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GUIDELINE

Acute pain guidelines

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.

Acknowledgements

The authors acknowledge being granted access to the following document as one of the primary references for these guidelines: *Acute Pain Management: Scientific Evidence 2015,* published by

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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:

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

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

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 Aδ 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 phe-

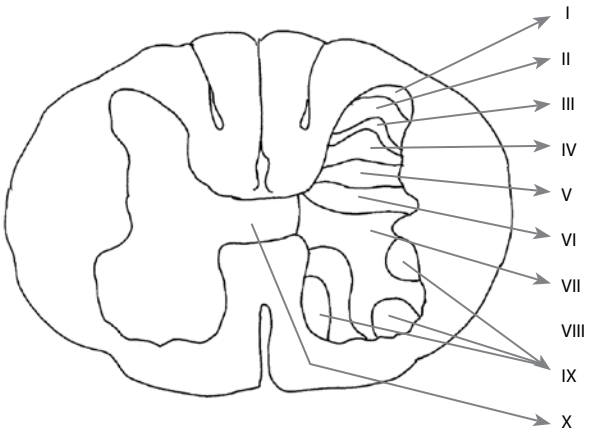


Figure 1: Laminae in the dorsal horn

nomenon of wind-up and temporal summation. 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 rhisotomy).

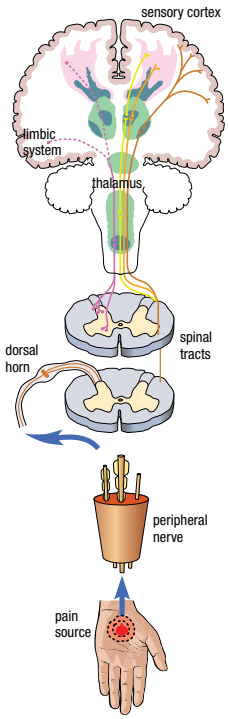


Figure 2: Basic afferent pain pathway

Collateral branches of the small fibres Aδ 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), glycin 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 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 spinomesencephlic 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.

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	HI	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, PGE_2: prostaglandin 2, $PG1_2$: prostacyclin, TRP: transient receptor potential

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 glucoronide, which antagonises opioid analgesia.

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

GABA and the gylcine 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 clonidin). 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.

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

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.

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.

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 lypolysis
Water and electrolytes
Water retention
Potassium loss

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

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 adrenocorticotropic hormone, cortisol, antidiuretic hormone, cathecolamines, 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.

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 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.

