Pharmacology of Nonsteroidal Antiinflammatory Drugs and Opioids

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ABSTRACT

Chronic pain affects up to 50 million Americans every day. Traditional treatment has included acetaminophen, nonsteroidal antiinflammatory drugs (NSAIDs), or opioids. The combination of NSAIDs and opioids can provide effective treatment for up to 90% of patients with chronic pain, but the NSAIDs have the potential for significant, even life-threatening side effects. Additionally, the nonselective cyclooxygenase inhibitors with 16,000 deaths per year in the United States might not be any safer. The opioids are great for short-term pain, but may need to be adjusted or changed frequently due to the development of tolerance. Understanding of the mechanism of opioids and NSAIDs has improved greatly over the past decade, but is still incomplete.

KEYWORDS: NSAIDs, opioids, analgesics, mechanisms, pharmacology

Objectives: Upon completion of this article, the reader should be able to evaluate pain physiology and state how opioids and NSAIDs produce their analgesic effect as well as side effects.

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Pain has plagued humans since the origin of the species, and other living creatures for eons before that. Over the millennia pain has been attributed to demons, bad luck, or divine punishment. Only in the last several decades has the pathophysiology of pain been partially elucidated. Despite our growing understanding of the physiologic underpinnings of pain, up to 40% of Americans experience pain on a daily basis, including 50 million individuals with chronic pain.¹ Pain is undertreated in nearly half of patients with cancer.² Untreated pain is considered such a significant problem that 111th United States Congress is attempting to pass the National Pain Care Policy Act.³

Interventional pain therapy includes control of procedural pain by the traditional methods used for acute pain control including oral, transdermal, intravenous (IV), and intramuscular (IM) delivery of pharmaceuticals. It also includes minimally invasive delivery of pain medications by other routes such as intrathecal, epidural, intraarticular, intraarterial, or paraganglionic. In the case of the neuropathic pain, interventional techniques can be used to deliver medications to the peripheral or central nervous systems to interrupt a positive feedback system for pain, ablate nerve axons or ganglia, alter receptors, or to simply provide temporary relief of pain. In very specific instances, medications to eliminate the

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nociceptive stimulus can be effectively administered by interventional radiology techniques. Several examples would include ozone in the treatment of degenerative disk disease, methyl-methacrylate treatment of compression fractures, radioactive strontium to treat bone metastases, or radioactive yttrium-90 to treat painful liver tumors. Because of space limitations, we will concentrate on the pharmacology of the two most commonly employed classes of analgesics: nonsteroidal antiinflammatory drugs (NSAIDs) and opioids.

Systemic analgesics and adjuvant medications have been the mainstay of pain control. Numerous medications have been developed to help alleviate pain, and researchers are attempting to develop additional pain medications. To simplify the study of the many different pain medications, it is helpful to divide them into smaller groups. The traditional medications comprise NSAIDs, opiates, anesthetics, antiinflammatory steroids, and adjuvant medications such as neurolytics, antidepressants, ketamine, and anticonvulsants. Each of these groups contains multiple medications with slightly differing properties. In addition, the effect of each medication will depend on its route of administration. Besides the traditional medications, recent efforts have tended to target cell membrane receptors or intracellular enzymes. These include cannabinoids and agonists or antagonists for sodium-calcium channels, *N*-methyl-D-aspartate receptors, vanilloid receptors, G protein inhibitors, thermal channel receptors, or α receptor agonists.⁴ Most of these medications are still in the investigational stage.

PAIN PATHOPHYSIOLOGY

To understand how the numerous medications can mitigate pain, a brief review of the current understanding of pain physiology is helpful. Pain mechanisms are usually divided into nociceptive and neuropathic pain. Nociceptive pain is acute pain caused by potentially injurious stimuli. Neuropathic pain implies alteration of the normal nervous system so hyperpathia is present. Hyperpathia comprises dysesthesia (unpleasant sensation with or without a stimulus), allodynia (perception of nonnoxious stimuli as pain), hyperallodynia (amplified perception of pain to noxious stimuli), hyperesthesia (exaggerated response to mild stimuli), or anesthesia dolorosa (perception of pain in an area that lacks sensation, e.g., phantom limb pain).

The earliest abstraction of pain was simplistic: a peripheral receptor was stimulated by a noxious stimulus. The peripheral nerve carried the signal to the spinal cord where it relayed the signal to an ascending neuron. This neuron carried the signal to the cerebral cortex where it was perceived as pain. Unlike this simplistic view, the current conceptualization of pain perception is considerably more complex.

