

# Optimising pain management- An update

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## Abstract

The key to optimal pain management is the ability to effectively monitor the patient to ensure pain relief, whilst minimising or managing the side-effects of pain medication. This will only be possible through the collaborative work of all healthcare professionals managing the patient. This article provides an overview of the requirements for optimising pharmacotherapeutic pain management.

**Keywords:** pain, opioids, non-steroidal anti-inflammatory drugs, acute pain, chronic non-malignant pain, cancer pain, post-caesarean section pain, analgesics

## Introduction

Pain is a health problem in its own right, not 'just' an indicator of an underlying disease or injury process.<sup>1</sup> It is subjective; the fact that an individual may not be able to adequately describe or explain the pain being experienced does not refute the need for an appropriate pain-relieving strategy.<sup>2</sup>

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.'<sup>3</sup>

## Types of pain

There are three types of pain, namely acute pain, chronic non-cancer (non-malignant) pain and cancer pain (chronic malignant pain). These types are explained in more detail below.

### Acute pain

This is defined as pain of recent onset and of short or limited duration. The pain is related to an identifiable cause. It includes nociceptive (somatic or visceral pain), namely pain caused by surgery, medical procedures, post-traumatic pain, burn trauma, labour, spinal cord injury, acute headache, HIV/AIDS, sickle cell crisis, trigeminal neuralgia, pancreatitis and other forms of colic, myocardial infarction and other major cardiac events, as well as so-called acute-on-chronic pain.<sup>1,3-5</sup>

### Chronic non-cancer or non-malignant pain

This is pain in one or more anatomic regions of the body that persists for longer than three to six months and/or beyond an expected time frame for tissue healing. It may be continuous or intermittent, and may continue in the presence or absence of

any evident pathology. This kind of pain usually causes a form of disability or distress, is usually not amenable with routine pain control methods and complete resolution of the pain may never occur. Examples of such pain are chronic musculoskeletal pain (fibromyalgia), chronic headache, irritable bowel syndrome, back pain, migraine, bone pain, neuropathic pain, visceral pain and chronic pain in sickle cell anaemia.<sup>1,5-7</sup>

### Chronic malignant or cancer pain

Cancer is the abnormal growth of cells, in any part of the body, and can invade and spread to distant sites of the body. Cancer can have severe health consequences, and is a leading cause of death. Effective treatment, including pain relief and palliative care, help increase cancer survival rates and reduces suffering.<sup>8</sup>

Debilitating pain can be caused either by the cancer itself or as a result of the cancer treatment through surgery, chemotherapy or radiotherapy. It may also be intermittent or continuous. The ideal goal in cancer management or treatment is to cure or considerably prolong the life of patients and to ensure the best possible quality of life to cancer survivors. However majority of cancer patients may be in the advanced stage of the disease when first seen by a doctor. Thus providing relief from pain and other distressing symptoms may be the best option for such patients. The focus on this kind of pain is more on symptom control than function, when compared to chronic non-malignant pain that has more of a rehabilitative focus.<sup>5,7,8</sup>

### Providing optimal therapy for pain management

Optimal pain management involves utilizing a combination of non-opioid, opioid analgesics, adjuvants and non-pharmacologic strategies. The approach must be adapted such that it is possible in resource limited areas as well. Treatment

guidelines should therefore consider the acute and chronic phase of the pain state, and recommend the appropriate pharmacologic or non-pharmacologic treatment using evidence based recommendations. They should also indicate when a single mode of treatment is appropriate and when multiple modes are required.<sup>1,9</sup>

The multimodal approach to pain management involves administering two or more analgesics with different mechanisms of action. The routes of administration may also be different. This approach is aimed at providing a synergistic effect of analgesia using the lowest possible doses of these medications than if they were used alone.<sup>10</sup>

### Access to new drugs and new formulations

Newer formulations available for the management of moderate to severe pain can assist in achieving effective levels of analgesia in patients. This section will focus on the latest developments in pain management in South Africa, with the emphasis on:

- Oxycodone Hydrochloride
- Buprenorphine
- Hydromorphone
- Tapentadol
- Fentanyl
- Lornoxicam.