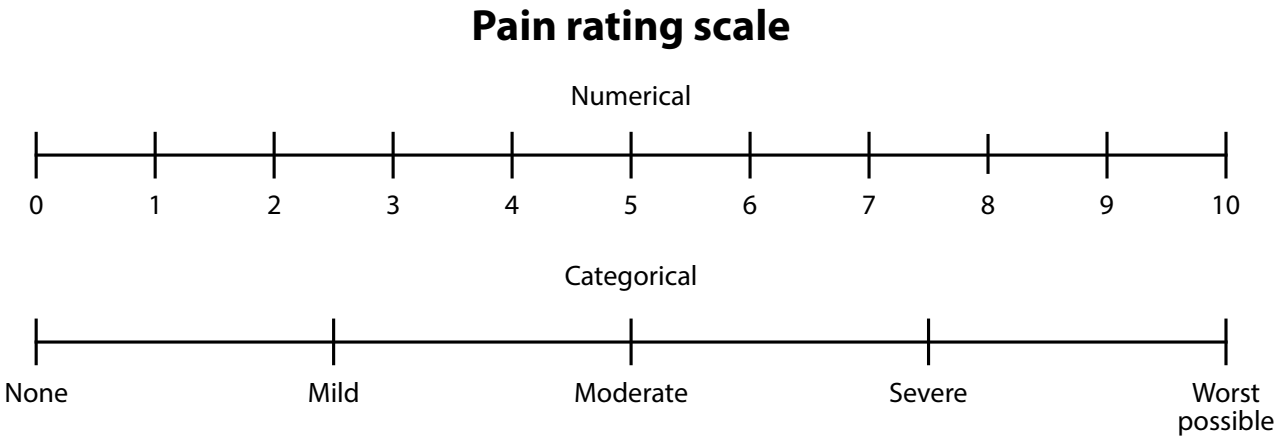


Figure 1: Pain rating scale

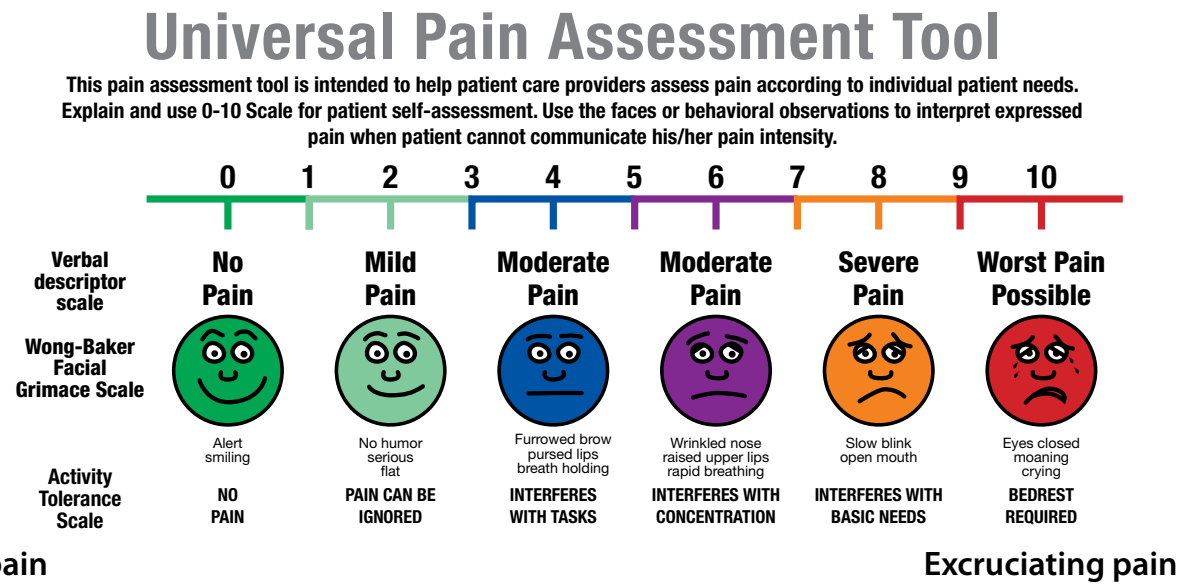


Figure 2: A universal pain assessment tool

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.

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

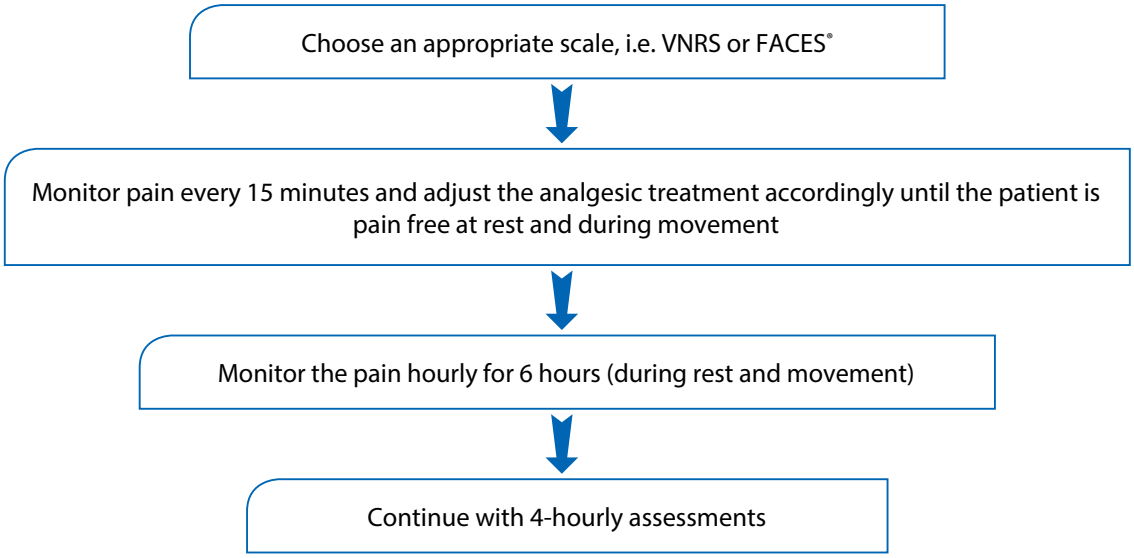
"Smiling" is characterised by upturned corners of the mouth, brightening of the eyes and a look of pleasure or contentment. Inexpressive refers to a neutral, at ease, relaxed or blank look.