For nociceptive pain, a noxious stimulus such as extreme heat, cold, pressure, stretching, cutting, inflammation, or some other potentially tissue-injuring stimulus excites nociceptors that transduce the stimulus into an action potential along an axon contained in a C (nonmyelinated) or A-delta (myelinated) nerve fiber in the peripheral nervous system. The action potential is carried through the afferent axons to the neuron cell body in the dorsal root ganglion, then through an efferent axon to the dorsal horns of the spinal cord where the peripheral neuron finally synapses with a central neuron in the spinal cord. The signal from the peripheral nerve can be modulated by astrocytes, microglia, other neurons (descending pathways from the brain, local neuronal circuits, or additional input from the peripheral nervous system) and potentially analgesic medications before it is carried to the brainstem and thalamus through ascending pathways such as the spinal thalamic tract. The signal is further processed by the brainstem, thalamus, and the cerebral cortex, where it is finally perceived as pain. Descending pathways from the cortex, thalamus, or brainstem can affect pain perception by modulating the transmission of signals in the dorsal horns.⁵ Pharmaceuticals or image-guided interventions can alter pain perception by decreasing the sensitivity of nociceptors; interfering with neuronal transmission of pain signals along axons or across synapses; reducing pain signals in the ascending spinal thalamic tract by downregulating signals from the pain network in the spinal dorsal horns, brainstem, or thalamus; by interfering with the perception of pain in the cerebral cortex; or by modulating the descending pathways from the brain (see Fig. 1).

The anatomic sites where pharmaceuticals can alleviate pain include

1. Nociceptors and surrounding tissue
2. Axons of the A-delta and C nerve fibers in the peripheral nervous system
3. Peripheral nerve cell bodies in the dorsal root ganglia
4. Dorsal horn synapses, neurons, microglia, and surrounding tissue
5. Ascending pathways in the spinal cord such as the spinothalamic tract
6. Brainstem, thalamus, or cerebral cortex
7. Descending pathways such as the corticospinal tract

Neuropathic pain, defined by the International Association for the Study of Pain as pain "initiated or caused by a primary lesion or dysfunction in the nervous system," is quite difficult to treat because even once the injurious stimulus has terminated, the induced change in the nervous system persists, resulting in chronic pain.⁶ The change in the nervous system could be a change in cell membrane receptors, cytoplasmic proteins, neuronal circuits, or a transdifferentiation of astrocytes and

Figure 1 Anatomic targets for analgesics. 1. Nociceptors and surrounding tissue. 2. A-delta and C fibers. 3. Dorsal root ganglia. 4. Dorsal horn synapses. 5. Ascending pathways. 6. Intracranial neurons and glial cells. 7. Descending pathways.

microglia surrounding the neurons (especially in the dorsal horns of the spinal cord).⁷

The first opportunity to alleviate pain is to reduce the sensitivity of nociceptors in the peripheral nervous system. Following most injuries, mast cells, macrophages, and the injured cells release a host of chemicals or initiate biochemical pathways that produce numerous compounds comprising an inflammatory soup that increases the sensitivity of nociceptors and can alter ion channels in peripheral nerves. Some of these chemicals include protein kinase A and C that can activate other membrane-bound receptors and gene transcription, 5-hydroxytryptamine, interleukin, nitric oxide, platelet-activating factor, prostaglandins, reactive oxygen species, and tumor necrosis factor.⁸

Both steroidal and nonsteroidal antiinflammatory medications exert much of their effect at this initial step in pain perception. Anesthetics work by interfering with

action potential propagation in axons of the A-delta and C nerve fibers. Opioids have limited effect on the first step of pain perception and exert most of their effect in the spinal cord and brain.

NSAIDS AND ACETAMINOPHEN (PARACETAMOL)

The World Health Organization (WHO) three-step analgesic ladder portrays a progression in the doses and types of analgesic drugs for effective pain management. This three-step plan is purported to adequately control pain in up to 90% of cancer patients. The first step in this approach involves the use of acetaminophen, aspirin, or another NSAID for mild to moderate pain.⁹

Mechanism of NSAIDs

NSAIDs exert their antiinflammatory effect by inhibiting prostaglandin H₂ synthetase, also known as cyclooxygenase (COX), an enzyme needed for synthesis of prostaglandins from cell membranes. The antiinflammatory effect is responsible for part of the analgesia derived from NSAIDs. Cell injury leads to release of lysosomal enzymes from leukocytes that liberate arachidonic acid (AA) from cell membranes. Arachidonic acid is converted into prostaglandins (PG), prostacyclins, thromboxanes, leukotrienes, lipoxins, and other eicosanoids. Some prostaglandins, especially PGE₂ and PGF_{2a}, are important in inflammation and in sensitizing the nociceptors innervated by small myelinated (A-delta) and unmyelinated (C) nerve fibers, but other prostaglandins are needed for homeostasis.¹⁰ The NSAIDs inhibit cyclooxygenase, which is necessary for the conversion of arachidonic acid into prostaglandins, prostacyclin, and thromboxanes (see Fig. 2). COX inhibitors reduce inflammation and pain, but they can also interfere with homeostatic functions such as proper renal blood flow and gastric mucosa protection.

