An update on oral opioids for the management of pain

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Abstract

Pain is an uncomfortable experience associated with various pathologies, including cancer. Advances in medical science have allowed for the development of effective analgesics, and opioids are the most effective in combating pain. Concerted efforts from healthcare workers and an understanding of the characteristics of different opioid drugs are cardinal in the effective use of these chemical entities in the effective management of pain. This short review focuses on discussing the currently available opioids for the management of pain.

Keywords: pain, opioids

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Pain

Definition

According to the International Association on the Study of Pain, pain can be defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with actual or potential tissue damage".[1] Although the acknowledgement of pain as a pathological entity in its own right is debated,[2] it poses a huge burden in the healthcare system.[3] The continuous rehabilitation of patients with pain sensations, hinders them from conducting day-to-day activities, which has a detrimental effect on the economy.[3] According to the Global Burden of Disease Study in 2016, pain and pain-related pathologies are a leading cause of disease burden and disability.[4] The study further reaffirmed that the global burden caused by pain is increasing, as 1.9 billion people were found to have recurrent-type headaches.[4]

Types of pain

Pain can be classified according to the pattern of occurrence's duration into acute and chronic pain.[3] Acute pain is temporary, and typically results from specific stimulus (chemical, thermal and mechanical). The four classic features of acute pain are that it is time-limited, has a triggering event, has a sudden onset, and can potentially develop into a pathologic condition.[5] In contrast, chronic pain persists for three to six months beyond the expected time frame. Chronic pain can either be intermittent or continuous and may persist regardless of the presence of any obvious stimuli or pathology. Cancer and associated surgery, chemotherapy or radiotherapy can result in a debilitating amount of pain, known as chronic malignant or cancer pain.[6] On the other hand, chronic pain resulting from other pathologies is known as chronic non-cancer or non-malignant pain.[6]

Alternatively, symptoms, mechanisms and syndromes can be used to classify pain into nociceptive, neuropathic, and inflammatory pain.[7] Neuropathic pain occurs as a response to actual or potential damage to visceral and somatic, non-neural tissue. Such stimuli activate nociceptors (Aδ- and C fibres), which are ultimately responsible for detecting chemical, mechanical and thermal stimuli.[3] Neuropathic pain is associated with nerve damage or nerve impairment and is commonly associated with allodynia – a central pain sensitisation that happens due to repetitive non-painful stimulation of receptors. Such sensitisation triggers a pain response to stimuli that normally does not provoke pain.[3] The inflammatory process is a natural response to tissue damage, that serves to remove necrotic cells and initiate the tissue healing process.[8] Upon tissue injury, neutrophils gather at the site of inflammation, followed by the release of chemical mediators. Such chemical mediators interact with nociceptors in the inflamed area, leading to inflammatory pain. Inflammation can result in allodynia, hyperalgesia or sympathetic maintained pain.[8]

Pain pathways

Pain is perceived in three stages, namely-transduction, transmission, and modulation.[3] Following the presence of a noxious stimuli, nociceptors in the peripheral primary afferent fibres located alongside the spinal cord's dorsal root ganglia are activated. The transmission of pain signals occurs via two routes, the ascending and the descending pathways.[3] Transduction and transmission are major events in the ascending pathway. During transduction, noxious stimuli are converted from chemical events into electrical events that get subsequently transduced in the form of chemical neurotransmitters (substance P, glutamate, and other excitatory neurotransmitters) onto primary and secondary neurons in the spinal cord. Following transduction, electrical events are transmitted along the neuronal pathways, through the thalamus into the somatosensory cortex of the brain, leading to the perception of pain.[3]

In the descending pathway, spinothalamic nerves go downwards from the midbrain brain periaqueductal grey (PAG) via the spinal

