Guidelines for the management of acute pain in specific scenarios

2022
## CONTENTS

1. Foreword .............................................. 1
2. Introduction ........................................ 4
   List of acronyms...................................5
3. The physiology of acute pain .............11
   3.1 Definitions ...................................... 11
   3.2 Understanding nociceptive pathways .............. 12
       3.2.1 Primary afferent fibres .......................13
       3.2.2 Dorsal horn.............................................14
   3.3 Neurotransmitters .............................. 14
       3.3.1 At the periphery ...................................14
       3.3.2 Dorsal horn.............................................14
   3.4 Intracellular events .............................15
   3.5 Receptors and ligands ........................15
   3.6 Nociceptive pathways .........................16
       3.6.1 Ascending pathways ..........................16
       3.6.2 Descending inhibition .......................17
       3.6.3 Neuropathic pain .................................18
   3.7 Receptors ............................................. 18
       3.7.1 Opiate receptors .................................18
       3.7.2 GABA and the glycine receptors ...19
       3.7.3 Adrenoreceptors ..................................19
       3.7.4 N-methyl-D-aspartic acid receptor 19
       3.7.5 Transient receptor potential receptors.............................................19
   3.8 Autonomic nervous system .............20
   3.9 Psychological aspects of acute pain .............20
   3.10 The progression of acute to chronic pain .............................................20
   3.11 Adverse effects of pain .......................21
4. Assessment of acute pain ...................22
   4.1 Introduction ........................................ 22
   4.2 Pain measurement tools .....................22
       4.2.1 Pain history ............................................22
       4.2.2 Visual analogue scale ..........................24
       4.2.3 Numerical rating scale ........................25
   4.3 Measurement considerations in special populations .......... 27
       4.3.1 The Wong-Baker FACES pain scale.............................................27
       4.3.2 The pain assessment in advanced dementia ....................................27
       4.3.3 The behavioural pain scale.............................................27
   4.4 Monitoring guidelines .........................28
5. Drug listing – enteral and parental ... 30
   5.1 Opioids – mainly for severe pain ...... 30
   5.2 Paracetamol ......................................... 35
   5.3 Nonsteroidal anti-inflammatory drugs for mild to moderate pain relief .............................................36
   5.4 Approach to oral combination analgesics .............38
   5.5 Local anaesthetics.................................41
6. Paediatric guidelines .........................44
   6.1 Principles of pain management in children .........................44
   6.2 The neurobiology of pain ..................44
       6.2.1 Postoperative pain ..........................45
       6.2.2 Procedural pain ..................................45
   6.3 Pain assessment in children .............45
       6.3.1 Pain history ............................................45
       6.3.2 Pain behaviours ......................................45
6.3.3 Pain assessment tools ......................47

6.4 Pain management .............................. 49
6.4.1 Pharmacological strategies ..........49
6.4.2 Local anaesthetics ..........................50
6.4.3 Simple analgesics ..........................51
6.4.4 Nonsteroidal anti-inflammatory drugs ................................................. 51
6.4.5 Opioids .........................................52
6.4.6 Alpha-2 agonists: clonidine and dexmedetomidine ..................54
6.4.7 Gabapentin ......................................55
6.4.8 Ketamine ........................................56

6.5 Recommended analgesia strategies for specific surgical procedures ..............................56
6.5.1 Ear, nose, and throat procedures ...56
6.5.2 Common procedures performed in children and suggested regional anaesthesia techniques ................................................. 57
6.5.3 Principles of postoperative analgesic prescription ......................... 58
6.5.4 Pain in children with cerebral palsy, deformities and cognitive impairment ................................................. 59
6.5.5 Pain in children with autism spectrum disorders ................................................. 60
6.5.6 Patients with obstructive sleep apnoea ................................................. 60
6.5.7 Pain in children with cancer ..........60

7. Acute pain management in elderly patients ................................................. 62

7.1 Factors affecting pain control in elderly patients ................................................. 62
7.1.1 Age-related alterations in pharmacokinetics and pharmacodynamics ................................................. 62
7.1.2 Altered perception of pain and potential difficulties in assessment ..........64
7.1.3 Diminished physiological reserve and concurrent diseases ..................64
7.1.4 Polypharmacy, leading to an increased risk of drug interactions ....64

7.2 Measurement of pain ......................... 64
7.2.1 Patient self-report measures of pain ................................................. 64
7.2.2 Other measures of pain ................................................. 65

7.3 Analgesic techniques in the elderly .. 65
7.3.1 Patient-controlled analgesia .......... 65
7.3.2 Epidural analgesia ..........................65

8. Analgesia during pregnancy, childbirth, the puerperium and lactation ................................................. 68
8.1 Pregnancy ................................................. 68
8.1.1 First trimester ................................................. 68
8.1.2 Second trimester ................................................. 69
8.1.3 Third trimester ................................................. 69

8.2 Childbirth ................................................. 69
8.2.1 Analgesia for vaginal delivery .......... 69
8.2.2 Analgesia for caesarean section ....71

8.3 The puerperium .................................... 73
8.3.1 Analgesia following vaginal delivery ................................................. 73
8.3.2 Analgesia following a caesarean section ................................................. 74

8.4 Lactation ................................................. 74

9. Routes of systemic drug administration: enteral and parenteral .................................... 76
9.1 Enteral administration .......................... 76
9.1.1 Oral route (p.o.) ................................................. 76
9.1.2 Rectal route (PR) ................................................. 78
9.1.3 Sublingual and buccal administration ................................................. 78
9.1.4 Feeding tubes (orogastric, nasogastric, postpyloric, gastrostomy and enterostomy) ................................................. 79

9.2 Parenteral administration ........................ 79
9.2.1 Noninvasive systemic drug administration ................................................. 79
9.2.2 Invasive systemic drug delivery ....81
10. Locally and regionally administered analgesic drugs .................................................. 85

10.1 Drugs used for local and regional analgesia ......................................................... 85
  10.1.1 Local anaesthetics ......................................................... 85
  10.1.2 Opioids ........................................................................ 86
  10.1.3 Adjuvant drugs .......................................................... 86
  10.1.4 Anti-inflammatory drugs ................................................. 86

10.2 Regional and local analgesic techniques .......................................................... 87
  10.2.1 Peripheral nerve blocks and the infusion of local anaesthetics .............. 87
  10.2.2 Interfascial plane blocks ................................................. 88
  10.2.3 Surgical site administration of analgesics .............................................. 89
  10.2.4 Intravenous regional analgesia ........................................... 91
  10.2.5 Topical analgesia .......................................................... 91

10.3 Safety considerations for regional and local analgesic techniques ................. 91
  10.3.1 Anticoagulation .......................................................... 91
  10.3.2 Nerve injury ............................................................... 92
  10.3.3 Toxicity ...................................................................... 92
  10.3.4 Infection .................................................................... 92

11. Patient-controlled analgesia and neuraxial analgesia techniques ................. 93

11.1 Clinical guidelines on the use of patient-controlled analgesia ....................... 93
  11.1.1 Rationale for use .......................................................... 93
  11.1.2 Standards of care .......................................................... 94
  11.1.3 Medication .................................................................. 97
  11.1.4 Equipment and programme variables/settings ....................................... 98

11.2 Neuraxial techniques ......................................................................................... 100
  11.2.1 Epidural analgesia ......................................................... 100
  11.2.2 Spinal (intrathecal) analgesia ......................................... 106
  11.2.3 Neuraxial techniques and concurrent anticoagulant medication ...... 108

12. Non-pharmacological pain techniques .......................................................... 114

Section A: Adults ......................................................................................... 114

12.1 Physical interventions .............................................................................. 114
  12.1.1 Massage ..................................................................... 114
  12.1.2 Heat and cold .............................................................. 115
  12.1.3 Transcutaneous electrical nerve stimulation ....................................... 115
  12.1.4 Acupuncture ............................................................... 115
  12.1.5 Progressive muscle relaxation .............................................. 116

12.2 Psychological interventions ................................................................. 116
  12.2.1 Cognitive behaviour therapy ............................................ 116
  12.2.2 Mindfulness-based stress reduction ............................................. 116
  12.2.3 Acceptance and commitment therapy ........................................... 116
  12.2.4 Guided imagery ............................................................ 117

12.3 Other interventions ................................................................................. 117
  12.3.1 Spirituality and religion .................................................. 117
  12.3.2 Music therapy ............................................................. 117
  12.3.3 Patient education .......................................................... 117

12.4 Conclusion ............................................................................................... 118

Section B: Paediatrics ............................................................................... 118

12.5 Pain management ...................................................................................... 118

12.6 Preparation ............................................................................................... 118

12.7 One Voice ................................................................................................. 119

12.8 Language .................................................................................................. 119

12.9 Positions of comfort ................................................................................. 120

12.10 Coping strategies ..................................................................................... 120
  12.10.1 Deep breathing ............................................................ 121
  12.10.2 Alternate focus ............................................................. 121
  12.10.3 Visualisation or imagination .............................................. 121
  12.10.4 Visual schedules ........................................................... 121
  12.10.5 Relaxation therapies ....................................................... 121
  12.10.6 Rehearsal ....................................................................... 122
12.10.7 Coping strategies according to age ........................................ 122

13. Management of acute pain in specific scenarios in adults ........ 125

13.1 Introduction .................................................. 125

13.2 General principles ............................................. 126
  13.2.1 Anatomical consideration ................................ 126
  13.2.2 Pathophysiological considerations ...................... 127
  13.2.3 Interventional considerations (what to do about the pain) .... 127
  13.2.4 Monitoring considerations .............................. 129
  13.2.5 Facilities and socioeconomical considerations ........... 129
  13.2.6 Routes of administration of analgesics ................. 129
  13.2.7 Management of acute nociceptive pain according to the visual analogue scale ........................................ 130

13.3 Acute pain in the emergency department ....................... 132
  13.3.1 Analgesics used in the emergency department ........... 133
  13.3.2 Anaesthetic agents in the emergency department ......... 135
  13.3.3 Specific conditions commonly seen in the emergency department ...... 135
  13.3.4 The discharge prescription from the emergency department .... 145

13.4 The intensive care unit .................................... 145
  13.4.1 Analgesics used in the ICU ............................... 147

13.5 Postoperative pain ........................................... 152
  13.5.1 Preoperative strategies ........................................ 153
  13.5.2 Intraoperative strategies ..................................... 153
  13.5.3 The postoperative care unit ............................... 153
  13.5.4 The postoperative prescription ............................. 154

13.6 Other measures to avert postoperative pain ..................... 166
  13.6.1 The discharge prescription ................................. 167

13.7 Specific considerations in different surgical disciplines .......... 167
  13.7.1 General surgery ........................................ 167
  13.7.2 Vascular surgery .......................................... 168
  13.7.3 Cardiothoracic surgery .................................... 168
  13.7.4 Neurosurgery ............................................ 168
  13.7.5 Orthopaedic surgery ..................................... 169

13.8 Acute burn injuries ......................................... 169
  13.8.1 Evaluation and classification of burn wounds .......... 170
  13.8.2 Pain in the burn victim ..................................... 171
  13.8.3 Analgesia is required in the following scenarios ........ 171

13.9 Headaches ................................................... 175
  13.9.1 General considerations: primary and secondary headaches .... 175
  13.9.2 Types of presentation of acute headaches ................ 177
  13.9.3 Carbon monoxide poisoning ............................ 187
  13.9.4 Temporal arteritis (giant cell arteritis) .................. 187
  13.9.5 Disorders of abnormal intracranial pressure .......... 188
  13.9.6 Paranasal sinusitis ....................................... 191
  13.9.7 Occipital neuralgia and cervicogenic headache ......... 192
  13.9.8 Hyposic headache ........................................ 193
  13.9.9 Cluster headache ......................................... 194
  13.9.10 Chronic headache because treatment is not working:
          medication overuse headache ................................ 196

13.10 Acute neuropathic pain ..................................... 197
  13.10.1 General considerations ................................. 197
  13.10.2 Central neuropathic pain ............................... 198
  13.10.3 Peripheral neuropathic pain ........................... 198
  13.10.4 General management of acute neuropathic pain ....... 199
  13.10.5 Pharmacological management of acute neuropathic pain .... 199
13.10.6 Algorithm for the pharmacological management of acute neuropathic pain ..........................204

13.10.7 Acute herpetic neuralgia ..................205

13.11 HIV-associated pain ..........................205
   13.11.1 Principles of managing HIV-related pain ..........................206

13.12 Acute cancer pain ............................207

13.13 Opioid tolerance .............................208

14. Opioid minimisation for acute pain management ........................................218
   14.1 Prescription opioid addiction and overdose ...........................................218
   14.2 Postoperative opioid respiratory depression ...........................................218
   14.3 Interventions to reduce opioid requirements following general anaesthesia ..........218
      14.3.1 Non-pharmacological interventions ............................................219
      14.3.2 Pharmacological interventions ...................................................220
   14.4 Opioid-free analgesia .........................222
   14.5 Conclusion ......................................223
1. Foreword

Pain is inevitable. Suffering is optional. (Haruki Murakami)

The Japanese novelist might not necessarily have had physical pain in mind, but this quote is eminently applicable to acute pain of patients. Acute pain sensations accompany many diseases and all surgery. The prevention and treatment of pain have made great surgical progress possible, particularly over the past two centuries. All doctors have a responsibility to relieve pain and suffering. This responsibility is particularly applicable to doctors, usually anaesthesia providers, in treating perioperative pain.

All patients, whether from rich or poor countries, can experience pain. The International Association for the Study of Pain (IASP) declared that access to pain management is a fundamental human right. Yet, they found that pain management is inadequate in most of the world, including rich countries, due to a lack of access, knowledge deficits, stigma, inadequate national policies, status of pain medicine as specialist area, and restrictions to and unavailability of opioids and other drugs needed for the treatment of pain. This finding is also true for South Africa, where people live in both first- and third-world conditions. Recent studies showed that perioperative outcomes are far worse in Africa than in developed, richer countries. Pain most likely plays a role in this as adequate pain relief reduces inflammation and aids recovery, and may reduce the development of chronic postoperative pain.

People use the word ‘pain’ to describe emotional, psychological, social and other unpleasant human conditions. This emphasises that the nature of pain is not merely physical, but relates to individual patients as well as environmental factors. This should alert the medical practitioner to the physio-psycho-social aspects which need attention when physical pain is addressed and treated according to these guidelines.

Pain treatment requires an understanding of not only the physiology and nature of pain, but also the drugs and interventions available for treatment as well as the impact thereof on patients. The current opioid epidemic as seen in the USA is, to a large extent, the result of irresponsible and inappropriate prescribing of medication for postoperative pain. The SASA Guidelines for the management of acute pain in specific scenarios provides guidance on the effective and appropriate treatment of pain. Though it is not a protocol, it does provide information which can be adapted to the unique circumstances of each individual patient. Treatment and approaches within different clinical contexts are covered in these guidelines. Also, a health economic approach should be followed in limited resource contexts to ensure that pain treatment is affordable for both rich and poor patients.

The SASA Guidelines for the management of acute pain in specific scenarios comprehensively addresses the treatment of acute pain in a wide range of situations. We owe gratitude to a team
that spent countless hours reviewing and updating these guidelines to be aligned with current best practice in simple to sophisticated pain treatment. With these guidelines, SASA hopes to play a role in relieving the suffering of patients with acute pain.

**Prof. Johan Diedericks**

SASA Guidelines Convener
2. Introduction

Welcome to the third edition of the Guidelines for the management of acute pain in specific scenarios. 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.

Guideline development and revisions thereof is a dynamic process. The Regulation Business Unit of the South African Society of Anaesthesiologists therefore would appreciate inputs on these guidelines from all sectors of the medical profession over the next few years. Contributions and opinions can be addressed to the SASA CEO via email (ceo@sasaweb.com), who will ensure that the contributors and councillors responsible for these guidelines, are informed.

The COVID-19 pandemic caused many challenges in completing this third edition review. However, through the dedication and perseverance of the contributors and councillors, we have produced an excellent guideline of international standard once again.

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.

On behalf of the consensus group:

- Prof. Sean Chetty
- Dr Eric Hodgson
- Prof. Analee Milner
- Dr Anthony Travers
- Dr Cecile van Rooyen
- Prof. Johan Diedericks
- Dr Sudha Bechan
- Dr Faheem Baba
- Dr Anisa Bhetty
- Dr Annemie Burke
- Prof. Frans Smith
- Dr Chloe van den Bosch
- Dr Gary Simpson
- Dr Theresa Samuel
- Dr Karen van Zijl
## List of acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>per cent</td>
</tr>
<tr>
<td>5-HT</td>
<td>5-hydroxytryptamine</td>
</tr>
<tr>
<td>AA</td>
<td>arachidonic acid</td>
</tr>
<tr>
<td>AACT</td>
<td>acceptance and commitment therapy</td>
</tr>
<tr>
<td>ABM</td>
<td>adjusted body mass</td>
</tr>
<tr>
<td>ACEI</td>
<td>angiotensin I converting enzyme inhibitor</td>
</tr>
<tr>
<td>ACT</td>
<td>activated clotting time</td>
</tr>
<tr>
<td>ACTH</td>
<td>adrenocorticotropic hormone</td>
</tr>
<tr>
<td>ADH</td>
<td>antidiuretic hormone</td>
</tr>
<tr>
<td>ADMA</td>
<td>asymmetrical dimethylarginine</td>
</tr>
<tr>
<td>ADP</td>
<td>adenosine diphosphate</td>
</tr>
<tr>
<td>AHN</td>
<td>acute herpetic neuralgia</td>
</tr>
<tr>
<td>AIDS</td>
<td>acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>AMPA</td>
<td>α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid</td>
</tr>
<tr>
<td>ANP</td>
<td>acute neuropathic pain</td>
</tr>
<tr>
<td>ANS</td>
<td>autonomic nervous system</td>
</tr>
<tr>
<td>APTT</td>
<td>activated partial thromboplastin time</td>
</tr>
<tr>
<td>ARA</td>
<td>angiotensin II receptor antagonist</td>
</tr>
<tr>
<td>ARV</td>
<td>antiretroviral drugs</td>
</tr>
<tr>
<td>ASD</td>
<td>autism spectrum disorders</td>
</tr>
<tr>
<td>ASIC</td>
<td>acid-sensing ion channel</td>
</tr>
<tr>
<td>ATP</td>
<td>adenosine triphosphate</td>
</tr>
<tr>
<td>BBB</td>
<td>blood–brain barrier</td>
</tr>
<tr>
<td>bd</td>
<td>twice daily</td>
</tr>
<tr>
<td>BK</td>
<td>bradykinin</td>
</tr>
<tr>
<td>BMI</td>
<td>body mass index</td>
</tr>
<tr>
<td>BPS</td>
<td>behavioural pain scale</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>calcium</td>
</tr>
<tr>
<td>CB1-2</td>
<td>cannibinoids</td>
</tr>
<tr>
<td>CBT</td>
<td>cognitive behaviour therapy</td>
</tr>
<tr>
<td>CGH</td>
<td>cervicogenic headache</td>
</tr>
<tr>
<td>CGRP</td>
<td>calcitonin gene-related polypeptide</td>
</tr>
<tr>
<td>CI</td>
<td>continuous infusion</td>
</tr>
<tr>
<td>CL</td>
<td>clearance</td>
</tr>
<tr>
<td>cm</td>
<td>centimetre</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>HGF</td>
<td>hepatocyte growth factor</td>
</tr>
<tr>
<td>HH</td>
<td>hypnic headache</td>
</tr>
<tr>
<td>HITT</td>
<td>heparin-induced thrombocytopenia and thrombosis</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>HS</td>
<td>hyperserotonergic syndrome</td>
</tr>
<tr>
<td>HSV</td>
<td>herpes simplex virus</td>
</tr>
<tr>
<td>IASP</td>
<td>International Association for the Study of Pain</td>
</tr>
<tr>
<td>IBS</td>
<td>irritable bowel syndrome</td>
</tr>
<tr>
<td>ICP</td>
<td>intracranial pressure</td>
</tr>
<tr>
<td>ICU</td>
<td>intensive care unit</td>
</tr>
<tr>
<td>IHS</td>
<td>International Headache Society</td>
</tr>
<tr>
<td>IIH</td>
<td>idiopathic intracranial hypertension</td>
</tr>
<tr>
<td>IL</td>
<td>interleukin</td>
</tr>
<tr>
<td>IM</td>
<td>intramuscular</td>
</tr>
<tr>
<td>IMI</td>
<td>intramuscular injection</td>
</tr>
<tr>
<td>IN</td>
<td>intranasal</td>
</tr>
<tr>
<td>INR</td>
<td>international normalised ratio</td>
</tr>
<tr>
<td>IO</td>
<td>intraosseous</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous</td>
</tr>
<tr>
<td>IVI</td>
<td>intravenous injection</td>
</tr>
<tr>
<td>kg</td>
<td>kilogramme</td>
</tr>
<tr>
<td>LA</td>
<td>local anaesthetic</td>
</tr>
<tr>
<td>LAST</td>
<td>local anaesthetic toxicity</td>
</tr>
<tr>
<td>LD</td>
<td>loading dose</td>
</tr>
<tr>
<td>LMA</td>
<td>laryngeal mask airway</td>
</tr>
<tr>
<td>LMWH</td>
<td>low-molecular-weight heparin</td>
</tr>
<tr>
<td>LPH</td>
<td>low intracranial pressure headache</td>
</tr>
<tr>
<td>MAD</td>
<td>mucosal atomisation device</td>
</tr>
<tr>
<td>MAOI</td>
<td>monoamine oxidase inhibitor</td>
</tr>
<tr>
<td>Mcg</td>
<td>microgram</td>
</tr>
<tr>
<td>MD</td>
<td>maintenance dose</td>
</tr>
<tr>
<td>mg</td>
<td>milligram</td>
</tr>
<tr>
<td>mg/kg</td>
<td>milligram per kilogram</td>
</tr>
<tr>
<td>MI</td>
<td>myocardial infarction</td>
</tr>
<tr>
<td>MIAs</td>
<td>mechanically insensitive afferents/nociceptors</td>
</tr>
<tr>
<td>ml</td>
<td>millilitre</td>
</tr>
<tr>
<td>mm</td>
<td>millimetre</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>MME</td>
<td>milligram morphine sulphate equivalents</td>
</tr>
<tr>
<td>Mmol/l</td>
<td>millimol per liter</td>
</tr>
<tr>
<td>MOBID</td>
<td>Mobilization-Observation-Behavior-Intensity-Dementia</td>
</tr>
<tr>
<td>MOH</td>
<td>medication overuse headache</td>
</tr>
<tr>
<td>N/A</td>
<td>not applicable</td>
</tr>
<tr>
<td>N₂O</td>
<td>nitrous oxide</td>
</tr>
<tr>
<td>NA</td>
<td>noradrenalin</td>
</tr>
<tr>
<td>Na⁺</td>
<td>sodium</td>
</tr>
<tr>
<td>NIPS</td>
<td>Neonatal Infant Pain Scale</td>
</tr>
<tr>
<td>NK-1</td>
<td>neurokinin 1</td>
</tr>
<tr>
<td>NMDA</td>
<td>N-methyl-D-aspartate</td>
</tr>
<tr>
<td>NNT</td>
<td>numbers needed to treat</td>
</tr>
<tr>
<td>NO</td>
<td>nitric oxide</td>
</tr>
<tr>
<td>NPO</td>
<td>nil per os</td>
</tr>
<tr>
<td>NRI</td>
<td>noradrenaline reuptake</td>
</tr>
<tr>
<td>NRS</td>
<td>numeric rating scale</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>NTS</td>
<td>nucleus tractus solitarius</td>
</tr>
<tr>
<td>OFA</td>
<td>opioid-free analgesia</td>
</tr>
<tr>
<td>OIH</td>
<td>opioid-induced hyperalgesia</td>
</tr>
<tr>
<td>ON</td>
<td>occipital neuralgia</td>
</tr>
<tr>
<td>OSA</td>
<td>obstructive sleep apnoea</td>
</tr>
<tr>
<td>OTC</td>
<td>over-the-counter</td>
</tr>
<tr>
<td>OWS</td>
<td>opioid withdrawal syndrome</td>
</tr>
<tr>
<td>p.o.</td>
<td>per os/orally</td>
</tr>
<tr>
<td>PaCO₂</td>
<td>partial pressure of carbon dioxide</td>
</tr>
<tr>
<td>PACSLAC</td>
<td>Pain Assessment Checklist for Seniors with Limited Ability to Communicate</td>
</tr>
<tr>
<td>PACU</td>
<td>postanaesthetic care unit</td>
</tr>
<tr>
<td>PAG</td>
<td>periaqueductal grey matter</td>
</tr>
<tr>
<td>PAINAD</td>
<td>pain assessment in advanced dementia</td>
</tr>
<tr>
<td>PCA</td>
<td>patient-controlled analgesia</td>
</tr>
<tr>
<td>PCEA</td>
<td>patient-controlled epidural analgesia</td>
</tr>
<tr>
<td>PDPH</td>
<td>postdural puncture headache</td>
</tr>
<tr>
<td>PE</td>
<td>pulmonary embolism</td>
</tr>
<tr>
<td>PET</td>
<td>preeclampsia</td>
</tr>
<tr>
<td>PF</td>
<td>preservative free</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>PG</td>
<td>prostaglandin</td>
</tr>
<tr>
<td>PGD2</td>
<td>prostaglandin D2</td>
</tr>
<tr>
<td>PGE2</td>
<td>prostaglandin 2</td>
</tr>
<tr>
<td>PGF2α</td>
<td>prostaglandin F2 alpha</td>
</tr>
<tr>
<td>PGG2</td>
<td>prostaglandin G2</td>
</tr>
<tr>
<td>PGH2</td>
<td>prostaglandin H2</td>
</tr>
<tr>
<td>PGI2</td>
<td>prostacyclin</td>
</tr>
<tr>
<td>PHN</td>
<td>postherpetic neuralgia</td>
</tr>
<tr>
<td>PK-PD</td>
<td>pharmacokinetic-pharmacodynamic</td>
</tr>
<tr>
<td>PLA2</td>
<td>phospholipase A2</td>
</tr>
<tr>
<td>PMA</td>
<td>post menstrual age</td>
</tr>
<tr>
<td>PMC</td>
<td>post conceptual age</td>
</tr>
<tr>
<td>PNP</td>
<td>peripheral neuropathic pain</td>
</tr>
<tr>
<td>PNS</td>
<td>peripheral nervous system</td>
</tr>
<tr>
<td>PO₂</td>
<td>partial pressure of oxygen</td>
</tr>
<tr>
<td>PPI</td>
<td>proton pump inhibitor</td>
</tr>
<tr>
<td>PR</td>
<td>per rectal</td>
</tr>
<tr>
<td>PRN</td>
<td>per request needed</td>
</tr>
<tr>
<td>RCT</td>
<td>randomised control trial</td>
</tr>
<tr>
<td>RR</td>
<td>respiratory rate</td>
</tr>
<tr>
<td>RVM</td>
<td>rostral ventromedial medulla</td>
</tr>
<tr>
<td>Rx</td>
<td>treatment</td>
</tr>
<tr>
<td>SAH</td>
<td>subarachnoid haemorrhage</td>
</tr>
<tr>
<td>SAMF</td>
<td>South African Medicines Formulary</td>
</tr>
<tr>
<td>SBP</td>
<td>systolic blood pressure</td>
</tr>
<tr>
<td>SC</td>
<td>subcutaneous</td>
</tr>
<tr>
<td>SIH</td>
<td>spontaneous intracranial hypotension</td>
</tr>
<tr>
<td>SL</td>
<td>sublingual</td>
</tr>
<tr>
<td>SNRI</td>
<td>serotonin and noradrenalin reuptake inhibitor</td>
</tr>
<tr>
<td>SR</td>
<td>slow-release</td>
</tr>
<tr>
<td>SRI</td>
<td>serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>SSRI</td>
<td>selective serotonin uptake inhibitor</td>
</tr>
<tr>
<td>Stat</td>
<td>immediately</td>
</tr>
<tr>
<td>TAP</td>
<td>transversus abdominis plane</td>
</tr>
<tr>
<td>TCA</td>
<td>tricyclic antidepressants</td>
</tr>
<tr>
<td>TD</td>
<td>trans dermal</td>
</tr>
<tr>
<td>TENS</td>
<td>transcutaneous electrical nerve stimulation</td>
</tr>
<tr>
<td>Abbr</td>
<td>Definition</td>
</tr>
<tr>
<td>-------</td>
<td>------------------------------------------------</td>
</tr>
<tr>
<td>TIA</td>
<td>transient ischaemic attack</td>
</tr>
<tr>
<td>TNF</td>
<td>tumour necrosis factor</td>
</tr>
<tr>
<td>tNSAIDs</td>
<td>traditional nonsteroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>TRP</td>
<td>transient receptor potential</td>
</tr>
<tr>
<td>TRPA</td>
<td>transient receptor potential ankyrin</td>
</tr>
<tr>
<td>TRPV1</td>
<td>transient receptor potential vanilloid 1</td>
</tr>
<tr>
<td>TRPV2</td>
<td>transient receptor potential vanilloid type-2</td>
</tr>
<tr>
<td>TTH</td>
<td>tension-type headache</td>
</tr>
<tr>
<td>TXA2</td>
<td>thromboxane A2</td>
</tr>
<tr>
<td>UFH</td>
<td>unfractionated heparin</td>
</tr>
<tr>
<td>UP-3</td>
<td>uvulo-palato-pharyngoplasty</td>
</tr>
<tr>
<td>UWC</td>
<td>use with caution</td>
</tr>
<tr>
<td>UWECO</td>
<td>use with extreme caution</td>
</tr>
<tr>
<td>VAS</td>
<td>visual analogue scale</td>
</tr>
<tr>
<td>Vd</td>
<td>volume of distribution</td>
</tr>
<tr>
<td>VDS</td>
<td>verbal descriptor scale</td>
</tr>
<tr>
<td>VNRS</td>
<td>verbal numeric rating scale</td>
</tr>
<tr>
<td>WDR</td>
<td>wide dynamic range</td>
</tr>
</tbody>
</table>
3. The physiology of acute pain

3.1 Definitions

**Pain** is defined by the International Association for the Study of Pain (IASP) as an “unpleasant sensory and emotional experience, associated with actual or potential tissue damage or described in terms of such damage” (Mersky). It is a complex interaction of sensory, emotional and behavioural factors. Nociception is mostly modulated at the spinal cord level and eventually interpreted by the cortex, resulting in varying degrees of discomfort and pain. Perceived pain, however, does not necessarily correlate with the degree of tissue damage.

**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. Acute and chronic pain can be represented on a continuum of a process which includes inflammatory, neuropathic, visceral and somatic pain. The nervous system is not a hard-wired system. It allows for peripheral, central, intracellular and synaptic modifications. Acute pain can result in long-term changes and, subsequently, modified responses to sensory input (neuroplasticity).

**Acute physiological pain** is defined as pain of short and limited duration. It is well localised, transient and well differentiated from touch. The pain relates to an identifiable cause (trauma, surgery or inflammation) and its purpose is to act as a protective mechanism.

**Clinical pain,** on the other hand, outlasts the stimulus and spreads to nondamaged areas, leading to primary hyperalgesia. Peripheral sensitisation occurs as part of the inflammatory response and results in activation of the Aβ-fibres which leads to the pain to touch (allodynia). Antidromic impulses (travelling in the direction opposite of nociceptive impulses conducted to the higher centres) result in the release of neurotransmitters from nerve endings of a primary afferent in response to noxious stimulation. In turn, these additional neurotransmitters have modulating effects on further impulse transmission.

<table>
<thead>
<tr>
<th>Table I: Pain physiology definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Allodynia</strong></td>
</tr>
<tr>
<td><strong>Central sensitisation</strong></td>
</tr>
<tr>
<td><strong>Gate control theory</strong> (Melzack and Wall)</td>
</tr>
<tr>
<td><strong>Hyperalgesia</strong></td>
</tr>
<tr>
<td><strong>Neuroplasticity</strong></td>
</tr>
</tbody>
</table>
Peripheral sensitisation

Decreased threshold of nociceptors and increased output, caused by mediators released during tissue injury.

Primary hyperalgesia

Increased pain perception from the injury site due to the release of inflammatory mediators peripherally.

Secondary hyperalgesia

Increased pain perception due to CNS mechanisms sensitising central neurons.

Wind-up phenomenon

A form of central plasticity. Repeated stimulation of C-fibres results in an increased number of discharges per stimulus, an expansion of receptive field size and an increase in spontaneous discharge rate.

3.2 Understanding nociceptive pathways

The experience of pain involves a series of neurophysiological processes that reflect the following four components:

1. **Transduction**: A noxious stimulus is converted to electrical impulses in sensory nerve endings.

2. **Transmission**: The conduction/propagation of impulses via peripheral afferent fibres to the CNS. Voltage-gated sodium channels play an important role in this component.
   - Peripheral sensory afferent fibres travel from the site of transduction to the spinal cord dorsal horn on the ipsilateral side.
   - Second-order neurons cross the midline to ascend in the contralateral spinothalamic tract.
   - Third-order neurons project from the thalamus to the sensory cortex.

Figure 1: Elements of pain processing and antagonists acting at these sites

3. **Modulation:** This is the alteration of pain transmission. Inhibition or excitation of ascending and descending pathways in the peripheral nervous system (PNS) and CNS result in inhibitory or facilitatory effects. Modulation involves the periaqueductal grey matter (PAG) and rostral ventromedial medulla (RVM) from descending projections from cortical sites to the spinal cord. Modulation involves the gate control theory, wind-up phenomenon and glial activation. Glial cells become activated after an insult (e.g. nerve injury or chronic opioid therapy), which subsequently release several substances. This causes a change in membrane potentials that cause normally inhibitory inputs to become excitatory.

4. **Perception:** This occurs in the thalamus and the sensory cortex, and produces a subjective pain sensation.

3.2.1 **Primary afferent fibres**

Peripheral nociceptors are free nerve endings of afferent nerves which respond to pressure, temperature and chemical stimuli. The cell bodies of these afferent nerves are located in the dorsal root ganglia, except for the fibres innervating the head, whose cell bodies are located at the trigeminal ganglion.

Sensory fibres are classified as Aβ-fibres that are large-diameter, myelinated fibres and conduct the fastest. They are activated by nonnociceptive stimuli and not involved in noxious transmission.

There are two main categories of nociceptive afferent fibres.

- **Aδ-fibres** are thin, myelinated and transmit mechano-thermal stimuli. They terminate in laminae I, III, IV, V of the dorsal horn of the spinal cord, and act as fast-conducting fibres involved with immediate pain.

- **C-fibres** make up 80–90% of nociceptive afferents. They are thin, unmyelinated and polymodal (i.e. they respond to thermal, mechanical and/or chemical stimuli). They terminate in the dorsal horn laminae I and II, and are slow conducting fibres, involved in dull, burning or throbbing, poorly localised pain. An important subgroup is nociceptors insensitive to mechanical stimuli (mechanically insensitive afferents/nociceptors [MIAs]) and is thought to play an important role in central sensitisation.

The Aδ- and C-fibres are high-threshold fibres. An ‘inflammatory soup’ of chemicals sensitise high-threshold nociceptors after surgery and trauma. Sensitised nociceptors react to a painful stimulus at a lower threshold (peripheral sensitisation). Silent nociceptors can become active in the presence of inflammation and also play a part in peripheral sensitisation.
3.2.2 Dorsal horn

Primary afferents (first-order neurons) interact extensively with other afferents, as well as with interneurons and the endings of descending tract fibres.

Second-order neurons comprise both high-threshold neurons (nociceptive specific) and WDR neurons. Once sensitised, the WDR neurons respond to and discharge upon tactile, nonnoxious stimuli (allodynia).

Central sensitisation can result from the activation of N-methyl-D-aspartate (NMDA) receptors on second-order neurons. Increased activity in the dorsal horn following repetitive stimulation from primary nociceptors causes increased excitability of second-order neurons. This leads to secondary hyperalgesia, wind-up, temporal summation and long-term potentiation. A low-threshold stimulus then results in both an increased magnitude and a prolonged duration of depolarisation at the second-order neurons.

Collateral branches of the small Aδ- and C-fibres may travel in the lateral part of the entry zone for several segments before synapsing in the dorsal horn (Lissauer’s tract).

3.3 Neurotransmitters

3.3.1 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, among others, hydrogen and potassium ions, bradykinin (BK), histamine, noradrenalin (NA), 5-hydroxytryptamine (5-HT), prostaglandins (PGs), leukotrienes, nerve growth factor, glutamate and substance P.

3.3.2 Dorsal horn

*Excitatory*

Glutamate, substance P and neurokinin 1 (NK-1) activate the low-threshold α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and NK-1 receptors, which in turn, sensitise and activate the high-threshold NMDA receptors on the second-order neurons.

*Inhibitory*

Noradrenalin, dopamine, serotonin, histamine, oxytocin, vasopressin, acetylcholine, γ-aminobutyric acid (GABA), glycine and opioids predominantly occur in the descending pathways.
### Table II: Neurotransmitters

<table>
<thead>
<tr>
<th>Neurotransmitter</th>
<th>Receptor</th>
<th>Effect on nociception</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substance P</td>
<td>Neurokinin-1</td>
<td>Excitatory</td>
</tr>
<tr>
<td>Calcitonin gene-related peptide</td>
<td></td>
<td>Excitatory</td>
</tr>
<tr>
<td>Glutamate</td>
<td>NMDA, AMPA, kainite, quisqualate</td>
<td>Excitatory</td>
</tr>
<tr>
<td>Aspartate</td>
<td>NMDA, AMPA, kainite, quisqualate</td>
<td>Excitatory</td>
</tr>
<tr>
<td>Adenosine triphosphate (ATP)</td>
<td>P₁, P₂</td>
<td>Excitatory</td>
</tr>
<tr>
<td>Somatostatin</td>
<td></td>
<td>Inhibitory</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>Muscarinic</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>Enkephalins</td>
<td>μ, δ, κ</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>β-endorphine</td>
<td>μ, δ, κ</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>α₂</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>Adenosine</td>
<td>A₁</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>Serotonin</td>
<td>5-HT₁, 5-HT₂</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>γ-aminobutyric acid (GABA)</td>
<td>A, B</td>
<td>Inhibitory</td>
</tr>
<tr>
<td>Glycine</td>
<td></td>
<td>Inhibitory</td>
</tr>
</tbody>
</table>

NMDA – N-methyl-D-aspartate, AMPA – 2-(aminomethyl)phenylacetic acid, 5-HT – 5-hydroxytryptamine

### 3.4 Intracellular events

NMDA activation in the CNS (by means of removal of the magnesium plugs) leads to i) calcium ($Ca^{2+}$) influx to the cell, ii) the production of nitric oxide and secondary messengers, and iii) prostaglandin production.

### 3.5 Receptors and ligands

Ligands transduce the specific stimulus into an action potential which is sodium ($Na^+$) channel dependent. Local anaesthetics (LA) act at this level, but as $Na^+$ channels are present in all nerve fibres, blocking of the autonomic motor and sensory fibres can occur to some degree.

Pain modulation can be achieved by i) decreasing excitation (opioids, $Na^+$ channel blockers and ketamine) and/or ii) increasing inhibition (NA, glycine, GABA at the level of the spinal cord).

The most common receptors and ligands are outlined in Table III.
Table III: Receptors, stimuli and ligands

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Receptor subtypes</th>
<th>Ligands and stimuli</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transient receptor potential</td>
<td>TRPV1, TRPV2, TRPA</td>
<td>Heat, H+ and capsaicin</td>
</tr>
<tr>
<td>receptors (TRPs)</td>
<td></td>
<td>Heat</td>
</tr>
<tr>
<td>Acidsensing</td>
<td>ASIC, DRASIC</td>
<td>Protons</td>
</tr>
<tr>
<td>Purine</td>
<td>P2X3</td>
<td>ATP</td>
</tr>
<tr>
<td>Serotonin</td>
<td>5-HT₁</td>
<td>5-HT</td>
</tr>
<tr>
<td>NMDA receptor</td>
<td>NRI Glutamate</td>
<td>Glutamate</td>
</tr>
<tr>
<td>AMPA</td>
<td>iGlutR1</td>
<td>Glutamate</td>
</tr>
<tr>
<td>Kainate</td>
<td>iGlutR5</td>
<td>Glutamate</td>
</tr>
<tr>
<td>Prostanoids</td>
<td>EP1-4 IP</td>
<td>PGE₂, PGI₂</td>
</tr>
<tr>
<td>Histamine</td>
<td>HI</td>
<td>HA</td>
</tr>
<tr>
<td>Serotonin</td>
<td>5-HT₁, 5-HT₂a, 5-HT₄</td>
<td>S-HT</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>BK1 and BK2</td>
<td>BK</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>CB1-2</td>
<td>Anandamide</td>
</tr>
<tr>
<td>Opioids</td>
<td>Mu, delta and kappa</td>
<td>Enkephalin, dynorphin and beta-endorphin</td>
</tr>
<tr>
<td>Tachykinin</td>
<td>NK-1</td>
<td>Substance P and neurokinin A</td>
</tr>
</tbody>
</table>

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, NMDA – N-methyl-D-aspartate, PGE₂ – prostaglandin 2, PGI₂ – prostacyclin, TRP – transient receptor potential

3.6 Nociceptive pathways

3.6.1 Ascending pathways

The spinothalamic tract originates in laminae I, II and V of the opposite dorsal horn, and after crossing the midline, it ascends to the thalamus and 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 components of the nociceptive stimulus. Autonomic and sensory coordination is provided by this pathway.

The cingulate cortex, insula, PAG, reticular formation and prefrontal cortex receive multiple inputs from the ascending pathways, and facilitate the coordination of autonomic and emotional responses.
3.6.2 Descending inhibition

These pathways modulate nociception by action on the primary nociceptive afferents and interneurons at the level of the dorsal horn. They mainly inhibit transmission towards the cortex and other higher centres. These tracts originate in the cortex, PAG and brainstem nuclei. Their fibres terminate in the dorsal horn, facilitating inhibition and modulating nociceptive input. Inhibitory neurotransmitters include opioids, 5-HT, NA and GABA. Tricyclic antidepressants (TCAs), opioids and alpha-2 agonists exert their effects on modulating nociception via the descending pathways.
3.6.3 Neuropathic pain

By definition, neuropathic pain is pain that originates in the nervous system. There is no clear distinction between neuropathic and nociceptive pain as clinically defined entities, and they often co-exist. Trauma and surgery cause nociceptive as well as neuropathic pain due to the cutting of nerve endings.

3.7 Receptors

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

3.7.1 Opiate receptors

They respond to endogenous and exogenous opiates. Note that opiate receptors are also located peripherally along the nerve fibre from the dorsal horn. This explains the effect of
opioids when administered intra-articularly or into the subcutaneous (SC) tissue. The opiate receptors are mainly located presynaptically (75%). Activation of the opioid receptors reduces the release of neurotransmitters from the first-order neurons while inflammation and nerve injury result in the presynaptic loss of opioid receptors.

3.7.2 GABA and the glycine receptors

GABA and the glycine receptors in the CNS have an inhibitory function. When GABA binds to its receptor, it increases chloride ion flow through chloride channels resulting in hyperpolarisation of the neuron membrane. GABA-A receptors occur mainly postsynaptically and respond to endogenous GABA ligand and to benzodiazepines. GABA-B receptors occur presynaptically and respond to endogenous GABA and to baclofen. Barbiturates, anaesthetic drugs and corticosteroids are also thought to activate GABA-B receptors.

3.7.3 Adrenoreceptors

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

3.7.4 N-methyl-D-aspartic acid receptor

Glutamate and substance P are released from the nociceptive first-order afferents, which activate the low-threshold AMPA and NK-1 receptors which, in turn, activate the NMDA receptors. The removal of the Mg\(^{2+}\) plug is followed by an influx of Ca\(^{2+}\) into the cells and subsequent depolarisation.

Ketamine is an indirect 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.

3.7.5 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, leukotrienes, interleukins (ILs) and N-arachidonoyl dopamine. Stimulation of these receptors, once opened, allows for the influx of charged portions of large molecules (i.e. charged fraction of local anaesthetic drugs, thereby increasing intracellular availability of local anaesthetic drugs to bind to the Na\(^{+}\) channel).

Other TRP ion channels have been described and found to be important in nociceceptor activation. TRPV2-4, as well as TRPM8 and TRPA1, are all activated by temperature in the noxious and nonnoxious range, and together encode the entire temperature spectrum.
3.8 Autonomic nervous system

The autonomic nervous system (ANS) is closely linked to the nociceptive pathways. The sympathetic system is an efferent system and 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), and
- peripheral level (somatic and visceral nociception causes vasodilatation, tissue damage and the subsequent release of neurotransmitters; circulating catecholamine and NA released from the sympathetic fibres perpetuate the noxious stimulus).

3.9 Psychological aspects of acute pain

Pain is an individual biopsychosocial phenomenon and is largely influenced by culture, previous pain experience and the ability to cope. It is a personal and subjective experience. Preoperative anxiety has been shown to contribute to increased postoperative pain, and preoperative depression is a predictor of postoperative pain.

3.10 The progression of acute to chronic pain

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

Risk factors for the development of chronic pain include the following:

- Intense and prolonged preoperative and/or postoperative pain
- Repeated surgery
- Perioperative chemotherapy and/or radiotherapy
- Postoperative complications (e.g. infection)

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

Table IV: Surgical procedures with an increased incidence of chronic pain

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental surgery</td>
<td>5–13</td>
</tr>
<tr>
<td>Vasectomy</td>
<td>0–37</td>
</tr>
<tr>
<td>Cholecystectomy</td>
<td>3–56</td>
</tr>
<tr>
<td>Mastectomy</td>
<td>11–57</td>
</tr>
<tr>
<td>Inguinal hernia repair</td>
<td>0–63</td>
</tr>
<tr>
<td>Thoracotomy</td>
<td>5–67</td>
</tr>
<tr>
<td>Amputations</td>
<td>30–85</td>
</tr>
</tbody>
</table>
Central sensitisation and wind-up phenomena are the pathophysiological mechanisms postulated to be involved in chronic pain development.

3.11 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 both provide pain relief as a humane measure and minimise the multisystem 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 adrenocorticotropic hormone (ACTH), cortisol, antidiuretic hormone (ADH), catecholamines, angiotensin II, interleukin (IL)-1 and IL-6, and tumour necrosis factor (Table V).

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 (DVT). Anxiety, helplessness, loss of control, an inability to interact and sleep deprivation all contribute to psychological disturbances, which can also increase the risk of persistent pain developing.

Table V: Adverse effects of pain

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

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

Bibliography

4. Assessment of acute pain

4.1 Introduction

A reliable assessment of acute pain is necessary to ensure appropriate, safe and effective pain management. The assessment of pain should form part of all routine vital observations so that therapy can be individualised according to patient response.

Pain should be assessed within a biopsychosocial model which recognises the influence of physiological, psychological, cultural and environmental factors on the overall pain experience. Therefore, a particular pain rating should not be the only factor that determines a specific intervention.

4.2 Pain measurement tools

Self-reporting is an important part of pain assessment. However, it is also important to acknowledge that self-reporting is affected by the language, culture, perceptions of disease, and cognitive skills of both the patient and the caregiver.

4.2.1 Pain history

The assessment of acute pain includes a thorough general medical history, a specific ‘pain history’ (Table I), a physical examination and an evaluation of associated functional impairment. It may help to distinguish between different underlying pain states, such as nociceptive (somatic and visceral) and neuropathic pain, which require different treatment modalities.

Characteristics of somatic pain include the following:

- sharp
- hot or stinging
- well localised
- associated with local and surrounding tenderness

Characteristics of visceral pain include the following:

- dull
- cramping or colicky
- poorly localised
- associated with local tenderness and/or referred pain
- can be associated with ANS phenomena, including nausea, sweating and cardiovascular (CV) changes

While nociceptive pain typically predominates in the acute pain setting, neuropathic pain may co-exist.
Features of neuropathic pain include the following:

- circumstances associated with a high risk of nerve injury (e.g. thoracic or chest wall procedures, amputations and hernia repairs)
- pain descriptors such as burning, shooting or stabbing
- paroxysmal or spontaneous nature of the pain, without clear precipitating factors
- presence of dysaesthesias (spontaneous or evoked unpleasant abnormal sensations)
- hyperalgesia (increased response to a normally painful stimulus), allodynia (pain due to a stimulus that does not normally evoke pain, such as light touch) or areas of hypoaesthesia
- regional autonomic features (changes in colour, temperature and sweating)
- phantom phenomena

**Table I: Fundamentals of a pain history**

| Site of pain            | a. Primary location  
|                        | b. Radiating pain   
|                        | c. Referred pain    
| Circumstances associated with pain onset | a. Trauma or surgical procedures 
| Intensity of pain       | a. Current pain, highest intensity 
|                        | b. At rest and during movement 
|                        | c. Temporal factors: duration, during last week, continuous or intermittent 
|                        | d. Aggravating and relieving factors 
| Associated symptoms    | a. Effect of pain on daily activity and sleep 
|                        | b. Autonomic phenomena: nausea, sweating, CV changes 
| Treatment              | a. Current and previous medications: dose, frequency of use, efficacy, adverse effects 
|                        | b. Other treatment (e.g. transcutaneous electrical nerve stimulation) 
|                        | c. Health professionals consulted 
| Medical history        | a. Previous or co-existing pain conditions and treatment outcomes 
|                        | b. Previous or co-existing medical conditions 
| Factors affecting symptomatic treatment | a. Belief concerning the causes of pain 
|                                                | b. Knowledge, expectations and preferences for pain management 
|                                                | c. Reduction in pain required for patient satisfaction or to resume reasonable activities 
|                                                | d. Effect of anxiety or psychiatric disorders (e.g. depression or psychosis) on the coping response 
|                                                | e. Family expectations and beliefs about pain, stress and postoperative care |
4.2.2 Visual analogue scale

The visual analogue scale (VAS) is the most commonly used scale for rating pain intensity in clinical trials. It is a 100 mm or 10 cm (or 10 or 100 units) horizontal line. The left end represents ‘no pain’ and the right end is ‘worst pain imaginable’, with no other tick marks along the length of the line (Figure 1).

A ‘pain meter’ consists of five coloured emoticon faces on the front of a ruler, with corresponding VAS scores on the back. The patients move a slider to mark the intensity of the pain they are experiencing. On the back of the ruler, the slider indicates the VAS in cm or mm, with ‘no pain’ indicated at VAS = 0 and ‘worst pain imaginable’ indicated at VAS = 100 mm or 10 cm (or units). The minimal translation difficulties have led to an unknown number of cross-cultural adaptations of the VAS.

The VAS must be presented to the patient in person (it cannot be used over the telephone). Patients mark the point along the line which they feel corresponds to the level of pain that they are experiencing, and the pain score is recorded as the measurement in millimetres, centimetres or units from the left end of the scale to the patients’ mark. Caution is required when the scale is photocopied as this may change the length of the 10-cm line. Also, the same alignment of the scale should be used consistently with the same patient.

A VAS rating of ≥ 70 mm (units) is indicative of ‘severe pain’ while 0–5 mm (units) indicates ‘no pain’. ‘Mild pain’ is 5–44 mm (units) and ‘moderate pain’ is 45–69 mm (units). The emoticon faces on the VAS may also allow for the evaluation of other aspects of the pain experience (e.g. affective components, patient satisfaction or adverse effects).

Figure 1: Visual analogue scale
The VAS requires concentration and coordination. This could mean that the assessment of pain immediately after surgery is more difficult, leading to greater interpatient variability in pain scores because of transient anaesthetic-related cognitive impairments and decreases in visual acuity. It also cannot be used in patients with visual or cognitive impairment.

The VAS has similar sensitivity to the numeric rating scale (NRS) when comparing acute postoperative pain intensity, and has greater sensitivity than a four-category verbal descriptor scale. VAS is more sensitive to small changes than simple descriptive ordinal scales in which symptoms are rated, for example, as mild or slight, moderate, or severe to agonising. The VAS is meaningful when used with the same patient over time, but not necessarily between patients.

4.2.3 Numerical rating scale

The eleven-point (0–10) NRS is similar to the VAS, but can be administered either verbally or in a written format. Patients are asked to rate the intensity of their pain according to a point scale from 0 (‘no pain’) to 10 (‘worst pain imaginable’). A pain score of 1–3 is considered ‘mild pain’, 4–7 is considered ‘moderate pain’ and a score of > 7 is ‘severe pain’. Pain relief may be measured in the reverse direction with 0 representing ‘no relief’ and 10 representing ‘complete relief’.

The NRS does not require any physical materials and is widely accepted in clinical practice. Strengths of the NRS over the VAS are that it can be administered either verbally or in writing, and its simplicity of scoring. The NRS can easily be adapted for use across different cultures and languages. However, scores are subject to social, cognitive and contextual influences. As with the VAS, the NRS is meaningful if used with the same patient over time, but not necessarily between patients.

A disadvantage of the NRS is that it evaluates only one component of the pain experience and intensity; therefore, it does not capture the complexity and idiosyncratic nature of the pain experience or improvements due to symptom fluctuations.

Figure 2: Numerical rating scale
This photo by an unknown author is licensed under CC BY-ND
Pain scales are useful for the assessment of the effectiveness of postoperative analgesia. The VAS and the 11-point NRS are the most commonly used. A reduction in the pain score itself, however, may not equate to an improvement in the patient’s experience. Pooled data from two postoperative analgesic studies found that VAS pain scores of up to 44 mm are consistent with a patient rating of mild pain. Current guidelines recommend titrating analgesia to achieve a VAS pain score of 40 mm or less. Postoperative pain studies using patient-controlled analgesia (PCA) typically titrate to a VAS or NRS pain score of 30 mm.

Pain is both subjective and multidimensional. Neither the VAS nor the NRS captures the complete pain experience. Clinical decisions are made on the basis of existing pain count.

### 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 behavioural observations to interpret expressed pain when patient cannot communicate his/her intensity.

<table>
<thead>
<tr>
<th>Items</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verbal Descriptor Scale</td>
<td></td>
</tr>
<tr>
<td>NO PAIN</td>
<td>0</td>
</tr>
<tr>
<td>MILD PAIN</td>
<td>1</td>
</tr>
<tr>
<td>MODERATE PAIN</td>
<td>2</td>
</tr>
<tr>
<td>SEVERE PAIN</td>
<td>4</td>
</tr>
<tr>
<td>WORST PAIN POSSIBLE</td>
<td>10</td>
</tr>
<tr>
<td>Wong-Baker Facial Grimace Scale</td>
<td></td>
</tr>
<tr>
<td>Alert smiling</td>
<td>0</td>
</tr>
<tr>
<td>No humor</td>
<td>1</td>
</tr>
<tr>
<td>Furrowed brow</td>
<td>2</td>
</tr>
<tr>
<td>Wrinkled nose</td>
<td>4</td>
</tr>
<tr>
<td>Slow blink</td>
<td>8</td>
</tr>
<tr>
<td>Eyes closed</td>
<td>10</td>
</tr>
<tr>
<td>Activity Tolerance Scale</td>
<td></td>
</tr>
<tr>
<td>NO PAIN</td>
<td>0</td>
</tr>
<tr>
<td>CAN BE IGNORED</td>
<td>1</td>
</tr>
<tr>
<td>INTERFERS WITH TASKS</td>
<td>2</td>
</tr>
<tr>
<td>INTERFERS WITH CONCENTRATION</td>
<td>4</td>
</tr>
<tr>
<td>INTERFERS WITH BASIC NEEDS</td>
<td>8</td>
</tr>
<tr>
<td>BEDREST REQUIRED</td>
<td>10</td>
</tr>
<tr>
<td>The pain assessment in advanced dementia scale</td>
<td></td>
</tr>
</tbody>
</table>

- **Breathing independent of vocalisation**
  - Normal
  - Occasional laboured breathing, short period of hyperventilation
  - Noisy laboured breathing, 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

**Figure 3: Universal pain assessment tool and the pain assessment in advanced dementia (PAINAD) scale**
Therefore, it is important to know what changes from a particular baseline is clinically significant from a patient’s perspective. The extremes of pain indicated on a VAS, typically ‘no pain’ and ‘worst pain imaginable’, may not accurately represent absolute limits of perception.