Although the NSAIDs exert some of their analgesic effects by inhibiting the inflammatory cascade in cells surrounding the injury site, they also appear to exert changes directly upon the central nervous system. For example, intrathecal ibuprofen or aspirin counteracts the hyperalgesia caused by *N*-methyl-D-aspartate (NMDA) and substance P.¹¹ In addition, NSAIDs have 10 to 100 times the potency when administered intraspinally compared with systemic administration.¹²

Two isoforms of cyclooxygenase (COX-1 and COX-2) exist in many tissues. COX-2 is normally absent in most cells, but is induced during inflammation and amplifies the inflammatory response. COX-1 does not play a major role in inflammation, but instead tends to be involved in homeostatic functions.¹¹ For example, PGE₁ produced by COX-1 enzymes in the stomach provides gastric epithelial cytoprotection by promoting

Figure 2 Cell membrane depicting phospholipid conversion into arachidonic acid and then into prostaglandins, thromboxanes, prostacyclins under the influence of COX enzymes. Also demonstrated is a G-protein with an endorphin / morphine receptor in the extracellular matrix and an intracellular gamma subunit ready to activate a potassium GIRK channel.

secretion of mucus and bicarbonate to reduce gastric acidity. In addition to stimulating epithelial cells to release more bicarbonate and mucus, prostaglandins can reduce the permeability of the epithelium and thus reduce acid back-diffusion.¹² Although COX-2 is absent in most cells until it is induced by inflammation, it also has homeostatic functions in the kidney and cardiovascular system where it is constitutionally present in endothelial cells and is responsible for producing

PGI₂, a potent vasodilator and platelet-aggregation inhibitor.¹³

Side Effects of NSAIDs

In 1997, there were ~107,000 hospitalizations and 16,500 deaths related to nonselective NSAID use and associated gastrointestinal (GI) complications among people with arthritis in the United States.¹⁴ Because

the COX-2 isoform is induced during inflammation, highly selective COX-2 inhibitors have been developed and marketed with the belief that such selective inhibitors would be just as effective as nonselective COX inhibitors without the GI side effects caused by COX-1 inhibition. In fact, COX-2 inhibitors such as celecoxib, valdecoxib, and rofecoxib have successfully halved the adverse GI side effects and have essentially no effect on platelet aggregation at their usual doses, but still maintain efficacy in their analgesic, antipyretic, and antiinflammatory effects.¹⁵

Unfortunately, there has been an increased incidence of cardiovascular deaths in patients at risk for a myocardial event who take selective COX-2 inhibitors. Gislason et al identified 107,092 patients surviving their first hospitalization because of heart failure between January 1, 1995, and December 31, 2004. They tracked the use of NSAIDs from individual-level linkage of nationwide registries of hospitalization and drug dispensing by pharmacies in Denmark and their subsequent death rates. The hazard ratio (95% confidence interval) for death was 1.70 (1.58–1.82), 1.75 (1.63–1.88), 1.31 (1.25–1.37), 2.08 (1.95–2.21), 1.22 (1.07–1.39), and 1.28 (1.21–1.35) for rofecoxib, celecoxib, ibuprofen, diclofenac, naproxen, and other NSAIDs, respectively.¹⁶ These data demonstrate a significant risk of myocardial infarct or congestive heart failure in patients taking COX-2 inhibitors with a prior history of heart failure. For example, for rofecoxib, the number of patients needed to treat for one year to cause one death was just nine; the corresponding number for celecoxib (Celebrex[®], Pfizer, New York, NY) was 14, and for diclofenac was 11.¹⁶

COX-2 is constitutionally present in endothelial cells and is responsible for producing PGI₂, a potent vasodilator and platelet aggregation inhibitor. The inability to inhibit platelet aggregation and the absence of a key vasodilator may be largely responsible for the increased risk of coronary infarcts for patients taking COX-2 inhibitors. Both COX-1 and COX-2 are important for regulating renal blood flow, natriuresis, and systemic blood pressure.^{17–19} As a consequence, selective COX-2 inhibitors should be avoided in patients at risk for coronary artery disease, congestive heart failure, or who have a hypercoagulopathy such as protein C or S deficiency. Nonselective COX inhibitors have a greater propensity for causing GI ulcers and bleeding and hence should be avoided in patients at risk for peptic ulcer disease. In some conditions, at least in rats, COX-2 inhibitors may eventually prove to slow down progression of renal disease,²⁰ but most authors recommend that COX-1 and COX-2 should be avoided in humans with reduced creatinine clearance, especially a creatinine clearance below 30 mL/minute.^{21,22}

Other side effects common to all the NSAIDs include rashes, allergic reactions, pruritus, abnormal

liver-associated enzymes and rarely liver failure, neutropenia, tinnitus, hypertension, dyspepsia, fluid retention, and rarely aplastic anemia.

