia *per se*, or as an analgesia technique. This risk is increased by:

- Anticoagulation; the most important risk factor.
- Any other coagulopathy.
- Advanced age.
- Indwelling catheter techniques.
- Difficulty in needle placement.
- Abnormalities of the vertebral canal or spinal cord.

Absolute recommendations cannot be made in many clinical situations. The opinions of experts in the field should be considered. For example, the Consensus Conference of the American Society of Regional Anesthesia and Pain Medicine can be found at <http://www.asra.com>.

Medications, indications and information continue to evolve. Knowledge should be current.

Individualise every case according to risk versus benefit in that situation. What may be feasible to the expert in a specialised environment may not be a worthwhile risk to the regular anaesthetist in routine practice. Err on the side of safety.

It is prudent to raise the level of vigilance as the haemostatic compromise increases, and to evaluate the patient every two hours if the risk is deemed to be high. The implication of this is that the anaesthetist cannot perform the neuraxial technique and consider that to be the end of the commitment to that patient's care.

Take care to prevent a combination of anticoagulation effects.

Low-molecular-weight heparin has a longer duration of action compared to unfractionated heparin, cannot be monitored, and is not completely reversed by protamine.

The novel oral anticoagulants have a long duration of action, and care must be taken when considering neuraxial anaesthetic techniques for patients on these agents. It is important to ensure that the patient has not taken the drug for a long enough period prior to inserting an epidural or spinal needle.

It can be foreseen that inadvertent or unavoidable anticoagulation would be instituted in a patient with a neuraxial catheter in situ. In this case, the treating physicians should consider the safest compromise and optimal timing to remove the catheter.

A reasonable approach to the practical management of neuraxial anaesthesia and analgesia in the patient on anticoagulation medication is summarised in Table 7. The recommendations are not absolute and the risk versus benefit must be considered in every clinical scenario.

Table 7: Clinical approach to neuraxial analgesia in the patient on medication with anticoagulation effects

Medication	Indication	Is performing epidural or spinal anaesthesia reasonable?	Monitor	Timing to insert	Timing to remove	Remarks
Herbal (ginkgo, garlic and ginseng)	Random, non-medical	Yes	None	Any time	Any time	Combinations with others may be unsafe
NSAIDs (COX-2 inhibitors preferred)	Anti-inflammatory and pain	Yes	No wholly accepted test	Any time	Any time	Combinations with others may be unsafe
Aspirin	Cardiovascular indications (60-325 mg/day)	Yes	Bleeding time not proven	Any time	Any time	Combinations with others may be unsafe
SC unfractionated heparin	DVT prophylaxis (12-hourly)	Yes	APTT	≥ 6 hours after dose, ≥ 2 hours before the next	≥ 6 hours after dose, ≥ 2 hours before the next	Consider HITT if ≥ 4 days on heparin, and perform a platelet count
Full IV heparin during surgery	5 000–10 000 U for vascular surgery	Yes	APTT, ACT	Conduct ≥ 1 hour before heparin	2-4 hours after dosing or reversal	"Bloody tap" is not an absolute indication to cancel surgery
LMWH	DVT prophylaxis	Yes	None	≥ 12 hours after the last dose ≥ 2 hours before the next dose	≥ 12 hours after the last dose, ≥ 2 hours before the next dose	Enoxaparin 40 mg/day subcutaneously, for example, or 30 mg q 12-hourly, or dalteparin 5 000 U q 12-hourly subcutaneously
Warfarin (prophylaxis)	DVT prophylaxis	Yes, if ≤ 24 hours after first dose	INR ≤ 1.5 useful if ≥ 24 hours	Do within 24 hours of the first dose	INR ≤ 1.5 If ≥ 3, cut warfarin	Warfarin is usually started the evening before surgery
IV heparin (cardiac surgery)	Intravenously for cardiopulmonary bypass	Not known	APTT, ACT	Conduct ≥ 1 hour before heparin	4 hours after dosing or reversal	Certainly not routine practice. Some place the epidural 12 hours preoperatively
Thrombin inhibitors (hirudin group)	HITT	Not known	APTT	Not known	Not known	Given intravenously, with an effect for up to 3 hours No antagonist
Fondaparinux	DVT prophylaxis	Not known	Not known	Not known	Not known	Avoid catheter effect for days

IV heparin maintenance	Full therapeutic	No	APTT	N/A	N/A	Often replaced with LMWH
Warfarin	Established, therapeutic	No	INR	N/A	N/A	Can conduct if feasible to stop for 5 days
LMWH for DVT, PE or acute MI	Therapeutic, e.g. enoxaparin 1 mg/kg bd	No	None	If feasible, stop and wait ≥ 24 hours	Unknown	Usually also on others, i.e. aspirin and clopidogrel
Antiplatelets (clopidogrel [†] and ticlopidine ^{††})	Acute MI Vascular disease	Most likely No	Platelet ADP	If feasible, wait ≥ 7–14 ^{***} days	Remove before starting Rx	Given <i>p.o.</i> Inhibits ADP platelet aggregation
Antiplatelets (GPIIb/IIIa antagonists)	Acute MI	No		Feasible? Waiting time of 4–48 hours	N/A	Usually also on others, i.e. aspirin and LMWH
Fibrinolysis and thrombolysis	Acute MI + thromboembolism	No	Fibrinogen	N/A within 10 days	Not known	Effect may last 27 hours Also has an effect on platelets

ACT: activated clotting time, ADP: adenosine diphosphate, APTT: activated partial thromboplastin time, bd: twice daily, COX: cyclo-oxygenase, DVT: deep vein thrombosis, HIT: heparin-induced thrombocytopenia and thrombosis, INR: international normalised ratio, IV: intravenous, LMWH: low-molecular-weight heparin, MI: myocardial infarction, N/A: not applicable, NSAIDs: nonsteroidal anti-inflammatory drugs, PE: pulmonary embolism, *p.o.*: per os, Rx: treatment, SC: subcutaneous

12. Non-pharmacological techniques

Examples of non-pharmacological interventions are detailed in Table 1.

Table 1: Examples of nonpharmacological interventions

Cognitive-behavioral
<ul style="list-style-type: none">• Reassurance• Education and information• Relaxation• Imagery• Distraction• Biofeedback• Hypnosis• Traditional healing
Physical
<ul style="list-style-type: none">• Heat and cold application• Massage and manual therapy• Transcutaneous nerve stimulation• Acupuncture and acupressure

12.1 Psychological interventions

Most psychological interventions used in acute pain management are seen as adjuncts to the pharmacological and physical therapeutic modalities. Evidence to support this form of intervention has grown over the last decade.

Psychological interventions can be classified as separate entities, but these groups share some common features. The treatment provider is encouraged to establish rapport with the patient. Information on the purpose and nature of the intervention should be imparted, as well as the expected outcome clearly defined. These aspects are necessary to gain the active cooperation of the patient. A skilled combination of psychological and medical and surgical modalities may lead to better outcomes than the application of either modality in isolation.

Psychological interventions may be divided into four broad categories. These are rarely standalone interventions, and the practitioner combines the elements of all four categories to try to achieve a positive outcome.

The categories are:

- Information provision (procedural or sensory).
- Stress and tension reduction (relaxation and hypnotic strategies).
- Attentional strategies.
- Cognitive behavioural intervention.

12.1.1 Provision of information

Procedural information has been found to be effective in improving postoperative recovery and reducing pain, pain medication use and length of hospital stay. Sensory information is information that describes the sensory experience which the patient may expect during treatment. Positive effects result from sensory information alone being given to the patient. The provision of sensory information has been shown to reduce self-rated pain more than the provision of procedural information. Combined sensory and procedural information yield the strongest and most consistent benefits in reducing negative effects, pain and other related distress.

Giving too much information, or asking certain patients to make too many decisions, may exacerbate anxiety and pain, especially in those with an avoidant coping style. Clinicians should assess a patient's normal approach to managing stress in order to identify the better of the two options for specific patients.

12.1.2 Stress and tension reduction

Relaxation training

Teaching patients to calm themselves through breathing control, altering their muscle tension, employing relevant imagery (i.e. conjuring mental pictures of relaxing scenes) and by giving them written or spoken instructions, as well as the use of music, are usually implied in this form of therapy. These methods are similar to meditation and self-hypnosis.

Relaxation techniques, when used alone for the management of pain after surgery and during procedures, seem to improve the desired outcome. Employing relaxation techniques in cancer patients with acute pain is effective in improving nausea, pain, pulse rate and blood pressure, as well as emotional adjustment variables (depression, anxiety and hostility).

Hypnosis

As techniques differ, hypnosis is difficult to assess. There is evidence that acute procedural pain for minor procedures can be managed by hypnosis effectively.

When dealing with acute pain in cancer patients, hypnosis has been found to be superior to other psychological interventions in reducing pain. This also applies to acute pain associated with procedures such as bone marrow aspiration, breast biopsy or lumbar puncture.

12.1.3 Attentional techniques

Attentional techniques include distraction from the pain, paying attention to imagined scenes or sensations, and music and aromatherapy. A common feature of these techniques is to attempt to alter the patient's emotional state from stress or fear, to comfort or peace.

Distraction is effective in needle-related, procedure-related pain in children and adolescents. Listening to music reduces pain intensity and opioid requirements after surgery, but the benefit is limited.

The use of mindfulness meditation is a type of attentional technique which may be effective in chronic pain states, but there are no reports on its use in the management of acute pain.

12.1.4 Cognitive behavioural interventions

Cognitive behavioural interventions involve applying a range of principles which can change the behaviour of a patient. Examples of this include positive reinforcement of desired behaviour, the identification and modification of unhelpful thoughts, and goal setting, in order to achieve a change in the targeted behaviour. Cognitive behavioural interventions aim to reduce the distressing or threat value of pain, and enhance a patient's sense of his or her ability to cope with it.

12.2 How are pain coping strategies applied to a cognitive behavioural intervention?

Identifying and reducing catastrophic thoughts about pain has become a key intervention within this approach, whether the pain is acute or persistent.

In preparation for surgery, painful medical procedures and post-surgical pain and distress, training in cognitive coping methods and behavioural instructions, in addition to relaxation training and procedural information, improve pain measures and reduce the postoperative use of analgesics. The treatment of procedure-related pain in children and adolescents is considered to be well established treatment in this setting.

Treatments include breathing exercises and other forms of relaxation and distraction, imagery and other forms of cognitive coping skills, filmed modelling, hypnosis, reinforcement and incentives, behavioural rehearsal and active coaching by a psychologist, parents, and/or medical staff members. The methods are not equally effective, and hypnotic-like methods, involving relaxation, suggestion and distracting imagery, hold the greatest promise for pain management in acute treatment-related pain.

12.3 The role of traditional healers in Africa

The role of the traditional healers must not be underestimated as tribal beliefs play a major role in pain management. According to tribal custom, pain expression could be viewed as a form of weakness, leading to symptom denial by believers. Caution is necessary as in addition to psychological counselling, these practitioners may prescribe remedies for ailments which are devoid of therapeutic value. However, many of these mixtures contain active substances, including anticoagulant and cardioactive agents, such as digitalis and belladonna alkaloids.

Clinical practice points

1. Listening to music produces a small reduction in postoperative pain and opioid requirements.
2. The evidence that information is effective in reducing procedure-related pain is tentatively supportive and insufficient for recommendations to be made.
3. Distraction is effective in procedure-related pain in children.
4. Training in coping methods or behavioural instruction prior to surgery reduces pain, negative effects and analgesic use.
5. Evidence of the benefit of hypnosis in the management of acute pain is inconsistent.
6. Immersive virtual reality distraction is effective in reducing pain in some clinical situations.
7. Evidence of any benefit from relaxation techniques in the treatment of acute pain is weak and inconsistent.

12.4 Transcutaneous electrical nerve stimulation

Transcutaneous electrical nerve stimulation (TENS) is not thought to be effective in postoperative pain. Opinions differ in this regard, as the maximal tolerable stimulation must be used to be effective. These parameters are a current amplitude ≥ 15 mA, a strong or subnoxious stimulus, and/or a maximal nonpainful stimulus. The superiority of high-intensity TENS, compared with low-frequency TENS, regardless of frequency used, has been demonstrated.

High frequency TENS is effective for dysmenorrhoea, but ineffective for labour analgesia.

Clinical practice points

1. There is no evidence that TENS is effective in treating pain during labour.
2. Certain stimulation patterns of TENS are effective in some acute pain settings.

