Opioid analgesics – a 2018 update

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Abstract

The opioid analgesic drugs constitute one of the most important groups of pharmacotherapeutic agents in the clinical practice setting. They are vital to pain management, especially moderate to severe cancer and visceral pain, in a myriad of healthcare settings. The key to optimal pain management is the ability to effectively manage patients to ensure optimal pain relief, whilst also minimising or managing the side-effects of their pain medication. This necessitates effective collaboration between all the healthcare professionals managing the patient. This article provides an updated overview of the opioid analgesics, and their usefulness in clinical practice.

Introduction

As a class, the opioid analgesics are arguably one of the most important groups of pharmacotherapeutic agents in the clinical practice setting. These drugs are either related to morphine in structure and action, or they are synthetic derivatives with different chemical structures. Morphine is the most important of the opioid analgesics. It is a plant alkaloid (i.e. an organic base substance, which is found in, and extracted from, plant material) that is extracted from the wild opium poppy, *Papaver somniferum*. A second alkaloid, codeine, is extracted from the same plant. Codeine and morphine are classified as phenanthrenes (opioid alkaloids that act as narcotic analgesics). The benzylisoquinolines are alkaloids that do not display the typical effects of the opioid analgesics. Papaverine acts as an antispasmodic and noscapine as a cough suppressant. The opioid analgesics suppress the neurotransmission of pain sensations due to their primary action in the spinal cord and brain (i.e. where their supraspinal receptors are located). They are the drugs of choice in the management of visceral and severe pain.[1]

The opioid peptides and their receptors (μ, δ, κ and σ)

The following receptors are utilised by the endorphins, dynorphins, enkephalins and other endogenous opioid peptides, with their subtypes[1-4]:

- Mu- (μ) and delta- (δ) receptors, also referred to as the mu opioid peptide (MOP) and delta opioid peptide (DOP) receptors.
- Kappa- (κ) receptors, also referred to as the kappa opioid peptide (KOP) receptors.
- Sigma- (σ) receptors (σ-receptors are not considered to be true opioid peptide receptors, but they do explain many of the unwanted effects of some opioid analgesics, such as pentazocine).
- Nociceptin opioid peptide (NOP) receptors have also been identified; these are G-protein-coupled receptors for the endogenous opioid-like ligand known as nociceptin or orphanin FQ, which does not seem to display any affinity towards the MOP, DOP, or KOP receptors (naloxone also does not act as an antagonist at these receptors).

The neurotransmitters that act on these receptors include: endorphins (especially β-endorphin), dynorphins, enkephalins (e.g. leu- and met-enkephalin), and other endogenous opioid peptides.[1]

The most significant physiological effects of these neurotransmitters are seen within the central nervous system (CNS), and may be summarised as follows[1-4]:

- The opioid peptides act as inhibitory neurotransmitters within the CNS. Opioid receptors are found throughout the brain, especially in the limbic system, as well as the brain stem and the posterior (dorsal) horn of spinal cord grey matter.
- Some notable CNS functions, which are influenced by these receptors, are: emotions and the processing of pain stimuli (the emotional aspects of pain perception), mood and consciousness. Stimulation of these peptide receptors may also suppress brain stem functions such as coughing and respiration.
- All the receptor-subtypes are present within the CNS.
- Stimulation of the μ, δ and κ-receptors will result in a decrease in the concentration of cyclic adenosine monophosphate (cAMP), will inhibit the opening of calcium-channels, and facilitate the opening of potassium-channels.

Mu- (μ) and delta- (δ) receptors

These two receptor subtypes closely resemble one another in their functionality. A huge problem with opioid analgesics, however, is tolerance (especially in chronic pain management and chronic care settings).[1] According to Sommers,[5] patients who develop tolerance to the analgesic effects of mu-receptor agonists could still obtain satisfactory levels of pain relief with delta-receptor stimulation.