"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.

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	



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

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

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.

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 • SRM-Rhotard® • MST Continus® • Merck Morphine Sulphate® • Micro Morphine injection® • Morphine Sulphate-Fresenius® *Combination:* Morphine + cyclizine = cyclimorph	**Oral** 10-20 mg q 12 hourly **IM** 0.1-0.3 mg/kg q 4 hourly **IV** *Bolus:* 1-5 mg q 1 hourly* *Infusion*:* 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 unit[2]) *PCA* Bolus 1–2 mg, with 5-10 minutes lockout time *Neuraxial*	Use[1]	• 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 naivity • Infusions may readily cause excessive accumulation of the drug with respiratory depression, and if undetected, death • PCA is a safer option[3] • 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 administration[4] • 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 drugs[6]

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 **PCA** 10–20 mg bolus with 5–10 minute lockout	Use[1]	• 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 SSRIs[6]
Papaveratum • Omnopon-Fresenius®	**IM** 0.15 mg q 4 hourly		• Not for children aged ≤ 1 year
Dihydrocodeine tartrate • DF- 118®	**Oral** 30 mg q 4–6 hourly **IM** 25-50 mg q 4–6 hourly	Use[1]	• Not for children aged ≤ 4 years • 30 mg of DF-118® exhibits comparative analgesia to 10 mg morphine • May worsen asthma
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		• For moderate to severe pain
Propoxyphene • Doloxene®	**Oral** 65 mg (1 capsule) q 4 hourly *p.o.* to a maximum of 390 mg/day		• For mild to moderate pain • Low-affinity agonist
Codeine • Lennon-Codeine Phosphate	**Oral** 15–60 mg daily *p.o.*	Use[1]	• Mild to moderate pain • Low affinity agonist • May not have any analgesic activity, but 10% is demethylated to morphine, and this is probably active[6]

Oxycodone • Oxycontin® • Oxynorm®	**Oral** *Oxycontin tablets (sustained release):* 5 mg, 10 mg, 20 mg and 40 mg, depending on the severity of the pain Start with 5–10 mg *p.o.* bd in an opioid-naïve patient *Oxynorm:* 5 mg, 10 mg, 20 mg for severe postoperative pain Start with 5 mg *p.o.* q 4–6 hourly	Use[1]	• 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 failure[6]

bd: twice daily, PCA: patient-controlled analgesia, *p.o: per os*, IM: intramuscular, IV: intravenous, MAOIs: monoamine oxidase inhibitors, SSRIs: selective serotonin reuptake inhibitors, Use[1]: 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** *Tablets*: 50 mg q 6–8 hourly. May increase to 100 mg for 2 doses only. *Drops:* 10–20 drops q 6–8 hourly	UWECO[1]	• Not for infants aged ≤ 1 year • For moderate to severe pain • 1 drop = 2.5 mg[7] • 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
Pentazoncine • Pentazozine-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]	• 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 children[8]
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]	• 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 deep[9]