### 4.3 Measurement considerations in special populations

It is important to recognise that patients with impairment or a limited ability to communicate verbally could also experience pain and be in need of pain-relieving treatment. Limiting factors include old age, dementia, unconsciousness or sedation. Other circumstances that pose a particular challenge when assessing pain include breakthrough pain either in cancer patients or those with chronic noncancer pain, as well as patients with a history of, or current, drug misuse. Physiological signs can be useful to indicate the presence of pain in elderly patients – particularly those with cognitive impairment. These clinical signs include hypertension, tachycardia or bradycardia, sweating and increased muscle tone.

#### 4.3.1 The Wong-Baker FACES pain scale

For those patients with some, albeit limited, ability to communicate, the Wong-Baker FACES pain scale (FPS) (Figure 3) can be useful. Patients are shown a range of faces indicating varying degrees of distress, and they are asked to select the expression that corresponds to the amount of pain which they are currently experiencing.

#### 4.3.2 The pain assessment in advanced dementia

The pain assessment in advanced dementia (PAINAD) scale is an observer-rated tool for assessing pain-related behaviour, and it is partly based on the FLACC (face, legs, activity, cry, consolability) scale.

#### 4.3.3 The behavioural pain scale

Assessing pain in patients who are critically ill is a challenge, particularly when patients are nonverbal due to sedation or lack of consciousness. This is especially true where altered mental state is the main risk factor for patients receiving no pain assessment.

The behavioural pain scale (BPS) has been validated for use in critically ill, sedated and mechanically-ventilated patients. The BPS score is calculated as the sum of three subscales (facial expression, upper limb movements and compliance with mechanical ventilation). Of the pain scales developed for use in adult patients receiving intensive care, the BPS is considered to be one of the most valid and reliable (Table II).
Table II: The behavioural pain scale

<table>
<thead>
<tr>
<th>Score</th>
<th>Facial expression</th>
<th>Verbalisation</th>
<th>Body position</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Neutral/positive facial expression, composed, calm</td>
<td>Normal conversation laugh, crow</td>
<td>Inactive, laying relaxed with all extremities, sitting, walking</td>
</tr>
<tr>
<td>1</td>
<td>Negative facial expression, concerned</td>
<td>Completely quiet or sobbing and/or complaining but not because of pain</td>
<td>Restless movements, shifting fashion and/or touching wound or wound area</td>
</tr>
<tr>
<td>2</td>
<td>Negative facial expression, grimace, distorted face</td>
<td>Crying, screaming and/or complaining of pain</td>
<td>Lying rigid and/or drawn up with legs and arms to the body</td>
</tr>
</tbody>
</table>

4.4 Monitoring guidelines

In acute pain management, assessment must be undertaken at appropriate intervals. At these times, an evaluation of pain intensity, functional impact and adverse effects of treatment must be undertaken. Assessment tools and scales must be consistent, valid and reliable. In addition, pain assessment should lead to re-evaluation of and changes in pain management to ensure improvements in the quality of care (Figure 4).

Figure 4: Pain assessment and re-evaluation
Mild – follow from step 1 or 2
Moderate – follow from step 1 + 2 or 3
Severe – starts at step 3 + 2 + 1 or 4

Figure 5: Treatment guide for acute pain

Bibliography

5. Drug listing – enteral and parental

Note that while examples of generic drugs are listed below, the list should not be considered comprehensive. Drugs are regularly added and removed by pharmaceutical companies and the latest drug indices should be consulted if necessary.

5.1 Opioids – mainly for severe pain

Opioids are grouped into the following categories:

1. Opioid agonists
2. Opioid antagonists
3. Opioid dualists – with agonist and antagonist properties, theoretically cancelling side effects
4. Atypical opioids

Side effects of all opioids include the following:

1. Respiratory depression – opioid patches should not be used for acute pain
2. Sedation (best indicator of incipient respiratory depression)
3. Nausea and vomiting
4. Constipation
5. Pruritis
6. Tolerance
7. Addiction
### Table I: Relevant information for opioids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult</th>
<th>Porphyria</th>
<th>Relevant information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphine</strong>&lt;br&gt;MST Continus&lt;br&gt;• Jurnista (hydromorphone HCl)&lt;br&gt;• Morphine Sulphate-Fresenius&lt;br&gt;• Pharm-Q Morphine injection&lt;br&gt;• Cyclimorph (Morphine + Cyclizine)</td>
<td>Oral&lt;br&gt;10–20 mg q 12-hourly&lt;br&gt;<strong>Intramuscular</strong>&lt;br&gt;0.1–0.3 mg/kg q 4-hourly&lt;br&gt;<strong>Intravenous</strong>&lt;br&gt;<strong>Bolus</strong>&lt;br&gt;1–5 mg q 1-hourly&lt;br&gt;<strong>Infusion</strong>&lt;br&gt;Loading dose followed by titration guided by pain and sedation scale – 3–5 mg/hr&lt;br&gt;<strong>PCA</strong>&lt;br&gt;Bolus 1–2 mg with 5–10 min lockout time</td>
<td>USE&lt;br&gt;a. Oral morphine&lt;br&gt;• Preparations are used in the treatment of chronic pain&lt;br&gt;• Dosage is dependent upon the severity of pain and patients’ previous analgesic history (i.e. opioid naïve or not)&lt;br&gt;b. Intravenous morphine&lt;br&gt;• IV titrations should be done in ICU&lt;br&gt;• Infusions may readily cause excessive accumulation of the drug with respiratory depression and, if undetected, could lead to death&lt;br&gt;• PCA (patient-controlled analgesia) is a safer option&lt;br&gt;• IV opioid PCA provides better analgesia than conventional parenteral opioid regimens&lt;br&gt;• Patient preference for IV PCA is higher when compared with conventional regimens&lt;br&gt;c. Neuraxial morphine&lt;br&gt;• Neuraxial opioids should be preservative free (PF)&lt;br&gt;• Extreme caution with neuraxial morphine is advised because the onset of respiratory depression only occurs 8–12 hours after administration&lt;br&gt;• Respiratory depression in the elderly is more prevalent and the neuraxial dose of opioids should be drastically decreased</td>
<td></td>
</tr>
<tr>
<td><strong>Pethidine</strong>&lt;br&gt;• Pethidine HCl-Fresenius&lt;br&gt;• Pharma-Q Pethidine</td>
<td><strong>Intramuscular</strong>&lt;br&gt;1–1.5 mg/kg q 3–4-hourly&lt;br&gt;<strong>PCA</strong>&lt;br&gt;10–20 mg bolus with 5–10 min lockout time</td>
<td>USE&lt;br&gt;a. Pethidine has never been shown to be superior to other opioids&lt;br&gt;b. It is no longer considered a ‘first line’ analgesic&lt;br&gt;c. Use depends on the preference and experience of the prescriber&lt;br&gt;d. Pethidine commonly causes euphoria/dysphoria&lt;br&gt;e. Drug interactions with MAOI and SSRI</td>
<td></td>
</tr>
<tr>
<td><strong>Papaveratum</strong>&lt;br&gt;• Omnopon-Fresenius</td>
<td><strong>Intramuscular</strong>&lt;br&gt;0.15 mg q 4-hourly</td>
<td><strong>Not for children under the age of 1 year</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Dihydrocodeine Tartrate</strong>&lt;br&gt;• Df-118</td>
<td>Oral&lt;br&gt;30 mg q 4–6-hourly&lt;br&gt;<strong>Intramuscular</strong>&lt;br&gt;25–50 mg q 4–6-hourly</td>
<td>USE&lt;br&gt;a. 30 mg of DF-118 gives analgesia comparative to 10 mg morphine&lt;br&gt;b. May worsen asthma</td>
<td></td>
</tr>
<tr>
<td><strong>Opioid agonists</strong>&lt;br&gt;<strong>Relevant information</strong>&lt;br&gt;a. Oral morphine&lt;br&gt;b. Intravenous morphine&lt;br&gt;c. Neuraxial morphine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Guidelines for the management of acute pain in specific scenarios 2022

#### Codeine
- Lennon-Codeine Phosphate
  - Dose: 15–60 mg daily p.o.
  - USE

#### Mild to moderate pain
- Codeine is a prodrug with low receptor affinity
- Only 10% is demethylated via CYP2D6 enzymes to morphine
- Ultra-rapid metabolisers may produce high levels of morphine which in turn may lead to respiratory depression in children
- Conversely, poor metabolisers may produce such low levels of morphine that no analgesia will be evident
- Respiratory depression may also occur in patients with obstructive sleep apnoea (OSA)
- The FDA has contraindicated the use in children under 12 years of age

#### Oxycodone
- Oxynorm – injection and immediate-release tabs
- Oxycotin – prolonged-release tabs
- TarginAct – prolonged-release tabs
- Oxycorrell – caps

#### Oxynorm tablets (sustained-release)
- Dose: 5 mg, 10 mg, 20 mg, 40 mg, 80 mg
- Recommendation is to start with 5–10 mg p.o. bd in an opioid naïve patient

#### Oxynorm injection
- 1–10 mg/ml slowly over 1–2 minutes IV
- For PCA and infusion check package insert

#### Oral
- 5 mg, 10 mg, 20 mg
- For severe postoperative pain
- Start with 5 mg p.o. q 4–6-hourly

#### TarginAct (prolonged-release)
- 5 mg, 10 mg, 20 mg, 40 mg q 12-hourly

#### Oxycorrell
- 5 mg, 10 mg, 20 mg q 4–6-hourly

#### Mild to moderate to severe pain
- Has identical opioid side effect and contraindication profile
- Opioid alkaloid thebaine is the main ingredient and works on µ₁-receptor
- Pharmacology depends on age of patient; elderly patients have a 15% higher plasma level
- Excreted in urine, drastically decrease dose in renal failure
- The combination of oxycodone and naloxone in TarginAct® decreases constipation
- This combination may also be a deterrent of abuse potential
<table>
<thead>
<tr>
<th><strong>Fentanyl</strong></th>
<th><strong>Transdermal patches</strong></th>
<th>• These patches are only recommended in chronic pain management</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ADCO Tenyl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Durogesic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Fendermal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Opioid dualists**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult</th>
<th>Porphyria</th>
<th>Relevant information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tilidine</strong></td>
<td>Drops</td>
<td>UWECO</td>
<td><strong>For moderate to severe pain</strong></td>
</tr>
</tbody>
</table>
| • Valeron | 10–20 drops q 6–8-hourly |  | • 1 drop = 2–5 mg  
• Probably better to calculate dose according to **weight** rather than age  
• **Not for children under the age of 1 year**  
• Do not exceed single dose of **1 mg/kg**  
• Drops are useful in **adults** requiring analgesia and having dysphagia |

<table>
<thead>
<tr>
<th><strong>Pentazocine</strong></th>
<th>Injection</th>
<th>AVOID</th>
<th><strong>For moderate to severe pain</strong></th>
</tr>
</thead>
</table>
| • Sosenol | 30–40 mg q 3–4-hourly IM/IV/SC  (if IV, only 30 mg/dose)  Maximum of 360 mg/24 hours |  | • Not a potent analgesic, but proponents claim superior postoperative analgesia for varicose vein operations  
• Also increases peripheral vascular resistance that may be detrimental in elderly patients  
• Respiratory depression is prevalent in children |

<table>
<thead>
<tr>
<th><strong>Buprenorphine</strong></th>
<th>Transdermal patch</th>
<th>USE</th>
<th><strong>For moderate to severe pain</strong></th>
</tr>
</thead>
</table>
| • Sovenor (transdermal)  
• Subutex (high dose for addicts)  
• Temgesic (sublingual and parenteral for analgesia) | 5, 10 or 20µg/hr  
**Sublingual** 0.2–0.4 mg q 6–8-hourly  
(Dose for opioid addiction is higher)  
**Deep IM/slow IV infusion** 0.3–0.6 mg q 6–8-hourly |  | • Transdermal patch (Sovenor) recommended for chronic pain  
• High doses (Subutex) used for weaning patients with opioid addiction  
• Patients may experience excitation/hallucinations  
• Contraindications:  
◦ Concomitant MAOI  
◦ Acute asthma  
◦ Not for children under the age of 12 years  
◦ IM injection must be ‘deep’ |

**Opioid antagonists**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult</th>
<th>Porphyria</th>
<th>Relevant information</th>
</tr>
</thead>
</table>
| **Naloxone** | IV |  | • May cause pulmonary oedema if entire calculated dose is rapidly administrated  
• Ampoule contains 0.4 mg; this should be diluted in 10 ml prior to administration  
• Naloxone reverses all opioid effects  
• The half-life may only be 15–60 minutes  
• Unwanted opioid side effects may re-occur, warranting re-administration of naloxone |
| • Naloxone HCl Fresenius  
• Pharma-Q Naloxone HCl | 0.006 mg/kg |  |  |
### Atypical opioid

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult</th>
<th>Porphyria</th>
<th>Relevant information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tramadol</td>
<td></td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td>• Austell-Tramadol</td>
<td>Capsules</td>
<td>USE</td>
<td>Not for children under the age of 12 years</td>
</tr>
<tr>
<td>• Dojotram</td>
<td>50–150 mg q</td>
<td></td>
<td>• It is a prodrug and reduced metabolism via CYP 2D6 may result in reduced active metabolite in 10% of the caucasian population</td>
</tr>
<tr>
<td>• Domadol</td>
<td>4–6-hourly to a maximum of</td>
<td></td>
<td>• Tramadol acts on μ1-receptors, noradrenaline and serotonin receptors</td>
</tr>
<tr>
<td>• Synotram</td>
<td>400 mg/day</td>
<td></td>
<td>• Avoid/caution using concomitant 5-HT3-antagonists (anti-emetics), SSRIs, antimigraine medication, as serotonergic syndrome may occur</td>
</tr>
<tr>
<td>• Tamostra</td>
<td>SR tabs</td>
<td></td>
<td>• Avoid higher doses and rapid IV administration which may lead to an increased incidence of nausea and vomiting</td>
</tr>
<tr>
<td>• Tramacet</td>
<td>100–150 mg q</td>
<td></td>
<td>• Therapeutic range: moderate to severe pain</td>
</tr>
<tr>
<td>• Tramal</td>
<td>12-hourly</td>
<td></td>
<td>• Combinations with paracetamol will be discussed in oral combination analgesics</td>
</tr>
<tr>
<td>• Tramahexal</td>
<td>Drops (unavailable)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Tramaspen</td>
<td>100 mg = 1 ml = 40 drops</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Tramazac</td>
<td>100 mg IM</td>
<td>IV/IM</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tapentadol</th>
<th>Oral</th>
<th>?</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Palexia</td>
<td>50–100 mg q</td>
<td></td>
<td>• Recommended for short-term use in moderate to severe pain</td>
</tr>
<tr>
<td></td>
<td>4–6-hourly</td>
<td></td>
<td>• This synthetic drug is a single enantiomer and therefore genetic CYP variations do not influence its pharmacokinetic profile</td>
</tr>
<tr>
<td></td>
<td>SR</td>
<td></td>
<td>• It works on μ1-receptors and has a degree of selectivity for NRI</td>
</tr>
<tr>
<td></td>
<td>50–200 mg q</td>
<td></td>
<td>• There is minimal SRI and, therefore, less chance of serotonin syndrome</td>
</tr>
<tr>
<td></td>
<td>12-hourly</td>
<td></td>
<td>• There is reduced nausea and vomiting compared to oxycodone</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Used for moderate to severe postoperative pain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• May be of use for neuropathic pain and chronic pain syndromes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• There are decreased ‘opioid like’ side effects</td>
</tr>
</tbody>
</table>

bd – twice daily, PCA – patient-controlled analgesia, p.o. – per os (orally), IM – intramuscular, IV – intravenous, MAOIs – monoamine oxidase inhibitors, SSRIs – selective serotonin reuptake inhibitors, USE – safe, UWC – use with caution, UWECO – use with extreme caution, may be unsafe, AVOID – unsafe, SR – slow-release, NRI – noradrenaline reuptake
5.2 Paracetamol

- Excessive dosage may cause irreversible liver failure.
- Use with caution or decrease the dose for the following:
  - Acute liver disease
  - Alcohol-related liver disease
  - Glucose-6-phosphate dehydrogenase deficiency

### Table II: Relevant information on paracetamol

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult</th>
<th>Porphyria</th>
<th>Relevant information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enteral</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| **Oral**  | 0.5–1 g q 4-hourly to a maximum of 4 g/day | USE | Mild to moderate pain only
| 500 mg/tab |       |           | • Package insert does not recommend for babies under the age of 3 months |
| • Actomol  |       |           |                                                           |
| • Adco-Napamol |       |           |                                                           |
| • Austell-Paracetamol |       |           |                                                           |
| • Calpol GSK |       |           |                                                           |
| • Feverpain |       |           |                                                           |
| • Painamol  |       |           |                                                           |
| • Panado    |       |           |                                                           |
| • Parafizz  |       |           |                                                           |
| • Painamol  | 2 caplets q 8-hourly, maximum 6 caplets/24 hours | USE | Do not crush, chew or dissolve the extended-release caplets |
| • Panado    |       |           |                                                           |
| **Rectal** | N/A   |           | Rectal absorption is inconsistent                         |
| • Empaped  |       |           | Caution in renal and liver disease                       |
| **Parenteral** |       |           |                                                           |
| **Intravenous** | (> 50 kg) | Intravenous dose | Prescription carefully according to weight, age and comorbidity |
| • Cetafuse IV | 1 g q 6-hourly to maximum dose of 4 g/24 hours | | Administration of infusion should occur over 15 minutes |
| • Paracetamol Biotech IV |       | | Registered use only for 24–48 hours |
| • Paracetamol Fresenius IV |       | | Hypotension is known to occur and may be due to mannitol in some formulations |
| • Paraspen IV |       | | Dose not administer any other oral paracetamol concomitantly, check combination analgesics for paracetamol |
| • Perfalgan IV |       | | An inadvertent IV overdose should be treated with N-acetylcysteine |

N/A – not applicable, USE – safe, UWC – use with caution, UWECO – use with extreme caution, may be unsafe, AVOID – unsafe
5.3  Nonsteroidal anti-inflammatory drugs for mild to moderate pain relief

NSAIDs can be divided into the following categories:

1. COX inhibitors
2. Selective COX-2 inhibitors
3. Specific COX-2 inhibitors

Side effects of NSAIDs include:

1. Renal damage, especially if prior renal impairment or hypovolaemia
2. Platelet impairment
3. Gastric erosions and haemorrhage
4. Possible poor wound healing
5. Asthma may be exacerbated in some patients

Sole drug for parenteral administration is parecoxib.

Table III: Relevant information on NSAIDs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult</th>
<th>Porphyria</th>
<th>Relevant information</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin</strong></td>
<td></td>
<td>USE</td>
<td>• Associated with Reye’s syndrome</td>
</tr>
<tr>
<td>• Disprin</td>
<td>300–900 mg q</td>
<td></td>
<td>• Caution in:</td>
</tr>
<tr>
<td>• Dr Du Toit’s Pain</td>
<td>4–6-hourly to a</td>
<td></td>
<td>◦ elderly</td>
</tr>
<tr>
<td>Expeller tablets</td>
<td>maximum of 4 g</td>
<td></td>
<td>◦ renal function</td>
</tr>
<tr>
<td>• Ecotrin</td>
<td>daily</td>
<td></td>
<td>◦ gastric bleeds</td>
</tr>
<tr>
<td><strong>Diclofenac</strong></td>
<td></td>
<td>UWECO</td>
<td></td>
</tr>
<tr>
<td>• Adco-Diclofenac</td>
<td>Oral</td>
<td></td>
<td><strong>Mild to moderate pain</strong></td>
</tr>
<tr>
<td>• Austell-Diclofenac</td>
<td>25–50 mg q 8-hourly</td>
<td></td>
<td>• Available as drops</td>
</tr>
<tr>
<td>Sodium</td>
<td>to a maximum of</td>
<td></td>
<td>• Not for children under the age of 2</td>
</tr>
<tr>
<td>• Bio Diclofenac</td>
<td>150 mg/day</td>
<td></td>
<td>years via any route</td>
</tr>
<tr>
<td>injection</td>
<td></td>
<td></td>
<td>• Good COX1:COX2 ratio</td>
</tr>
<tr>
<td>• Cataflam</td>
<td></td>
<td></td>
<td>• Avoid in the following:</td>
</tr>
<tr>
<td>• Catafast D</td>
<td></td>
<td></td>
<td>◦ Asthma</td>
</tr>
<tr>
<td>• Diclofenac SR</td>
<td></td>
<td></td>
<td>◦ GIT/renal disease</td>
</tr>
<tr>
<td>Biotech</td>
<td></td>
<td></td>
<td>◦ Intra- and postoperative</td>
</tr>
<tr>
<td>• Dicloflam</td>
<td></td>
<td></td>
<td>hypovolaemia</td>
</tr>
<tr>
<td>• Fortfen</td>
<td></td>
<td></td>
<td><strong>Intramuscular injections</strong></td>
</tr>
<tr>
<td>• K-Fenak</td>
<td></td>
<td></td>
<td>• Must be deep intraluteral</td>
</tr>
<tr>
<td>• Mylan Diclofenac</td>
<td></td>
<td></td>
<td>• May cause necrotising fasciitis –</td>
</tr>
<tr>
<td>+ tabs</td>
<td></td>
<td></td>
<td>therefore, change to oral therapy ASAP</td>
</tr>
<tr>
<td>• Veltex</td>
<td></td>
<td></td>
<td>• Inadvertent injection into nerve may</td>
</tr>
<tr>
<td>• Voltaren</td>
<td></td>
<td></td>
<td>cause irreversible neural damage</td>
</tr>
<tr>
<td>• Voltaren Acti-Go</td>
<td></td>
<td></td>
<td>• Suppositories can cause proctitis,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>avoid use for longer than 5 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Controversial for posttonsillecotomy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Swallow tablet whole with food; do not</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>chew</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Combination with prostacyclin may</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>decrease NSAID side effects</td>
</tr>
<tr>
<td>• Arthrotec</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Diclofenac 75 mg +</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>misoprostol 200 µg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ibuprofen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>• Advil</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>• Betagesic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>• Betaprofen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>• Bren-400</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>• Brufen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>• Ibucare</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>• Ibugesic Fever and Pain</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>• Nurofen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>• Pedea</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>200–400 mg q 4–6-hourly to a maximum of 1 200 mg/day</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**USE**

- Beware of GIT bleeds
- Beware of asthma
- For moderate pain

<table>
<thead>
<tr>
<th><strong>Indomethacin</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>• Arthrexin</strong></td>
</tr>
<tr>
<td><strong>• Betacin</strong></td>
</tr>
<tr>
<td><strong>• Flamecid</strong></td>
</tr>
<tr>
<td><strong>• Mediflex</strong></td>
</tr>
<tr>
<td><strong>25–50 mg q 6–8-hourly to a maximum of 200 mg/day</strong></td>
</tr>
</tbody>
</table>

**USE**

- Take with food/antacid/milk
- GIT bleeds/asthma/renal insufficiency
- CNS disturbances

<table>
<thead>
<tr>
<th><strong>Ketoprofen</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>• Fastum Gel</strong></td>
</tr>
<tr>
<td><strong>5–15 cm to affected area q 12-hourly</strong></td>
</tr>
</tbody>
</table>

**USE**

- Not for children under the age of 6 months or weighing less than 10 kg
- Do not administer for longer than 5 days

<table>
<thead>
<tr>
<th><strong>Mefenamic acid</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>• Adco-Mefenamic Acid</strong></td>
</tr>
<tr>
<td><strong>• Ponac</strong></td>
</tr>
<tr>
<td><strong>• Ponstan</strong></td>
</tr>
<tr>
<td><strong>• Ponstel</strong></td>
</tr>
<tr>
<td><strong>500 mg q 8-hourly</strong></td>
</tr>
</tbody>
</table>

**USE**

- Not for children under the age of 18 years
- GIT, renal and platelet concerns

<table>
<thead>
<tr>
<th><strong>Lornoxicam</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>• Xefo</strong></td>
</tr>
<tr>
<td><strong>8–16 mg/day in 2–3 divided doses</strong></td>
</tr>
</tbody>
</table>

**USE**

- Not for children under the age of 5 years
- Caution if:
  - Diathesis for GIT bleeding
  - Renal compromise
  - Asthma
  - Drug interactions with hydantoins/anticoagulants/sulphonylureas
  - For mild to moderate pain

<table>
<thead>
<tr>
<th><strong>Naproxen</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>• Adco-Naproxen</strong></td>
</tr>
<tr>
<td><strong>• Aleve</strong></td>
</tr>
<tr>
<td><strong>• Bio-Naproxen</strong></td>
</tr>
<tr>
<td><strong>• Litha Naproxen</strong></td>
</tr>
<tr>
<td><strong>• Mylan Naproxen</strong></td>
</tr>
<tr>
<td><strong>• Nafasol</strong></td>
</tr>
<tr>
<td><strong>• Napflam</strong></td>
</tr>
<tr>
<td><strong>• Vimovo + esomeprazole</strong></td>
</tr>
<tr>
<td><strong>500 mg q 12-hourly</strong></td>
</tr>
</tbody>
</table>

**USE**

- Not for children under the age of 5 years

- Caution if:
  - Usual concerns with NSAIDs
  - Caution if hepatic insufficiency
  - Long half-life, may be given as a single daily dose
  - For moderate pain

<table>
<thead>
<tr>
<th><strong>Piroxicam</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>• Brexecam</strong></td>
</tr>
<tr>
<td><strong>• Piroxicam Actor DT</strong></td>
</tr>
<tr>
<td><strong>• Pixicam</strong></td>
</tr>
<tr>
<td><strong>• Pyrocaps</strong></td>
</tr>
<tr>
<td><strong>• Rheugesic</strong></td>
</tr>
<tr>
<td><strong>• Xycam</strong></td>
</tr>
<tr>
<td><strong>20–30–40 mg daily</strong></td>
</tr>
</tbody>
</table>

**USE**

- Not recommended for children
- Usual concerns with NSAIDs
- Caution if hepatic insufficiency
- Long half-life, may be given as a single daily dose
- For moderate pain
### Selective COX-2 inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult</th>
<th>Porphyria</th>
<th>Relevant information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meloxicam</td>
<td>7.5 mg q 12-hourly or 15 mg daily</td>
<td>USE</td>
<td>Give with food&lt;br&gt;Selective COX-2 inhibitor – however, in very high doses may have COX-1 inhibition as well</td>
</tr>
<tr>
<td>• Adco-Meloxicam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Coxflam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Coxitec</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Flamaryx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Flexocam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Loxiflam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Medoxicam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Meloxicam</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Melzy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Mobic</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Selective COX-2 inhibitors (COXIB)**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adult</th>
<th>USE</th>
<th>Relevant information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etoricoxib</td>
<td>60 mg, 90 mg and 120 mg q 24-hourly</td>
<td></td>
<td>Moderate to severe pain</td>
</tr>
<tr>
<td>• Adco-Etoricoxib</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Arcoxia</td>
<td>100–200 mg q</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Coricib</td>
<td>12-hourly to a maximum of 400 mg/day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Exinef</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Extrib</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Celecoxib</th>
<th>USE</th>
<th>Not for children under the age of 18 years&lt;br&gt;Contraindicated for sulphonamide allergy&lt;br&gt;Selective COX-2 inhibitor (COXIB), i.e. only has COX-2 effects even at very large doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Celebrex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Celecoxib Unicorn</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Coxleon</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parecoxib</th>
<th>Not for children under the age of 18 years&lt;br&gt;Contraindicated for sulphonamide allergy</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Rayzon</td>
<td>40 mg q 6–12-hourly IV/IM, maximum 80 mg/day</td>
</tr>
</tbody>
</table>

COX – cyclo-oxygenase, GIT – gastrointestinal tract, CNS – central nervous system, NSAIDs – nonsteroidal anti-inflammatory drugs, USE – safe, UWC – use with caution, UWECO – use with extreme caution, may be unsafe, AVOID – unsafe

---

**5.4 Approach to oral combination analgesics**

Combinations of all the above oral drugs are used extensively in South Africa. It is, therefore, not possible to include all combinations in this section. The rationale for drug combination is to reduce the dose of each drug and, hence, improve the side effect profile. The list below gives some components in these combination preparations and highlights specific effects or side effects.

1. Paracetamol
   - The dose is usually lower in combination preparations.
   - Always check that the patient has not received paracetamol via the intravenous (IV) or the rectal route, as overdose may occur.
2. Caffeine hydrate
   - This has a vasodilatory effect and may be good for migraines.

3. Codeine phosphate
   - This has a mild analgesic effect and has to be metabolised to morphine. In a subset of patients, excessive sedation is problematic (see above).

4. Aspirin
   - Use caution if patient has prior history of dyspepsia or bleeding diathesis.

5. Propoxyphene napsylate
   - This has a weak analgesic effect, but some sedation.

6. NSAIDs
   - Use caution if a patient has prior history of dyspepsia or bleeding diathesis and renal impairment.

7. Meprobamate
   - It is a weak analgesic.
   - Probable addiction after 10 days of use; this is a physical as well as emotional addiction.

8. Doxylamine succinate
   - There is not a clear rationale for inclusion in analgesic drugs.

9. Promethazine
   - Phenothiazine with anti-emetic and sedatory effects.
   - ‘Blackbox’ in the USA due to ↑QT interval.

10. Orphenadrine
    - This has an antimuscarinic effect.

11. Diphenhydramine
    - Antihistamine with sedatory effect (blackbox).

Table IV: Relevant information to the approach to combination analgesics

<table>
<thead>
<tr>
<th><strong>NMDA receptor antagonists (excitatory amino acid antagonists)</strong></th>
<th><strong>Drug</strong></th>
<th><strong>Porphyria</strong></th>
<th><strong>Relevant information</strong></th>
</tr>
</thead>
</table>
| Ketamine | Oral | USE | - Side effects:
  - hallucinations
  - excessive salivation
- Synergism with opioids as supposedly decreases opioid tolerance
- No decrease in opioid side effects
- May give some pre-emptive analgesia
- May reduce opioid requirements in opioid-tolerant patients |
| | 0.25 mg/kg, PCA | | |
| | May be added to PCA in combination with morphine | | |
| **Magnesium** | 30 mg/kg at start of induction and then 25 mg/kg/hr | USE | • Concern regarding potentiation of muscle relaxation  
• Decrease in blood pressure, which is usually easily managed  |
| --- | --- | --- | --- |
| **Nitrous oxide** | Nitrous oxide (N₂O) 50%/Oxygen (O₂) 50% | USE | • Do not store cylinders in temperatures below 7 °C  
• Used in labour for analgesia  
• Used in dental chair  
• Appropriate monitoring should always be applied  
• Bone marrow depression occurs with prolonged use  |
| • Entonox |  |  |  |
| **Dextrometorphan** | 45 mg p.o. preoperatively | USE | • Use as premedication for pre-emptive analgesia  
• Said to decrease use of other analgesics post tonsillectomy in adults  
• Addiction potential as no prescription is required  |
| Benylin Original  
Benylin Dry Cough  
Benylin |  |  |  |

### α2-agonists

| **Clonidine** | Oral  
2.5 µg/kg as a premedication  
**Intravenous**  
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/hypotension may manifest  
• Bradycardia may be problematic  |

| **Dexmedetomidine** | LD = 1 µg/kg slowly over 30 minutes  
**MD** = 0.2–0.7 µg/kg/hr | For moderate to severe pain | • Expensive  
• Loading dose should be given slowly over 10–30 minutes  
• Patients on an infusion should always go to ICU for monitoring of level of sedation, bradycardia and hypotension  
• Arterial line is essential for monitoring if drug is given as an infusion  
• Side effects:  
◦ Hypotension  
◦ Sedation  
◦ Bradycardia  
• Bonus: analgesia |
| • Precedex |  |  |  |

PCA – patient-controlled analgesia, LD – loading dose, MD – maintenance dose, NMDA – N-methyl-D-aspartate, USE – safe, UWC – use with caution, UWECO – use with extreme caution, may be unsafe, AVOID – unsafe
5.5 **Local anaesthetics**

LAs are divided into short-acting (e.g. lignocaine) or long-acting (e.g. bupivacaine, ropivacaine) anaesthetics.

The following are possible side effects:

1. Toxic doses
2. Cardiotoxicity
3. Neurotoxicity

<table>
<thead>
<tr>
<th>Table V: Relevant information regarding local anaesthetics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td><strong>Lignocaine 2%</strong></td>
</tr>
<tr>
<td>- Lignocaine-HCl Braun</td>
</tr>
<tr>
<td>- Lignocaine HCl Fresensius Vials</td>
</tr>
<tr>
<td>- Remicaine</td>
</tr>
<tr>
<td>- Xylopect</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Toxic dose</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Topicalisation of mucous membranes</strong></td>
</tr>
<tr>
<td><strong>UWC</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Neurotoxicity occurs before cardiotoxicity</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Do not use intrathecally as toxicity to spinal cord and nerves are a concern</strong></td>
</tr>
<tr>
<td><strong>Continuous perineural infusions of lignocaine result in less effective analgesia and more motor block than long-acting LAs</strong></td>
</tr>
<tr>
<td><strong>Postoperative systemic administration for analgesia is an option. After abdominal surgery doses, an LD (1.5 mg/kg over 15 minutes) followed by continuous infusion (2 mg/kg/hr) has shown to shorten duration of ileus and decrease nausea and vomiting as well as need of analgesia</strong></td>
</tr>
<tr>
<td><strong>Bupivacaine</strong></td>
</tr>
<tr>
<td>- Macaine</td>
</tr>
<tr>
<td>- Pharma-Q Bupivacaine</td>
</tr>
<tr>
<td><strong>Toxic dose</strong></td>
</tr>
<tr>
<td>2 mg/kg</td>
</tr>
<tr>
<td><strong>Cardiotoxicity occurs before neurotoxicity</strong></td>
</tr>
<tr>
<td><strong>Intralipid may be used for cardiotoxicity 1–1.5 ml/kg IV stat</strong></td>
</tr>
<tr>
<td><strong>More potent than isomers as described below and thus motor block and cardiotoxicity may be more pronounced</strong></td>
</tr>
<tr>
<td><strong>However, there are no consistent differences between ropivacaine and bupivacaine when given in low doses for regional analgesia in terms of quality of analgesia or motor blockade</strong></td>
</tr>
<tr>
<td><strong>Ropivacaine</strong></td>
</tr>
<tr>
<td>- Adco- Ropivacaine</td>
</tr>
<tr>
<td>- Naropin</td>
</tr>
<tr>
<td><strong>Toxic dose</strong></td>
</tr>
<tr>
<td>2 mg/kg</td>
</tr>
</tbody>
</table>
Volatile agent – self-inhalation

**Methoxyflurane**
- **Penthrop**

Inhaler is known as the ‘green whistle’
- It is handheld, single-use, portable and disposable

**Maximum adult dose**
- 6 ml/day, i.e. two 3 ml doses
- \(LD = 6–10\) breaths/minute
- 3 ml will last 25 minutes with continuous breathing but with intermittent use can last up to an hour

Avoid
- This was a popular volatile agent in the 1960s but was withdrawn due to nephrotoxicity in doses required for general anaesthesia
- Generally used by paramedics at the roadside or in casualty
- For moderate to severe pain
- May be used in paediatrics, but use caution in children under the age of 5 years, as deep sedation has been reported
- Should never be used on consecutive days due to threat of renal failure and disturbances of hepatic metabolism
- Contraindications include:
  - renal and hepatic impairment
  - head injuries
  - respiratory failure
- Sevoflurane should be avoided if prior use of MOF inhaler, as high concentrations of fluoride ions may be a concern

MOF – methoxyflurane, LD – loading dose, USE – safe, UWC – use with caution, UWECO – use with extreme caution, may be unsafe, AVOID – unsafe

**Bibliography**


• WMIC. Drugs that are considered to be SAFE for the use in the acute porphyrias. Welsh Medicines Information Centre (WMIC) and Cardiff Porphyria Service; 2015. p. 1-2.
6. Paediatric guidelines

Children are often subjected to a variety of painful diagnostic and therapeutic procedures. Immaturity and cognitive impairment may preclude competent expression of pain during such experiences. Therefore, the need for analgesia may not be sufficiently addressed.

Pain assessment and measurement are prerequisites to optimal pain management. Pain measurement tools are available for children of all ages and cognitive ability. Methods of pain assessment as well as treatment guidelines for the paediatric population are well established, but not widely used. The use of pain scores allows the practitioner to select appropriate analgesia for the severity of pain, which improves pain control. Reassessment and regular documentation after initiating management indicate efficacy in pain management. The correct tool is appropriate both developmentally for the child and to the clinical context, and can be used consistently.

Inadequate pain management has physiological, psychological, social and economic consequences, and is an ethical and legal dilemma. Neonates and infants are particularly vulnerable due to the neuroplasticity of their immature nervous systems, with emerging evidence of poorer neurodevelopmental outcomes as a result of repeated painful stimuli without adequate analgesia. There is a dearth of literature demonstrating moderate to severe pain in the paediatric inpatient population, regardless of a medical or surgical diagnosis, as a result of inappropriate and inadequate pain management.

6.1 Principles of pain management in children

- Anxiety, fear and pain in children are intricately linked.
- Intermittent intramuscular (IM) injections are distressing to children and are less effective in achieving pain control than IV infusions or intranasal (IN) administration. Therefore, IM injections are strongly discouraged.
- Avoid per request needed (PRN) dosing as far as possible. Where used, inform and empower the child/caregiver to request analgesia if the child is in pain.
- Always use pain scoring tools to assess pain and to direct appropriate pain management.

6.2 The neurobiology of pain

Even extremely premature neonates are able to process and experience pain. Repeated painful stimuli experienced in the neonatal period have been associated with adverse long-term consequences, including poor cognitive outcomes. Neonates and infants are particularly vulnerable because of the plasticity of their nervous systems. Inhibitory descending pathways only develop after the ascending nociceptive pathways, which possibly, in theory, results in increased susceptibility to painful stimuli.
6.2.1 Postoperative pain

The type and extent of surgery are the main predictors of the severity of postoperative pain. Aspects that should be considered are the degree of tissue damage, the presence of preoperative pain, and the likely duration of pain. This will guide the choice of regional anaesthesia technique and whether catheter techniques or additives should be used. Pain is typically moderate to severe for 48–72 hours after intermediate or major surgery. However, pain can persist for longer under certain conditions, such as ileus or significant nerve injury. Surgical pain usually includes neuropathic elements, which do not respond to simple or opioid analgesia. Also, other sources of pain should be considered (e.g. vascular cannulae, nasogastric tubes, urinary catheters and chest drains).

6.2.2 Procedural pain

The aim of procedural pain management is to minimise physical discomfort, pain, movement and psychological disturbance, without compromising patient safety. For a comprehensive guideline on paediatric procedural sedation and analgesia, please refer to the SASA paediatric guidelines for the safe use of procedural sedation and analgesia for diagnostic and therapeutic procedures in children: 2021–2026.

6.3 Pain assessment in children

Children are able to reliably articulate pain from approximately 5 years of age. However, at this age, localisation of pain is still poor, which explains the frequent reports of abdominal pain, despite the actual source. Localisation of pain becomes reliable only at approximately 7 years of age.

6.3.1 Pain history

Self-reporting is the gold standard of pain assessment and the child should be engaged at a developmentally appropriate level. Where the child is nonverbal, a collateral history from the caregiver is important. Make every effort to get information regarding the type, severity and localisation of pain, as well as any associated symptoms. Enquire about the impact of pain on daily activities, including sleep, school attendance and performance, as well as interaction with peers, play and participation in sport. Explore pain descriptors; allow the child to use their own words in their home language.

6.3.2 Pain behaviours

The expression of pain is influenced by the interplay between bio-psycho-social factors (see Figure 2). In children, previous experiences and fear are important drivers of pain behaviour.
There is no scientific evidence to suggest that gender affects pain, but societal norms and pressures often regulate how boys behave when they are in pain.

Figure 1: Pain assessment and management in children algorithm

Figure 2: A bio-psycho-social model of pain behaviour
6.3.3 Pain assessment tools

The routine use of pain scoring tools is strongly encouraged, as it is associated with better pain management. Three kinds of pain assessment tools are used, namely physiological, behavioural and self-report. If the practitioner cannot rely on self-report, behavioural tools should be used. Physiological variables such as heart rate, blood pressure and respiratory rate (RR) are unreliable indicators of either the presence or the absence of pain. Choose an appropriate pain assessment tool depending on the child’s age and cognitive development. This facilitates the quantification of pain so that a pain diagnosis can be made. Pain is diagnosed as mild, moderate or severe.

Neonates: behavioural pain assessment tool

The Neonatal Infant Pain Scale (NIPS) is used in neonates and infants up to 2 months of age. The patient is observed for 1 minute and each is then parameter scored.

Table I: Neonatal Infant Pain Scale

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Facial expression</strong></td>
<td>Relax</td>
<td>Contracted</td>
<td></td>
</tr>
<tr>
<td><strong>Cry</strong></td>
<td>Absent</td>
<td>Mumbling</td>
<td>Vigorous</td>
</tr>
<tr>
<td><strong>Breathing</strong></td>
<td>Relaxed</td>
<td>Different than basal</td>
<td></td>
</tr>
<tr>
<td><strong>Arms</strong></td>
<td>Relaxed</td>
<td>Flexed/stretched</td>
<td></td>
</tr>
<tr>
<td><strong>Legs</strong></td>
<td>Relaxed</td>
<td>Flexed/stretched</td>
<td></td>
</tr>
<tr>
<td><strong>Alertness</strong></td>
<td>Sleeping/calm</td>
<td>Uncomfortable</td>
<td></td>
</tr>
</tbody>
</table>

Two months to 18 years old: behavioural pain assessment tool

The revised FLACC tool can be used in children aged 2 months to 18 years, and includes descriptors for cognitively impaired children. It allows for the diagnosis of pain with a sensitivity of 87% and specificity of 80%. The clinician assigns a score to each characteristic and tallies a score out of 10. The final score is used to diagnose mild, moderate or severe pain, which must then be treated accordingly.

Table II: Revised FLACC tool

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Face</strong></td>
<td>No particular expression/smile</td>
<td>Occasional grimace/frown</td>
<td>Constant grimace/frown, quivering chin, clenched jaw, jerking</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Withdrawn or disinterested</td>
<td>Looks distressed, expression of fright/panic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Appears sad/worried</td>
<td></td>
</tr>
<tr>
<td><strong>Legs</strong></td>
<td>Normal position or relaxed</td>
<td>Uneasy, restless, tense</td>
<td>Kicking or legs drawn up</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Occasional tremors</td>
<td>Spasticity, constant tremors, jerking</td>
</tr>
</tbody>
</table>
### From 5–7 years old: self-reporting pain assessment tools

The following are self-reporting tools.

For the FACES pain scale (Figure 3), the child indicates which facial expression correlates best with their level of pain. Younger children sometimes find this tool confusing and tend to choose FACES that are at the extremes of the spectrum.

<table>
<thead>
<tr>
<th>Activity</th>
<th>Lying quietly, normal position, moves easily</th>
<th>Squirming, shifting back and forth, tense, mildly agitated</th>
<th>Arched, rigid, jerking</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Shallow, splinting respirations, intermittent sighs</td>
<td>Severe splinting</td>
</tr>
<tr>
<td>Crying</td>
<td>No cry (awake/asleep)</td>
<td>Moans or whimpers, occasional complaint, verbal outburst/grunt</td>
<td>Crying steadily, screams, sobs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Frequent complaints/outbursts, constant grunting</td>
</tr>
<tr>
<td>Consolability</td>
<td>Content, relaxed</td>
<td>Reassured by occasional touching, ‘talking to’, hugging</td>
<td>Difficult to console/comfort</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Distractable</td>
<td>Pushing away caregiver or comfort measures</td>
</tr>
</tbody>
</table>

#### Pain measurement scale

![Image of FACES pain scale](image)

**Figure 3: FACES pain scale**

![Image of numeric rating scale](image)

**Figure 4: Numeric rating scale**
Older children are able to use the NRS (Figure 4) which assigns a number to their level of pain. Note that, even though younger children (younger than 7 years) may be able to count to ten, they lack the ability to seriate.

Scores from both the FACES pain scale and the NRS are used to diagnose mild, moderate or severe pain (0 to 10).

For neonates/infants, use the NIPS:
- 0–2 points = no pain
- 3–4 points = moderate pain
- > 4 points = severe pain

For older children, use R-FLACC and NRS:
- 0 = no pain
- 1–3 = mild pain
- 4–7 = moderate pain
- 8–10 = severe pain

Once the severity of pain has been diagnosed, an appropriate level of pain management should be initiated.

6.4 Pain management

Non-pharmacological pain management strategies should always be included in pain management. Preoperative anxiety, catastrophising, depression and other mental health as well as neurodevelopmental issues can amplify or confuse a patient’s expression of discomfort/pain. Addressing these aspects are important in adequately managing acute pain.

6.4.1 Pharmacological strategies

Multimodal analgesia refers to the use of a variety of treatment strategies, including both pharmacological and non-pharmacological. By employing these strategies, the complex pathophysiology of pain is addressed as multiple receptors are targeted, resulting in improved analgesia. Additionally, this allows for reduced doses of agents with unfavourable side effect profiles (e.g. opioids). These adjuvant agents include simple analgesics, opioids, \( \alpha_2 \)-receptor agonists (clonidine and dexmedetomidine), NMDA receptor antagonists (ketamine, tramadol, magnesium sulphate), inhalational agents, anxiolytics (Table III) and LAs (Table IV). Neuropathic pain is an important component of postoperative pain. Certain surgeries (e.g. amputations, thoracotomy, scoliosis, neurosurgical) have a higher component of neuropathic pain. This type of pain typically does not respond to simple analgesia or opioid therapy.
Table III: Pharmacological management of pain

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-pharmacological strategies are beneficial for pain of any severity</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Simple analgesics</th>
<th>Paracetamol with or without NSAIDs</th>
</tr>
</thead>
</table>

Opiate analgesics

<table>
<thead>
<tr>
<th>Not usually required</th>
<th>Tilidine SL or Morphine p.o. or Tramadol IV/p.o.</th>
<th>Morphine IV or Fentanyl IN</th>
</tr>
</thead>
</table>

Titrate IV morphine for safety. Consider PCA for ongoing moderate to severe pain > 24 hrs.

Adjuvant agents

<table>
<thead>
<tr>
<th>Ketamine, clonidine, dexmedetomidine, gabapentin</th>
</tr>
</thead>
</table>

Useful for neuropathic elements of pain.

Interventional modalities

<table>
<thead>
<tr>
<th>Regional anaesthesia</th>
</tr>
</thead>
</table>

6.4.2 Local anaesthetics

LAs are sodium channel blockers. They are used for wound infiltration, nerve blocks and neuraxial blockade; all with or without catheters. Some of these techniques require specialist expertise. Additives are used to prolong the duration of analgesia (Table V).

Table IV: Guidelines for local anaesthetic doses in children

<table>
<thead>
<tr>
<th>Lignocaine</th>
<th>Topical</th>
<th>Infiltration or nerve block</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Spray (Xylocaine spray 10 mg per spray) 5 mg/kg/dose</td>
<td>With adrenaline: 7 mg/kg/dose</td>
</tr>
<tr>
<td></td>
<td>• Gels: 2%</td>
<td>Without adrenaline: 3–4 mg/kg/dose</td>
</tr>
<tr>
<td></td>
<td>• Eutectic mixture of local anaesthetic cream: 2.5% lignocaine + 2.5% prilocaine 1.5 g/10 cm² under occlusive dressing for 1–3 hours, effective after 45 mins</td>
<td></td>
</tr>
</tbody>
</table>

Bupivacaine

| Maximum dose: 2–3 mg/kg/dose (with and without vasoconstrictor) |

Ropivacaine

| Maximum dose: 2–3 mg/kg/dose |

Table V: Adjuvants for neuraxial anaesthesia

<table>
<thead>
<tr>
<th>Additive</th>
<th>Dose</th>
<th>Effect</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>1–2 mcg/kg</td>
<td>Improved quality and duration of analgesia with approximately 4 hours</td>
<td>Systemic absorption causes some sedation. Can cause apnoea in neonates</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>1 mcg/kg</td>
<td>Improved quality and duration of analgesia with approximately 4 hours</td>
<td>Marked sedation can occur</td>
</tr>
<tr>
<td>Ketamine*</td>
<td>1 mcg/kg</td>
<td>Improved quality and duration of analgesia for single-dose caudal injections only</td>
<td>Not for use if child is under 1 year</td>
</tr>
</tbody>
</table>
6.4.3 Simple analgesics

Simple analgesics include paracetamol, NSAIDs and local anaesthetic agents. They are generally safe provided dosing instructions and other cautions are adhered to, and have favourable side effect profiles. These agents should be considered as part of any analgesic strategy and can reduce the amount of opioids needed to achieve equivalent levels of analgesia.

Table VI: Guideline for paracetamol doses in children

<table>
<thead>
<tr>
<th>Route</th>
<th>Loading dose</th>
<th>Maintenance dose</th>
<th>Maximum daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO</td>
<td>20 mg/kg</td>
<td>20 mg/kg 6-hourly</td>
<td>90 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neonates: 60 mg/kg/day in divided doses</td>
</tr>
<tr>
<td>PR</td>
<td>40 mg/kg</td>
<td>30 mg/kg/dose 6-hourly</td>
<td>5 g/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Neonates: 60 mg/kg/day in divided doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Other infants and children: 90 mg/kg/day</td>
</tr>
<tr>
<td>IV</td>
<td>20 mg/kg</td>
<td>Neonates: PMC 28–31 weeks 10 mg/kg 12-hourly; PMA 32–44 weeks 10 mg/kg 6-hourly Other infants and children: 15 mg/kg 6-hourly</td>
<td>30 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>60 mg/kg/day</td>
</tr>
</tbody>
</table>

PMC – post conceptual age, PR – per rectal, PMA – post menstrual age

6.4.4 Nonsteroidal anti-inflammatory drugs

- Owing to the risk of Reye’s syndrome, aspirin should be avoided in febrile children, particularly those with concurrent viral infections.
- NSAIDs may cause pulmonary hypertension and alterations in cerebral, gastrointestinal (GI) and renal blood flow in infants under 3 months of age.
- Serious adverse events after administering NSAIDs are rare in children above 6 months of age.
- Ensure adequate hydration, avoid concomitant nephrotoxic drugs and exercise caution in children who are not fed orally.
- While it is acknowledged that certain NSAIDs have the potential to increase surgical bleeding, this blood loss remains clinically insignificant (i.e. it does not lead to increased reoperation rates, haemodynamic compromise or blood transfusions).
• The concern that NSAIDs cause delayed bone healing remains unproven in children and the use of NSAIDs is recommended as part of a multimodal approach in otherwise healthy children. Where the risk of nonunion is high, a risk/benefit approach must be followed.

• Paediatric trial data regarding the use of selective COX-2 inhibitors is limited. The understanding of the degree of COX-2 selectivity, the pharmacokinetic-pharmacodynamic (PK-PD) relationship and adverse effects of these agents in children remains poor and paediatric use is off-label.

### Table VII: Guideline for NSAID doses in children

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Age Group</th>
<th>Dose Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>Under 3 months of age</td>
<td>Oral: 5–10 mg/kg/dose, 8-hourly, maximum 400–800 mg</td>
</tr>
<tr>
<td></td>
<td>1–12 years of age</td>
<td>Oral: 1–2 mg/kg/dose, 8-hourly, maximum 50 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rectal: 1–2 mg/kg/dose, 12-hourly, maximum 50 mg</td>
</tr>
<tr>
<td>Diclofenac</td>
<td></td>
<td>Oral: 0.2 mg/kg/dose, 4–6-hourly, maximum 10 mg or 0.8 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV: 0.2–0.6 mg/kg/dose, 6-hourly, maximum 30 mg or 120 mg/day; use for 5 days only, then de-escalate</td>
</tr>
<tr>
<td>Ketorolac</td>
<td></td>
<td>Oral: 0.2 mg/kg/dose, 4–6-hourly, maximum 10 mg or 0.8 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IV: 0.2–0.6 mg/kg/dose, 6-hourly, maximum 30 mg or 120 mg/day; use for 5 days only, then de-escalate</td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td></td>
<td>Oral/rectal: 10 mg/kg/dose, 8-hourly</td>
</tr>
<tr>
<td>Parecoxib*</td>
<td>Above 2 years of age</td>
<td>IV: 1 mg/kg (maximum 40 mg), 6–12-hourly, maximum 80 mg/day</td>
</tr>
</tbody>
</table>

* Not licensed for use in children younger than 18 years; this dosing is derived from study data

### 6.4.5 Opioids

• IV opioids can be used safely and effectively in children of all ages.

• The initial dose of opioids should be based on the age and weight of the child, and then titrated against response. There is no maximum or ceiling dose.

• Unwanted side effects should be anticipated and treated (e.g. prescribe antiemetics as needed in children at risk for nausea/vomiting).

• There is no lower age limit for PCA use in children. Children need to possess the physical dexterity to use the PCA, display a reasonable understanding of how it works and how to use the device. Effective PCA prescription in children incorporates a bolus and may include a low-dose background infusion to improve efficacy and sleep. The child needs to be cared for in a monitored environment with continuous oxygen saturation monitoring and appropriately trained nursing staff.