There are at least two important mu-receptor subtypes[1-4]:

- μ1-receptors: These receptors are involved in the analgesic and euphoric effects of the opioids and are found in the CNS.

- μ2-receptors: These receptors are found in the CNS, where they are implicated in the respiratory depression caused by the opioid analgesics, and also peripherally in the GIT, where they cause constipation.

The delta-receptors are also of importance in peripheral tissues. Further subtypes of these receptors, as well as subtypes of the kappa- and sigma-receptors, also exist.[1]

Effects of opioid peptide receptor stimulation

Table I gives an exposition of the most significant effects that stimulation of the opioid receptors have on nervous system functioning. It also highlights the usefulness and some of the expected side-effects of the opioid analgesics.

Opioid analgesia

Across the globe, millions of people with cancer and other disease states experience moderate to severe pain, many without access to adequate treatment. These people face severe suffering for months on end, and eventually die in unnecessary agony due to pain, which is almost always preventable and treatable.[6,7] Many developing countries lack the necessary economic, human and logistic resources to provide optimal pain treatment to their population.[6]

Pain is defined as "…an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage".[8] Pain is one of the most prevalent and most feared symptoms in patients with cancer and other non-malignant diseases. Hence, good pain management is one of the central pillars of good patient care.[9]

The World Health Organization's (WHO) analgesic ladder serves as the mainstay of treatment for the relief of pain, combined with the relevant and necessary psychological and rehabilitative modalities.[10] This multidimensional approach offers the greatest potential for maximising the effectiveness of analgesia, whilst minimising the adverse effects thereof. According to literature, about 70–90% of cancer pain is relieved when clinicians apply the steps of the WHO's pain ladder appropriately.[10] According to the WHO,[11] the key to effective pain management is contained in the following principles:

- **By mouth:** If possible, analgesic should be given by mouth.

- **By the clock:** Analgesics should be given at fixed time intervals

Table I. The major effects of opioid receptor stimulation[1]				
	Mu (μ)	**Delta (δ)**	**Kappa (κ)**	**Sigma (σ)***
Pain	Strong analgesic effects at spinal and supraspinal (brain) level, as well as peripherally	Spinal analgesic effects	Peripheral and some spinal analgesic effects	
Mood and consciousness	Euphoria, sedation		Sedation, dysphoria	Dysphoria, hallucinations and nightmares
Breathing	Suppresses the respiratory centre (also suppresses the cough centre)	Some respiratory depression		Stimulation, tachypnoea
Blood pressure and pulse rate	May cause bradycardia			Increases blood pressure and pulse rate
Gastrointestinal tract	Smooth muscle contraction with spastic paralysis of the small intestine, leading to constipation; increased biliary sphincter tone**; also causes nausea and vomiting	Reduced gastrointestinal motility		
Other	Miosis, physical dependence			Mydriasis, hypertonia

*Not a true opioid receptor.
**The increased tone of the sphincter of Oddi is less pronounced with pethidine (syn. meperidine).
Note: This table only highlights the most prominent effects that are associated with stimulation of each of the listed receptor subtypes.

and the dosages should be titrated according to the needs of individual patients. Subsequent dosages should be given before the previous dosage has fully worn off.

- **For the individual:** The choice of agent and dosages of the selected analgesics should be tailored to the patient.

- **By the ladder:** The WHO ladder, illustrated in Figure 1, advocates the following stepped approach to the use of analgesics[11]:

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 a non-opioid.

Step 3: Strong opioids (e.g. morphine, hydromorphone, oxycodone, buprenorphine and tapentadol (the latter is not available on the South African market yet) may be used alone or in combination with a non-opioid for **severe pain**.