### Oxycodone

Oxycodone is a mu ( $\mu$ ) agonist with partial kappa ( $\kappa$ ) activity, use to treat moderate to severe pain.<sup>11</sup>

It is a semisynthetic analgesic derived from the opium alkaloid thebaine.<sup>9,10</sup> It has been used for many years in combination with paracetamol for chronic pain, but the latest clinical trial data pointed out that it may be more efficacious and safe when used alone as a controlled-release or an immediate-release formulation.<sup>12,13</sup>

Therefore, the two different formulations are:<sup>9,14</sup>

- **Immediate-release preparations (conventional):** The conventional preparations of oxycodone can be used orally for the management of moderate to severe pain in conditions such as bursitis, dislocations, etc. It may also be used for postoperative pain management, post-extraction and postpartum pain.<sup>14</sup> These preparations may be available as capsules in 5, 10 and 20 mg strengths.<sup>9</sup> After oral administration an analgesic effect may occur within 10-15 minutes, and may persist for 3-6 hours.<sup>14</sup>
- **Extended-release preparations:** Used orally in moderate to severe pain, in situations where continuous analgesia is needed, for instance in cancer and non-malignant pain, or pain during rehabilitation.<sup>14</sup> The extended-release tablets are **not** for use in preoperative analgesia, or for pain during the immediate phase post-surgery, nor for mild short-term or acute use. The preparation should also **not** be used on an as-needed ('*prn*') basis.<sup>13-15</sup> Available preparations include 10, 20, 40 and 80 mg. Due to its abuse potential the 160 mg extended-release formulation has been withdrawn from the market.<sup>13,14,15</sup> After administration the onset of analgesia may occur within one hour and may provide analgesia for up to 12 hours.<sup>14</sup> The

extended-release tablets **should not be** broken, crushed or chewed as this may result in a toxic dosage due to the rapid release of the drug. Patient counseling should include dietary advice (intake with a high-fat meal may increase peak plasma levels) and the fact that the matrix core can be passed in the stool as it does not completely dissolve.<sup>14,15</sup>

Oxycodone has been implicated in its use in other countries as one of the most abused opiate agonists. Patient information should include information about its abuse potential and the risk of theft of their medicine.<sup>14</sup> Side-effects are similar to those that occur with the other strong opioids, including nausea, vomiting, sedation, constipation, dizziness and pruritus.<sup>14, 15</sup> It may cause respiratory depression and these effects should be monitored. In patients suffering from renal impairment (with a creatinine clearance of  $\leq 60$ ml/min) the initial dosage of the extended-release formulation should be reduced and adjusted according to the patient's clinical status.<sup>14,15</sup> In patients with hepatic impairment extended-release formulations should be initiated at 33-50 % of the normal dosage.<sup>14, 15</sup>

### Hydromorphone

Hydromorphone is a hydrogenated semi-synthetic potent mu ( $\mu$ ) -opioid with a weak affinity for kappa ( $\kappa$ ) receptors that is used to treat moderate to severe pain.<sup>12,16,17</sup> It is 5-10 times more potent than morphine and due to alterations in its chemical structure (a keto-group instead of hydroxyl group at position 6 – when compared to morphine) it has enhanced distribution to the central nervous system.<sup>18</sup>

A controlled-release formulation of oral hydromorphone (OROS<sup>®</sup>) is the only one that is currently approved for the South African market (4 and 8 mg - Jurnista<sup>®</sup>), (although powder and oral solutions, injections and rectal suppositories are available in the USA).<sup>14</sup> This formulation maintains consistent hydromorphone plasma concentrations throughout the 24-hour dosing interval, ensuring long-lasting analgesia. The hydromorphone is released from the matrix system actively by the dosage form itself with minimal effects from food and alcohol (as it is not influenced by pH or gastric motility).<sup>14,16,17</sup>

Hydromorphone is well absorbed orally and when compared to morphine it has a faster onset of action but with a shorter duration of action. This can be used as an advantage in the use of short-term analgesia.<sup>18</sup>

Hydromorphone has the same side-effect profile as other opiate agonists; however, nausea, vomiting, constipation and euphoria may be less pronounced with hydromorphone than when compared to morphine.<sup>14,19</sup> Safety and efficacy has not been established in children, and in patients over the age of 65 years (clinical trials did not involve enough subjects to determine response in this population as compared to younger patients).<sup>14,5</sup>

### Buprenorphine

Buprenorphine is a partial opioid receptor agonist (i.e. an agonist/antagonist). It binds to the mu ( $\mu$ ) receptors with greater affinity but has a low intrinsic activity. It also has affinity for the kappa ( $\kappa$ ) receptor. The rate of dissociation from the  $\mu$  receptors is slow, which results in an antagonistic effect to any other opioids that

may be co-administered with buprenorphine.<sup>19,20</sup> Buprenorphine is a partial agonist, and when compared with full agonists, has a lower liability for the induction of physical dependence.<sup>5,20</sup>