Acetaminophen

N-acetyl-*p*-aminophenol is known as acetaminophen in the United States and as paracetamol in other countries. Brand names include Tylenol[®] (Ortho-McNeil-Janssen Pharmaceuticals, Titusville, NJ), Crocin[®] (GlaxoSmithKline, Brentford, London, UK), Tempra[®] (Bristol-Myers Squibb, New York, NY), Datril[®] (Bristol-Myers Squibb, New York, NY), Panadol[®] (GlaxoSmithKline, Brentford, London, UK), and many others. Acetaminophen is the active metabolite of phenacetin, which was derived from coal tar.²³ Acetaminophen incompletely inhibits COX-1 and COX-2 enzymes and has little antiinflammatory effect.²⁴ There may be a COX-3 enzyme in the brain that is inhibited by acetaminophen or its effect may be secondary to activation of descending serotonergic pathways or activation of cannabinoid receptors, but despite many years of use, the precise mechanism of action for acetaminophen is still not known.²⁵ Acetaminophen is an antipyretic and its analgesic effect appears additive to the NSAIDs. Acetaminophen has minimal effect on the incidence of peptic ulcer disease or renal function, but has a proclivity to cause hepatic injury in higher doses. For patients with mild hepatic insufficiency the daily dose should be reduced to no more than 2000 mg per day. For patients with no underlying liver disease, 4000 mg per day is considered the maximum safe dose.²⁶

Because of the low incidence of side effects, acetaminophen is often the first-choice analgesic. It can be used by itself or in combination with NSAIDs and opioids. In the United States, it is currently available for oral or rectal administration; in 60 other countries, it is also available intravenously. The U.S. Food and Drug Administration (FDA) is currently considering approval of an IV formulation of acetaminophen for use in the United States; a decision is forthcoming.

Aspirin

Willow bark extract has been used for thousands of years by the Chinese, Egyptians, Native Americans, and others to relieve fever and aches. The Latin name for white willow, *salix alba*, was the namesake for the salicylates. “Aspirin” was coined from Meadowsweet (*Spiraea ulmaria*) because its extract had similar ameliorating effects as willow bark. In 1763, Reverend Edmund Stone wrote a letter to the Royal Society documenting the medicinal effects of willow bark. In 1899, Hoffman recognized the reduced side effects of acetyl salicylic acid that had been formulated in 1853 by

Gerhardt, and Bayer Laboratories began marketing aspirin in 1899.²⁷

Unlike the other NSAIDs, aspirin binds irreversibly to cyclooxygenase. Aspirin will continue to inhibit COX until new COX has been synthesized in the body. In most cells, this takes only minutes so that after aspirin has been cleared from the bloodstream, nucleated cells will synthesize new COX to initiate the synthesis of prostaglandins and restart the inflammatory response or to restart the homeostatic processes interrupted by aspirin. Anucleated platelets cannot synthesize new COX; instead, new platelets need to be produced to overcome aspirin's inhibition of platelet aggregation. This explains why aspirin can have a profound effect on platelet function for up to a week even though aspirin is cleared from the body in a few hours.²⁸

In addition to its analgesic effect, aspirin lowers the risk for stroke and myocardial infarction for people at risk for cardiovascular events. Doses of 75 to 160 mg are as effective as larger doses.²⁹ Chronic aspirin use reduces fatal colon cancer in men by up to 50%.³⁰ Aspirin has been linked to Reyes syndrome and aspirin should not be given to children less than 18 years old if they have a febrile illness.³¹

Choosing NSAIDs

Because the NSAIDs provide nearly equal analgesia, the choice of NSAID usually depends on side effects, available route of administration, and cost. See Table 1 for common dosages, costs, and comments. Aspirin, with its prolonged inhibition of platelets can increase bleeding, especially in patients on anticoagulation or with thrombocytopenia. Ketorolac tromethamine can be taken orally or given IM or IV, but it has a strong association with both renal failure and peptic ulcer disease so its use is limited to 5 days. Ibuprofen can be given orally or IV; in addition, topical preparations and oral gels are available. It has been widely used and has one of the best safety profiles.²⁸ All NSAIDs increase the risk of GI erosions, ulcers, and bleeding. This can be mitigated by the concomitant ingestion of omeprazole, a proton pump inhibitor, or misoprostol, the prostaglandin needed for homeostasis of gastric mucosa.³² Diclofenac and meloxicam have a relatively greater inhibition of COX-2 than other nonselective NSAIDs, and they appear less likely to cause peptic ulcer disease than other nonselective NSAIDs. Selective COX-2 inhibitors such as Celebrex[®] and preferential COX-2 inhibitors such as diclofenac and meloxicam have an increased risk of causing congestive heart failure or myocardial infarction, so their use should be limited in patients at risk for cardiovascular disease.³³