TENS: transcutaneous electrical nerve stimulation

12.5 Acupuncture and acupressure

Acupuncture, compared with sham controls, has been shown to reduce postoperative pain (at eight hours and 72 hours), opioid consumption, as well as nausea (not vomiting), sedation, pruritus and urinary retention. The magnitude of the reduction is small.

Acupuncture may be effective for pain in childbirth, idiopathic cluster headaches and for dental pain. It has also been shown that acupuncture reduced analgesic requirements in postoperative pain.

Acupressure is a technique derived from acupuncture, where physical pressure is applied to the acupuncture points. Studies are limited, but acupressure performed during pre-hospital transport using “true points” led to better pain relief than acupressure using “sham points”.

Clinical practice points

1. Acupuncture reduces postoperative pain, as well as opioid-related adverse effects.
2. Acupuncture may be effective in other acute pain settings.

12.6 Other physical therapies

12.6.1 Massage and manual therapy

This form of therapy usually involves physiotherapy, osteopathy, chiropractic and massage. Most studies relate to low back and musculoskeletal pain.

Massage therapy has little use in postoperative pain. It may aid in recovery from acute back pain. The other forms of therapy have definite value in acute musculoskeletal and back pain, but little evidence is available to support their use in the management of other forms of acute pain, including postoperative pain.

12.6.2 Heat and cold therapy

The application of heat or cold may reduce opioid consumption after orthopaedic trauma, but is of no help after other major surgery.

There is limited evidence to support the use of local cooling for pain relief from perineal trauma after childbirth.

A beneficial effect of cold therapy is seen in acute sports injuries, and cold therapy (rather than heat therapy) should be instituted in this setting.

Heat therapy may provide some benefit in acute back pain.

12.6.3 Static magnetic therapy

There is no evidence to support the use of static magnetic therapy for the treatment of pain, and the use of this therapy had no effect on postoperative pain or analgesic requirements.

12.6.4 Transcranial magnetic stimulation

Postoperative transcranial magnetic stimulation used in patients after gastric bypass surgery led to significantly lower patient-controlled analgesia opioid requirements.

12.6.5 Millimetre wave therapy

There is no evidence to support the use of this therapy in acute pain.

Clinical practice points

1. Combined sensory procedural information can be effective in reducing pain and distress.
2. Hypnosis reduces procedure-related pain.
3. Training in coping methods or behavioural modification must be performed prior to surgery in order to be effective. It may not be of any use in other acute pain scenarios.
4. Certain TENS stimulation patterns may be effective in some acute pain settings.
5. Acupuncture has some efficacy in reducing acute pain.
6. Cold therapy has value in the management of orthopaedic postoperative pain and in acute sports injuries.

TENS: transcutaneous electrical nerve stimulation

References

1. Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine. Acute pain management: scientific evidence. Third edition 2012. ANZCA [homepage on the Internet]. 2012. c2015. Available from: <http://www.anzca.edu.au/resources/college-publications/pdfs/Acute%20Pain%20Management/books-and-publications/Acute%20pain%20management%20-%20scientific%20evidence%20-%20third%20edition.pdf>
2. Johnston M, Vogele C. Benefits of psychological preparation for surgery: a meta analysis. *Ann Behav Med.* 1993;15:245-256.
3. Suls J, Wan CK. Effects of sensory and procedural information on coping with stressful medical procedures and pain: a meta-analysis. *J Consult Clin Psychol.* 1989;57(3):372-379.
4. Seers K, Carroll D. Relaxation techniques for acute pain management: a systematic review. *J Adv Nurs.* 1989;27(3):466-475.
5. Luebbert K, Dahme B, Hasenbring M. The effectiveness of relaxation training in reducing treatment-related symptoms and improving emotional adjustment in acute non-surgical cancer treatment: a meta-analytical review. *Psychooncology.* 2001;10(6):490-502.
6. Patterson DR, Jensen MP. Hypnosis and clinical pain. *Psychol Bull.* 2003;129(4):495-521.
7. Uman LS, Chambers CT, McGrath PJ, et al. Psychological interventions for needle-related procedural pain and distress in children and adolescents. [Cochrane review]. In: *The Cochrane Library, Issue 4, 2006.* Update: Oxford Software.
8. Sullivan MJ, Thorn B, Haythornthwaite JA, et al. Theoretical perspectives on the relation between catastrophizing and pain. *Clin J Pain.* 2001;17(1):52-64.
9. Bjordal JM, Johnson MI, Ljunggreen AE. Transcutaneous electrical nerve stimulation (TENS) can reduce postoperative analgesic consumption. A meta-analysis with assessment of optimal treatment parameters for postoperative pain. *Eur J Pain.* 2003;7(2):181-188.
10. Sun Y, Gan TJ, Dubose JW, et al. Acupuncture and related techniques for postoperative pain: a systematic review of randomized controlled trials. *Br J Anaesth.* 2008;101(2):151-160.
11. Kober A, Scheck T, Greher M, et al. Prehospital analgesia with acupressure in victims of minor trauma: a prospective, randomized, double-blinded trial. *Anaesth Analg.* 2002;95(3):723-727.
12. Brandner B, Munro B, Bromby LM, et al. Evaluation of the contribution to postoperative analgesia by local cooling of the wound. *Anaesthesia.* 1996;51(11):1021-1025.
13. Cepeda MS, Carr DB, Sarquis T, et al. Static magnetic therapy does not decrease pain or opioid requirements: a randomized double-blind trial. *Anaesth Analg.* 2007;104(2):290-294.
15. Borckardt JJ, Weinstein M, Reeves ST, et al. Postoperative left prefrontal repetitive transcranial magnetic stimulation reduces patient-controlled analgesia use. *Anesthesiol.* 2006;105(3):557-562.

13. Management of acute pain in specific scenarios

An acute pain treatment ladder is depicted in Figure 1.

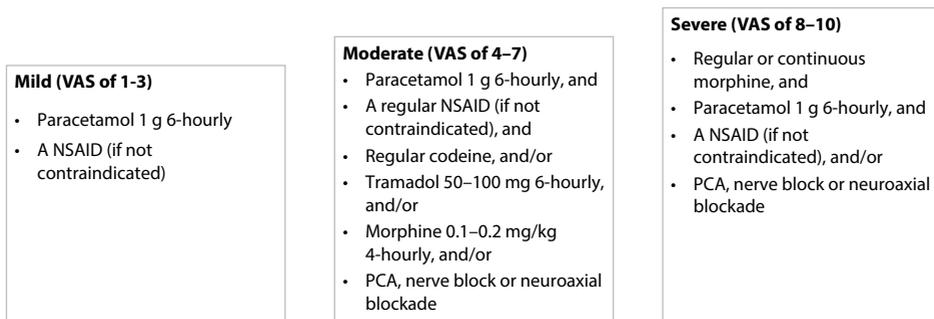


Figure 1: Acute pain treatment ladder

NSAID: nonsteroidal anti-inflammatory drug, PCA: patient-controlled analgesia, VAS: visual analogue scale

13.1 Acute pain as an outpatient

The management of minor and moderate acute pain as an outpatient is usually easily achieved with the use of routine oral agents. Severe, recurring, unrelenting or intractable acute pain usually mandates admission and specialist investigation.

Paracetamol, aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), cyclo-oxygenase inhibitors (coxibs) and opioid derivatives are the most commonly prescribed agents. Generally these agents are safe for routine usage as a short course of therapy for acute pain.

Only a short course of pain medication should be prescribed following an acute episode of acute pain. It is seldom necessary for therapy in medical conditions for ≥ 5 days. Twenty-four hour therapy is more than adequate in many acute medical conditions. Acute pain medication should never be prescribed for ≥ 10 days without a review.

Analgesics can mask the progression of many clinical scenarios, and patients should be advised to return for a review should their pain not settle completely within an appropriate time. Patients should also be warned about common side-effects, special precautions relating to their prescribed analgesics and serious drug interactions.

Topical analgesic agents are useful tools in treating outpatient conditions, especially trauma. This can decrease reliance on oral drug therapy.

Generally, modes of analgesic administration, other than oral or topical, are inappropriate for routine outpatient therapy. Rectal suppositories should only be considered in infants and patients who are unable to tolerate oral medication (usually due to nausea and vomiting). Rectal therapy should be avoided in young children and teenagers. Currently, available sublingual and transdermal analgesic formulations cannot be considered to be appropriate as acute pain therapy.

There is no role for ongoing routine parenteral analgesic therapy as an outpatient, unless under the supervision of an appropriate medical specialist.

13.2 The emergency department

Pain is the single most common complaint with which patients present at emergency rooms throughout the world. The management of pain in the majority of routine non-critical and non-severe cases is for the same as that for any outpatient scenario. Similarly, severe pain and serious disease entities usually entail admission into the facility.

However, conditions which are associated with severe pain but are non-serious and for which admission is not required are unique to this setting, for example:

- Extensive abrasions requiring cleansing and dressing.
- Serious conditions which may be adequately settled in the casualty department, thereby allowing the patient to be discharged, e.g. joint dislocation.
- Several minor conditions which necessitate a single dose of a potent analgesic to relieve the associated severe pain, e.g. a migraine headache.

Clearly, these patients require significant and potent analgesia, but their subsequent discharge affects their management.

IV titrated opioid therapy remains the therapy of choice for severe acute pain in the emergency department. Usually, IV access is routine, and appropriate monitoring equipment, resuscitation equipment and medical and nursing expertise is available.

The reversal agent, naloxone (Narcan®), should always be available in any situation in which IV narcotics are used. Repeated doses of naloxone may be required in cases of opioid overdose reversal, owing to its relatively short half-life.

Morphine is still the most widely available and utilised agent, and is safe and reliable when used correctly.

Other potent opioids, such as pentazocine (Sosenol®), meperidine (Pethidine®), dihydrocodeine (DF118®) and a morphine and papaveretum combination (Omnopon®), are also available, and can be used instead, but offer no significant advantage over morphine sulphate.

Renal colic is the only clinical scenario in which meperidine (Pethidine®) has been shown to be potentially more effective. NSAID analgesics have been shown to be as effective as opioids in this scenario. Meperidine superiority in biliary colic remains controversial and unsubstantiated.

When opioids are used in the emergency department, the patient must be kept for observation before discharge for a sufficient length of time, bearing in mind the half-life of the narcotic selected, concomitant medication which may affect respiration or haemodynamics, and the age and mass of the individual patient.

Nalbuphine (Nubain®) is an effective and safe opioid which has been available in South Africa intermittently. It is less potent than morphine, and has a lower side-effect profile, making it a reasonable choice for use in the emergency department scenario, when available.

Tramadol (Tramal®) has emerged as a very useful drug in the emergency department scenario, and this trend is to be encouraged. Tramadol has a far lower serious side-effect profile than other narcotics, enabling safer discharge of the patient from the hospital. The potency of analgesia is usually adequate for the vast majority of conditions and in the majority of patients. The standard adult dosage of tramadol is an IV bolus of 50–200 mg/dose.

Tramadol is also a very useful agent in the emergency department in cases where the severity of the condition mandates admission. The significantly lower risk of respiratory depression, hypotensive collapse and oversedation are major advantages in these serious cases. The use of tramadol in the trauma scenario is increasing and is appropriate.

When opioids cannot safely be administered intravenously, they may be given by intramuscular (IM) injection. However, this is not ideal in the emergency department because of longer onset of action and a less predictable and titratable response. A far longer observation period is usually necessary thereafter. Occasionally sublingual, oral or rectal routes may be indicated.

IV bolus doses of NSAIDs and coxibs are also extremely useful for the treatment of severe pain in the emergency department.

Lack of sedation, respiratory depression or haemodynamic instability are the major advantages of IV NSAIDs in patients who can be sent home subsequently.

Parecoxib (Rayzon®) is an IV selective COX-2 inhibitor and is available in South Africa. Evidence suggests that it is as effective for acute pain therapy as a nonselective IV NSAID.

Parecoxib is safer than nonselective NSAIDs in patients likely to undergo a surgical procedure.

The IV NSAID, ketorolac (Toradol®), has been shown to be efficacious and opioid-sparing in the emergency setting. However, caution should be exercised in patients with renal insufficiency.

Lornoxicam (Xefo®) is a balanced (COX-1:COX-2) inhibitor, and is also useful for acute nociceptive pain. It is available in both IV and oral formulations.