When taken orally, buprenorphine undergoes first-pass hepatic metabolism with N-dealkylation and glucuroconjugation in the small intestine. It is oxidatively metabolised by cytochrome P450 CYP3A4 and by glucuroconjugation of the parent molecule and the dealkylated metabolite (norbuprenorphine).<sup>5, 20</sup> Distribution is rapid and the half-life is two to five hours. The conjugated metabolites are excreted mostly in the faeces by biliary excretion (80%), but also in the urine.<sup>20</sup>

Due to its high potency, low molecular weight and lipophilicity, it is also suitable for transdermal administration.<sup>13</sup>

In South Africa, the following transdermal patches are available: 5, 10 and 20 mg formulations.<sup>13</sup> Also, it is currently available as sublingual tablets (0.2 mg) and in an injectable form.

The following interactions have been identified with the use of buprenorphine:<sup>14</sup>

- Non-selective MAO inhibitors enhance the effect of buprenorphine. This can result in anxiety, confusion and respiratory depression. It should not be used concomitantly, or by patients who took MAO inhibitors in the prior 14 days.
- Inhibitors of CYP3A4 result in higher plasma concentrations, e.g. macrolide antibiotics, protease inhibitors and calcium antagonists. There is also an efficacy reduction from increased hepatic clearance with concurrent use of CYP3A4 enzyme inducers, e.g. carbamazepine, phenytoin and phenobarbitone.
- Central nervous system (CNS) depressants and muscle relaxants. Caution must be taken when using drugs that depress respiration and the CNS, e.g. sedatives or hypnotics, general anaesthetics, other opioid analgesics, phenothiazines, centrally-acting antiemetic agents, benzodiazepines and alcohol.

The most commonly-experienced adverse effects are constipation, headaches, insomnia, asthenia, drowsiness, nausea and vomiting, fainting and dizziness, orthostatic hypotension and sweating. Pruritus or erythema at the application site of the transdermal patches are rare.<sup>5, 13, 20,21</sup>

### **Tapentadol**

Tapentadol is the first oral agent approved to act centrally, for acute pain in adults. It was approved in the United States in 2008 for the treatment of moderate to severe pain in adults.<sup>22</sup> It has been proposed for use in chronic pain management, e.g. in chronic lower back pain and in the treatment of neuropathic pain, but further research is required.<sup>23</sup> The drug has a dual mechanism of action as a  $\mu$  ( $\mu$ )-opioid receptor agonist and as a noradrenaline reuptake inhibitor.<sup>23</sup> The chemical structure of tapentadol is unlike other opioids such as morphine, but resembles tramadol the most.<sup>22</sup> The combination of  $\mu$ -opioid receptor agonism and noradrenalin reuptake inhibition offers the following mechanisms in pain management:<sup>23</sup>

- The  $\mu$ -opioid receptor agonism of the afferent pain fibres inhibits the release of excitatory neurotransmitters and reduces the upward transmission of pain signals. The effects on the

brain include an influence on the release of neurotransmitters by the descending pain pathways, providing further inhibition of pain.

- The noradrenaline reuptake inhibition has an anti-nociceptive effect via the descending pain pathways by reducing pain signals to the brain via its effects on presynaptic  $\alpha_2$ -receptors.<sup>22,23</sup>

These two mechanisms act synergistically to provide an overall analgesic effect.<sup>22</sup> Current formulations available in the United States include tablets and film coated-tablets in strengths of 50, 75 and 100 mg.<sup>14</sup> Patients with mild to moderate renal impairment, and mild hepatic impairment do not require dosage adjustments.<sup>14, 22</sup> However, clinical studies have not been done in patients with severe renal or hepatic impairment and should not be used in this patient population. Patients with moderate hepatic impairment should use the drug with caution and dose adjustments should be made.<sup>14,22</sup> The drug is contra-indicated in the following settings:<sup>14</sup>

- Concurrent or recent (within two weeks) use of a monoamine oxidase (MAO) inhibitor.
- Substantial respiratory depression in a setting, where it cannot be monitored or where there is no resuscitation equipment.
- Acute or severe bronchial asthma, where the condition cannot be monitored or where there is no resuscitation equipment.

