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NSAIDs, Opioids, and Beyond

Coti Phillips, Edwin Contreras and Jessica Oswald

Abstract

Medications are prescribed throughout the world for a variety of reasons including pain. NSAIDs, opioids, and other non-opioid modalities have been used to treat both acute and chronic pain. In this chapter we will discuss the pharmacokinetics, indications, function and associated complications for commonly used pain medications to include NSAIDs, opioids, antidepressants, cannabinoids, and ketamine.

Keywords: acute pain, chronic pain, NSAIDs, opioids, antidepressants, cannabinoids, ketamine

1. Introduction

Acute and chronic pain is a complex disease process that can be difficult to treat. Despite new developments in medications and technology, nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids are among the most widely prescribed medications in the world [1, 2]. In addition to NSAIDs and opioids, adjunctive pharmacologic agents to include antidepressants, cannabinoids and ketamine have increased in popularity. This chapter aims to review commonly prescribed pain medications with a focus on their classification categories, mechanisms of action, and major side effect profiles.

2. NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) were first introduced in the 1960s and are the most prescribed medication class in the world. The United States issues more than 100 million prescriptions annually [3] with approximately 20% of its citizens using NSAIDs on a frequent monthly basis at some point during their lifetime [4].

NSAIDs are a diverse group of compounds with varying chemical structures that possess anti-inflammatory, antipyretic, and analgesic properties [5]. They represent a class of drugs with a primary mechanism of action that involves inhibition of the pro-inflammatory cyclooxygenase (COX) enzymes. This includes both non-selective COX inhibitors (COX-1 and COX-2) including aspirin, indomethacin, and ibuprofen as well as the newer selective COX-2 inhibitors such as celecoxib. NSAIDs have an established short-term efficacy in the treatment of osteoarthritis (OA) and associated chronic low back pain as well as an opioid sparing effect when combined with most chronic pain management regimens [6, 7]. Despite the well-documented efficacy of NSAIDs, there are serious side effects associated with routine use that include gastrointestinal irritation (gastritis and ulceration of the stomach and small

intestine), cardiovascular events (myocardial infarction, hypertension exacerbation) and renal toxicity (acute renal failure, electrolyte and fluid abnormalities).

2.1 Mechanism of action

Prostaglandins are lipid compounds that are physiologically active and have a diverse range of homeostatic and inflammatory effects in the human body that modulate fever and pain. They are the primary mediators of inflammatory cascades resulting in peripheral sensitization, hyperalgesia and chronic pain. Prostaglandin H_2 (PGH_2) is a common precursor for prostaglandins (PGE_2 , PGI_2 , and PGF_2) and thromboxane. It is synthesized from arachidonic acid via the rate limiting enzyme cyclooxygenase (COX) (**Figure 1**). By inhibiting the cyclooxygenase (COX) enzymes and thus inhibiting prostaglandin synthesis, NSAIDs are able to produce their analgesic and anti-inflammatory effects. COX exists in two isoforms, COX-1 and COX-2. COX-1 is expressed throughout the body and is a normal component of most cells. It is a necessary in the production of protective gastric mucosal secretions and regulation of gastric acid, promotion of platelet aggregation and the maintenance of renal blood flow [9]. COX-2, however, is minimally expressed and tightly regulated under normal conditions but is induced with the pro-inflammatory stimuli seen with cellular injury (IL-1, TNF-alpha tumor necrosis factor-alpha, and cytokines) [10]. Given some of the beneficial aspects of COX-1 and the specific pro-inflammatory aspect of COX-2, newer NSAIDs are directly targeted at selective