### Table VIII: Guideline for opioid doses in children

<table>
<thead>
<tr>
<th>Opioid doses in children</th>
<th>Additional comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine (intermediate-acting)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>0.1–0.2 mg/kg/dose 4–6-hourly</td>
</tr>
</tbody>
</table>
| **Oral** | **Neonates:** 0.05 mg/kg  
1 month–1 year of age: 0.05–0.2 mg/kg  
Above 1 year of age: 0.1–0.4 mg/kg/dose, 4–6-hourly | Peak analgesic effect at 1.5 hours |
| --- | --- | --- |
| **Infusion** | 5–40 mcg/kg/hour | 0.5 mg/kg of morphine sulphate in 50 ml normal saline  
Run at 5–40 mcg/kg/hour (0.5–4 ml/hr) (1 ml = 10 mcg/kg morphine) |
| **PCA** | 20 mcg/kg bolus with 5–15 minute lockout time  
If a background infusion is used, dose at 4 mcg/kg/hour | Weight in kg = mg of morphine, dilute up to 50 ml volume  
This will give 20 mcg/kg/ml |

**Tilidine hydrochloride (Valoron®)** (intermediate-acting)

| **Sublingual** | 1 mg/kg/dose 6-hourly | 1 drop = 2.5 mg  
Weight (kg) divided by 2.5 = number of drops |
| **Pethidine** (intermediate-acting) | IV 0.5–1 mg/kg/dose stat | Avoid repeat dosing  
Metabolites can cause seizures |

**Tramadol** (intermediate-acting)

| PO/IV Above 1 year of age and less than 50 kg: 0.5–1 mg/kg/dose 4–6-hourly  
More than 50 kg: 50–100 mg | Max daily dose 6 mg/kg  
Lowers the seizure threshold; avoid repeat dosing in seizure prone patients |

**Fentanyl** (short-acting)

| IV 0.5–3.0 mcg/kg/dose  
Titrate at 5–10 minute intervals to desired effect | Clearance in preterm neonates is slow  
Can cause prolonged respiratory depression |
| IV infusion 1.0–5.0 mcg/kg/hour | Only in theatre or ICU environment (careful, unfavourable context sensitive t1/2) |
| Intranasal 1.5–2.0 mcg/kg/dose stat | Use neat fentanyl with or without atomiser  
Peak analgesia within 5 minutes |

**PC** 0.3 mcg/kg bolus with lockout time  
If a background infusion is used, dose at 0.3 mcg/kg/hr  
15 mcg/kg fentanyl diluted to 50 ml with 0.9% saline  
For children more than 50 kg: maximum 750 mcg fentanyl in 50 ml 0.9% saline bolus = 15 mcg Background 15mcg/hr  
Alternative to morphine in patients with renal or hepatic impairment  
Caution: unfavourable context sensitive t1/2 |

**Alfentanil HCl** (short-acting)

| IV 10 mcg/kg/dose titrate at 10–15 minute intervals | Shorter t1/2 in children |

**Sufentanil**

**Remifentanil** (ultra-short-acting)

| IV Infusion: 0.05–1 mcg/kg/minute | Only in theatre or ICU |

*The use of slow/modified/controlled-release opioids is not recommended in children with acute pain*
Monitoring in patients receiving opioids

- All patients receiving opioids MUST have the following monitored and documented:
  - Heart rate
  - Oxygen saturation via continuous saturation monitoring for the first 15 minutes
  - Respiratory rate
  - Level of consciousness
  - Pain score
- Frequency of monitoring
  - Observe closely for 15 minutes after administering opioid dose
  - Then do observations every 30 minutes for the first hour
  - Thereafter, observations must be documented 2-hourly
- A suitably trained nurse must be available to monitor, initiate management and escalate care, or call the doctor when necessary
- Resuscitation equipment must be readily available, checked and in working order
- Naloxone must be immediately available: the dose is 10 mcg/kg slowly IV or IM or subcutaneously; can also be given intranasally 1 mg; repeat if necessary

6.4.6 Alpha-2 agonists: clonidine and dexmedetomidine

Clonidine has excellent analgesia and opioid-sparing properties. In addition, it has anxiolytic effects, which are beneficial in the paediatric population. The associated bradycardia is usually not clinically significant, and rarely requires any intervention, unless when associated with hypovolaemia and bleeding. It is a cost-effective drug that is well tolerated and has been extensively studied for a wide variety of indications in paediatric practice. Clonidine is available as a 25 mcg tablet. In order to make administration easier, consider prescribing the following convenient doses: 25 mcg, 50 mcg, 75 mcg and 100 mcg.

If the patient has received clonidine for more than 7 days, it is necessary to wean to avoid withdrawal symptoms. Withdrawal is characterised by peripheral hyperactivity of the sympathetic nervous system, including anxiety, sweating, insomnia, nausea and vomiting, severe hypertension, and palpitations. If the dose was administered three times per day, reduce the dosage interval to twice daily (bd) for two days, followed by once daily for two days and then stop.

Dexmedetomidine is more $\alpha_2$-selective with similar pharmacodynamics. It is available as an intravenous injection (IVI) only and administered as an infusion. It can also cause withdrawal syndrome when stopped abruptly.
Table IX: Guideline for the use of alpha-2 agonists

<table>
<thead>
<tr>
<th>Clonidine</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PO</strong></td>
<td>1–5 mcg/kg/dose</td>
<td>Start at 1–3 mcg/kg nocte, increase to 12-hourly, then 8-hourly over 3 days</td>
</tr>
<tr>
<td>6–8-hourly</td>
<td></td>
<td>If pain is moderate to severe, initiate treatment with a full dose 6–8-hourly</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IV</th>
<th>Bolus: 1–2 mcg/kg</th>
<th>Slow bolus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion: Loading dose</td>
<td>1–3 mcg/kg, followed by 0.7–1 mcg/kg/hr</td>
<td>Infusion</td>
</tr>
<tr>
<td></td>
<td>Limited to theatre and ICU</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IN</th>
<th>4 mcg/kg stat</th>
<th></th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Dexmedetomidine</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IV</strong></td>
<td>Infusion: Loading dose 0.5–1 mcg/kg over 10–20 minutes, followed by 0.5–1 mcg/kg/hr</td>
<td>Bolus can cause bradycardia and hypertension</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IN</td>
<td>1–4 mcg/kg</td>
<td>Higher doses will cause sedation</td>
</tr>
<tr>
<td>Buccal</td>
<td>3–4 mcg/kg</td>
<td></td>
</tr>
</tbody>
</table>

6.4.7 Gabapentin

Gabapentin has been shown to decrease the incidence of chronic pain after scoliosis surgery, reduce morphine consumption after multilevel scoliosis repair, and decrease phantom limb pain after amputation. Gabapentin has also been successfully used to treat visceral hyperalgesia and neuropathic pain in children with cerebral palsy. The dose range is 3–10 mg/kg/dose 8-hourly. The starting dose is 3–5 mg/kg and the maximum dose is 10 mg/kg.

- Gabapentin is available as a 100 mg capsule. When dissolved in 10 ml of water, it produces a solution of 10 mg/ml. To facilitate administration, consider prescribing the following convenient doses: 25 mg, 50 mg, 75 mg, 100 mg, 150 mg and 200 mg.

- **Initiating** gabapentin
  - Day 1 – start with a dose at night
  - Day 2 – increase to a dose twice per day
  - Day 3 – increase to three times per day, then titrate upward as required

- **Stopping (weaning)** gabapentin
  - If gabapentin has been used for more than seven days, titrate the dose down to avoid withdrawal symptoms
  - If receiving a dose three times per day, reduce the frequency to bd for two days, then once daily for two days and then stop administration
  - Alternatively, retain the frequency and halve the dose every two days
6.4.8 Ketamine

Ketamine is an NMDA receptor antagonist which is known for its haemodynamic and respiratory stability. It is effective in the management of acute, chronic and neuropathic pain, as well as allodynia and hyperalgesia. It displays synergism with opioids, resulting in reduced opioid requirements with a better side effect profile. This agent should be considered for patients with high opioid requirements or opioid tolerance, or where there is a significant component of neuropathic pain (e.g., scoliosis, amputation, neurosurgical procedures, burns, mucositis of chemotherapy) or severe surgical pain. When used with morphine in PCA, ketamine has been found to result in improved sleep and pain control with no increase in side effects (nausea, hallucinations). The IV infusion dose is 5 mg/kg diluted to 50 ml 0.9% saline (0.1 mg/kg/ml) and administered at 0.2–0.5 mg/kg/hr IV (2–5 ml/hr).

6.5 Recommended analgesia strategies for specific surgical procedures

6.5.1 Ear, nose, and throat procedures

Myringotomy

- Oral paracetamol, ibuprofen or diclofenac, in suitable doses and administered 30 minutes preoperatively, can achieve adequate early postoperative analgesia.
- 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 to simple analgesics.

Tonsillectomy

- Tonsillectomy is associated with moderate to severe pain, behavioural disturbance, sleep disruption and altered activity which can persist for up to two weeks.
- Surgical technique is an important determinant of posttonsillectomy pain; cold dissection techniques are associated with less pain.
- NSAIDs do not increase the risk of re-operation for bleeding. However, ketorolac has been associated with increased bleeding and should be avoided.
- Intraoperative analgesia: a multimodal analgesic strategy is imperative, which includes a combination of individually titrated (short- and intermediate-acting) opioids, paracetamol, an NSAID and an alpha-2 agonist. Alpha-2 agonists are particularly advantageous in patients with obstructive sleep apnoea (OSA), where cautious use of opioids is recommended.
- Local anaesthesia either injected into the tonsillar fossa or applied topically improves postoperative pain scores and reduces the time to the first oral intake and the incidence of referred ear pain.
- Dexamethasone (0.5 mg/kg)
- Analgesic dose of ketamine (0.2 mg/kg)
- Postoperative analgesia: the *regular (around the clock)* administration of paracetamol and NSAIDs.
- Information given to caregivers on pain assessment and medication use following discharge is particularly important.

6.5.2 Common procedures performed in children and suggested regional anaesthesia techniques

Regional anaesthesia techniques, such as wound infusion catheters inserted at the end of the procedure, increase the time to opioid request, improve pain scores, and reduce opioid consumption.

In addition to prolonged analgesia with caudal blocks, IV clonidine added to local anaesthetic solution increases the duration of analgesia with the following nerve blocks: sciatic, penile, saphenous, brachial plexus, ilioinguinal and iliohypogastric. Add 1–2 mcg/kg to the local anaesthetic solution or administer it intravenously.

**Table X: Suggested regional anaesthesia techniques for specific procedures**

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Regional nerve block options</th>
<th>Dosing* (volume)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umbilical herniorrhaphy</td>
<td>Rectus sheath</td>
<td>0.1–0.3 ml/kg/side</td>
</tr>
<tr>
<td>Inguinal herniorrhaphy</td>
<td>Caudal</td>
<td>0.15–0.2 ml/kg/side</td>
</tr>
<tr>
<td></td>
<td>Ilioinguinal/iliohypogastric nerve block</td>
<td></td>
</tr>
<tr>
<td>Orchidopexy</td>
<td>Caudal</td>
<td>0.2–0.3 ml/kg/side</td>
</tr>
<tr>
<td></td>
<td>Ilioinguinal and iliohypogastric</td>
<td></td>
</tr>
<tr>
<td>Circumcision</td>
<td>Dorsal penile nerve</td>
<td>1 ml/kg</td>
</tr>
<tr>
<td></td>
<td>Caudal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pudendal nerve</td>
<td></td>
</tr>
<tr>
<td>Laparotomy (supraumbilical)</td>
<td>Thoracic paravertebral</td>
<td>0.5 ml/kg/side</td>
</tr>
<tr>
<td></td>
<td>Subcostal transversus abdominus plane”</td>
<td>0.3–0.5 ml/kg/side</td>
</tr>
<tr>
<td></td>
<td>Erector spinae plane</td>
<td>0.5 ml/kg/side</td>
</tr>
<tr>
<td></td>
<td>Epidural with catheter</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Wound infusion catheter</td>
<td>0.5 ml/kg/side</td>
</tr>
</tbody>
</table>

| Laparotomy (infra umbilical) | Caudal                                      | 0.5 ml/kg/side |
|                            | Epidural + catheter                           |                 |
|                            | Quadratus lumborum                            | 0.5 ml/kg/side |
|                            | Lumbar paravertebral plane                    | 0.5 ml/kg/side |
|                            | Erector spinae plane                          | 0.3–0.5 ml/kg/side |
|                            | Transversus abdominus plane”                 | 0.3–0.5 ml/kg/side |
|                            | Wound infusion catheter                       |                 |
### Laparotomy (midline)
- Rectus sheath block**
- Caudal (only block lower midline reliably)
- Erector spinae plane
- Epidural with catheter
- Wound infusion catheter

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Anaesthetic Approach</th>
<th>Dose (ml/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracic paravertebral</td>
<td>Intercostal nerves</td>
<td>0.5</td>
</tr>
<tr>
<td>Thoracic paravertebral</td>
<td>Erector spinae plane</td>
<td>0.5</td>
</tr>
<tr>
<td>Thoracic paravertebral</td>
<td>Epidural with catheter</td>
<td>0.5</td>
</tr>
<tr>
<td>Thoracic paravertebral</td>
<td>Wound infusion catheter</td>
<td></td>
</tr>
</tbody>
</table>

* Adhere to maximum doses (mg/kg) detailed in Table IV

** Provides somatic analgesia only

### Thoracotomy
- Transversus abdominus plane**
- Quadratus lumborum

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Anaesthetic Approach</th>
<th>Dose (ml/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendicectomy (laparoscopic)</td>
<td>Transversus abdominus plane**</td>
<td>0.3–0.5</td>
</tr>
<tr>
<td>Appendicectomy (laparoscopic)</td>
<td>Quadratus lumborum</td>
<td>0.5</td>
</tr>
</tbody>
</table>

### Femur fracture
- Fascia iliaca
- Femoral nerve, with or without sciatic or popliteal nerves
- Caudal, epidural with catheter

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Anaesthetic Approach</th>
<th>Dose (ml/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appendicectomy (laparoscopic)</td>
<td>Fascia iliaca</td>
<td>0.5</td>
</tr>
<tr>
<td>Appendicectomy (laparoscopic)</td>
<td>Femoral nerve, with or without sciatic or popliteal nerves</td>
<td>0.5</td>
</tr>
<tr>
<td>Appendicectomy (laparoscopic)</td>
<td>Caudal, epidural with catheter</td>
<td></td>
</tr>
</tbody>
</table>

### 6.5.3 Principles of postoperative analgesic prescription

- The oral route is well tolerated and is usually cheaper. Adhere to the World Health Organization’s (WHO) ‘by the mouth’ recommendation. Monitor for any factors that may cause poor absorption (e.g. vomiting, ileus).
- IM injections are distressing and painful and are not recommended.
- Prescribe regular analgesia – i.e. ‘around the clock’.
- Where de-escalation to ‘when required’ dosing is used, educate/empower both the patient and caregivers to request analgesia if the analgesia is insufficient.
- Small studies on the use of IV lignocaine infusions in children have shown encouraging results. However, further studies are needed before dosing recommendations can be made.
- Where PCA is used, the use of standardised protocols is recommended for safety reasons.

### An important note on codeine

The efficacy of oral codeine is variable, and individual differences in the ability to generate the active metabolite – morphine – may reduce the efficacy or increase the side effects, including respiratory depression. A number of combination preparations contain codeine (e.g. Stopayne®, Myprodol® and Syndol®). Their use is not recommended in children who are under 2 years of age and should be used with caution in children above 2 years of age.
Table XI: Principles of postoperative analgesic prescription

<table>
<thead>
<tr>
<th>Predicted postoperative pain</th>
<th>Recommended analgesia (inpatient)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild*</td>
<td>Paracetamol with or without an NSAID</td>
<td></td>
</tr>
<tr>
<td>Moderate**</td>
<td>Paracetamol with or without an NSAID Tilidine or Tramadol Consider clonidine</td>
<td>Clonidine improves neuropathic pain and anxiety, and improves sleep</td>
</tr>
<tr>
<td>Severe***</td>
<td>Paracetamol with or without an NSAID Morphine p.o. or morphine infusion Consider clonidine Consider low dose ketamine infusion</td>
<td>Adhere to monitoring recommendations for morphine infusion</td>
</tr>
</tbody>
</table>

* Mild pain such as inguinal herniorrhaphy, myringotomy, incision and drainage of an abscess
** Moderate pain such as displaced fractures, tonsillectomy, orchidopexy, laparoscopic appendicectomy (unruptured) and Nissen’s fundoplication
*** Severe pain such as laparotomy, tonsillectomy, thoracotomy with intercostal drain in situ, osteotomy, laparoscopic appendicectomy (ruptured)

6.5.4 Pain in children with cerebral palsy, deformities and cognitive impairment

A systematic approach to identifying the source of pain is suggested. Children who suffer from cerebral palsy or other deformities are not necessary cognitively impaired. Therefore, caregivers, including anaesthesiologists, must first attempt to communicate with the patients – not with their caregivers. However, caregivers could provide useful information on pain behaviours. The R-FLACC tool is used to assist with the diagnosis of pain and its severity.

Pain is a frequent and significant problem in children with cognitive impairment (from any cause), with the highest frequency and severity occurring in children with the greatest impairment. These patients are vulnerable to underrecognition and undertreatment of pain. Barriers to treatment include uncertainty in identifying pain, limited experience and fear about the use of analgesics (largely opiophobia).

Sources of pain include neuropathic pain (peripheral or central) due to altered excitability of the nervous system, muscle spasms, positioning and GI impairment (constipation, gastritis, ulcers or pancreatitis). New-onset pathology (e.g. otitis, urinary tract infection, nephrolithiasis, appendicitis, lower respiratory tract infection, dental pain, fractures or hip subluxation) should also be considered.

A trial of gabapentin is suggested for children with neuropathic pain, visceral hyperalgesia or autonomic dysfunction. Spasticity can be managed pharmaco logically with baclofen, benzodiazepines or an alpha-2 agonist (clonidine). Interventional options include botulinum toxin injections or dorsal rhizotomy.

Non-pharmacological strategies for spasticity and dystonia include brace and positioning, passive stretching, massage and warm baths.
6.5.5 Pain in children with autism spectrum disorders

Autism spectrum disorders (ASDs) is a neuro-developmental spectrum of disorders, which comprise the following:

1. Impaired social functioning
2. Impaired communication skills
3. Disordered sensory processing
4. Restricted, repetitive behaviours

Pain behaviours in these patients may differ and distort pain diagnoses. Behavioural pain tools may be problematic and inaccurate. Every effort should be made to individualise care and minimise sensory stimuli by (i) providing a consistent environment with as much familiarity as possible, (ii) facilitating minimal separation between caregiver and patient, and (iii) minimising the use of restraint which help to alleviate psychological and emotional distress to the patient and family. It is important to seek expert advice or consultation.

6.5.6 Patients with obstructive sleep apnoea

Children with OSA have an increased sensitivity to opioids and are particularly susceptible to respiratory depression. Opioids must be used with caution, titrated wherever possible, with strict adherence to monitoring and, where appropriate, an escalated level of care.

6.5.7 Pain in children with cancer

The South African Cancer Pain Working Group published the Guide to Treatment of Cancer Pain in South Africa which can be referenced for guidelines.

Bibliography

- Red Cross War Memorial Children's Hospital Acute Pain Management Protocol.
7. Acute pain management in elderly patients

As a greater proportion of the population falls into the ‘elderly’ category (aged ≥ 65 years), more and more elderly patients are presenting for treatment of acute pain. Medical conditions which often lead to acute pain are more likely in older adults.

These conditions include the following:
- Acute exacerbations of arthritis
- Osteoporotic fractures
- Cancer
- Acute medical conditions, such as ischaemic heart disease, vascular disease and herpes zoster
- Traumatic injuries
- Surgery

7.1 Factors affecting pain control in elderly patients

Factors that make effective pain control more difficult in elderly patients 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.

In addition, the elderly may fail to report pain because they think it is a common aspect of ageing, they acquiesce to family members/medical staff, or they have fears about intervention or the unwanted effects of analgesics, especially opioids.

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 because of increasing age and the increasing likelihood of concurrent disease. These changes are summarised in Table I.

Table I: Physiological changes in older people, resulting changes in pharmacokinetic and pharmacodynamics variables and consequences for pharmacological treatment (2020 ANZCA Pain Guidelines)

<table>
<thead>
<tr>
<th>Bodily system or process</th>
<th>Parameter and changes</th>
<th>Resulting pharmacokinetic/pharmacodynamic changes</th>
<th>Changes in pharmacological treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body composition</td>
<td>Body fat 10–50%</td>
<td>For lipophilic medicines Vd t1/2</td>
<td>Calculate doses of lipophilic medicines on total body weight</td>
</tr>
<tr>
<td></td>
<td>Muscle 20%</td>
<td>No relevant effect</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>Body water 10%</td>
<td>For hydrophilic medicines Vd</td>
<td>Calculate doses of hydrophilic medicines based on lean body weight</td>
</tr>
<tr>
<td></td>
<td>Plasma volume ↔</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Organ</td>
<td>Function</td>
<td>Impact on Drugs</td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>----------</td>
<td>-----------------</td>
<td></td>
</tr>
</tbody>
</table>
| Liver | Liver size 25–40% | Bioavailability of oral medicines
|       | Hepatic blood flow 25–40% | Hepatic clearance (CL) of high extraction medicines (e.g. morphine)
|       | Phase 1 metabolism 25% | Hepatic CL of some low-extraction medicines (e.g. ibuprofen)
| Heart | Cardiac output ↔ or to 20% | Central compartment volume
|       |                          | Peak concentration after IV bolus
|       |                          | Initial IV bolus doses
| CNS   | Cerebral blood flow, volume and metabolism 20% | Distribution to the CNS
|       |                          | Apparent volume in the CNS
|       | Blood–brain barrier transport (medicine-specific effect) | Apparent volume in the CNS
|       |                          | Apparent increase in CNS sensitivity
| Absorption | Oral and transmucosal absorption | No relevant effect of ageing
|          | IM absorption | ↔
|          | SC absorption | ↔
|          | Transdermal absorption | Hydrophilic medicines ↔ lipophilic medicines
| Protein binding | Plasma albumin 20% | Unbound fraction of medicines
|          | Alpha-1-acid glycoprotein 30–50% | Cerebral uptake of medicines
|          |                          | ↔ hepatic clearance of high-extraction medicines hepatic clearance of low-extraction medicines
| Kidneys | Kidney size 30% | clearance of renally excreted medicines ↔ effect on opioids, but often clearance of metabolites (e.g. morphine [M6G], tramadol [M1])
|       |                          | Maintenance dose of renally excreted medicine (alpha-2-delta ligands: gabapentin, pregabalin) or medicines with renally excreted metabolites (morphine, tramadol, pethidine) Monitor for accumulation of renally excreted medicines
The information in Table I centres on opioids, given its widespread use. These changes have variable prevalence and are generally attributable to ageing alone. However, these changes may be compounded by a higher incidence of degenerative and other concurrent diseases in elderly patients.

7.1.2 Altered perception of pain and potential difficulties in assessment

The assessment of pain, and the evaluation of the efficacy of treating this pain, are often more difficult in elderly patients. This may be due to differences in pain perception and the reporting of pain, cognitive impairment and difficulties in measuring pain. Thresholds to pain are often increased in elderly patients, making diagnoses more difficult in conditions such as acute myocardial infarction (MI) and peritonitis, where pain is usually the presenting symptom. Importantly however, pain tolerance can be reduced in elderly patients, necessitating its immediate treatment. Elderly patients often underreport pain for a number of reasons, including fear, anxiety, depression and cognitive impairment. Cognitive impairment may make the measurement of pain very difficult, especially if the patient is noncommunicative. Behaviour, such as restlessness, grunting and grimacing, needs to be assessed in these circumstances.

The need for specific methods to assess pain in elderly patients is recognised in international guidelines. There is also a need to educate healthcare staff in the use of patient-appropriate pain assessment tools in order to make valid assessments of pain in elderly patients.

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 elderly patients receive PCA. The concomitant administration of long-acting CNS depressants (e.g. benzodiazepines) should be avoided.

7.2 Measurement of pain

7.2.1 Patient self-report measures of pain

Unidimensional measures of pain intensity are more commonly used than multidimensional measures to quantify pain in the acute pain setting. Unidimensional measures used in younger adult patients, which have been shown to be appropriate for use in elderly patients, include the verbal numeric rating scale (VNRS), FACES pain scale (FPS), verbal descriptor scale (VDS) and the NRS, while there is equivocal support for the use of the VAS.
Testing of different self-assessment scales may be warranted, including in patients with severe impairment, as elderly patients may need more time to understand and respond to questions regarding pain. Immediate reports of present pain may be reasonably accurate and as valid as reports of cognitively intact patients, but recall of past pain is less likely to be as reliable.

7.2.2 Other measures of pain

Assessment of pain in noncommunicative patients is more difficult. Behaviours such as restlessness, frowning and grimacing, or sounds such as grunting or groaning, have been used in attempts to assess pain. In cognitively intact adults, some of these behaviours have been shown to correlate with patient self-report of pain. However, these may not always be valid indicators of pain in the nonverbal adult and can be difficult to interpret.

More than 28 different observational pain assessment scales have been developed and are used in patients with varying degrees of dementia. Scales with the strongest evidence of usefulness in patients with dementia include FPS, Abbey Pain Scale (APS), Pain Assessment in Advanced Dementia (PAINAD – a simple, reliable and validated five-item observational tool), Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC), and Mobilization-Observation-Behavior-Intensity-Dementia Pain Scale (MOBID).

7.3 Analgesic techniques in the elderly

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

7.3.1 Patient-controlled analgesia

PCA should not be withheld from elderly patients simply because of their age. The basic requirements for PCA 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 should be avoided.

7.3.2 Epidural analgesia

Elderly patients can be safely managed with an epidural, providing there is appropriate monitoring and staff education. The following are five important guidelines regarding opioid analgesia in elderly patients:

- The 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 elderly patients; it is advised that lower doses and infusion rates are used.
• Elderly patients may be more prone to side effects (e.g. hypotension) and spinal stenosis may predispose them to neurological complications.

• Elderly patients are more likely to have ischaemic heart disease where coronary blood flow may be reduced rather than increased in response to sympathetic stimulation.

• Many elderly patients may be taking anticoagulants as chronic medication, therefore, neuraxial analgesia may not be feasible.

Analgesic drugs in the elderly are outlined in Table II.

Clinical practice points are as follows:

1. Pain thresholds increase in elderly patients, but their pain tolerance decreases.

2. PCA and epidural analgesia are more effective in elderly patients.

3. Acute pain may be underreported.

4. Self-report measures of pain can be used in elderly patients, as opposed to other measures.

5. There is an age-related decrease in opioid requirements in elderly patients.

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.

Table II: Analgesic drugs in elderly patients

<table>
<thead>
<tr>
<th>Opioids</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure agonists are good, but the dose should be decreased in the event of renal dysfunction. The effective duration of a single dose can be increased, if desired. Pruritis, nausea and vomiting decrease with opioid use. Thus, the routine administration of antiemetics is not recommended owing to their side effects. Agonist-antagonists are not recommended because of the increased incidence of delirium.</td>
<td></td>
</tr>
</tbody>
</table>

| Pethidine | Pethidine is best avoided because a significant accumulation of the metabolite norpethidine might occur. It can also cause cognitive dysfunction. |

| Fentanyl | Fentanyl is a good drug in elderly patients, particularly those with renal impairment. It also causes less confusion than other analgesic drugs. |

| 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. |

<p>| NSAIDs and COX-2 inhibitors | There is an increased risk of complications, such as renal impairment, cardiac failure and hypovolaemia. There is an increased risk of gastrointestinal side effects and an increase in cognitive dysfunction in frail elderly patients who take NSAIDs. |</p>
<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>Paracetamol is a safe drug in the elderly. There is no need to reduce the dosage unless the patient is very frail.</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>Ideally, nitrous oxide should not be used in elderly patients because of the likelihood of vitamin B₁₂ deficiency occurring.</td>
</tr>
</tbody>
</table>

COX – cyclo-oxygenase, NSAIDs – nonsteroidal anti-inflammatory drugs, PCA – patient-controlled analgesia
8. Analgesia during pregnancy, childbirth, the puerperium and lactation

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

Chronic abdominal pain is present in 10–20% of women up to a year after delivery which has been found to increase postpartum depression threefold. Breastfeeding and bonding with their infant are adversely affected if the mothers experience pain, while immobilisation due to pain can lead to thrombo-embolic disease.

It is possible for pregnant women to be on chronic pain medication for chronic pain syndromes. Pregabalin and gabapentin are unlikely to be major teratogens and can be used for neuropathic pain. Parturients can also be on antidepressants, either for depression or as part of their chronic pain medication regime. Serotonin-norepinephrine reuptake inhibitors and TCAs, has reassuring safety data.

While this group of women frequently require analgesia, pain control is often poorly managed. By focusing on reducing unacceptably high maternal mortality rates in a resource-limited environment, pain may be overlooked. 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, which results in many healthcare providers incorrectly labelling these drugs as unsafe.

8.1 Pregnancy

8.1.1 First trimester

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

Analgesia following the termination of pregnancy should include NSAIDs and paracetamol. Short-acting opiates can be used for the procedure.
8.1.2 Second trimester

There is a lower risk of teratogenesis during the second trimester, as well as a lower risk of miscarriage following stress. This is also considered the safest period during which to perform a procedure if a delay until after delivery is not a feasible option.

8.1.3 Third trimester

There is a high risk of onset of premature labour during this period, and the wellbeing of the foetus should be considered after any stressful experience. There is minimal risk of teratogenesis during the third trimester as growth occurs during this period. However, all drugs given to the mother may cross over to the foetus via the placenta. Therefore, side effects of drugs on the foetus must be taken into account. Drugs affect the same organ systems in both the mother and the foetus. Analgesia throughout pregnancy is outlined in Table I.

Table I: Analgesia throughout pregnancy

<table>
<thead>
<tr>
<th>Paracetamol</th>
<th>1 g orally, 6-hourly</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opioids</strong></td>
<td>The prescription of any opiate should be undertaken with due caution. The duration of opioid analgesia should be limited to a maximum of 3–5 days. Opioids should be prescribed with symptomatic relief of constipation. All opioids pose the risk of addiction and neonatal abstinence syndrome should be monitored if opioids are used in the third trimester.</td>
</tr>
<tr>
<td>Short-acting oxycodone up to 5 mg orally, 4–6-hourly. Oxycodone is extremely potent and addictive.</td>
<td></td>
</tr>
<tr>
<td><strong>NSAIDs</strong></td>
<td>If pain is not controlled with paracetamol and opiates, a short-course low-dose NSAID may be prescribed, taking into account that the use of NSAIDs in pregnancy is off label. All NSAIDs are to be avoided after 30 weeks’ gestation to avoid the risk of premature ductal closure in the foetus. Ibuprofen is safe during lactation.</td>
</tr>
<tr>
<td>Ibuprofen 200 mg orally, 8-hourly</td>
<td></td>
</tr>
</tbody>
</table>

NSAID – nonsteroidal anti-inflammatory drug

8.2 Childbirth

All women should be offered methods of managing pain regularly throughout labour. Appropriate analgesia options should be available at 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 which is subjective. This includes distraction techniques (e.g. breathing exercises and white noise), which 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).
Non-pharmacological adjuncts could decrease anxiety as oxytocin and endogenous endorphins are secreted with a feeling of wellbeing.

**Systemic analgesia**

There are two ways of administering systemic analgesia:

i. **Opiates:** Morphine provides good analgesia during labour. However, it should not be given within four hours of delivery. Naloxone must also be available for the infant immediately after delivery. Pethidine was offered traditionally, but it is not recommended for use during labour or delivery. 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.

ii. **Patient-controlled analgesia (PCA) pump:** Usually, morphine is used in a PCA pump. The analgesia quality is 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 should only be used by specialised practitioners in a monitored environment.

**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 monitored regularly (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 (i.e. not fully supine unless a wedge is used to raise the right side at least 15 degrees). Walking should not be allowed unaidered, as there may be some motor block and proprioception is lost. Mothers can walk if supported on both sides.

Combined spinal and epidural (CSE) anaesthesia, an intrathecal injection of opiate, is given before the epidural is sited and used. This allows for faster onset of analgesia, but offers no other benefits, requiring special sets and added skill as well as respiratory monitoring. Analgesia during vaginal delivery is outlined in Table II.

**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.

Table II: Analgesia during vaginal delivery

<table>
<thead>
<tr>
<th>Non-pharmacological methods</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Morphine:</strong> 10 mg intramuscularly 4-hourly</td>
</tr>
<tr>
<td><strong>PCA pump:</strong> morphine 1 mg bolus with an 8-minute lockout</td>
</tr>
<tr>
<td><strong>Epidural:</strong> 0.1% bupivacaine + fentanyl 2 µg/ml, at 8–10 ml/hour</td>
</tr>
<tr>
<td>• Top up with 5–10 ml 0.1% bupivacaine (low dose top-up for haemodynamic safety)</td>
</tr>
<tr>
<td>• If for a CS, top up with 5–15 ml 0.5% bupivacaine, or 5–15 ml 1–2% lignocaine</td>
</tr>
<tr>
<td>• <strong>CSE:</strong> intrathecal injection 10–15 µg fentanyl (25 µg increases pruritus, NV) as well as the epidural mix, as described (0.1% bupivacaine 10 ml)</td>
</tr>
</tbody>
</table>

**Nitrous oxide 50% in oxygen (Entonox®):** Self-administered via a face mask

CS – caesarean section, CSE – combined spinal and epidural anaesthesia, PCA – patient-controlled analgesia, NV – nausea and vomiting

8.2.2 Analgesia for caesarean section

A South African study showed more than 80% of patients experienced moderate to severe pain after caesarean section (CS). More than 50% of these patients did not receive the fixed-interval morphine prescribed. Because complete elimination of pain is not likely, complete analgesia should be balanced with the risk of side effects and delayed mobilisation.

Pain after a CS is somatic and visceral. Individualised pain management requires trained and motivated staff and increases the workload impact. Analgesia in resource-limited environments should include freely available, inexpensive drugs with maximal analgesic efficiency and minimal side effects or monitoring for both mother and infant.

**Neuraxial block**

Neuraxial blocks are recommended for most mothers, unless there are contraindications such as severe hypotension, coagulopathy, raised intracranial pressure (ICP) and local sepsis. This provides analgesia for both the operation itself and approximately 2–3 hours postoperatively.

The addition of fentanyl 10–15 µg or sufentanil 2.5–5 µg improves and prolongs the quality of the block, which allows for less bupivacaine to be used, hence less haemodynamic compromise. Intrathecal opioids reduce the need for intraoperative analgesic supplementation, reduce nausea and vomiting, but increase pruritus.

Intrathecal morphine is the gold standard single dosage. Adding intrathecal preservative-free morphine to bupivacaine can prolong the duration of analgesia for more than 24 hours. If an ultra-low dose morphine (50 µg) is used intrathecally, healthy patients can return to the ward with routine postoperative monitoring. Low dose morphine (100 µg) intrathecally needs 2-hourly respiratory and sedation monitoring for 12 hours in a high care environment.
If intrathecal morphine has been administered, parturients with cardio-pulmonary or neurological comorbidities, a BMI > 40 kg/m², known or suspected OSA, chronic opioid use, hypertension or receiving magnesium need continual additional monitoring in a high care environment.

To prevent respiratory embarrassment, postoperative parenteral or oral opioids should not routinely be administered after intrathecal morphine. However, a pain specialist can prescribe additional parenteral or oral opioids for breakthrough pain.

Adding both fentanyl and morphine to the neuraxial block improves the intraoperative quality of the block with the added benefit of excellent postoperative analgesia.

If the spinal block works out after 2–3 hours, the patient has no level of analgesia. Intraoperatively, IV paracetamol and morphine should be considered. If there are no contraindications to NSAIDs (e.g., preeclampsia [PET] or renal insufficiency), excellent analgesia can be obtained from suppositories, IV or IM NSAIDs.

**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 be blunted (e.g. in PET), long-acting opiates should be avoided, if possible. Alfentanil or magnesium sulphate is recommended (unnecessary if the patient has been loaded with magnesium recently).

The mother should be kept adequately anaesthetised. Short-acting opiates are used for analgesia. From induction until delivery, the infant is exposed to all the drugs given to the mother. Therefore, the person receiving the infant must be informed if opiates were used and naloxone must be available in the theatre.

Once the infant has been delivered, multimodal analgesia is administered to the mother, as is done with all open abdominal procedures. Local anaesthetic agents can be infiltrated into the wound at the end of the procedure, or a bilateral transversus abdominis plane (TAP) block can be performed. Analgesia during a CS is outlined in Table III.

**Table III: Analgesia during a caesarean section**

<table>
<thead>
<tr>
<th>Neuraxial block</th>
<th>Recommended intrathecal injections are as follows:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• 2.0–2.2 ml 0.5% heavy bupivacaine (i.e. bupivacaine with dextrose)</td>
</tr>
<tr>
<td></td>
<td>• 1.8–2.0 ml 0.5% heavy bupivacaine, with 10–15 µg fentanyl or 2.5–5 µg sufentanil</td>
</tr>
<tr>
<td></td>
<td>• 1.8–2.0 ml 0.5% heavy bupivacaine (i.e. with 50 µg morphine, 10–15 µg fentanyl or 2.5–5 µg sufentanil)</td>
</tr>
</tbody>
</table>
General anaesthesia

If the intubation response must be blunted, the following applies:

- Magnesium sulphate: 40 mg/kg IV infusion preinduction
- Alfentanil: 0.5–1.0 mg intravenously, or remifentanil 0.5–1 mcg/kg/min IV until after intubation

Intraoperative analgesia following delivery of the infant

- 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)

---

8.3 The puerperium

The use of multimodal analgesia allows for decreased doses of the individual component drugs, which benefit the breastfeeding infant as fewer drugs cross over into the breastmilk.

8.3.1 Analgesia following vaginal delivery

Mothers experience pain from ongoing contractions, vaginal tears, episiotomies and breast pain. They also have headaches from prolonged labour, emotional turmoil, prolonged pushing, dural puncture during insertion of the intrathecal, or inadvertent dural puncture with an epidural needle.

Perineal pain is acute and may be severe. In combination with multimodal analgesia, sitting in ice water or using ice packs may be useful.

Other forms of pain can be managed by using a combination of paracetamol and an NSAID around the clock (this combination is very effective), and adding a short-course opiate as required. The breastfeeding infant should be monitored for sedation if high doses of opiates are used. Parenteral analgesia (including paracetamol) is not superior to oral analgesia and has the added benefit of increased patient mobility.

Codeine is not recommended. Pharmacogenomic metabolic variability in efficiency can lead to high levels of active metabolites, excreted into breastmilk with respiratory depression in the infant.

Oxycodone or dihydrocodeine have similar analgesic potency as codeine with a better side effect profile.

Tramadol also has pharmacogenomic polymorphisms; some patients lack the enzyme to produce the active metabolite, while others are extensive metabolisers. Adverse reactions in breastfed infants may include excessive sleepiness, difficulty breastfeeding or breathing.
problems. Therefore, if infants are exposed to tramadol through breastmilk, they should be monitored for excessive sedation and respiratory depression.

8.3.2 Analgesia following a caesarean section

As with all abdominal surgeries, postoperative pain is considerable. Multimodal analgesia should be used and patients should be discharged with oral medication.

Paracetamol given regularly is 20–40% opioid-sparing, while NSAIDs is a key component in multimodal analgesia and is 30–50% opioid-sparing. Gabapentinoids, ketamine and dexamethasone are adjuncts with potential peri-operative analgesic benefits. Analgesia during the puerperium is outlined in Table IV.

### Table IV: Analgesia during the puerperium

<table>
<thead>
<tr>
<th>Following normal vaginal delivery</th>
<th>Following a caesarean section</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Paracetamol: 1 g 6-hourly; and</td>
<td>• Paracetamol: 1 g 6-hourly; and</td>
</tr>
<tr>
<td>• NSAIDs: ibuprofen 400 mg 6-hourly, or diclofenac 50–100 mg, 8–12-hourly; and</td>
<td>• NSAIDs: ibuprofen 400 mg 6-hourly, or diclofenac 50–100 mg 8–12-hourly; and</td>
</tr>
<tr>
<td>• Short-course opiates: such as dihydrocodeine 30–60 mg 4–6-hourly; or</td>
<td>• Short-course opiates if no intrathecal morphine has been given: These should be nurse administered, such as morphine 10 mg IM/SC 3–6-hourly, as required; or</td>
</tr>
<tr>
<td>• Oxycodone: 5–10 mg 6-hourly; or</td>
<td>• PCA: PCA morphine 1 mg bolus with 8-minute lockout, while in hospital, then an oral short-course opiate; or</td>
</tr>
<tr>
<td>• Combinations containing paracetamol, with or without NSAIDs, and with or without an opioid available.</td>
<td>• Short-acting oxycodone: 5 mg 4–6-hourly (oxycodone in lactating mothers is off label); or</td>
</tr>
<tr>
<td>• Check the relative doses of each component, and supplement with individual components, rather than increasing the doses of all of these.</td>
<td>• Dihydrocodeine: 30–60 mg 4–6-hourly; or</td>
</tr>
<tr>
<td></td>
<td>• Tramadol: 50–100 mg 6-hourly</td>
</tr>
</tbody>
</table>


8.4 Lactation

Breastfeeding mothers can experience pain for a number of reasons. Breast pain is common, especially after the first few days, and results from engorgement and cracked nipples.

While most drugs cross into the breastmilk, the concentrations are usually too low to be of concern regarding the wellbeing of the infant if the drugs and the doses are carefully considered. Analgesia for lactating mothers is outlined in Table V.
Table V: Analgesia for lactating mothers

<table>
<thead>
<tr>
<th>Pain Level</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild pain</td>
<td>Paracetamol: 1 g 6-hourly, with the possible addition of a short-course of low dose NSAID (e.g. ibuprofen 400 mg, 6-hourly)</td>
</tr>
<tr>
<td>Moderate pain</td>
<td>Paracetamol + NSAIDs at regular intervals</td>
</tr>
<tr>
<td>Severe pain</td>
<td>Paracetamol + NSAIDs + a short-course opiate (i.e. dihydrocodein)</td>
</tr>
</tbody>
</table>

NSAID – nonsteroidal anti-inflammatory drug

Bibliography

9. Routes of systemic drug administration: enteral and parenteral

Analgesia prescriptions should be individualised based on actual or expected pain severity, patient characteristics and available resources. Attention must be paid to both the effectiveness and the adverse effects of analgesic agents. Monitoring will be directed by the drug class and route of administration.

Analgesics should be prescribed regularly, rather than on a pro re nata (‘as the thing is needed’) basis.

9.1 Enteral administration

9.1.1 Oral route (p.o.)

The cost per dose of oral preparations is usually lower and should be used if possible. No patient who can swallow or who is not vomiting should receive parenteral analgesics. Not only are oral dosage forms usually cheaper, but also no further cost is incurred with infusion sets, IV solutions and time to administer the drugs. Moreover, every time a patient is exposed to an IVI, there is always the risk of introducing microorganisms if aseptic technique is not strictly adhered to.

The efficacy of oral drugs is determined by the following factors:

- **GI motility** considerations include delayed gastric emptying, nausea and vomiting, and delayed ‘dumping’.

- **Drug formulation affects absorption rate** as liquids are absorbed faster than capsules, while tablets are absorbed the slowest. The enteric coatings of tablets and capsules delay dissolution until they have left the stomach with its low pH. This protects acid-labile drugs from stomach acid. Enterically coated tablets and capsules should never be crushed or opened, respectively. Slow-release preparations release the active ingredient at a controlled rate at different areas of the gut. This allows for the delivery of a larger dose, with slower onset, longer duration and reduced peak levels, and hence reduced adverse effects. Several slow-release analgesic agents are marketed. They are usually administered 12-hourly. These drugs are most useful for providing baseline analgesia for acute pain, and for the long-term therapy of chronic and cancer pain.

- **Hepatic first-pass metabolism** occurs with all enteral dosage forms, except sublingual (SL) preparations.

Details about drug classes that are administered orally are given in Chapter 5.
Morphine

Oral morphine is available as a liquid (most commonly formulated as 20 mg/5 ml), immediate-release tablets and a slow-release formulation. Oral morphine is effective for acute pain relief at a dose of 20 mg every 30 minutes, until an adequate level of pain relief has been established. Thereafter, 10–20 mg can be administered 4-hourly. The main concern with this therapy, particularly with poorly-staffed wards, is the diversion of the oral morphine to visitors for illicit use.

With longer-term use, the total daily oral morphine use should be quantified. This dose is taken in a slow-release formulation bd. An immediate-release formulation, taken for breakthrough pain, is gradually added to the slow-release dose, while immediate release doses are still available.

Oxycodone

Oxycodone has a similar onset and duration of action to morphine, and is available as an immediate (Oxynorm® 5, 10 or 20 mg) or slow-release (Oxycontin® 5, 10, 20, 40 or 80 mg) preparation. Differences to morphine include reduced first-pass metabolism, which improves oral bioavailability. With longer-term use, daily oral oxycodone use should be quantified. Fifty per cent of the daily requirements is administered as a 12-hourly slow-release formulation, while breakthrough pain is managed with a short-acting tablet (usually 5 mg) administered 4–6-hourly. The newest formulation of oxycodone is Targinact® which combines oxycodone and naloxone in a 2:1 ratio. Naloxone undergoes 97% hepatic first-pass clearance. Therefore, it does not antagonise the analgesic effect of oxycodone, and reduces the GI adverse effects by up to 60%, excluding nausea (which is mediated through a CNS effect).

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 norpethidine.

Procedural sedation (with analgesia)

This is especially helpful in the paediatric population. The IV formulations of ketamine (containing 50 mg/ml) 5 mg/kg and midazolam (containing 5 mg/ml) 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 intended for parenteral use mixed with a suitable syrup.) The onset time is 20–30 minutes and the duration of sedation is 30–45 minutes.
Secondary analgesics

Clonidine

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

9.1.2 Rectal route (PR)

Per rectum NSAIDs and paracetamol are commonly used in South Africa.

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 and must be specifically obtained.

Rectal paracetamol still undergoes hepatic first-pass metabolism; hence, absorption may be slow in hypovolaemic patients with reduced splanchnic blood flow.

The GI adverse effects of NSAIDs include systemic anti-cyclo-oxygenase effects. Therefore, the rectal administration of these agents does not prevent GI adverse effects. Similarly, the renal and antiplatelet effects are independent of the route of administration.

Tramadol is the only opioid available for rectal administration. Dosage adjustment is not necessary. Currently, this preparation is not available in South Africa.

Suppositories may be administered via intestinal stomas. However, the level of the stoma determines the suitability of this application of suppositories; that is, the absorbing surface (small bowel) available, as well as the transit time. Discussion with the surgeon is advised, especially with freshly-formed stomas and complex diversion procedures. This is an unreliable route and its routine use is not advocated.

9.1.3 Sublingual and buccal administration

Drugs administered sublingually are absorbed directly into the systemic circulation. This results in a faster onset and a higher peak level because of direct absorption with no hepatic first-pass
metabolism. The SL and buccal routes may be useful when IV administration is not feasible, or in low peripheral perfusion, such as hypothermia or any cause of low cardiac output (e.g. hypovolaemia).

Drugs in an IV formulation may be given sublingually before the establishment of IV access. For drugs that usually require a loading dose (LD) (e.g. dexmedetomidine), buccal administration appears to provide onset of effect, approaching that of an IV LD. In adults, buccal administration (the solution must not be swallowed) of the IV preparation of dexmedetomidine, 2 µg/kg has an absolute bioavailability of 84% and is an effective route of administration if IV access is not available.

In emergency settings, the SL administration of drugs, such as morphine 0.5 mg/kg and fentanyl (100 µg tablets and wafers; neither of which is available in SA), provide adequate analgesia.

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 with the lollipop have been raised, but not validated. However, neither is available in South Africa.

The anti-emetic ondansetron, is available as a rapidly dissolving SL lyophilisate wafer (Zofran Zydis™).

9.1.4 Feeding tubes (orogastric, nasogastric, postpyloric, gastrostomy and enterostomy)

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

9.2 Parenteral administration

9.2.1 Noninvasive systemic drug administration

**Intranasal (IN) droplets**

The IV formulation of morphine, fentanyl, midazolam, dexmedetomidine and ketamine may be given intranasally.
The aim of administering the drug via the nasal mucosa is fast onset and high peak levels of the drug, providing efficacy similar to IV administration. However, more than 70% of medication administered via this route passes through the nasal passage into the nasopharynx and is then swallowed. The swallowed medication is absorbed via the gastrointestinal tract (GIT), with a slow onset and low peak due to hepatic first-pass metabolism, as with any orally administered drug.

Most IV formulations have a bitter taste. 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.

The administration of an opioid (particularly synthetic fentanyl derivatives) via the nasal route is associated with intense pruritis, which may be due to large numbers of degranulated histamine-releasing immune cells in the nasal mucosa when exposed to opioids.

**Nasal transmucosal administration**

A device known as the LMA (laryngeal mask airway) MAD (mucosal atomisation device) Nasal® (Teleflex Medical, USA), produces a fine mist (droplet size < 0.2 µm) when the medication is injected from a standard syringe through the MAD (Figure 1). More than 90% of the medication in the droplets from the MAD is absorbed by the nasal mucosa, with less than 10% swallowed. The result is that MAD-administered drugs, such as morphine, midazolam and dexmedetomidine, achieve fast onset and 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.

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

Figure 1: LMA MAD Nasal® (Teleflex Medical, USA)
Passive transdermal drug delivery

The transdermal route 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, particularly in opioid-sensitive patients.

Fentanyl and buprenorphine are both 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.

Cutting transdermal patches to reduce the rate of drug delivery in the acute pain setting is a negligent practice which cannot be justified, and that carries significant medicolegal consequences in the event of an adverse outcome.

Transdermal fentanyl or buprenorphine are best suited to the maintenance of opioid analgesia in patients with either chronic or cancer pain. Transdermal fentanyl or buprenorphine does not have a role in acute pain management but must be part of an analgesia plan for patients who are already using these for chronic and cancer pain.

9.2.2 Invasive systemic drug delivery

This includes the subcutaneous (SC), intramuscular (IM), IV and intraosseous (IO) routes.

Apart from adverse and toxic effects of drugs administered via the IV, IM, SC and IO routes, a potentially more serious complication of these routes of administration is infection and sepsis. Nothing should ever be administered through an injection port (including stopcocks) or the skin without proper disinfection. Line sepsis has both a high morbidity and a high mortality. The stopcocks hygiene is extremely important. Injection ports must always be capped; caps must never be removed from the port, kept in the (always contaminated) palm of the hand and then used to cover the injection port as the cap will be contaminated.

A manner in which to avoid contaminating the injection port of a stopcock is the following (for right-handed persons):

Hold the needle-capped syringe containing the solution to be injected in your right hand with the needle pointing downwards. Place the needle in the web between your left thumb and index finger. Remove the capped needle from the syringe by holding it in the web between your left thumb and index finger. Remove the cap from the sterile injection port of the stopcock using your right thumb and index finger. Place the sterile cap onto the open end of the sterile needle between the left thumb and index finger. Stabilise the stopcock with the left hand, still holding the needle capped with the stopcock cap. Insert the syringe nozzle into the sterile
injection port and open the injection port with your right hand. Inject the content of the syringe, and close the port with your right hand. Detach the syringe by holding it between the thumb and index finger of your right hand. Remove the stopcock cap from the capped needle using your right hand and replace the cap onto the injection port of the stopcock. Still holding the needle between the left thumb and index finger, put the (still sterile) syringe nozzle onto the (still sterile) needle. QID!

**Subcutaneous drug delivery**

Analgesics that are formulated for IV use may usually be administered SC if the volume is limited to approximately 1.5 ml. A volume of up to 3 ml is tolerated SC when administered into the abdominal wall. Aqueous solutions formulated for IV administration should ideally also be registered for SC use and indicated on the ampoule label. The acceptability of a solution (pain injection, tissue damage) is determined by excipients (buffers, stabilisers and preservatives), pH and osmolality. SC administration of drugs is unpredictable in patients with poor peripheral perfusion (hypothermia, hypovolaemia, etc.) because a large dose may enter the circulation as soon as perfusion is restored.

Drugs that are formulated for IM administration are not always suitable for SC administration as the volume is excessive and the solution is an irritant (e.g. diclofenac).

An indwelling SC cannula dedicated for analgesic drugs simplifies the administration of analgesics in wards. Patients are spared the pain and inconvenience of multiple injections, while staff are exposed to needles less and the risk of needle-stick injuries is reduced.

In patients undergoing surgery and who are likely to require systemic opioids and/or NSAIDs for postoperative pain relief, the SC cannula should be inserted in the operating theatre intraoperatively. The anterior upper arm area is one of the most comfortable sites for cannula insertion, with optimal consistency in drug absorption.

A 20 or 22 G IV cannula is inserted into the SC tissue and connected to a low-volume extension (approximately 10 cm in length and 1 mm in diameter) with a needle-free injection port. The tubing should be primed with the solution intended for SC administration. The cannula with connection is covered with a clear semi-permeable dressing (e.g. OpSite™ or Tegaderm™), leaving the injection port accessible for drug administration. Sites need to be changed every 2–3 days, as long as the injection site is not painful or infected (redness and swelling).

The rate of SC boluses with infusions (bolus-basal administration) should not exceed 1 ml in a single bolus, or a total volume of 3 ml/hour. 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 PCA systems.
SC PCA 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 cannula removal and replacement at an alternative site. The following are a number of advantages to SC PCA administration:

- PCA may be continued when IV access is no longer required or feasible (palliative care).
- 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 removed.

**Intramuscular drug delivery**

The IM route is a common route of opioid delivery in postoperative patients, despite well-recognised complications, including drug toxicity from intra- and perivascular injection, inadequate analgesia, nerve damage and injection abscesses. Injection abscess complications are increased with a high injection volume, increasingly irritant injectate and in immunocompromised patients. Two-hourly rather than 4-hourly intervals are required.

Examples of inadequate IM analgesia include the following:

- **Inappropriate dosing:** morphine is commonly dosed at 10–15 mg, and pethidine at 50–100 mg, both 4–6-hourly. These prescriptions provide adequate postsurgical analgesia in < 50% of patients, but will cause significant respiratory depression in up to 2%.
- **Reduced blood muscle and skin flow:** this occurs particularly after surgery (hypothermia) and in emergency situations (hypovolaemia). IM drug administration in the emergency management of moderate to severe acute pain is inappropriate.
- Injection into fat or SC tissue.

**Intravenous drug delivery**

IV drug delivery provides the most rapid onset of action through direct access to the systemic circulation. However, side effects (including overdose) may also be more common.

Principles of safe medication administration should always be followed, regardless of the route of administration, and heightened vigilance is required when using opioids.

Paracetamol and NSAIDs may have more benign acute adverse effects but can also result in life-threatening complications that require ongoing monitoring. Opioids have the potential to cause respiratory depression and patients should be constantly monitored by trained personnel who are able to identify a reduction in RR and/or tidal volume and level of consciousness, and who have access to naloxone and are trained to administer it. Using pulse oximetry may only alert personnel to respiratory depression at a late stage when desaturation occurs; supplementary
oxygen is then unlikely to resolve the true underlying mechanism of respiratory compromise (i.e. hypoventilation or obstructed airway).

**Intraosseous drug delivery**

An IO needle may be placed in both children and adults, commonly using the tibia or proximal humerus (also femur, iliac crest and sternum). It is unlikely that an IO device will be placed solely for analgesic purposes, but it can be used if in situ.

Almost all IV administrations may be given via the IO route. Drugs administered intraosseously have similar bioavailability, posology and pharmacokinetics.

The Arrow® EZ-IO® Intraosseous Vascular Access System (Teleflex, USA), is available in South Africa. Many techniques for insertion and attachment are available in the literature. An 18 G Tuohy needle can be used for IO access.