Note: Although the package inserts of certain opioid analgesics may display a registered indication of "moderate to severe" pain, the WHO ladder recommends the weaker opioid agents for the former, and the stronger ones for the latter level of severity. If, at the initial consultation, the patient's pain can already be regarded as severe, it is recommended that the physician move to the third level of the ladder directly, rather than starting with the first two.[11]

As illustrated in 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.[12] However, certain barriers limit the effective use of opioids in the management of pain, as explained below[13]:

- Concerns about the use of opioids from healthcare professionals, family members and patients; such concerns may be related to the side-effect profile and perceived risk of dependence when using the opioids.
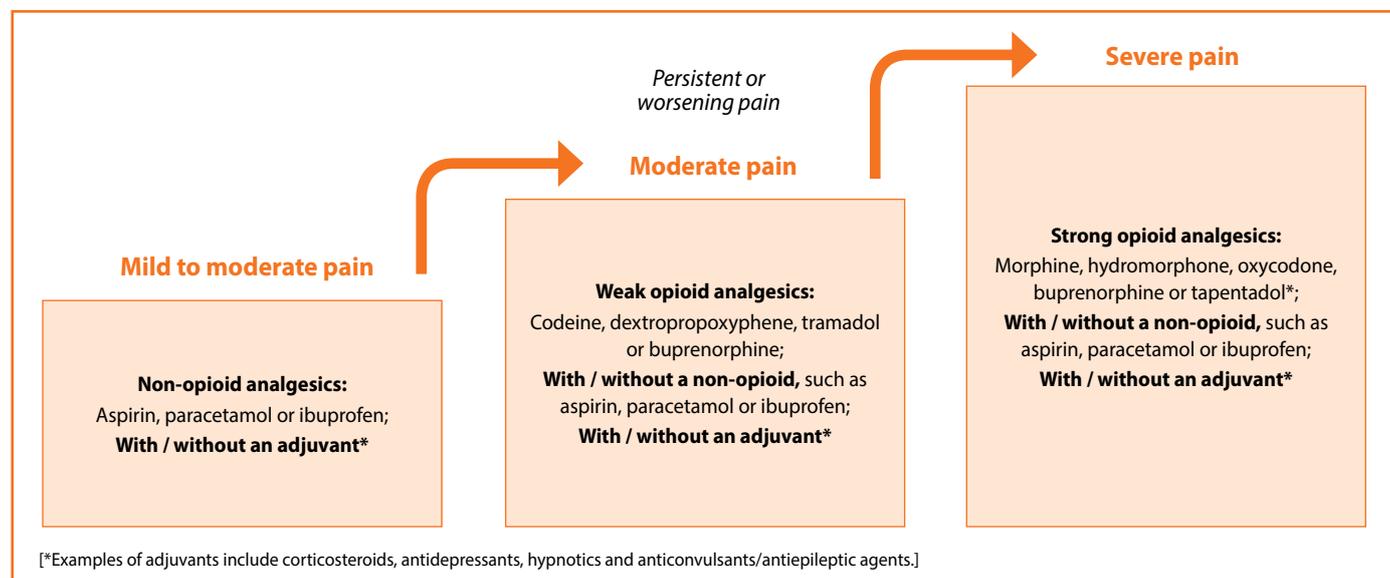
- The development of tolerance (tachyphylaxis) to the chronic use of opioids.

- Successful pain management with the use of opioid analgesics may be achieved by balancing the adverse effects with the level of analgesia in each individual patient.[13] The newer, oral opioid formulations that are available for the management of moderate to severe pain, can assist in achieving effective levels of analgesia in patients.

The opioid drugs

Two major drug groups are utilised in the pharmacotherapeutic management of pain, namely the opioid analgesics for [moderate to] severe pain, and the non-opioid analgesics that are generally used in the management of mild to moderate pain.[1]

The opioid analgesics may be classified in a variety of ways. In clinical practice, however, the most practical classification is based upon the degree of efficacy that may be expected from each one of the more commonly used drugs. Therefore, a distinction is made between high-potency agents, low-potency agents, and opioid agents of intermediate potency. Some authors choose to refer to high-, low- and intermediate-efficacy agents. Their degree of potency, or efficacy, is dependent on whether they act as full agonists at μ-receptors, since most of the currently available opioid analgesics exert their analgesic effects via these receptors, whether they are high- or low-affinity μ-agonists, or whether they are μ-receptor dualists. Naloxone is an opioid-receptor antagonist.[1-4]