Arachidonic acid, a 20-carbon fatty acid containing four double bonds, is liberated from the *sn*2 position in membrane phospholipids by phospholipase A_2 , which is activated by diverse stimuli. Arachidonic acid is converted by cytosolic prostaglandin G/H synthases, which have both cyclooxygenase (COX) and hydroperoxidase (HOX) activity, to the unstable intermediate prostaglandin H_2 . The synthases are colloquially termed cyclooxygenases and exist in two forms, cyclooxygenase-1 and cyclooxygenase-2. Coxibs selectively inhibit cyclooxygenase-2. Prostaglandin H_2 is converted by tissue-specific isomerases to multiple prostanooids. These bioactive lipids activate specific cell-membrane receptors of the superfamily of G-protein-coupled receptors. Some of the tissues in which individual prostanooids exert prominent effects are indicated. IP denotes prostacyclin receptor, TP thromboxane receptor, DP prostaglandin D_2 receptor, EP prostaglandin E_2 receptor, and FP prostaglandin $F_{2\alpha}$ receptor.

Figure 1.
Production and actions of prostaglandins and thromboxane (adapted from [8]).

inhibition of COX-2 and are collectively referred to as coxibs. NSAIDs are otherwise non-selective in their inhibition of COX-1 and COX-2 although with varying affinity (Table 1).

2.2 Side effects

The same mechanism of action that provides the therapeutic effect of NSAIDs is also most commonly responsible for the side effects associated with chronic use. By inhibiting prostaglandin synthesis, NSAIDs increase the risk of gastrointestinal bleeding [12–16], thrombosis [17], and myocardial infarction [18]. COX-1 mediated synthesis of PGE₂ is responsible for gastric mucosa integrity. Inhibiting PGE₂

NSAID	COX-2 selectivity*	Gastrointestinal risk	Cardiovascular risk	Clinical use
Aspirin	Low	Moderate	Low	Prevention of cardiovascular events, mild pain, and inflammation
Ibuprofen	Moderate	Low	Moderate to high	Osteoarthritis, rheumatoid arthritis, fever, dysmenorrhea, mild to moderate pain, headache, migraine, myalgia
Diclofenac	High	Moderate	High	Osteoarthritis, rheumatoid arthritis, fever, dysmenorrhea, mild to moderate pain, migraine
Indomethacin	Low	Moderate to high	Moderate to high	Osteoarthritis, rheumatoid arthritis, bursitis, tendinitis, mild to moderate pain, or severe pain
Naproxen	Low	Moderate to high	Low	Gouty arthritis, mild to moderate pain, tendonitis, fever, rheumatoid disorders, osteoarthritis, dysmenorrhea, migraine prevention
Meloxicam	High	Low	Moderate to high	Osteoarthritis, rheumatoid arthritis
Celecoxib	High	Low	Moderate to high	Osteoarthritis, ankylosing spondylitis, rheumatoid arthritis, acute pain, dysmenorrhea

Adapted from [11].
*Only generic names provided. List not all inclusive. Keep in mind NSAIDs carry varying risks of rare liver toxicity and renal failure.
*Selectivity is based on in vitro assay studies and should be interpreted with caution as different assay methods give different results. No assay method can predict what will happen when the drug is given to patients. Clinical studies are the best way to determine the effects of NSAIDs in patients.

Table 1.
Safety comparison of some of the most commonly used NSAIDs.*

production with traditional non-selective NSAIDs results in gastric mucosal impairment and injury. Gastroduodenal ulcers are commonly identified with endoscopy after chronic non-selective NSAID use with double-blind trials showing incidence as high as 46% after 24 weeks of ibuprofen use [19]. Extra care must be taken with NSAID use in special populations including the elderly and those with underlying gastric irritation, stress related gastric mucosal injury (SRMD), and portal hypertensive gastropathy.