NSAIDs appear safe for short-term usage, but have significant risk of causing GI hemorrhage, renal

failure, or cardiovascular events with long-term use, especially in the elderly.

OPIOIDS

Enkephalins, endorphins, endomorphins, dynorphins, and nociceptin are a group of five polypeptides that compose the known endogenous opioids. These polypeptides are a part of a natural internal system that modulates pain through a complex interplay between the endogenous opioids, opioid receptors, neurons, and microglia. The exogenous opioids mimic the endogenous opioids by competing as ligands to activate cell membrane opioid receptors.³⁴

Exogenous opioids achieve analgesia by interfering with the pain signaling at several distinct anatomic sites (see Fig. 1). First, activated opioid receptors in peripheral tissue can produce antiinflammatory effects by inhibiting cells that release bradykinins and other proinflammatory peptides. Opioid receptors can also inhibit activation of peripheral nociceptors.^{35,36} Second, activated opioid receptors in the dorsal horn of the spinal cord block the release of neurotransmitters from the afferent dorsal root neurons by inhibiting voltage-dependent calcium channels.^{37,38} Third, potassium channels in the dorsal horn postsynaptic neurons are opened by opioid receptors to hyperpolarize the postsynaptic membrane and preventing the propagation of action potentials along the efferent ascending spinal thalamic tracts.³⁹ The combined effect upon the dorsal horn synapse is to dampen pain signals through the ascending spinal pathways. Opioid receptors also inhibit synapses in the medulla, pons, ventral tectal area, ventral caudal nucleus of the thalamus, and in the cerebral cortex to further reduce pain signals and pain comprehension. Descending cortical spinal tracts inhibit dorsal horn nuclei, but the descending pathways are themselves normally inhibited by basal tone from other neurons in the cortex, midbrain, and pons. Activated opioid receptors in the brainstem inhibit the inhibitory tone upon the descending inhibitory pathways, resulting in increased inhibition of the dorsal horn synapses and decreased pain signals to the brain.⁴⁰

On the cellular level there are four main opioid receptors: μ , δ , κ , and the nociceptin opioid receptor (aka opioid receptor-like receptor). Current standard terminology replaces traditional labels μ , δ , κ , and nociceptin receptors with MOR, DOR, KOR, and NOR, respectively.⁴¹ Each of the four receptors is encoded by a separate gene and only one gene has been identified for each receptor. The different subtypes (e.g., MOR1, MOR2, MOR3, DOR1, DOR2, KOR1, KOR2, KOR3, NOR1, and NOR2) are splice variants from the premessenger RNA copied from each gene. All four of the principal opioid receptors (MOR, DOR, KOR, NOR) are guanine nucleotide-binding proteins

Table 1 Nonsteroidal Antiinflammatory Drugs: Generic, Brand Names, Doses, Prices, and Comments