Also note that the opioid analgesics, in contrast to the nonsteroidal anti-inflammatory drugs (or NSAIDs), cannot be used in the management of pyrexia (fever) or inflammation. The non-opioid analgesics act within peripheral tissues, where they facilitate the inhibition of pain impulse formation. The prostaglandins are important mediators of somatic pain sensations, or so-called dermal, subcutaneous and musculoskeletal pain.[1]

Mild to moderate pain

Non-opioid analgesics:
Aspirin, paracetamol or ibuprofen;
With / without an adjuvant*

Persistent or worsening pain

Moderate pain

Weak opioid analgesics:
Codeine, dextropropoxyphene, tramadol or buprenorphine;
With / without a non-opioid, such as aspirin, paracetamol or ibuprofen;
With / without an adjuvant*

Severe pain

Strong opioid analgesics:
Morphine, hydromorphone, oxycodone, buprenorphine or tapentadol*;
With / without a non-opioid, such as aspirin, paracetamol or ibuprofen;
With / without an adjuvant*

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

Figure 1: The World Health Organization's three-step analgesic ladder (adapted and examples added)[11]

In patients with severe pain, morphine is typically regarded as the gold standard for strong opioids. However, careful consideration needs to be given to the following agents as well:

• Oxycodone

• Hydromorphone

• Buprenorphine

• Tapentadol (currently not marketed in South Africa)

Each of these drugs will be looked at in more detail.

Oxycodone

Oxycodone is classified as a mild-to-moderate, partial agonist at the mu- (μ) and kappa- (κ) opioid receptors, with strong analgesic properties.[4,14] It is a semisynthetic agent, derived from the opium alkaloid, thebaine.[4,14] It has been used for many years, in combination with paracetamol, for chronic pain, but more recent clinical trial data revealed that it might be more efficacious and safe when used by itself, in a controlled-release, or an immediate-release formulation.[4,14] In addition, it has been shown that conversion to oxymorphone is not required for its bioactivity; meaning that the drug has a high oral bioavailability and is twice as potent as morphine.[14]

Both immediate-release (IR) and prolonged-release (PR) preparations are marketed in South Africa.[15,16]

• **Immediate-release preparations (Oxynorm® capsules):** 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.[16] The approved indication for Oxynorm® is as follows: indicated for the treatment of moderate to severe pain in patients with cancer, and postoperative pain, once gastrointestinal function has returned. It is also indicated for the treatment of severe pain requiring the use of a strong opioid analgesic. This product is available in 5, 10 and 20 mg strengths, in packs of 28 capsules.[15] The capsules should be taken at 4–6 hourly intervals. After oral administration, an analgesic effect may occur within 10–15 minutes, and may persist for 3–6 hours.[16]

• **Prolonged-release preparations (Oxycontin® prolonged-release tablets):** This product may be used orally for the relief of moderate to severe pain in situations where continuous analgesia is needed, for instance in cancer and persistent, non-malignant pain, or pain during rehabilitation.[16] The approved indication for Oxycontin® is as follows: indicated for the treatment of moderate to severe pain in patients with cancer, and postoperative pain, once gastrointestinal function has returned. It is also indicated for the treatment of severe pain requiring the use of a strong opioid analgesic. The prolonged release tablets are not indicated for use in preoperative analgesia, or for pain during the immediate (i.e. the first 24 hours) phase post-surgery, nor for mild, short-term or acute use. The preparation should also not be used on an "as-needed" basis.[14,16,17] The available preparations include 5, 10, 20, 40 and 80 mg in packs of 28 tablets. The tablets should be taken at 12-hourly intervals. After administration, the onset of analgesia may occur within 37 minutes and it provides an analgesic effect for up to 12 hours.[16] Prolonged-release tablets should not be broken, crushed or chewed, as this may result in a toxic dosage of the drug being delivered. Patient counselling should include dietary advice (intake with a high-fat meal may increase peak plasma levels) and information on the fact that the matrix core can be passed in the stools, since it does not dissolve completely.[16,17] In addition, patients need to be informed of the abuse potential of any strong opioid agonist, as well as the risk of theft of their pain medication.