Lack of a sedative effect is an advantage of an IV NSAID in a patient who is to be admitted subsequently. This is of major importance when the patient has to sign consent for procedures or surgery.

NSAIDs are contraindicated in anyone at risk of renal failure, including a pre-renal insult (such as shock and dehydration), cardiac patients, peptic ulcer patients, those at risk of haemorrhage, including those on an anticoagulant agent, and those at risk of an allergic reaction.

IV paracetamol (Perfalgan®) is similarly as safe as NSAIDs in these patients, but can also be used safely in almost every clinical scenario, including those previously mentioned. (Care must be taken not to exceed the maximal daily dose, especially in the elderly and in hepatically impaired patients).

Although usually not adequate for analgesia alone, the opioid-sparing effect of IV paracetamol is extremely attractive in patients who can be discharged. Also, the lack of side-effects or sedation is of benefit to patients who are being admitted. The analgesic efficacy of IV paracetamol has been shown to be similar to 10 mg of IM morphine.

Inhalational analgesia is now also available in South Africa. Methoxyflurane (Penthrop®) is an anaesthetic volatile agent with analgesic properties at subanaesthetic doses. The delivery of this agent in the outpatient setting is now possible owing to a disposable inhalational delivery system. The drug offers good analgesia for short intense periods of pain, such as during dressing changes or wound debridement.

It is necessary for completeness sake to mention that ketamine is an option for analgesia in pain relief and anaesthesia for certain casualty-based procedures. It has largely been discarded as a modality because of its side-effects and owing to the introduction of newer agents, but may be appropriate in selected scenarios and peripheral areas, provided that the practitioner is experienced in its usage. Adequate analgesia can usually be achieved with IV doses of up to 0.5 mg/kg, and the well-known psychological side-effects usually only occur with doses ≥ 1 mg/kg. An initial dose of 2–4 mg/kg intravenously for anaesthesia usually produces anaesthesia within 30 seconds and lasts up to 10 minutes. Thereafter, repeated increments of half the induction dose can usually be given every 5–10 minutes without significant accumulation. The administration of 10 mg/kg intramuscularly is an alternative which induces anaesthesia in 3–4 minutes, and which lasts approximately 15–20 minutes.

Appropriate monitoring during casualty-based procedures in general is advised. Oxygen, monitoring equipment and resuscitation equipment that is in good working order are mandatory.

It is often routine in casualty-based sedation to combine an opioid with a benzodiazepine. This increases the risk of respiratory depression and oversedation, and dramatically lengthens the post-procedure observation time prior to safe discharge.

When performed, only short-acting benzodiazepines, such as midazolam, should be used for emergency room and outpatient sedation, and these should be titrated.

Caution is also required when reversing benzodiazepine sedation with flumazenil (Anexate®) as this agent's half-life is also short, and re-sedation may occur after its effect wears off.

Anaesthetic induction agents, such as propofol, thiopentone (Pentothal®) and etomidate (Hypnomidate®), should never be used in the emergency department unless a decision has been taken that the patient requires intubation and ventilation, and thus hospital admission.

The risk of aspiration must always be considered whenever a sedative agent is administered to a patient, especially in the case of agents which exacerbate nausea, and in patients who are not starved.

Inhaled nitrous oxide may be a useful adjunct for pain control in the emergency room scenario and in the pre-hospital scenario. It may also be useful as analgesia for minor procedures.

13.3 The intensive care unit

The availability of well trained support staff, excellent monitoring facilities and resuscitation equipment in intensive care units (ICUs) allows more potent agents to be used more safely.

The IV titration of opioid narcotics remains the method of choice in conscious and orientated patients. Morphine is effective, the cheapest agent that is readily available, and the agent with which most

practitioners have the most experience. Its length of action is well suited to this environment. Fentanyl is emerging as a useful agent in this scenario, but remains more costly than morphine.

There is a definite role in experienced hands for the use of potent short-acting narcotics, i.e. alfentanil (Rapifen®) and sufentanil (Sufenta®), for acute, severe pain. These are similarly titrated intravenously, and are especially of use in patients immediately post major surgery.

Ventilated patients are unable to vocalise when they are in pain. Thus, regular potent analgesia must be administered regularly to all patients who are likely to experience it. It is important that patients' vital organs are monitored for signs which may be suggestive of pain, e.g. tachycardia and hypertension.

It is a wise policy to routinely administer the analgesia before the sedation, which should reduce the risk of inadequate pain control in sedated patients.

It is routine practice to include an opioid analgesic in the sedation regimen of ventilated patients, even in patients who are unlikely to experience pain, as this augments the sedation and alleviates the discomfort associated with interventions and procedures.

Nonpharmacological issues are extremely important in the ICU setting and affect both pain level and pain perception. These include nursing care, pressure care, devices, masks, oxygen gas flow, humidification, physiotherapy, secretion formation, noise levels, day-night routines, visitation and sleep.

Usually, morphine is the preferred analgesic sedative in mechanically ventilated patients, and remains a very popular choice in combination with the short-acting benzodiazepine, midazolam (Dormicum® and Midacum®).

Other narcotic potent analgesics can be substituted for morphine, but are more expensive, have no additional benefits and staff are less familiar with their use.

Morphine should be used with care in renal failure owing to the accumulation of the active metabolite of the drug.

Fentanyl (Sublimaze®) is the best alternative opioid for use in the ICU if an alternative to morphine is required. Fentanyl has the advantage of being associated with lesser haemodynamic instability, but may accumulate with prolonged use because of its half-life.

Partial opioid agonists should be avoided in the ICU because of the risk of dependency developing with prolonged use, without additional benefits in efficacy.

Similarly, other benzodiazepines, such as diazepam (Valium® and Pax®) or lorazepam (Ativan®), can be used in place of midazolam, but these are all longer acting and prone to accumulate more, hence negatively affecting the weaning process.

Usual precautions are required when monitoring ventilated patients during sedation and analgesia with morphine. Although respiratory depression and oversedation are less of a concern in ventilated patients, these become extremely important during weaning from mechanical ventilation. Other negative effects of narcotics, especially hypotension, remain a concern.

Remifentanyl (Ultiva®) is also a very useful agent for use in the critical care environment. It is an ultra-short-acting, very potent opioid and is easily titratable as an adjustable IV infusion.

Remifentanyl is currently a superior agent for analgesia in ventilated patients undergoing invasive, uncomfortable or painful procedures. It is easily titrated for the duration of the procedure, irrespective of its duration (useful in short procedures, e.g. the placement of invasive monitoring lines, catheters and chest drainage tubes; and in longer procedures, such as major burn dressings).

The recommended dosage of remifentanyl in this setting is a 0.1–0.5 µg/kg/minute infusion in adults. Children may require a higher dosage of up to 1 µg/kg/minute.

Remifentanyl infusion is effective for ongoing analgesia in the immediate postoperative phase following major surgery associated with significant pain. When used intraoperatively in these cases, it is advantageous to continue this into the early postoperative period.

Remifentanyl can be used effectively in combination with propofol (Diprivan®) for the sedation and analgesia of ventilated patients as an alternative to morphine and midazolam. This combination is even more short acting and titratable than the more popular combination, but cannot be advocated for routine usage because of the significantly higher cost of both agents. In addition, the propofol infusion should not be used for ≥ 3 days because of the risk of propofol infusion syndrome.

A major indication for using the remifentanyl plus propofol regimen is cases of major surgery in which postoperative ventilation is required, and where patients can rapidly be weaned from ventilation within 48 hours.

Remifentanyl is useful for ICU sedation in patients with renal failure as its clearance is independent of renal function. The dosage of remifentanyl required for ICU sedation is usually 0.025–0.200 µg/kg/minute. The recommended dosage for propofol for ICU sedation is 5–50 µg/kg/minute.

Dexmedetomidine (Precedex®) is another useful agent for use during ICU procedures, and combines analgesia with anxiolysis. This agent is an alpha 2-receptor agonist. It causes sedation which mimics natural sleep, and also provides limited analgesia.

The recommended dosage for dexmedetomidine in the ICU is 0.5–3.0 µg/kg/single dose as a slow IV bolus (usually 1 µg/kg for procedures), and 0.2–1.0 µg/kg/hour (usually 0.6–0.7 µg/kg/hour) for continuous infusion. Dexmedetomidine is not registered for more than 24 hours of continuous use.

IV paracetamol (Perfalgan®) may be used for pain and fever, if not contraindicated.

13.4 Postoperative pain

The management of postoperative pain in hospital is generally the scenario in which medical, pharmacy and nursing staff have the most experience. Experience gleaned in this scenario has been extrapolated to guide pain control in most other medical scenarios. Failure to treat the pain may result in a physiological stress response, which may lead to myocardial ischaemia.

Immediate postoperative pain control in the recovery room, and subsequently if the patient is transferred to a high dependency or critical care environment, is best achieved by titrating an IV opioid agent. Alfentanil, fentanyl or sufentanil are the most common agents that are used immediately postoperatively by anaesthesiologists.

It is common practice to administer a longer-acting IV opioid, such as morphine, towards the end of the surgical procedure to ensure sustained and adequate analgesia on waking. The importance of appropriate monitoring is stressed.

Generally, it is also routine to administer an IV nonsteroidal analgesic during the surgical procedure, providing there are no contraindications. This practice is to be encouraged.

IV NSAID administration is preferable to rectal suppository NSAID administration when IV access is available.

Initially and preferably, a NSAID should be given intravenously, and thereafter an oral course of on average five days is appropriate for most routine post-surgical scenarios.

NSAIDs provide effective and sustained analgesia, enhance multimodal analgesic efficacy, and decrease opioid requirements. They should be given routinely after all major, invasive and severely painful operations, except where a specific contraindication exists.

Inherent contraindications to the administration of an NSAID include an allergy to these agents, asthma, ischaemic heart disease, hypertensive cardiac disease, peptic ulcer disease, vascular disease, renal disease, significant hepatic disease, coagulopathies and concomitant anticoagulation therapy. Routine postoperative prophylactic anticoagulation is not a contraindication to NSAID therapy.

Intraoperative complications that constitute a contraindication to NSAID therapy include significant blood or fluid loss, hypotensive insult, the use of significant dosages of anticoagulation, and procedures which enhance the risk of postoperative complications. For example, aortic cross-clamping would increase the risk of renal failure developing.

It is appropriate in the vast majority of cases to use the newer coxibs and NSAIDs, as opposed to the older nonselective NSAIDs or COX-2 inhibitors, for most scenarios of postoperative pain control.

The use of COX-2 inhibitors and selective NSAIDs preferentially reduces postoperative complications, especially the risks of gastrointestinal haemorrhage due to peptic ulceration, and all complications relating to over-anticoagulation. Cardiac cases and cardiovascular surgery are exceptions.

IV paracetamol is a useful adjunct in postoperative pain control, and should be used routinely postoperatively for its multimodal effects, and to decrease the amount of narcotic needed.

Failure to achieve appropriate pain control postoperatively has been shown to be a major risk factor for the development of neuropathic pain and the conversion of acute pain into a chronic pain syndrome. Early and effective pain relief reduces this risk dramatically. Various agents have been used with variable success in an attempt to diminish this incidence and/or to treat the condition. Agents with some benefit include calcitonin, ketamine, morphine, gabapentin, pregabalin, lignocaine, carbamazepine and amitriptyline.

Day case surgery also warrants specific mention. The severe pain incidence in these procedures is usually approximately 5%. However, inadequate pain control is common because of concerns with administering powerful agents to patients who are being discharged, and reluctance on the part of staff to delay the discharge process. Orthopaedic, plastic surgical and laparoscopic procedures, as well as hernia repair, are common scenarios in which pain control is often inadequate. Patients with an increased body mass index (BMI), and procedures in which longer general anaesthesia is required, are risk factors for the development of severe pain.

The use of local anaesthesia, and regional anaesthesia, where possible, in the day case scenario is strongly advocated.

13.4.1 General surgery

The fact that patients are kept *nil per os* for varying lengths of time is of particular importance in gastrointestinal and other intra-abdominal procedures.

A prolonged period *nil per os* increases the risk of peptic or stress ulceration, and nonselective NSAIDs should be used with caution, or avoided where possible. When NSAIDs are utilised in this scenario, the risk of gastric or duodenal erosions and ulceration can be decreased by the simultaneous administration of IV proton-pump inhibitors (PPIs) or H₂-receptor blockers, or alternatively sucralfate via the nasogastric or orogastric tube. These practices are common and accepted as routine, despite evidence that these regimens may increase septic complications, especially pneumonia, in ventilated patients.