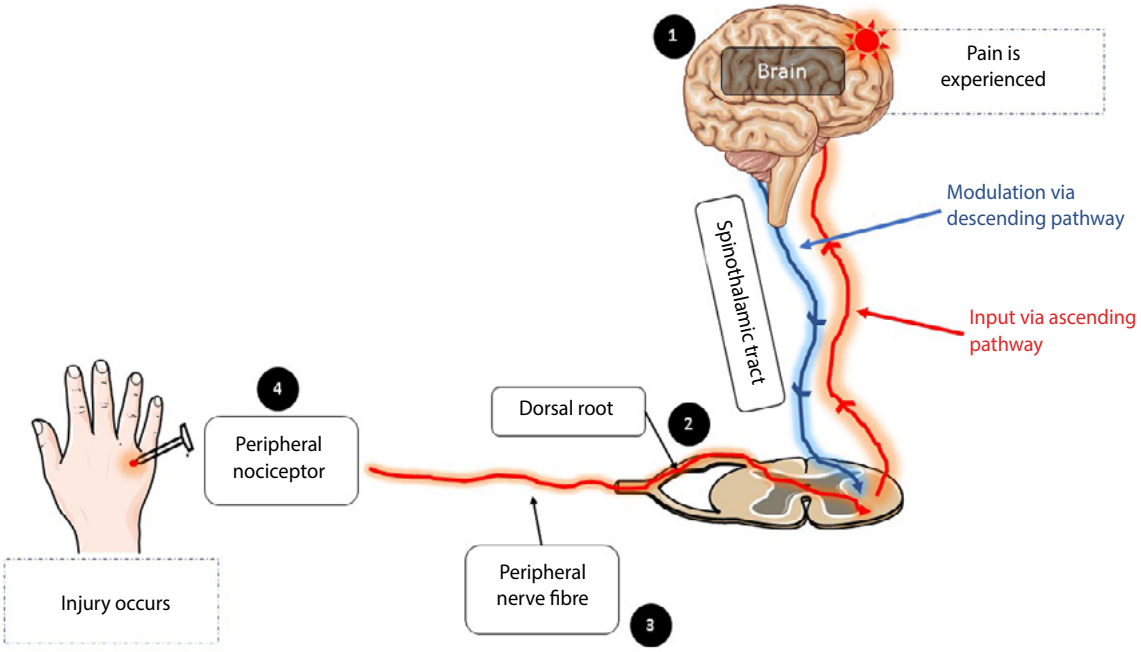

Figure 1: Adapted diagram showing the pain pathways and various targets for treatment options.[9] The target sites of the various treatment options are: (1) Opioids and α_2-adrenergic agonists in the brain; (2) Opioids, local anaesthetic agents and α_2-adrenergic agonists at the dorsal horn; (3) Local anaesthetics peripheral nerve fibre; (4) Local anaesthetics agents and non-steroidal anti-inflammatory drugs at peripheral nociceptors.

cord to the effector organs. Some AB fibres from peripheral tissues are also involved in the descending pathway.[3] The modulation of pain is facilitated through the inhibition of the spinothalamic tract by large fibres that impinge these neurons. Inhibition of the AB fibres stimulates the release of Mer-enkephalin from interneurons in the spinal cord.[3] Additionally, serotonergic fibres arising from the nucleus magnus raphe (NMR) release serotonin and norepinephrine fibres arising from the locus ceruleus (LC) release norepinephrine. When both these neurotransmitters are released, they inhibit the dorsal spinal neurons that transmit pain to the supraspinal structures. The pain pathways and various therapeutic targets are briefly outlined in Figure 1.