• General side-effects are similar to the ones associated with other strong opioids, including nausea, vomiting, sedation, constipation, dizziness and pruritus.[16,17] It may cause respiratory depression and these effects should be monitored. In patients suffering from renal impairment (with a creatinine clearance of ≤ 60 ml/min), the initial dosage of the prolonged-release formulation should be reduced and adjusted according to the patient's clinical status.[16,17] In patients with hepatic impairment, the prolonged release formulations should be initiated at 33–50% of the dosage that would otherwise be recommended.[16,17]

The release of oxycodone from Oxycontin® prolonged release tablets is biphasic with an initial, relatively fast release providing an early onset of analgesia, followed by a more controlled release, which ensures the 12-hour duration of action.

Hydromorphone

Hydromorphone is a hydrogenated, semi-synthetic, potent mu- (μ) receptor agonist with a weak affinity for kappa- (κ)receptors. It is used to treat moderate to severe pain.[4,18,19] It is five to ten times more potent than morphine and due to alterations in its chemical structure (a keto-group instead of a hydroxyl group at position 6, when compared to morphine), it has enhanced distribution into the CNS.[20]

A controlled-release formulation of oral hydromorphone is the only one that is currently approved for the South African market (Jurnista®, 8 and 16 mg tablets), although powder and oral solutions, injections, and rectal suppositories are available in the USA.[16] These formulations maintain consistent hydromorphone plasma concentrations throughout the 24-hour dosing interval, ensuring long-lasting analgesia. The hydromorphone is actively released from the matrix system by the dosage form itself, with minimal effects from food and alcohol (as it is not influenced by gastric pH or motility).[16,18,19]

Hydromorphone is well absorbed after oral intake, and when compared to morphine it has a faster onset of action, but with a shorter duration of action. This can be advantageous in the short-term analgesia setting.[20]

Hydromorphone has the same side-effect profile as other opiate agonists; however, nausea, vomiting, constipation and euphoria may be less pronounced with hydromorphone, when compared

to morphine.[16,21] Safety and efficacy has not been established in children, and in patients over the age of 65 years.[16,22]

Buprenorphine

Buprenorphine is a partial opioid receptor agonist (i.e. an agonist-antagonist). It binds to the mu- (μ) receptors with great affinity, but has a low intrinsic activity. It also has an affinity for the kappa- (κ) receptors. The rate of dissociation from the μ-receptors is slow, which results in an antagonistic effect to any other opioids that may be co-administered with buprenorphine.[23,24] Buprenorphine is a partial agonist, and when compared with full agonists, has a lower liability for the induction of physical dependence.[22,23]

When taken orally, buprenorphine undergoes first-pass hepatic metabolism with N-dealkylation and glucoroconjugation in the small intestine. It is oxidatively metabolised by CYP3A4 and by glucoroconjugation of the parent molecule and the dealkylated metabolite (norbuprenorphine).[22,23] Distribution is rapid and the half-life is two to five hours. The conjugated metabolites are excreted, mostly in the faeces, via biliary excretion (80%), but also in the urine.[23]