Avoid[1]: Unsafe, IM: intramuscular, IV: intravenous, MAOI: monoamine oxidase inhibitor, SL: sublingual , UWC[1]: Use with caution, UWECO[1]: Use with extreme caution; may be unsafe

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

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]	• May cause pulmonary oedema if the entire calculated dose is rapidly administrated • 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 naloxone[10]

IV: intravenous, Use[1]: 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 • Tramal® • Dolotram® • Tramahexal®	**Oral** • *Capsules:* 50-150 mg q 4–6 hourly to a maximum of 400 mg/day • *SR tablets:* 100-150 mg q 12 hourly • *Drops:* 100 mg = 1 ml = 40 drops. Start with 20 drops and titrate up, if necessary. Do not exceed 400 mg/24 hours **Rectal** 100 mg/suppository. Do not exceed > 400 mg/24 hours **IV/IM** • 100 mg IM • IV administration must be slow	Use[1]	• Not for children aged ≤ 12 years • Avoid using 5-HT_3 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 • *Therapeutic range:* Moderate to severe pain[6]

5-HT_3: 5-hydroxytryptamine, IM: intramuscular, IV: intravenous, SR: slow release , SSRIs: selective serotonin reuptake inhibitors, Use[1]: 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 • Adco-Paracetamol® • Antalgic® • Fevamol® • Go-Pain P® • Pacimol® • Painamol Be Tabs® • Panado® • Prolief® • Tylenol®	**Oral** (500 mg) tablet • 0.5–1.0 g q 4 hourly to a maximum of 4 g/day	Use[1]	• Not recommended for children aged ≤ 3 months Mild to moderate pain only
• Tylenol® Extended Release	2 capsules q 8 hourly, to a maximum of 6 capsules/24 hours	Use[1]	• Do not crush, chew or dissolve the extended-release capsules
• Varipan®			
Oral (paediatric syrup) • Adco-Paracetamol® • Antalgic® • Calpol GSK® • Go-Pain® • Napamol® • Painamol® • Panado® • Pyradol®		Use[1]	
• Empaped®	**Rectal** N/A	Use[1]	• Rectal absorption is inconsistent • Beware of renal and liver disease
• Parenteral • Perfalgan® • Paraspen®/Kabimol®	**IV** *Adults (≥ 50 kg):* 1 g q 6 hourly to a maximum dose of 4 g/24 hours		• 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 formulations[11] • **Do not administer other oral paracetamol concomitantly. Beware of combination analgesics which may contain paracetamol** • An inadvertent overdose should be urgently treated with N-acetylcystine.

IV: intravenous, NA: not applicable, Use[1]: 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 • Bayer Aspirin® • Be Tabs Aspirin® • Disprin® • Ecotrin® • Myoprin®	**Oral** 300–900 mg q 4–6 hourly to a maximum of 4 g daily	Use[1]	• Associated with Reye's syndrome • Use with caution in the elderly, in cases of poor renal function and when there is gastric bleeding
Diclofenac[12] • ACU-Diclofenac® inj • Adco-Diclofenac® • Austell-Diclofenac® Sodium • BE-TABS Diclofenac® inj • Cataflam D® • Dicloflam® • Diclohexal® • Diclohexal-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]	• 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 • *IM injections:* 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 prostacylin 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** *Drops (only Voltaren®)* 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		
Ibuprofen13 • 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]	• Beware of gatrointestinal 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]	• 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]	
Ketorolac[14] • 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]	• 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 • Adco-Mefenamic Acid® • Fenamin® • Ponac® • Ponstan® • Ponstel® • Sandoz Mefenamic Acid®	**Oral** 500 mg q 8 hourly		• Do not administer for ≥ 5 days • Not for children aged ≤ 6 months or weighing < 10 kg
Lornoxicam • Xefo®	**Oral** 8–16 mg/day, in 2–3 divided doses		• Not for children aged ≤ 18 years
Naproxen • Adco-Naproxen® • Aleve® • Aspen Naproxen® • Merck-Naproxen® • Nafasol® • Napflam® • Rolab-Naproxen® • Synflex®	**Oral** 500 mg q 12 hourly	Use[1]	• 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 hydantoins, anticoagulants and sulphonylureas • For mild to moderate pain[15]
Piroxicam • Adco-Piroxicam® • Brexecam® • CPL Alliance Piroxicam® • Pixicam® • Pyrocaps® • Rheugesic® • Rolab-Piroxicam® • Sandoz-Piroxicam® • Xycam®	**Oral** 20–40 mg daily		• Not recommended in children • The usual concerns with NSAIDs apply • Caution must be excercised in cases of hepatic insufficiency • The long half-life may be given as a single daily dose • For moderate pain
Sulindac • Adco-Sulindac®	**Oral** 100–200 mg q 12 hourly, to a maximum of 400 mg/day		• Caution should be taken in cases of renal and hepatic insufficiency, gastrointestinal bleeds and asthma
Tenoxicam • Tilcotil®	**Oral** 20 mg daily **IV/IM** 20 mg daily for 1–2 days only		• Parenteral use