Nonselective NSAIDs are often contraindicated in post-laparotomy patients. This means that opioid analgesics are the most commonly utilised agents in these scenarios. Opioids too should be used with caution, and sparingly, if possible, while ensuring adequate pain control. This relates to the unwanted side-effects of nausea and vomiting, which are common in any event in patients undergoing general surgery. They also delay gastrointestinal motility recovery, which further prolongs postoperative ileus and exacerbates post-surgical constipation.

Paracetamol and the coxibs are generally safe for use post gastrointestinal surgery, but are seldom adequate without opioids initially.

All classes of analgesics are generally used safely and routinely in all other general surgical procedures in which laparotomy is not involved.

Local anaesthesia and regional anaesthesia, especially lumbar epidural analgesia post laparotomy, are supported wherever possible too, depending on local expertise and monitoring.

13.4.2 Vascular surgery

Vascular patients are often cardiac and/or renal patients too. Hence, the use of NSAIDs, including coxibs, should be judicious in vascular patients, and is actively discouraged in patients with hypertensive or ischaemic heart disease, and in those with renal dysfunction.

In addition, these patients may be at added risk of haemorrhage, or may require concomitant anticoagulation therapy. This also contraindicates NSAID usage, although coxibs may be used cautiously in these cases.

Prostaglandin inhibition may be completely contraindicated in certain cases, especially peripheral vascular disease, as this may exacerbate ischaemia by vasoconstriction.

Opioid narcotics and paracetamol are generally safe in the majority of vascular patients.

Regional and spinal blockade and epidural anaesthesia are also encouraged in these patients, in that the concomitant sympathectomy effect generally causes vasodilatation and improves blood perfusion.

Contraindications to blockade and neuraxial analgesia include concomitant anticoagulation, patients with a fixed cardiac output state, those in whom hypotensive events could be a disaster, and those requiring peripheral limb monitoring, i.e. those requiring peripheral neurological function monitoring and those at risk of developing compartment syndromes.

13.4.3 Cardiothoracic surgery

Postoperative cardiac surgery patients are usually nursed in intensive care. Powerful, titratable narcotics, such as fentanyl derivatives or morphine, are routinely used initially.

NSAIDs are effective analgesics for sternotomy and thoracotomy wounds, but usually cannot be utilised due to anticoagulation therapy, or concomitant cardiac or renal disease.

Neuraxial blockade is often contraindicated because of anticoagulation therapy.

Nonselective NSAIDs and coxibs are useful adjuncts to opioid therapy in thoracic procedures. Multimodal therapy with coxibs and paracetamol may be beneficial in terms of opioid sparing and to decrease concerns about respiratory depression. Thoracic epidurals, and paravertebral, pleural and intercostal blocks, are all extremely useful adjuncts to pain management.

13.4.4 Neurosurgery

Pain control in most post-neurosurgical operations is managed similarly to that in other scenarios, i.e. with a multimodal approach, and usually by combining opioids and NSAIDs or coxibs.

Issues that warrant special mention are that accurate neurological assessments and level-of-consciousness monitoring may be severely impaired by the sedative side-effects of opioid narcotics, which limits their use in certain scenarios. Careful titration and experienced dosing is required to overcome these issues. Oversedation may be desirable in other circumstances, e.g. when wanting to limit stimuli that would raise intracranial pressure. Here, monitoring for overdosage, hypotension and respiratory depression is required.

Other side-effects of opioids may also be problematic. Patients with intracerebral tumours and/or raised intracranial pressure tend to suffer from severe nausea in any event, and vomiting may be exacerbated. Spinal patients are prone to constipation (spinal cord injury, autonomic dysfunction and prolonged bed rest are the culprits), and this is exacerbated by opioids.

NSAIDs also need to be used cautiously in certain neurosurgical patients, owing to the fact that any post-surgical haemorrhage in a neurosurgical patient may be disastrous, and because of the high incidence of peptic ulceration in these patients as a consequence of chronic NSAID usage (spinal patients), stress ulceration (head injury patients), irregular enteral feeding and concomitant steroid therapy (patients with raised intracranial pressure).

Coxibs are preferable to older nonselective NSAIDs in these patients, and evidence exists that COX-2 inhibitors are the drug of choice following spinal cord injury.

NSAIDs should be used cautiously in patients at risk of developing renal failure. These are mainly patients at risk of dehydration and pre-renal insult. This includes patients on diuretic therapy for raised intracranial pressure and those who have developed diabetes insipidus.

The use of local, regional and neuraxial blockade in these patients needs to be carefully considered. These offer excellent pain control in spinal and peripheral nerve surgeries and injuries, but impair motor and sensory neurological monitoring. They may also be contraindicated owing to sepsis and haemorrhage risks.

13.4.5 Orthopaedic surgery

Orthopaedic procedures are particularly painful procedures, and pain control is vital to allow early mobilisation, prevent complications (deep vein thrombosis, pulmonary embolism, contractures and pressure sores), and decrease chronic pain syndromes. Initial postoperative parenteral opioid usage is routine, followed by substitution with oral agents. NSAID therapy is extremely efficacious in these patients, but needs to be used judiciously.

Often, orthopaedic patients have utilised NSAIDs chronically preoperatively, and thus have a high incidence of known or occult peptic ulceration.

Routine upper gastrointestinal endoscopy at the time of major spinal, pelvic and lower limb surgery, especially joint arthroplasties, is encouraged to exclude a lesion at risk of haemorrhage. These patients are at particular risk of deep vein thrombosis. Postsurgical, prolonged anticoagulation is mandatory. The routine postsurgical usage of PPI therapy is advisable.

NSAIDs have been shown to delay bone healing times post surgery and after fractures. This is, however, not a clinically relevant problem in most cases.

The intra-articular instillation of analgesics, local anaesthetics and corticosteroids in joint surgery, day case arthroscopy and joint injury is controversial, and evidence in the literature is conflicting. Currently, there is evidence to support the instillation of a local anaesthetic in the acute situation, and cortisone in the chronic situation. There is some evidence to support intra-articular opioid instillation after some types of orthopaedic procedures.

Regional and neuraxial blocks are particularly useful in the early postoperative period. Routine post-surgical prophylactic anticoagulation does not contraindicate the use of epidural usage postoperatively, but experience is required when managing the dosing of such therapy to allow safe catheter removal without neuraxial haemorrhage risk.

13.5 Acute spinal cord injury

Pain can develop weeks, months or years following spinal cord injury. Pain resulting from spinal cord injury is termed central. Pain can be neuropathic, at the level, or above the level, of injury. Central pain is generally more difficult to treat, and tends to be resistant to many therapeutic options. Nociceptive pain, complex regional pain syndrome and phantom pain can also develop. Treatment of the condition is extrapolated from studies on chronic neuropathic pain.

Primary and secondary analgesics can be used, i.e. opioids, ketamine, local anaesthetics, antidepressants and anticonvulsants. Psychotherapy and rehabilitation must be included in the treatment regime for these patients.

13.6 Acute burn injuries

Post-burn injury pain is both nociceptive and neuropathic in origin. Therapy is required to manage the constant baseline pain, as well as acute intermittent exacerbations and exacerbations associated with procedures such as line or dressing changes.

Cooling is a major factor in the early management of these patients and is vital to limit burn tissue extension and pain alleviation. Evidence suggests that IV opioid titration is best at achieving adequate pain control in these patients. Patient-controlled analgesia (PCA) may be a useful tool in managing opioid administration in burn patients.

Single-dose boluses of a short-acting powerful opioid, such as alfentanil, are appropriate for pain exacerbations associated with quick procedures in these patients. Titrated remifentanyl infusion is a superior technique for longer procedures, especially major dressing changes, provided that respiratory support is available to the patient. Fentanyl or morphine titrations may be used when it is not available.

Ketamine is also particularly useful in burn patients as it provides both analgesia and sedation. Nitrous oxide and IV lignocaine are other agents that are used for burn pain control. These are predominantly used in peripheral areas and situations in which intensive monitoring is limited.

Topical adjunctive analgesics are available in the form of lignocaine-soaked dressings and morphine-infused creams, such as silver sulphadiazine (Flamazine®).

Concomitant sedation is useful and humane. Numerous agents are available, and have been successfully used according to local experience and expertise. These include benzodiazepines and antihistamines, such as lorazepam, midazolam and hydroxyzine (Aterax®), propofol, and occasionally phenothiazine-type drugs, such as chlorpromazine (Largactil®), haloperidol (Serenace®) or clotiapine (Etomine®).

13.7 Acute back pain

Acute spinal pain (cervical, thoracic, lumbar or sacral) affects the majority of people at some stage of their life. A self-limiting and benign course is expected once the “red flags” of fracture, infection, tumour and metastasis have been excluded.

Range of movement and a focused neurological examination are indicated. Psychosocial and occupational factors (“yellow flags”) need to be identified early.

Education and maintaining activity are the focus of management of the condition. A multidisciplinary approach is indicated, aimed at the prevention of chronic pain development. Treatment consists of short-term rest, hot or cold packs, nonspecific NSAIDs or coxibs and muscle relaxants. Physiotherapy is recommended.

13.8 Acute musculoskeletal pain

NSAIDs are generally the drug of choice in the scenario of acute musculoskeletal pain. Coxibs are preferable in the elderly and in patients in whom prolonged therapy is envisaged. Usually, oral opioids are also required in the acute phase, followed by an oral NSAID and paracetamol. Topical NSAIDs and cortisone injections are effective in selected cases.

Adjuvant therapy with physiotherapy, exercise, ultrasound, infrared therapy and laser, is beneficial. Evidence does not exist for the routine use of muscle relaxants, antidepressants or anticonvulsants.

13.9 Post-trauma pain

The management of acute pain due to trauma is similar to that of postoperative pain. Initial therapy for significant trauma pain is best achieved by the titration of IV opioids. Morphine remains the most widely used agent, and is cheap and effective. However hypotension, respiratory depression and oversedation are real concerns.

Tramadol and IV paracetamol are advocated as effective and safer alternatives to morphine. IV COX-2 inhibitors are also effective and useful, and should be administered early in the therapy of trauma. These are safer alternatives to the older, non-specific NSAIDs, but may be less efficacious.

Nonselective NSAIDs are extremely effective analgesics in the trauma setting, and are initially advocated for trauma by IV or IM injection. NSAIDs are generally safe and their use supported, but these agents should obviously not be used in patients at risk of haemorrhage, or in patients at risk of renal failure (shocked patients). Care should be taken when using NSAIDs in the elderly. IV paracetamol or coxibs are preferable in these patients. NSAIDs are usually continued post-hospital discharge in an oral formulation; alone or in combination with an opioid derivative, such as codeine. Topical NSAIDs are useful in gel or patch form, and decrease systemic analgesic requirements.

13.10 Pain management in sports medicine

The health benefits associated with increased physical activity have been established. However, a subsequent increase in sports and exercise-related injury accompanies increased participation in physical activity. The agents that are used for pain management in acute sports injury are reviewed, and a rational approach to the use of these agents suggested.

When tissue is injured, phospholipids are released from the cell membrane, and are converted into arachidonic acid by the enzyme, phospholipase A2. Arachidonic acid, in turn, is a substrate for the enzyme, COX, resulting in the production of various prostaglandins. This pathway and the substances which are produced are responsible for the pain and inflammation seen in sports injuries, but also initiate the healing process.

Medication attempts to change this process. It is believed that the use or abuse of analgesic medication and NSAIDs is widespread in sports medicine among professional and amateur athletes. The pressure is on the medical professional to relieve pain and to return the athlete to training and competition as soon as possible without compromising tissue healing. However, the acute and long-term use of some of these agents is problematic, and not without significant side-effects.

Analgesics are commonly used in the management of acute sports injury to reduce pain. The further use of analgesics depends upon the intensity and duration of pain. Agents in this group are used either as single agents or in combination, and include:

- Acetylsalicylic acid, in doses up to 300 mg.
- Paracetamol, up to 3–4 g/day.
- Codeine, reserved for more severe pain, with numerous side-effects.
- Tramadol, reserved for more severe injuries.

It is important to note that these medications do not inhibit the inflammatory response.