The elucidation of pain pathways and the physiology underlying pain has allowed for the development of analgesic agents. In the 1980s, the World Health Organization (WHO) developed a three-step ladder that has been used as a guideline for the pharmaceutical management of pain.[10] A major limitation of the initial guidelines is that they did not incorporate non-pharmacological interventions. The lack of consideration of alternative non-pharmacological strategies such as minimally invasive treatment can result in the irrational use of pharmacological agents (especially opioids), leading to unwanted side effects. As such, a revised four-step ladder that incorporates non-pharmacological treatments in conjunction with opioids and other analgesics has been proposed (Figure 2).[10]

As shown in Figure 2, opioids are critical in the management of

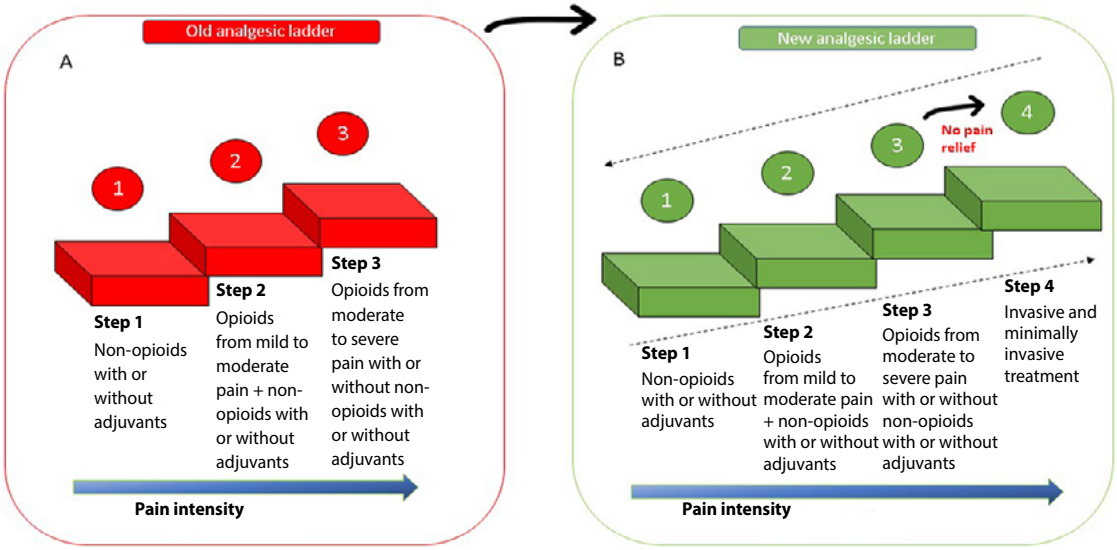

Figure 2: Transition from the initial WHO (A) three-step ladder to the (B) four-step ladder used as a guideline for the treatment of pain[10]

mild to moderate and severe pain. However, abuse and use-dependence preclude the optimal use of opioids in the management of pain.[11] This review aims to discuss oral opioids in the management of pain.

Mechanism of action of opioids

Opioid receptors

Opioid receptors are G protein-coupled receptors that are widely distributed in the brain, spinal cord, gastrointestinal tract, and skin.[12] There are three types of opioid receptors, the delta (δ), kappa (κ) and mu (μ) receptors.[13] Opioids and many metabolites bind to opioid receptors in the brain, leading to euphoria, respiratory depression and analgesia.[12] Although all three opioid receptors elicit an analgesic effect on the brain, they individually have distinct outcomes and distribution in various brain regions.[12] The μ receptors are found in the PAG, cerebral cortex, and thalamus, where they bind to endorphins and stimulate euphoria, use dependence and respiratory depression.[14] The δ receptors located in the PAG and hypothalamus bind to dynorphins to stimulate sedation and dysphoric effects.[14] The κ receptors are found in the basal ganglia, where they bind to enkephalins to induce an anxiolytic effect.[14]

Mechanism of opioid analgesia

Upon binding to receptors, opioids can modulate intracellular calcium disposition and alter protein phosphorylation.[15] Opioids exert their analgesic activity both pre- and postsynaptically. At the presynaptic level, they block the voltage-gated Ca^{2+} channels on afferent fibres. Consequently, neurotransmitters that contribute to nociception (e.g., substance P, serotonin, and glutamate) are reduced, leading to analgesia.[15] Postsynaptically, opioids result in the opening of K^{+} channels, leading to hyperpolarisation of neurons. This leads to decreased neuronal excitability, which ultimately results in analgesia.[15] Some opioids can inhibit serotonin uptake through various mechanisms, therefore, caution should be taken when administering opioids to patients already taking medication with serotonergic activity. Additionally, some opioids such as methadone act on the N-methyl-D-aspartate (or NMDA) receptors, where they antagonise glutamate. This is possibly why methadone has superior efficacy in combating neuropathic pain, compared to other opioids.[16]