Tapentadol is metabolized by hepatic microsomal enzymes and in particular cytochrome P450 (CYP) isoenzymes 2C9, 2C19 and 2D6. The only isoenzyme that was inhibited to a limited extent *in vitro* was CYP2D6, but the concentrations required are clinically irrelevant. Potential drug interactions may include the following drug groups:<sup>14,24</sup>

- Monoamine oxidase inhibitors as discussed in the text
- Serotonergic drugs causing serious to fatal 'serotonin syndrome', e.g. the triptans
- CNS depressants, e.g. sedatives, tranquilisers, etc.
- Alcohol.

Other precautions are similar to the general opiate agonist precautions.<sup>24</sup> Side-effects may include nausea, dizziness, vomiting, somnolence, constipation, pruritus, dry mouth, hyperhidrosis and fatigue.<sup>14,5</sup> Gastro-intestinal effects (nausea, vomiting and constipation) have been reported but tapentadol may have an 'opioid-sparing' effect with less opioid-related side-effects.<sup>14,23,24</sup>

### **Transmucosal immediate-release fentanyl (TIRF)**

Fentanyl is a narcotic analgesic. The formulations registered in South Africa are injections and transdermal patches. The focus will be on those formulations that can further enhance pain management but that are not registered in South Africa.

TIRF medicines are used to manage breakthrough pain in adults with cancer that are routinely taking other opioids around the clock for pain. They are also used to manage the pain of cancer patients that have become tolerant to regular opioid therapy. It is contraindicated for acute or post-operative pain as life-threatening hypoventilation may occur at any dose in patients not taking chronic opioids.<sup>25, 26</sup>

Breakthrough pain is defined as infrequent short episodes of increased pain occurring against a background of stable, well-controlled pain. In patients on continuous opioid therapy that experience breakthrough pain, as-needed immediate-release opioids may be useful as 'rescue analgesia'. However, the benefits and potential risks should be carefully considered before prescribing such medicines.<sup>4</sup>

Available formulations are the sublingual tablet (100, 200, 300, 400, 600 and 800mcg), buccal tablet (100, 200, 400, 600 and 800mcg), troche/lozenge ((200, 400, 600, 800, 1200 and 1600mcg), soluble film (200, 400, 600, 800 and 1200mcg), the sublingual spray (100,200, 400, 600 and 800mcg/spray), and the intranasal spray (100mcg/100mcl and 400mcg/mcl).<sup>25</sup>

Due to the potential risk of misuse, abuse, addiction, overdose and serious compliance due medication errors, in the United States of America, these formulations are only available for selected patients through the 'Risk Evaluation and Mitigation Strategy' (REMS) program of the United States Food and Drug Administration.<sup>27</sup>

### Lornoxicam

Lornoxicam belongs to the oxycam group of non-steroidal anti-inflammatory drugs (NSAIDs) and has potent anti-inflammatory and analgesic effects. It is a potent inhibitor of both the cyclooxygenase 1 and 2 isoenzymes (i.e. COX-1 and COX-2), thus inhibiting the process of inflammation.<sup>28,29</sup>

It is characterised by a relatively quick onset of action and a short elimination half-life of 3-4 hours. The new formulation technique used, results in the release of 90% of the active drug already in the ventricle after only five minutes. The entire drug is metabolised into an inactive substance and excreted through the liver (70%) and kidneys (30%). This formulation is bio-equivalent to its intramuscularly injected formulation.<sup>28,30</sup>

Research proved that it is as effective as opioid analgesics in reducing postoperative pain and, due to its opioid-sparing effect; lornoxicam might also be used in combination with opioid analgesics. It is comparable to other NSAIDs in treating musculoskeletal pain, like osteoarthritis and back pain. It has also showed great efficacy in the management of perioperative and postoperative pain associated with gynaecological, orthopaedic, abdominal and dental surgery.<sup>29,30</sup>

An advantage of lornoxicam over opioids is that, although they both have comparable efficacy in managing postoperative pain, it shows a better tolerability profile. In addition, the safety and tolerability profile of lornoxicam is better when compared to other NSAIDs in this setting. The reporting rate of adverse events was also very low in the available studies and this could be a positive effect of the short half-life.<sup>30</sup>

Lornoxicam is available as the conventional immediate-release tablets (4 and 8mg), injection for intravenous and intramuscular use (4mg/ml) and the most recent formulation that was registered in South Africa, was the **rapid-release tablet (Xefo® Rapid 8mg)** 44/3.1/0331. It is registered in South Africa for the short-term treatment of mild to moderate pain where intramuscular use is inappropriate (not to exceed 72 hours).<sup>31</sup>

## Management according to recommended guidelines

Appropriate medicine therapy should be based on the intensity or type of pain. There are recommended guidelines for the management of different categories of pain.