Due to its high potency, low molecular weight and lipophilicity, it is also suitable for transdermal administration.[15] Each buprenorphine-base transdermal patch provides a steady delivery of buprenorphine for up to seven days. Steady state is achieved during the first application. After removal of the buprenorphine-base transdermal patch, the buprenorphine concentration will decline; decreasing by approximately 50% in 12 hours (range 10–24 hours). The absorption does not vary significantly across the specified application sites. Mean exposure (i.e. the AUC) at each of the application sites is within ± 11% of the mean exposure for the four sites. Following buprenorphine-base transdermal patch application, buprenorphine diffuses from the patch through the skin. Buprenorphine is approximately 96% bound to plasma proteins. Buprenorphine metabolism in the skin, following buprenorphine-base transdermal patch application, is negligible. Norbuprenorphine, is the only known active metabolite of buprenorphine.[4,15,22-24]

In South Africa, three buprenorphine-containing products are currently being marketed, namely:

- Sovenor® 5, 10 and 20 mcg/hour transdermal patches
- Subutex® 2 and 8 mg sublingual tablets
- Temgesic® 0,2 mg sublingual tablets, as well as a solution for parenteral injection, of 0.3 mg/ml.

The Sovenor® transdermal patches are indicated for the treatment of chronic musculoskeletal pain of the joints and the lower back, when that pain is of moderate to severe intensity and sufficient to require an opioid to attain adequate levels of analgesia. There are three different strengths available, and the patches release 5 mcg, 10 mcg and 20 mcg, respectively, of buprenorphine per hour over a period of seven days. Therefore, they only need to be replaced once a week. The patches offer a convenient ultra-low dosage to start with.

The following important drug interactions have been identified with the use of buprenorphine[16]:

- Non-selective MAO-inhibitors enhance the effects of buprenorphine. This can result in anxiety, confusion and respiratory depression. These two agents should, therefore, not be used concomitantly, or by patients who took MAO-inhibitors in the prior 14 days.
- Inhibitors of CYP450 3A4 result in higher plasma concentrations, e.g. macrolide antibiotics, HIV 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.
- CNS depressants and muscle relaxants: Caution must be taken when using drugs that suppress respiration and the CNS, e.g. sedatives or hypnotics, general anaesthetics, other opioid analgesics, phenothiazines, centrally-acting antiemetics, 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.[15,22-24]

Tapentadol

Tapentadol is not available in South Africa yet. The drug has a novel, dual mechanism of action as a combined mu- (μ) opioid receptor (MOR) agonist, and as a noradrenaline-reuptake inhibitor (NRI). The chemical structure of tapentadol is unlike that of other opioids, such as morphine, but resembles tramadol the most. The combination of μ-opioid receptor agonism and noradrenalin reuptake inhibition offers the following mechanisms in pain management[25-27]:

- The μ-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 inhibitory influence on the release of neurotransmitters by the descending pain pathways, providing further inhibition of pain.
- The noradrenaline reuptake inhibition has an antinociceptive effect, via the descending pain pathways, through a reduction in pain signals to the brain.

These two mechanisms act synergistically to provide an overall state of analgesic pain relief.[26] Current formulations available in the United States include tablets and film-coated tablets in strengths of 50, 75 and 100 mg.[16] Patients with mild to moderate renal impairment, and mild hepatic impairment do not require dosage adjustments.[16,25] However, clinical studies have not been done in patients with severe renal or hepatic impairment and tapentadol should therefore not be used in this patient population. Patients with moderate hepatic impairment should use the drug with caution and any required dosage adjustments should be made.[16,25] The drug is contra-indicated in the following settings[16]:

- 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 at hand.

- Acute or severe bronchial asthma, where the condition cannot be monitored or where there is no resuscitation equipment available.

Tapentadol is metabolised by hepatic microsomal enzymes and, in particular, by cytochrome P-450 (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[16,27]:

- 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, alcohol, etc.