Morphine

Morphine is one of the several important alkaloids derived from the poppy plant, *Papaver somniferum*.[17] The drug has remarkable efficacy in the relief of moderate to severe pain and serves as a standard by which other analgesic agents are measured.[17] Preoperatively, morphine is used to reduce anxiety, reduce the anaesthetic dose, and cause sedation.[17] Due to its vasodilatory and bradycardic activity, morphine is used in the treatment of myocardial infarction. Tolerance, physical dependence, respiratory depression, gastrointestinal effects at therapeutic doses are common side effects associated with morphine.[17] As a result, morphine is subject to abuse and is tightly controlled by national and international regulatory agencies.[17]

Hydromorphone

Hydromorphone is a hydrogenated semi-synthetic opioid agonist, with potent activity on the μ receptors, and weak activity on the κ opioid receptors.[6] Hydromorphone is used in the treatment of moderate to severe pain. Due to alterations (a keto-group instead of the hydroxyl group at position 6), hydromorphone is 5 to 10 times more potent compared to morphine, and has better distribution to the central nervous system, leading to enhanced analgesic activity.[18]

Although injections, oral solutions, suppositories and powder formulations are available in the USA, OROS®, a controlled-release oral hydromorphone formulation is the only formulation currently approved in the South African market (4 and 8 mg Jurnista®).[6] This formulation allows for the maintenance of constant plasma concentration levels of the drug, ensuring prolonged analgesia. In comparison to morphine, hydromorphone is better absorbed orally, and has a faster onset but shorter duration of action. This can be used as an advantage when trying to achieve short-term analgesia.[18] Compared to morphine and other opioids, hydromorphone has a similar side effect profile, however, euphoria, nausea, vomiting and constipation may be less pronounced.[6,19]

Oxycodone

Oxycodone is a semi-synthetic opioid used to treat moderate to severe pain. Oxycodone has strong agonistic activity at the κ receptors, and to a lesser degree, at the μ receptor.[20] Despite the use of oxycodone in combination with paracetamol for many years, it has been demonstrated that oxycodone may be safe and efficacious when used alone.[6] There are two main formulations of oxycodone; an immediate-release (conventional) preparation, and an extended-release preparation.[21] The conventional formulation can be used orally for the treatment of moderate to severe pain in conditions such as bursitis, dislocations, and postoperative, post-extraction and postpartum pain.[6] This formulation is available in oral capsules, with doses of 5, 10 and 20 mg.[6] It has a 10–15 minute onset of action, and a 3–6 hours duration of action.[6] The extended-release preparation is used in the treatment of moderate to severe pain, where continuous analgesia is required. This formulation maybe be advantageous in the treatment of cancer-associated pain, and for treating pain during rehabilitation.[6] The preparations for the extended-release formulation may be available in 10, 20, 40 and 80 mg strength. This formulation has a 1-hour onset of action and analgesic action can last up to 12 hours.[6]

Fentanyl

Fentanyl is a narcotic analgesic that was developed in the 1950s and 1960s in an effort to produce opioid analgesics with greater potency, analgesic efficacy, and fewer side effects compared to morphine.[22] Only injections and the transdermal formulations are registered in South Africa, however, a transmucosal immediate-release (TIRF) formulation is available in other countries.[6] These

short-acting fentanyls are delivered through sublingual (100, 200, 300, 400, 600 and 800 µg) and buccal tablets (100, 200, 400, 600 and 800 µg), intranasal sprays (100 µg/100 µL and 400 µg/100 µL) and troche/lozenges (200, 400, 600, 800, 1 200 and 1 600 µg).[6] These formulations are primarily indicated for the treatment of breakthrough cancer pain, in patients that are routinely taking other opioids for pain.[23] To mitigate the potential of abuse, misuse and addiction, TIRF preparations are administered to selected patients through the Risk Evaluation and Mitigation Strategy program of the United States Food and Drug Administration.[6]