Generic	Brand Name	Typical Dose for 70 kg Adult	Cost per Day ⁱ	Comments
Acetaminophen/paracetamol	Tylenol [®] , Panadol [®] *	500 mg/4 h Reduce dose with liver failure	\$0.16	Minimal antiinflammatory effect; potential liver toxicity over 4 g
Acetaminophen/paracetamol suppository			\$2.50*	
Carboxylic acids				
Aspirin (acetylsalicylic acid)	Anacin [®] , Ecotrin [®] *	325–1500 mg/6 h	\$0.20	Irreversibly blocks COX enzymes
Choline magnesium trisalicylate	Trilisate [®] , Tricosal [®] *	1500 mg tid	\$1.11	Less GI distress than ASA
Diflunisal	Dolobid [®]	0.5–1.5 g/24 h bid	\$1.80	
Sodium salicylate	AlkaSeltzer [®] *	325–650 mg/4 h	\$0.81	
Salsalate	Amigesic [®] , Disalcid [®] *	1.5–3.0 g/24 h bid	\$1.20	
Magnesium salicylate	Doan's Pills [®] *	467 mg/4 h	\$0.32	
Propionic acids				
Fenoprofen	Nalfon [®]	300–600 mg qid	\$1.72	More renal side effects
Flurbiprofen	Ansaid [®]	100 mg bid-tid	\$0.78	Peptic ulcers in elderly
Ibuprofen	Motrin [®] , Nuprin [®] , Advil [®] , OTC*	400–800 mg qid	\$0.64	IV injection available
Ketoprofen	Orudis [®] , Oruvail [®]	75 mg tid	\$0.67	Lower dose for elderly
Naproxen; Enteric	Naprosyn [®] , Naprolin [®] , Alleve [®] , OTC*	500 mg bid	\$0.28	Usually well tolerated
Oxaprozin	Daypro [®]	600–1200 mg/day	\$0.56	
Acetic acid derivatives				
Diclofenac	Voltaren [®] , Cataflam [®]	50–75 mg bid or tid	\$0.99	Preferential COX-2 inhibitor
Diclofenac sustained release	Voltaren-XR [®]	100–200 mg/day	\$2.80	Preferential COX-2 inhibitor
Diclofenac/misoprostol 200	Arthrotec [®] 50 or 75	50–75 mg tid	\$2.52	
Etodolac	Lodine [®]	200–400 mg tid	\$2.58	Less GI distress
Indomethacin	Indocin [®] , Indocin SR [®]	25–50 mg bid or tid	\$0.48	GI and bone marrow effects
Ketorolac tromethamine	Toradol [®]	10 mg qid	\$1.00 PO \$5.60- IV	PO, IV, IM, limit to 5 days Caution with renal failure
Sulindac	Clinoril [®]	150–200 mg bid	\$0.70	Increased GI effects
Tolmetin	Tolectin [®]	200–600 mg qid	\$6.52	Increased side effects
Fenamates				
Meclofenamate	Meclofen [®]	50–100 mg qid	\$3.88	Diarrhea
Mefenamic acid	Ponstel [®]	250 mg qid	\$2.00	
Enolic acids				
Meloxicam	Mobic [®]	7.5 mg/day	\$0.14	Preferential COX-2
Piroxicam	Feldene [®]	10–20 mg/day	\$0.17	Increased GI bleeds
Naphthylkanones				
Nabumetone	Relafen [®]	500–2000 mg/day	\$2.00	Decreased ulcers
Selective COX-2 inhibitors				
Celecoxib	Celebrex [®]	100, 200 mg/day	\$0.55	Cross react with sulfonamides

*Multiple other brands.

ⁱBased on October 10, 2009 prices according to www.pharmacychecker.com.⁷²

ASA, aspirin; bid, twice daily; COX, cyclooxygenase; GI, gastrointestinal; tid, three times daily; IM, intramuscularly; IV, intravenously; OTC, over the counter; PO, orally; qid, four times daily.

(G-protein) coupled receptors located in cell membranes. These receptors are present throughout the central and peripheral nervous system as well as the immune system and GI system.^{42,43} Two of the recep-

tors were named for the first letter of the first chemical used to bind to the receptor. Morphine was the first drug to bind to MOR receptors. Ketocyclazocine was the first drug to attach to KOR receptors. The DOR

receptor was named for the vas deferens, the tissue first noted to contain DOR.⁴⁴

The μ -receptors are mostly located in the substantia gelatinosa of Rolando of the dorsal horn of the spinal cord, and in the periaqueductal gray matter.⁴⁵ The MOR1 receptor is the receptor most strongly associated with analgesia and physical dependence. The MOR2 receptor is associated with respiratory depression, euphoria, physical dependence, and miosis. The KOR1, KOR2, and KOR3 receptors also promote analgesia as well as sedation and miosis. The DOR1 and DOR2 receptors promote analgesia and physical dependence.⁴⁶

As mentioned above, opioid receptors are G-protein coupled receptors that bind to opioid ligands. Docking of the opioid ligands with the receptors cause conformational changes that result in separation from the cell membrane and activation of a G-coupled protein. The α subchain of the G-protein inhibits adenyl cyclase in the cytoplasm, which is needed to convert adenosinetriphosphate (ATP) into cyclic adenosinemonophosphate (cAMP). cAMP is a cellular second messenger that activates protein kinases and gene transcription proteins. Thus opioids binding to the G-protein coupled receptors lead to decreased c-AMP, decreased protein kinases, transcription of various proteins, and in particular to increased activity of the sodium-potassium (Na/K) ATP pump. This in turn leads to hyperpolarization of nerve axons and synapses, and to decreased neuronal activity. The β and gamma subunits of the guanine nucleotide binding protein released by the activated opioid receptor lead indirectly to inhibition of the voltage-dependent calcium channels (VDCC)^{47,48} on presynaptic neurons, and stimulation of the G-protein activated inwardly rectifying potassium (GIRK) channels. Inhibition of the VDCC's results in decreased release of presynaptic neurotransmitters, especially glutamate, but also norepinephrine, serotonin, acetylcholine, and substance P. Stimulation of the GIRK channels and Na/K ATPase pumps hyperpolarizes the postsynaptic membranes. These processes lead to a dampening of pain signals through the dorsal horn of the spinal cord.^{49,50} The same or similar mechanisms could lead to dampening of neuronal activity in the brain, leading to decreased pain perception.