13.10.1 Nonsteroidal anti-inflammatory drugs, including cyclo-oxygenase inhibitors

NSAIDs and coxibs are widely used and are effective in decreasing pain and swelling, but benefit in acute sport injuries has only been proved in a few studies. They have been widely tested in chronic arthritis models and the side-effect profile has been extensively discussed. These agents may even cause harm in acute sport injuries. A review of the literature suggests that anti-inflammatory agents, and indeed both nonselective NSAIDs and coxibs, have a significant negative effect on musculoskeletal tissue healing (bone, tendon, muscle and ligaments). Although this finding remains the subject of considerable debate, athletes who receive these agents in the first 48 hours after an injury may be disadvantaged.

13.10.2 Topical analgesics

The majority of topical analgesics are skin counterirritants, and contain a combination of substances, including methyl salicylate, eucalyptus, menthol, capsicum and camphor. The active ingredients cause erythema and blood vessel dilatation, as well as stimulate the pain and temperature receptors. These agents can be used in addition to a warm-up, and can be of some benefit in minor sprains and strains. Topical NSAIDs are effective in relieving the pain associated with soft tissue injuries, without causing serious adverse effects.

Clinical practice points

1. The inflammatory process seems to be an important part of the healing process in musculoskeletal tissue in humans. Only analgesics should be used in the first 48 hours following an injury to allow the first part of the physiological healing process to occur. Paracetamol, or paracetamol plus codeine, are examples of agents which can be used for pain management in this phase.
2. Rest, ice, compression and elevation are important elements of pain management in the first 48 hours of an injury occurring.
3. If a repeat assessment of the injury reveals the clinical signs and symptoms of excessive inflammation (swelling and pain) after 48 hours post injury, a NSAID or coxib should be used for up to five days as these agents have been shown to reduce pain and promote function following an injury.
4. If the athlete has a history of gastrointestinal side-effects or other side-effects following nonselective NSAID use, paracetamol should be continued, or a coxib, or a coxib plus PPI, considered.
5. Physiotherapy, including therapeutic ultrasound, followed by rehabilitation, forms an essential part of treatment from 24 hours after the injury.
6. Generally, if the use of a NSAID, coxib or analgesic is required for ≥ 5 days, the patient should be reassessed and the diagnosis revisited.
7. NSAIDs and coxibs should not be used prophylactically to prevent muscle soreness after exercise, or to prevent pain during sport.
8. There is evidence of the efficacy of use of NSAIDs in ligament sprains of the ankle, knee and shoulder joints, and in conditions where the pathological disorder is tissue entrapment or impingement of the nerves and other structures due to soft tissue swelling. These occur, for example, in carpal tunnel syndrome, Morton's neuroma, intervertebral disc prolapse, thoracic outlet syndrome, bursitis in rotator cuff disease, trochanteric bursitis and iliotibial band friction syndrome.
9. There is no role for NSAIDs in the management of chronic degenerative tendon conditions, including Achilles tendinosis, as the pathology has been shown not to be inflammatory in origin. Furthermore, there is no evidence to support the use of NSAIDs for long-term pain arising from a sports injury without impingement.
10. Sufficient time should be taken off from training in order to allow for complete tissue healing. Athletes sometimes ingest agents to facilitate an early return to sport, which can place them at risk of further injury. Adequate time for recovery, physiotherapy and rehabilitation should be allowed before returning to sport.
11. If opioids are considered at any stage in professional sports men and women, it must be noted that these drugs appear on the World Anti-Doping Agency prohibited list.

coxib: cyclo-oxygenase inhibitor, PPI: proton-pump inhibitor

13.11 Acute abdominal pain

Acute abdominal pain usually begins as visceral pain, and as the pathology progresses, the pain develops into somatic pain. Visceral pain can be acute or chronic, and is classically colicky in nature. Local inflammation results in progression to classical acute somatic pain, with localisation of the affected area and progression to the clinical picture of peritonism.

Adequate analgesia should be administered without fear of masking the clinical signs, as appropriate dosing will not interfere with the progression of the clinical signs and symptoms. Opioids are the drug of choice for treating severe acute abdominal pain with peritonism. Caution should be taken with respect to the side-effects, i.e. a decrease in gastrointestinal motility and the exacerbation of nausea and vomiting.

Parenteral opioid preparations are available in combination with an anticholinergic, antihistaminic-type of antiemetic drug (cyclizine), and certain parenteral opioids can safely be mixed with a phenothiazine-type antiemetic (prochlorperazine) for IM injection. Alternatively, an antiemetic can be administered separately as required. Antiemetics of the serotonin antagonist type, such as ondansetron (Zofran®) or granisetron (Kytril®), are currently the most efficacious agents available for the suppression of nausea in this scenario.

Other antiemetics of the dopamine antagonist type may be preferable, as these are prokinetic as well, and improve gastric emptying and enhance intestinal motility. They diminish the negative effects of the opioid and decrease the risk of aspiration. Metoclopramide (Maxalon® and Clopamon®) is the drug of choice in this group, and is available in parenteral and oral formulation. Alternatives are droperidol [Inapsin® (parenteral only)] and domperidone [Motilium® (oral only)].

Antispasmodic analgesics may be utilised with varying response for relief from gastrointestinal origin colic visceral pain. Smooth muscle relaxants and peppermint oil have been shown to be the most effective agents in acute exacerbations of chronic cramping pain, such as irritable bowel syndrome.

The debate as to whether pethidine or morphine is superior in the treatment of renal colic has persisted, but the agents are equivocal and effective in clinical practice.

NSAIDs have been shown to be as effective an analgesic as opioids in renal colic, and superior in one study. They are most effective in renal colic, and onset of action is most rapid when administered intravenously. The benefit of adding an anticholinergic or antispasmodic agent, e.g. hyoscine, in renal colic, is not found in medical evidence as these agents are less efficacious than opioids or NSAIDs, and combination therapy is equivalent to the usage of opioids or NSAIDs alone.

The debate as to whether pethidine is superior to morphine (an alleged lesser effect on the sphincter of Oddi) in acute abdominal pain of biliary or pancreatic origin continues. There is no evidence to suggest that pethidine paradoxically relaxes sphincter of Oddi spasm. Opioids increase sphincter spasm and hence bile duct pressure. However, pethidine appears to have the least effect in this regard. However, this is unlikely to have clinical relevance.

Opioids are excellent analgesics in biliary colic. The parenteral NSAIDs; ketorolac (Toradol®), tenoxicam (Tilcotil®) and diclofenac (Voltaren® and Veltex®), have been shown to be as efficacious as opioids in biliary colic. Antispasmodic agents have been shown to be inferior to opioids and NSAIDs in managing pain from biliary colic.

Nonselective coxibs or NSAIDs have been demonstrated to be the drugs of choice in the management of pain due to dysmenorrhoea. Ibuprofen (Brufen®, Nurofen®, Inza®, Advil®, Ibumax® and Ranfen®), naproxen (Naprosyn®, Nafasol®, Napflam® and Aleve®) and mefenamic acid (Ponstan®, Ponac® and Fenamin®) have all been shown to be efficacious in dysmenorrhoea. They are all more efficacious than aspirin or paracetamol alone.

Combination products of ibuprofen, together with paracetamol and/or codeine (Myprodol®, Mybulen®, Mypaid®, Lotem® and Betagesic®), are widely used and are popular for treating dysmenorrhoea in South Africa. However, these have not been compared with the use of ibuprofen alone in any studies.

The supplementation of vitamin B1 has been shown to be beneficial in treating dysmenorrhoea. The application of heat to the lower abdomen (by a hot water bottle or heating pad) has also been shown to be scientifically effective in easing dysmenorrhoea cramping.

13.12 Acute cardiac pain

Acute cardiac pain results from acute coronary ischaemic states, and includes acute myocardial infarction and unstable angina.

The restoration of adequate coronary blood flow, which limits cardiac muscle damage and reverses ischaemic pain, is the mainstay of treating acute cardiac pain. Optimising myocardial oxygen delivery is the prime goal, which, in turn, settles ischaemic pain. However, early pain control is important in decreasing myocardial oxygen demand as it decreases the stress response.

Supplemental oxygen is the most simple and quickest method of improving myocardial oxygenation, and is the first therapy that should be initiated, whenever possible.

Nitroglycerine administration decreases acute myocardial ischaemic pain, irrespective of the presence of coronary artery disease.

IV morphine has been shown to be very effective at suppressing acute cardiac ischaemic pain, usually within 20 minutes, and by utilising a relatively low dose (a total of only 7 mg, on average).

Alfentanil is as efficacious as morphine in treating ischaemic cardiac pain, and its onset of action is more rapid.

Buprenorphine and pethidine are equivalent in efficacy and side-effect profile to morphine in treating cardiac ischaemic pain.

IV tramadol has been demonstrated to provide adequate analgesia in this scenario.

Inhaled nitrous oxide has been shown to be effective at relieving acute cardiac ischaemic pain.

Acute cardiac pain due to pericarditis is somatic pain, as opposed to ischaemic pain, and is best treated with NSAIDs.

13.13 Acute headaches

Headaches are a very common cause of acute pain. Although the vast majority are not due to a serious underlying pathology, it is important to adequately investigate severe, unrelenting or headaches which return repeatedly as the cause can be due to a serious intracranial pathology, such as infection, tumour, a stroke, aneurysm, glaucoma or temporal arteritis.

Most commonly, acute headaches are due to migraines, episodic tension headaches, cluster headaches, post trauma, post-drug usage or withdrawal, or due to various less common primary headache causes.

Headaches also frequently have a non-cranial origin, usually a cervical pathology or cervicogenic, due to a neck muscle spasm, or may be due to other non-central nervous system (CNS) causes, such as sinusitis.

13.13.1 Migraines

Migraines are usually severe unilateral headaches, often retro-orbital and associated with nausea, vomiting, photophobia and phonophobia, and worsened by movement. They may be preceded by an aura, usually visual disturbances, but may also include other sensory, motor or speech disturbances.

They are vascular in origin, usually characterised by initial cerebral arterial vasoconstriction, followed by the release of inflammatory mediators and excessive compensatory vasodilatation, with painful pulsation. Migraines occur significantly more frequently in females, and attacks have been linked to fluctuations in the serum levels of oestrogen, and secondarily relate to the menstrual cycle, pregnancy, menopause, hormone therapy and oral contraceptives. Numerous other trigger factors have been identified.

Migraines are often debilitating in their severity. Most attacks occur repeatedly in sufferers, and are treated by the patients themselves so that they do not present to hospital. They are commonly seen in emergency departments. Eighty per cent of patients have attempted self-medication at home before presenting at the facility.

Minor migraine attacks can be treated successfully with the resolution of symptoms by two hours by utilising common analgesics, often combined with an antiemetic. Regimens, such as aspirin or paracetamol, combined with metoclopramide, have been shown to be as effective as the newer triptan agents in minor cases.

Severe attacks, unrelenting attacks, attacks with significant disability and recurrent attacks are most effectively treated with triptans, which have revolutionised the treatment of acute migraine attacks. Several triptan agents are available on the market. Oral agents are best tolerated by patients, but intranasal sprays and subcutaneous injections provide the most rapid onset of action and are more efficacious. This is probably due to impaired absorption and gastric stasis. Oral wafers for sublingual absorption and suppositories are also available and are better absorbed.

Side-effects with triptan therapy are common, but are generally non-serious. These include nausea, fatigue, dizziness, paraesthesia and sensory sensitivity to touch and temperature. Triptan therapy is contraindicated in active ischaemic heart disease and uncontrolled hypertension, and should not be used in combination with ergot preparations.

Ergot derivatives, such as ergotamine and dihydroergotamine, have been widely used in the past to treat acute migraine attacks. Caffeine has also been used in combination with ergot derivatives. Ergotamines are an effective medication, but are less efficacious than triptans, with a higher side-effect profile. Thus, they are being superseded by triptan therapy.

Opioids are not effective analgesics for treating migraine headaches and are not recommended, except as a last resort for acute, severe migraines in patients in whom triptans, ergot derivatives and other agents are contraindicated.

IV antiemetic therapy is effective in treating acute migraine. Prochlorperazine, metoclopramide, chlorpromazine and droperidol have all been utilised successfully.

The dangers of akinesias and athetosis (extrapyramidal side-effects) with antiemetics, especially in young female patients, should be noted. Should these occur, they can rapidly be reversed with biperiden (Akineton®), i.e. 5–10 mg slow bolus, intravenously.