Given the side effects associated with inhibition of COX-1, especially the GI toxicity noted above, selective COX-2 inhibiting NSAIDs were created with the intention of avoiding harmful GI events while continuing to retain the anti-inflammatory and analgesic benefits of COX-2 antagonism. The selective COX-2 inhibition that occurs with coxibs (celecoxib, rofecoxib) was, however, believed to be associated with increased cardiovascular (CV) events including hypertension and thrombosis. The CV side effects are attributed to the imbalance in vascular tone and clotting hemostasis that is in part regulated by arachidonic metabolites; with COX-1 mediated TXA₂ being an inducer of platelet aggregation and COX-2 mediated PGI₂ being an inhibitor of platelet aggregation [20]. This is highlighted with PGI₂ receptor deficient mice being more prone to thrombosis than wild type mice [21]. Ultimately, large randomized controlled trials showed that celecoxib in moderate doses was non-inferior to naproxen or ibuprofen (non-selective NSAIDs) in regards to a primary outcome of cardiovascular causes of death [22].

3. Opioids

Opioids have been used for the management of pain since the earliest records of human history. The Sumerians of Mesopotamia were the first to cultivate the poppy plant [23]. Further refinement paralleled the advancement of human growth with the first extraction of morphine from opium occurring in 1803 [24]. New formulations, concentrations, and routes of delivery were developed and there was a simultaneous increase in medicinal as well as recreational use. Opiate use peaked between 1999 and 2017 and was responsible for approximately 400,000 overdose related deaths [25]. This has culminated into the current state of affairs where narcotic prescription abuse has become a national crisis with strict regulations on prescribing now in place. The fine balance between proper medical uses for the treatment of acute and chronic pain versus inappropriate overprescribing is being heavily scrutinized requiring careful consideration of the appropriateness of initiating opioids and the risks and benefits of chronic use. The importance of this is demonstrated with meta-analysis showing roughly 5% of patients prescribed an opioid for pain developing iatrogenic opioid dependence or abuse [26]. One must have an intimate understanding of the various opioid medications available and take a careful and strategized approach to prescribing a chronic regimen to suitably navigate this dilemma. Nonetheless, opioids remain a mainstay in the treatment of acute and chronic cancer related pain. This is in contrast to the benefit of opioids used in chronic non-malignant pain with studies continuing to show little to no benefit in quality of life or functional capacity [27, 28].

3.1 Mechanism of action

The classification of *opioid* commonly refers to all compounds that bind to the opiate receptors. This includes the naturally occurring alkaloids derived from the opium poppy (morphine, codeine), semi-synthetic opioids which are synthesized

from naturally occurring opiates (oxycodone, heroin) and fully synthetic opioids (methadone, fentanyl). Opioids as a class are similar in that they all cause analgesia and have a common side effect profile. Opioid drugs impart their effects primarily through three receptors: Mu (μ), Delta (δ), and Kappa (κ) (**Table 2**). These receptors are found both peripherally and centrally and can be activated all along the neuroaxis including the cortex, brainstem, interneurons of the spinal cord and the nociceptors at the level of the primary sensory neurons. Activation of these receptors is responsible for both the analgesic properties of opioids as well as the major side effects. All opioid receptors are G-protein coupled receptors that inhibit adenylyl cyclase, decreasing conductance of voltage-gated Ca^{++} channels and/or opening rectifying K^{+} channels (**Figure 2**). This ultimately prevents calcium influx and the release of pronociceptive neurotransmitters (glutamate, substance P, and calcitonin gene-related peptide from the nociceptive fibers) [31]. By preventing the release of these pain-promoting neurotransmitters, opioids are able to impart their analgesic properties.

3.2 Opioid receptors

Mu receptors are largely thought of as the primary receptor responsible for analgesia with opioids; thus, the term “mu agonist” is often used to describe opioids used for the management of pain. Mu opioid receptors (MOR) are found in high density at the periaqueductal gray (PAG) of the midbrain. Agonism of MOR in this region is thought to eliminate a tonic gamma aminobutyric acid (GABA) tone thus