Opioid-Induced Tolerance and Hyperalgesia

With repeated use, tolerance develops to the analgesic effect of opioids as well as many of the side effects. Opioids can even induce allodynia and hyperalgesia rather than analgesia, although this is more common with short-acting opioids such as remifentanyl.⁵¹⁻⁵³ The mechanism for tolerance and hyperalgesia to opioids is poorly understood, but several theories have been proposed. Part of the tolerance may be an upregulation of cAMP which would lead to a less effective Na/K

adenosine triphosphatase pump and increased excitability of neurons. According to another theory, endogenous opioids bound to G-proteins in the cytoplasm induce endocytosis, leading to rapid efficient recycling of the opioid receptors. Exogenous opioids bound to opioid cell membrane receptors may not induce endocytosis and recycling of receptors as efficiently as endogenous polypeptide opioids. Other investigators have posited that chronic exogenous opioids may lead to fewer receptors on cell membranes, hence requiring ever-increasing doses of opioids to achieve the same effect. Another theory that has been gaining traction is based on observations that glial cells in the central nervous system modulate neurons by releasing pain-enhancing substances, including interleukin-1. It is possible that opioid-induced allodynia, or even much of neuropathic pain, is caused by transmigration of astrocytes and microglia rather than neurons.^{54,55} Another theory with practical implications is that long-term opioids lead to hypersensitization of *N*-methyl-D-aspartate receptors (NMDA); such stimulation of NMDA receptors causes intense pain. This theory would explain why coadministration of NMDA receptor antagonists, such as dextromorphan or ketamine, can decrease the dose of opioids needed for pain control. Low-dose naloxone or naltrexone can decrease the dose of opioids required for analgesia even though they are opioid antagonists.⁵⁶ Switching to methadone, which is another NMDA antagonist, also frequently overcomes opioid tolerance.⁵⁷ Finally, tolerance can often be overcome by switching to a different opioid.⁵⁸

Common Opioid Side Effects

CONSTIPATION, NAUSEA

Constipation and nausea are common side effects of opioids. The severity of these symptoms frequently diminishes or dissipates completely with continued administration, but these symptoms can persist to the point that patients stop taking the opioids altogether. Methylnaltrexone is a new MOR-specific antagonist that is proving effective for opioid-induced nausea and constipation.⁵⁹ Alvimopan is another new drug showing promise to lessen the GI side effects from opioid administration.⁶⁰

RESPIRATORY DEPRESSION

Opioid doses can usually be increased without fear of respiratory compromise if patients are still in pain, but if the level of pain decreases and patients continue on the same dose of opioid, respiratory depression can become quite profound or even cause death. Respiratory depression, along with the analgesia, can be reversed with IV naloxone (15 μ g/2 kg). The reversal may be shorter than respiratory depression caused by opioids, so patients

will need to be observed carefully for recurrent respiratory depression and may require a second dose of naloxone. Nalbuphine (1 mg) can also reduce the respiratory depression caused by opioids but has less effect on reversing analgesia effects of opioids.⁶¹

HYPOGONADISM

Long-term use of opioids leads to gonadal atrophy and loss of libido. These effects are usually reversed a few months after cessation of opioids.⁶²

Opioid Use in Patients with Impaired Hepatic or Renal Function

Most opioids undergo phase I metabolism in the liver by various modification reactions such as dealkylation, hydroxylation, oxidation, or deamination facilitated by the CYP-450 cytochrome enzyme system. The majority of these reactions involve the CYP3A4 and CYP2D6 enzymes. Because the CYP3A4 enzyme metabolizes more than 50% of all drugs, opioids metabolized by this enzyme have a high risk of drug-drug interactions. Oxycodone, methadone, fentanyl, and tramadol are commonly prescribed opioids metabolized by the CYP3A4 system and hence have a greater likelihood of interacting with other medications. Morphine, hydromorphone, and oxymorphone do not undergo phase I metabolism and therefore have the lowest chance of interacting with other medications. Codeine and hydrocodone are metabolized by the CYP2D6 system, and have an intermediate chance of interacting with other medications. Codeine is converted into morphine by the CYP2D6 system. Up to 10% of patients have allelic variations of the CYP2D6 enzyme that only slowly converts codeine into morphine so that codeine will provide little analgesic effect for them. Most opioids undergo phase 2 (conjugation) metabolism in the liver. Most opioids also undergo glucuronidation, which makes the metabolite more hydrophilic and more easily excreted by the kidneys. As a general rule of thumb, doses of opioids may need to be reduced in patients with either advanced liver disease or renal failure.⁶³

Special Considerations for Individual Opioids

Numerous opioids are available. Some of the more commonly prescribed brands and their generic name are listed in Table 2.