**Bibliography**

10. Locally and regionally administered analgesic drugs

10.1 Drugs used for local and regional analgesia

10.1.1 Local anaesthetics

LAs exert analgesic effects by blocking sodium channels, impeding neuronal excitation and conducting impulses. LA consist of a hydrophilic amine and a lipophilic aromatic ring connected by an intermediate chain, which can have either an ester or amide linkage. Commonly used amide agents available in South Africa are lignocaine (injectable and topical), bupivacaine, levobupivacaine and ropivacaine, with articaine and mepivacaine available in cartridge form (mainly for dental use). Prilocaine is available in a topical formulation as part of EMLA. Ester LA available are cocaine, amethocaine (tetracaine) and benzocaine, all for topical application.

Short-duration LAs

- Lignocaine is the most widely used short-duration LA in acute pain management.
- Although the plasma half-life of lignocaine is approximately 90 minutes, the duration of the LA effect is also determined by the site of administration, the dose and the presence or absence of vasoconstrictors.
- The hydrophilic nature of lignocaine is overcome by delivering the drug in high concentrations. This results in good diffusion into nerve bundles with little separation of sensory and motor blocking actions.

Long-duration LAs

- The three commonly used long-duration LA agents are bupivacaine, levobupivacaine and ropivacaine.
- These drugs are structurally related. Bupivacaine is a racemic mixture of the S- and R-enantiomers, while both levobupivacaine and ropivacaine are solely S-(levo)-enantiomers.
- Duration of action is 2–9 hours and is influenced by site of administration and dose, but is minimally influenced by the addition of vasoconstrictors.

Summary of evidence-based efficacy and safety features of LA agents

- A continuous perineural infusion of lignocaine provides less effective analgesia and results in denser motor block than ropivacaine, levobupivacaine or bupivacaine.
- 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.
- Ropivacaine and levobupivacaine cause less severe CV and CNS toxic effects than racemic bupivacaine.
• A lipid emulsion (20% intralipid) is effective in the resuscitation of circulatory collapse due to local anaesthetic toxicity (LAST) and must be used in conjunction with advanced cardiac life support.
• Resuscitation following accidental overdose with ropivacaine is more likely to be successful than resuscitation after a bupivacaine overdose.

10.1.2 Opioids

• Although peripheral opioid receptors have been identified, there is currently little clinical evidence to support the use of opioids for possible peripheral or local effects.
• When compared to placebo, intra-articular morphine following knee arthroscopy does not improve analgesia.
• There is currently no conclusive evidence that opioids have a peripheral effect at perineural level.
• Evidence for clinically-relevant peripheral opioid effect after topical administration is also inconclusive.

10.1.3 Adjuvant drugs

Alpha-2 agonists

• Clonidine prolongs the duration of analgesia and anaesthesia when added to LAs for plexus blocks, peribulbar blocks and peripheral nerve blocks, but is associated with increased hypotension and bradycardia.
• Adding clonidine to lignocaine IV regional anaesthesia delays tourniquet pain.

Magnesium

• Magnesium sulphate improves intra- and postoperative analgesia and tourniquet tolerance when added to lignocaine IV regional analgesia.
• The long-term effects of perineural magnesium are unknown and adding magnesium to LA when performing nerve blocks is not advised.

Ketamine

• 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 various clinical settings.
• Subacromial injections of corticosteroids are more effective than oral NSAIDs when treating rotator cuff tendonitis.

• Intra-articular steroids, in combination with an LA, 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.

• Adding dexamethasone (perineural or IV) to LA increases duration of peripheral nerve blocks significantly compared to LA only. Perineural dexamethasone prolongs the LA nerve block by about three hours compared to IV dexamethasone.

**Nonsteroidal anti-inflammatory drugs**

Administering NSAIDs at the site of pain is an attractive alternative to oral or parenteral routes, potentially minimising systemic side effects of the drug.

• Topical NSAIDs (possibly excluding indomethacin) are effective in treating acute strains and sprains, providing short-term functional improvement with side effects comparable to placebo. Gel formulations of diclofenac, ibuprofen and ketoprofen, as well as diclofenac patches, work best.

• Topical NSAIDs also provide effective analgesia for traumatic corneal abrasions and are effective for short-term relief of sore throat following tracheal intubation (benzydamine, e.g. Andolex® and flurbiprofen, e.g. Strepsils intensive®).

• Adding a non-selective NSAID to an LA solution for IV regional anaesthesia improves postoperative analgesia.

**10.2 Regional and local analgesic techniques**

10.2.1 Peripheral nerve blocks and the infusion of local anaesthetics

• Peripheral nerve blocks may be performed either as a single-shot or via an indwelling perineural catheter.

• Evidence of efficacy of peripheral nerve blocks has been confirmed in various clinical settings:
  ◦ Continuous peripheral nerve blocks, 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).
  ◦ Continuous peripheral nerve blocks have been shown to be safe when used at home provided that there are adequate resources and patient education is provided.
  ◦ Single-shot infraclavicular blocks provide effective analgesia and less nausea following hand and wrist surgery, and earlier ambulation and hospital discharge compared to GA.
Following open shoulder surgery, single-shot or continuous interscalene analgesia provides better analgesia and improved patient satisfaction, with reduced opioid-related side effects compared to opioid-based IV PCA.

A femoral nerve block provides better analgesia than parenteral opioid-based techniques after total knee arthroplasty.

An adductor canal femoral nerve block, with quadriceps muscle function sparing, may facilitate earlier mobilisation after total knee arthroplasty.

A continuous femoral nerve block is equianalgesic to epidural analgesia, but with fewer side effects following total knee arthroplasty.

Continuous posterior lumbar plexus analgesia and continuous femoral analgesia are equally effective following total knee arthroplasty.

When compared to 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.

The advantages and disadvantages of peripheral nerve blocks are outlined in Table I.

<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent analgesia</td>
<td>Small risk of bleeding with anticoagulation</td>
</tr>
<tr>
<td>Avoids the complications of systemic analgesics</td>
<td>Continual monitoring of analgesia, together with an adjustment of the dose or infusion rate, is mandatory</td>
</tr>
<tr>
<td>Promotes early mobilisation and physiotherapy</td>
<td>Potential local anaesthetic toxicity with prolonged infusion (a rare complication)</td>
</tr>
<tr>
<td></td>
<td>Catheter migration with resulting ineffective analgesia</td>
</tr>
<tr>
<td></td>
<td>Infection risk with indwelling catheter</td>
</tr>
<tr>
<td></td>
<td>Possible nerve damage</td>
</tr>
</tbody>
</table>

10.2.2 Interfascial plane blocks

Interfascial plane blocks, in which LA are introduced into fascial planes where sensory nerves usually course, have been widely applied over the last 10 years.

Transversus abdominus plane (TAP) 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. Breathing and coughing is more comfortable, and early mobilisation and discharge are facilitated. A reduction in persistent postoperative pain with TAP blocks after CS is reported.

Paravertebral blocks have been shown to be effective after breast surgery as well as thoracotomy.
• Randomised controlled data is currently lacking regarding newer plane blocks, but indications may be summarised as follows:
  ◦ Breast surgery: pectoralis II, erector spinae plane block or serratus plane block
  ◦ Mini thoracotomy: pec II plus erector spinae block
  ◦ Thoracotomy: serratus plane or erector spinae plane
  ◦ Midline abdominal surgery, including abdominal hernia repair: four-quadrant TAP or erector spinae or quadratus lumborum plane block
  ◦ Lumbar spine surgery: erector spinae plane blocks

10.2.3 Surgical site administration of analgesics

Analgesia administered into or surrounding a surgical wound is an attractive and safe method of blocking noxious stimuli resulting from a surgical insult. This method can take the form of intracavity analgesia (intraperitoneal and intra-articular), musculofascial and subdermal infiltration.

• Peri-articular surgical wound infiltration
  ◦ In hip and knee surgery, single-dose, large-volume, low-concentration LA infiltration of capsule, ligaments and other soft tissue is effective in reducing short-term pain and hospital stay.
  ◦ This technique has been proven beneficial in patients undergoing total knee replacement, with less conclusive data in hip replacement.
  ◦ Periarticular catheter techniques are not recommended due to concerns of catheter-related sepsis.
  ◦ Periarticular techniques for shoulder surgery have not been studied adequately enough to make recommendations.

• Intra-articular techniques
  ◦ When compared with placebo, intra-articular morphine alone following knee arthroscopy does not improve analgesia.
  ◦ Postoperative pain is reduced to a limited degree by single-shot intra-articular LA. Intra-articular bupivacaine infusions have been associated with chondrolysis and are not recommended.
  ◦ Intra-articular NSAIDs, such as ketorolac, result in improved pain relief after surgery. However, long-term follow-up has not been undertaken and the effect on bone healing is unknown.
  ◦ Following knee joint arthroscopy, intra-articular steroids, in combination with either an LA or opioid, reduce pain, analgesic consumption and the duration of immobilisation.
• Local infiltration and continuous wound infusions for abdominal surgery
  ◦ In order for analgesia to be effective, infiltration of peritoneal, musculofascial and subdermal planes are required.
  ◦ Continuous LA wound infusions after laparotomy lead to a reduction in pain at rest and during movement, most notably during first 24 hours postoperatively. 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.
  ◦ The infiltration of the wound with LA agents provides good and long-lasting analgesia after inguinal hernia repair, abdominal hysterectomy and ventral hernia repair, but is of limited value in laparoscopic cholecystectomy. With ventral hernia repair, additional infiltration of LA around the perimeter of the mesh creates a field block which covers the fascia closure as well as the mesh fixation sites. Preperitoneal or subfascial catheters allow for continuous LA infusion and prolonged analgesia.
  ◦ There are no studies that compare surgical site infiltration with interfascial plane blocks. Current evidence suggests that a TAP block offers comparable degrees of analgesia to surgical site infiltration with significantly longer duration of action.

• Intraperitoneal LA
  ◦ May reduce early postoperative pain scores following laparoscopic cholecystectomy, but the generalised use of intraperitoneal LA in laparoscopic surgery is of unproven benefit.
  ◦ The benefits of adding adjuncts like magnesium and dexmedetomidine to the mixture remain unproven.

LA doses and infusion rates for peripheral nerve blocks, interfascial plane blocks and surgical site infiltration in adults are covered in Table II.

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

<table>
<thead>
<tr>
<th>Technique</th>
<th>Drugs</th>
<th>Adult dose</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plexus block</td>
<td>Bupivacaine</td>
<td>LD: 0.25–0.50%, 20–40 ml Cl: 0.12–0.25%, 5–10 ml/hour</td>
<td>Maximum 2 mg/kg or 6 mg/kg/24 hours Maximum 150 mg or 1 ml/kg bolus</td>
</tr>
<tr>
<td></td>
<td>Levobupivacaine</td>
<td>As for bupivacaine</td>
<td>As for bupivacaine</td>
</tr>
<tr>
<td></td>
<td>Ropivacaine</td>
<td>LD: 0.50–0.75%, 10–40 ml Cl: 0.20%, 0.10 ml/kg/hour</td>
<td>Maximum 800 mg/24 hours or 28 mg/hour dose/kg? Maximum 1 ml/kg bolus</td>
</tr>
<tr>
<td>Minor nerve blocks, surgical site infiltration and interfascial plane blocks</td>
<td>Bupivacaine</td>
<td>0.25–0.50%, 1–60 ml</td>
<td>Maximum 2.5 mg/kg or 150 mg</td>
</tr>
<tr>
<td></td>
<td>Levobupivacaine</td>
<td>0.25–0.50%, 1–60 ml</td>
<td>Maximum 2.5 mg/kg or 150 mg</td>
</tr>
</tbody>
</table>

LD – loading dose, CI – continuous infusion
10.2.4 Intravenous regional analgesia

IV regional analgesia is a less commonly used technique of administering peripherally-acting analgesics. IV regional analgesia doses are outlined in Table III.

Table III: Intravenous regional analgesia doses

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lignocaine</td>
<td>Maximum dose of 200 mg or 2 mg/kg</td>
<td>Dilute to 40 ml total volume</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adding dexamethasone or ketorolac may prolong analgesia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adding clonidine and magnesium delay tourniquet pain</td>
</tr>
</tbody>
</table>

10.2.5 Topical analgesia

Topical application of locally-acting analgesics is potentially associated with a favourable drug side effect profile. The evidence-based topical use of several drugs is summarised in Table IV.

Table IV: Clinical use of topically applied analgesic agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Application</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMLA</td>
<td>Venous ulcer debridement</td>
<td></td>
</tr>
<tr>
<td>Amethocaine</td>
<td>IV cannulation in children</td>
<td>Superior to EMLA</td>
</tr>
<tr>
<td>Local anaesthetic on swab</td>
<td>Direct application to tonsil bed with tonsillectomy</td>
<td>Similar analgesia to local anaesthetic infiltration</td>
</tr>
<tr>
<td>Ketamine</td>
<td>Mouthwash</td>
<td>Reduced pain from oral mucositis</td>
</tr>
<tr>
<td>NSAID</td>
<td>Eyedrops</td>
<td>Traumatic corneal abrasions</td>
</tr>
<tr>
<td>Transdermal</td>
<td>Lozenges/oral sprays (benzydamine, flurbiprofen)</td>
<td>Postanaesthesia sore throat following intubation</td>
</tr>
<tr>
<td></td>
<td>Gel formulations of diclofenac, ibuprofen and ketoprofen, and diclofenac patches</td>
<td>Acute soft tissue strains and sprains</td>
</tr>
</tbody>
</table>

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

10.3 Safety considerations for regional and local analgesic techniques

10.3.1 Anticoagulation

Caution is advised when performing blocks in patients with impaired coagulation where direct pressure in the event of a traumatised blood vessel is not possible (e.g. during a lumbar plexus block, psoas compartment block or infraclavicular brachial plexus block), as a plexopathy may follow haematoma-induced pressure. Guidelines for the removal of peripheral catheters from noncompressible sites are the same as 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 resolve within 3–6 months.
- The incidence of late neurological injury persisting for more than 6–12 months is approximately 0.04%. (4 per 10 000).
- Permanent neurological injury has been reported following the injection of a LA directly into the cervical spinal cord while an interscalene block was performed GA.
- 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 IV injection or the rapid absorption of a LA in vascular-rich areas can lead to LAST.

- The highest incidence is seen with paravertebral blocks, followed by upper and lower extremity peripheral nerve blocks.
- Risk factors for LAST include small muscle mass, extremes of age and pre-existing heart disease or carnitine deficiency.
- Half the cases of LAST have a delayed onset (> 1 hour) or atypical presentation, with no seizures and only CV toxicity.
- Minimising LAST-related morbidity requires correct patient selection, block choice, drug and dose, complete monitoring and use of ultrasound-guided regional anaesthesia when possible.

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 ≥ 48 hours, and repeated dressing changes are risk factors for colonisation. Catheter tunnelling significantly reduces bacterial colonisation to 6%.

The strongest recommendations for preventing infections 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.

Bibliography

11. Patient-controlled analgesia and neuraxial analgesia techniques

PCA and neuraxial analgesia techniques offer alternative nonconventional methods for postoperative pain management.

11.1 Clinical guidelines on the use of patient-controlled analgesia

11.1.1 Rationale for use

PCA refers to a method of analgesia through which a patient self-administers small doses of an analgesic, usually an opioid, delivered with a programmable infusion pump.

Efficacy

The proposed benefits of PCA, compared to conventional parenteral opioid regimens, include the following:

- Improved pain control
- Higher patient satisfaction
- Decreased risk of overdose
- Less labour-intensive for the nursing staff

However, IV PCA with opioids may result in higher opioid consumption and pruritus compared to intermittent opioid administration. There may also be no difference in efficacy in settings with a high nurse-to-patient ratio.

The decision to provide PCA depends on availability and resources (financially and staffing), and is taken after discussion with the patient. Ongoing communication regarding, for example, the adjustment of demand dosing, may influence the success of PCA management.

PCA is only effective after the initial rapid pain control under supervision of the prescribing physician, for example, in the postoperative care unit. Initial doses should be individualised, taking into account factors such as previous opioid use and age.

The concept of PCA continues to develop in children. Patient-controlled epidural analgesia (PCEA), SC PCA and intranasal (IN) PCA are extensions of this method. 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 above the age of 5 years.
Cost

Although equipment cost is higher, the possible benefits of reduced adverse effects and nursing time must also be considered.

11.1.2 Standards of care

The safety of PCA can be improved upon by adopting standardised protocols regarding methods and documentation (see Chart 1). 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 by the nursing staff

**Prescription**

Prescription date & time: ____________________________

<table>
<thead>
<tr>
<th>Opioid name:</th>
<th>Opioid concentration (mg/ml):</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additive 1 name:</td>
<td>Additive 1 dose or amount:</td>
</tr>
<tr>
<td>Additive 2 name:</td>
<td>Additive 2 dose or amount:</td>
</tr>
</tbody>
</table>

**Treatment changes**

| Continuous infusion (ml/hr) | | |
| Loading dose opioid (mg) | | |
| PCA bolus opioid (mg) | | |
| Lockout time (minutes) | | |
| 4-hour maximum opioid (mg) | | |
| Total amount opioid (mg) | | |

**Bag change?**

Yes | No

**Prescription for repetition of bag:**

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Additive 1</th>
<th>Additive 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount (mg)</td>
<td>Amount (mg)</td>
<td>Amount (mg)</td>
</tr>
<tr>
<td>Type of solution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bag size (ml)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Doctor: __________________ Signature: __________________ Contact no: __________________

**Monitoring (hourly)**

<table>
<thead>
<tr>
<th>Pain (use VAS)</th>
<th>Findings</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate to severe</td>
<td></td>
<td>Contact doctor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sedation</th>
<th>Findings</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficult to wake</td>
<td></td>
<td>Administer Narcan® 0.2 mg stat IV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Respiratory rate</th>
<th>≤ 10/minute</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Administer Narcan® 0.2 mg stat IV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pupil size</th>
<th>≤ 2 mm</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Contact doctor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>SBP &lt; 90 mmHg</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Contact doctor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Heart rate</th>
<th>≤ 50/minute or ≥ 100/minute</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Contact doctor</td>
</tr>
</tbody>
</table>

**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 (PE) or myocardial infarction, should also be uncovered.

2. Monitoring addresses the prevention of complications, and assures that repeated assessment is conducted with regard to the adequacy of pain management.

Figure 1: Proposed treatment algorithm for patient-controlled analgesic management (adapted, not revised; used with permission)
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 IV 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 (see Table I).

5. A standardised treatment algorithm may improve pain management by integrating pain assessment and side effects with a clear reaction pathway. A treatment algorithm for PCA management is detailed in Figure 1.

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:** Included in the adult hospital level Essential Medicines List. A background infusion increases the risk of respiratory depression with no additional benefit.
- **IV tramadol:** Recommended for inclusion in the adult hospital level Essential Medicines List, for regional hospitals only. It provides effective analgesia comparable to morphine.
- **IV pethidine:** Pethidine should not be prescribed. It may cause neurotoxicity owing to the accumulation of norpethidine.
- **IV remifentanil:** Offers analgesia equivalent to morphine and may be associated with less nausea and vomiting.
- **IV fentanyl:** There is limited evidence of a difference between IV fentanyl and morphine.
- **IV oxycodone:** It has similar effects to morphine.

**Adjuvant medicines in PCA**

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

**Antiemetic drugs**

The routine addition of antiemetic drugs to a PCA infusion is not advocated as there is no additional benefit over selective administration when indicated.
Droperidol is an effective antiemetic, but may cause unacceptable sedation at the dose necessary to prevent nausea and vomiting.

The benefit of adding 5-hydroxytryptamine-3 antagonists (e.g. ondansetron) to PCA, is unclear. 5-HT-3 receptor antagonists should not be used with tramadol.

**Ketamine**

The addition of ketamine to PCA may benefit patients after major surgery with regard to analgesia as well as the adverse effects of opioids.

**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 variables/settings

Several PCA products are available in South Africa. Systems can be broadly categorised into the following two groups:

- Durable (often bulky) pumps with disposable cartridges, which usually offer multiple programmable options.
- Pumps composed of disposable components with built-in mechanisms for bolus administration. These 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, although these may provide a cost benefit.

All PCA infusion systems must incorporate anti-syphon valves, as well as anti-reflux valves in nondedicated lines.

**Pump settings**

**Bolus dose**

The optimal bolus dose should provide adequate pain relief with minimal adverse effects. Age and a history of previous opioid exposure can influence the response to the bolus dose. The usual PCA bolus dose for morphine is 1 mg (15–20 µg/kg).
**Lockout time**

The lockout time interval should allow the analgesic to reach its peak effect. The optimal lockout time 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 that can be attributed to these limits, does not exist. The impact of decreased clearance should be kept in mind (e.g. liver impairment, kidney failure, cardiac failure and any cause of a decreased cardiac output).

**Background infusions**

The risk of respiratory depression is higher when a background infusion is used, and it does not improve pain control or sleep, or reduce the number of PCA demands. It may be useful in opioid-tolerant patients, but its routine use is not advised.

**Loading dose**

No good evidence of any benefit exists when using this option on programmable pumps. Pain should be controlled first by titrated LDs before PCA is started.

**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 I.

**Table I: Examples of IV patient-controlled analgesia management regimens**

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Opioid dilution</th>
<th>Additive</th>
<th>Additive dilution</th>
<th>Pump settings for opioid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>1 mg/ml</td>
<td>Dexmedetomidine</td>
<td>2–5 μg/ml</td>
<td>• Bolus of 1 mg (1 ml)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or ketamine</td>
<td>2 mg/ml</td>
<td>• Lockout time of 7–11 minutes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>droperidol</td>
<td>15–100 μg/1 mg</td>
<td>• Maximum 30 mg in 4 hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>or ondansetron</td>
<td>5 mg/100 ml</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16 mg/100 ml</td>
<td></td>
</tr>
<tr>
<td>Tramadol</td>
<td>5 mg/ml</td>
<td>Dexmedetomidine</td>
<td>1–2 μg/ml</td>
<td>• Bolus of 10–20 mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Lockout time of 5–10 minutes</td>
</tr>
</tbody>
</table>
### 11.2 Neuraxial techniques

11.2.1 Epidural analgesia

Epidural analgesia (i.e. the provision of pain relief by the continuous administration of 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. Epidural analgesia at the correct level for an appropriate duration may decrease pulmonary complications, ventilator requirements or MI, and may improve bowel motility. However, data on improved outcomes are controversial, and the focus should be on pain relief and patient satisfaction.

**Clinical practice points regarding epidural analgesia**

1. The decision to perform an epidural, and the technique selected, should be appropriate for the intensity of pain anticipated and congruent to the level of tissue damage (i.e. head and neck, torso or limbs).

2. All techniques of epidural analgesia, except when using a lipophilic opioid only, for all types of surgery, provide better postoperative pain relief than parenteral opioids (including PCA).

3. The complete absence of pain is seldom achievable, and never realistic, even with neuraxial techniques. The objective should therefore be the balance between analgesia, patient satisfaction, safety and available resources. A VAS count of < 4/10 (40/100) is usually a satisfactory goal.

4. Combinations of low concentrations of LAs and opioids provide better analgesia than either component alone, and reduce the dose requirements of both drugs.

5. Permanent neurological damage with epidural techniques is a rare, but devastating, occurrence and all efforts should be made to prevent, diagnose and treat it immediately. Immediate decompression of a haematoma or an abscess increases the likelihood of recovery. Therefore, the risks and benefits should be discussed with the patient and informed consent obtained.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Concentration</th>
<th>Dosing Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remifentanil</td>
<td>50 μg/ml</td>
<td>• Bolus of 50 μg over 5 minutes (background 0.075–0.15 μg/kg/minute)</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>1 μg/ml</td>
<td>• Bolus of 4–6 μg (background of 1.15 μg/hour)</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>1 μg/ml</td>
<td>• Bolus of 30–40 μg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Maximum 300 μg in 4 hours</td>
</tr>
</tbody>
</table>

### S100

- Remifentanil 50 μg/ml • Bolus of 50 μg over 5 minutes (background 0.075–0.15 μg/kg/minute) • Lockout time of 5 minutes
- Sufentanil 1 μg/ml • Bolus of 4–6 μg (background of 1.15 μg/hour) • Lockout time of 1 minute
- Fentanyl 1 μg/ml • Bolus of 30–40 μg • Lockout time of 5–8 minutes • Maximum 300 μg in 4 hours
6. The insertion of an 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.

7. Infusions of epidural LA 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. In many hospital wards, this may not be available or possible.

8. Epidural catheters are inserted under sterile conditions for obvious reasons. A sterile theatre gown, mask, cap and gloves must be worn. It is prudent to use an alcoholic chlorhexidine solution to disinfect the skin, adhere to antiseptic technique 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. Whenever the epidural filter gets disconnected from the catheter, both the filter and the catheter must be regarded as contaminated and the epidural catheter must be removed.

9. The level of the epidural is determined by the level of trauma. 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. Although an incision-congruent level of block supplies somatic analgesia, visceral analgesia requires a block that includes a few segments above and below the incision level (Table II). According to NYSORA, a generally accepted guideline for dosing epidural anaesthesia in adults is 1–2 ml per segment to be blocked.

<table>
<thead>
<tr>
<th>Surgery</th>
<th>Level of the epidural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thoracotomy</td>
<td>T4–T8</td>
</tr>
<tr>
<td>Upper abdominal</td>
<td>T6–T8</td>
</tr>
<tr>
<td>Middle abdominal</td>
<td>T8–T10</td>
</tr>
<tr>
<td>Lower abdominal</td>
<td>T8–T12</td>
</tr>
<tr>
<td>Lower extremity</td>
<td>L1–L4</td>
</tr>
</tbody>
</table>

**Epidural local anaesthetics**

LAs available for epidural use in South Africa are outlined in Table III.
Table III: Local anaesthetics for epidural use available in South Africa

<table>
<thead>
<tr>
<th>Duration of action</th>
<th>Drug</th>
<th>Formulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting</td>
<td>Lignocaine</td>
<td>Various</td>
</tr>
<tr>
<td></td>
<td>Bupivacaine</td>
<td>Macaine* 0.5% (5 mg/ml), with or without adrenaline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Macaine* 0.1% (1 mg/ml) polybag</td>
</tr>
<tr>
<td>Long-acting</td>
<td>Levobupivacaine</td>
<td>Chirocaine® 5.0–7.5 mg/ml</td>
</tr>
<tr>
<td></td>
<td>Ropivacaine</td>
<td>Naropin® 5.0, 7.5 and 10 mg/ml, and 2 mg/ml as the 100/200 ml polybag</td>
</tr>
</tbody>
</table>

There are no consistent differences between ropivacaine, levobupivacaine and bupivacaine when given in low doses for regional analgesia in terms of quality of analgesia and 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 either by intermittent bolus dose or by infusion. With bolus dose regimens, the risk of respiratory depression is higher and analgesia is less effective. Lipophilic opioids (e.g. fentanyl, sufentanil and alfentanil) have a faster onset, but shorter duration of action, compared with hydrophilic drugs. Contrary to epidural morphine, epidural lipophilic opioids reach analgesic systemic concentrations, which contributes substantially to their analgesic effects.

The levels of the required level of the epidural blocks are outlined in Table II.

**Epidural test doses**

This procedure is standard when the epidural commences, 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 adrenaline and LA before bolus dosing for pain may prevent complications (e.g. high or total spinal anaesthesia and neurotoxicity) associated with the accidental administration of LAs into this space. After negative aspiration, 45 mg of lignocaine plus 15 µg of adrenaline, can be administered as a test dose. This is prepared as follows:

- Adrenaline 2 mg is diluted to 10 ml = 20 µg/ml.
- Add 1 ml of this adrenaline dilution (20 µg) to 3 ml of lignocaine 2% (20 mg/ml) in a 5 ml syringe. This solution contains 60 mg of lignocaine plus 20 µg of adrenaline in 4 ml. Therefore, 3 ml will contain 45 mg of lignocaine and 15 µg of adrenaline.
• Since the dead space of the epidural catheter and filter is approximately 1 ml, 4 ml can be administered in a bolus. If the filter and catheter has been primed with the solution, 3 ml is administered.

According to NYSORA: “The intrathecal injection of 45 mg of lidocaine should produce a significant motor nerve block if the catheter is in the subarachnoid space, although recent evidence suggests that this is not always reliable. A change in heart rate of 20% or greater (or, alternatively, an increase in heart rate of 10 to 25 beats per minute) within 1 minute suggests that the catheter has been placed in (or has migrated into) a vessel and should be replaced. If the heart rate does not increase by 20% or greater or if a significant motor nerve block does not develop within 5 minutes, the test dose is considered negative. Exceptions to this rule have been observed in labouring patients, anaesthetised patients, and patients receiving β-adrenergic blocking agents.”

**Patient-controlled epidural analgesia**

The use of patient-controlled epidural analgesia (PCEA) is based on the individualisation of therapy, similar to other patient-controlled techniques. The optimal settings of PCEA will vary, based on the epidural vertebral level, type of surgery, as well as patient factors.

**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.

<table>
<thead>
<tr>
<th>Table IV: Complications of epidural analgesia treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complications</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>Pruritus</td>
</tr>
<tr>
<td>Urinary retention</td>
</tr>
<tr>
<td>Postdural puncture headache</td>
</tr>
<tr>
<td>Hypotension</td>
</tr>
<tr>
<td>Scenario</td>
</tr>
<tr>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>Motor block</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Respiratory depression</td>
</tr>
<tr>
<td>Local anaesthetic systemic toxicity (LAST)</td>
</tr>
<tr>
<td>Epidural haematoma or abscess</td>
</tr>
<tr>
<td>Permanent neurological damage</td>
</tr>
</tbody>
</table>

LA – local anaesthetic, LAST – local anaesthetic systemic toxicity, CPR – cardiopulmonary resuscitation

**Respiratory depression by epidural solutions**

A strategy to detect and treat this complication should be in place. The incidence of respiratory depression is between 1% (decreased RR) and 15% (desaturation) depending on the criteria used, but is clinically significant in less than 1% of patients. High-risk patients (e.g. sleep apnoea and obesity) should be identified preoperatively.

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 injection with morphine, or continuously during an infusion. The absence of a decreased RR is not a reliable warning sign of respiratory depression, but it is almost always preceded by sedation. (Exclude motor block, high block, sympathetic nervous system block, migration of catheter, etc.)

Supplemental oxygen should be available to patients receiving neuraxial opioids, and administered to those with an altered level of consciousness, respiratory depression or hypoxaemia. In the infrequent event of life-threatening apnoea, the airway should be maintained, and the patient bag-mask ventilated pending naloxone administration. The naloxone dose should be titrated to effect (40–80 μg IV increments), followed by an infusion at a dose sufficient to maintain an adequate RR until the effect of the opioid has worn off (e.g. 1–2 μg/kg/min).
The reason for the respiratory depression should be assessed and the dose of the neuraxial infusion of opioids decreased if this is the cause. If an epidural infusion is stopped, alternative pain treatment should be prescribed to prevent rebound pain.

The patient should be transferred to a higher level of nursing for care and monitoring.

**Duration of epidural analgesia**

The epidural 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.

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Onset</th>
<th>Duration</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lipophilic opioid infusion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fentanyl</strong></td>
<td>Dilute the single dose in 10 ml normal saline:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Loading dose = 50–100 μg</td>
<td>5–10 minutes</td>
<td>2–4 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Infusion dose = 25–100 μg/hour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sufentanil</strong></td>
<td>Loading dose = 10–50 μg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infusion dose = 10–20 μg/hour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hydrophilic opioid infusion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Morphine</strong></td>
<td>Loading dose = 1–5 mg</td>
<td>30–60 minutes</td>
<td>6–24 hours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infusion dose = 0.1–1 mg/hour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Local anaesthetics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bupivacaine</strong></td>
<td>5–8 ml/hour of 1.25–2.5 mg/ml solution or incremental doses of 3–5 ml of 1.25–2.5 mg/ml solution</td>
<td>10–20 minutes</td>
<td>3–4 hours</td>
<td></td>
</tr>
</tbody>
</table>

*Establish the block with a 0.5% bolus of 15–30 ml

*Recommendation: Limit to 2 mg/kg in 4 hours and 400 mg/24 hours
Levobupivacaine

10–15 ml/hour of
1.25 mg/ml, or
5–7.5 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

Local anaesthetic-opioid infusions

<table>
<thead>
<tr>
<th>Ropivacaine</th>
<th>2 mg/ml + fentanyl 4 μg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bolus: 10–20 ml</td>
<td>6–14 ml/hour</td>
</tr>
<tr>
<td>Duration: 15–20 minutes</td>
<td>140–200 minutes</td>
</tr>
</tbody>
</table>

This combination is marketed as a polybag in some countries (not in South Africa)

Bupivacaine

1 mg/ml + fentanyl 4 μg/ml

5–10 ml/hour

Bupivacaine 0.625 mg/ml + fentanyl 2–5 μg/ml

8–16 ml/hour

Local anaesthetic-opioid epidural PCA (infusion + demand)

<table>
<thead>
<tr>
<th>Continuous infusion (ml/hour)</th>
<th>Demand dose (ml)</th>
<th>Lockout (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levobupivacaine 1.25 mg/ml + fentanyl 4 μg/ml</td>
<td>Initial rate of 4 ml/hour</td>
<td>2</td>
</tr>
<tr>
<td>Stability proven for up to 40 hours at 20 °C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bupivacaine 1 mg/ml + fentanyl 5 μg/ml</td>
<td>6 ml/hour (3–4 ml/hour for thoracic block)</td>
<td>2</td>
</tr>
<tr>
<td>Ropivacaine 1–2 mg/ml + fentanyl 2–5 μg/ml</td>
<td>3–5 ml/hour</td>
<td>2</td>
</tr>
</tbody>
</table>

* Not commonly used alone in an analgesic infusion, CSF – cerebrospinal fluid

11.2.2 Spinal (intrathecal) analgesia

A single injection of intrathecal LA 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

LAs 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 VI.

**Table VI: Drugs for intrathecal analgesia**

<table>
<thead>
<tr>
<th>Drug (preservative free)</th>
<th>Intrathecal single dose</th>
<th>Onset</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fentanyl</td>
<td>5–25 µg</td>
<td>5–10 minutes</td>
<td>1–4 hours</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>2–10 µg</td>
<td>5–10 minutes</td>
<td>2–6 hours</td>
</tr>
<tr>
<td>Morphine</td>
<td>50–300 µg</td>
<td>45–75 minutes</td>
<td>18–24 hours</td>
</tr>
</tbody>
</table>

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 during the first 24 hours. 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 for doses above 200 µg. Significant side effects associated with intrathecal morphine are as follows:

- Respiratory depression in 3% of patients (partial pressure of carbon dioxide $[\text{PaCO}_2] \geq 50$ mmHg, and/or an RR ≤ 8/minutes)
- Pruritus (itching) in up to 30% of patients
- Nausea and vomiting in 25% of patients
- Urinary retention in 35% of patients

When intrathecal morphine is 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 efficacy 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 is opioid-sparing for up to 24 hours.
2. Intrathecal morphine doses of ≥ 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.
11.2.3 Neuraxial techniques and concurrent anticoagulant medication

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

- Anticoagulation (the most important risk factor)
- Any other coagulopathy
- Advanced age (older than 65 years)
- Female gender
- Difficult needle placement
- Abnormalities of the vertebral canal or spinal cord
- Indwelling catheter techniques (especially during sustained anticoagulation)

Absolute recommendations cannot be made in many clinical situations and 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.

Every case should be individualised according to risk versus benefit in each particular 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. Take care to prevent a combination of anticoagulation effects. Neuraxial techniques should not be performed in patients who receive more than one anticoagulant simultaneously (especially when early postoperative use of other anticoagulant drugs is anticipated).

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 most common presenting symptoms of a neurologically significant haematoma are a progressive sensory and motor block (68%) or bowel/bladder dysfunction (8%); however, severe radicular back pain is uncommon. Spinal cord ischaemia tends to be reversible in patients who undergo surgical decompression within 8 hours of onset of neurological dysfunction. The implication of this is that the anaesthetist cannot perform the neuraxial technique and consider that to be the end of their commitment to the patient’s care.
The novel oral anticoagulants have a long duration of action, and care must be taken when considering the timing of neuraxial anaesthetic. Generally, the decision whether or not to continue the anticoagulant up to the time of the surgical procedure, is made by weighing the risk of thrombosis if the anticoagulant is stopped versus the bleeding risk of the procedure. This should be a multidisciplinary discussion.

Recommendations on timing of neuraxial techniques after stopping the anticoagulant are usually pharmacologically based. For example, recommended time intervals between discontinuation of a drug during therapeutic anticoagulation and subsequent neuraxial block are 5 half-lives (and is dependent on renal function). This will allow for resolution of 97% of anticoagulant effect. With lower levels of anticoagulation associated with prophylaxis, only a 2-half-life interval is required. Subsequent dosing of anticoagulation therapy is based on 8 hours (the time it takes for a platelet plug to become stable) minus the time it takes the anticoagulant to reach peak effect.

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 VII. The recommendations are not absolute and the risk versus benefit must be considered in every clinical scenario.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Is epidural or spinal reasonable?</th>
<th>Time from last dose to neuraxial block insertion</th>
<th>Administration of drug while catheter in situ</th>
<th>Time from dose (while catheter in situ) to catheter removal</th>
<th>Time from block/removal of catheter to next dose</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herbal (ginkgo, garlic and ginseng)</td>
<td>Yes</td>
<td>Anytime</td>
<td>Can continue</td>
<td>Anytime</td>
<td>Combination with others may be unsafe</td>
<td>Combination with others may be unsafe</td>
</tr>
<tr>
<td>NSAIDs (COX-2 inhibitors preferred)</td>
<td>Yes</td>
<td>Anytime</td>
<td>Can continue</td>
<td>Anytime</td>
<td>Combination with others may be unsafe</td>
<td>Combination with others may be unsafe</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Yes</td>
<td>Anytime</td>
<td>Can continue</td>
<td>Anytime</td>
<td>Combination with others may be unsafe</td>
<td>Combination with others may be unsafe</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>Yes</td>
<td>Anytime</td>
<td>Can continue</td>
<td>Anytime</td>
<td>≥ 6 hours</td>
<td>Combination with others may be unsafe</td>
</tr>
</tbody>
</table>

Table VII: Clinical approach to neuraxial analgesia in the patient on medication with anticoagulation effects
<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Duration After Block</th>
<th>Action Upon Dose</th>
<th>APTT Requirement</th>
<th>Duration Before Dose</th>
<th>Risk</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dipyridamole/aspirin combination</td>
<td>Yes</td>
<td>24 hours</td>
<td>Stop combination drug, aspirin may be continued</td>
<td>N/A</td>
<td>≥ 6 hours</td>
<td>Increased risk of bleeding with combination therapy</td>
</tr>
<tr>
<td>SC UFH prophylaxis (low-dose) ≤ 15 000 U/day</td>
<td>Yes</td>
<td>≥ 4–6 hours or confirm normal aPTT</td>
<td>Can continue</td>
<td>≥ 4–6 hours or confirm normal aPTT</td>
<td>≥ 1 hour</td>
<td>Consider HITT if ≥ 4 days on heparin, and perform a platelet count</td>
</tr>
<tr>
<td>SC UFH prophylaxis (high-dose) ≤ 20 000 U/day</td>
<td>Caution advised</td>
<td>≥ 12 hours and confirm normal aPTT</td>
<td>Safety not established</td>
<td>N/A</td>
<td>≥ 1 hour</td>
<td>Consider HITT if ≥ 4 days on heparin, and perform a platelet count</td>
</tr>
<tr>
<td>SC UFH therapeutic ≥ 20 000 U/day</td>
<td>Caution advised</td>
<td>≥ 24 hours and confirm normal aPTT</td>
<td>Safety not established</td>
<td>N/A</td>
<td>≥ 1 hour</td>
<td>Consider HITT if ≥ 4 days on heparin, and perform a platelet count</td>
</tr>
<tr>
<td>IV UFH therapeutic</td>
<td>Caution advised</td>
<td>≥ 4–6 hours and confirm normal aPTT</td>
<td>Caution advised</td>
<td>≥ 4–6 hours and confirm normal aPTT</td>
<td>≥ 1 hour</td>
<td>Bloody or difficult needle placement may increase bleeding risk with subsequent IV heparin</td>
</tr>
<tr>
<td>IV heparin during surgery (5 000–10 000 U for vascular surgery)</td>
<td>Yes</td>
<td>Conduct ≥ 1 hour before heparinisation</td>
<td></td>
<td>≥ 2–4 hours and confirm normal aPTT</td>
<td>“Bloody tap” is not an absolute indication to cancel surgery</td>
<td></td>
</tr>
<tr>
<td>IV heparin (cardiopulmonary bypass)</td>
<td>Not known</td>
<td>Conduct ≥ 1 hour before heparinisation</td>
<td></td>
<td>≥ 4–6 hours and confirm normal aPTT</td>
<td>Certainly not routine practice; some place the epidural 12 hours preoperatively</td>
<td></td>
</tr>
<tr>
<td>SC LMWH prophylaxis once daily dose</td>
<td>Yes</td>
<td>≥ 12 hours</td>
<td>Can continue: 1st postop dose ≥ 12 hours after block; 2nd dose given ≥ 24 hours after 1st dose</td>
<td></td>
<td>≥ 4 hours</td>
<td>Traumatic placement: no need to postpone surgery, but delay LMWH 24 hours</td>
</tr>
<tr>
<td>Treatment</td>
<td>Caution Advised</td>
<td>Dose</td>
<td>If Feasible, Stop and Wait</td>
<td>Warfarin Prophylaxis</td>
<td>monitored INR</td>
<td>Warfarin Established, Therapeutic</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-----------------</td>
<td>------</td>
<td>-----------------------------</td>
<td>----------------------</td>
<td>---------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>SC LMWH Prophylaxis</td>
<td>Caution Advised, Bd Dose Associated with Increased Risk of Spinal Haematoma</td>
<td>≥ 12 hours</td>
<td>No</td>
<td>N/A</td>
<td>≥ 4 hours</td>
<td>Traumatic Placement: No Need to Postpone Surgery, but Delay LMWH 24 Hours</td>
</tr>
<tr>
<td>SC LMWH Therapeutic</td>
<td>No</td>
<td>If Feasible, Stop and Wait ≥ 24 Hours; Consider Checking Antifactor Xa</td>
<td>No</td>
<td>N/A</td>
<td>≥ 4 hours</td>
<td>Traumatic Placement: No Need to Postpone Surgery, but Delay LMWH 24 Hours</td>
</tr>
<tr>
<td>Warfarin Prophylaxis</td>
<td>Yes, If ≤ 24 Hours After First Dose</td>
<td>Can Do If ≤ 24 Hours After First Dose</td>
<td>Yes, Monitor INR Daily</td>
<td>INR ≤ 1.5 and ≤ 48 Hours After First Dose If ≥ 3, Cut Warfarin</td>
<td>N/A</td>
<td>Warfarin Is Usually Started the Evening Before Surgery</td>
</tr>
<tr>
<td>Warfarin Established, Therapeutic</td>
<td>No</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Can Conduct If Feasible to Stop for 5 Days; Verify Normal INR</td>
</tr>
<tr>
<td>Direct Thrombin Inhibitors (Parenteral)</td>
<td>No</td>
<td>Not Recommended</td>
<td>N/A</td>
<td>N/A</td>
<td>Not Known</td>
<td>Given IV, With an Effect for Up to 3 Hours; No Antagonist</td>
</tr>
<tr>
<td>Carefully and Individually Considered; Advised Against in Pts With CrC of ≤ 30 ml/min</td>
<td>≥ 5 Days</td>
<td>No</td>
<td>N/A</td>
<td>N/A</td>
<td>Unanticipated Administration, Wait 34–36 Hours</td>
<td>Highly Dependent on Renal Excretion</td>
</tr>
<tr>
<td>Anti-Factor Xa Inhibitors Fondaparinux</td>
<td>Not Known, Limited Clinical Experience</td>
<td>Not Known</td>
<td>N/A</td>
<td>N/A</td>
<td>Avoid Catheter</td>
<td>Anti-Fxa Effect for Days</td>
</tr>
<tr>
<td>Direct Oral Anti-Factor Xa Agents (Rivaroxaban*, Apixaban***)</td>
<td>Not Known</td>
<td>≥ 72 Hours</td>
<td>No</td>
<td>N/A</td>
<td>Unanticipated Administration, Wait 22–26* Hours or 26–30** Hours</td>
<td>≥ 6 Hours</td>
</tr>
<tr>
<td>Antiplatelets thienopyridines (clopidogrel* and prasugrel**)</td>
<td>Most likely no</td>
<td>If feasible, wait ≥ 5–7* days or ≥ 7–10** days</td>
<td>No</td>
<td>N/A</td>
<td>Stat if no LD given; if LD, ≥ 6 hours</td>
<td>Given p.o.; inhibits ADP platelet aggregation</td>
</tr>
<tr>
<td>Antiplatelets ticagrelor</td>
<td>Not known</td>
<td>≥ 5–7 days</td>
<td>No</td>
<td>N/A</td>
<td>Stat if no LD given; if LD, ≥ 6 hours</td>
<td>Antiplatelet effect within 30 minutes with maximum effect within 2 hours</td>
</tr>
<tr>
<td>Antiplatelets (GPIIb/IIIa antagonists) abciximab* eptifibatide** tirofiban**</td>
<td>No</td>
<td>Waiting time of 4–8** hours or 24–48* hours</td>
<td>No</td>
<td>N/A</td>
<td>N/A</td>
<td>Contraindicated for 4 weeks after surgery; usually also on others (i.e. aspirin and LMWH)</td>
</tr>
<tr>
<td>Fibrinolysis and thrombolysis</td>
<td>No</td>
<td>≥ 48 hours and normal clotting studies including fibrinogen</td>
<td>No</td>
<td>N/A</td>
<td>Remove and wait 10 days before starting Rx</td>
<td>Effect may last 27 hours; also has an effect on platelets</td>
</tr>
</tbody>
</table>

Bibliography


- Van Dyk D. Anticoagulation and bridging in Obstetric Anaesthesia. UCT Part II Anaesthesia refresher course; 2019.


12. Non-pharmacological pain techniques

Section A: Adults

Non-pharmacological pain techniques refer to interventions that do not involve the use of medication to treat pain. These techniques may be used as an adjunct to pharmacotherapy and are usually not used in isolation.

The goals of non-pharmacological techniques are to decrease fear, distress and anxiety, as well as to reduce pain and provide patients with a sense of control. The advantages of non-pharmacological techniques are that they are relatively inexpensive and safe. Further advantages include reducing analgesic drug doses and the potential adverse effects thereof, reducing the focus on the pain, anxiety, stress and pain behaviour, and enhancing muscle strength, functional capacity and activity.

Non-pharmacological techniques are typically categorised into the following:

- **Physical (sensory) interventions** that reduce the nociceptive input and pain perception.
- **Psychological interventions** that are used where a therapeutic relationship, or rapport, is developed with the patient. These techniques are important because recurrent and continuous acute pain may lead to maladaptive physical and psychological functioning. Patients who suffer from this may experience depression, anxiety and posttraumatic stress due to their vulnerability. In addition, preoperative anxiety has been associated with the development of chronic regional pain syndrome (CRPS).

- **Other interventions**

12.1 Physical interventions

12.1.1 Massage

Massage is the process of rubbing and kneading muscle groups and joints, using either hands or other implements such as hot stones, to help relieve pain and reduce tension, tightness and spasms in these muscle groups and joints. Massage may help to increasing blood circulation and lymphatic drainage, as well as reducing inflammation and oedema. It may also increase endogenous endorphin and dopamine levels and promote lower blood pressure, improved circulation, a strengthened immune system, and reduced pain and anxiety in surgical and nonsurgical patients. In cancer patients, massage has been shown to improve mood and quality of life.
12.1.2 Heat and cold

Historically, hot-water bottles have been used to alleviate backache and sore abdomens. These days, this technique has been modified to use wheat-based heat packs and electrical pads to reduce the potential risk of burn injury.

Active warming may be used to treat appendicitis, colitis, cystitis and urolithiasis. Heat therapy has been shown to reduce pain, anxiety, nausea and heart rate. It has been postulated that heat therapy may work in several different ways: heat reduces spasm in striated muscle, and reduces muscles spindle excitability and tension in trigger points; heat also stimulates the thermoreceptors in the skin and deeper tissues and reduces pain by closing the gate in the spinal cord; and lastly, heat reduces the viscosity of synovial fluid in joints, and alleviates pain and stiffness, thereby improving the range of movement.

Conversely, cold and ice have been used to treat acute injuries and to reduce swelling, inflammation and pain.

12.1.3 Transcutaneous electrical nerve stimulation

Electrical stimulation may be used to treat mild to moderate acute pain, including back pain, labour pains and musculoskeletal pain. Transcutaneous electrical nerve stimulation (TENS) is administered through a battery-operated electrical device which consists of 2–4 leads that are connected to sticky pads. These sticky pads are applied to the painful area. The TENS device delivers a low voltage alternating electrical impulse at a low frequency of 540 Hz. Patients feel a mild tingling sensation in the area where the pads are placed.

TENS stimulates the large β-nerve fibres and, according to the gate theory, thereby blocks transmission of pain from the smaller C- and Aδ-fibres. It may also modulate pain by enhancing descending inhibition and blocking sympathetic outflow. TENS is contraindicated in patients with cardiac conditions such as dysrhythmias and those with pacemakers. However, TENS has no adverse effects.

12.1.4 Acupuncture

Acupuncture began in China more than 5 000 years ago. It consists of inserting extremely thin needles into specific points along invisible meridians in the body. These needles stimulate the nerves and the immune system, increase blood flow, and promote wound healing, pain modulation and analgesia. In addition to treating acute pain, acupuncture has been used for, among others, allergies, anxiety and depression, hypertension, insomnia, menstrual cramps and migraines.
12.1.5  Progressive muscle relaxation

Progressive muscle relaxation involves the patient tightening and relaxing different groups of muscles in the body in a progressive manner (e.g. starting at the toes and feet and moving up the body, tightening and relaxing each muscle group). This proves a sense of relaxation and comfort. This technique may be used for all types of pain and may be combined with psychological techniques such as guided imagery.

12.2  Psychological interventions

12.2.1  Cognitive behaviour therapy

In terms of the bio-psycho-social-spiritual model of pain, psychological factors may influence pain and pain behaviours. By targeting cognition, cognitive behaviour therapy (CBT) may modify the maladaptive behaviour associated with pain. It teaches patients coping skills which improve cognitive and psychological functioning, and change negative behaviours to positive choices. These techniques include structured relaxation therapy, recalling and scheduling pleasurable and enjoyable activities and events, positive assertions and reinforcements, and pacing strategies. CBT can also reduce maladaptive thoughts and pain catastrophising thoughts and behaviours.

12.2.2  Mindfulness-based stress reduction

There is a range of attention-based techniques such as distraction, attention, imagined scenery, or external stimuli. Mindfulness-based stress reduction was popularised in the western world by Kabat-Zinn, and is adapted from yoga meditation. Therefore, it is a technique similar to other strategies such as awareness and meditation. The aim is to uncouple, or create a disconnect between, the sensory elements of the pain and the emotional and consequential overlays thereof.

12.2.3  Acceptance and commitment therapy

In this technique, patients are taught that they do not need to change their thoughts, but rather accept these and modify their responses to ameliorate the negative consequences and achieve a more positive outcome. This technique emphasises non-judgement and acceptance and may help to augment the patients’ wellbeing and sense of purpose. Therefore, in conducting acceptance and commitment therapy (AACT), patients may be able to improve purposeful awareness and pain acceptance, divert the focus from the pain, and thereby modify their behaviour to achieve more fulfilling outcomes.
12.2.4 Guided imagery

Guided imagery is a technique whereby an experienced practitioner helps the patient create a particular calm, relaxing and blissful state of mind, and/or create soothing and relaxing mental images (e.g. walking on the beach, or watching a daytime or nighttime sky). It may also take the form of storytelling and metaphors. These images elicit a physiological response via modulation of the ANS which results in changes in the respiratory system (i.e. deep breathing and lower RR), CV system (i.e. reduced heart rate and blood pressure), and reduced stress response via the endocrine and immune systems. Many trials have been conducted and have shown a reduction in the pain score when used either alone or in combination with hypnosis or CBT.

12.3 Other interventions

12.3.1 Spirituality and religion

Spirituality and religion are an important part of many people’s lives. The meaning assigned to the pain experience may therefore be seen in terms of the spiritual and/or religious context (e.g., pain may be seen as either a consequence of their actions, or as a sign of punishment from God [Christianity/Hinduism], or as a sign of suffering caused by attachment [Buddhism]). Patients may not see pain as merely a sign of disease or ailment, but it may have added meaning for them, which may either interfere with treatment and worsen the pain or improve it, depending on the particular patient’s beliefs and context. The power of prayer and the place it has in the patients’ lives also plays a role and this will either improve or negatively impact on the patient’s pain experience. Therefore, pain needs to be addressed holistically within the bio-psycho-social-spiritual model pain.

12.3.2 Music therapy

Music has been shown to enhance wellbeing and reduce pain and suffering. Since ancient times, it has been used as a tool to improve wellness, emotion and quality of life. It has been shown that music played during operations reduces pain and the consumption of morphine or other analgesic, and improves sedation and anxiolysis. Many randomised controlled trials (RCTs) have demonstrated lower pain scores, and less sedation requirements in patients undergoing procedures. Women in labour, elderly patients with osteoarthritis, and cancer patients have all reported lower pain scores and analgesia requirements when receiving music therapy.

12.3.3 Patient education

It is very important to provide patients with adequate information regarding surgery and procedure, anatomy, pathophysiology of their disease/injury, expected pain and treatment options, and recovery timelines. The well-informed patient has an enhanced recovery and reduced analgesia requirements, compared to the uninformed patient.
12.4 Conclusion

In general, non-pharmacological interventions are inexpensive, safe and have a low adverse effect profile. Patient-, procedure- and context-specific non-pharmacological interventions may be harnessed and may be used as an adjunct to pharmacotherapy to improve pain management and patient outcomes.

Section B: Paediatrics

12.5 Pain management

It is imperative that effective pain management is standardised for all paediatric patients. Even minor painful events or procedures, such as needle pricks, can affect children's long-term emotional wellbeing. Timely administration of pain management techniques can affect the paediatric patient's entire medical experience and have a lasting effect on future medical experiences.

A child can experience a seemingly benign examination as distressing. The emotional context can influence the individual child's perception of the intensity of pain. Without appropriate pain management, posttraumatic stress symptoms can occur after procedures or stressful medical experiences, which can in turn lead to difficulty coping with future procedures. Studies have shown that early exposure to painful experiences and undertreated pain at crucial developmental periods can cause changes in the activity and structure of the CNS, and could cause long-term effects in a child's perception of pain at later stages of childhood.

12.6 Preparation

Research proves that children who are prepared for health care experiences in a manner that is developmentally appropriate, show more positive outcomes regarding their behaviour, recovery and ability to cope with stressful events. Preparation and medical play leads to less emotional distress, better overall coping, clearer understanding of medical interventions, and a more positive physical recovery.

By using developmentally appropriate communication as well as preparation for medical procedures, children gain knowledge and skills that reduce distress and anxiety and increase their coping skills. Uncertainty and lack of clear information causes anxiety and increased distress that heightens the child’s perception of pain. By lowering their anxiety and promoting their adaptive coping skills, their perception of pain can be reduced.

The developmental level of functioning as well as the level of cognitive functioning will have an effect on the child’s understanding of the medical procedure. It will thus influence the manner
and content of preparation. The goal is to enhance understanding and facilitate coping, thereby reducing distress. Distress is generated when there is a discrepancy between expectations of an event and the actual experience.