Other precautions are similar to general opiate agonist precautions.[27] Side-effects may include nausea, dizziness, vomiting, somnolence, constipation, pruritus, dry mouth, hyperhidrosis and fatigue.[16,22] Gastrointestinal effects (nausea, vomiting and constipation) have been reported, but tapentadol may have an 'opioid-sparing' effect with less opioid-related side-effects.[16,26,27]

In summary

Four key drug examples have been discussed in the aforementioned section. However, a few over-all remarks are herewith summarised for the opioid analgesics in general[1-4]:

- The opioid analgesics act as either full agonists (of high or low affinity) or partial agonists (dualists) at the opioid receptors. Morphine is more water-soluble than codeine. It is a high-affinity agonist at μ-receptors and a very potent opioid. Codeine is not nearly as potent as morphine (it is a low-affinity agonist). The μ-agonists also cause smooth muscle contraction, and therefore produce a spastic paralysis of the small intestine, which leads to constipation. At dosages that are lower than those required for effective analgesia, codeine may be used as an antitussive (i.e. a cough suppressant) as well as an anti-diarrhoeal agent. Dihydrocodeine is a more potent analgesic than the latter.

- Pethidine, dipipanone and fentanyl (as well as sufentanil, alfentanil and remifentanil) are examples of full agonists. Opioid dualists with analgesic effects, which act on the κ- and σ-receptors, are pentazocine and tilidine. Pentazocine produces a feeling of dysphoria and increases the blood pressure and pulse rate. Tilidine must be administered orally, since it is a pro-drug and only its active metabolite is pharmacologically active. Buprenorphine is a high-affinity dualist.

- Tramadol is a low-affinity μ-agonist which has negligible effects on the other opioid receptors. Unlike other opioid analgesics it also has serotonergic and noradrenergic properties.

- There is a very real danger that the full μ-receptor agonists will cause dependency; the dualists generally do not cause this problem.

- Pethidine (also known as meperidine) has a rapid onset of action, but its analgesic effects are limited to a few hours in duration. It has a toxic metabolite that accumulates with repeated administration, which makes it poorly suited to the management of chronic pain, but it is still suited to the postoperative setting. It is the opioid drug of choice in obstetrics, ureter colic and biliary obstruction (its action on smooth muscle is less pronounced than that of the other opioid analgesics).

- Other examples of opioid analgesics include methadone (high potency) and dextropropoxyphene (low potency). In addition, oxycodone and hydromorphone (both phenanthrenes) are two more examples of high-potency opioids that may be used in cases of severe pain. Furthermore, methadone has the ability to act as an antagonist at NMDA-receptors and to block the reuptake carriers of the monoaminergic transmitters, and it is long-acting.

- Morphine, and the other opioid analgesics to varying degrees, can elicit adverse effects such as respiratory depression, truncal rigidity, sedation, nausea and vomiting, urinary retention, constipation, miosis, tolerance and dependence.

- Naloxone is a competitive antagonist at the opioid receptors but has a shorter half-life than morphine has, for instance. It may be used in cases of morphine and other opioid overdosage.

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 should 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.

References

1. Schellack G. Pharmacology in clinical practice: application made easy for nurses, pharmacists and allied health professionals. 3rd ed. Lansdowne: Juta and Company (Pty) Ltd.
2. Brenner GW, Stevens CW. Pharmacology. 4th ed. Philadelphia: Saunders Elsevier.
3. Brunton LL, Chabner BA, Knollmann BC, editors. Goodman and Gillman's The Pharmacological Basis of Therapeutics. 12th ed. New York: McGraw-Hill Medical.
4. Katzung BG, Masters SB, Trevor AJ, editors. Basic and Clinical Pharmacology. 12th ed. New York: McGraw-Hill Medical; 2012.
5. Sommers De K. Sommer's Pharmacology. Pretoria: De K Sommers, 2000.
6. World Medical Association (WMA). Resolution on the Access to Adequate Pain Treatment. 2011. Available from: http://www.wma.net/en/30publications/10policies/p2/index.html (Accessed 27 Feb 2013).
7. Taylor AL, Gostin LO, Pagonis KA. Ensuring effective pain treatment: a national and global perspective. JAMA, 299(1):81-91.2008. Available from: http://scholar.edu/ois_papers/10 (Accessed 02 Feb 2013).