There must be practical strategies and therapy to reduce or treat the side-effects of opioids, such as sedation, nausea, vomiting, pruritus, urinary retention, constipation, etc., as well as to provide symptom relief for breathlessness, nausea, vomiting and other symptoms associated with the advanced stages of cancer, and to manage or treat associated stress or anxiety, and manage other related inflammatory or neuropathic conditions as a result of the disease.<sup>1</sup>

### Acute pain

#### *Post-operative pain: post-caesarean section*

Pain following caesarean delivery can significantly impact the new mother. The aims of postoperative pain treatment are to provide subjective comfort, inhibit nociceptive impulses and blunt the neuro-endocrine response to pain, thus enhancing early mobilization to prevent the risk of thromboembolic disease. These patients need to be pain free to care for their newborn infants and breastfeed them effectively.

Multimodal analgesia is the most effective way of alleviating this type of pain. The choice of drugs should be based on knowledge of their potential impact on breastfeeding and on the breastfed infant, as a result of transfer in human milk. In addition, the lowest possible effective maternal dosage of analgesia is recommended, breastfeeding is best avoided at times of peak drug concentration in milk, and the infant should be observed for effects of medication transferred in breast milk.<sup>3,33</sup>

Analgesics may be administered via a neuraxial block (epidural), intramuscular route, intravenous patient controlled analgesia (IV-PCA) or orally. Pain relief with IV-PCA has shown to be superior to conventional intramuscular opioids for women having had a caesarean section. This is because patients are able to control their pain, without having to wait for the nurses and doctors to provide analgesia. Patient satisfaction is high for this approach even though it is less effective than epidural analgesia.<sup>33</sup>

The goal of pain management is to obtain synergistic or additive analgesia with fewer side-effects by combining lesser amounts of each drug with different mechanisms of action. Some of the medications used for post-caesarian section pain are highlighted below.<sup>33</sup>

It is preferable to use Non-selective NSAIDs instead of aspirin, because salicylates are eliminated slowly by the neonate, cause platelet dysfunction and have been associated with Reye's syndrome.<sup>3,34</sup>

The short-term use of opioids is generally considered safe for the infant during lactation as most opioids are secreted into breast milk in low dosages. They should, however, be avoided if the neonate experiences apnoea and cyanosis during the first week of life.<sup>3</sup>

Morphine is the recommended opioid if choice if potent analgesia is required in breastfeeding mothers. Although it is

transferred in breast milk, only a small amount reaches the infant as the oral bioavailability is low.<sup>3</sup>

Breastfed infants whose mothers received pethidine were less alert and oriented to auditory stimuli after caesarean section than the babies of mothers receiving morphine. Another disadvantage of pethidine is that its neurotoxic metabolite of, which is norpethidine, accumulates in breast milk with repeated use and has very slow neonatal elimination; pethidine use during breastfeeding is not recommended.

Oxycodone is one of the components of multimodal analgesia in the first 72 hours after caesarean section. Although it is concentrated in breast milk there may be minimal risk as only a low volume of milk is ingested during this period.<sup>3</sup>

Short-term use of tramadol is also considered to be safe. Studies have shown that although it is found in breast milk, there were no detectable behavioural effects in the infants for this duration of therapy.<sup>35</sup>

The recommended approach in the South African acute pain guidelines is as follows:<sup>3</sup>

- Paracetamol (1g 6 hourly)
- NSAIDs (ibuprofen 200-400 mg 8 hourly)
- Short-course opiates: nurse administered (e.g. morphine 10 mg 4 hourly/*prn*), or patient administered (PCA morphine 1 mg bolus with 6 min lockout) while in hospital, then oral opiates (codeine 15-40 mg 4-6 hourly or propoxyphene 65 mg 4 hourly) at home, for a few days. Codeine should be given along with symptom relief for constipation. Patients should be discharged with oral medication and/ or suppositories.<sup>3</sup>

### Chronic non-cancer or non-malignant pain

Some people with chronic pain are able to manage without medication; however it becomes necessary to use medications once the overall quality of life or mobility becomes impaired. Management of this type of pain requires a multidisciplinary approach as medications alone are sometimes not effective.<sup>4</sup>

Opioids are increasingly being used to treat persistent pain. They can be effective therapy for a carefully selected group of patients as part of a wider management plan, which focused on reducing disability and improving quality of life.