The goal, therefore, of psychological preparation is to increase children’s sense of predictability of and control over potentially overwhelming experiences, allowing them to proceed in these situations with a sense of mastery and the lowest possible level of distress.

12.7 One Voice

One Voice is a method used during procedures to reduce a child’s anxiety due to noise and overstimulation, and to increase coping for both the patient and the caregiver. When a child has multiple people giving directions or words of encouragement at the same time, the child may become more anxious or agitated. To help a child focus their attention and to facilitate better coping skills, the One Voice philosophy recommends that only one person communicates with the child during a procedure. That one person speaking can be a parent, child life specialist, doctor, nurse, technician, etc. The voice can be selected prior to the procedure and can change during the procedure as needed. Using the One Voice method during invasive procedures along with other interventions, such as alternative focus, can help manage a patient’s fear, anxiety and pain, allowing the patient and family to have the best experience possible.

12.8 Language

During the administration of a medical procedure, it is helpful to use language that invites hope and courage and that assures the child of some release from suffering, fear and pain. Remind the child that the pain will come to an end. Avoid words that might conjure up fear, uncertainty or anxiety.

The appropriate time to inform the child of potential discomfort and to explain how it will be managed, is before the medical procedure. This is done by:

- providing clear and honest information about the procedure,
- providing explanations at a language level appropriate to the child’s abilities,
- focusing on the positive and incorporating positive or neutral or ‘every day’ words into your language,
- using language that is more descriptive and concrete and that avoids the use of medical terms which can be confusing to children, and
- speaking the child’s home language.
Table I: Language to avoid and language to use

<table>
<thead>
<tr>
<th>Language to avoid</th>
<th>Language to use</th>
</tr>
</thead>
<tbody>
<tr>
<td>We are going to make an incision.</td>
<td>We are going to make a small opening that we will close very carefully afterwards.</td>
</tr>
<tr>
<td>You will be okay, there is nothing to worry about.</td>
<td>What did you do at school today?</td>
</tr>
<tr>
<td>This won’t hurt.</td>
<td>It might feel like a pinch.</td>
</tr>
<tr>
<td>You are acting like a baby.</td>
<td>Let’s get your mind off it, tell me about that movie.</td>
</tr>
<tr>
<td>This won’t take long.</td>
<td>The procedure will be shorter than (child's favourite television programme).</td>
</tr>
<tr>
<td>The medicine will burn.</td>
<td>Some children say they feel a warm feeling.</td>
</tr>
<tr>
<td>I am sorry</td>
<td>You are being so brave.</td>
</tr>
<tr>
<td>Don’t cry</td>
<td>That was hard, I am proud of you.</td>
</tr>
<tr>
<td>It’s over</td>
<td>You did a great job doing the deep breathing and holding still (as we practised).</td>
</tr>
<tr>
<td>You will have to say goodbye to your parents.</td>
<td>That will be the time when you say: ‘See you later’.</td>
</tr>
<tr>
<td>You will have a sore throat when you wake up.</td>
<td>Your throat may feel dry and scratchy when you wake up.</td>
</tr>
</tbody>
</table>

12.9 Positions of comfort

Positions of comfort is a support measure used to incorporate reassurance, comfort and control for patients during medical procedures. Children may feel a loss of control if they are put in a supine position during a procedure, which could result in fear. The child may associate this fear with invasion of privacy and body space and may not understand why a member of the medical team is inflicting pain on them. Comfort positions allow the caregiver to hold the child during a procedure, for example, in either a chest-to-chest or back-to-chest position.

Comfort positions can be used during a variety of procedures, including intramuscular injections (IMIs), IV placements, nasogastric tube placements, sutures or staples, and can be initiated as soon as a child has gained head and trunk control (3–5 months of age).

The goals for comfort positions include promoting a sense of control for the child, allowing the caregiver to participate in a positive way, providing comfort through close contact with the caregiver, limiting the number of people needed to complete a procedure, and successfully immobilising an extremity for a procedure. The intention with positions of comfort is for the parent to soothe and comfort the child, not to restrain the child.

12.10 Coping strategies

Coping strategies are defined as specific cognitive or behavioural actions taken to manage tension-generating events. The following sections contain descriptions of various coping strategies.
12.10.1 Deep breathing

Facilitate deep breathing by breathing in through the nose and out through the mouth, blowing bubbles, blowing away the ‘bad’ feeling or pain, smelling the imaginary flowers and blowing the imaginary bubbles, or blow out all the birthday candles.

12.10.2 Alternate focus

The gate control theory serves as a conceptual framework for the use of alternate focus to aid children in coping with pain. This theory proposes that pain impulses are moderated by a gating mechanism that opens to allow nerve impulses to reach the brain or closes to decrease impulse transmission. Anxiety, anticipation and distress may open the gate and thus increase the perception of pain. Cognitive activities such as alternate focus, relaxation and imagery tend to close the gate and prevent sensory transmission of pain.

By actively distracting the child’s attention and focusing it on a cognitive task or playful activity, the child’s perception of pain can be reduced. The rationale is that distraction and alternate focus interrupt the processing of the sensory and emotional impulses in the brain. Examples of alternate focus include reading a book or pop-up books, playing ‘I spy’ or ‘Where’s Wally?’, playing electronic games, watching videos, playing with puppets, playing with sensory toys such as light spinners, glitter wands, Geoflux and oil drippers.

12.10.3 Visualisation or imagination

Help the child to visit a favourite place in their imagination. Encourage the child to experience detailed pleasing sensory experiences associated with their favourite place. For example, feel the sand between your toes, smell the fresh air, feel the cool breeze against your face, and feel the warm sunshine on your skin.

12.10.4 Visual schedules

Take photographs of the various stages of the procedure, laminate them and put them on a communication board. As the procedure progresses, allow the child to remove the pictures of the stages that have been completed. This will provide the child with a sense of control and predictability during the administration of the procedure.

12.10.5 Relaxation therapies

Help the child to tense various muscle groups for seven seconds and then relax the muscles. Aid the child to concentrate on the sensation of relaxation (e.g. pretend that you feel warm sunshine on your face, then your shoulders and torso, feel how your body relaxes in the sunlight).
12.10.6 Rehearsal

Role play the procedure. The child acts out the procedure using/implementing coping techniques. Show the child a video recording of other children undergoing the procedure and coping well.

12.10.7 Coping strategies according to age

**Infants**

Distraction or alternate focus – use a rhythmic voice, gentle massage, soft soothing music, breathe slowly and rhythmically while holding the infant, skin-to-skin contact, or breastfeeding during the administration of the procedure.

**Toddlers and preschool children**

Distraction or alternate focus, imagination flights, deep breathing, blowing bubbles, rehearsal of the procedure beforehand, or visual schedules of the steps of the procedure.

**School-age children**

Distraction or alternate focus, progressive relaxation, guided imagery, deep breathing and blowing bubbles, rehearsal of the procedure beforehand, or visual schedules of the sequential steps of the procedure.

**Adolescents**

Adolescents might be afraid of losing control and looking like a baby. They are often hesitant to express feelings of pain. They should not be shamed or ridiculed. This age group might need more rehearsal and practice time than other age groups.

Distraction, progressive relaxation, guided imagery, deep breathing and blowing bubbles, rehearsal of the procedure beforehand, or visual schedules of the sequential steps of the procedure.
Table II: Non-pharmacological pain management strategies for children

<table>
<thead>
<tr>
<th>Contextual measures</th>
<th>Physical measures</th>
<th>Cognitive measures</th>
<th>Emotional support</th>
<th>Environment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cluster procedures to avoid overhandling</td>
<td>Breastfeeding</td>
<td>Explain procedures</td>
<td>Presence of parent/caregiver</td>
<td>Clean and neat, child-friendly environment</td>
</tr>
<tr>
<td>Reduce noise level</td>
<td>Non-nutritive sucking (dummy)</td>
<td>Reassurance</td>
<td>Structured parental involvement</td>
<td>Monitors fully functional and alarms appropriately set</td>
</tr>
<tr>
<td>Dim lights</td>
<td>Facilitated tucking/swaddling</td>
<td>Pain and neuroscience education</td>
<td>Caregivers voice</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Kangaroo care, parental cuddles</td>
<td>Mindfulness</td>
<td>Voice: calm, soothing tone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Massage</td>
<td>Yoga</td>
<td>Active reassurance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sucrose syrup</td>
<td>Distraction</td>
<td>Positive affirmations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immobilise/splint fractures</td>
<td>Imagery</td>
<td>Praise</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dress burns/bleeding wounds</td>
<td>Favourite toy</td>
<td>Rewards system</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Explain procedures</td>
<td>Music therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reassurance</td>
<td>Music stimulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pain and neuroscience education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mindfulness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yoga</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Distraction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Imagery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Favourite toy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Music therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Music stimulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Bibliography


13. Management of acute pain in specific scenarios in adults

13.1 Introduction

This chapter describes the general principles in the management of acute pain using oral and parenteral routes of administration in the adult population.

Acute pain is a physical sign and experience that points to real (existing or potential) recent tissue injury. It results from stimulation of sensory (afferent) nerve endings in areas of tissue injury, whether mechanical (incision, pressure or stretching), chemical, thermal, ischaemia, or other stimulation.

In both threatening injury and real injury, the tissue releases several substances which stimulate nociceptors (the respective receptors on the nerve endings). These nerve endings depolarise (are activated) and transport the impulses to the CNS (spinal cord and brain).

Up to this point, the process is called nociception (i.e. reception of signals reporting tissue injury), and the pain initiated in this manner is referred to as nociceptive pain. Nociception is processed in the spinal cord and brain and is eventually delivered to the sensory cortex, where it is interpreted and experienced as ‘pain’. Therefore, pain tells the patient that something is hurting some tissue.

The types of tissue that are injured or potentially injured, give rise to different types of acute pain: either somatic or visceral pain.

Somatic pain originates from nociceptors either in the skin and mucus membranes (superficial somatic pain) or from soft tissue, fascia, muscle, joints, tendons and periosteum (deep somatic pain). Superficial somatic pain is well-localised, intense, sharp, burning, pricking and sharp. This type of pain is experienced with mucosal ulcers, mucositis and burns.

Deep somatic pain arises from SC tissue and the musculoskeletal structures (i.e. muscle, tendons, bones and joints). It is described as being sore, dull or aching. Deep somatic pain is caused by fractures, dislocations, ischaemia, rupture of muscle and ligament sprains. It is less well-localised, depending on the extent of tissue injury (e.g. a toe fracture causes localised pain that resembles superficial pain, whereas a hip fracture causes deep aching pain spreading throughout the upper leg, hip joint and knee).

Visceral pain is frequently accompanied by nausea, vomiting and sweating. While treatment recommendations for visceral pain are the same as for somatic pain, visceral pain processing is distinctly different from somatic nociception and as a result should perhaps be treated differently from somatic pain.
Visceral pain can point to injury of either hollow organs (stomach, intestines, ureter and bladder) or solid organs (or rather their capsules). Injury is caused by stretching, distension, inflammation and ischaemia.

*Visceral pain differs from somatic pain both physiologically and clinically.* Since internal organs have a dual nerve supply (sensory autonomic as well as somatic nerve supply) ending in several spinal cord segments, visceral pain is poorly localised, diffused and referred, and is commonly accompanied by signs of activation of autonomic nerves (vagal nerve, sacral nerves and sympathetic nerves). Pain is described as poorly localised, vague, dull, deep, aching, twisting, spasmodic or cramping, or severe discomfort. *Autonomic features* include sweating, nausea, vomiting, hyper- or hypotension, and tachycardia. When visceral pathology (e.g. visceral peritonitis) spreads to structures that are innervated by somatic nerves (e.g. parietal peritoneum), visceral pain displays deep somatic pain, often accompanied by increased tone of abdominal wall muscles.

Owing to the wide innervation of internal organs, visceral pain is not only poorly localised, but also often *radiate*, making pain more unpleasant. Cardiac pain radiates to the arms (usually left), jaws or epigastrium. Blood under the right diaphragm and pathology of the gallbladder radiate to the right shoulder, and pain from a perforated peptic ulcer radiates to the back. Bladder pain radiates to the perineum, while kidney stones cause back pain.

Sometimes, pain is not felt in the area adjacent to the area of injury at all, but is *referred* to distant structures (e.g. cardiac pain may present with only neck or jaw pain and testicular pathology may only present with periumbilical pain).

### 13.2 General principles

When treating any disease, including acute pain, the following factors should always be taken into consideration:

#### 13.2.1 Anatomical consideration

Anatomical defects are congenital, iatrogenic (e.g. caused by surgery), trauma-related, neoplastic or endocrine, among others. Anatomical abnormalities may also follow pathophysiological processes, such as allergy or endocrine disease (acromegaly, goitre, diabetic arthropathy, obesity, etc.). These anatomical defects will always have some physiological consequence such as the functioning of the upper and lower airway, respiratory, CV, haemodynamic (circulatory shock, hypovolaemia, hypoproteinaemia), neurological (central and/or peripheral), haematological, renal or hepatic, among others. A typical anatomical concern in analgesia is the anatomical features that affect the airway that may cause airway obstruction (e.g., in patients with OSA).
13.2.2 Pathophysiological considerations

Physiological derangements may result from anatomical abnormalities, such as iatrogenic (e.g. surgery or pharmacological), trauma, neoplasms, endocrine disease, and others. Pathophysiological processes often result in anatomically identifiable complications, such as renal tubular necrosis, liver necrosis, brain ischaemia, MI, compartment syndrome, and airway and pulmonary oedema. Physiological conditions often change the volume of drug distribution as well as free drug concentrations (pharmacokinetics).

The risk of aspiration must always be considered whenever a sedative agent is administered. The trauma-related stress response as well as opioids delay gastric emptying and patients run the risk of aspirating if they regurgitate or vomit. For example, a patient who ate an hour before injury may still have a significant amount of stomach content several hours after injury.

13.2.3 Interventional considerations (what to do about the pain)

Interventions are pharmacological and physical (e.g. immobilisation of fractures, including the neck and facial fractures). These interventions may have anatomical effects (e.g., on the airway or vascular access) and the physiology of multiple systems, namely, CV, haemodynamic, haematological, ventilatory, renal, endocrine, etc.

There are hundreds of drug interactions. Therefore, clinicians must always refer to a reliable source to identify drug interactions, such as The South African Medicines Formulary (SAMF). Drug–drug interactions may be either pharmacodynamic or pharmacokinetic. Pharmacodynamic interactions refer to the enhancement or diminution of effects, such as the enhancement of opioid-related respiratory depression by sedatives. Pharmacodynamic interaction refers to the mutual effects of drugs on enteral absorption, plasma protein binding, metabolism and excretion. Regarding pharmacokinetic interactions, liver enzyme induction and suppression may affect the formation of active metabolites and drug clearance. Moreover, several pharmacogenetic effects may impact on drug activation (e.g. metabolism of codeine to morphine). The most common suppressors of cytochrome enzymes in the liver include antiretroviral protease inhibitors (ritonavir, lopinavir and atazanavir), conazole antifungal agents, cimetidine and clarithromycin.

Drug–disease interactions must also be considered, such as the combination of anxiolytics and opioids, SSRI antidepressants and tramadol, anti-inflammatory agents in the elderly, hypertensive vasculopathy receiving an ACEI or ARA and diuretics. A patient with OSA may be very sensitive to respiratory suppression of sedatives (including all of the opioids), a patient who may develop a compartment syndrome should probably not receive a neuraxial or limb nerve block, and a patient on anticoagulants may not receive a neuraxial block or non-selective cyclooxygenase inhibitors (the traditional nonsteroidal anti-inflammatory drugs [tNSAIDs]).
Regarding pharmacokinetics and pharmacodynamics, remember the following principles:

- Depending on its severity, vital organ comorbidity affects other vital organ functions, pharmacokinetics and pharmacodynamics, which make the patient more prone to adverse effects of drugs and drug interactions.
- CV and haemodynamic disease can affect respiratory, liver and kidney function.
- Lung disease can affect haemodynamic function.
- Liver and kidney disease can affect pulmonary and haemodynamic function.
- All of the above can affect neurological and haematological function, and blood biochemistry (electrolytes, proteins).
- Metabolic diseases (including obesity) can affect all of the above.
- Physiological age (the very young and the elderly) affect all of the above.
- Pharmacological agents can affect all of the above.

- **All of the above can decrease the elimination of analgesics**, which increase its blood levels, prolong its activity and increase sensitivity (adverse effects and toxicity), as well as those of active metabolites. Keep this in mind when treating pain with any opioid, paracetamol, NSAIDs, and analgesic adjuvants (antidepressants, antiepileptics, etc.) in the patient with impaired vital organ system of any aetiology.

- Whenever possible, **multimodal analgesia** should be prescribed: a combination of drugs have the least additive effects, which allows lower doses and, consequently, fewer adverse effects.

- Since it is difficult to remember the pharmacokinetic characteristics of all drugs, clinicians must have a **source** where these characteristics can be looked up (e.g. the SAMF or package inserts).

- **Doses** are often given according to body mass. Drugs are usually tested in nonobese persons. The bodies of obese patients, however, do not only have an increased percentage of fat, but also an increased lean body mass (mainly due to an increase in muscle mass and blood volume). Some obese or overweight patients may have a normal BMI due to a loss of lean body mass (mainly bone, muscle and a decrease in blood volume). This is called sarcopaenic obesity and often occurs in the elderly, Cushing’s syndrome, invalids, amputees, among others. Oedematous patients have an increased BMI in spite of a decreased percentage of fat. Athletes may have a high BMI but a low percentage of fat. Cachectic patients have a low fat and muscle mass.

In obese patients, an adjusted body mass (ABM) is safer to use initially:

The ABM is calculated as follows:

\[ \text{DBM} = \text{Ideal body mass} + 0.4(\text{body mass} - \text{ideal body mass}) \]

Ideal body mass in men = Height in cm – 100 kg
Ideal body mass in women = Height in cm – 105 kg
For example, the ABM in a woman with a mass of 100 kg and height of 1.7 m is

\[ 65 + 0.4(100 - 65) \text{ kg} = 65 + 0.4(35) = 65 + 14 \text{ kg} = 79 \text{ kg} \]

13.2.4 Monitoring considerations

Anatomical, pathophysiological and interventional factors must always be assessed by imaging, chemical, haematological, pharmacological, pain assessment, etc.

Pain monitoring assesses the following pain characteristics: what is the location of the pain (localised or referred), what happened before the pain started (activity, visual symptoms, nausea), duration, onset (when, suddenly, gradually), constant or fluctuating, type of pain (stabbing, dull, throbbing, cramping), pain severity (pain scale), other symptoms (e.g., swelling, deformity, visual symptoms, motor or sensory symptoms, nausea, vomiting, dizziness, dyspnoea, skin discolouration or a rash), what gives relief, the effect of analgesics, and were there previous episodes?

13.2.5 Facilities and socioeconomical considerations

The choice of analgesia is often determined by the location (outpatient, inpatient, high dependency unit), socioeconomical factors (e.g., income, distance from health facility, housing, availability of caregivers).

*These five considerations (anatomical, pathophysiological, interventional, monitoring, and facilities and socioeconomical) never operate in isolation.* The interplay among these considerations determines the intervention (type, dose, route, etc.). In this chapter, the emphasis is on the pharmacological intervention in the management of *acute pain*. When treating acute pain, the practitioner must always base their choice of analgesia on the above principles, namely the pharmacokinetic and pharmacodynamic effects of the particular anatomical, pathophysiological, and interventional factors in a particular patient in particular circumstances.

13.2.6 Routes of administration of analgesics

The route of administration of analgesics is preferably either *orally (p.o.)* or *IV*. Patients who are nil per os (NPO) can receive analgesics p.o. or sublingually. *IV administration* is indicated only in patients who either cannot swallow or has a nasogastric tube in situ. *IMI and SC* injections are painful and drug absorption is unpredictable, especially in patients with a low cardiac output, oedema or vasoconstriction, and is contraindicated in patients receiving therapeutic doses of anticoagulants. Often, patients receive an IV infusion to keep a vein open just for IV analgesics. It is uncomfortable and increases the risk of infection and thrombophlebitis.

Generally, routes of administration other than *oral* or *topical* should be avoided, if possible. *Suppositories* should only be considered in infants and patients who are unable to tolerate
oral medication (nausea and vomiting). The use of suppositories should be avoided in young children and teenagers and needs consent from the patient or guardian. Transdermal formulations should not be used in acute postoperative pain, but may be used when prolonged pain is expected (e.g. cancer pain).

Topical analgesia is useful in treating outpatient conditions, especially superficial lesions such as abrasions and oral mucositis. This can decrease reliance on oral drug therapy.

13.2.7 Management of acute nociceptive pain according to the visual analogue scale

From the classification of acute pain, it should be clear that several organs (visceral, somatic, superficial, deep) and different innervations are involved. A host of neurotransmitters are involved in this circuitry. Moreover, the activity of nociception and pain experience is influenced by genetic factors, previous exposure to analgesics (tolerance and addiction) and chronic pain. If agonists, antagonists or modifiers of these transmitters were freely available, analgesia could be tailored to manage a particular pain in a particular patient. To date, only a handful of groups of analgesics are available. These factors form the basis of the use of different groups of analgesics simultaneously (i.e. multimodal analgesia).

Only the groups of analgesics that are freely available will be mentioned, namely:
- Paracetamol
- NSAIDs
- The steroid anti-inflammatory drug, dexamethasone
- Opioid agonists, dualists and atypical opioids, tramadol and tapentadol
- NMDA antagonists, ketamine and magnesium
- Gabapentanoids, gabapentin and pregabalin
- The α2-receptor agonist, dexmedetomidine
- Antidepressants

The SAMF is indispensable for the safe prescription of drugs, including analgesics.

The analgesia ladder

Mild pain (VAS of 1–3)
- paracetamol
- an NSAID

Moderate pain (VAS of 4–7)
- Paracetamol, and
- a regular NSAID, and
- an opioid.
• PCA
• Nerve block or neuraxial blockade

**Severe (VAS of 8–10)**
• Regular or continuous opioid, and
• paracetamol, and
• an NSAID, and/or
• PCA, nerve block or neuraxial blockade.
• Other adjuvants: ketamine, dexmedetomidine, pregabalin, TCAs

Each analgesic has characteristic pharmacodynamics and pharmacokinetics, and of course, also a particular dose in a particular patient. Regarding opioids, it is useful to regard them as morphine-like substances and to compare their potency to that of morphine. They all work to some extent on µ-receptors (agonists or dualists), but may also affect other receptors (e.g. κ-receptors) and neurotransmitters (noradrenaline, serotonin). However, the well-known adverse effects of opioids are effects on the µ-receptors.

Opioids have pharmacodynamic and pharmacokinetic characteristics that make these either very potent (doses expressed in µg, e.g. sufentanil), or weak (doses expressed in mg, e.g. tramadol). However, when given at a particular (equivalent) dose, the drug effects on the µ-receptors are similar in terms of adverse effects and addiction potential to that of morphine.

**Milligram morphine sulphate equivalents**

It is useful to have an idea of the potency of opioids compared to that of morphine sulphate. This is called the milligram morphine sulphate equivalent (MME). If an opioid has a dosage interval different from that of morphine sulphate, it is more convenient to use the daily MME (DMME) and divide that dose by the number of daily doses. Doses are applicable to nontolerant patients.

Regarding oral preparations, the dose refers to the simple not-sustained release (long-acting) preparation.

The DMME refers to the effect of 1 mg/day of a drug relative to that of morphine sulphate via the same route (Table I). For example, oxycodone has an oral DMME of 1.5. That means that 1 mg/day of oxycodone p.o. has the activity of $1.5 \times 1 \text{ mg/day of morphine sulphate p.o.} = 1.5 \text{ mg/day}$.

Since drugs have different oral bioavailabilities (the fraction of drug that reaches the systemic circulation after oral administration), an opioid may have a larger IV MME. For example, oxycodone has an IV MME of 3. That means that when given via IVI, oxycodone 1 mg/day has the effect as morphine sulphate 3 mg/day p.o. If IV morphine sulphate is to be replaced with oral oxycodone, how much oxycodone is needed? The IV MEE of morphine sulphate = 3 mg/
day IVI. Therefore, 1 mg/day of morphine sulphate IVI = 3 mg/day p.o. If the patient receives morphine sulphate 45 mg/day IVI, 3 × 45 mg = 135 mg/day p.o. is needed. What is the equivalent of oral oxycodone? The oral MME of oxycodone = 1.5. Therefore, the oxycodone dose is 135 mg/1.5 mg/day = 90 mg/day. Or, from Table I, it is seen that morphine sulphate 3 mg/day IVI = oxycodone 3 mg/day IVI. But oxycodone has an oral MME = 1.5. Therefore, the oral dose of oxycodone is 3 × 45/1.5 mg/day = 90 mg/day. 

<table>
<thead>
<tr>
<th>Drug</th>
<th>MME p.o. to p.o.</th>
<th>MME IV to p.o.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine phosphate</td>
<td>0.13 mg/day</td>
<td>Not IVI</td>
</tr>
<tr>
<td>Tramadol</td>
<td>0.15 mg/day</td>
<td>0.1 mg/day</td>
</tr>
<tr>
<td>Tapentadol</td>
<td>0.4 mg/day</td>
<td>-</td>
</tr>
<tr>
<td>Morphine sulphate</td>
<td>1 mg/day</td>
<td>3 mg/day</td>
</tr>
<tr>
<td>Oxycodone HCl</td>
<td>1.5 mg/day</td>
<td>3 mg/day</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>35.5 mg/day</td>
<td>75 mg/day</td>
</tr>
</tbody>
</table>

### 13.3 Acute pain in the emergency department

In South Africa, patients with acute painful conditions may report to an outpatient or emergency department. In the private sector, these departments function in the same facility. In state hospitals, these may differ according to the grading of the hospital or clinic.

Patients usually report to the emergency department and after assessment, they are managed according to the gravity of the problem, including resuscitation, optimisation and stabilisation. Analgesia will always form part of the resuscitation process and the choice of analgesia will be determined by anatomical and physiological findings, as well as on special investigations and the interventional options available at the particular facility. The management of acute pain due to trauma and nontrauma is similar to that of postoperative pain (see section 13.5).

Although acute pathology in different organ systems present with acute pain, the analgesics used are often similar. Some conditions, however, may need a different approach and different drugs.

Pathology may be trivial, justifying oral analgesics and discharge after minor procedures (e.g. management of minor wounds or splinting of fractures). More serious pathology or trauma may need resuscitation, admission for medical management or surgery, or be referred for further management. Recurring, intractable acute pain usually requires admission and further investigation.
13.3.1 Analgesics used in the emergency department

**Paracetamol and NSAIDs**

The management of minor or moderate acute pain in an outpatient is usually easily achieved with the use of oral agents. Paracetamol, an NSAID with or without an opioid, are usually prescribed. The NSAID may be either a tNSAID or a selective cyclooxygenase-2 (COX) inhibitor (coxib). Paracetamol and all NSAIDs are opioid-sparing, but lack the opioid-related adverse effects. See section 13.5. for a further discussion on the use of paracetamol and NSAIDs.

**Use of opioids in the emergency department**

Parenteral analgesic should only be used under medical supervision. When potent opioids are used, patients must be kept for observation for long enough before discharge, bearing in mind the half-life of the narcotic, and the concomitant use of other sedatives which potentiate respiratory and haemodynamic effects in the specific patient (e.g. age, comorbidity and antihypertensive treatment). All opioids can cause hypotension and subsequently dizziness in absolutely hypovolaemic patients, patients with cardiac disease and relatively hypovolaemic patients, especially in patients on antihypertensives, patients who are elderly, and those with concomitant use of other sedatives. This is a major concern since sedative analgesics and other sedatives are a common cause of falls and fractures in elderly patients in and out of hospital.

**IV morphine sulphate** is still the most widely-available and widely-used agent to treat severe acute pain. The dose is 50 µg/kg every 3 minutes until the VAS is ≤ 3. In a patient with a mass of 70 kg, this is about 3 mg every 5 minutes. **Oxycodone, tramadol, and papaveretum** (Omnopon) are not superior to morphine sulphate.

**Some perspectives regarding papaveretum:**
- It is a combination of morphine chloride, codeine and papaverine.
- Note that papaveretum 20 mg contains 10 mg morphine base, which is equivalent to 13.3 mg morphine sulphate, while morphine sulphate 10 mg and 15 mg injections contain 7.6 mg and 11.4 mg of morphine base, respectively.

**Tramadol:**
- It is a prodrug that is metabolised to desmetramadol, which is a µ agonist responsible for most of the analgesia, and an activity and adverse effect similar to that of morphine and oxycodone.
- It is not safer than the so-called ‘potent opioids’.
- Tramadol 100 mg IV is equivalent to approximately 10 mg of morphine sulphate.
- It is not safer to administer tramadol and discharge the patient immediately.
- The standard adult dosage of tramadol is an IV bolus of about 1–3 mg/kg over 3 minutes.
• Tramadol is renowned for nausea and vomiting. The same problem can occur with codeine in some patients.
• For further perspective, see section 13.5.

**Pethidine:**
• It has several unpleasant and therapeutic adverse effects and should not be used.

**Pentazocine:**
• It is a κ agonist and should not be used.
• It has several adverse effects, including hallucinations and skin ulcers.

**Dihydrocodeine (DF118):**
• It should not be administered intravenously, and therefore it has no place in the emergency scenario.

In the absence of venous access, opioids may be administered by IMI. However, this is not ideal in the emergency department because of the longer onset of action and a less predictable and titratable response, which requires a longer observation period before discharge.

The *combination of an opioid with a benzodiazepine* increases the risk of respiratory depression and oversedation, and lengthens the postprocedure observation time before safe discharge. These agents usually act synergistically. Therefore, the doses of both should be decreased by at least 50%. The *short-acting benzodiazepine midazolam* is preferred in the emergency department. Midazolam is titrated to effect at doses of 0.03–0.3 mg/kg depending on the hydration state, hypotension, vital organ function and age. Usually, 0.05 mg/kg is a safe titration dose.

**Naloxone and flumazenil**

The µ opioid antagonist, naloxone, should be available whenever IV narcotics are used. The dose is 5 µg/kg IVI (usually 0.4 mg). Since naloxone has a half-life of approximately 30–80 minutes, which is shorter than those of other opioids (except remifentanil), repeated doses may be required. Therefore, the patient must be observed for at least 2 hours (4 × 30 minutes = 120 minutes) to ensure that the opioid effect does not resurface.

Flumazenil is a benzodiazepine antagonist used to reverse benzodiazepine-related sedation, as well as hypoventilation. It has an elimination half-life of approximately 60 minutes, which is shorter than that of the shortest-acting benzodiazepine midazolam (120 minutes). The reversal effect of flumazenil lasts for approximately 2 hours, depending on the dose of the agonist, after which resedation from the agonist may occur. The dose is 3 µg/kg titrated over 15 seconds and repeated every 60 seconds up to 2 mg. The usual dose is 5–10 µ/kg.
13.3.2 Anaesthetic agents in the emergency department

Ketamine is an option for analgesia and it may be appropriate in selected scenarios. Adequate analgesia can usually be achieved with IV doses of up to 0.5 mg/kg, titrated at approximately 0.2 mg/kg. An initial dose of 2–4 mg/kg intravenously produces anaesthesia within 30 seconds, which 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 IM is an alternative which induces anaesthesia or deep sedation (dissociation) within 3–4 minutes, which lasts approximately 15–20 minutes. Oral ketamine 10 mg/kg also produces sedation adequate to either establish venous access or perform short painful procedures in uncooperative patients. Although ketamine has been used intranasally in children, more studies are needed to establish the appropriate dose for procedural sedation and analgesia. The effective doses varied from 6–10 mg/kg.

Ketamine is not useful for procedures where decreased muscle tone is required (e.g. shoulder or hip dislocations). Hallucinations commonly occur during ketamine sedation and while waking up from ketamine anaesthesia.

Methoxyflurane (Penthrup) is a volatile anaesthetic agent with analgesic properties at sub-anaesthetic doses. The delivery of this agent in the outpatient setting is now possible owing to a disposable inhalational delivery system. The drug offers adequate analgesia for short intense periods of pain, such as during dressing changes or wound debridement.

Anaesthetic induction agents, such as propofol and etomidate, should not be used unless the doctor knows the effect of these potent agents in healthy and injured patient, changes in pharmacokinetics, and airway management (laryngoscopy, intubation, prevention of aspiration, influence of burns, and maxillofacial and neck injury). As soon a patient has been intubated, they become an intensive care patient and must be managed as such.

13.3.3 Specific conditions commonly seen in the emergency department

- Acute cardiac pain
- Acute abdominal pain: biliary colic, renal colic, dysmenorrhoea
- Posttraumatic pain
- Acute musculoskeletal pain (including acute spinal pain)
- Pain management in sports medicine
- Headaches

Acute cardiac pain

Acute cardiac pain results from acute myocardial ischaemia and includes acute MI and unstable angina. Pain or discomfort is typically precordial, radiating or referred to the left arm and jaw,
but patients may also experience pain in either arms, left shoulder, back, neck or stomach. This is accompanied by dyspnoea, sweating, stomach discomfort (indigestion or heartburn), nausea and vomiting. Depending on the extent and location of ischaemia, patients may be dizzy (hypotensive due to myocardial failure or dysrhythmias). Sympathetic activation (sweating), radiating pain, referred pain, nausea and vomiting are typical of visceral pain (see the next section).

The restoration of adequate myocardial oxygenation is the mainstay of treatment. This is done by increasing arterial partial pressure of oxygen (PO₂), increasing coronary blood flow, and decreasing myocardial oxygen demand. These steps limit cardiac muscle damage and reverses ischaemic pain. However, early pain control is important in decreasing myocardial oxygen demand as it decreases the stress response.

Supplemental oxygen is usually administered as soon as possible. IV morphine is analgesic, anxiolytic, decreases blood pressure and suppresses the stress response. These effects decrease oxygen demand. Concurrent management includes nitrates, antihypertensives, antiplatelet agents and interventions to restore myocardial perfusion.

Morphine sulphate has been shown to be very effective at suppressing acute cardiac ischaemic pain. It is titrated at a dose of 50 µg/kg every 5 minutes. Keep in mind that morphine delays the antiplatelet effect of ticagrelor.

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

Acute abdominal pain

A wide spectrum of conditions present with acute abdominal pain. These conditions may be due to abdominal pathology (intra- or extraperitoneally), radiating or referred pain from extra-abdominal pathology, or systemic conditions presenting with abdominal pain. Therefore, it is once again important to not only manage the pain, but also consider anatomical, physiological (including functional disturbances and psychological) and pharmacological factors (including toxins), as well as conducting appropriate investigations before deciding on the management (intervention).

Abdominal pain can have its origin intra-abdominally (intra- or extraperitoneally) or extra-abdominally. Pain can radiate or refer from the abdomen to extra-abdominal regions, for example, to the right shoulder (the gallbladder, liver or right diaphragm), to the back (stomach, pancreas, retroperitoneal blood or kidney) and to the groin (kidneys and ureters). Conversely, pain due to extra-abdominal pathology can radiate or refer to the abdomen, for example, MI, pericarditis, testicular pathology, pleural pathology (pneumonia or PE), herpes zoster (may
present like gallbladder pain), among others. Functional disturbances also present with acute abdominal pain, for example, irritable bowel syndrome (IBS).

Acute abdominal pain can be caused by a wide range of systemic conditions, including the following:

- Infections and infestations: gastroenteritis, typhoid, tuberculosis, malaria, intestinal parasites
- Metabolic diseases: ketoacidosis, uraemia, porphyria, hypercalcaemia
- Haematologic and immunological: sickle cell crisis, haemolytic crisis, retroperitoneal haemorrhage in patients on anticoagulants, enlarged lymph nodes, intestinal angioedema (C1 esterase deficiency, ACEI)
- Toxins: corrosive substances, arsenic, heavy metals (lead and mercury), spider and snake poison
- Neurologic disease: substance withdrawal syndromes, abdominal migraine, IBS, toxin-mediated peripheral neuropathy (heavy metals)

Acute abdominal pain due to abdominal pathology usually begins as visceral pain, but becomes somatic once the parietal peritoneum is affected. Visceral pain can be acute or chronic, and is classically colicky in nature. Local inflammation results in progression to typical acute somatic pain, with localisation of the affected area and progression to the clinical picture of peritonism.

Pathology causing acute abdominal pain is often accompanied by nausea and vomiting. Similar to abdominal pain, nausea and vomiting are caused by a wide range of conditions. The afferent input for nausea, the nausea centre, and the vomiting centres are responsible for the symptoms of nausea and vomiting.

The nucleus tractus solitarius (NTS) can be regarded as the ‘nausea centre’ and the dorsal motor nucleus of the vagal nerve forms the so-called ‘vomiting centre’. The NTS is a cluster of afferents where various central and peripheral afferents converge. From here a common efferent pathway enters the dorsal motor nucleus of the vagal nerve, which coordinate the autonomic (sweating and salivation) and somatic (contraction of the diaphragm, abdominal wall and retroperistalsis of the stomach and oesophagus) phenomena of the act of vomiting.

The NTS receives input from the following centres:

- The chemoreceptor trigger zone is stimulated by toxins, drugs (several, including opioids) and metabolic derangement (ketoacidosis, uraemia, hypoxia and ketoacidosis). This stimulus is mediated by serotonin and dopamine. These causes are treated with serotonin-3-receptor (5-HT3) antagonists (ondansetron, granisetron) or dopamine antagonists (droperidol, metoclopramide, prochlorperazine, promethazine).
- Extramedullary brain structures, such as vestibular and cerebellar (motion sickness), olfactory, taste, cortex (emotion, severe pain), brain trauma and increased ICP. These are mediated by
acetylcholine and histamine. Nausea due to these stimuli is treated with the antimuscarinics (hyoscine, promethazine) and the H1 blockers (promethazine, cyclizine).

- GI visceral afferents from the GIT (vagal or sympathetic afferents) are stimulated by GI irritation (mucosal irritation, i.e. acid, alkali or bacterial toxins, distention, spasm, peritoneum) and are mediated by 5-HT3 and dopamine receptor stimulation. It is treated with 5-HT3 and dopamine antagonists.

- Extragastrointestinal stimulation (hepatobiliary [biliary colic]), peritoneum, heart, genitourinary (kidney colic, torsion or an ovary of ovarian cyst) is mediated by serotonin and treated with 5-HT3 blockers.

The management of abdominal pain consists of the management of the primary cause, as well as of the pain, hypermotility (spasm/colic), and nausea and vomiting.

This discussion is limited to conditions where urgent or emergency management is not considered, for example, bowel obstruction or GI haemorrhage.

Pharmacological treatment usually consists of analgesics and antispasmodics. Apart from atropine and glycopyrrolate, the antimuscarinic agent hyoscine butylbromide is the only injectable antispasmodic available in South Africa for management of GI, biliary (including the sphincter of Oddi) and genitourinary colic (renal colic). The dose is 0.2 mg/kg IV/SC 6–8-hourly.

**Renal colic**

Kidney stones do not cause pain until these obstruct the ureter. Ureter obstruction causes the renal capsule to stretch and the smooth muscle in the ureter to spasm. These events activate the release of prostanoids and serotonin which cause colic pain, and nausea and vomiting, respectively. There is also a decrease in renal function. The severe pain usually requires a combination of drugs. NSAIDs, such as ketorolac, form the mainstay of treatment. An opioid is added as second-line drug. Paracetamol is of less value in this setting. NSAIDs do not aggravate nausea and vomiting and patients need fewer rescue analgesics than those receiving opioids.

Lignocaine can be used for intractable renal colic pain not responding to NSAIDs and opioids. Lignocaine 120 mg in 100 ml normal saline is infused IV over 10 minutes. A lignocaine-morphine combination is also useful: morphine sulphate 0.1 mg/kg plus lignocaine 1.5 mg/kg over 2–4 minutes.

When NSAIDs are contraindicated, an IV opioid with IV paracetamol must be used. An antispasmodic may be added. Patients presenting with renal colic are usually admitted to hospital for further management.
**Biliary colic**

Biliary colic is characterised by colic pain in the right hypochondrium, spreading to the epigastrium and back.

Obstruction of the biliary tree may occur in the left or right hepatic duct, common hepatic duct, cystic duct or common bile duct. The common bile duct is joined by the pancreatic duct after which it opens into the duodenum through the sphincter of Oddi. Obstruction can be caused by gallstones, fibrosis due to previous stones and cholangitis, malignancy, parasites, external pressure, as well as spasm of the sphincter of Oddi. Proximal and incomplete obstructions are often asymptomatic. Acute complete obstruction of the cystic or common bile duct is usually caused by a gallstone and may be intermittent, but may also require urgent exploration or cholecystectomy.

Acute obstruction of the cystic or common bile causes increased pressure in the gallbladder and intrahepatic bile ducts. *Mucosal irritation and contraction* of the smooth muscle in the walls of these ducts cause the release of *prostanoids*, which are responsible for colic pain and *serotonin*, which causes nausea and vomiting.

Prolonged obstruction (approximately one day) causes cholecystitis and cholangitis, which is characterised by the Charcot’s triad (biliary colic, rigours and jaundice). Biliary colic may be intermittent. A stone that obstructs the outlet of the gallbladder may fall back into the gallbladder and the pain will subside. Stones in the common bile duct may be passed into the duodenum, or cause intermittent obstruction in the duct or at the sphincter of Oddi. A gallstone may cause obstruction of the pancreatic duct, causing pancreatitis.

Biliary colic should be referred for imaging, which will direct further management. The trend is to perform a laparoscopic cholecystectomy on an urgent basis. Protracted biliary colic is best managed by urgent laparoscopic cholecystectomy.

An NSAID is the first-choice treatment. NSAIDs have the same efficacy as opioids and significantly reduce the proportion of patients with severe complications. They are as effective as opioids, do not increase the tone of the sphincter of Oddi, do not cause nausea and vomiting, and prevent progression to cholecystitis.

If NSAIDs are used, it should be given parenterally since nausea and vomiting may make oral medication ineffective. Any parenteral NSAID may be used, but the following have been used in trials:

- Diclofenac 75 mg IMI
- Ketorolac 60 mg IMI, or 30 mg IVI
Besides pethidine and butorphanol, no reference could be found regarding the use of any other opioids in the management of biliary colic pain. These drugs were compared to an NSAID, and since these do not have any advantage over NSAIDs, it is not recommended but may be used in patients in whom NSAIDs are contraindicated.

Regarding the influence of opioids on the tone of the sphincter of Oddi: pethidine may decrease the tone, morphine may increase the tone, and tilidine does not affect the tone and may be used. The increase in tone caused by morphine is reversed by naloxone. The efficacy of the smooth muscle relaxant hyoscine bromide is inferior to that of NSAIDs.

**Dysmenorrhoea**

Primary dysmenorrhoea is explained by an overproduction of prostanoids in the endometrium when progesterone levels decline. A non-selective NSAID is the first-line treatment in the management of pain of dysmenorrhoea. Several of these agents are effective and are better than paracetamol. No reference regarding the use of opioids could be found.

**Posttraumatic pain**

Everybody, including babies, children, fit athletes and the frail elderly, is vulnerable to trauma. Trauma patients do not only differ in age, but also with regards to the type of trauma, comorbid conditions and medications – including analgesics. These factors must be considered when treating their pain.

Initial therapy for significant trauma pain is best achieved by the titration of IV opioids. Morphine sulphate remains the most widely-used agent, but adverse effects such as nausea and vomiting, hypotension, respiratory depression and oversedation occur commonly. The dose is 50 µg/kg every 5 minutes until the VAS is ≤ 3/10.

NSAIDs are effective analgesics in the trauma setting. These should preferably be administered IV, but IMI administration may be necessary if IV access is not available. NSAIDs (non-selective and selective COX-2 inhibitors) are generally safe, but should not be used in patients at risk of haemorrhage; that is CNS injury, head and neck injury, vascular injury, patients with premorbid diseases such as GI ulcers and bleeding diathesis (e.g. liver disease), antiplatelet agents, and anticoagulants. These should not be used in patients at risk of renal failure (hypovolaemia, the elderly, use of ACEIs, ARAs and diuretics) and IV paracetamol is preferable in these patients.

NSAIDs are usually continued after hospital discharge in an oral formulation either alone or in combination with an opioid derivative, such as codeine. **Topical NSAIDs in gel or patch form are useful and decrease systemic analgesic requirements.**
Acute musculoskeletal pain and acute spinal pain

Musculoskeletal injury may be present in any patient who has sustained other trauma, and it is managed according to the extent of injury and other injuries. In this section, focus will be on the musculoskeletal aspect alone.

Patients presenting with spinal pain (neck, thoracic, lumbar or sacral) must be evaluated by taking a thorough systemic history followed by a clinical examination. Take note of the following: the type of pain (duration, location, constant, intermittent, referred, spreading), chills and fever, local tenderness, physical activity, overuse injury, other skeletal pains, age (aortic aneurism), neurological complaints (spreading or referred pain, numbness, spasticity, weakness), GI complaints (peptic ulcer, jaundice, weight loss, faecal incontinence), genitourinary system (haematuria, incontinence, difficulty to pass urine) and haematological problems (anaemia, bruising). Also examine the breasts and thyroid.

Acute musculoskeletal pain usually follows injury (muscle injury, ligament injury, fracture, haemarthrosis or septic arthritis), overuse, gout and exacerbations of inflammatory arthropathies, such as rheumatoid arthritis and osteoarthritis. However, less common but very important causes must be kept in mind, including malignancy and haematological disorders.

The same approach is followed as with spinal pain. Usually, the diagnosis is obvious from the age of the patient and their history. Important information suggested in the history should not be overlooked. For example, an elderly person presenting with acute hip pain after a fall may have a fractured hip, but why did they fall? Dizziness and falls could be caused by, among others, autonomic neuropathy, diabetes mellitus, cardiac disease, carotid disease, epilepsy and drugs such as antihypertensive agents and analgesics (tramadol and meprobamate-containing preparations). Remember, shoulder pain may be referred cardiac pain.

Sports injuries

These are usually associated with musculoskeletal injury and pain and include skeletal injury (stress fractures, fractures, sprains, strains, joint dislocations, muscle haematomas, muscle rupture, etc.). These injuries may heal completely leaving no pain; others may be complicated by long-term morbidity, including dysfunction and chronic pain. Yet, the pain associated with sports injury is not always of a musculoskeletal nature. The apparent good health of persons presenting with sports-related pain may be misleading. Moreover, sports-related pain may not be of (the expected) musculoskeletal origin or even sports-related. Pain may also be out of proportion to the injury.

Patients may present with headache. Primary headaches (migraine, tension headache and cluster headache [CH]) occur commonly, but secondary headaches should always be suspected in a patient partaking in contact sports. These are trauma-related, vascular or nonvascular
types, or infection and substance abuse. Therefore, persons presenting with sports-related pain should be evaluated by taking a history, a clinical examination, and appropriate special investigations regarding the following:

- **Anatomical:** What sports were played (e.g., contact and collision sports, athletics, running, boxing, wrestling, rock climbing, surfing)? Look for associated injury, such as nerve injury, spinal injury, abdominal injury, thoracic injury, among other. Pain is also not limited to musculoskeletal injury (e.g. surfing complicated by sunburn, bites and stings, ocular trauma, and (important, but rarely) paraplegia due to vascular-related myelopathy).

- **Physiological:** Apart from the obvious or expected musculoskeletal pain, look for other functional disturbances, such as hyper- or hypothermia, neurological (change in consciousness, headache, weakness, paralysis, loss of sensation, pain out of proportion to the injury, radiating or referred pain), CV (dehydration, hypertension, dyspnoea, dysrhythmias, chest pain, blood pressure, pulses, compartment syndrome), respiratory (dyspnoea, chest pain), abdominal (abdominal pain, tenderness, groin pain) and genito-urological (flank pain, haematuria, testicular torsion).

- **Pharmacological:** What has the patient taken for pain? Has the patient taken any analgesics (opioids, NSAIDs, glucocorticoids)? Is there an indication of drug abuse (analgesics (opioids), sedatives (alcohol, benzodiazepines), hormones (anabolic steroids, thyroxine), psychostimulants and diuretics)? Does the patient display any drug-seeking behaviour? Athletes usually believe that illicit drug use has pleasant short-term consequences, such as increased physical and mental ability, but usually deny long-term detrimental health consequences. Alcohol is often abused and affects several neurological functions, which affects performance, memory, vigilance, reaction time and dexterity. They may also present with sports-related pain due to loss of muscle strength, and incomplete and delayed recovery. Drug abuse has also been implicated in serious adverse effects, including sudden death during competition. Persons taking anabolic steroids usually also use several other substances. They have often been diagnosed with a substance dependence disorder, and often suffer from psychiatric illness. These factors will influence pain management. Therefore, the practitioner who treats sports-related pain must have a sound knowledge of all the drugs used and abused by these patients; including the indications, adverse effects and abuses.

- **Special investigations:** The history and clinical examination will usually be straightforward or may need further investigation to dictate further management.

*Professional or serious athletes may be demanding patients.* Keep notes of the history, clinical findings, and special investigations, and refer the patient for further investigation or management. Fortunately, the majority of patients seeking help for sports-related pain are uncomplicated, undemanding, ‘normal’ patients. They can be treated with the usual analgesics.
**Pharmacotherapy of sports injury**

**Paracetamol**

Paracetamol is always prescribed. It should be taken around the clock at a dose of 15 mg/kg p.o. 6-hourly.

**NSAIDs**

Tissue injuries (including fractures) triggers the *inflammatory cascade* starting with phospholipase A2 (PLA2) that starts the formation of prostanoids. Apart from mediating nociception, these mediators of the inflammatory process initiate the repair process by hyperaemia, and recruitment of inflammatory cells that secrete mediators that promote the formation of granulation tissue, collagen formation by fibroblasts, and vascularisation. This early surge in the inflammatory response lays the foundations for eventual healing and return of function. Therefore, early NSAIDs inhibit the early inflammatory response and can impair healing. The clinical impact of this theoretical negative impact of NSAIDs on fracture healing is not clear.

Regarding fractures, retrospective studies have implicated the use of NSAIDs in delayed healing, delayed union, and nonunion of long bone fractures. It has been advised that NSAIDs should be avoided in complete fractures and stress fractures. If an NSAID is prescribed, the dose and duration should be limited as far as possible.

Healing of ligaments takes place in three phases, namely an early inflammatory response, the proliferation phase which is responsible for collagen formation, and finally remodelling. This phase may take up to a year. In one study, patients who received an NSAID for an ankle sprain, had less pain, decreased swelling and earlier return to activity. However, these ankles demonstrated less stability and range of movement. The faster return to activity may be due to analgesia, while joint instability and decreased range of movement points can be ascribed to blunting of the early healing process.

Findings of studies in animals regarding the effect of NSAIDs on ligament injury are conflicting. In humans, the effect on joint stability and range of movement is uncertain. Therefore, as is the case with fractures, an NSAID may be prescribed at the lowest effective dose for approximately 3–7 days. The emphasis should be on early immobilisation of the joint.

Healing of muscle injury also consists of three phases, namely inflammatory response, repair and remodelling. However, the inflammatory phase is accompanied by muscle destruction due to the proteolytic effect of inflammatory cells. Theoretically, by limiting proteolysis, NSAIDs may attenuate local tissue damage, limit pain, and promote healing and recovery.
NSAIDs are useful in muscle injury as these are not only analgesic, but also promote recovery, and earlier return to activity after muscle strain and eccentric injury (lengthening of the muscle during contraction). However, long-term use may be detrimental to repair and regeneration.

NSAIDs are useful in entrapment- or swelling-related disorders (e.g. carpal tunnel syndrome, interdigital neuroma, intervertebral disc prolapses, thoracic outlet syndrome, rotator cuff bursitis, trochanteric bursitis, and iliotibial band syndrome).

The adverse effects of NSAIDs should be discussed with the athlete, namely early advantages, risks and long-term outcomes.

NSAIDs are usually prescribed, taking into account its adverse effects and contraindications, including dehydration, kidney disease, ischaemic heart disease and peptic ulceration. The tNSAIDs are not necessarily safer than the coxibs. These drugs should not be prescribed to contact athletes on the day of competition. In the scenario of musculoskeletal injury, NSAIDs may be prescribed at the lowest effective dose for approximately 3–7 days.

Topical NSAIDs penetrate into soft tissues while systemic drug levels remain low. These are effective in relieving the pain associated with soft tissue injuries, without causing serious systemic or local adverse effects.

Corticosteroids

These agents are potent inhibitors of PLA2, which initiates the production of prostanoids. Corticosteroids have potent anti-inflammatory properties and are prescribed to avoid the well-known adverse effects of NSAIDs. For tissue repair (including scarring) to take place, it needs inflammation to bring along several mediators for granulation tissue and collagen formation, fibroblasts and vascularisation. Glucocorticoids inhibit these processes. Where inflammation is the primary process (not preceded by trauma, e.g., rheumatic and connective tissue disorders), corticosteroids are useful and are often prescribed for long-term use. However, secondary (injury-related) inflammation forms part of the healing process and corticosteroids may be prescribed for a short period of time. A short course (< 7 days) has not been shown to affect ultimate healing. Therefore, athletes should not receive these drugs during the competition season, where repeated injury is unavoidable and short-term repair is important.

Oral glucocorticoids are useful for acute radiculopathy and osteitis pubis, but should not be prescribed for noninflammatory degenerative conditions such as plantar fasciitis and Achilles tendinitis. Chronic back pain caused by disc herniation or radiculopathy can be treated with epidural corticosteroids.
Opioids

Besides the type of injury occurring in particular sports, sports injury is characterised by repeated injury and pain. The prescription of opioids every time an athlete seeks help, should therefore be done with circumspection to prevent abuse of opioids. All opioids are habit-forming and related to the number (milligrams) of MMEs – not the type of opioid (so-called weak and potent opioids). When prescribing opioids, the MME for the different opioids should be kept in mind to prevent inadvertent overdosing when switching between opioids.

The use of NSAIDs for sports injuries is controversial. Taking into account the (probable) effects of NSAIDs on healing, paracetamol and opioids are the only analgesics useful for the management of acute sports-related pain. However, the adverse effects of NSAIDs have not been demonstrated to impact significantly on the outcome, and are often prescribed. Paracetamol and the NSAID must be taken around the clock, while the opioid must be reserved for breakthrough pain. Physical measures are opioid-sparing (e.g. limb elevation and cold therapy to decrease swelling). A prescription for more than five days is usually unnecessary and it should never be prescribed for longer than 10 days without a review.

13.3.4 The discharge prescription from the emergency department

A patient should not receive a prescription for analgesics without a diagnosis. If a diagnosis is not clear, the patient must be referred for further evaluation as either an in- or outpatient. If the doctor is of the opinion that it is safe to discharge the patient, they must be advised on the symptoms to look for and instructed to return if necessary.

A prescription consisting of paracetamol and an NSAID is usually safe. The drugs should be taken around the clock for approximately 24 hours and longer if necessary. An opioid may be added for breakthrough pain or when NSAIDs are contraindicated. The number of opioid tablets/capsules should not exceed 10 units containing approximately 5 mg MMEs. This practice may decrease the availability of unused opioids that can land up in the hands of people who misuse opioids.