8. Baumann TJ, Strickland J. Pain management. Pharmacotherapy: a physiologic approach. Edited by Dipiro JT, Talbert RL, Yee GC, et al. 2008. United States of America: McGraw-Hill.

9. Auret K. Pain management in palliative care – an update. 2006. Australian Family Physician, (35)10:762-765.

10. Christo PJ, Mazloomdoost D. Cancer pain and analgesia. 2008. Annals of the New Academy of Sciences, (1138):278-298.

11. World Health Organization (WHO). A community health approach to palliative care for HIV/AIDS and cancer patients, Geneva: World Health Organization. 2002. Available from: http://www.who.int/hiv/pub/prev_care/palliativecare/en/print.html (Accessed 21 Jan 2013).

12. Likar R. Transdermal buprenorphine in the management of persistent pain – safety aspects. Therapeutics and Clinical Risk Management. 2006:2(1):115-125.

13. Ballantyne JC (Editor in Chief). Opioids in cancer pain: new considerations: the clinical problem of persistent cancer pain. International Association for the Study of Pain (IASP). 2010. Volume XVIII (1).

14. Franceschi F, Marini M, Ursella S, et al. Use of oxycodone in polytrauma patients: The "Gemelli" experience. European Review for Medical and Pharmacological Sciences. 2008;12:123-126.

15. Raff M. What's new in pain management? South African Journal of Anaesthesia and Analgesia. 2012;18(1).

16. McEvoy G (Editor-In-Chief). AHFS Drug Information. Published by the American Society of Health-System Pharmacists. American Hospital Formulary Service. 2011.

17. Gaskell H, Moore DS, McQuay HJ. Single dose oral oxycodone and oxycodone plus paracetamol for acute postoperative pain in adults (Review). The Cochrane Library. 2010;11.

18. Hanna M, Tuca A, Thipphawong J. An open-label, one-year extension study of the long-term safety and efficacy of once-daily OROS hydromorphone in patients with chronic cancer pain. 2009;8(14).

19. Hanna M, Thipphawong J. 118 Study Group. A randomized, double-blind comparison of OROS hydromorphone and controlled-release morphine for the control of chronic cancer pain. BMC Palliative Care. 2008;7:17.

20. Felden L, Walter C, Harder S, et al. Comparative clinical effects of hydromorphone and morphine: a meta-analysis. British Journal of Anaesthesia. 2011. doi:10.1093/bja/aer232 Accessed from http://bja.oxfordjournals.org on 4 Feb 2013.

21. Wirz S, Wartenberg HC, Nadstawek J. Less nausea, emesis, and constipation comparing hydromorphone and morphine? A prospective open-labeled investigation on cancer patient. Support Care Cancer. 2007. doi: 10.1007/s00520-007-0368-y.

22. Baumann TJ, Strickland J. Pain management. Pharmacotherapy: a physiologic approach. Edited by Dipiro JT, Talbert RL, Yee GC, et al. 2008. United States of America: McGraw-Hill.

23. Lintzeris N, Clark N, Muhleisen P, et al. 2001. Clinical guidelines and procedures for the use of buprenorphine in the treatment of heroin dependence. Bupronephrine clinical guidelines. Edited by Vorrath E.

24. Gray A. Systematic review of the safety of buprenorphine methadone and naltrexone. Department of Therapeutics and Medicines Center for the AIDS Programme of Research in South Africa. Congella, South Africa. 2007.

25. Kee V. Tapentadol IR: A Gain for Pain? World of Drug Information (Division of Drug Information Service). 2009;20(2).

26. Pergolizzi J, Alon E, Baron R, et al. Tapentadol in the management of chronic low back pain: a novel approach to a complex condition? Journal of Pain Research. 2011:4203-210.

27. National Horizon Scanning Centre (NHSC): University of Birmingham. Tapentadol (Paelxia) prolonged release for chronic pain. 2009. National Institute for Health Research (NHS).