There is no evidence that antiepileptic medication, e.g. sodium valproate, or antiarrhythmic agents, e.g. IV lignocaine, are effective in treating migraines. The use of these medications in this scenario is discouraged.

Research is currently underway to assess IV magnesium sulphate as therapy for acute migraines, and this may prove to be useful in the future. Currently, it cannot yet be recommended.

NSAIDs are effective in treating acute migraines, and less effective than triptans or antiemetics when used alone. The combination of a NSAID with an antiemetic and caffeine was proven to be more effective than a triptan in a single study.

Aspirin, ibuprofen and indomethacin (orally) and IV NSAIDs (Ketorolac and lornoxicam) have all been used successfully in acute migraine headaches. NSAIDs can also be given by suppository should vomiting prove a challenge.

Intravenous NSAIDs are the drugs of choice in emergency department therapy, and should be combined with an IV antiemetic. An intravenous COXIB (Parecoxib) could be substituted if there is a major contraindication to nonselective NSAID therapy.

Overall, parenteral triptan therapy is the therapy of choice for the current emergency department treatment of acute migraines, unless a major contraindication exists.

Preventative measures are also important components of therapy. Patients should avoid triggers, such as chocolate and red wine. Strong evidence exists for the use of botulinum toxin as a preventative treatment for migraine headaches.

Therapy for migraines in children is similar to that in adults, with the following provisos:

- Triptans are effective and constitute the drug of choice in children aged ≥ 12 years. Evidence is not yet available to support the safety and use of triptans in younger children.
- Nasal sumatriptan is well tolerated.
- Paracetamol and NSAIDs are effective and safe as acute therapy in younger children.
- Aspirin should not be used in young children because of the rare, but real danger of, Reye's syndrome.
- Antiemetics should be used with care in children owing to the higher incidence of extrapyramidal side-effects.

13.13.2 Tension headaches

Tension-type headaches may be episodic or chronically recurrent in nature. They are classically bilateral and characterised by a pressing or tight cranial sensation. Generally, tension-type headaches are not exacerbated by movement nor associated with nausea.

Paracetamol and aspirin have both been shown to be effective agents when used alone and in combination with other NSAIDs.

NSAIDs alone are more effective than paracetamol alone in treating this type of headache. Ibuprofen, naproxen and ketoprofen have all been shown to be effective therapy for tension-type headaches.

13.13.3 Cluster headaches

Cluster headaches occur almost exclusively in males, and are characterised by recurrent brief attacks of severe, unilateral, periorbital pain, often associated with tear formation and conjunctival injection.

Triptan therapy is the treatment of choice for cluster headaches and has been proven to be effective. Oxygen therapy is an effective second-line therapy, and is indicated in patients who are unable to use triptans, and in those who experience multiple attacks daily.

Ergot derivatives are also effective, but have largely been replaced by triptans.

13.13.4 Postdural puncture headaches

Acute postdural puncture headaches warrant special mention. They may occur after spinal anaesthesia, a spinal tap, block or lumbar puncture. The incidence is higher in younger patients and in pregnancy. These headaches are usually postural in nature, and may be relieved by lying flat. Bed rest does not prevent these headaches, but difficulty with mobilisation is common once the headache has begun.

Preventing this type of headache is preferable to attempting to cure it, and there is a lower incidence of headaches if small-gauge needles are used to perform the puncture, and if the needles are of the non-cutting or non-bevelled type.

A blood patch remains the standard treatment, using 15 ml of the patient's blood, although evidence of efficacy is scanty. A blood patch is contraindicated in sepsis, human immunodeficiency virus (HIV), coagulopathy and malignant blood dyscrasias.

Routine oral analgesic agents (opioid and non-opioid types) provide temporary relief. Caffeine has also been shown to be effective in this regard. IV rehydration is also an important component in the treatment of these patients. Complete resolution of the headache occurs in the vast majority of patients within 10 days.

There is no evidence-based medicine to support the use of triptans, neuraxial opioids, epidurally administered fluids or fibrin glue in these patients.

13.14 Neurological disorders

Acute pain associated with a neurological disorder is often neuropathic in nature, but may have a nociceptive component as well. Neurological origin pain may be acute or chronic, with acute exacerbations. The pain can be peripheral in origin, e.g. peripheral neuropathy, or central in origin, e.g. multiple sclerosis.

Nociceptive pain components, e.g. due to muscle spasm, are treated with routine analgesics. Data are still lacking on the use of muscle relaxants and antispasticity agents, e.g. baclofen.

Neuropathic pain is treated with an array of agents, in different combinations and with differing responses. These regimens have been extrapolated from the treatment of chronic neuropathic pain states with varying success. Tricyclic antidepressants (TCAs), anticonvulsant drugs, membrane-stabilising drugs, N-methyl-D-aspartate (NMDA) receptor antagonists and opioids may be used. Other agents used for neuropathic pain include carbamazepine (for trigeminal neuralgia), various anticonvulsant agents (for pain associated with multiple sclerosis), and TCAs, lamotrigine and gabapentin (for pain following a stroke).

13.15 Acute orofacial pain

Scientific evidence does not exist of a comparison of analgesics used for therapy for pain due to sinusitis or otitis media. Therapeutic decisions derive from the evidence of treating other causes of orofacial pain, such as dental pain.

NSAIDs, coxibs, paracetamol, aspirin, tramadol and codeine are all useful agents in treating acute orofacial pain. Combination preparations are widely and effectively used in these scenarios in South Africa, although various combinations have never been compared in an evidence-based manner. Popular combinations include paracetamol with ibuprofen and codeine, paracetamol with tramadol, and aspirin with codeine.

Other medications commonly utilised are those which provide symptomatic relief from these conditions, and which may augment pain relief secondarily although they are not analgesic themselves. Additional benefits of these agents, i.e. antihistamines, decongestants and beta stimulants, have not been assessed in any trials. Various preparations are available on the market in which these agents are combined with genuine analgesics (paracetamol, aspirin and/or ibuprofen, most commonly), and are actively marketed for the symptomatic treatment of sinusitis and otitis media.

Additional pain relief when treating pharyngitis and tonsillitis may be achieved by adding mouth washes and gargle solutions which contain topical local anaesthetic agents.

Antiseptic and local anaesthetic solutions, pastes, lozenges and gels can provide analgesia in acute oral mucosal ulceration due to trauma, burns, infection or drugs.

13.16 Herpes zoster infection

Acute shingles (herpes zoster infection) is associated with acute, severe pain in the dermatome distribution of the affected nerve roots. Spinal and cranial nerves can be infected by the varicella-zoster virus, and hence are involved in the distribution of severe zoster pain.

Shingles pain may progress to a chronic pain syndrome, called postherpetic neuralgia (PHN), which is pain that persists for more than three months after the onset of the disease. This is common in elderly and immunocompromised patients.

Early management of the zoster infection has been shown to decrease the incidence of PHN developing. Antiviral therapy given early after the onset of the rash, i.e. within three days, has been demonstrated to effectively decrease the duration and severity of the attack. This results in earlier resolution of skin lesions, less pain and a lower risk of PHN developing. Acyclovir, famcyclovir and valacyclovir have all demonstrated efficacy.

Amitriptyline, started at the onset of the disease and continued for 90 days, has been shown to decrease the incidence of PHN developing. Pregabalin and gabapentin have also been shown to be effective in the treatment of PHN.

Corticosteroids have been demonstrated to decrease the acute pain of shingles, but not alter the incidence of PHN developing. They should only be used in combination with an antiviral agent, as their use alone may immunosuppress the patient and aid in dissemination of the infection.

The topical application of aspirin to lesions has been effective in achieving acute pain relief. Topical NSAIDs have not been effective. Systemic aspirin and NSAIDs do not offer effective analgesia.

Anticonvulsants have been ineffectual at decreasing acute zoster pain, but are efficacious in diminishing pain associated with chronic PHN.

13.17 Acute pain in patients with HIV

Pain is a common symptom in people infected with HIV, with the prevalence ranging from approximately 30% in the early stages of infection, to 80% in those with acquired immunodeficiency syndrome (AIDS).

Pain relating to HIV/AIDS may be due to:

- The effects of HIV on the peripheral or CNS.
- Opportunistic infections or neoplasms as a result of immunosuppression.
- *The side-effects of treatment:* Despite the potentially neurotoxic effect of certain antiretroviral (ARV) drugs, the prolonged use of highly active antiretroviral therapy (HAART) has been shown to result in a decrease in neuropathic pain incidence and severity.

13.17.1 Principles of management

The treatment of pain in patients with HIV/AIDS is based on similar principles to those employed in the management of cancer and chronic pain. It has been well documented that pain in HIV patients is frequently undertreated. This needs to be rectified. Multiple clinician-, patient- and system-related barriers to adequate pain management account for this, including underestimation of the patient's pain by the clinician, fear of the analgesic side-effects by both the clinician and patient, and the challenge of polypharmacy in patients who are already using several disease-specific agents.

A meticulous clinical assessment is essential to determine the likely cause of the pain and the most appropriate treatment. HIV infection should be treated with HAART, and an assessment conducted of the associated disease that is complicating the HIV and the pain itself.

Management of the pain must be individualised and directed, depending on the type of pain. Often, HIV-associated pain is neuropathic. The South African clinical practice guidelines for the management of neuropathic pain recommend TCAs, gabapentanoids or serotonin and noradrenaline reuptake inhibitors as first-line therapy for neuropathic pain.

The acute component of the pain can be addressed using the World Health Organization (WHO) analgesic ladder. According to the WHO stepladder approach to pain management, moderate to severe pain should be managed with opioid agents, in addition to non-opioids, such as paracetamol and NSAIDs. Tramadol, morphine and fentanyl are the most frequent opioid agents used. Opioids should be administered by the least invasive and safest route capable of providing adequate analgesia. Adjuvant agents, where appropriate, can be used at any level of the analgesic ladder. These include agents such as antidepressants, anticonvulsants and corticosteroids. Explanation, reassurance and acceptance are of particular importance in the management of acute HIV-related pain, since aspects such as stigma, fear and poor socio-economic conditions frequently aggravate the pain experienced by patients with HIV/AIDS.

Capsaicin and lignocaine patches can also be considered for the management of HIV-associated neuropathic pain. However, at the time of publication these agents were not registered for use in South Africa.

13.17.2 Drug interactions between analgesics and antiretroviral drugs

Drugs which inhibit the cytochrome P450 (CYP) 3A4 enzymes, such as ritonavir, nelfinavir, ketoconazole, itraconazole and clarithromycin, can reduce the clearance of fentanyl and lead to severe respiratory depression. Therefore, ritonavir-treated patients receiving IV bolus fentanyl require longer respiratory monitoring. The doses for those receiving continuous dosing with fentanyl should be reduced.

The ARV drug, ritonavir, also inhibits the CYP2D6 enzyme which is involved in converting tramadol from a prodrug to an active metabolite. The concomitant use of ritonavir with tramadol may lead to the decreased analgesic efficacy of tramadol.

Rifampicin, used in the treatment of tuberculosis, may decrease the analgesic effect of morphine. Increased doses may be required.

13.17.3 Approach to pain in HIV/AIDS

The recommended approach to pain in HIV/AIDS is outlined in Table 1.