Buprenorphine

Buprenorphine is an opioid derivative with higher potency (25–40 times) and has longer lasting analgesic effects compared to morphine.[24] The drug acts as a partial agonist at µ receptors, where it binds with great affinity but with low intrinsic activity.[24] It also has partial agonist effects at the κ receptors and is an antagonist at the delta receptors.[6] 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.[24] Due to such antagonistic activity, buprenorphine is an effective treatment for opioid use disorder.[25] Approved oral preparations include a buprenorphine/naloxone tablet (2/0.5, 0.7/0.18, 1.4/0.36, 2.9/0.71, 5.7/1.4, 8.6/2.1, 11.4/2.9 mg/mg).[25] Constipation, asthenia, drowsiness, nausea and vomiting, fainting and dizziness, orthostatic hypotension, sweating, headaches, and insomnia are the most common side effects associated with buprenorphine use.[6]

Tilidine

Nortilidine, the main active metabolite of the opioid drug tilidine, has a high affinity to µ-receptors, but not to δ- or κ-receptors, and has typical opioid effects and side effects.[26] Tilidine is indicated for postoperative and severe pain, and is usually considered prior to stronger opioids.[27] Tilidine is available as Valoron® drops for use undiluted perilingually or sublingually with or without sugar.

Tramadol

Tramadol is a centrally acting opioid analgesic that has a multimode of action. In addition to acting as an agonist at the µ receptors, tramadol also acts as a noradrenaline reuptake inhibitor.[28] Tramadol is indicated for the treatment of moderate to severe pain, and does not cause much serious adverse side effects when compared with other opioids like morphine.[28] Although other formulations of tramadol exist, oral preparations include; Tramal® 50 mg capsules and 100 mg sustained-release tablets, Austell-tramadol® 50 mg capsules, Dolatram® and Domadol® 50 mg capsules, Tramahexal® 50 mg capsules, and Tramaspen® and Tramazac® 50 mg capsules. Tramadol is also available in combination with paracetamol as Tramacet® at a dose of 325 mg/37.5 mg respectively.[28]

Tapentadol

Tapentadol is a newer opioid that has dual activity as a µ receptor agonist, and a noradrenaline reuptake inhibitor.[6] In comparison to other opioids like morphine, tapentadol resembles tramadol the most and similar multimode mechanism of action. However, in contrast with tramadol, tapentadol additionally inhibits the reuptake of norepinephrine. Consequently, tapentadol has an additional anti-nociceptive activity at the descending pathway, by reducing the transmission of pain signals to the brain.[29] Although not currently registered in South Africa, tapentadol is available in the form of tablets and film-coated tablets with modified release patterns under the trade name Palexia.[30]

Conclusion

Pain is a devastating experience and has a detrimental effect on patients suffering from it, and poses a huge burden on the healthcare system. Fortunately, advances in medical science have allowed for the elucidation of the mechanisms driving pain, which has led to the development of effective analgesics. Opioids form a cardinal part of the pain treatment ladder proposed by the WHO, as they are effective treating moderate to severe pain. However, due to the wide distribution of opioid receptors, opioid drugs are associated with various side effects, and the most concerning ones are use dependence and addiction. This short review highlighted the different oral opioids available. Each opioid drug has its unique mechanism of analgesic action and side effect profile. Where possible, the use of opioid analgesics should be limited when invasive and minimally invasive approaches can result in analgesia. This will strengthen the patient's experience of symptomatic relief, while side effects are avoided.

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