COX: cyclo-oxygenase, IM: intramuscular, inj: injection, IV: intravenous, NSAIDs: nonsteroidal anti-inflammatory drugs, Use[1]: Safe, UWECO[1]: 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)

Drug	Means of administration and dosage	Use in porphyria[1]	Relevant information
SELECTIVE COX-2 INHIBITORS			
Meloxicam • 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]	• 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 • Celebrex®	**Oral** 100–200 mg q 12 hourly, to a maximum of 400 mg/day	Use[1]	• 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 • Rayzon®	**IV/IM** 40 mg q 6–12 hourly IV/IM, to a maximum of 80 mg/day		• Not for children aged ≤ 18 years • Contraindicated if there is a sulphonamide allergy
Etoricoxib • Arcoxia®	60mg osteoarthritis daily 90mg Rheumatoid arthritis daily 120mg Acute gouty arthritis daily		• 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 anatagonists)

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]	• *Side-effects:* 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]	• Concern regarding the potentiation of muscle relaxation • Decrease in the blood pressure, but easy to manage
Nitrous oxide • Entonox®	**Oral** N_2O 50%/O_2 50%	Use[1]	• 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 • Benylin Original® • Benylin Dry Cough® • Benalin®	**Oral** 45 mg *p.o.* preoperatively	Use[1]	• Use pre-emptively preoperatively • Said to decrease the use of other analgesics post tonsillectomy in adults • Usually only prescribed with the premedication

N_2O: nitrous oxide, NMDA: N-methyl-D-aspartate, O_2: oxygen, PCA: patient-controlled analgesia, *p.o.*: *per os*, Use[1]: Safe

5.6 α2 agonists

Table 6 details the relevant information on α2 agonists.

Table 6: Relevant information on α2 agonists

α2 AGONISTS			
Drug	**Means of administration and dosage**	**Use in porphyria[1]**	**Relevant information**
Clonidine	**Oral** 2.5 µg/kg as premedication **IV** 2.5 µg/kg slow injection **Epidural/caudal** 2–10 µg/kg epidurally in 10 ml saline		• Premedication - Sedation - Pre-emptive analgesia • Partial agonist, therefore hyper- or hypotension may manifest • Bradycardia may be problematic
Dexmedetomidine[17]	**IV** *LD:* 1.0 µg/kg slowly over 30 minutes *MD:* 0.2–0.7 µg/kg/hour		• 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% • Renucaine®	**Toxic dose** • *Without adrenaline:* 5 mg/kg • *With adrenaline:* 7 mg/kg • *For mucous membranes:* • 9 mg/kg		• 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 • Microbupivacaine® • Macaine®	**Toxic dose** 2 mg/kg		• 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 • Chirocaine®	**Toxic dose** 2 mg/kg		
Ropivacaine • Naropin®	**Toxic dose** 2 mg/kg		

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