13.4 The intensive care unit

The duration of sedation and analgesia in the intensive care unit (ICU) should be limited to decrease the duration of ventilatory support and limit the complications thereof. To this end, the availability of well-trained staff, good monitoring and resuscitation equipment allow for more potent agents to be used more safely.

- Multiorgan physiological derangements may develop or exist in most patients. These abnormalities affect pharmacokinetics to some extent or may be aggravated by analgesics. Owing to large organ reserves, biochemical indicators may be within normal limits, but show a downward trend or deteriorate rapidly once the reserve has been exhausted. For example,
serum creatinine and the glomerular filtration rate (GFR) remain within the normal range in the presence of a severe renal insult. In fact, the baseline GFR may remain within the normal range until as much as 50% of nephrons have been lost.

- **Liver function** is determined by liver perfusion and hepatocyte volume and function. Low liver perfusion and hepatocyte dysfunction commonly occur, impairing excretory, anabolic and catabolic liver functions. These may be due to preadmission conditions (trauma, medical conditions), or pre-, intra-, or postoperative insults. **Hypoalbuminaemia** is very prevalent and may indicate a decrease in anabolic liver function, but is often a finding in several clinical situations, including catabolic states, systemic inflammation disorders (including sepsis), nephrotic syndrome, GI protein loss, and HIV infection.

- A low plasma albumin concentration increases the free (active) fraction of most analgesics, while loss of hepatocytes decrease the clearance of several analgesics. Clearance from the plasma is not only affected by metabolism and excretion, but also by redistribution to muscle and fat. Apart from remifentanil that is metabolised rapidly, it should be appreciated that the longer a sedative is infused, the longer the patient will take to wake up after termination of infusions (up to several days). This also accounts for propofol infusions.

- **Ventilated patients are unable to verbalise their pain.** It is often difficult to differentiate between discomfort caused by ventilatory failure (dyspnoea, hypoxaemia, hypercapnia), the endotracheal tube, artificial ventilation, awkward body posture, withdrawal of opioids or ethanol, and surgical and nonsurgical pain. All these factors can cause restlessness and haemodynamic instability (e.g. tachycardia and hypertension). Therefore, all the nonnociceptive elements of care must be attended to before resorting to analgesics.

- **When the presence of moderate to severe pain is unlikely**, nonanalgesic interventions (including sedatives) may suffice. However, when pain and discomfort is the likely cause of restlessness, analgesic-based sedation (**analgesedation**) is preferred to hypnotic-based sedation (**hypnosedation**).

- **Non-pharmacological interventions can 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, visits and sleep. If pain is the likely main cause of restlessness, it is a wise policy to administer analgesics before sedatives, which should reduce the risk of inadequate pain control in sedated patients. All opioid analgesics have sedative properties and may address the sedative component adequately. Usually, morphine sulphate is the preferred analgesic in mechanically-ventilated patients, often in combination with the short-acting benzodiazepine, midazolam or propofol.

- Patients may receive analgesics p.o. or via nasogastric tube, but GI motility may be unpredictable, which may affect absorption.
13.4.1 Analgesics used in the ICU

Paracetamol

Paracetamol should be used for pain and fever, if not contraindicated. Paracetamol forms the basis of analgesia in the ICU. The dose of paracetamol is 15 mg/kg 6-hourly by any route, but should be decreased in patients with liver and renal impairment and elderly patients. Paracetamol has a plasma protein binding of < 50%. Therefore, free drug concentrations are less affected by hypoalbuminaemia.

NSAIDs

NSAIDs should probably not be used in the ICU setting. For a discussion of paracetamol and anti-inflammatory drugs, see section 13.5.

Opioids

Opioids are the most important analgesics in ICU. These can be given intravenously or enterally, but must be administered IV if it forms part of sedation. Opioid analgesia is usually started by titration to effect. The analgesic is administered as boluses, every 5 minutes until the VAS is < 3/10. This is followed by an infusion, the effect of which must be monitored regarding pain, sedation and haemodynamic effects.

Analgesia and sedation should be monitored. Not only using a pain scale, but also by keeping an eye on haemodynamic changes. Haemodynamic suppression (due to central sympatholysis) usually correlates with the analgesic/sedative effect (e.g. hypotension and bradycardia) when sedation is too deep, and vice versa. When analgesia is inadequate, a bolus of approximately 15% of the hourly dose is administered over 30 minutes, while the infusion rate is increased by 15–20% until a new steady state is reached. Similarly, when analgesia/sedation is too deep, the infusion is decreased by 15–20% until a new steady state is reached.

Tolerance of all opioid agonists develop and is a normal physiological phenomenon. It should be taken into account if a patient needs higher doses of opioids or becomes restless when weaned from an opioid infusion. Tolerance to the analgesic effect of opioids should not be overlooked and is managed by administering a muscle relaxant or restraining the patient.

Tolerance manifests as opioid-induced hyperalgesia (OIH) in the postoperative period and doses need to be increased to maintain adequate analgesia and sedation, while it manifests as opioid withdrawal syndrome (OWS) when an opioid infusion is stopped. OWS occurs in adults and in more than 50% of children. The degree and manifestation of tolerance (dose needed, OIH and OWS) vary and are probably determined by pharmacogenetic factors. The potent
shorter-acting opioids such as fentanyl and remifentanil are often used in the ICU and have often been implicated in the development of tolerance.

OWS manifests as severe restlessness and haemodynamic instability when the infusion of a potent opioid is stopped. It can be prevented by decreasing opioid infusion rates over several hours or days, while the drug that the patient is being weaned from is replaced by an infusion of a longer-acting opioid such as morphine sulphate (opioid rotation). The infusions should be titrated downward using the 20%-rule. For example, if the infusion runs at a rate of 10 ml/h, it is changed to 8 ml/h for 6 hours → 6.4 ml/h for 6 hours → 5 ml/h for one hour → 4 ml/h for 6 hours → 3 ml/h for 6 hours → 2.4 ml/h for 6 hours → 2 ml/h for 6 hours → stop. The longer the patient has received an opioid, the longer the weaning period should be and could even last days.

Tolerance to the analgesic effect of opioids may be overcome by using the dualist (partial µ agonist) buprenorphine instead of the pure µ agonist or by adding low dose ketamine or dexmedetomidine. The dose of buprenorphine is 0.2–0.4 mg sublingually or 0.3 mg IV 6-hourly. Since buprenorphine binds strongly to µ-receptors, its effect on respiration is not readily reversible by naloxone.

**Morphine sulphate**

Morphine sulphate is an effective analgesic and, in combination with paracetamol, forms the basis of analgesia in the ICU. It is cheap, readily available, and the agent with which most practitioners have the most experience. Its length of action is well-suited to this environment. Morphine sulphate is titrated at a dose of approximately 50 µg/kg every 5 minutes until the VAS is < 3. In a patient with a mass of 70 kg, this is about 3 mg every 5 minutes. This is followed with an infusion of 50–300 µg/kg/hour.

Morphine is metabolised in the **liver** to the active metabolite morphine-6-glucuronide (M6G) and other nonactive metabolites, all of which are excreted by the **kidneys**. Approximately 10% of morphine is excreted unchanged in the urine. Morphine has a half-life of about 2 hours. However, M6G is twice as potent as morphine and has a longer half-life. Therefore, the dose of morphine should be adjusted in patients with decreased liver and kidney function of any cause. Both morphine and M6G have low plasma protein binding (15–30%), which make their effects more predictable in the presence of low plasma protein concentrations.

When morphine is contraindicated, the short-acting potent opioids alfentanil, fentanyl, sufentanil and remifentanil can be used. The analgesic potencies of alfentanil, fentanyl, remifentanil and sufentanil relative to that of morphine are approximately 10, 100, 100 and 1 000 times more potent, respectively. Alfentanil, fentanyl and sufentanil are all cleared by the liver and can accumulate in patients with liver impairment.
**Fentanyl and remifentanil**

Fentanyl and remifentanil can be used as morphine alternatives. These opioids are similarly titrated intravenously. Although these work quicker, better analgesia is not offered than morphine after about 30 minutes. Since these are highly plasma protein bound, dosages should be lowered in hypoproteinaemic patients.

*Fentanyl* is effective after 1–2 minutes. The initial bolus dose in nontolerant patients is 1–2 µg/kg, followed by an infusion of 1–1.5 µg/kg/h (up to 10 µg/kg/h in tolerant patients). Fentanyl is metabolised in the liver and has no active metabolites. Therefore, it accumulates in patients with liver impairment but usually not in patients with kidney failure. Fentanyl has a plasma half-life of 2–4 hours. Since fentanyl has a long context-sensitive half-time, the duration of action increases as infusion time increases.

*Remifentanil* is cleared by nonspecific esterases, which makes it independent of renal and liver function. It has no active metabolites. Remifentanil works within 1–3 minutes. The LD is 1 µg/kg and the maintenance dose (MD) is 0.05–2 µg/kg/min (3–120 µg/kg/h). Remifentanil is ideal for infusions in the ICU since it has a short half-life (3–10 minutes) and a constant context-sensitive half-time of approximately 3 minutes.

Remifentanil is useful for analgosedation in ventilated patients and when performing uncomfortable or painful procedures. It can be used in combination with propofol for analgosedation. The dosages of remifentanil plus propofol sedation are 0.025–0.200 µg/kg/minute and 5–50 µg/kg/minute, respectively. Both remifentanil and propofol are very expensive. In addition, a propofol infusion should not be used for longer than three days because of the risk of propofol infusion syndrome.

**Dexmedetomidine**

*Dexmedetomidine* is a selective α₂ agonist with hypnotic and analgesic properties synergistic with that of opioids. It is an opioid-sparing adjunct to opioid-based analgosedation. Dexmedetomidine improves analgesia in opioid-tolerant patients (e.g. patients with major burns and in patients with a history of substance addiction). Dexmedetomidine and clonidine are useful in the management of OWS. However, evidence does not support the routine use with opioids. It is a useful analgosedative for short stressful procedures, such as fiberoptic bronchoscopy and tracheal intubation.

Adverse effects include hypotension and bradycardia. Abrupt cessation of an α₂ agonist infusion can result in life-threatening hypertension and, rarely, withdrawal syndrome. The rapid administration of a bolus can cause severe hypertension and bradycardia.
The LD is 1 µg/kg over not less than 10 minutes. However, an LD may be omitted when converting from another sedative to dexmedetomidine. The maintenance infusion dose is 0.2–0.7 µg/kg/h and should not be used for more than 24 hours. The dose should be decreased in the presence of hepatic impairment, elderly patients, and when used concomitantly with anaesthetics, hypnotics or opioids.

When used in ventilated patients, it is unnecessary to wean the patient from dexmedetomidine since it can be continued after extubation. This makes dexmedetomidine a useful drug during weaning analgosedatives such as morphine, fentanyl and remifentanil.

**Ketamine**

Ketamine is a pluripotential agent with several mechanisms of action and, consequently, applications. It is analgesic and hypnotic, and useful in painful procedures such as burn dressings and gaining venous access, especially in children. The pharmacodynamic characteristics that come in handy in the ICU scenario include the following:

- It is an indirect NMDA receptor antagonist in dorsal spinal ganglia. This anti-NMDA effect mediates (potentiates) opioid-mediated antinociceptive effect (analgesia) and reduces OIH. The hypnotic effect of ketamine results from a combination of NMDA channel blockade and activation of cation channels at supra spinal sites.
- Ketamine suppresses induction of nitric oxide (NO) synthase and protein expression by endotoxin. This results in an anti-inflammatory effect in sepsis, as well as a reduction of OIH.

Ketamine causes dose-dependent profound analgesia, catalepsy, amnesia, sedation and anaesthesia. Its sedative properties differ from that of other sedatives in that it produces a dissociative state; patients appear to be awake, but are detached from their surroundings and their eyes often remain open.

Ketamine increases muscle tone, causes minimal respiratory suppression, is a bronchodilator, and increases salivation and tracheobronchial secretions. Since airway reflexes remain intact, laryngospasm occurs more commonly. Different from other analgosedatives, it increases blood pressure and heart rate. Adverse effects of ketamine include delirium, hallucinations, nausea and vomiting.

Ketamine is metabolised in the liver and has an active metabolite that is excreted by the kidneys. Therefore, dosages should be adjusted in patients with decreased liver and kidney function. Ketamine has a low plasma protein binding (about 30%). Therefore, free plasma concentrations are less affected by low plasma protein concentrations.

Ketamine can be administered p.o., IM and SC. The dosage via these non-IV routes is 5–10 mg/kg. The oral bioavailability is 20%. The oral route (often combined with midazolam 0.2–0.5 mg/kg) is often used in children. This oral combination produces sedation within about 20
minutes and usually allows for painful procedures such as venous cannulation. IV ketamine of 1–2 mg/kg and 0.1–0.2 mg/kg produces anaesthesia and sedation, respectively. These IV dosages are effective within 1 minute and the effect lasts for up to 10 minutes. IM and SC administration produce deep sedation or anaesthesia within 10 minutes, which lasts up to 20 minutes. The analgesia and psychological adverse effect of ketamine lasts longer than the sedative effect.

Ketamine infusions are used in the ICU, usually in selected patients (e.g. to decrease delirium in ventilated patients). The sedation dose is 0.1–1.0 mg/kg followed by 0.125–0.5 mg/kg/h (usually 0.2 mg/kg followed by 0.2 mg/kg/h).

Caution should be exercised in patients with ischaemic heart disease, significant hypertension and psychotic states. In spontaneously breathing patients, ketamine should be used cautiously if there is increased intracranial pressure. However, this applies to all sedatives. In ventilated patients who maintain PaCO₂, ketamine can be used safely, usually in combination with other sedatives such as midazolam or propofol.

Ketamine is often used as co-analgosedative with other agents in nonventilated and ventilated patients. This includes ketamine-midazolam and ketamine-propofol. The dose of midazolam when used as monosedative in ventilated patients is an LD of 10–50 µg/kg over several minutes, which may be repeated every 5–15 minutes until the required level of sedation is reached. The MD is 20–100 µg/kg/h infusion. A low dose ketamine-midazolam infusion of ketamine (≤ 0.25 mg/kg/h) with midazolam (7–15 µg/kg/h) reduces morphine requirements.

**Propofol**

Propofol is commonly used as a sedative in the ICU. The dose of propofol sedation in the ICU is 5 µg/kg/min for 5 minutes. This is titrated upwards with approximately 20% every minute until an adequate level of sedation has been reached. The MD is 5–50 µg/kg/min IV titrated to response. Cognisance should be taken of the danger of propofol infusion syndrome and prolonged emergence with prolonged administration.

Numerous mg:mg combinations of ketamine and propofol (ketofol) have been described, varying from 1:10–1:1, but the optimum dose of combinations remains unclear.

**Drug combinations in the ICU**

The principle with respect to combinations of analgosedatives and hipnosedatives is that these combinations should be regarded as a drug with unique characteristics and adverse effects. Furthermore, the effect of a combination should be assumed to be at least a synergistic effect of these combinations (i.e., 2 + 2 = an effect of (2 + 2)² = 16) while an additive effect is produced.
when $2 + 2 = 4$. When synergism is assumed, the dose can be titrated to the required endpoint of sedation or analgesia.

Several binary drug combinations have been reported in the literature and are widely used. These combinations give rise to several caveats.

- Firstly, numerous dose combinations on numerous patient profiles formed part of study protocols, and are therefore difficult to apply universally.
- Secondly, the pharmacokinetics of the drugs used in these combinations differ, resulting in different times to maximal effect of the individual drugs. Consequently, a clear effect of the combination (‘new drug’) may be delayed. Moreover, the effect of the drugs may dissipate at different rates when the infusion is stopped.
- Thirdly, there may be physicochemical incompatibility of the different agents in the same syringe or the same infusion line. Incompatibilities may manifest as precipitation of the drugs, which may make the solution cloudy or degrade components (propofol containing mixtures obscure precipitation). The absence of any visible change does not necessarily exclude incompatibility. Precipitation is impossible in propofol combinations. Propofol is compatible with fentanyl, alfentanil, sufentanil and ketamine; however, propofol is incompatible with remifentanil and midazolam. Ketamine is compatible with propofol, midazolam, morphine sulphate, fentanyl and sufentanil.

### 13.5 Postoperative pain

Failure to treat postoperative and posttraumatic pain adequately result in increased psychological and physiological stress and contributes to the development of chronic pain. Perioperative clinicians are the most experienced in the management of postoperative pain and their experience in this scenario has been extrapolated to guide pain control in most other medical scenarios, including the outpatient department, emergency department, and the ICU.

Day case surgery also warrants specific mention. The incidence of severe pain following these surgeries is approximately 5%. However, inadequate pain control is common because of concerns of administering powerful agents to patients who will be discharged soon, and reluctance on the part of staff to delay the discharge process. Orthopaedic, plastic surgery, laparoscopic procedures and hernia repair are common scenarios in which pain control is often inadequate. Patients with an increased BMI, and procedures that requires longer GA, are risk factors for the development of severe pain.

The use of multimodal analgesia, including local and regional anaesthesia, is strongly advocated in the day case scenario where possible. This means that analgesics of different classes or pharmacodynamics are co-prescribed. These different drugs may have additive or synergistic effects, which allows for lowering the doses of the different analgesics (e.g. opioid-sparing).
These low-dose combinations decrease adverse effects. Whenever possible, multimodal analgesia should be prescribed.

Several strategies are used to pre-empt postoperative analgesia. These include neuraxial block (intrathecal LA and/or epidural opioid), nerve block (nerve plexus, peripheral nerves, infiltration or intra-articular LAs), or NSAIDs before incision, and paracetamol and a longer-acting opioid such as morphine sulphate before the end of surgery. Opioid-free anaesthesia (OFA) has been shown to decrease postoperative analgesic consumption.

Acute pain is usually caused by tissue injury which can be managed by using pre-, intra- and postoperative strategies.

13.5.1 Preoperative strategies

Paracetamol, approximately 15 mg/kg p.o., and an NSAID p.o. are cheap and as effective as intraoperative IV formulations. For surgery lasting more than approximately two hours, intraoperative administration of paracetamol is probably more effective. A long-acting NSAID, such as naproxen/esomeprazole 500/20 mg, is useful. A gapentanoid such as pregabalin 150 mg one hour preoperatively is opioid-sparing, but is associated with postoperative dizziness. If PCA is planned, the use of the device must be explained to the patient.

13.5.2 Intraoperative strategies

Both paracetamol and an NSAID are usually given intravenously intraoperatively. The NSAID is usually administered at induction anaesthesia, while paracetamol is given near the end of surgery, depending on the duration of the surgery. If non-opioid non-NSAID analgesics (e.g. ketamine and dexmedetomidine), form part of postoperative analgesia, these are usually administered at low doses during surgery and continued during the postoperative period. An opioid-free anaesthetic technique decreases postoperative opioid requirements. If IV or epidural PCA is planned, these can be activated before the end of the surgery. An opioid can be started at the end of surgery (e.g. if buprenorphine is prescribed as the postoperative opioid, buprenorphine can be administered IV about 30 minutes before the end of surgery).

13.5.3 The postoperative care unit

If the patient is not transferred to a high care unit (HCU) or the ICU directly from the operating room, immediate postoperative pain control in the postanaesthetic care unit (PACU) in the operating theatre complex is usually accomplished by titrating an IV opioid to an adequate effect. *Morphine sulphate* is usually used at a dose of approximately 50 µg/kg every 5 minutes until VAS has decreased to < 3/10. Other IV opioids can also be used, including oxycodone, tramadol and buprenorphine.
If the patient has not received paracetamol intraoperatively, a dose of 15 mg/kg is immediately given intravenously. This dose of intravenous paracetamol has a morphine-sparing effect of up to 60%; the analgesic efficacy of IV paracetamol 1 g (approximately 15 mg/kg) is similar to 10 mg of IV morphine sulphate over 15 minutes.

Ideally, the first dose of analgesics prescribed on the postoperative prescription should be offered as soon as the patient arrives in the PACU (hopefully, the patient is awake and with no airway in situ). This practice will ensure a smoother transition of analgesia from theatre to ward, since it often occurs that the postoperative analgesics are not fetched from the pharmacy for several hours after the patient has arrived back in the ward. Any analgesic for postoperative pain administered intraoperatively and in the PACU must be documented on the postoperative prescription to prevent overdosage when the patient is transferred to the ward.

13.5.4 The postoperative prescription

The postoperative prescription should follow the same principles given in the analgesic ladder earlier. For moderate to severe pain, the prescription should include paracetamol, an NSAID, as well as an opioid.

**Paracetamol**

Paracetamol is safe in almost every clinical scenario. On its own, it is effective for mild to moderate postoperative pain at the most. Paracetamol improves analgesia when prescribed with other analgesics. However, evidence is conflicting and the efficacy of combinations seems to depend on the type of surgery and the doses of analgesics used in combination with paracetamol. For example, in surgery complicated by severe pain (e.g. spinal surgery), the role of paracetamol is less clear. Paracetamol and NSAIDs have at least additive analgesic effects. Therefore, this combination is more effective than the individual drugs. Combinations preparations containing paracetamol, an NSAID (usually ibuprofen) with or without codeine, is useful for mild to moderate pain. It should be noted that the contribution of paracetamol to the analgesia offered by a high dose of NSAIDs may be negligible. The lower-dose combination of paracetamol and tramadol is as effective as higher doses of either drug.

The dose of the oral and IV formulations is 15 mg/kg 6-hourly, but 8-hourly in patients with kidney or liver impairment. Care must be taken not to exceed the maximal IV dose of approximately 15 mg/kg 6-hourly or 60 mg/kg/day, especially in elderly patients and patients with decreased liver function. The analgesic efficacy of IV paracetamol 1 g (approximately 15 mg/kg) is similar to 10 mg (0.15 mg/kg) of IV morphine sulphate over 15 minutes. Although usually not adequate for severe pain, the opioid-sparing effect of IV paracetamol is useful in patients who can be discharged. The lack of adverse effects or sedation is of benefit to patients...
who remain in hospital. If paracetamol was administered pre- or intraoperatively, it must be recorded on the prescription chart to prevent an overdose postoperatively.

Although IV paracetamol has been shown to be opioid-sparing, oral paracetamol strictly scheduled (6-hourly) is not necessarily inferior to IV paracetamol. When paracetamol forms part of multimodal analgesia, the IV route does not produce better analgesia than the oral preparation. Although IV propacetamol achieves therapeutic levels quicker than tablets, analgesia was not better at 30 minutes; however, it was better two hours after oral paracetamol. Effervescent tablets halve the time to peak blood levels as compared to conventional tablets. Therefore, paracetamol should form part of multimodal analgesia, but IV paracetamol should be reserved for patients in whom the enteral route (including the oral, nasogastric or gastrostomy) is not accessible. Oral formulations (including effervescent tablets) are far cheaper than the IV formulations.

**NSAIDs**

NSAIDs should, if not contraindicated (see below), form part of multimodal analgesia. Although these drugs form a definite and very useful part in the treatment of pain, notice must be taken of important adverse effects. The discussion that follows is to emphasise the group adverse effects of NSAIDs. These belong to a diverse group of drugs that are analgesic, antipyretic and anti-inflammatory. To appreciate its adverse effect profile (and one side effect used therapeutically as antiplatelet agents), its group pharmacodynamics (its effect on body systems) must be appreciated. NSAIDs affect prostanoid production throughout the body.

**Cyclooxygenase**

Phospholipase A2 (PLA2) enzymes are a group of enzymes that occur in all tissues. These occur intra- and extracellularly and are activated by diverse stimuli, such as cell membrane injury. PLA2 cleave fatty acid from phospholipid to form arachidonic acid (AA). The cyclooxygenase (COX) and peroxidase activities of the COX isoforms COX-1 and COX-2 change AA to PGG2 and PGG2 to PGH2. Tissue-specific isomerases and synthases transform PGH2 to the three groups of prostanoids: prostaglandins (PGE2, PGF2α and PGD2), PGI2 (prostacyclin), and thromboxane A2 (TXA2).

The production (stimulus, type and output) of a particular PG by particular cells depends on the expression of the particular COX enzyme (COX-1 and COX-2) and of the particular enzymes distal to PGH2 to render the different cell-specific prostanoids.

The different prostanoids interact with its respective cell-membrane receptors occurring in different tissues where these play important tissue-specific physiological functions and pathophysiological responses. These include:
• Fever (PGE2), modulation of fever and inflammation (PGE2) and its resolution (including erosion of cartilage and juxta-articular bone)
• Haemodynamics (including coronary artery blood flow and ischaemia and renal hemodynamics (PGI2) and progression of kidney disease)
• Renal water and electrolyte homeostasis (PGE2) and oedema formation
• Gastric and intestinal (GI) cytoprotection (PGE2 and PGI2) and ulceration
• Haemostasis (TXA2 and PI2) and thrombosis
• Embryo implantation, uterine function and labour (PGF2α)
• The sleep cycle (PGD2)
• Anti-atheroma effect and progression of atherosclerosis
• Angiogenesis and cancer

**COX-1 is expressed constitutively** (it is active all the time) in most cells. It has a housekeeping function in homeostasis and is not normally inducible. From a therapeutic viewpoint, COX-1 has important functions regarding GI cytoprotection and platelet activation.

**Platelet COX-1**

COX-1 is the only COX present in mature platelets. AA is released when thrombin and adenosine diphosphate (ADP) interact with their specific platelet receptors. COX-1 transforms AA to PGH2, which isomerises to TXA2. TXA2 causes platelet aggregation, is a potent vasoconstrictor, and promotes vascular smooth muscle proliferation.

Low-dose aspirin irreversibly and almost completely (> 95%) inactivate COX-1 activity resulting in decreased platelet function for the duration of the life of the platelet (i.e. approximately ten days). Since even a very low concentration of TXA2 activates platelets, complete (> 95%) and continuous suppression of platelet COX-1 is essential for cardio-protection. Therefore, the traditional non-selective COX blockers (tNSAIDs), which reversibly, incompletely and intermittently inhibit platelet COX-1, are not cardio-protective. The exception is naproxen. At a high dose of 500 mg bd (which is the therapeutic dose), it inhibits platelet COX-1 > 95%, even at the end of the 12-hour dosing interval.

The use of NSAIDs does not significantly increase postoperative bleeding or the need for blood transfusion. Regarding aspirin withdrawal, the risk and benefit of stopping the drug should be assessed. If low-dose aspirin is used for the secondary prevention of CV events, patients should continue taking aspirin perioperatively. Withdrawing aspirin may increase the risk of serious thromboembolic complications. Usually, continuing with aspirin carries a minimal risk of perioperative bleeding, as compared to the risk of developing thromboembolic complications when aspirin is withdrawn. Procedures where the risk of withdrawal of aspirin is
justified include intracranial, middle ear, posterior segment of the eye, intramedullary spinal, and perhaps transurethral prostatectomy surgery.

_Gastric COX-1_

The protection of gastric mucosa by PGs is mediated by inhibition of acid secretion and increased production and secretion of mucus, bicarbonate and surfactant-like phospholipid. PGs also promote healing of gastric lesions. This function is mediated by hepatocyte growth factor (HGF) expressed in gastric mucosal cells. HGF stimulates gastric epithelial growth as well as the maintenance of gastric mucosa.

COX-1 is expressed constitutively in gastric mucosa. It is responsible for the production of the cytoprotective prostanoids PGE2 and PGI2. Gastro-duodenal ulceration in many patients taking tNSAIDs is ascribed to suppression of COX-1 activity. Although the inhibition of mucosal COX-1 is responsible for ulceration, the high grade inhibition of platelet COX-1 by tNSAIDs in some patients is responsible for serious haemorrhage, which may be fatal. Selective COX-2 inhibitors have a better safety profile since these spare both mucosal and platelet COX-1 activity. Therefore, the GI advantage of COX-2 selective inhibitors (coxibs) is lost when patients receive low-dose aspirin.

Regarding gastric cytoprotection, both COX-1 and COX-2 are essential in mucosal defence, where each has specific functions under various physiological and pathophysiological conditions. In normal gastric mucosa, inhibition of neither COX-1 nor COX-2 induces gastric lesions, but during pending injury (e.g. when the mucosa is exposed to acid), inhibition of COX-1 but not of COX-2 leads to mucosal lesions.

_COX-2 occurs both constitutive and inducible_ (mostly). Expression of COX-2 is low under basal physiological conditions. It is _constitutively_ expressed in several tissues, notably the kidney and brain. Therefore, COX-2 has regulatory functions under basal physiological conditions and does not only catalyse the production of mediators under nonbasal pathophysiological conditions (inducible).

COX-2 is induced in various cells, including monocytes, macrophages and endothelium. COX-2 is induced at sites of inflammation, infection and cancer. Induction occurs in response to inflammatory cytokines, endotoxin, vascular laminar shear stress and growth factors. The products of COX-2 activity include PGE2 and prostacyclin. In both physiologic and pathologic conditions, COX-2 is the rate-limiting enzyme in PGI2 biosynthesis. PGE2 and prostacyclin (PGI2) are involved in a variety of physiological and pathophysiological processes, such as renal haemodynamics, blood pressure control, resistance of the endothelium to thrombosis, pain, and triggers of inflammation, such as endotoxin.
COX-2 is involved in GI mucosal protection in concert with other factors, such as NO and afferent nerve function. Severe mucosal lesions develop when COX-2 is inhibited when the function of any one of these defence mechanisms is compromised. Moreover, isolated COX-2 inhibition harms gastric mucosa during ischaemia-reperfusion (an ubiquitous phenomenon during haemodynamic instability, when periods of hypoperfusion alternates with periods of reperfusion). This suggests that COX-2 is upregulated to attenuate ischaemia-reperfusion-induced injury. This effect is ascribed to the effect of the products of COX-2 on the regulation of cytokine release by inflammatory cells.

**The interaction between the effect of Helicobacter pylori and COX-2 should be remembered.**

The gastric mucosal toxicity of *H. pylori* infection involves release of inflammatory cytokines including IL-1, IL-6, IL-8 and TNFα. These cytokines increase vascular permeability, and leukocyte infiltration. *H. pylori* also stimulates gastric mucosa fibroblasts to produce COX-2 and PGE2. The latter probably stimulates production of HGF by gastric fibroblasts. Therefore, the bacterium induces the production of PGE2 and HGF, which decreases its mucosal toxicity. This counterbalance balance is called chronic gastritis and may be present without destruction of the mucosa. However, this counterbalance is easily disturbed by the inhibition of PGE2 and HGF production resulting in ulceration. This is probably the pathophysiology of NSAID-induced GI ulceration.

COX-2 selective inhibitors suppress PG and HGF released by gastric fibroblasts to the same degree as the non-selective COX inhibitors (tNSAIDs) and since COX-2 is important in the healing of gastric ulcers, these delay ulcer healing to the same degree as the non-selective inhibitors (tNSAIDs) do. The ulcer-preventing balance between the noxious effect of *H. pylori* toxicity (ulceration) and the protecting effect of PGE2 and HGF from gastric fibroblasts (cytoprotection and healing) is disturbed. Therefore, both tNSAIDs and selective COX-2 inhibitors swing the scale in favour of ulceration and delayed ulcer healing.

**Endothelial cells** form a dynamic barrier which reacts to local and systemic stimuli, such as platelets and inflammation as well as shear stress, generated by pulsatile blood flow along the arterial network. COX-2 is up-regulated by physiological laminar shear stress stimulation.

**Endothelial COX-2** controls the production prostacyclin, PGD2 and PGE2 of which PG12 is the most important prostanoid in the macrocirculation. Prostacyclin regulates the activation of circulating blood cells and underlying smooth muscle cells. It is a potent inhibitor of platelet aggregation, platelet TXA2 production, leukocyte-endothelium interactions, and vascular smooth muscle proliferation. It is a potent vasodilator that antagonises the vasoconstriction caused by TXA2.

Selective COX-2 inhibition is associated with an increased risk of MI, especially in patients (phenotype) who are dependent on the availability of PG12 (vasodilatation and decreased
platelet function). If these patients receive coxibs over a long time, an initial low risk for or stable ischaemic heart disease and peripheral vascular disease may lead to accelerated development of CV disease. Therefore, selective inhibition of COX-2-dependent endothelial PGI2 without inhibition of platelet COX-1 (production of TXA2) results in an increased CV risk. Dose reduction of these agents decreases their anti-inflammatory and analgesic efficacy. This is particularly important in vasculopaths, especially when presenting for surgery, including vascular surgery.

In the kidney, constitutive COX-2 is involved in renal perfusion and glomerular blood flow. In the medulla, it plays a crucial role in the regulation of a cardioprotective gene networks, which fulfils an important role in the CV adverse effects of NSAID (cardiorenal adverse effects). COX-2 inhibitors increase blood levels of asymmetrical dimethylarginine (ADMA), a naturally occurring endothelial nitric oxide synthase (eNOS) inhibitor, which contributes to the CV adverse effects of NSAI Ud. These include the development of new hypertension and deterioration of renal function, especially in patients with underlying renal failure, hypertension, concomitant treatment with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor antagonists (ARA), and elderly patients.

**Pharmacodynamic classification of COX inhibitors**

The COX-1 and COX-2 selectivity of NSAIDs are determined by measuring its IC50s. The IC50 is the concentration of the drug to decrease the activity COX-1 and COX-2 by 50%. The lower the IC50, the more selective (a low concentration can inhibit the particular COX); the higher the IC50, the less selective (a higher concentration is needed to inhibit the particular COX). From these findings COX-1/COX-2 IC50 ratios were calculated. Therefore, the lower the COX-2s IC50, the higher the COX-1/COX-2 IC50 ratio and the higher COX-2 selectivity.

These ratios demonstrate that selectivity is a continuum; from pure COX-1 to pure COX-2 selectivity. In between selectivity varies between balanced (non-selective) blockers, such as the tNSAIDs ibuprofen, ketoprofen, flurbiprofen and naproxen towards COX-1 and COX-2 activities. However, the group of COX-2 selective (COX-2 CI50 < COX-1 CI50) also includes the tNSAIDs meloxicam and diclofenac. In vitro, the IC50s of diclofenac indicates that it is approximately 29 times more COX-2 than COX-1 selective. Regarding the selective COX-2 inhibitors (coxibs) the ratios vary: celecoxib 30, valdecoxib (the active metabolite of parecoxib) 61, rofecoxib 272, and etoricoxib 344. However, plasma concentrations necessary for therapeutic effect may be much higher than their in vitro IC50s (e.g. daily doses of ibuprofen and naproxen inhibit both COX-1 and COX-2 by 80% [not 50%]). Similar observations have been made regarding COX-2 selective inhibitors.

Note that diclofenac has a ratio of 29 and celecoxib of 30. These also demonstrate similar pharmacodynamics; namely, these do not affect the antiplatelet effect of low-dose aspirin, and display similar long-term GI and CV adverse effects.
All the NSAIDs increase the alternative pathway from AA to leukotrienes. Leukotrienes, also involved in inflammation, are powerful bronchoconstrictors and increase vascular permeability causing tissue oedema. Leukotrienes are involved in allergic reactions, rhinitis and asthma.

Cross-hypersensitivity to NSAIDs (including aspirin) may exist. Patients at risk to develop allergic reactions include asthmatics and patients suffering from rhinitis, as well as patients with nasal polyps. Allergic reactions are more common in NSAIDs with sulphonamide in its molecule, including all the oxicams and coxibs.

From the above discussion, it should be clear that NSAIDs, from tNSAIDs (balanced COX-1/COX-2 inhibitors) to selective COX-2 inhibitors, should be prescribed taking into account (patho) physiological and pharmacological factors in the particular patient.

The patients who are at risk are the following:

- Those with any cardiac disease (elderly, ischaemic, failure).
- Those with any vascular disease or haemodynamic disorders (elderly, hypovolaemia, dehydration, hypertension, atherosclerosis, peripheral arterial disease, cerebrovascular disease, renovascular disease, diabetes mellitus). NSAIDs should not be administered pre- or intraoperatively if conditions are foreseen that will cause intraoperative haemodynamic instability (especially hypotension), particularly in patients with preexisting vital organ dysfunction. These conditions include use of antihypertensive agents (ACEIs, ARAs and diuretics), and hypovolaemia. Intraoperative conditions include large fluid shifts, the type of surgical intervention (e.g. aortic cross-clamping), deliberate hypotension, and administration of IV radiocontrast. All these conditions may compromise vital organ function in patients with premorbidity – in particular myocardial ischaemia, kidney failure and liver failure. NSAIDs should not be administered intra- or postoperatively in patients undergoing free flap surgery since they have been implicated in flap failure (thrombosis of the vascular pedicle).
- Those with any renal disease, including elderly patients, hypertension, diabetes, hypovolaemia or dehydration (physical exertion, such as running). Remember the dangerous triad NSAID + diuretic + ACEI/ARA.
- Those with a history of gastritis or GI ulceration (consider coprescribing a PG [misoprostol], a proton pump inhibitor [PPI] [esomeprazole], or an H2-blocker [ranitidine]).
- Those with a history of rhinitis or asthma.
- Those with bleeding disorders (concomitant use of antithrombotic agents and anti-platelet agents). These drugs are not contraindicated in patients taking low-dose aspirin or on thromboprophylactic low-molecular-weight heparins (LMWHs). In fact, low-dose aspirin protects against the CV side effects of the coxibs – but eliminates its (alleged) GI advantage. Since all the NSAIDs are highly plasma protein bound, it can displace warfarin from albumin, which increases the free fraction of warfarin resulting in an increased INR. Moreover, a low plasma protein level increases their free fractions, which increase their toxicity. This should
be taken into account in patients that undergo haemodilution (resuscitation fluids, fluid retention).

- NSAIDs should be avoided in pregnancy, especially during the first and third trimester.

**Pharmacokinetics of NSAIDs**

The pharmacokinetics of NSAIDs vary between and within chemical groups. In general, the following principles should be remembered:

- These are acids.
- These are absorbed from the stomach where it can cause local irritation. Therefore, these should be taken with food, although food may dilute the drug, which may delay absorption. **However, its effect on cytoprotection is a systemic effect and is not prevented by IV or rectal administration.**
- These are highly plasma protein-bound (mainly albumin). Therefore, these drugs have a low volume of distribution (Vd). Therefore, doses should be calculated according to ideal or lean body mass. Moreover, these can displace other highly protein-bound drugs, notably warfarin and oral hypoglycaemic agents (the sulphonylureas).
- These are metabolised in the liver to inactive metabolites and excreted by the kidneys. Therefore, if used at all, patients with significant liver and kidney impairment should not receive these drugs.
- Elderly patients have a lower lean body mass, decreased clearance of drugs and should therefore receive lower doses.

**Analgesic equivalence of NSAIDs and routes of administration**

NSAIDs have similar analgesic effects at equivalent doses and are useful for the treatment of acute moderate to severe pain, and provide better analgesia during mobilisation than opioids. Regarding bone fractures and orthopaedic procedures, little evidence supports a detrimental effect of NSAIDs on bone healing, but these should be limited to a few days.

NSAIDs are all opioid-sparing and lack the adverse effects of opioids, namely sedation, nausea, vomiting, dizziness and confusion – the latter two especially in elderly patients.

Not all the analgesic effects of NSAIDs are explained by its effect on peripheral nerve endings, that is at the site of injury. These also affect COX activity in dorsal root neurons (afferent neurons) outside the blood–brain barrier (BBB), as well as in the CNS (spinal cord and brain) inside the BBB. Since most of these agents are highly hydrophilic, the latter mechanism has been questioned. However, diclofenac affects dorsal root neurons and parecoxib crosses the BBB and may contribute to analgesia – similar to that of paracetamol.
An NSAID may be administered preoperatively (p.o. or IV; in the ward or during induction of anaesthesia) or intraoperatively. Preoperative administration attenuates the inflammatory response before tissue injury starts and may contribute to better postoperative analgesia and mobilisation. Etoricoxib 1.5 mg/kg (90–120 mg) p.o. preoperatively is an effective analgesic for more than 20 hours.

Postoperatively, it is unnecessary and expensive to continue with IV NSAIDs. If a patient is NPO and receives IV fluids only, the safety of any NSAIDs is questionable. Several NSAIDs can be given p.o., IV, IM, as well as rectally, topically, as surgical site infiltration and intra-articularly. The route of administration does not affect its efficacy and adverse effect profile. However, the latter three applications provide better analgesia with lower drug blood levels.

The following NSAIDs can be administered IVI:

- **Ketorolac** is a balanced (COX-1:COX-2) inhibitor. It is available in both IV and oral formulations. The dose is 0.5 mg/kg (one 30 mg injection) followed by about 0.15 mg/kg (one 10 mg injection) 6-hourly, with a maximum of about 1 mg/kg/day (0.8 mg/kg/day in the elderly).
- **Lornoxicam** is a balanced (COX-1:COX-2) inhibitor. It is available in both IV and oral formulations. The IV dose is 0.1 mg/kg bd.
- **Parecoxib** is a COX-2 selective inhibitor available as injection only. The dose is 0.5 mg/kg followed by 0.5 mg/kg 12-hourly.
- **Diclofenac** can be given IV as a buffered solution over 15–60 minutes – no bolus IV injection. The LD is 0.5–1.0 mg/kg in 200 ml of a buffered solution, followed by an infusion of 70 µg/kg/h not exceeding a dose of 2 mg/kg/hour. The buffered solution is prepared as follows: add 0.5 ml of an 8.4% sodium bicarbonate injection (or 1 ml of 4.2%) to 200 ml of sodium chloride 0.9% solution or glucose 5% solution. Discard the solution if crystals or precipitates are observed after the addition of diclofenac.

The following oral (or rectal) NSAIDs are useful postoperatively:

- **Diclofenac**: 0.7 mg/kg 8-hourly with a maximum of 2 mg/kg/day. In patients with a history of peptic ulceration, the diclofenac/misoprostol combination is safer.
- **Lornoxicam**: 0.1 mg/kg 12-hourly; a fast-acting tablet is available.
- **Ibuprofen**: 4–5 mg/kg 6-hourly to a maximum of 20 mg/kg/day. Several combinations with paracetamol and paracetamol as well as codeine are available.
- **Naproxen** is a balanced COX-1/COX-2 inhibitor. Different from other tNSAIDs, it blocks platelet COX-1 activity > 95%, which decreases CV risk. This anti-cytoprotective gastric effect is prevented by the co-formulation with esomeprazole. Naproxen/esomeprazole 500/20 mg is taken 12-hourly and it can be given preoperatively.
- **Etoricoxib**: 1–2 mg every 24 hours and it can be given preoperatively.
Dexamethasone

Glucocorticoids are anti-inflammatory by blocking PLA2, which prevents the formation of AA, and therefore of PGs. This glucocorticoid is a potent, long-acting steroid that is also used as part of multimodal antiemetic treatment postoperatively. A single antiemetic dose of approximately 0.15 mg/kg at induction, is opioid-sparing for at least 24 hours. It has not been associated with glucocorticoid adverse effects.

Opioids

Opioids are used to treat moderate to severe pain. Opioids are often prescribed ‘when necessary’ for fear of accumulation and respiratory suppression. On the other hand, prescribing an opioid at fixed intervals may result in opioid plasma levels that vary between excessive (overdose) and insufficient (pain). This problem may be overcome by PCA, constant drug infusion and sustained-released drug formulations. The former two methods should preferably be offered in HCU's where patient surveillance is more reliable.

All the opioid agonists (morphine, codeine, dihydrocodeine, oxycodone), buprenorphine, a dualist (tilidine), and atypical opioids (tramadol and tapentadol) are widely used in a wide variety of pain scenarios. Buprenorphine at lower doses (such as used for postoperative analgesia) is a potent agonist (about 30 times more potent than morphine), but it is a dualist/antagonist at high doses. However, all of these share the same dose-dependent dangers (respiratory depression, sedation, hypotension) and troublesome adverse effects (nausea and vomiting, constipation). All opioids are addictive (except dualist buprenorphine that is used in opioid addicts). The sedative effects of this group of analgesics should be taken into account in patients with a history of OSA. All opioids suppress respiration and should be prescribed cautiously in a patient who is dependent on the central drive of respiration by CO₂ (lung disease) or with increased intracranial pressure. Morphine releases histamine, causing a maculopapular rash along the vein if given IVI, or at the site of injection if given subcutaneously. The histamine may provoke bronchospasm in sensitive patients.

What dose of opioid is prescribed?

Doses should be individualised to provide adequate analgesia at the smallest dose to minimise adverse effects. This strategy decreases the adverse effects and misuse. Respiration and blood pressure should be closely monitored for the first 24–72 hours and following dose increases.

Co-prescribing different opioids may theoretically be justified (e.g. α μ agonist such as morphine plus α μ and κ agonist such as oxycodone). However, this combination has not proven useful. Combining different opioids should be avoided. On the one hand, its intrinsic activity (full agonist or dualist) at, and affinity for, opioid receptors may differ. Therefore, the effect of two agonists may be increased (more adverse effects), or the effect of a dualist with a high
affinity may decrease the effect of the full agonist. However, opioids which act on more than one opioid receptor may have favourable effects. Oxycodone (µ + κ agonist + serotonin agonist) may be a better analgesic for visceral pain. The combination of buprenorphine and tramadol have an additive analgesic effect and improved analgesia in a patient with an opioid abuse disorder stabilised on buprenorphine (usually transdermal patch).

Tramadol deserves some comment. Tramadol is a serotonin and noradrenaline reuptake inhibitor and releaser. It is a weak opioid and often regarded as a safe opioid with fewer adverse effects and addiction potential. However, the active metabolite of tramadol is a potent opioid responsible for the risk of abuse, where short-term use becomes prolonged abuse, similar to other opioids.

The parent drug tramadol is a weak opioid, while the analgesic effect is related to the inhibition of norepinephrine and serotonin reuptake. However, in the liver, it is metabolised to desmetramadol (O-desmethyltramadol) by the CYP2D6 enzyme. The affinity of desmetramadol for µ-receptors is 700 times greater than that of tramadol, and is similar to that of morphine, and is responsible for its abuse potential.

Polymorphisms of CYP2D6 influence the metabolism of tramadol to desmetramadol and varies from 3% in poor metabolisers to 86% in extensive metabolisers. Therefore, the extensive metabolisers may be more prone to addiction to tramadol. Although tramadol is a Schedule 5 drug, desmetramadol is an opioid similar to morphine and oxycodone, which are Schedule 6 opioids. Therefore, the number of tramadol capsules and tablets on discharged prescriptions should be limited to not more than 10 units.

• **Codeine** on its own is a poor analgesic. Approximately 10% is metabolised to its active metabolite morphine. This metabolic path is under genetic control and much larger fractions may be metabolised to morphine. Therefore, the analgesic activity is unpredictable. It is usually included in analgesic combinations with paracetamol and an NSAID, such as ibuprofen.

• **Morphine chloride** oral solution (1, 2 and 5 mg/1 ml). The oral dose is approximately 25 µg/kg 4-hourly.

• **Morphine sulphate** injection (10 and 15 mg/ml). The IV dose is 50 µg/kg every 5 minutes until the VAS is < 30/100 mm. This is followed by an infusion of approximately 50–100% of the titrated dose/hour and titrate down or up by approximately 15%. The dose varies between 50 and 300 µg/kg/h.

• **Tramadol** (50 and 100 mg capsules and injection). IV loading (if necessary) with up to 1.5 mg/kg followed by 0.7 mg/kg every 30 minutes up to a maximum of 3 mg/kg. This is followed by 0.7–1.5 mg/kg 4–6-hourly p.o. (or intravenously) to a maximum of 8 mg/kg/day.

• **Tapentadol** (50 and 100 mg tablets). 0.7–1.5 mg/kg 4–6-hourly.
- **Buprenorphine** (0.2 mg [200 µg] and 0.4 mg [400 µg] SL tablets and 0.3 mg [300 µg] injection). The dose is 3–5 µg/kg sublingually or intravenously 6–8-hourly.
- **Tilidine** (50 mg capsules and drops with 2.5 mg/drop). The dose is 0.8 mg/kg 6-hourly.
- **Oxycodone hydrochloride.** Oxycodone base and morphine base are approximately equipotent. Oxycodone HCl 10 mg Oxycodone base 9 mg.
- Immediate-release tablets (5, 10 and 20 mg): 0.07–0.15 mg/kg 4–6-hourly.
- Prolonged-release tablets (5, 10, 20, 40 and 80 mg). This preparation is not indicated for acute postoperative pain, but for palliative care. The dose (according to the level of tolerance) is one tablet 12-hourly.
- SR tablets with oxycodone/naloxone 5/2.5 mg, 10/5 mg and 20/10 mg. Naloxone has an oral bioavailability of less than 2% and blocks opioid receptors in the GIT. It is included to counteract constipation (opioid tolerance does not develop to constipation) and to prevent IV abuse. The tablet releases oxycodone in two peaks; one at approximately 40 minutes and at 7 hours. The dose is approximately 0.3–0.6 mg/kg around the clock 12-hourly.
- For breakthrough pain, the 0.7 mg/kg 4-hourly of the short-acting oxycodone can be given in between, keeping in mind the peak delivered by the SR tablet is at about 7 hours. The maximum dose is approximately 1.0 mg/kg 12-hourly.
- **Oxycodone injection.** 10 mg oxycodone chloride is titrated postoperatively and maintained in an HCU or the ICU. The titration dose is 50–100 µ/kg over 2 minutes. This dose can be given 4-hourly or followed by an infusion of approximately 2 mg/hour (approximately 25 µg/kg/h).

**Please note: sedatives are not analgesic and should not be co-prescribed with opioids.**

The following drugs and drug combinations should be avoided:

*Pethidine* is a dirty drug renowned for nausea and vomiting as well as increase in heart rate and increased peripheral resistance. Moreover, its active metabolite accumulates in patients with renal failure.

*Sedation, delirium, hypotension and dizziness* may be troublesome and dangerous in elderly patients. Falls in these patients give rise to head injury and fractures. There is a significant association between hip fractures and elderly patients receiving tramadol or meprobamate.

*Sedatives* such as the benzodiazepines suppress the peripheral drive of respiration in the carotid body and aortic arch by a low arterial PO₂ and acidosis. Therefore, co-prescribing opioids and benzodiazepines can cause severe respiratory suppression.

*Sedatives* in analgesic combinations are unnecessary and dangerous. These include the sedative antihistamines such as hydroxyzine, doxylamine, and phenothiazines such as promethazine, and the anxiolytic meprobamate. These sedatives cause sedation and delirium, especially in...
elderly patients, which contribute to falls. **Meprobamate is addictive and has been withdrawn from the market in Canada and Europe.**

Sedatives increase the risk of respiratory complications, especially in elderly patients, obese patients, and patients with OSA (enquire about snoring).

**Tramadol** should not be prescribed for patients receiving an SSRI, serotonin and noradrenalin reuptake inhibitor antidepressants (SNRIs), or monoamine oxidase inhibitor (MAOI). Tramadol in combination with an SSRIs can give rise to hyperserotonergic syndrome (HS) that can be fatal. Tapentadol has also been implicated. Although sertraline inhibits the transformation of tramadol to its active metabolite, which is responsible for its effect on µ-receptors, the serotoninergic and noradrenergic mechanisms of analgesia is not affected. Other analgesics with serotoninergic effects and which have also been implicated are fentanyl, oxycodone, pethidine, codeine, buprenorphine and ketamine. Although HS is not often diagnosed, it should be considered in patients receiving analgesics and presenting with a change in mental status, increased muscle tone or autonomic instability.

The diagnosis of HS is made in a patient who has received serotonergic agents and may vary from subtle psychiatric signs to the complete life-threatening syndrome.

HS is a triad of clinical signs consisting of the following:
- **Mental status and neurological signs:** restlessness, confusion, anxiety, agitation, hypomania, hallucinations, convulsions and coma.
- **Neuromuscular:** muscle rigidity, trismus, tremors, hyperreflexia, myoclonus, ocular clonus, nystagmus and ataxia.
- **Autonomic instability:** tachycardia, hyper- or hypotension, tachypnoea, diarrhoea, mydriasis, sweating and hyperthermia.

Management of HS consists of discontinuation of the suspected agents, administration of antiserotonergic agents (oral cyproheptadine or IV chlorpromazine), sedative-anticonvulsants such as a benzodiazepine, neuromuscular blockade, and intubation and ventilation.

Being a serotonin agonist, tramadol causes severe nausea in some patients. The analgesic effect of tramadol is antagonised by the 5-HT3 receptor antagonist antiemetics, such as ondansetron.

The sedative effect of other opioids is increased by MAOIs and patients may fall into a deep coma.

**13.6 Other measures to avert postoperative pain**

Mechanisms underlying severe postoperative pain may include sociodemographic influences, previous postoperative pain experiences, surgery-related variables (some procedures are more painful than others) and psychological factors. Patients with better coping mechanisms
with preoperative pain, usually experience less postoperative pain. In this regard, adequate preoperative analgesia and CBT may be useful. It has been demonstrated in patients undergoing lower limb amputation, that preoperative anxiety is associated with more postoperative acute phantom limb pain. Preoperative anxiety affects the patients’ ability to cope with pain. Catastrophising may aggravate postoperative pain experiences. These patients may benefit from anxiolytics.

13.6.1 The discharge prescription

The aim of the discharge prescription is to bridge the in-hospital moderate to severe pain to minor to moderate pain that justifies discharge. The former requires high doses of potent analgesics, while the latter should be managed with a time-limited multimodal analgesic prescription, usually consisting of paracetamol, an NSAID and a limited number of opioids for breakthrough pain. The discharge prescription should not turn into a long-term abuse of analgesics. It is not uncommon to find patients who remain on opioids and sedatives for years postoperatively.

A higher in-hospital total dose of opioids predicts the number of MMEs prescribed on the discharge prescription and use after discharge. Opioid use after discharge is predicted by younger age, men, lower socio-economic status, baseline preoperative substance abuse, admission to ICU, and the number of MMEs on the discharge prescription. Opioid use after discharge can be limited by limiting the number of MMEs prescribed postoperatively. In-hospital strategies can be used to achieve this goal, namely multimodal analgesia, decreasing the daily MMEs while in hospital, and physical interventions to decrease swelling (limb elevation and cold therapy).

The number of opioid tablets should be limited. It has been demonstrated that for patients who received paracetamol and ibuprofen, 5 tablets oxycodone 5 mg (7.5 mg MME) were enough to manage breakthrough pain after laparoscopic cholecystectomy and appendicectomy. It has also been demonstrated that patients discharged from the emergency department, took a median of < 10 tablets of morphine sulphate 5 mg MME and that 15 tablets of MME 5 mg were enough in 95% of patients for the first three days. Physicians should prescribe smaller quantities of opioids and ask the pharmacist to supply the total number of tablets in portions. This may minimise the number of unused units. If surgery was of a palliative nature, opioids should not be limited.

13.7 Specific considerations in different surgical disciplines

13.7.1 General surgery

Local anaesthesia and regional anaesthesia, especially epidural analgesia after laparotomy, should be offered whenever possible.
13.7.2 Vascular surgery

Patients presenting for vascular surgery often suffer from several comorbidities, including hypertension, ischaemic heart disease, lung disease, renal impairment and diabetes mellitus. Hence, the use of NSAIDs, including coxibs, is discouraged. Opioid narcotics and paracetamol are generally safe in the majority of vascular patients. Regional, spinal and epidural anaesthesia are also encouraged in these patients, in that the concomitant sympathectomy causes vasodilatation and improves peripheral perfusion.