CODEINE

Codeine is considered a weak opioid and is often recommended for the second step in the WHO analgesic ladder. Codeine itself has no analgesic properties and must be metabolized to morphine to have any effect. The enzyme responsible for this phase I modification, CYP2D6, has significant allelic variation so that up to

Table 2 Generic and Brand Names of Commonly Prescribed Opioids

Brand Name	Generic Name/Component(s)
Darvocet [®]	Propoxyphene
Darvon [®]	Propoxyphene
Demerol [®]	Meperidine
Dilaudid [®]	Hydromorphone
Dolophine [®]	Methadone
Fioricet with Codeine [®]	Butalbital, acetaminophen, codeine
Fiorinal with Codeine [®]	Butalbital, acetaminophen, codeine
Levo-Dromoran [®]	Levorphanol
Lortab [®]	Acetaminophen, hydrocodone
MS Contin [®]	Duramorph
Numorphan [®]	Oxymorphone
OxyContin [®]	Oxycodone
Soma with Codeine [®]	Carisoprodol
Synalgos-DC [®]	Dihydrocodeine bitartrate
Talacen [®]	Pentazocine, acetaminophen
Talwin NX [®]	Pentazocine, naloxone
Tylenol with Codeine [®]	Acetaminophen, codeine
Vicodin ES [®]	Hydrocodone bitartrate, acetaminophen
Wygesic [®]	Propoxyphene, acetaminophen

10% of some populations will not convert codeine to morphine and will receive no analgesia from codeine. Others may metabolize codeine very rapidly so that they receive more of a bolus effect from codeine.⁶⁴

TRAMADOL

Tramadol is a weak opioid agonist of MOR, but it may have a role in chronic pain control because it has a lower tendency to cause tolerance than other opioids. It appears to exert its effect not only upon MOR, but also inhibits serotonin reuptake and has an effect on several other monoamines; it also antagonizes NMDA. It has a low potential for abuse or significant side effects.⁶⁵

MORPHINE

Morphine is the epitome of opioids and is among the first choices for treatment of moderate to severe pain. It is available in oral, rectal, and parenteral forms. It does not undergo phase I metabolism and so has fewer interactions with other medications than some of the other opioids. It was the first opioid given FDA-approval for epidural administration.⁶⁶

METHADONE

Because of its use as a maintenance drug for opioid addicts for nearly half a century, a wealth of experience has been accumulated regarding methadone's safety profile and side effects. It has not been used as frequently as other opioids for analgesia until recently, but its unique properties make it one of the best choices for

chronic neuropathic pain. It is not only a MOR agonist, but also inhibits NMDA, and inhibits reuptake of serotonin and norepinephrine. This may explain why many patients receive superior pain relief with methadone compared with other opioids. Methadone has a long but variable half-life ranging from 13 to 58 hours. The long half-life obviates the need for extended release forms, but it also mandates that caution be used when starting methadone to prevent toxic accumulations. It is available both orally and parenterally, and is also less expensive than most opioids. For these reasons, methadone is rapidly becoming more popular as a first-line opioid for chronic pain control.⁶⁷

FENTANYL

Fentanyl is frequently used along with a benzodiazepine for moderate sedation and procedural pain control. Because it is lipophilic, it can cross the blood-brain barrier more easily than most opioids. The rapid onset and short time-to-peak analgesia make it ideal for use in moderate sedation. It is available in parenteral, transmucosal, and transdermal formulations.⁶⁸

MEPERIDINE

Meperidine is decreasing in popularity largely due to the possible accumulation of its metabolite, normeperidine, especially in patients with renal failure.⁶⁹

ADJUVANT ANALGESICS

Many adjuvant pharmaceuticals are available for pain control. Some of the more common ones include corticosteroids; anticonvulsants such as gabapentin, carbamazepine, and pregabalin; antidepressants such as duloxetine or amitriptyline; NMDA antagonists (e.g., ketamine or dextromethorphan); anesthetics (e.g., lidocaine patch or oral mexiletine); α -2 agonists (e.g., clonidine); α -1 antagonists (e.g., terazosin); and epidural ion channel blockers (e.g., verapamil and ziconotide (snail venom)).^{70,71}

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