Table 1: Recommended approach to pain in HIV/AIDS

Pain in HIV/AIDS	Aetiology	Treatment
Neuropathic pain*	<ul style="list-style-type: none"> HIV HAART: Stavudine and didanosine Isoniazid Cancer Cancer therapy Herpes zoster 	<p>The following are based on their efficacy in providing relief from neuropathic pain due to other diseases:</p> <ul style="list-style-type: none"> TcAs Calcium-channel $\alpha_2\text{-}\delta$ ligands, such as gabapentin or pregabalin SNRIs, such as duloxetine and venlafaxine <p>Lamotrigine is useful as second-line therapy, or for neuropathy associated with ART</p> <p>Patients with acute severe neuropathic pain require rapid pain relief during titration of one of the first-line agents. Oral or parenteral tramadol, or a strong opioid, i.e. morphine or fentanyl, is suggested in this situation, or as second-line therapy</p>
Abdominal pain and headaches	<ul style="list-style-type: none"> Infections and neoplasmas 	Progressively stronger analgesics

Pain in HIV/AIDS	Aetiology	Treatment
Oral and pharyngeal pain	<ul style="list-style-type: none"> • Aphthous ulcers • HSV • CMV ulcers • Acute necrotising gingivitis 	Antibiotics for gingivitis, oral or IV acyclovir, or oral valacyclovir, are used for HSV. A rinse containing benzydamine and topical corticosteroids should be used for minor aphthous ulcers
Genital ulceration	<ul style="list-style-type: none"> • Usually HSV 	Acyclovir or valacyclovir, plus standard analgesia
A stroke (pain relates to muscle spasticity)	<ul style="list-style-type: none"> • Muscle spasms 	Oral baclofen as the first choice, and diazepam and dantrolene alternatively
Brain-related central neuropathic pain	Following a stroke or intracranial neoplasms	TCAs, calcium-channel α_2 - δ ligands and SSNRIs are considered to be first line treatments in the management of this pain Consider IV morphine in acute severe central neuropathic pain
Oesophageal pain and odynophagia	Oesophagitis, most commonly caused by <i>Candida</i> infection <i>Other causes:</i> CMV infection, idiopathic aphthous ulcers, and less commonly, HSV infection	Start with empiric antifungal therapy of fluconazole 200-400 mg daily for 14-21 days, or intravenously in patients who are unable to swallow Upper endoscopy ulcer appearance, biopsy and viral cultures help to make a definitive diagnosis if the pain does not improve Treat HSV with IV acyclovir 15 mg/kg/day, or 200 mg 5 times daily <i>p.o.</i> , provided the patient can swallow, for 14-21 days IV ganciclovir is used to treat CMV, but has many side-effects
Kaposi's sarcoma	Malignancy	Pain medication and radiotherapy
Acute herpes zoster infection**	Herpes zoster	Treat early and aggressively to limit PHN Antiviral therapy, such as acyclovir, valacyclovir or famcyclovir, should be initiated within 72 hours of the onset of pain or rash, together with the aggressive use of analgesics, which may include opioids Consider amitriptyline 25 mg daily for 90 days

* Frequently due to a distal sensory polyneuropathy and comprises burning pain, pins and needles, numbness and allodynia. It begins in both feet and progresses to the legs, with loss of sensory function, and particularly pain and vibration sense.

Neuropathic pain is also due to postherpetic neuralgia

** This is covered under the neuropathic pain section

AIDS: acquired immune deficiency syndrome, ART: antiretroviral therapy, CMV: cytomegalovirus, DSP: distal sensory polyneuropathy, HAART: highly active antiretroviral therapy, HIV: human immunodeficiency virus, HSV: herpes simplex virus, IV: intravenous, *p.o.*: *per os*, PHN: postherpetic neuralgia, SNRIs: serotonin and noradrenaline reuptake inhibitors, TCAs: tricyclic antidepressants

13.18 Acute cancer pain

Acute pain in cancer patients is commonly an acute exacerbation of underlying chronic pain. Acute exacerbations of pain should be treated aggressively and expeditiously. Practitioners should be aware that acute changes in pain levels may signify progression of the underlying disease locally, or in terms of metastases. Every incident should be appropriately investigated and treated.

Cancer patients are frequently on chronic, slow-release opioid maintenance analgesia. The correct management in acute exacerbations of pain is the urgent administration of rapid-release narcotics, repeated every half an hour until complete pain resolution is achieved. Appropriate patient monitoring is required to prevent adverse effects. This is in effect a titration of opioid therapy.

A general guide to proper analgesia for cancer patients is to use increments of the analgesic dose equal to one-sixth of the usual daily maintenance opioid requirement. IV fentanyl is the standard therapy in this scenario, and is effective and reliable.

Nausea and vomiting are common in this situation and antiemetic therapy should be routinely considered. Serotonin inhibitors, such as ondansetron and granisetron, are effective. Small-volume morphine delivered parenterally (via injection) is also available, which includes a combination antiemetic, i.e. cyclizine (Cyclimorph®).

For a more detailed discussion and explanation of cancer pain management, the reader is referred to the *Guide to the treatment of cancer pain in South Africa 2015*. Blanchard C, Chetty S, Ganca, et al. Figshare [homepage on the Internet]. c2015. Available from: <http://dx.doi.org/10.6084/m9.figshare.1612170>

13.19 Specific patients with medical conditions

13.19.1 Respiratory patients, including asthmatics

The practitioner must be wary of using analgesic agents which may cause respiratory depression in patients who have respiratory (restrictive or obstructive) disease. Potent narcotic opioids are the agents that are most dangerous in these patients.

It is assumed that the IV administration of opioids is the most risky, and this is especially true if large or repeated doses are given. This risk increases in elderly patients.

With proper monitoring and supervision, IV administration is the safest way to give potent opioids. This allows the careful titration of dosing under direct clinical supervision, and also monitoring of the clinical response and side-effects. IV opioid titration provides the most consistent and predictable dose needed to maintain the serum blood level.

All other modes of opioid administration have a variable absorption rate, which varies according to the individual and according to a host of other factors, e.g. BMI, time of the last meal, the activity level after administration and concomitant medications. These result in variations in the duration of onset of action, efficacy and adverse effects. The half-life and hence duration of activity may also vary in different patients according to similar parameters, e.g. volume of distribution and organ function.

The asthmatic

Avoiding precipitating or exacerbating acute bronchospasm is of particular importance when managing acute pain in asthmatic patients. Aspirin and nonselective NSAIDs should be avoided in asthmatic patients. These agents may precipitate bronchospasm directly or via cross-allergy, which is not uncommon.

Aspirin may directly induce an acute severe asthmatic attack. Cross-hypersensitivity has been reported with respect to almost all nonselective NSAIDs. The sensitivity appears to relate to COX-1 inhibition, and the less selective the COX-1, the less the risk of inducing asthma.

Selective coxibs have also been reported to occasionally induce bronchospasm, but the risk is far lower. These agents should be used preferentially in asthmatic patients when NSAID therapy is deemed necessary.

Paracetamol has rarely been reported to cause bronchospasm in these patients, and represents the safest overall option of all COX-inhibiting agents.

Opioids should also be avoided, whenever possible, in asthmatic patients. Morphine, codeine and tramadol have all been reported to induce acute asthma or worsen current bronchospasm.

Hypersensitivity and bronchospasm relate to the histamine release which often accompanies opioid administration. This is common. Thus, opioids should only be used in asthmatic patients when truly justified. Antihistamine premedication (diphenhydramine) may attenuate the response and should be given, when possible.

Sensitivity to opioids appears to be class specific within opioids as a group. Phenanthrenes (morphine, codeine and dihydrocodeinone) are the most common causes thereof, followed by phenylpiperadines (fentanyl and pethidine). Patients who react to these drugs may still tolerate phenylheptanes (propoxyphene). However, alternate classes should be trialled cautiously. Propoxyphene is currently not available in South Africa. True major allergy and anaphylaxis to opioids is rare in all patients.

Regional and neuraxial blockade, where possible, are useful tools in asthmatic patients undergoing surgery, and in those who sustain an injury.

Ketamine, an NMDA receptor antagonist, which has an analgesic effect, can be useful in asthmatic patients owing to its bronchodilatory effects.

13.19.2 Cardiac patients

NSAID drugs should be used cautiously in cardiac patients. Paracetamol represents the only truly safe COX-inhibiting agent in these patients.

NSAIDs are known to exacerbate hypertension in certain patients and to diminish the efficacy of certain antihypertensive medication. NSAIDs may exacerbate known hypertension or unmask previously unknown, borderline, new-onset cases.

Loop diuretics and thiazide diuretics may have diminished efficacy with the concomitant administration of NSAIDs.

Recently, considerable attention has focused on the negative cardiac effects of coxibs. Several agents [valdecoxib (Bextra®)] were withdrawn from the South African market because of these concerns. It appears that true selective COX-2 inhibition with minimal COX-1 activity increases the cardiac risks of these agents. This is mainly in hypertensive, ischaemic and cardiac failure patients, and predominantly in the elderly. It was demonstrated in the Multinational Etoricoxib Versus Diclofenac Arthritis Long-Term Study (MEDAL)

study that coxibs had the same risk profile as nonselective NSAIDs with regard to thrombotic cardiovascular events. Therefore, coxib cardiac risks are similar to those of other nonselective NSAIDs in non-hypertensive patients.

NSAIDs may also worsen other vascular pathologies which are common in cardiac patients. They may occasionally precipitate a stroke in patients with cerebrovascular disease, may cause deterioration in renal function in renal vascular (atherosclerotic or hypertensive) disease, while prostaglandin inhibition can worsen critical ischaemic peripheral vascular disease.

Opioids are generally safe in cardiac patients, except in those at risk of their blood pressure dropping. The careful titration of IV opioids is advocated in severe pain in these patients in order to avoid hypotension.

Caution is required with respect to analgesia given to patients on concomitant anticoagulation therapy.

Aspirin and NSAIDs should be avoided in patients on other anticoagulant therapies because they have their own cumulative anticoagulant effect. This includes:

- Oral clotting factor inhibiting agents, i.e. warfarin (Coumadin®).
- Injectable heparins, including newer low-molecular-weight heparins.
- The novel oral anticoagulants, i.e. dabigatran.
- Oral antiplatelet agents, i.e. dipyridamole (Persantin®).
- Glycoprotein IIIa/IIb inhibitors, i.e. clopidogrel (Plavix®).

Opioids are generally safe in patients on anticoagulants, as are coxibs and paracetamol, providing cardiac risk factors are not present.

NSAIDs and aspirin should also be avoided in patients on thrombolytic therapy, owing to the increased risk of major haemorrhage. This includes patients on streptokinase, urokinase or tissue plasminogen activator (Actalysse®).

13.19.3 Analgesia in the presence of liver and kidney dysfunction

The liver and kidneys are central to the metabolism and excretion of drugs. The main role of the liver is converting lipid-soluble analgesic and antihyperalgesic drugs into a more soluble form for renal, or less commonly, biliary, excretion. Thus, liver failure tends to result in the accumulation of the unmetabolised drug.

The kidney plays a limited role in the biotransformation of drugs, but a major role in the excretion of both metabolised lipid-soluble drugs and non-metabolised, water-soluble drugs. Thus, kidney failure tends to result in the accumulation of water-soluble hepatic drug metabolites which are occasionally more active than the parent compound.

Organ system failure changes the composition of the body's fluid compartments with consequent alterations in the drug pharmacokinetics, particularly on initial administration.

Principles of analgesic and antihyperalgesic prescription with organ failure are as follows:

- *Define the pain experienced:* This refers to the likely aetiology, nociceptive versus neuropathic, intensity, duration, and response to previous therapy.
- *Quantify the degree of organ dysfunction:* Kidney (urine output, serum creatinine and creatinine clearance) and liver (Childs-Pugh score).
- *Review current medications:* This is to avoid interactions between the pain-relieving drugs to be prescribed and the medication that the patient is already taking.
- *Select appropriate analgesics and antihyperalgesic agents:* The use of these results in minimal metabolism with the inactive metabolites, organ-independent elimination, limited drug interactions, and short duration of action
- *Start low and go slow:* Commence pain therapy with the lowest effective dose, and escalate over weeks, rather than days.
- *Monitor:* Monitor the response to therapy with downward titration or withdrawal, if possible; the occurrence of side-effects with prophylaxis, if predictable; and the progression of organ failure.

Liver failure

Paracetamol

The recommended dose of paracetamol of no more than 20 mg/kg (1 g in adults) as a single dose, and no more than 80 mg/kg (4 g) in a single day, should be reduced by at least 20% in the presence of clinically detectable liver failure.

IV paracetamol is preferred in the postoperative setting as liver exposure is reduced by 80%, compared with oral or rectal dosing, where 100% of the administered paracetamol has to pass through the liver before reaching the systemic circulation.

NSAIDs (including coxibs)

Aspirin has been associated with Reye's syndrome, which includes liver damage, leading to the recommendation that aspirin should be withheld from infants and children.

Liver failure may be precipitated by NSAIDs owing to genetically determined variations in the hepatic metabolism.

Diclofenac hepatocyte toxicity, as well as cholestasis with sulindac, has been described. Lumiracoxib was withdrawn after reports of hepatotoxicity following clinical release.

Nonselective NSAIDs and coxibs are relatively contraindicated in liver failure because of the reduced intravascular volume in cirrhotic patients. The administration of a nonselective NSAID or coxib is likely to result in the development of renal failure and/or the precipitation of hepatorenal syndrome.