	Mu (μ)	Delta (δ)	Kappa (κ)
	Mu 1: Analgesia Mu 2: Sedation, vomiting, respiratory depression, pruritus, euphoria, anorexia, urinary retention, physical dependence	Analgesia, spinal analgesia	Analgesia, sedation, dyspnea, psychomimetic effects, miosis, respiratory depression, euphoria, dysphoria, dyspnea
Endogenous peptides			
Enkephalins	Agonist	Agonist	
Beta-endorphin	Agonist	Agonist	
Dynorphin A	Agonist		Agonist
Agonists			
Morphine	Agonist		Weak agonist
Codeine	Weak agonist	Weak agonist	
Fentanyl	Agonist		
Meperidine	Agonist	Agonist	
Methadone	Agonist		
Antagonists			
Naloxone	Antagonist	Weak antagonist	Antagonist
Naltrexone	Antagonist	Weak antagonist	Antagonist

Adapted from [29, 30].

Table 2.
Analgesic effects at opioid receptors.

Figure 2.
Mechanisms of opioid action in the spinal cord.

indirectly stimulating descending inhibitory pathways at the level of the spinal cord [32]. MOR receptors are also in high density on dorsal horn neurons and elicit their analgesic effect through inhibition of glutamine release decreasing the transmission of nociceptive information from A-delta and C nerve fibers.

The drugs that are able to fully activate these mu receptors in a dose dependent fashion are referred to as full agonists. This is in contrast to the drugs that are either weak agonists at the mu receptor (while preventing other full agonists from binding) or are antagonists at the mu receptor while being an agonist at another receptor. These are referred to as agonist-antagonist drugs and include buprenorphine+naloxone (suboxone), nalbuphine, and pentazocine. Reversal of the effects caused by mu agonists is accomplished with competing antagonists (naloxone), which are crucial in the medical management of opioid overdoses and the associated respiratory depression. Kappa and delta receptors also contribute to analgesia and the other clinical effects seen with acute and chronic use including respiratory depression and sedation. Kappa receptors, in particular, are localized in the brain stem and spinal cord and are chiefly responsible for providing spinal analgesia [29]. Opioid receptors also bind to endogenous opioid

peptides (endorphins, enkephalins, and dynorphins), which are important in overall pain modulation.

The clinical use of opioids is dependent upon more than just the receptor specificity and relies on deep understanding of the pharmacokinetics of these drugs for optimal use. In a basic sense, opioids can be classified into either short or long acting agents although this terminology inappropriately simplifies complex pharmacodynamic and pharmacokinetic properties of these drugs.

3.3 Side effects

The interaction between exogenous opioids and opioid receptor activation has a diverse side effect profile with variable differences seen with acute and chronic use. These side effects include constipation, nausea and vomiting, hyperalgesia, opioid induced hormonal changes, and respiratory depression. Opioid induced constipation (OIC) is one of the most commonly seen side effects with roughly one half of patients experiencing OIC with long-term use [33]. OIC can cause significant morbidity with associated adverse effects including fecal impaction with obstruction, reflux, dyspepsia, cramping/pain, and lengthened hospitalization [34]. For this reason, all chronic opioid regimens should include prophylactic laxatives. Mu opioid receptors are abundant in the respiratory rhythm generating regions of the brainstem and pons. Agonism of these receptors causes opioid induced breathing alterations including significant reduction in respiratory rate and minute ventilation with associated hypercapnia. This can ultimately lead to fatal apnea, especially with lipophilic opioids and intravenous administration that allows for quick equilibration at the effect compartment (central respiratory centers) [35]. Given the euphoria that occurs with opioids, addiction is another potential iatrogenic side effect seen with acute and chronic use. This can be associated with tolerance to opioids, which is defined as a decreased objective and subjective effect with a stable dose over time as well as requiring increasing amount of an opioid to achieve the same effect. Increasing tolerance also develops to the other effects of opioids including respiratory depression [24]. This is problematic in patients abusing opioids given the tendency for relapse back to a previous dose that will now cause profound respiratory depression due to the loss of tolerance during abstinence.