However, before clinicians prescribe chronic opioid therapy, they should first consider non-opioid therapies (e.g. analgesics, antidepressants and anxiolytics), psychotherapeutic interven-

tions, functional restoration and other medical and social interventions.<sup>6</sup>

### Management of chronic malignant or cancer pain

The World Health Organisation's (WHO) 'analgesic ladder' serves as the mainstay of treatment for the relief of pain together with psychological and rehabilitative modalities.<sup>36</sup> This multidimensional approach offers the greatest potential for maximising analgesia and minimising adverse effects. According to literature about 70-90% of cancer pain is relieved when clinicians apply the WHO ladder appropriately.<sup>36</sup> According to the WHO<sup>6</sup>, the key concepts to the effective management of pain are as follows:

- By mouth: If possible analgesics should be given by mouth.
- By the clock: Analgesics should be given at fixed time intervals and the dosage should be titrated according to the patient's pain, and the next dosage should be given before the previous dosage has fully worn off.
- For the individual: The choice and dosages of the analgesics should be tailored to the needs and circumstances of the particular patient.
- By the ladder: The well-known WHO ladder, illustrated in Figure 1, advocates a step-wise approach to the use of analgesics, as explained below.

**Step 1:** Non-opioids (e.g. aspirin, paracetamol or ibuprofen) are used for mild to moderate pain.

**Step 2:** Weak opioids (e.g. codeine phosphate, dihydrocodeine, tramadol and buprenorphine) are recommended for moderate pain, used alone or in combination with one of the non-opioids mentioned in step 1.

**Step 3:** Strong opioids (morphine, hydromorphone, oxycodone, buprenorphine and tapentadol) may be used alone or in combination with a non-opioid (from the first step) for severe pain.

If the patient's pain is already severe, it is recommended that the physician should move to the third level of the ladder immediately, rather than starting with the first two.

As illustrated by Figure 1, opioids play an important role in the management of, not only acute and chronic pain, but also in the management of moderate to severe pain.<sup>38</sup> However, certain barriers limit the effective use of opioids in the management of pain:<sup>39</sup>

**Table 1:** Pharmacological management of chronic non-cancer or non-malignant pain<sup>5</sup>

Type of pain	NSAIDs and other analgesics	Opioids	Other medications
Chronic low back pain	Paracetamol, NSAIDs <b>First-line</b>	Short term use for mild to moderate flare-ups <b>Selected patients</b>	TCAs, AEDs <b>if neuropathic symptoms are present</b>
Musculoskeletal pain (fibromyalgia)	Paracetamol, NSAIDs <b>First-line</b>	Long-term use not recommended	TCAs, AEDs
Neuropathic pain	Paracetamol, NSAIDs are rarely effective	Considered first-line therapy, but usually are tried after AEDs and/ or TCAs, lidocaine 5% patch	TCAs, AEDs, SNRIs, topical <b>First-line</b>

[AEDs: antiepileptic drugs; NSAIDs: non-steroidal anti-inflammatory drugs; SNRI: serotonin-noradrenaline reuptake inhibitor; TCA: tricyclic antidepressant]

- Concerns about the use of opioids from health care workers, family members and patients; these concerns may be related to the side-effects and risk of dependence when using the opioids.
- Development of tolerance to the chronic use of opioids.

### Adjuvant therapy

Adjuvantive therapy is sometimes necessary to manage the side-effects of medications for pain, provide symptom relief, treat anxiety and manage related or underlying conditions. This is because chronic pain patients are more likely to report anxiety, depression neuropathic pain and significant activity limitations.<sup>37</sup> Examples of adjuvant medicines are steroids, anxiolytics, antidepressants, hypnotics and anticonvulsants/antiepileptic agents.<sup>40</sup>

In the case of cancer pain in children, however, the WHO recommends a two-step ladder. Although there are a limited number of analgesic medicines that can be safely used in children, it is still possible to provide adequate analgesia with this two-step approach. This strategy consists of a choice of category of analgesic medicines according to the child's level of pain severity: for children assessed as having mild pain, paracetamol and ibuprofen should be considered as first options and in children assessed as being in moderate to severe pain, the administration of an opioid should be considered.<sup>9</sup>

**Step one:** For mild pain, paracetamol and ibuprofen are the medicines of choice in the first step (mild pain). Both paracetamol and ibuprofen need to be given together for treatment in this step. For children below three months of age **only** paracetamol should be given.