Nonselective NSAIDs have the added disadvantage of platelet inhibition, which, together with the defects in the clotting cascade owing to impaired factor synthesis, can precipitate bleeding.

Opioids

Severe liver failure results in a reduction of the conversion of opioids to their water-soluble metabolites, with accumulation of the administered opioid. The dose of the opioid should be reduced and the dose interval prolonged in established liver failure.

Tramadol and buprenorphine have theoretical advantages in liver failure owing to their lack of active metabolites and limited potential to cause respiratory depression.

Codeine is not converted into active metabolites in liver failure so is ineffective. Pethidine should not be used in liver failure because of unpredictable metabolite levels. The active metabolite of oxycodone, oxymorphone, accumulates in moderate to severe liver failure.

Adjuvant drugs

Manufacturers recommend that clonazepam and sodium valproate should be avoided, and that dosages of fluoxetine, lamotrigine, valproic acid, venlafaxine, tramadol, topiramate and duloxetine should be reduced, in liver failure.

Amitriptyline is hepatically metabolised so will persist for a long period. Gabapentin and pregabalin are excreted unchanged in the urine. Thus, they are unaffected by changes in liver function.

Kidney failure

Paracetamol

Paracetamol, unlike phenacetin, does not cause renal failure when taken at recommended doses for ≤ 3 months. Prolonged exposure at doses which exceed recommendations has been associated with the development of renal failure. Paracetamol remains the foundation of the WHO pain ladder in established renal failure, with no requirement for a dose adjustment.

NSAIDs (including coxibs)

NSAIDs can precipitate renal failure, particularly in hypovolaemic patients, and thus should be avoided in patients with renal dysfunction who do not require dialysis, particularly when creatinine clearance is ≤ 30 ml/minute.

However, NSAIDs may be used in established chronic renal failure where patients are already on dialysis, particularly for postoperative pain and soft tissue injury. Coxibs are preferred as they do not affect the platelets. Thus, they are unlikely to cause bleeding complications in the face of uraemic platelet dysfunction and the requirement for anticoagulation during dialysis.

Opioids

Opioids are converted to water-soluble metabolites in the liver to be excreted in the urine.

The two most common metabolites are:

- *Demethylation to the nor-metabolite:* These may be toxic (norpethidine) and reduce seizure threshold, thus predisposing to seizures.

- *Glucuronidation:* The resulting metabolites are commonly inactive. However, morphine-6-glucuronide is more potent than morphine, has better CNS penetration and a longer half-life.

Buprenorphine, oxycodone and tramadol are preferred in renal failure because they lack active metabolites and have limited potential to cause respiratory depression.

If more potent opioid analgesia is required, oxycodone is preferred to morphine because the active metabolite of oxycodone, oxymorphone, is hepatically metabolised, and has the same duration as oxycodone, independent of renal function. Oxycodone is not available in state practice, so morphine is still going to be used. The drug should be titrated to effect with a dose reduction and an extension of the dosage interval. Sufentanil may be used in PCA devices or inpatients, particularly postoperatively, in preference to morphine, as Sufentanil has no active metabolites and does not have the same propensity to cause hyperalgesia as fentanyl.

Adjuvant drugs

The nor- and glucuronide metabolites of amitriptyline and the other TCAs accumulate in renal failure and may contribute to excessive sedation and arrhythmias.

Both gabapentin and pregabalin are excreted unchanged via the kidneys, and thus also accumulate in renal failure. Carbamazepine undergoes hepatic metabolism with inactive metabolites, so a dosage adjustment is not required in renal failure.

Experience with newer drugs such as venlafaxine and duloxetine is limited, but the principle of starting at the lowest dose likely to be effective, and only titrating upwards in the absence of side-effects, should be applied.

13.20 Acute pain management in the patient with obstructive sleep apnoea

Mild obstructive sleep apnoea (OSA) affects one in five people, whereas moderate to severe OSA affects one in 15 people. Anaesthesia in the presence of OSA presents a multidimensional problem, and analgesia is just as challenging, particularly as OSA is often undiagnosed in many patients requiring pain relief.

Available evidence on the risks of opiates in patients with OSA is limited. Nevertheless, in many cases when complications occur in these patients, opiates appear to be a common factor, together with inadequate appropriate monitoring. To date, opioids and non-opioid techniques have not been compared in studies on patients with obstructive sleep apnoea.

Therefore, the recommendations for pain management in patients with OSA are as follows:

- Preferably, the patient should be managed in a high dependency area, with appropriate monitoring, such as capnography and sedation levels (not just respiratory rate monitoring).
- Supplemental oxygen is recommended, and not continuous positive airway pressure (CPAP) necessarily, unless the patient has severe OSA and is being managed with CPAP.
- Opioid-sparing analgesia techniques are recommended. Thus, non-opioid multimodal therapy is advocated, including local and regional techniques.

13.21 Analgesic options for patients with opioid tolerance

Opioid analgesics are used extensively in the treatment of acute, chronic, cancer and non-cancer pain. Opioids provide excellent pain relief, but may provide insufficient analgesia in a small but significant number of patients. Prior exposure to an opioid, particularly as a sole analgesic agent, is the major risk factor for inadequate opioid analgesia, and results in tolerance.

Tolerance may be a result of:

- Alterations in G-protein coupling to the opioid receptor.
- Changes in receptor trafficking between the neuronal surface and cytoplasm.
- An increase in the number and sensitivity of NMDA receptors as a result of central sensitisation.

Tolerance is only seen in a small proportion of patients (< 5%) who receive opioids, but any or all of the previously mentioned mechanisms may be active in these patients.

13.21.1 Perioperative analgesic adjuvants

In addition to ketamine and the alpha 2 agonists, a number of other drugs have demonstrated promise in providing effective analgesia to opioid-tolerant patients, or providing opioid-free analgesia should this be required, e.g. to recovering addicts and those who are morbidly obese.

These drugs have been studied in unselected populations, where efficacy has been variable owing to the profound effects of opioid analgesia in opioid-naïve patients.

Gabapentin and pregabalin are inhibitors of voltage-gated calcium channels containing the $\alpha 2\delta$ -1 subunit, with demonstrated efficacy in the management of chronic neuropathic pain. These drugs have been used at doses of 400–1200 mg twice daily (gabapentin) and 75–300 mg twice daily (pregabalin) in the perioperative period.

They should be continued for the duration of the surgical pain stimulus, i.e. 10–14 days, but are usually given only until the patient starts mobilising. Dizziness is a major side-effect of both drugs when given at effective doses. This limits mobilisation.

TCAs provide sedation superior to that provided by the benzodiazepines, which may be useful for night sedation and premedication, if required. TCAs are also excellent secondary analgesics by the augmentation of descending inhibition of pain transmission by serotonin and noradrenalin. Anticholinergic side-effects may be troublesome, especially in fasting patients.

Dexamethasone, a potent glucocorticoid, is recognised as an antiemetic at a dose of 0.05 mg/kg. There is now good evidence that a higher dose of 0.1 mg/kg also provides significant pain relief.

Lignocaine may be given systemically at a dose of 1 mg/kg + 1–2 mg/kg/hour. The sodium-channel blockade provided by lignocaine provides excellent pain relief, and also preserves or possibly enhances bowel function after abdominal surgery.

Magnesium, a physiological calcium antagonist, may be given at a similar dose to that used in pre-eclampsia, i.e. 30 mg/kg + 10–15 mg/kg/hour. The aim should be to maintain levels of 2–3 mmol/l. Magnesium requirements are markedly reduced with renal dysfunction.

Mulier (Belgium) describes a technique for opioid-free anaesthesia for bariatric surgery using the following combination: 1 litre saline + 100 mg ketamine + 100 µg dexmedetomidine + 100 mg lignocaine + 5 g magnesium. It should be run at 12 ml/hour via a mechanical PCA pump or elastomeric infusion pump (<http://www.publicationslist.org/jan.mulier>).

This technique has been used successfully by anaesthesiologists in Pretoria.

13.21.2 Management of opioid tolerance (multimodal approach)

Antihyperalgesic drugs

Patients with acute or chronic pain deemed to be nociceptive or inflammatory in nature will benefit from the institution of paracetamol and a NSAID that is appropriate to the patient in the absence of contraindications.

Patients who have not previously been assessed by clinicians familiar with chronic pain are commonly treated with opioids alone or with NSAIDs. There is often an element of neuropathic pain in a patient with chronic pain that will need to be addressed by appropriate adjuvant drugs, as discussed in appropriate sections of this guideline and summarised briefly as follows:

- *TCAs*: Amitryptiline 10–75 mg at night.
- *Anticonvulsants*: Gabapentin 100–1 200 mg divided into four daily doses; pregabalin 150 mg - 300 mg divided into two daily doses daily; or clonazepam 0.5–3.0 mg twice daily.

Regional blocks

The addition of a regional block should be considered. This approach is particularly useful in the perioperative period when neuraxial, regional or nerve blocks can be employed. Continuous wound infiltration is possible as at least two wound infiltration catheters are now available in South Africa.

Neuraxial opioids should not be used in patients receiving systemic opioid therapy. However, systemic opioids should be continued.

A small subgroup of patients may benefit from the implantation of a continuous epidural or spinal catheter which can be refilled once they are outpatients. These patients need to be managed under the supervision of a pain specialist who is familiar with the technique.

13.21.3 Additional opioid medication

Additional opioid medication may be necessary. Patients should continue on their usual dose of opioid by the usual route. However, if oral administration is not possible, particularly perioperatively, systemic administration is required. This may be given transcutaneously by means of an opioid patch, which avoids the need for an infusion device, or subcutaneously using a continuous infusion, which may be administered using a mechanical or disposable infusion device. IV administration may be used in the perioperative period, particularly if a central line has been placed.

Opioid “resensitisers”

Opioid rotation may be necessary. There are significant differences in the interaction between different mu agonists and the mu receptor which go beyond the effect on second messenger systems after binding, and include the rate of receptor trafficking, and possibly even effects on receptor synthesis affinity. In view of this, a patient experiencing inadequate analgesia from one opioid drug may be switched to slow-release morphine, or oxycodone. Transdermal fentanyl should be avoided due to the likely development of hyperalgesia. A switch back to the previous drug may prove effective should analgesia on the new drug become inadequate over time.

A patient on maintenance opioids for chronic pain in the perioperative setting should be managed with a different opioid for perioperative analgesia.

Ketamine

NMDA receptors are central to the pathogenesis and maintenance of chronic pain states. Chronic upregulation of the NMDA receptors is one of the best accepted mechanisms for tolerance to opioids. The administration of low-dose ketamine to patients with inadequate opioid analgesia has been shown to restore opioid sensitivity for a prolonged period. Doses demonstrated to be effective are as follows:

- *Perioperative dose:* 0.5 mg/kg on induction, repeated 30 minutes prior to estimated emergence from an operation lasting for ≥ 2 hours.
- *PCA:* Ketamine may be mixed with an appropriate opioid at a concentration of 1–3 mg/ml. For example, ketamine 100 mg + morphine 100 mg in 50 ml with saline, given as a 1 ml bolus, with a 10-minute lockout; or fentanyl 2.5 mg + ketamine 250 mg in 50 ml with saline, given as a 1 ml bolus, with a 10-minute lockout.
- *Oral:* Ketamine undergoes extensive first-pass metabolism so a dose of 5 mg/kg is required for the drug to be effective. A typical mixture is morphine 5 mg/ml with ketamine 10 mg/ml, given as a dose of 5 ml, 1–4 hourly, as needed.

Alpha 2 agonists

The activation of alpha 2-receptor agonists results in hyperpolarisation of the presynaptic neurons involved in pain transmission. This reduction in input to the dorsal horn and thalamus results in improved analgesia. Alpha 2 agonists provide analgesia independent of the opioid receptors by facilitating the descending inhibition of pain transmission mediated by noradrenalin from the periaqueductal grey matter and nucleus *raphe magnus*.

Both clonidine and dexmedetomidine are effective adjuvants to neuraxial anaesthesia. Dexmedetomidine is also effective when administered systemically as a component of a multimodal PCA regimen as follows:

- Dexmedetomidine 200 μ g + ketamine 250 μ g + fentanyl 2.5 mg + granisetron 3 mg, dosed with a 1 mg bolus and 10-minute lockout.
- Dexmedetomidine 200 μ g + ketamine 250 μ g + morphine 500 mg + granisetron 3 mg, dosed with a 1 mg bolus and 10-minute lockout.

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