4. Antidepressants

Antidepressants have a long established efficacy in the treatment of neuropathic predominant chronic pain disorders [36]. Neuropathic pain disorders develop from a multitude of disease processes that directly arise from lesions or other damage to the central or peripheral somatosensory nervous system [37]. Associated diseases and processes include diabetes mellitus (diabetic peripheral neuropathy), HIV (HIV polyneuropathy), herpes zoster (post-herpetic neuralgia), and medical interventions (e.g., post-mastectomy pain, chemotherapy). Tricyclic antidepressants (TCAs) including amitriptyline, imipramine, and nortriptyline are routinely used as first line options in the management of neuropathic pain [36, 38]. TCAs can be started and maintained at doses lower than the doses used in depression thus reducing some of the side effects commonly seen at depression doses such as dry mouth, sedation, urinary retention and orthostatic hypotension. TCAs must be used cautiously in patients taking other serotonergic drugs or in patients with a history of cardiovascular disorders, glaucoma, or urinary

retention given the anticholinergic side effects TCAs can produce. Of note, TCAs are beneficial to both depressed and non-depressed patients as well as having the added value of helping with depression in the depressed subpopulation [36]. Serotonin-norepinephrine reuptake inhibitors (SNRIs) are also commonly used in the management of chronic pain with duloxetine having FDA approval for the management of fibromyalgia and venlafaxine showing superiority to placebo in the treatment of diabetic neuropathy [39, 40].

The primary mechanism of action of TCAs in the treatment of neuropathic pain involves the reuptake inhibition of norepinephrine (NE) and serotonin (5-hydroxytryptamine [5-HT]), which causes a blockade of the neuronal membrane ion channels and increases the activation of descending inhibitory pathways in the midbrain and spinal cord [41, 42]. SNRIs also elicit their effect through inhibition of NE and 5-HT blocking their role in descending pain pathways.

5. Cannabinoids

The term cannabinoid is used to collectively describe all naturally occurring and synthetic compounds that are structurally similar to and elicit similar effects as the cannabinoid plants, most notably *cannabis*. In addition to the cannabinoids derived from plants (phytocannabinoids), there are also endogenously produced cannabinoids (endocannabinoids) and synthetic cannabinoids now being produced for medical use. Endocannabinoids are fundamental in human homeostasis with established behavioral, metabolic, immunologic, and physiologic functions [43]. Cannabinoids bind to two isotypes of G protein coupled receptors, CB₁ and CB₂ [44]. The CB₁ receptor is found predominantly in the CNS including the brain, spinal cord, and the sensory nerve terminals and along primary pain pathways. Activation of CB₁ receptors at these sites results in membrane hyperpolarization and the modulation of nociceptive neurotransmitters contributing to both the pain relief and psychotomimetic properties of cannabinoids [45]. This reduced pain with cannabinoid receptor agonists can occur at multiple levels of the CNS both peripherally and centrally. CB₂ receptors are concentrated in the hematopoietic cells of the immune system and are involved in a diverse range of immunomodulatory effects including the inhibition of cytokine release [46, 47].

Cannabis contains over 500 chemical compounds including over 150 phytocannabinoids with the most studied being Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD). THC is the chief psychotropic compound of *cannabis* and is found in varying concentrations in different strains of the plant. THC has a strong affinity for CB₁, which is regarded as the primary receptor responsible for the psychoactive effects seen with cannabis. In contrast, CBD does not activate CB₁ so it does not produce psychoactive effects and is associated more with the anti-inflammatory effects of cannabinoids [48]. There are currently three cannabinoid drugs available for use in the United States. Epidolex® is a CBD based drug used to treat epileptic disorders and is derived from cannabis. Dronabinol and Nabilone are synthetic THC compounds approved for use in chemotherapy associated nausea and as an appetite stimulant in HIV/AIDS [49]. Molecular and preclinical evidence continues to support the anti-nociceptive properties of cannabinoids although experimental human studies are more heterogeneous with varying results although ongoing research is being conducted [50]. With major legislative changes in the USA, thirty-three states and the District of Columbia have passed laws broadly legalizing cannabis in some form at the time of this writing.