13.7.3 Cardiothoracic surgery

Postoperative cardiac surgery patients are usually admitted to an ICU. Powerful, titratable narcotics, such as fentanyl derivatives or morphine, are routinely used initially. Paracetamol is safe and should be used.

NSAIDs are effective analgesics after thoracic surgery but are contraindicated after cardiac surgery and in anticoagulated patients. Cardiac output and renal function are often compromised after cardiac surgery, which preclude the use of NSAIDs.

Neuraxial blockade is useful but contraindicated when anticoagulants or therapeutic anti-platelet agents are used.

13.7.4 Neurosurgery

Pain control after neurosurgery is managed in a similar manner than in other scenarios, that is, with a multimodal approach. Issues that warrant special mention are that accurate neurological assessments and level-of-consciousness monitoring may be severely impaired by the sedative adverse effects of opioid narcotics. Sedation may be desirable in certain circumstances (e.g. reaction to external stimuli can increase ICP). On the other hand, sedation can cause hypotension, which can compromise cerebral perfusion pressure.

Adverse effects of opioids may be problematic. Opioids increase vomiting in patients with intracerebral tumours and/or raised ICP. Patients with spinal cord lesions often suffer from constipation (due to spinal cord injury, autonomic dysfunction and prolonged bed rest), which is exacerbated by opioids.

NSAIDs should be used cautiously in neurosurgical patients, since postoperative surgical haemorrhage may be disastrous. Furthermore, there is a high incidence of peptic ulceration due to chronic NSAID usage (spinal patients), stress ulceration (head injury patients), irregular enteral feeding and concomitant steroid therapy (patients with raised ICP). NSAIDs should be used cautiously in patients at risk of dehydration, including diuretic therapy for raised ICP and diabetes insipidus.
13.7.5 Orthopaedic surgery

Orthopaedic procedures are particularly painful procedures, and pain control is vital to allow for early mobilisation, prevent complications (DVT, PE, contractures and pressure sores) and decrease chronic pain syndromes. Opioids are usually prescribed, either orally or using PCA. NSAID therapy is efficacious in these patients, but needs to be used judiciously.

Orthopaedic patients often take NSAIDs chronically. Between 1% and 5% of these patients run the risk of postoperative GI bleeding. Therefore, a history of GI ulceration must be excluded. If NSAIDs are prescribed postoperatively, especially after major orthopaedic procedures, a PPI, misoprostol or ranitidine should also be prescribed.

If a patient is admitted to an HCU or the ICU postoperatively, a low-dose ketamine is morphine-sparing. Ketamine 0.12 mg/kg/h IVI is effective after hip arthroplasty. It facilitates rehabilitation and decreased pain for up to 6 months after surgery.

The intra-articular instillation of opioids, LAs and corticosteroids in joint surgery, day case arthroscopy and joint injury is controversial, and evidence is conflicting. There is evidence that supports intra-articular opioid instillation after some orthopaedic procedures.

Regional and neuraxial blocks are particularly useful in the early postoperative period. Routine postoperative prophylactic anticoagulation does not contraindicate epidural analgesia.

13.8 Acute burn injuries

Burn wounds are caused by thermal injury (flame, scalds, explosives or any hot material), cold injury (frostbite), electrical shock, chemicals or radiation.

Depending on the extent of injury, burn injury is probably the most drastic insults regarding pain, anxiety, number of procedures and duration of hospitalisation. Burn injuries often have vast anatomical and physiological complications. It is probably the type of trauma that can launch the biggest stress response. These patients have suppressed immunity, are prone to infection and have special nutritional demands. Moreover, burn injury is renowned for severe and protracted pain. Each of these aspects form part of the management and caregivers must be cognisant of the behaviour of burns: these aspects vary over time, which necessitates adjustment of management.

Although anatomical and physiological aspects take preference during immediate (resuscitation, early wound care, management of associated injury) and subsequent management, analgesia should be part of immediate/early management. It is not only anatomically and physiologically necessary, but also humane – even in patients with a poor prognosis.
Poorly managed pain aggravates the stress response and the subsequent sequelae. Inadequate early analgesia leads to the development of chronic pain. Moreover, the psychological consequences such as anxiety, depression and posttraumatic stress disorder can impact on the healing process.

13.8.1 Evaluation and classification of burn wounds

Burn injury can be trivial and the patients are usually discharged home with advice regarding wound care and analgesics such as paracetamol, an NSAID and codeine.

Evaluation of the burn patients is the same as that of other trauma patients: anatomically (issues associated with burn injury such as the face, airway, circumferential and torso burns) and physiologically (including breathing and circulation), as well as pharmacologically/toxicologically. These aspects will determine the appropriate investigations and interventions. Burn-specific evaluations include the mechanism of injury (thermal, chemical, inhalation or electrical) and a physical examination to exclude associated injuries, including inhalational injury.

Burn wounds are classified according to their extent (body surface area) and depth. However, wounds are usually not uniform in depth, varying from deep (third-degree) in the centre to partial-thickness (second-degree) and superficial (first-degree) at the periphery, and are often underestimated regarding depth and area. Therefore, the initial grading of wound depth and area affected does not necessarily correlate with pain intensity. This may also vary while healing takes place or when infection sets in. Nonetheless, classification according to depth and area directs initial management regarding resuscitation and wound management.

In children, associated trauma and distribution of burns, lesions indicative of previous injury, conflicting stories and delayed presentation for help, can indicate the possibility of drug misuse. This should be referred for further investigation.

The following are the classifications of burn wounds:

- **First-degree (superficial)** burns are damage to the epidermis and are often caused by intense sun exposure. The wounds are red and dry. Since the cutaneous nerves are intact, these wounds are may be very painful.

- **Second-degree (partial-thickness)** burns involve the dermis (‘dermal burns’) and do not penetrate beyond the dermis and are either superficial or deep. This depth of injury is seen typically after exposure to hot liquid or steam. These wounds have fluid-filled blisters and are red and wet, and since deeper nerves may be spared, the wound may be excruciating.

- **Third-degree (full-thickness)** burns extend beyond the dermis to the SC tissue, muscle, tendons, joints and bone. These wounds are usually caused by a flame or prolonged exposure to any hot material. The wounds are dry and leathery, and since all nerves have been destroyed,
these are insensate. However, shallower burns and inflammation at the periphery cause severe pain. Furthermore, when nerve regeneration starts, neuropathic pain may set in.

• Circumferential wounds of the torso and limbs may cause hypoventilation and ischaemia, respectively.

13.8.2 Pain in the burn victim

Pain experienced directly after injury usually differ from pain that patients experience during the healing process. It can either improve or increase in intensity and character, becoming more complex and chronic.

Pain evolves during management and healing. Management of burn wounds involves wound debridement and skin grafts. These procedures cause further tissue injury and acute pain, which may be worse than the original wound. Nerve injury and regeneration cause protracted neuropathic pain, manifesting as tingling and itching.

It is important to believe the patient regarding their pain intensity. Complete absence of pain is preferable, but often not attainable – except under GA. Analgesia is adequate when the pain level is a VAS ≤ 3/10, the patient is comfortable, and the pain does not interfere with nighttime sleep.

It must be stressed from the outset, that early and adequate multidisciplinary pain management is essential. Adequate wound care prevents physical scaring, but psychological scarring should also be prevented. Psychological scarring results from pain (it is inhumane to tolerate pain in patients), anxiety, experience of disfigurement, loss of function (and limbs), prolonged hospitalisation, loneliness, financial and educational losses, etc. Management of all these aspects from the outset ensures less pain and better functioning over different fronts after discharge. The larger and the more disfiguring the injury (face, head, neck, hands, perineum), the higher the morbidity and challenges.

13.8.3 Analgesia is required in the following scenarios

• Immediate pain
• Background pain and breakthrough pain
• Procedural pain
• Chronic pain

In all these circumstances, changes in pharmacokinetics (vasoconstriction, hypovolaemia, anaemia, hypoalbuminaemia, weight loss) and pharmacodynamics (multimodal analgesia, tolerance) should be kept in mind.
Immediate pain

Immediate pain and the efficacy of analgesics are determined by the nature of injury (depth, area and other injuries), previous experience, anxiety and drug tolerance. Immediate pain is aggravated by the initial evaluation process. This pain should be minimised by prompt IV analgesia.

IV opiates are usually indicated for large wounds. Incremental doses of opiates (usually morphine sulphate) are titrated until the patient is comfortable and less anxious (VAS of approximately 3/10). The titration dose of morphine sulphate is 50 µg/kg every 5 minutes. In the absence of IV access, oxycodone 5–10 mg p.o. or buprenorphine 0.2–0.4 mg sublingually can be used. PCA may be offered in the acute setting. Paracetamol 15 mg/kg is administered p.o. or IV. NSAIDs are not safe during the period of resuscitation (hypovolaemia, pigmenturia).

Background and breakthrough pain

Background pain occurs at the site of injury and skin donor sites and is constantly present between interventions (wound dressings, physiotherapy, surgery). Breakthrough pain occurs when background pain is adequately addressed but not pain during movement, physiotherapy, etc. The intensity and character of pain varies from day to day and over time depending on healing, interventions, complications, inappropriate analgesia (caregivers’ misconception about addiction and tolerance) and mood. Background pain can persist even after the wounds have healed. Over time, background pain may become more intense, change in character (chronic pain), and is often accompanied by itching, which is indicative of nerve regeneration (neurogenic pain).

Protracted background pain can, to some extent, be prevented by early and appropriate analgesia and non-pharmacological measures. Therefore, comforting patients (analgesia, anxiolysis and psychotherapy) must be individualised according to pain intensity and character, complications and healing. To this end, pain intensity and character monitoring during the day and day-to-day must be used to preempt exacerbations of pain to prevent chronicity.

Managing background and breakthrough pain

Multimodal analgesia must be used. Adequate and timely management of background and breakthrough pain improves pain associated with wound interventions. Patients are less apprehensive since they are confident that their pain will be addressed adequately. Therefore, it is advised that preemptive doses of analgesics be allowed before wound care procedures. Nighttime sleep is important. If pain is responsible for insomnia, it must be addressed; if it is caused by anxiety or depression, it must be managed. As healing progresses, background pain and anxiety decrease and the patient may get more involved in wound care and active
movement physiotherapy without the need for analgesics and sedatives. Patients who are treated on an outpatient basis must follow the same principles as inpatients.

The ladder approach applied for postoperative pain is followed for background pain, namely paracetamol; paracetamol + NSAID; paracetamol + NSAID + opioid. If burn injury has justified hospitalisations, opioids are usually appropriate from the beginning. Long-acting opioids are useful. Of course, patients who are admitted for observation (e.g. facial or inhalational injury), do not necessarily need opioids.

Analgesics must be given around the clock, but adult patients (and even children) must, over time, be allowed to manage their own analgesia; they may refuse analgesics if they are comfortable, but analgesics must be available to allow for doses of opioids preemptively as well as for breakthrough pain.

**Breakthrough pain** and preemptive analgesia can be afforded with shorter-acting analgesics such as morphine sulphate or morphine chloride syrup and oxycodone.

Adjuncts such as pregabalin (it is opioid-sparing and addresses emerging central hyperalgesia of neuropathic pain), clonidine, antidepressants (amitriptyline, not more than 75 mg daily, at night), and anxiolytics may be added. Subcutaneous ketamine has been used in the hospice setup for the triad of depression, anxiety and chronic pain. Oral ketamine has also been used, but more prospective studies are needed to prove its efficacy and safety. The dose of racemic ketamine that has been used is 0.5 mg/kg p.o. 8-hourly.

**Procedural pain**

Additional tissue trauma during wound management, such as wound dressings, debridement, skin grafting, as well as physiotherapy, is unavoidable. For these procedures, preemptive analgesia is required (see above), as well as postoperative analgesia if the procedures are done under GA. Hyperalgesia in both the healing and the newly traumatised parts will be aggravated, and background pain will often shift to a higher level. However, wound dressing and sloughectomy may improve pain. Therefore, analgesia should be adjusted after wound interventions. The frequency of these intercurrent procedures decrease over time, but may contribute to sustained background pain and subsequent chronic pain.

**Managing procedural pain**

Depending on the extent of injury and degree of healing that has taken place, procedures can be done without any extra analgesia or sedation, under sedation, or under GA.

When done under sedation, preemptive analgesia and/or sedation may be necessary. Paracetamol and NSAIDs must be given as close as possible to the procedure. Analgesia and sedation are achieved with a dose of opioid used for breakthrough pain and a sedative administered approximately 30 minutes before wound care.
Sedation can be accomplished with midazolam and the opioid-sparing sedative analgesics ketamine and dexmedetomidine (which are very expensive). Opioids and ketamine are administered p.o. or IV. IV sedation using propofol and short-acting opioids can be used, but should preferably be done in the operating theatre and by an anaesthesiologist.

When using ketamine or other potent sedatives, patients should be NPO for 6 hours. Keep in mind that opioids slow gastric emptying. Therefore, dressings should be done early in the morning or 6 hours after early breakfast. Patients must eat lunch.

One of the following regimens may be used:

- **Ketamine**
  - *IV ketamine combined with an opioid* (the opioid is administered p.o. 30 minutes before or IV just before the procedure): ketamine approximately 1.0 mg/kg IV with additional doses of 0.1 mg/kg IV. Midazolam 0.05 mg/kg IV may also be added.
  - Without *venous access* and with *preemptive opioids*: 0.5–3.0 mg/kg (2.5 mg/kg) p.o. approximately 15 minutes before wound care. (This is much lower than the dose of 5–10 mg/kg needed for procedural sedation in children.) Midazolam approximately 0.1 mg/kg p.o. (the oral bioavailability is about 50%) can be given.
  - Without *an opioid*: 6 mg/kg p.o.
- **Dexmedetomidine** 4 µg/kg p.o., but it is less effective than ketamine.
- A methoxyflurane inhaler has been used with success, but should be studied further in this setting. This method is probably useful in the outpatient setting.
- If more extensive wound care involving GA is done, postoperative analgesia should be tailored to the procedure and preoperative needs.

**Chronic pain after burn injury**

Chronic pain correlates with wound area, depth, the efficacy of wound care, analgesia, management of psychological issues, and complications such as scarring, contractures and nerve entrapment. Amputation often results in phantom pain. Some patients experience pain at the site of injury after the wound has healed. Opioids, antidepressants (SSRIs, amitriptyline) and antiepileptics (gabapentin and pregabalin) are used.

*Itching* in or around the healing wounds or in scars (keloid) commonly occur and may persist for decades after injury. Scratching damages healing wounds and normal skin. Itching is either a manifestation of local mediators such as histamine and prostanoids secreted in healing tissue or may be a manifestation of central or peripheral neurogenic origin (an indication of neuropathic pain). Itching is often aggravated by movement, heat and psychological factors. *It is managed* by skin cooling, fragrance-free skin moisturisers, oral antihistamines (cetirizine), NSAIDs, gabapentanoids, antidepressants such as amitriptyline, and topical anaesthetics. Several antihistamines are anxiolytic and sedating and improve nighttime sleep.
13.9 **Headaches**

13.9.1 **General considerations: primary and secondary headaches**

Acute headaches account for approximately 8% of visits to the emergency department. Common headaches occur generally, but when a patient presents with a new-onset (something else) severe headache, it should be managed as an urgent matter. Delayed diagnosis and management may have catastrophic consequences. Some of the headaches discussed in this section occur rarely, but should be considered to prevent morbidity and mortality.

The patient may present with either an old or a new problem. However, the new headache may be the first of recurring headaches, or the headache may be different from the known recurring headaches. The pain may have been present at different times, or the frequency has changed; they are familiar with the pain, or it has changed character, or it has become associated with other symptoms.

If a patient presents with a headache, the attending doctor must always assess the patient as if they present for help for the first time. This includes a complete history (when, what happened, suddenly/gradually, associated symptoms, other diseases [including HIV], history of head or neck injury, dental or jaw problems, medication, medication overuse, family history, etc.) as well as a general clinical examination (all the vital signs, pregnancy test, targeted ENT and neurological examination, assessment of visual acuity, including fundoscopy). Never miss the signs of increased ICP, namely headache, vomiting without nausea, diplopia (due to ocular paresis), decreased vision (due to papilloedema), deteriorating consciousness, and back pain. The aim of the history and clinical examination is to exclude secondary causes and thereafter to manage the more common acute headaches, namely the primary headaches.

Headaches can be primary or secondary (Table II and Table III). Primary headaches are much more prevalent, and although the pathophysiology may be known and have a predictable character, the causes may remain obscure, and these may have a high morbidity, but low mortality. The causes of secondary headaches are known, it may be from intra- or extracranial origin, have a character that is determined by the cause, may be treatable, and have, depending on the cause, a high morbidity and mortality (Table III). Treatable causes include mass lesions (hydrocephalus, tumours, cysts, abscesses, subdural and extradural haematomas), and vascular lesions (stroke, aneurysms, subarachnoid haemorrhage [SAH], vascular malformations and cerebral venous sinus thrombosis).

The doctor must never get use to a patient’s headache. The first task of the caregiver is to decide whether further investigations are justified to exclude secondary causes (red flags). The SNNOOP10 is a screening tool, depicted in Table III.
Table II: Primary and secondary headaches

<table>
<thead>
<tr>
<th>Primary headaches</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Migraine</td>
<td>2. Tension-type headache (TTH)</td>
</tr>
<tr>
<td>3. Cluster headache (CH) and other trigeminal autonomic cephalalgias</td>
<td>4. Other primary headaches</td>
</tr>
<tr>
<td>Secondary headaches</td>
<td></td>
</tr>
<tr>
<td>1. Headache attributed to head and/or neck trauma</td>
<td>2. Headache attributed to cranial or cervical vascular disorder</td>
</tr>
<tr>
<td>3. Headache attributed to nonvascular intracranial disorder</td>
<td>4. Headache attributed to a substance or its withdrawal</td>
</tr>
<tr>
<td>5. Headache attributed to infection</td>
<td>6. Headache attributed to disorder of homoeostasis</td>
</tr>
<tr>
<td>7. Headache or facial pain attributed to disorder of cranium, neck, eyes, ears,</td>
<td>8. Headache attributed to psychiatric disorder</td>
</tr>
<tr>
<td>nose, sinuses, teeth, mouth, or other facial or cranial structures</td>
<td></td>
</tr>
<tr>
<td>Cranial neuralgias, central and primary facial pain, and other headaches</td>
<td></td>
</tr>
<tr>
<td>1. Cranial neuralgias and central causes of facial pain</td>
<td>2. Other headaches, cranial neuralgia, central or primary facial</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table III: Secondary headache: SNNOOP10 list of red flags</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sign or symptom</td>
<td>Related secondary headaches</td>
</tr>
<tr>
<td>Systemic symptoms including fever</td>
<td>Headache due to infection or nonvascular intracranial disorders,</td>
</tr>
<tr>
<td></td>
<td>carcinoid, pheochromocytoma</td>
</tr>
<tr>
<td>Neoplasm in history</td>
<td>Neoplasms of the brain, metastases</td>
</tr>
<tr>
<td>Neurologic deficit or dysfunction (including consciousness)</td>
<td>Attributed to vascular, nonvascular intracranial disorders, brain abscess/other infections</td>
</tr>
<tr>
<td>Onset sudden or abrupt</td>
<td>Subarachnoid haemorrhage, other attributed to cranial or cervical</td>
</tr>
<tr>
<td></td>
<td>vascular disorders</td>
</tr>
<tr>
<td>Older age (&gt; 50 years)</td>
<td>Giant cell arteritis, other due to cranial or cervical vascular disorders</td>
</tr>
<tr>
<td>Pattern change, recent onset</td>
<td>Neoplasms, other nonvascular intracranial disorders</td>
</tr>
<tr>
<td>Positional headache</td>
<td>Intracranial hypertension/hypotension</td>
</tr>
<tr>
<td>Precipitated: sneezing, coughing, exercise</td>
<td>Posterior fossa malformations, Chiari malformation</td>
</tr>
<tr>
<td>Papilloedema</td>
<td>Neoplasms/nonvascular intracranial disorders, intracranial hypertensive disorders</td>
</tr>
<tr>
<td>Progressive, atypical presentations</td>
<td>Neoplasms, nonvascular intracranial disorders</td>
</tr>
<tr>
<td>Pregnancy, puerperium</td>
<td>Headaches due to cranial/cervical vascular disorders, postdural puncture headache, hypertension-related disorders (e.g. preeclampsia), cerebral sinus thrombosis, hypothyroidism, anaemia, diabetes</td>
</tr>
<tr>
<td>Painful eye with autonomic features</td>
<td>Pathology in posterior fossa, pituitary region, or cavernous sinus Tolosa-Hunt syndrome, ophthalmic causes</td>
</tr>
<tr>
<td>Posttraumatic onset</td>
<td>Acute, chronic posttraumatic headache Subdural haematoma, other headache due to vascular disorders</td>
</tr>
<tr>
<td>Pathology of immune system</td>
<td>Opportunistic infections, HIV</td>
</tr>
<tr>
<td>Pain killer overuse, new drug at onset</td>
<td>Medication overuse, drug incompatibility</td>
</tr>
</tbody>
</table>
Shortened SNOOP

- Systemic symptoms (fever, weight loss, HIV, systemic cancer)
- Neurologic symptoms or signs (confusion, impaired alertness or consciousness)
- Onset (sudden, abrupt, split-second)
- Older (new onset, progressive, especially middle-age > 50 years [giant cell arteritis])
- Previous headache history (first headache, different [frequency, severity, features])

In order to identify the cause and decide on the most appropriate management, the doctor must appreciate the clinical features of the different disorders that present with acute headaches. Remember that nonneurological disorders can present with acute headache.

13.9.2 Types of presentation of acute headaches

New-onset headache with fever: exclude meningitis

The most common cause of acute headache associated with fever is systemic illness headache. The headache is usually self-limiting and improves when the systemic infection resolves, but may be complicated by a nonspecific persistent headache. The most common causes of acute headache with fever are acute paranasal sinusitis and viral infections, such as influenza.

The most important cause to exclude is that of acute bacterial meningitis. The most common causes of bacterial meningitis are meningococcal, pneumococcal and tuberculous infections. If the history and clinical examination points to meningitis, a lumbar puncture should be performed to exclude aseptic meningitis (which occurs more commonly) and to direct antibacterial therapy. IV ceftriaxone must be started immediately. If there is no history of HIV, convulsions, the patient is fully conscious, and there is no lateralisation (abscess), further imaging is unnecessary, but should be left to the discretion of a specialist.

Headache accompanied by focal neurological symptoms: migraine

These headaches are accompanied by sensory, motor and vision complaints. The most common cause of this triad is migraine with an aura. However, if this is the first time the patient presents with these complaints, imaging is indicated to exclude vascular (stroke, haemorrhage) and mass lesions.

Migraine is the most common cause of headache in patients visiting the emergency department. It occurs in approximately 16% of the population; an aura precedes the headache in a third of patients. It is more prevalent among women. Migraine may occur either without a preceding aura or with a preceding aura, but rarely present with an aura only (silent migraine).

Migraine is a neurovascular disorder that is characterised by a usually unilateral frontotemporal pulsating (throbbing) headache and several hypersensitivity-related symptoms (aura), such
as photophobia, phonophobia and olfactophobia. It is often accompanied by autonomic symptoms (lacrimation, nausea, vomiting), sensory symptoms (paresthesiae, scotomata and other visual disturbances), motor symptoms (focal weakness or paralysis), cognitive symptoms (amnesia), or fluctuation in consciousness. It is often associated with a trigger, including emotional stress, sleep disturbances, hormonal changes, fasting, noise, light, etc. It seems as though migraines are the result of a brain state of altered sensitivity (hyperexcitability), which can activate the trigeminovascular system in genetically susceptible people.

*The aura is caused by cortical spreading depression (CSD).* CSD occurs in genetically predisposed individuals. It is a physiological response to irritant stimuli in the cerebral cortex. In these patients, the cortex is hyperexcitable, which is caused by a disturbed excitatory/inhibitory imbalance. This response of the cortex in response to irritant stimuli occurs before the onset of the headache.

In CSD, the stimulus induces a slowly spreading (2–8 mm/minute) wave of depolarisation across the cortex, followed by slow repolarisation. The depolarised cortical tissue becomes isoelectric and does not function properly. The evolving nature of the aura is indicative of CSD. The areas affected determines the characteristics of the aura. *Serotonin* (increased levels) and *dopamine* (hypersensitivity due to chronic dopamine deficiency) may be involved in CSD.

The aura reaches a peak within approximately 5–20 minutes and persists for about 30 minutes, followed by complete resolution. In about 4% of patients, the neurological deficit may last for more than a day.

**Central and peripheral sensitisation** occurs when there is a reduction in the excitatory thresholds of peripheral and central trigeminal neurons (spinal trigeminal nucleus and cervical spinal neurons 1–3). Peripheral sensitisation results in hypersensitivity of trigeminal afferents in the face, scalp and neck. This results in a pain response to a normally nonpainful stimulus, including vascular pulsations in arteries supplying the scalp, face or arms. Note: it is not dilatations or extracranial arteries that cause pain, but hypersensitivity of afferents that cause the pain with a throbbing character.

**Central sensitisation** also involves activation of the trigeminovascular system, which causes *intracranial (pial) arterial vasodilatation* causing traction on blood vessel walls. These arteries are accompanied by trigeminal afferents and when stimulated (sensitised), nociceptive signals are transmitted via the trigeminal nerve. The intracranial vasodilatation is responsible for the headache. Extracranial arteries do not dilate.

During CSD, neurons, glia and vascular cells release ADP, H⁺, and K⁺, while perivascular nerves (trigeminal afferents) release NO and calcitonin gene-related polypeptide (CGRP). These substances trigger a *neurogenic inflammatory response* involving the release of inflammatory cytokines, prostanoids and histamine. These substances trigger neurogenic inflammation-
causing intracranial vasodilatation. They also diffuse to the surface of the cortex where they stimulate pial nociceptors in trigeminal afferents and cause vasodilation. The patient becomes more sensitive to the slight increase in ICP caused by the vasodilation, resulting in the throbbing quality of migraines.

Migraine without aura is diagnosed if the patient experiences:

A. At least five attacks fulfilling criteria B through D
B. Headache lasting 4–72 hours (untreated or unsuccessfully treated)
C. At least two of the following pain characteristics: unilateral location, pulsating, moderate or severe, or aggravating routine physical activity
D. At least one of the following during the headache: nausea and/or vomiting or photophobia and phonophobia

*Cranial autonomic symptoms* may also be present, including nasal congestion, ptosis, eye lid oedema, tearing, conjunctival injection and miosis. *Cutaneous* allodynia may also occur during attacks.

Migraine with aura is diagnosed if a patient experiences:

A. The diagnostic criteria for migraine without aura
B. At least two attacks fulfilling criteria C
C. At least three of the following during a headache:
   1. One or more symptoms indicating focal, cerebral, cortical and/or brainstem dysfunction; a sensory aura may consist of unilateral paresthesiae and sensory aphasia, while a motor aura consists of focal weakness or paralysis; visual auras may present as shimmering lights or zigzagging lines of different colours and/or brainstem dysfunction (fainting, unconsciousness, disorientation, tinnitus, loss of balance, dizziness, vertigo, diplopia, dysarthria) or retinal symptoms; an aura may also present as transient amnesia.
   2. At least one of the aura symptoms develops gradually over more than 4 minutes, or two or more symptoms in succession.
   3. No aura symptom lasts more than 60 minutes.
   4. The aura is followed by a headache, with a free interval of less than 60 minutes.
   5. The aura is unilaterally spreading over more than 5 minutes, lasts less than 60 minutes and are followed by a headache within 60 minutes; the headache may begin before or during the aura.
Management of acute migraine

The patient who seeks help for a headache is either a known migraineur, or a patient with a ‘new’ headache. Regarding the latter, the priority is to exclude secondary causes and to treat the headache while a diagnosis is being made. The migraineur knows that the headache is a migraine, and visits the healthcare facility due to failure of home medication.

Management of acute migraine attempts to address the neurologic and vascular processes by targeting receptors involved in neural, vascular and inflammatory responses.

General principles

1. By the time a patient arrives at the healthcare facility, they may be dehydrated due to an inability to eat or from vomiting. These patients should receive an IV infusion of Ringer’s lactate of approximately 10 ml/kg.
2. The infusion also facilitates the administration of other drugs, especially for inpatients who vomit.
3. The time between the start of the attack and the treatment should be kept as short as possible. All treatment modalities, especially the triptans, are more effective if administered early in the episode. Early treatment is recommended for migraine without aura. Regarding migraine with aura, it is suggested that a triptan should be taken at the onset of the headache. However, taking an oral triptan during the aura appears to be effective and safe.
4. Patients react differently to treatment; analgesics (paracetamol and NSAIDs) may suffice in some, while a particular triptan is required in others (genetic factors). Moreover, the severity, duration of the headache, and vomiting determine the modalities, dosages and drug formulations used.
5. Drug combinations are useful. Drug combinations are often more effective than the components alone. These include a triptan + NSAID + a dopamine antagonist (antiemetic).
6. The choice of drug formulation is determined by the characteristics of the attack: severity, duration and vomiting. If an attack builds up rapidly to a severe headache, especially if accompanied by vomiting, an SC or IN triptan should be used first. When the attack is less severe, oral and nasal preparations can be used. Oral formulations that facilitate faster absorption may be used, including oral dispersible tablets or wafers and effervescent tablets.
7. A measure of the efficacy of treatment modalities is the pain-free period after administration. These endpoints are usually the 2-hour and the 24-hour pain-free rate (sustained effect of mild or no pain).
   - Headache syndromes, including migraine, is often complicated by medication-overuse-induced headache. This is a headache that is exacerbated by the frequent use of over-
the-counter (OTC) analgesic combinations. These usually contain paracetamol, NSAIDs, a sedative (usually an antihistamine), as well as codeine. Opiates should not be used as these are less effective than the other drugs used for the management of migraine headaches, are habit-forming, and lead to medication overuse headache (MOH).

8. In patients in whom vasoconstrictors (the triptans) are contraindicated, treatment is limited to paracetamol, an antiemetic (sedating antihistamine), and an NSAID. Owing to its better CV and antiplatelet effect, naproxen sodium is the first-choice NSAID. An opioid may be added in exceptional cases.

**Drugs used for a migraine attack**

**Antidopaminergic antiemetics**

*Metoclopramide and domperidone* are not only antiemetics, but are also prokinetics, which promote the absorption of oral drugs, including the triptans. The dose of *metoclopramide* is 10 mg p.o. or IVI up to 6-hourly. *Domperidone* 10 mg is given p.o. 8-hourly. Domperidone has several drug interactions, is affected by liver and kidney function, and prolongs the QT interval (see the SAMF).

*Prochlorperazine* can be added for refractory vomiting. The dose is 20 mg p.o. followed by 5–10 mg 6-hourly, if necessary. If nausea prevents oral administration, prochlorperazine 12.5 mg can be administered IMI or 25 mg per rectum.

*Droperidol* is an effect antiemetic. The dose is 20 µg/kg. This drug can prolong the QT interval.

All antidopaminergic drugs, especially prochlorperazine and droperidol, have extrapyramidal adverse effects. It can be treated with centrally acting anticholinergic *biperiden* 30 µg/kg IVI or IMI and repeated every 30 minutes if necessary. The maximum daily dose is approximately 150 µ/kg.

**Paracetamol and NSAIDs**

These drugs may suffice for mild to moderate migraine attacks, but are always used for severe attacks. Except for naproxen, NSAIDs have a rapid onset of action. NSAIDs improve the 2-hour and 24-hour pain-free rate. Oral preparations should be used if possible.

*Paracetamol* on its own is suitable only for mild attacks, but is additive to the effect of NSAIDs. The dose is 15 mg/kg p.o. or 15 mg/kg IVI 4–6-hourly with a maximum of 60 mg/kg/day.

*Ibuprofen* is often used by migraineurs. A maximum effective and appropriate dose is approximately 7 mg/kg, which can be repeated 6-hourly.
Diclofenac can be given p.o. (diclofenac sodium tablets or diclofenac potassium powder for oral solution), IMI, IVI or rectally. The dose is 0.7 mg/kg p.o. 8-hourly, 1 mg/kg IMI, or IV infusion over at least 30 minutes (see postoperative pain), or 1–1.5 mg/kg per rectum. The maximum dose of diclofenac is approximately 2 mg/kg/day.

Ketorolac has been used with success for migraine headaches. It has a relatively long half-life of 5 hours. The dose is 0.5 mg/kg IVI, followed by 0.15 mg/kg 6-hourly with a maximum of approximately 1 mg/kg/day. The oral dose is 10 mg 4–6-hourly.

Naproxen is commonly used for acute migraine headaches. It is available as the base and the sodium salt. Naproxen sodium is preferred since it is absorbed quicker than the base. Naproxen has a half-life of 14 hours, but the 2-hour pain-free characteristic is inferior to that of ibuprofen and diclofenac. The long half-life of naproxen reduces the recurrence rate of migraine. Moreover, the CV and antiplatelet profile of naproxen is better than those of other NSAIDs. The dose is 3.5–7.0 mg/kg 12-hourly.

The triptans

During a migraine attack, intracranial arteries dilate on the side of the headache and to a lesser extent on the nonpainful side. The extracranial arteries do not dilate. The anti-migraine effect of the triptans is still unclear. Possibilities include extracranial vasoconstriction, suppression of neuropeptide release from trigeminovascular afferents, and antinociceptive activity in the brainstem. The triptans are agonists at 5-HT1B and 5-HT1D receptors, causing peripheral vasoconstrictors. These constrict extracranial arteries (making them less pulsatile with less release of neuropeptides from the hyperexcitable trigeminovascular afferents).

Sumatriptan does not cross the intact BBB, which also stays in tact during a migraine attack. Since the anti-migraine effect of sumatriptans does not rely on intracranial vasoconstriction and cerebral antinociceptive effects, it is also unlikely that the triptans drugs blunt the migraine generator (focus). This may explain the recurrence of headache once the extracranial vasoconstrictor effect of the triptans has worn off.

Owing to possible genetic factors, triptans are not equally effective in all patients. The adverse effects may also differ between patients. Therefore, a patient may prefer a particular triptan.

Subcutaneous sumatriptan has the best 2-hour pain-free rate. Regarding the oral preparations, eletriptan and rizatriptan are better after 2-hours, while eletriptan has the highest 24-hour pain-free rate. Oral eletriptan and zolmitriptan works faster than oral sumatriptan. Nasal sprays work faster than oral triptans, may offer relief if the oral dose has failed, and is useful in patients who cannot take tablets due to vomiting.
If a triptan is ineffective, a follow-up dose usually does not offer any additional relief. A triptan failure may be rescued by naproxen sodium 550 mg p.o.

Triptans are administered when paracetamol and an NSAID has failed to control the headache. All three of these are often co-administered for moderate to severe migraine. Both IV or oral metoclopramide and oral domperidone are antiemetic as well as prokinetic and promote the absorption of oral triptans.

Triptans are contraindicated in patients with vascular disease, namely hypertension, coronary artery disease, Prinzmetal angina, cerebrovascular disease and peripheral artery disease. Triptans and ergot alkaloids have additive vasoconstrictive effects and should be given more than 24 hours apart. These should not be given for ophthalmoplegic, basilar artery and hemiplegic migraines.

These are also contraindicated in patients on drugs that increase serotonin levels, including SSRIs and SNRIs. Sumatriptan and eletriptan contain a sulfur-containing moiety, which makes them contraindicated in patients allergic to sulfas. Zolmitriptan is sulfur-free. Triptans should be avoided in patients taking MAOIs and lithium.

The following triptans are available in SA: Sumatriptan, eletriptan, zolmitriptan, and naratriptan.

- **Sumatriptan** is administered by SC injection for a severe migraine attack, while oral tablets or wafers or IN sprays can be used for less severe attacks. The IN spray may be effective if the oral route fails to control the attack. The SC dose is approximately 80 µg/kg. SC sumatriptan may be effective if another triptan has failed to give adequate relief. The oral dose is 50 mg and the IN dose is 20 mg. The SC dose can be repeated after an hour and the oral and IN doses, after two hours.

- **Eletriptan** is a sulfur free triptan. It has a short onset of effect and a high 2-hour and 24-hour pain-free rate. The dose is approximately 0.5 mg/kg p.o. The metabolism of eletriptan is decreased by suppressors of liver CYP3A4, including erythromycin and its derivatives, the conazole antifungal agents, and the ARV ritonavir.

- **Naratriptan**: the dose is approximately 30 µg/kg p.o.

- **Zolmitriptan**: it is a fast-acting oral triptan. The dose is approximately 30 µg/kg p.o.

- **Rizatriptan**: the dose is approximately 0.15 mg/kg p.o.

**The ergot alkaloids**

These drugs should not be used any longer. These are non-selective vasoconstrictors affecting serotonin, adrenergic and dopaminergic receptors. This non-selectivity gives rise to several potentially long-lasting adverse effects, including hypertension, myocardial ischaemia, peripheral ischaemia (ergotism), and nausea and vomiting. These have several drug interactions,
including the erythromycin derivatives and the protease inhibitors, such as ritonavir (slower metabolism), and with other vasoconstrictors, non-selective beta-blockers, and the triptans.

**Opioids**

Opioids should not be used routinely for migraine headaches. It may also promote the development of MOHs, which may make the routine antimigraine agents less effective.

**Corticosteroids**

Although evidence is lacking regarding the efficacy of corticosteroids for the management of migraine headache, dexamethasone 4–16 mg IVI may prevent recurrence of headache for up to 72 hours.

**Migraine during pregnancy and lactation**

Acetaminophen, metoclopramide and codeine are safe during pregnancy. NSAIDs should be avoided. Prochlorperazine is not teratogenic, but should be avoided in the peripartum period since it can cause extrapyramidal effects in the neonate. An occipital nerve block (greater and lesser occipital nerves) may be helpful.

During lactation, paracetamol and the tNSAIDs are safe, but aspirin should be avoided. Sumatriptan and the antiemetics are safe. Opioids should be avoided if possible, especially if the mother breastfeeds an infant with a postconceptional age of less than 60 weeks or when the mother experiences drowsiness after taking an opioid. In the case of codeine, she may be an extensive metaboliser of codeine to morphine.

**Thunderclap headache: sudden onset of severe headache**

The onset of a severe headache may be abrupt with maximal intensity from the start. These headaches are not transient (seconds) and are repetitive in nature, such as neuralgic head pain. A thunderclap headache is severe, persistent and distressing. However, the severity does not correlate with the gravity of the underlying pathology. This group of headache-causing disorders is mentioned since patients with a known primary headache disorder may also present with a ‘sudden severe different headache’.

Although these headaches occur infrequently (approximately 40 cases per 100 000 adults per year) it is essential to exclude possible deadly secondary disorders that have a potentially good prognosis if treated correctly and urgently.

It is important to exclude a ruptured cerebral aneurism. This lesion may present with rapidly deteriorating focal neurological signs and consciousness, or with the headache only. The diagnosis is facilitated by urgent imaging and lumbar puncture.
In the majority of these cases, a secondary cause is not identified and the diagnosis of a primary headache disorder is made. The most important secondary causes are neurovascular in origin, including SAH from a cerebral aneurism, arterial dissection, reversible cerebral vasoconstriction syndrome and dural sinus thrombosis. Other rare causes include MI, phaeochromocytoma, pituitary apoplexy, spontaneous intracranial hypotension (SIH), and idiopathic physical-activity-related thunderclap headache.

**New-onset persistent headache**

This is a person with no prior history of headache who presents with several days or weeks of a new headache. These patients may have a history of ‘normal’ headaches, but now presents with new headaches. Several of these patients visit the emergency department for help. These headaches do not present as abruptly as a thunderclap type headache, but is new in character and persists. These headaches have a wide differential diagnosis. As is the case with thunderclap headaches, it is important not to miss an important secondary cause.

**Tension-type headache**

TTH is a primary headache. It occurs commonly and is probably the kind of headache that occurs ‘normally’. It is also referred to as a stress or muscle tension headache. Since there is an overlap in symptomatology, pathophysiology, as well as the co-occurrence of the two headaches in the same patient, migraine is often erroneously diagnosed as TTH, and vice versa.

A diagnosis (International Headache Society [IHS] diagnostic criteria for migraine without aura and episodic tension-type headache [ETTH]) of TTH is mainly based on the absence of certain other symptoms, while migraine is diagnosed by the presence of typical symptoms, namely nausea and vomiting, photo- and phonophobia, headache exacerbated by physical activity. However, the absence of differentiating characteristics of TTH contributes to the diagnosis of TTH instead of migraine. The overdiagnosis of TTH may explain its high prevalence of ETTH of approximately 40% in adults. The misdiagnosis may deprive the migraineur of appropriate therapy, which may cause suffering unnecessarily, and vice versa.

The nonspecific nature of TTHs must be investigated further for a secondary cause, especially if the pattern of headache changes (e.g. if starting during the night or if therapy does not give relief anymore). In this regard, the doctor must recommend a visit to the dentist to exclude temporomandibular pathology, bruxism and impacted wisdom teeth. Also consider cervical spine disorders, including cervicogenic headaches (CGHs).

For differentiation between these primary headache types, the reader is referred to the diagnostic criteria of the IHS for migraine without aura and ETTH.
TTH can be episodic (ETTH) or chronic (CTTH). In ETTH, the headache occurs for less than 14 days per month and typically last from 30 minutes to 7 days. In CTTH, the headache is experienced for more than 14 days per month and is present relatively continuously. The pathogenesis of ETTH and CTTH differ.

Headaches usually start during waking hours and get worse during the day. TTH is triggered by increased psychological (depression, anxiety and panic disorder), or physiological stress (including disturbed sleep patterns, overexertion, hunger, dehydration, female hormonal fluctuations and caffeine withdrawal). However, these stressors are also frequently present in migraineurs.

**Pathophysiology**

The pathophysiology of ETTH and CTTH differ, but there may be an overlap in patients. Both peripheral myofascial and CNS sensitisation are involved. Pericranial myofascial mechanisms are implicated in ETTH. Continuous stimulation of trigger points in the pericranium and cervical muscle cause sensitisation of peripheral nociceptors followed by sensitisation of second-order neurons in the spinal nucleus of the trigeminal nerve.

CNS sensitisation is involved in the pathogenesis of ETTH and CTTH, leading to decreased pain thresholds. These patients are hypersensitive to noxious stimulation of muscle, tendon, nerve, at cephalic and extracephalic points, and during and between headaches. Patients with CTTH also have decreased central nociceptive inhibition.

**Management of tension-type headaches**

Management consists of avoiding triggers (i.e. stressful situations), following a stress-avoiding lifestyle (get more sleep and apply sleep hygiene, physical exercise, regular healthy meals), psychological aspects (overcome depression and stress through CBT), physiotherapy and pharmacological management.

ETTH attacks are managed with paracetamol (15 mg/kg p.o. 6-hourly) combined with an NSAID such as ibuprofen (4 mg/kg p.o. 6-hourly) or naproxen (7 mg/kg bd; available with esomeprazole). Caffeine improves the efficacy of paracetamol and ibuprofen. It is available in several paracetamol combinations. To prevent the development of analgesic overuse headache, the use of these drugs should be limited to 3 days and opioids and sedatives should not be prescribed. Triptans are ineffective.

If a patient experiences headache more than twice a week (CTTH), preventative medication is indicated. Amitriptyline is the drug of choice. Start with a low dose (10 mg) at night and increase it gradually up to 75 mg at night. The effective dose is prescribed for 6–12 months.
Thereafter, the patient can be weaned from amitriptyline. Other TCAs may be used instead of amitriptyline. The SSRIs and botulinus toxin are ineffective.

13.9.3 Carbon monoxide poisoning

Most patients with chronic carbon monoxide (CO) poisoning present with the symptom of nonspecific headaches. These patients usually work close to internal combustion engines in poorly ventilated spaces. CO poisoning can cause permanent neurological impairment and even death. The diagnosis is made from the occupational history and an arterial blood gas analysis.

13.9.4 Temporal arteritis (giant cell arteritis)

Giant cell arteritis (GCA) is a rare disease (incidence of approximately 20/100 000/year). The disease affects elderly people, usually in their eighties, and women are affected more often than men. Although GCA is a rare cause of acute headache, it has a high morbidity if not treated promptly.

GCA is an autoimmune disease that affects large and medium size arteries. It is the most common systemic arteritis in elderly people. It usually affects the branches of the external carotid artery, namely the superficial temporal, maxillary, ophthalmic, posterior ciliary and vertebral arteries. These arteries supply the structures of the temporal, frontal (including the orbit), facial and temporomandibular joints.

Systemic signs of inflammation are often present, including fever, malaise and anorexia (flu-like symptoms). Less commonly, coronary arteries, cerebral arteries and the aorta are affected, causing MI, stroke and an aortic aneurism, respectively.

The typical symptoms form the triad of a severe, unilateral throbbing, temporal headache, jaw claudication and blindness. The painful areas are also hyperalgesic, and may be aggravated by chewing and swallowing. Patients may also complain of diplopia and both eyes are affected in > 50% of cases. The temporal arteries are tender and swollen. Patients may also present with ataxia, tinnitus and deafness.

The diagnosis is made by a raised erythrocyte sedimentation rate and biopsy of the temporal artery.

Management of acute giant cell arteritis

Once the diagnosis of GCA is suspected, treatment must be started immediately to prevent blindness or a stroke. Prompt administration of a corticosteroid before visual symptoms occur, decreases the prevalence of blindness from 50% to 1%. Corticosteroids are the only confirmed
treatment for GCA. Start with prednisone approximately 1.0 mg/kg/day p.o. In the presence of visual loss, start with methylprednisolone 15 mg/kg/day IVI for three days.

13.9.5 Disorders of abnormal intracranial pressure

These disorders include the following:

- Idiopathic intracranial hypertension (IIH) (pseudotumor cerebri)
- Low intracranial pressure headache (LPH): postdural puncture headache (PDPH) and SIH

Patients suffering from these disorders may present to the emergency department with severe persistent headaches.

**Idiopathic intracranial hypertension**

IIH is defined as elevated ICP, normal CSF composition, and the absence of intracranial pathology. It occurs in obese persons, more often in young women, but may also occur in children. It is also associated with a recent steep increase in BMI.

A wide range of conditions have been associated with IIH, including medication (hyper-vitaminosis A and retinoids [used for acne], growth hormone [GH], tetracycline, the quinolone antibiotics), OSA, and several endocrine disorders.

Patients complain of a persistent severe headache (> 90% of cases) accompanied by nausea, pulse-synchronous tinnitus (turbulent blood flow in cerebral venous sinuses), diplopia (loss of N. abducens), blurred vision, restricted visual fields, tunnel vision or even loss of vision. Visual loss correlates with increased BMI – in adults and children. Symptoms are exacerbated when the ICP is raised (e.g. by lying down).

Patients often present complaints similar to those of migraine, including headache, nausea, vomiting, and photo- and phonophobia. As is the case with other headaches, different headache disorders may occur in the same patient. IIH also occur in migraineurs.

As with all headaches, the doctor must be on the lookout for symptoms and signs of increased ICP (see above). Secondary causes of elevated ICP must be excluded, especially venous sinus thrombosis. Investigations include imaging, CSF pressure studies and biochemistry. The patient should be referred to a neurologist and ophthalmologist.
**Management of acute IIH-related headache**

Symptoms usually present acutely and are self-limiting, but the condition may become chronic. The aim of treatment of an acute headache is to alleviate pain and other symptoms and to prevent vision loss.

Although weight loss is the most important long-term treatment to improve the headache and the visual outcome, these patients need symptomatic treatment in the emergency setting. Headaches may be alleviated by an NSAID, an antiemetic, a glucocorticoid and a triptan. However, the most important component of acute therapy is to decrease CSF production and intracranial and intraocular pressure by the carbonic acid anhydrase inhibitor, acetazolamide and the antiepileptic agent topiramate. Acetazolamide may be combined with a loop diuretic such as furosemide. Acetazolamide causes a hypokalaemic metabolic acidosis. Furosemide also lowers the potassium. Therefore, serum electrolytes should be monitored.

The advantages of topiramate are that it is useful in preventing migraine and suppresses appetite. However, it has several adverse effects, including cognitive decline, dysgeusia, acral paraesthesiae, metabolic acidosis, acute narrow-angle-glaucoma, renal calculi and is teratogenic.

The following drug combination is useful for an acute attack of IIH:

- Acetazolamide 500 mg p.o. immediately, then bd, increased to 2–4 g/day
- Ketorolac 30 mg IVI
- Dexamethasone 8 mg IVI
- An antidopaminergic antiemetic such as metoclopramide 10 mg p.o. or IVI up to 6-hourly, or domperidone 10 mg p.o. 8-hourly, or prochlorperazine 20 mg p.o. followed by 5–10 mg 6-hourly if necessary or 12.5 mg IMI or 25 mg per rectum.

If the headache and visual loss do not respond to weight loss or medical treatment, surgery should be considered, including CSF diversion with a ventriculo- or lumboperitoneal shunt, optic nerve sheath fenestration, or venous sinus stenting. Bariatric surgery is indicated if dietary measures are ineffective.

**Low intracranial pressure headache**

PDPH is the most common cause of an LPH. This follows subarachnoid anaesthesia or analgesia and correlates with needle size used (< 25 G), number of attempts and age. PDPH occurs more commonly in young patients and rarely in the elderly.

SIH is a rare cause of LPH and usually follows a tear in the spinal dura or dural sheath of a spinal nerve. The tear is caused by known or unrecognised trivial trauma involving the spine. CSF leaks into the spinal epidural space resulting in LPH. Patients present with acute (thunderclap)
disabling headache, or the headache may develop over several days. The diagnosis of SAH is high on the differential diagnosis list in patients presenting with severe acute headache. If imaging does not confirm SAH or any cause of increased ICP, SIH should be considered.

Postural headaches can be relieved by lying down or by sitting up. A headache that is relieved on lying down (orthostatic headache) is typical of PDPH and SIH. In contrast to orthostatic headache, meningitis-associated headache is exacerbated by supine position.

Loss of SCF causes sagging of the brain in the upright position, resulting in traction on the pain-sensitive meninges, sensory cranial nerves V, VII, IX, and X, cervical spinal nerves C1–3, motor cranial nerves (VI, VII) and NVIII. Traction on these nerves explains the symptoms of frontal and occipital headache, nausea, vomiting, tinnitus, vertigo, muffled hearing, diplopia and cervical myelopathy; all which improve in the horizontal position.

LPH is treated with paracetamol, an NSAID and caffeine, but these drugs do not contribute to sealing of the CSF leak. LPH may disappear spontaneously over time (days to months), but intervention is often necessary. The most common remedy is an epidural blood patch (EBP).

The EBP may be done using the loss of resistance technique or with the help of a radiologist under fluoroscopic or computed tomography (CT) guidance. The EBP is a sterile procedure. The patient may sit or lie on the side. The epidural space is identified with an epidural needle (usually an 18 G). With the needle in place, the assistant draws 15–20 ml blood from the patient (also applying a strictly sterile technique). The blood is injected into the epidural space over approximately one minute. After the EBP, the patient must stay in bed for a day and avoid exercise for a few days. The EBP has a success rate of more than 90%, but may be repeated.

The EBP may be difficult in patients with SIH. The epidural space may be filled with CSF under pressure. When the needle is inserted, CSF may flow back through the epidural needle and it may seem as if the tip has perforated the dura. In these cases, fluoroscopy may facilitate the procedure.

PDPH may also be treated with neostigmine and atropine. Neostigmine increases CSF production and blocks CSF reabsorption by the cerebral vessels on the brain surface, which is the main reabsorption mechanism of CSF (not the subarachnoid villi). Both neostigmine and atropine cause cerebral vasoconstriction. The doses are neostigmine 20 µg/kg and atropine 10 µg/kg slowly IVI over approximately 5 minutes 8-hourly. Two doses are usually sufficient. Adverse effects are abdominal cramps (20%), muscle twitches (15%) and urinary bladder hyperactivity (12%).
13.9.6 Paranasal sinusitis

When the cause of headache cannot be identified clinically, the clinician should refer the patient for imaging, including the paranasal sinuses to exclude sinusitis. Pain management consists of antibiotics, paracetamol, an NSAID and decongestants.

**Isolated sphenoid sinus pathology**

Infection/inflammation is the most common pathology (bacterial and fungal sphenoiditis), followed by polyps and neoplasia.

Pathology of the sphenoid sinus should be considered in severe, refractory new-onset headaches. Isolated sphenoid sinusitis is an uncommon condition, which can often be overlooked. Patients may present with nonspecific symptoms and the clinical examination often do not reveal pathology. Different from pathology in the other paranasal sinuses, patients do not often present with nasal obstruction, rhinitis, tenderness or nasal secretions. Only approximately 20% of patients are febrile. The diagnosis is often missed even after the patients have developed neurological signs. Sphenoid sinusitis has a high morbidity and mortality (7–30%) if diagnosis and management are delayed.

Situated at the center of the skull, the sphenoid sinus is in contact with several structures, including the dura, cavernous sinus, internal carotid artery, optic nerve and optic chiasm, pituitary gland, and cranial nerves III, IV, VI, and all three divisions of V (V1 is the nerve supply of the sphenoid sinus), and is close contact with the sphenopalatine ganglion. These relationships explain the (non)specific symptomatology, variations in pain, the referred nature of the pain, and the wide range of complications.

All patients with inflammatory/infective pathology (usually pneumococcal or staphylococcal, and fungal) present with headache, while only 30% with neoplastic lesions experience headaches. The headache may present gradually or may present as an acute thunderclap headache. The pain is referred to any part of the head and is worse at night. It may involve any part of the head: pancephalic, hemicranial (migraine-like), retro- or periorbital, maxillary, frontal, fronto-occipital, vertex, parietal, temporal (arteritis-like) or postauricular.

Patients with cranial nerve involvement present with diplopia (NIII, NIV and VI), and pain or numbness over the distribution of the trigeminal nerve. Photophobia and loss of vision are caused by inflammation of the optic nerve and retinal ischaemia. The latter is caused by occlusion of the retinal artery and vein by thrombosis, oedema or vasculitis.

Other complications of sphenoiditis include osteitis, extra- and subdural empyema, meningitis, brain abscess, and cavernous and superior sagittal sinus thrombosis.
Sphenoiditis needs emergent surgery and antimicrobial therapy. Pain is managed by paracetamol, an NSAID and an opioid (e.g. buprenorphine).

13.9.7 Occipital neuralgia and cervicogenic headache

Occipital neuralgia (ON) and CGH present with occipital pain. Symptoms point to involvement of the upper cervical and trigeminal nerves. The upper cervical afferents and trigeminal afferents converge to form the trigeminocervical complex. Therefore, nociceptive stimuli from the upper cervical afferents (C1–3) are referred to areas that are innervated by trigeminal afferents, causing referred cervical, parietal, frontal or orbital pain.

The greater occipital nerve (C2) supply the skin overlying the posterior skull to the vertex. The lesser occipital nerve (C2 and C3) supply the skin overlying the posterior third of the temporal fossa, and the area of the neck superior and posterior of the ear. The third occipital nerve (C3) supplies the skin of the lower occipital scalp and upper neck.