**Step two:** If the pain severity associated with a medical illness is assessed as moderate or severe, the administration of a strong opioid is necessary. Morphine is the medicine of choice for the second step, although other strong opioids should be considered and made available to ensure an alternative to morphine in case of intolerable side-effects.

According to this guideline, the decision to prescribe and administer opioid analgesics, bypassing the first step, should be

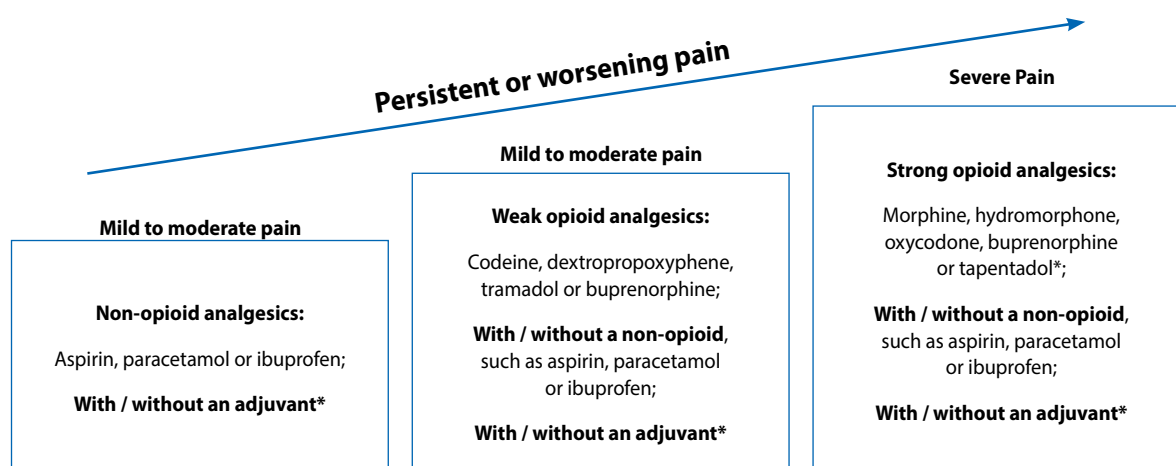
based on the clinical judgement of the severity of a child's pain, on careful considerations of the disability caused by the pain, on the cause of the pain, and on the expected prognosis and other relevant aspects.<sup>9</sup>

### Collaborative work between doctors, pharmacists and nurses

Pharmacists play an important role in pain management, both in the hospital setting and in the community setting. In many societies, the pharmacist is the first point of health care to the public when one feels pain. They are in several cases the final person who dispenses and counsels patients on medications prescribed for them. They can be big advocates for pain relief in directing patients to the right health care facility or doctor and also in discussing with patients, the importance of pain treatment. In certain instances however, nurses and pharmacists are hesitant to use or recommend opioids appropriately due to unfounded fears and biases that they will be prosecuted or investigated. This often contributes to the 'under-treatment' of all types of pain. Also, many of them are fearful that they may cause drug dependence syndrome by using, dispensing or suggesting opioids.<sup>1</sup> However, with collaborative work with doctors with the goal of improving the quality of life of the patient, optimum pain management can be achieved.

### Conclusion

The effective management of pain requires a multidisciplinary healthcare approach. The clear, step-wise escalation pathway, as recommended by the WHO in its analgesic 'ladder', provides strong guidelines in terms of the escalation to opioid-based analgesia (in cases of moderate to severe pain and discomfort). Healthcare professionals need to make appropriate recommendations and provide effective advocacy for the use of the more potent opioid analgesics, whenever these have become appropriate and necessary. In addition, the use of adjuvant treatment options should be considered during each one of the three steps in the pain ladder, since the augmentation of pure analgesia will strengthen the patient's experience of symptomatic relief. Pharmacists need to have a clear understanding of the various treatment options, as well as their indications, side-effects and contra-indications.



[\*Examples of adjuvants include corticosteroids, antidepressants, hypnotics and anticonvulsants/antiepileptic agents.]

**Figure 1:** The World Health Organization's three-step analgesic ladder.<sup>37,40,41</sup>

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