6. Ketamine

Ketamine is a dissociative analgesic and amnestic medication that acts as a non-competitive antagonist of the N-Methyl-D-Aspartate (NMDA) receptor in the central nervous system [51]. It has been used since the 1960s as an anesthetic agent and continues to be studied and adapted for novel psychiatric and anesthetic purposes. Ketamine has multiple sites of drug action but its principal nociceptive effects occur at the NMDA receptors. NMDA receptors have dense expression in the temporal cortex, hippocampus, basal ganglia, cerebellum and brain stem and are known to contribute to the neuronal process that mediate nociception via activation by glutamate, an excitatory amino acid [52]. By targeting this receptor, ketamine has profound attenuating effects on ascending nociceptive transmission and amplification of descending inhibitory pathways [52, 53]. Ketamine is currently utilized in the management of many diseases and other applications including the management of chronic pain disorders (e.g., complex regional pain syndrome, phantom limb pain, fibromyalgia), acute pain, conscious sedation, and intraoperatively for antihyperalgesia and induction of anesthesia [54].

7. Conclusions

NSAIDs have been used historically to treat both acute and chronic pain. They possess analgesic, antipyretic, and anti-inflammatory properties through the inhibition of the pro-inflammatory cyclooxygenase (COX) enzymes. Their mechanism of action allows them to establish efficacy in treating a variety of pain diseases but also allows their routine use to produce serious side effects. COX-1 receptors are expressed throughout our body and its inhibition can lead to gastric mucosal injury including gastroduodenal ulcers. Selective COX-2 inhibitors were created with hopes of avoiding the side effects connected with non-selective COX-inhibitors; however, they are associated with their own complications which include an increased risk for cardiovascular events (thrombosis and hypertension).

Opioids remain a popular option in treating pain due to their effect on the Mu (μ), Delta (δ), and Kappa (κ) receptors. By activating these receptors, opioids can prevent the release of pain-promoting neurotransmitters providing their analgesic effects. However, the activation of the same receptors is also responsible for the associated side effects. These side effects vary depending on either acute or chronic use but can be life-threatening in some cases. This includes respiratory depression which can lead to fatal apnea. Chronic opioid use is associated with opioid induced constipation that can cause significant morbidity. It is therefore recommended to include prophylactic laxatives with chronic regimens. It is important to remember that addiction and tolerance is associated with opioid use due to its euphoric effect. Therefore, the clinical use of these medications should not only depend on their mechanism of action but also on understanding the potential severe complications that arise with their use.

Neuropathic chronic pain disorders have been effectively treated with antidepressants. These disorders include, but are not limited to, diabetic peripheral neuropathy, HIV polyneuropathy, and post-herpetic neuralgia. One of the first line options are the tricyclic antidepressants (TCAs) which are usually started and maintained at lower doses versus the depression doses. This helps reduce some of their side effects including urinary retention, sedation, and dry mouth. Other antidepressants include serotonin-norepinephrine reuptake inhibitors that are also used in the management of neuropathic disorders.

Cannabinoids exhibit their effects by binding to CB₁ and CB₂ receptors, two iso-types of G-protein coupled receptors. The agonism of these receptors is responsible for cannabinoids' anti-inflammatory and analgesic effects. CB₁ receptor agonism is also predominately responsible for the psychoactive effect. Preclinical evidence supports anti-nociceptive effects and with recent legalization of cannabis, the use of cannabinoids to treat pain disorders will expand with ongoing research.

Ketamine has many uses in treating both acute and chronic pain including fibromyalgia. It is also used for conscious sedation due to both its dissociative and amnesic properties. Ketamine has multiple sites of interactions but it exhibits its principle nociceptive effect by acting as a non-competitive antagonist of the N-Methyl-D-Aspartate (NDMA) receptor.

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