Occipital neuralgia may be a primary headache disorder, or it may be caused by irritation of the occipital nerves. Patients complain of paroxysms of severe, usually unilateral, stabbing pain that last for seconds to minutes. The pain is in the distribution of the greater and lesser occipital nerves (i.e. occipital area) and radiates to the vertex and to the trigeminal areas, namely the temporal, frontal and orbital areas. In between attacks, patients may experience a dull pain and allodynia over the affected area.

Referred pain from cervical structures should be considered if the pain is persistent and allodynia is absent. Pain referred from the atlantoaxial or upper facet joints may point to CGH.

The diagnosis of CGH is made if a temporal relationship exists between the headache and disorders of the cervical spine or soft tissues. Clinical and/or imaging evidence may identify a disorder within the cervical spine and soft tissues of the neck, which are known causes of headache. In patients with CGH, neck mobility is limited and pain is aggravated by certain neck manoeuvres and pressure points on the nerve.

CGH may be caused by myelopathy involving C1, C2 and C3. Approximately 90% of patients suffering from a cervical myelopathy or radiculopathy, complain of headache. There may be an association between neck pathology and CGH, but the pathology is not necessarily the cause of the headache. Nevertheless, imaging may be necessary to exclude pathology such as tumours, fractures, spondylolysis, etc.

Both ON and CGH, as well as other primary headaches, such as migraine, CH, and TTH may improve with blockade of the occipital nerves. All these headache disorders may overlap clinically, including pericranial (periosteum of the skull) tenderness and neck pain. Connections
between the upper cervical nerves and cranial nerves VIII, IX, and X may explain tinnitus, dizziness and nausea.

Both ON and CGH respond to manual treatment (massage and manipulation of the neck). The value of pharmacological treatment is not clear but may be helpful. These include NSAIDs, amitriptyline, baclofen and an anticonvulsant such as gabapentin or carbamazepine. The cytokine TNF-α antagonist infliximab may also be helpful. Opioids should not be prescribed and doctors must be on the lookout for the development of MOH.

13.9.8 Hypnic headache

A hypnic headache (HH) is a rare primary headache. It usually occurs in persons older than 50 years and more commonly in women. It is a strictly sleep-associated headache, waking the patient up at approximately the same time, usually between 2:00 am and 4:00 am (alarm clock headache), and lasts for 2–3 hours. The headache is usually described as mild to moderate, is usually bilateral, frontotemporal, or diffuse. The headache improves after a few hours.

The clinical presentation and pathophysiology differ from other primary headaches, such as migraine. The strict association with sleep and the circadian nature suggest involvement of the hypothalamus, not the trigeminal nerve. It is not a REM sleep disorder, and not a manifestation of OSA, although OSA does occur more commonly in the elderly.

The acute attack is usually terminated by caffeine (a cup of strong coffee). Prophylactic treatment options are caffeine, indomethacin and lithium.

Caffeine (a cup of strong coffee at bedtime) is safe and promising. Patients do not usually complain of any sleep problems after taking caffeine.

The COX-1 inhibitor indomethacin may be an effective prophylactic drug. The dose is 0.3–2 mg/kg at bedtime. Since HH occurs more commonly in the elderly, the effect of NSAIDs on kidney function should be considered. A combination of indomethacin with a PPI prevents gastric mucosal effects.

Lithium carbonate may be effective. The dose is 2–8 mg/kg/day (plasma levels of 0.5–1.0 mmol/l). However, lithium has several adverse effects, including worsening of the headache, sedation, tremor, nausea, vomiting, diarrhoea, nephrogenic diabetes insipidus resulting in polydipsia and polyuria, chronic renal failure, hypothyroidism, acne and psoriasis. It is contraindicated in patients with kidney disease and CV disease. It should not be used in combination with NSAIDs and diuretics since they decrease the clearance of lithium.
13.9.9  Cluster headache

A CH is a rare (about 4/10 000) primary headache, occurring more often in men. Headache recurs (clusters) within active periods. CHs usually occur at night during the first three hours of sleep. The attack starts within 5–10 minutes, and lasts between 15 minutes to 3 hours (usually less than an hour). At least five headaches occur during a cluster, with frequency ranging from one every other day to eight per day. CHs can be episodic or chronic. Patients with episodic CH (about 90% of patients) have a series of attacks lasting from weeks to months followed by pain-free periods lasting months to years.

CHs are intense, stabbing, strictly unilateral in the periorbital and temporal region, and are accompanied by agitation and restlessness (which is not typical of migraine). Attacks usually remain on the same side. Ipsilateral autonomic activation occurs in approximately 90% of patients. These present as nasal congestion, ptosis, lacrimation and conjunctival hyperaemia.

CHs should be differentiated from dissection of the internal carotid artery, venous sinus thrombosis, and C2 nerve root pain. Internal carotid artery dissection presents with headache, pulsatile tinnitus, aphasia, eye pain, neck pain, Horner syndrome, inability to swallow and hemiparesis.

Venous sinus thrombosis may present with a thunderclap headache or a new-onset headache. Venous sinus thrombosis occurs in patients with pro-thrombotic risk factors. They present with neurological symptoms, including headaches, which may appear gradually or suddenly (thunderclap), aphasia, hemiparesis or bilateral weakness, seizures, depressed consciousness and coma. On examination, there are signs of severe increased ICP, including papilloedema, decreased level of consciousness, abnormal posturing, and a Cushing response.

Pathophysiology of cluster headache

The pathophysiology of CH is unclear. The circadian and seasonal nature of CH suggests a role of the hypothalamus in the pathophysiology. Neuroendocrine changes also point to hypothalamus dysfunction, including decreased melatonin levels; especially during attacks. Headaches can be provoked by vasodilatation in the hypothalamus. Nitroglycerin causes vasodilatation in the ipsilateral inferior hypothalamus during a nitroglycerin provoked attack.

Fibres from the hypothalamus to trigeminal nuclei can activate the trigeminovascular and cranial parasympathetic systems, which may explain the ocular autonomic symptoms.

Management of the acute cluster headache attack

Primary analgesics are ineffective.
Oxygen

When the patient seeks help while still experiencing a headache, the first step is the administration of 100% oxygen at 10 l/minute using a nonrebreathing mask for 25 minutes. The attack can recur after discontinuation of oxygen. Oxygen therapy is more effective in men.

The triptans

Sumatriptan 6 mg SC is the most effective treatment to abort a CH and is effective in more than 70% of patients within 15 minutes. Higher doses are not more effective. Sumatriptan 20 mg via nasal spray is effective in approximately 55% of patients within 30 minutes. The other triptans are also effective, especially when administered via nasal spray (see the section on migraines). For adverse effects and contraindication for triptans, see the section on migraines. Ergotamine and dihydroergotamine are not recommended.

Octreotide

Octreotide (somatostatin analogue) may be considered to improve the headache. The dose is octreotide 100 µg subcutaneously. However, the patient must be monitored for adverse effects, including bradycardia or tachycardia, and hyper- or hypoglycaemia. Minor adverse effects include urticaria at the injection site, nausea, flatulence, diarrhoea and lethargy. It should not be administered with calcium channel blockers.

Sphenopalatine ganglion topical anaesthesia

The sphenopalatine ganglion is situated posterior to the middle nasal turbinate. Lignocaine and cocaine swabs have been applied to the mucosa covering this area. Using lignocaine 4% spray, the pain relief was moderate or poor in 54% of patients, with no relief in the rest.

Prophylactic therapy

Only small studies have evaluated the use of drugs in the management of CH, and are used off-label. Patients suffering from CH should be monitored for the development of analgesia overuse headache.

Verapamil

Verapamil is the drug of choice and is tolerated well. It can be used in combination with other agents (except octreotide) during the acute attack. The prophylactic oral dose is approximately 4.5–9.0 mg/kg/day p.o. divided into three doses (i.e. approximately 1.5–3.0 mg/kg p.o. 8-hourly). The long-acting tablet (240 mg daily) may also be used. Verapamil is effective after approximately one week. Common adverse effects are constipation, hypotension and dizziness.
An electrocardiogram must be done to exclude conduction defects. The vascular selective calcium blockers nifedipine and nimodipine have been used.

**Lithium carbonate**

Lithium carbonate may be used for the long-term prophylaxis of CH. The dose is 4 mg/kg p.o. bd. The trough plasma concentration is measured 12 hours after the last dose and should not exceed 1.0 mmol/l. It may be used in conjunction with verapamil. For adverse effects and monitoring of lithium therapy, see hypnic headache.

**Melatonin**

Melatonin levels are controlled by the suprachiasmatic nucleus of the hypothalamus. Levels increase at nighttime and decrease during daytime. In patients suffering from CHs, melatonin levels are reduced, especially during headache. The dose is 2–10 mg/day p.o. Melatonin causes drowsiness and must be taken at bedtime.

**Civamide**

Civamide is a capsaicin receptor modulator. It depresses activity in type-C nociceptive fibres, and releases with repeated application, depletes neuropeptides algesic peptides, such as substance P and CGRP. Substance P and CGRP may trigger episodic CH. Civamide nasal spray has been effective in improving headache response.

**Baclofen**

The GABA<sub>B</sub> receptor agonist baclofen has been used with some success. The dose was 5 mg three times per day. The drug has several adverse effects, including drowsiness, hallucinations, depression, hypotension, dizziness and urinary retention.

No evidence supports the use of triptans and corticosteroids for prophylaxis in CHs.

**13.9.10 Chronic headache because treatment is not working: medication overuse headache**

These patients suffer from a chronic headache of known diagnosis and start to present more often because their medication does not give relief anymore. Although these patients may suffer from a primary headache, the doctor must be vigilant not to miss a new headache, or secondary headache where the underlying pathology is changing. This is especially true for patients with intracranial hypertension. The headache of intracranial hypertension may be ascribed to TTH, migraine, or MOH.

Patients presenting for medication failure suffer from chronic migraine. They experience headache almost daily and triptans do not give complete relief. It is important to look for a
new headache, but also to review their medication consumption. Very often, patients overuse tramadol and OTC analgesic combinations containing codeine and a sedative, such as meprobamate, doxylamine, promethazine and diphenhydramine. If patients use analgesics for headache for more than ten days per month, the diagnosis of MOH should be considered.

The reason for the MOH may be that the primary headache has not been addressed adequately. If the patient is in pain when presenting, the primary headache should be managed with a triptan, a neuroleptic (dopamine antagonist) and an IV NSAID. The doctor must ensure that the patient receives appropriate prophylactic medication. Lifestyle and psychological interventions may assist in addressing the drug overuse.

13.10 Acute neuropathic pain

13.10.1 General considerations

Owing to its severity and persistence (considered as chronic pain), neuropathic pain has a high morbidity and often results in disability.

Nociceptive pain differs from neuropathic pain. Neuropathic pain is usually described as being sharp, aching or throbbing. It usually occurs in the area of injury, is proportional to the extent of injury, and decreases as healing takes place.

Neuropathic pain may remain constant, but usually changes in character (i.e. distribution, triggers, severity, duration and frequency of attacks). It often persists even after healing or after the original stimulus has disappeared. The pain is dysfunctional since it no longer has a protective role, namely to protect the person from real or potential tissue harm:

- The person experiences pain in a body part that is not present anymore (phantom pain).
- Pain may be experienced in the absence of a stimulus (dysaesthesia).
- Pain may be experienced in response to nonharmful stimuli, such as touch (allodynia).
- The pain may be a disproportionate response to a stimulus that is painful (hyperalgesia).
- Pain may be accompanied by inappropriate sensations, such as pins and needles, crawling and tingling (paresthesia).
- Pain or other sensations are experienced in a different part than the part that is stimulated (alachaesthesia).
- Pain is experienced in a numb area (anaesthesia dolorosa).

Neuropathic pain is caused by lesions in the CNS or the peripheral nervous system (PNS). Injury of the CNS and PNS cause severe acute neuropathic pain (ANP) and may evolve into chronic pain complex regional pain syndromes.
13.10.2 Central neuropathic pain

Central neuropathic pain (CNP) is caused by pathology in the somatosensory tracts involving the spinothalamic tract, or trigeminothalamic tracts and the sensory cortex. Stroke, brain surgery and spinal cord injury are the most common causes of CNP. It affects approximately 8% of stroke victims and about 70% of patients with spinal cord injury. CNP also complicates multiple sclerosis, vascular malformations, tumours and infections (tuberculosis, syphilitic myelitis, abscesses, HIV).

Spinal cord injury can cause severe ANP, which is often complicated by chronic pain. Pain can develop weeks, months or years following spinal cord injury. Pain is experienced at the level or above the level of injury.

Stroke-related CNP appear soon, months or years after the stroke. It usually involves large parts of the body and is characterised by a sensation or mixture of sensations of aching, burning (causalgia), cold, crushing, shocking, stabbing, numbness, allodynia, hyperalgesia, allachaesthesia and hip pain. Other symptoms include intolerance to temperature change, fatigue, a vague numb sensation, hyperalgesia, allodynia, allachaesthesia and visceral pain. Nociceptive pain can also develop.

CNP is difficult to treat, and is resistant to many options. Treatment of the condition follows the principles used for the management of chronic neuropathic pain.

13.10.3 Peripheral neuropathic pain

Peripheral neuropathic pain (PNP) occurs after injury of the dorsal root ganglion, a peripheral nerve, or nerve plexus. Common aetiologies include metabolic disease (diabetes mellitus), infection (postherpetic neuralgia [PHN] following herpes zoster), ischaemia, injury (postsurgical, brachial plexus avulsion), entrapment (carpal tunnel syndrome, disc herniation with compression of a spinal nerve causing radicular pain, trigeminal neuralgia), autoimmune connective tissue disease (due to neurovasculitis), malignancy, drugs (antineoplastic agents, antiepileptic agents, vitamin deficiencies) and toxins (lead, mercury, arsenic, thallium, organic solvents [including glue sniffing]).

Approximately 1% of patients experience PNP after nonamputation surgery. In about half of these patients, pain persisted for at least a year. Procedures that carry a higher risk to develop ANP include limb amputation, thoracotomy, and mastectomy with axillary lymph node dissection. The mechanism of ANP in all these procedures involve peripheral nerve injury. Severity of postoperative pain may be the first indication of nerve injury and is a predictor of long-term pain. Insufficient postoperative analgesia is also complicated by prolonged postoperative pain.
Nerve injuries that are renowned for the most severe ANP include spinal cord injury, brachial plexus avulsion, burn injury and herpes zoster. Thermal injury and herpes zoster damage cutaneous nerves. This progresses to ANP and is often described as intense burning dysaesthesia (hot pain), stinging or pricking, beating and itching. These sensations often persist long after the lesions have healed.

Patients suffering from a neuropathic pain (CNP and PNP) often experience pain-related sleep disturbance, and vice versa. This aspect should be kept in mind when treating neuropathic pain.

At the end of this section, two very common ANP syndromes will be discussed, namely herpes zoster- and HIV-related pain.

13.10.4 General management of acute neuropathic pain
- If possible, manage the primary process that has led to ANP and prevent further damage (e.g., management of fractures, wound care and early adequate multimodal analgesia).
- Early pharmacological therapies to address the initiating process should be started as soon as possible. Once the doctor has missed the early therapeutic window, the risk of chronicity increases, which responds far less favourable to medication (e.g. herpetic neuralgia).
- Psychological support should be offered since psychological stress aggravates pain.

13.10.5 Pharmacological management of acute neuropathic pain

Several drugs have been tested and recommended for the management of CNP and PNP, irrespective of the causes. Although different drugs demonstrate better analgesic effects in some conditions, part of its beneficial effects may be ascribed to the effect on sleep and mood.

The efficacy of drugs in some painful neuropathies is unclear. For some conditions, a drug may be the ‘first-line recommendation’, while it may be an ‘add-on’ for another condition. However, several algorithms have been suggested, which can be applied (tried) in most conditions.

The difference in effects of drugs in different conditions may be ascribed to different pain mechanisms, different levels of pain, pharmacogenetic factors, etc. For example, pregabalin is useful in several conditions, but ineffective in the treatment of HIV-associated distal sensory polyneuropathy and radiculopathy. Apart from surgery, the best treatment option for trigeminal neuralgia is carbamazepine.

Regarding the influence of pathophysiology on treatment, painful neuropathies may have different mechanisms of injury, which may influence the efficacy of particular drugs in particular neuropathies. For example, neuropathies may be caused by either compression or noncompression mechanisms (toxic, trauma, ischaemic or infective). Compression neuropathy (e.g. radicular pain following disc herniation) has a different pathophysiology and is often not
successfully treated by the conventional drugs (e.g. the gabapentanoids). The same may apply to trigeminal neuralgia caused by vascular compression at the brain stem.

The efficacy of drugs is usually measured according to a global effect on pain (e.g. the VAS). However, the effect of analgesics used in neuropathic pain may be determined by the effect of the drug on a particular pain entity (e.g. the effect on mechanical [touch] allodynia and thermal allodynia). If these different aspects (total pain, differential pain) were tested, so-called responders to a particular agent reported in most studies, would not be real responders. For example, in central and peripheral nerve injury, IV lignocaine is not equally effective to suppress all the pain components, since patients experience relief of spontaneous pain and mechanical allodynia and hyperalgesia, but not thermal allodynia and hyperalgesia.

The recommendations in this section are based on the conclusions of several trials, review articles and meta-analyses. The recommendations include ‘should be offered’, ‘should be considered’, ‘less robust evidence’, or ‘no better than placebo’. These recommendations are based, for example, on meta-analyses that grouped recommendations on the size of the difference between treatment options, risk difference (reduction in pain in the active group minus that in the control group) and numbers needed to treat (NNT). For a difference in the proportions of patients with a pain reduction > 30–50%, a risk difference of > 20% is regarded as a large effect (NNT < 5), a risk difference of > 10–20% (NNT 5–10) as a moderate effect, and a risk difference of < 10% (NNT > 10) is regarded as a small effect. When reporting the mean reduction of pain from baseline on a Likert scale or VAS as compared to an alternative drug or placebo, a reduction difference of > 30% is considered a large effect, > 15–30% is a moderate effect, and < 15% is a small effect.

Several drugs are used off-label to treat neuropathic pain. This must be explained to the patient. Moreover, the patient must be aware that the drug does not change disease progression.

The following drugs are used to alleviate ANP: antidepressants, antiepileptic agents, membrane stabilisers, ketamine, opioids and capsaicin.

**Antidepressants**

These include the TCAs (e.g. amitriptyline, nortriptyline) and the SNRIs (e.g. venlafaxine and duloxetine).

Both TCAs have several adverse effects, including dizziness, insomnia or sedation, dry mouth, blurred vision, hypertension and tachycardia. These should not be used within two weeks of MAOIs and should not be used together with antihistamines, antihistamine-like agents (such as antipsychotic drugs) and antiemetics. TCAs have antimuscarinic effects and should be avoided in patients with glaucoma and prostate enlargement. These should also not be used with other serotonin reuptake inhibitors, including the SSRIs and tramadol.
Early amitriptyline reduces the development of PHN and has been used for relief of phantom limb pain, pain following hip surgery and painful diabetic peripheral neuropathy pain. However, amitriptyline is not beneficial in the treatment of HIV-related neuropathic pain. The dose of amitriptyline is a low dose (10 mg) at night, which is increased gradually up to 75 mg.

Blood levels of amitriptyline are increased by the inhibitors of cytochrome enzyme inhibitors, such as the protease inhibitor antiretroviral agents (e.g. ritonavir, lopinavir and atazanavir). Blood levels are decreased by the enzyme inducer carbamazepine.

Two SNRIs are recommended for neuropathic pain, namely venlafaxine and duloxetine. Neuropathic pain following chemotherapy and painful diabetic peripheral neuropathy can be treated with venlafaxine and duloxetine, while gabapentanoids are ineffective. Venlafaxine and duloxetine have a safer CV profile than the TCAs and these should not be prescribed within two weeks after stopping an MAOI.

Extended-release venlafaxine 75 mg daily for 2–6 weeks has been used with success. The dose of duloxetine is approximately 0.8 mg/kg at bedtime.

Duloxetine has several drug interactions: SSRIs (serotonin syndrome), neuroleptics (prolonged QT interval, dysrhythmias), anticoagulants (increased bleeding) and the triptans. The dose should be decreased in patients with decreased renal function. (See the SAMF for more complete information.)

**Antiepileptic drugs**

Antiepileptic agents, gabapentanoids (gabapentin and pregabalin), carboxamides (carbamazepine and oxcarbazepine), lamotrigine and topiramate have been used for ANP. Lamotrigine, topiramate and phenytoin have been used for trigeminal neuralgia.

- *Gabapentin* and *pregabalin* have been recommended as first-line treatment of several neuropathic pain syndromes. These drugs are GABA analogues with a structure similar to that of the amino acid leucine, but are inactive at GABA$_A$ (the benzodiazepines) and GABA$_B$ receptors (baclofen). Like opioids and ketamine, these agents inhibit the release of glutamate and aspartate from the dorsal root neurons to stimulate the sensory neuron in the spinal cord. The gabapentanoids affect the $\alpha2-\delta$-1 subunit of neuronal calcium channels on presynaptic membranes. Pregabalin has a higher affinity for the alpha-2-delta protein. Therefore, the dose of pregabalin is approximately six times lower than that of gabapentin.

Expression of calcium channels occurs in central and peripheral neurons following nervous system injury. The effect of the gabapentanoids on the $\alpha2-\delta$-1 subunit of these neuronal calcium channels may explain the efficacy of these drugs in CNP (spinal cord injury) and PNP (postherpetic neuralgia and diabetic peripheral neuropathy, trigeminal neuralgia). Although pregabalin is useful in several conditions, it is ineffective in the treatment of HIV-associated...
distal sensory polyneuropathy. Little evidence from randomised control trials support the use of gabapentanoids for the management of radicular and chemotherapy-induced neuropathic pain.

Apart from its effect on neuropathic pain, pregabalin improves sleep. This effect occurs within the first two days of treatment and contributes to its analgesic effect.

The adverse effects of gabapentin and pregabalin are similar and include sedation, fatigue, dizziness, irritability, cerebellar signs (dysarthria, tremor, ataxia, vertigo) and ocular symptoms (blurred vision, diplopia). Patients who experience adverse effects from one gabapentinoid usually experience the same effects from the other.

The gabapentanoids use the L-amino acid transporters in the gut for absorption. This transport system of gabapentin is saturable, while that of pregabalin is not saturated by large doses. The gabapentanoids are not metabolised by cytochrome enzymes and is excreted mainly by the kidneys. Therefore, the doses of these agents must be adjusted according to renal function tests.

The starting dose of gabapentin is approximately 2 mg/kg 12-hourly and may be increased gradually to a maximum of 20 mg/kg 12-hourly. The dose of pregabalin is approximately 1 mg/kg 12-hourly and may be increased gradually to 4 mg/kg 12-hourly. Pregabalin should not be stopped abruptly but withdrawn over no less than a week.

- Oxcarbazepines carbamazepine and oxcarbazepine are the first-line drugs for the management of trigeminal neuralgia. However, the most successful treatment of trigeminal neuralgia is surgery to decompress the nerve in the brainstem.

The dose of carbamazepine is approximately 1.5 mg/kg (100 mg) 12-hourly. This dose is increased by 1.5 mg/kg 12-hourly until pain is relieved. The maximum dose is approximately 16 mg/kg/day (1 200 mg). The MD is 5–10 mg/kg/day (400–800 mg).

Carbamazepine is not a ‘clean’ drug. It induces its own metabolism in the liver, necessitating an increase in doses. Therefore, blood levels should be monitored. It has several drug interactions, which should be investigated before prescribing the drug. Interactions occur with other anticonvulsants, antiretroviral drugs, TCAs, neuroleptics, MAOIs, lithium, SSRIs, cimetidine, erythromycin, tetracycline, rifampicin, calcium channel blockers (verapamil, diltiazem decrease metabolism of carbamazepine), oral contraceptives and glucocorticosteroids. Several of these drugs are also used for other pain conditions, and the necessary adjustments should be made.

Adverse effects of carbamazepine include drowsiness, nausea, dizziness, diplopia, ataxia, elevation of liver enzymes, lymph adenopathy, bone marrow suppression (agranulocytosis, thrombocytopenia, aplastic anaemia), and syndrome of inappropriate vasopressin secretion.
(hyponatremia). Therefore, blood levels, blood count and blood biochemistry should be performed after initiation of therapy.

Oxcarbazepine is a derivative of carbamazepine. It is cleaner than carbamazepine as it is converted into an active metabolite, which does not induce liver enzymes significantly. It has less adverse effects than carbamazepine, but also interact with calcium channel blockers, oral contraceptives, antiretrovirals and MAOIs.

The initial dose of oxcarbazepine is 4 mg/kg 12-hourly. This dose is increased gradually to effect weekly, up to a maximum of approximately 16 mg/kg/day. The effective dose is then decreased. The MD is 4–8 mg/g/day.

- Lamotrigine inhibits the release of glutamate (ketamine-like). Lamotrigine reduces pain experienced from HIV-related peripheral sensory neuropathy and trigeminal neuralgia. The dose is approximately 0.3 mg/kg/day, increased by 0.3 mg/kg/day after two weeks, and then increased by 1.5 mg/kg every two weeks if necessary. The total dose is divided and taken 12-hourly with a target dose of 3–4 mg/kg/day. Lamotrigine levels are decreased by enzyme inducers (carbamazepine and phenytoin) and by protease inhibitors (lopinavir, ritonavir). Adverse effects include sedation, insomnia, cerebellar signs, diplopia, blurred vision (myopia), dizziness, nausea, severe skin rash (Stevens-Johnson syndrome), desquamation and bone marrow suppression. This drug inhibits dihydrofolate reductase.

- Topiramate is a glutamate antagonist and GABA agonist. It is also a carbonic acid anhydrase inhibitor. The dose is the same as that for lamotrigine (i.e. approximately 0.3 mg/kg/day, increased by 0.3 mg/kg/day after two weeks, then increased by 1.5 mg/kg every two weeks if necessary). The total dose is divided and taken 12-hourly with a target dose of 3–4 mg/kg/day. Adverse effects are similar to that of lamotrigine. However, it also has several troubling adverse effects, including cognitive decline, dysgeusia, acral paraesthesia, metabolic acidosis, acute narrow-angle-glaucoma, renal calculi and it is teratogenic.

- Phenytoin may be used to manage a trigeminal neuralgia crisis. A dose of 14 mg/kg is administered intravenously over 20 minutes. This dose may be effective for up to two days, allowing other drugs to take effect.

**Membrane stabilisers**

Peripheral nerve injury increases expression of sodium channels, leading to a more positive membrane potential, which makes the nerves more excitable. Two sodium channel blockers have been tried, namely mexiletine and lignocaine. Evidence regarding the efficacy of mexiletine is lacking. Lignocaine is not absorbed orally, but the efficacy of IV lignocaine and lignocaine 5% patches have been used with success in PHN and trauma-related neuropathy. Several IV lignocaine ‘tests’ have been used. In CNP and PNP, lignocaine 5 mg/kg over 30 minutes improve spontaneous and mechanical allodynia and hyperalgesia for up to 6 hours (and for days
in some patients). Lidocaine 3 mg/kg over 3 minutes followed by 4 mg/kg over 60 minutes were effective in CNP and PNP. Although not investigated, these modalities may be useful in the management of an acute attack of neuropathic pain. Lignocaine 5% patches are used for herpes zoster- and HIV-related neuropathic pain.

**Opioids**

Despite several adverse effects, addiction potential and overuse pain syndromes, opioids may be used in the management of chronic nonmalignant neuropathic pain. Morphine, oxycodone and tramadol may be considered, but these have moderate effect sizes.

Although there is no firm evidence for its efficacy in neuropathic pain, tramadol is considered a second-line drug for ANP and exacerbations of neuropathic pain. It should not be used with SSRIIs and TCAs.

Tapentadol is a newer, weak μ-receptor agonist and norepinephrine reuptake inhibitor. It has been used for painful diabetic peripheral neuropathy.

**N-Methyl D-aspartate receptor antagonists: ketamine**

Ketamine 0.4mg/kg IVI has shown some efficacy in the treatment of ANP. This may be used for relief of acute exacerbations of neuropathic pain.

**Capsaicin receptor stimulation**

Capsaicin stimulates transient receptor potential vanilloid 1 (TRPV1) channels (capsaicin receptors) on nociceptors at the peripheral sensory nerve endings. TRPV1 is activated by exogenous and endogenous stimuli. These channels are activated by temperature higher than 43 °C, a low pH and substances in spices (e.g., capsaicin in chili peppers, and allyl isothiocyanate in mustard and wasabi). TRPV1 is involved in the detection of high temperature and thermoregulation. Stimulation of TRPV1 channels causes an intensely painful, burning sensation. Application of a high concentration causes overstimulation of nociceptors followed by a reversible reduction in nerve fiber density and extinguishing of nociceptor sensitivity. The capsaicin 8% patch does not have any systemic adverse effects, and a single application can provide pain relief for up to three months. It is useful in herpetic neuralgia as well as some painful HIV-related neuropathies.

13.10.6 Algorithm for the pharmacological management of acute neuropathic pain

- **First-line:** TCAs, gabapentanoids, SNRIs, topical agents (lignocaine, capsaicin)
- **Second-line:** opioids (tramadol), combinations of first-line agents (taking into account drug interactions)
- **Third-line:** antiepileptic agents, SNRI antidepressants, NMDA antagonists
13.10.7 Acute herpetic neuralgia

Acute herpetic neuralgia (AHN) results from reinfection by herpes varicella viruses that were dormant in a dorsal root ganglion or trigeminal ganglion for several years. The incidence of AHN increases with age. The pain of AHN often starts as paraesthesia, allodynia, hyperalgesia and dysesthesia (aching, severe itching, burning and electric shock-like pain). These symptoms often precede the typical dermatomal herpes zoster vesicular rash. In approximately 15% of patients, AHN is complicated by PHN (i.e. persistence of pain for more than three months after the rash has disappeared). Approximately 50% of patients experience pain for longer than a year.

Administering an antiviral agent within 72 hours and early medication for ANP decreases the incidence of PHN, which is often difficult to manage.

Systemic treatment should be offered as soon as possible. The systemic agents recommended for AHN is the same as for ANP, namely a TCA, gabapentin or pregabalin, and an opioid (oxycodone or morphine). Lidocaine 5% should be offered. Aspirin in ointment or cream may be tried.

A single application of a capsaicin 8% patch provides pain relief for up to 12 weeks and does not have any systemic adverse effects. Application of the patch causes pain or discomfort for approximately 6 hours, but is well tolerated. Patients with more pain before the application of the patch experience less capsaicin-related discomfort than patients with less pain. Adverse effects are limited to transient local erythema and treatment-related discomfort.

13.11 HIV-associated pain

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 following:

- The effects of HIV on the peripheral or CNS (neuropathic pain).
- Opportunistic infections or neoplasms as a result of immunosuppression.
- Antiretroviral drugs (ARVs) that may be neurotoxic. However, the prolonged use of highly active antiretroviral therapy (HAART) decreases the prevalence and severity of neuropathic pain.

As for any patient presenting with pain, anatomical, physiological, pharmacological, grading (distribution, type, duration, etc.) and psycho-social factors should be assessed to guide appropriate management. Nociceptive pain is treated with ‘typical’ analgesics, while neuropathic pain is treated with ‘atypical analgesics’.
Pain in HIV patients is frequently undertreated. Clinician-, patient- and system-related factors account for this, including underestimation of pain by the clinician, fear of analgesic adverse effects by the clinician and patient, and drug interactions between analgesics and ARVs.

13.11.1 Principles of managing HIV-related pain

Management of the pain must be individualised and directed, depending on the type of pain; whether nociceptive or neuropathic (Table IV). Acute nociceptive pain is managed according to the guidelines discussed under acute nociceptive pain, but may fail to relieve ANP. ANP is managed according to the guidelines discussed above.

Since the use of HAART decreases the occurrence of opportunistic infections, including that of the CNS, peripheral sensory polyneuropathy has become the most important HIV-related neurological complication. The most common forms of sensory neuropathy are infection-related distal sensory polyneuropathy (direct nerve injury by the virus, and effects of viral protein coat on chemokines and cytokines) and antiretroviral-induced mitochondrial dysfunction causing a toxic neuropathy.

Amitriptyline is not effective in the management of HIV-related neuropathic pain. Gabapentin improves pain and sleep disturbances, but pregabalin is ineffective. Lamotrigine of approximately 4 mg/kg/day relieves pain in HIV-related neuropathic pain. The lidocaine 5% patch and high-dose capsaicin cream are effective.

Table IV: Recommended approach to pain in HIV/AIDS

<table>
<thead>
<tr>
<th>Pain</th>
<th>Aetiology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-related neuropathic pain</td>
<td>HIV, HAART (stavudine, didanosine), isoniazid, neoplasms, oncotherapy, herpes zoster</td>
<td>Gabapentin or lamotrigine, topical lignocaine and capsaicin</td>
</tr>
<tr>
<td>Abdominal pain, headache</td>
<td>Infections, neoplasms</td>
<td>As for nociceptive and neuropathic pain</td>
</tr>
<tr>
<td>Oral, pharyngeal pain</td>
<td>Aphthous ulcers, herpes simplex virus, cytomegalovirus ulcers, necrotising gingivitis</td>
<td>Antibiotics for gingivitis, oral or IV acyclovir, or oral valacyclovir, are used for HSV Mouthwash containing benzydamine and topical corticosteroids</td>
</tr>
<tr>
<td>Genital ulceration</td>
<td>Herpes simplex</td>
<td>Acyclovir or valacyclovir, plus standard analgesia</td>
</tr>
<tr>
<td>Stroke</td>
<td>Spasticity, muscle spasms</td>
<td>Oral baclofen as the first choice, and diazepam and dantrolene alternatively</td>
</tr>
<tr>
<td>Central neuropathic pain</td>
<td>Following a stroke or intracranial neoplasms</td>
<td>Gabapentin, SSNRIs, IV morphine</td>
</tr>
</tbody>
</table>
Oesophageal pain and odynophagia  
Candida, cytomegalovirus, aphthous ulcers, herpes simplex  
Upper endoscopy ulcer appearance, biopsy and viral cultures help to make a definitive diagnosis  
Oral fluconazole 200–400 mg/day for 14–21 days, or IV if patient cannot swallow  
Treat HSV with acyclovir 15 mg/kg/day IVI or 200 mg 5 times/day p.o. for 14–21 days  
For CMV, ganciclovir IVI (but has many adverse effects)

Kaposi sarcoma  
Malignancy  
Analgesics, radiotherapy

Herpes neuropathy  
Herpes zoster  
Early treatment of PHN with antiviral agent and TCA

13.12 Acute cancer pain

This section focuses on nonsurgical pain in the palliative scenario. The aim of analgesia in this setting is a VAS of < 4/10 with movement. The analgesic plan may differ from the approach to nonmalignant pain, as the focus is more on patient comfort, while concerns about adverse effects are more in the background. Both the patient and the caregivers must understand this approach. Of course, this does not mean that clinicians have the freedom to prescribe drugs at dosages that may cause harm, even in uncompromised patients. Caregivers should take note of patients’ complaints, fears and concerns. No drug can replace empathy.

Changes in the characteristics of pain may signify progression of local or distant disease, a transition from acute nociceptive pain to ANP (CNP or PNP) or from acute to chronic pain, an appearance of drug tolerance, or changes in drug clearance due to a decline in vital organ function (cardiac, hepatic, renal, blood), and psychological changes (e.g. anxiety and depression). Moreover, the adverse effects of oncotherapy often cause severe pain. These include oncotherapy-related peripheral neuropathy and oral mucositis. The oncotherapy-related pain of mucositis can be treated effectively with a ketamine mouthwash. The concentration is 4 mg/ml and the dose is 5 ml (20 mg) 4-hourly, if necessary. The patient must rinse their mouth for a few minutes and then spit out the solution.

Patients and caregivers must take part in the analgesia plan; they should know what to expect, what to look for, how to manage adverse effects, how to adjust doses, and when to seek help.

Nociceptive and neuropathic pain is managed according to guidelines as discussed above; often a combination of drugs is used for both types of pain. Regarding opioids, long-acting dosage forms, namely slow-release oral tablets and transdermal delivery systems (patches), are often used. Transition from short-acting oral or IV opioids to sustained-release tablets or patches is usually not complicated. The total daily dose of a short-acting or parenteral dosage form is determined, and then replaced by the long-acting form. This can be done for an IVI to patch, short-acting oral to long-acting, or even from one opioid to another using the daily MME
(Table I). The following opioids will be discussed briefly: morphine, oxycodone, fentanyl and buprenorphine.

- **Morphine**: The total daily parenteral dose of morphine is determined. Morphine has an oral bioavailability of approximately 30%. Therefore, the total daily oral dose is approximately three times the IV dose. This oral dose is offered as a long-acting tablet containing the daily dose. These are available as 10 mg, 30 mg and 100 mg. The long-acting tablet is taken as 50% of the total dose 12-hourly. With the development of tolerance, higher doses will be required. The new dose is determined using the morphine solution/syrup (5 mg, 10 mg, 20 mg or 100 mg/5 ml). For breakthrough pain, the syrup is used. The dose is 0.2–0.5 mg/kg 4–6-hourly. The syrup is titrated up until the VAS has decreased to < 4/10 with movement. The new total daily dose is the total of the long-acting tablet plus the total of the solution. Once the total morphine dose has been established, this is replaced by a slow-release tablet with an adjusted morphine content.

- **Oxycodone**: It has an oral bioavailability of 50% (Table I). If the total IV dose is known, the oral dose is twice that amount. Half of this dose is given p.o. 12-hourly as the prolonged-release tablet (5 mg, 10 mg, 20 mg, 40 mg and 80 mg). The short-acting 5 mg tablet is used 4–6-hourly for breakthrough pain. The total daily dose is determined and the long-acting dose is adjusted accordingly.

- **Buprenorphine**: It has an oral bioavailability of 50%. The total IV dose is determined and the oral dose is twice the total IV dose. This amount is divided by 4 and taken 6-hourly. If the oral dose is known, the IV dose can be calculated (50% of the oral dose) and the IV dose per hour is calculated (total IV dose/24). The prolonged-release patch that delivers the calculated hourly dose, is used. The patches available are 5 µg/hour, 10 µg/hour and 20 µg/hour.

- **Fentanyl**: This is given IVI. The total daily dose is known, and the hourly dose can be calculated. The prolonged-release patch that delivers approximately that amount is then prescribed. These patches deliver 12 µ/hour, 25 µ/hour, 50 µ/hour, 75 µ/hour or 100 µ/hour. To adjust the patch dose, the patient must be admitted and fentanyl administered IVI using a PCA pump. The new total daily dose is determined and the most appropriate patch is applied.

### 13.13 Opioid tolerance

(Also see opioid tolerance in the ICU – section 13.4.1)

Opioid tolerance is a common cause for the failure of opioid analgesia. Exposure to an opioid, particularly as the sole analgesic, gives rise to pharmacodynamic tolerance (loss of activity, not due to faster drug clearance but to decreased analgesic effect). Tolerance develops to the adverse effects of opioids, namely sedation, hypoventilation and nausea, but not to constipation and miosis.
Tolerance results from alterations in G-protein coupling to the opioid receptor, changes in receptor trafficking between the neuronal surface and cytoplasm, and an increase in the number and sensitivity of NMDA receptors as a result of central sensitisation.

Tolerance in the perioperative setting can be attenuated by preventive and/or prolonged blocking of pain impulses along the pain pathway through the following non-opioid agents:

- Local analgesics as a *continuous* local, regional or neuraxial infusion.
- Paracetamol and an NSAID, used before considering opioids.
- De-escalating opioids as soon as possible.
- Multimodal analgesia (co-analgesia): apart from paracetamol and an NSAID, a combination of usually two analgesics with different pharmacodynamics (e.g. an opioid, ketamine, dexmedetomidine and a gabapentanoid).

Regarding multimodal analgesia, it is difficult to interpret studies due to the heterogeneity of the studies: number of studies included, number and type of participants, studies used different drug combination, different dose ratios. Studies also administer analgesics according to different regimens, for example, PCA of (usually) two drugs, always an opioid with a non-opioid in the same mixture, PCA an opioid with a concurrent non-opioid infusion, concurrent (in the same mixture) infusion of an opioid plus a non-opioid, concurrent (in the same mixture) infusion of two non-opioid with addition of a low-dose opioid on a prn basis, and different opioids.

Several of these combinations have been tested; anaesthesiologists, using fuzzy logic (an integration of a sound knowledge of experience), are very good at compiling these recipes. Very often, these recipes are found in meta-analyses, which often both confirm the utility of these combinations, and also point out the deficiencies of studies or the fallacies of some combinations.

*Primary outcomes* usually are postoperative pain intensity, opioid consumption over different periods, and patient satisfaction. *Secondary outcomes* usually include sedation, hallucinations, hypoventilation, hypoxaemia, hypotension, brady- or tachycardia, nausea, vomiting and pruritus.

Postoperative PCA opioid-dexmedetomidine combinations decrease pain intensity, opioid consumption and adverse effects, as compared to an opioid only.

An example of an opioid-dexmedetomidine PCA regimen is that of Nie et al.:

- **Mixture**: sufentanil 100 µg + dexmedetomidine 300 µg diluted to 100 ml (This is a very expensive mixture)
- **Background infusion**: sufentanil 0.015 µg/kg/h + dexmedetomidine 0.045 µg/kg/h
- **PCA dose**: sufentanil 0.023 µg/kg + dexmedetomidine 0.07 µg/kg
- **Lockout interval**: 8 minutes
An example of an opioid-ketamine PCA regimen is that of Javery et al.:
- **Mixture**: morphine 100 mg + ketamine 100 mg diluted to 100 ml
- **No background infusion**
- **PCA dose**: 1 ml
- **Lockout interval**: 6 minutes

Once opioid tolerance is diagnosed, the following steps may be taken:
- Management is similar to that of ANP, including amitriptyline or gabapentanoids.
- The patient may continue with the normal opioid dose, while additional doses are administered, either intravenously or via a transcutaneous patch.
- Opioid rotation may be applied in the tolerant patient. There are significant differences in the interaction between different µ agonists and the µ-receptor which go beyond the effect on second messenger systems after binding, including the rate of receptor trafficking, and possibly even effects on receptor synthesis and 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. The following approach to opioid rotation is used:
  - Calculate the equianalgesic dose of the new opioid based on equianalgesic tables.
  - Start the new opioid at a dose 25–50% lower than the calculated equianalgesic dose.
  - Select an appropriate dose within this window, using clinical judgment as to the applicability of the equianalgesic dose table to the specific characteristics of the opioid regimen (i.e. p.o. or IVI).
  - Reassess pain severity to determine whether an additional 15–30% dose increase or decrease should be allowed to improve efficacy or to minimise adverse effects.
  - Evaluate the response frequently and titrate dose of the new opioid up or down to optimise the effect. If supplemental doses are used, these should constitute 5–15% of the total daily dose and should be administered according to dose intervals appropriate for the particular opioid.

**Bibliography**


14. Opioid minimisation for acute pain management

For at least 10 000 years, opiates derived from the opium poppy were the only reliable analgesics used by humans. During the twentieth century, synthetic opioids were increasingly used, particularly in anaesthesia, to such an extent that editorials were written up to the mid-2007s decrying ‘oligoanalgesia’ due to unreasonable withholding of opioids.

Subsequently, there are increasing concerns regarding the use of opioids in medical practice, particularly anaesthesia, for two major reasons, namely (i) addiction and overdose and (ii) respiratory depression.

14.1 Prescription opioid addiction and overdose

- This has become a major problem, largely confined to the USA due to unique issues with the prescription of opioids in this country. Despite making up just less than 5% of the world population, Americans consume more than 80% of opiates and opioids used in the world. Regulation has lagged inappropriate industry promotion to the extent that emergency medical services now carry naloxone as a standard drug and even fire services regularly treat opioid overdoses.
- Opioids remain the ideal drug to manage severe pain such as postoperative pain. Presently, drugs which provide analgesia without addictive effects are undergoing trials and the first of these is oliceridine (TRV130). Animal trials have been promising and early human trials are underway.

14.2 Postoperative opioid respiratory depression

This has become an increasing problem in the so-called first world due to the epidemic of obesity:
- A BMI of more than 30 kg/m$^2$ is associated with an increasing incidence of OSA, which is further increased after surgery under GA.
- As a patient’s BMI rises to > 40 kg/m$^2$, reduction of weight purely through diet and/or exercise is unlikely and procedures such as gastric banding or bypass may be required to significantly reduce caloric uptake. These procedures require GA with persistent risk of airway obstruction from the morbidly obese state.
- However, OSA may also be present without a raised BMI. This may be managed surgically by procedures such as the uvulo-palato-pharyngoplasty (UP-3). Once again, airway patency will persist or be worsened in the immediate postoperative period.

14.3 Interventions to reduce opioid requirements following general anaesthesia

- The interventions discussed below exclude neuraxial, regional and LA blocks as these are extensively covered elsewhere in these guidelines.
There are two broad categories of intervention: non-pharmacological and pharmacological.

14.3.1 Non-pharmacological interventions

**Transcutaneous electrical nerve stimulation**

TENS is a pain relief technique that involves passing a low-intensity electric current between cutaneous electrodes through the painful area. TENS devices generate biphasic pulsed currents with adjustable pulse amplitude (1–60 mA), pulse frequency (1–200 Hz), pulse duration (50–200 μs), pulse patterns (continuous, intermittent trains or bursts) as well as modulated amplitude, modulated frequency and modulated duration. There are minor differences in the technical output specifications of standard TENS devices.

TENS can progress from paraesthesia to muscle twitching to pain different from the pain experienced before the application of TENS. It has been used for postoperative pain relief since the 1970s with inconsistent results and it has still not been subjected to a substantial RCT, mainly due to significant difficulties with blinding.

**Perioperative language**

Humans are sensitive to language use, particularly in stressful situations such as the perioperative period. In particular, negative expressions are not comprehended, the primary concept being understood without the minimising modifier (e.g. when taking blood, if a practitioner tells a patient it will be ‘just a little scratch’, ‘little’ will be ignored and ‘scratch’ will be emphasised).

This has been studied in a perioperative setting where a pain score was compared to a comfort score after a CS. One group of patients were asked to rate their pain from 0 to 10 with 0 = no pain to 10 = worst possible pain, compared to another group of patients who were asked to rate their comfort with a score of 0 = least comfortable to 10 = most comfortable. In the latter group, use of the word ‘pain’ was limited as far as possible. Pain scores and analgesic consumption were significantly reduced in the comfort group.

**Acupuncture**

The use of needles in specific locations has been done for centuries, particularly in Asian medicine. Acupuncture is largely applied in outpatient settings to deal with chronic pain. However, there is an increasing application to acute pain in perioperative settings. The major limitation, however, is the availability of practitioners who are able to apply acupuncture.

**Psychological therapies**

Low back pain is a condition that is associated with difficulty in successful treatment, particularly after surgery. In a randomised study of 90 patients from Denmark (59 study patients; 31
controls), CBT of 4 three-hour sessions was compared to standard care. The CBT group had superior mobility and postoperative pain relief. This is similar to studies that demonstrated small but consistent improvement in pain scores.

**Music**

Music has proven useful to reduce the perception of pain, particularly of procedural pain such as dressing changes for burns. Several anaesthesiologists will ask patients to bring their music player with their favourite tracks to the operating room with them. The practitioners can then play the music at a comfortable level during the time of induction. As hearing is the last sensation to be anaesthetised and the first to return, the music is continually played even in the recovery room. The pleasant sounds appear to improve postoperative outcomes.

**Hypnosis**

Hypnosis is defined as inducing a state of consciousness in which a person apparently loses the power of voluntary action and is highly responsive to suggestion or direction. It is used in therapy typically to allow modification of behaviour. In the context of this section, it is used to modify the response to pain. The usefulness of hypnosis is limited by the following:

i. The unavailability of suitably trained therapists.

ii. Up to 20% of patients do not respond to hypnosis.

iii. The effect of a hypnotic treatment varies in duration and may require frequent repetition.

**Sleep disorders**

Insomnia is exceedingly common in all hospital settings but particularly in HCUs. A consistent complaint from patients discharged from HCUs is the dreaded bath between 3 and 4 am. A major cause of disorientation leading to delirium in patients over the age of 60 is sleep deprivation. Yet this is very common in modern ICUs and a point which all can improve.

**Manual therapies**

This is beyond the scope of this guideline.

14.3.2 Pharmacological interventions

**NSAIDs and paracetamol**

These have been extensively covered in this guideline and will not be discussed further. These have a central role in reducing opioid requirements for pain relief.
**Ketamine**

The NMDA receptor antagonist, ketamine, is a drug widely used in veterinary practice. Since this drug causes the least CV depression of available anaesthetic agents, it is particularly useful in the management of unstable trauma and septic patients. Oral as well as relatively painless IM and SC administration make it a useful drug in paediatric applications such as suturing and establishing IV access.

For the management of acute pain, ketamine can provide profound analgesia, with a dose of 2 mg/kg intravenously, allowing for procedures as extensive as a CS to be performed. Ketamine is useful as an adjunct to other agents in analgesic regimens (e.g. an infusion of 0.2 mg/kg/hour and PCA with a bolus of 2.5–5 mg and a lockout time of 5–10 minutes).

**Lignocaine**

LA provided by lignocaine is well-recognised. Less well-known is that, as a sodium channel blocker, lignocaine is also an extremely effective analgesic. Owing to its short duration of action, lignocaine needs to be given as a continuous infusion (CI) at a rate of 1.0–1.5 mg/kg/hr.

**Dexmedetomidine**

The α₂-receptor agonist, dexmedetomidine, has largely replaced clonidine, particularly in South Africa, where clonidine is not available as an IV preparation. The oral formulation (Dixarit®) is a 25 µg tablet used for migraine treatment which is impractical for use in sedation.

Dexmedetomidine provides a unique form of sedation that includes profound analgesia. The patient is sedated but rousable, returning to sleep within a short time. RR and haemoglobin oxygen saturation are unaffected.

Sedation is initiated by a bolus dose of 0.5–1 mcg/kg delivered over 15–30 minutes. A push injection bolus can cause severe hypertension and bradycardia. Maintenance will require an infusion of 0.2–0.9 µg/kg/hr. Onset and offset of sedation is slow and functions as a baseline for other sedative agents. The requirement for other sedatives such as ketamine, lignocaine or opioids (rarely required) is reduced by at least 40%, up to 80%. During the management of difficult airways, dexmedetomidine is an extremely useful adjunct, improving patient comfort and cooperation without affecting airway obstruction.

**Magnesium sulphate**

The second most common intracellular cation is magnesium. In terms of pain management, magnesium acts synergistically with ketamine as an NMDA-receptor antagonist. Administration requires an LD of 30–50 mg/kg over 15 minutes followed by an infusion of 10–30 mg/kg/h aiming for a serum level of 2–4 mmol/l. Clinically, deep tendon reflexes can be monitored.
Magnesium administered to patients with postoperative pain reduces opioid consumption but has less effect on reducing opioid-related side effects.

Magnesium is excreted by the kidneys. Therefore, special care should be taken in patients with impaired renal function.

**Gabapentinoids**

These anticonvulsant drugs used extensively in chronic pain management, showed initial promise in the management of acute pain. However, after a comprehensive meta-analysis, these are no longer recommended.

**Esmolol**

Decreased opioid requirements with subsequent decrease in opioid side effects, both intra- and postoperatively. Intraoperatively a patient will respond to a noxious stimulus through increased heart rate, BP or both. Esmolol and fentanyl have similar haemodynamic effects, both reducing the heart rate and BP. Studies reviewed in a 2018 meta-analysis have demonstrated similar analgesic efficacy whether esmolol or fentanyl were administered in response to predetermined haemodynamic changes. Patients given esmolol had significantly fewer opioid-related side effects, including sedation, nausea and vomiting.

Unanswered questions, however, include the following:

1. Is the effect of esmolol on perioperative pain a class effect common to all β-blockers or unique to esmolol?
2. Should β blockade with esmolol or another β-blocker be extended into the postoperative period? If so, for how long?

### 14.4 Opioid-free analgesia

LA techniques were pioneered in KwaZulu-Natal, South Africa and remain the mainstay of postoperative pain relief from simple infiltration to complex ultrasound-guided blocks.

Baseline systemic analgesia is based on paracetamol 1 g 6-hourly in adults and an NSAID as indicated according to specific comorbidities.

J-P Mulier pioneered the concept of OFA (opioid-free anaesthesia/analgesia) in his hospital in Brugge, Belgium. This interest was born out of necessity, as he was anaesthetising an increasing number of super morbidly obese patients (BMIs > 60 kg/m²) with significant OSA who were exquisitely sensitive to opioids. He found no difficulty in providing OFA and very rarely resorted to a remifentanil infusion. Usually, he succeeded with a combination of desflurane and dexmedetomidine intraoperatively. During the latter stages of the operation, patients received IV paracetamol and ketorolac if there was no renal impairment.
In anticipation of the postoperative multimodal analgesic, infusion LDs of the component drugs would be given as follows:
1. Ketamine 0.5 mg/kg
2. Lignocaine 1 mg/kg
3. Magnesium 30 mg/kg

The infusion recommended by Dr Mulier is given in Appendix 1. This infusion commenced during the closing stage of surgery. At the end of surgery with muscle relaxation reversed and adequate breathing established, the patient was extubated.

Any complaints of pain were carefully evaluated and, if required, treated with no more than 1 mg of morphine at 30-minute intervals so that not all, but the vast majority of anaesthetics were opioid-free. Tramadol (50 mg) may be preferred. In the ward, the patient could be out of bed within two hours, walking in the ward within six hours and fully mobilised within 24 hours.

Dr Mulier’s results are reproducible as demonstrated by pro vs con articles assessing the efficacy of OFA in breast reduction surgery.

14.5 Conclusion

Pain is something we all have or will experience at some point in time. This short summary provides a few interventions that may assist not only the patients, but also the practitioner when that most terrible of masters makes its appearance.
Appendix 1

24-hour background analgesic infusion

J-P Mulier, Oostende-Brugge, Belgium

Based on an 80 kg patient over 24 hours (multiplication factor for each drug = 24 × 80 = 1,920).

Amounts are rounded off to available ampoule sizes.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/kg/hour</th>
<th>kg</th>
<th>Hours</th>
<th>Total/24 h</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine</td>
<td>0.05 mg</td>
<td>80</td>
<td>24</td>
<td>100 mg</td>
<td>2 ml of 50 mg/ml</td>
</tr>
<tr>
<td>Lignocaine</td>
<td>1 mg</td>
<td>80</td>
<td>24</td>
<td>2,000 mg</td>
<td>20 ml (10%; 100 mg/ml)</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>0.1 µg</td>
<td>80</td>
<td>24</td>
<td>200 µg</td>
<td>2 ml (100 µg/ml)</td>
</tr>
<tr>
<td>MgSO₄</td>
<td>2.5 mg</td>
<td>80</td>
<td>24</td>
<td>5 g</td>
<td>10 ml (50%; 0.5 g/ml)</td>
</tr>
<tr>
<td>Dextrose 5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>500 ml</td>
</tr>
</tbody>
</table>

Total volume 534 ml

Infusion rate 534/24 = 22 ml/hour

(Remark: As far as the author knows, DW5% 500 ml is not available in South Africa. Therefore, the total drug volumes (34 ml) can be added to 200 ml of DW5% = 234 ml and administered at 234 ml/24 hours = 9.75 ml/h ≈10 ml/h.)

Reviews


Bibliography


