Chapter 4
Opioid Pharmacology and Pharmacokinetics

Andrea M. Trescot

Introduction

Opioids are compounds that work at specific receptors in the brain to provide analgesia. Originally derived from the sap of the poppy plant (*Papaver somniferum*), opioids may be naturally occurring, semi-synthetic, or synthetic, and their clinical activity is a function of their affinity for the various opioid receptors in the brain. Opioids are useful for a wide variety of painful conditions, including acute pain, cancer pain, and chronic pain, and cough suppression and air hunger. However, opioid use is associated with a significant misuse, has legal ramifications, and carries the potential for addiction, which limits their use and contributes to the current "opioid-phobia."

Opioid Receptor Pharmacology

"*Opiates*" are naturally occurring compounds derived from the poppy and would include morphine and codeine. The term "*opioid*" is now used broadly to describe any compound that exerts activity at an opioid receptor [1]. The opioid receptors were first discovered in 1972 by Candice Pert as a graduate student [2], and the first endogenous opioid, "*endorphin,*" was identified in 1975 [3]. Multiple opioid receptors have now been identified, including **mu**, **kappa,** and **delta receptors** (Table 4.1), and opioids can work at one or several of these receptors. **Mu receptors** (where morphine molecules attach) are found primarily in the brain stem, ventricles, and medial thalamus; activation of these receptors can result in supraspinal analgesia, respiratory depression, euphoria, sedation, decreased

A.M. Trescot (✉)
Pain and Headache Center, 5431 Mayflower Lane, Suite 4, Wasilla, AK 99654, USA
e-mail: DrTrescot@gmail.com

P.S. Staats and S.M. Silverman (eds.), *Controlled Substance Management in Chronic Pain*, DOI 10.1007/978-3-319-30964-4_4

Table 4.1 Analgesic effects at opioid receptors

	Mu	Kappa	Delta
Endorphins			
Enkephalin	Agonist		Agonist
Beta endorphin	Agonist		Agonist
Dynorphin	Agonist	Agonist	
Opioids			
Morphine	Agonist	Weak agonist	
Codeine	Weak agonist		Weak agonist
Fentanyl	Agonist		
Methadone	Agonist		
Oxycodone	Agonist	Agonist	
Buprenorphine	Partial agonist	Antagonist	
Pentazocine	Partial agonist	Agonist	
Nalbuphine	Antagonist	Agonist	
Butorphanol	Partial agonist	Strong agonist	
Antagonists			
Naloxone	Antagonist	Weak antagonist	Antagonist
Naltrexone	Antagonist	Weak antagonist	Antagonist

Modified from Trescot et al. [1]

gastrointestinal motility, and physical dependence. They are now recognized to be at least 3 mu receptors—Mu_1, Mu_2, and Mu_3. Mu_1 is responsible for analgesia, euphoria, and serenity, while Mu_2 is related to respiratory depression, pruritus, prolactin release, dependence, anorexia, and sedation [4]; Mu_3 is proposed to be an important immune link [5]. **Kappa receptors** (named for ketocyclazocine that was used to find the receptor) are found in the limbic system, brain stem, and spinal cord and are felt to be responsible for spinal analgesia, sedation, dyspnea, dependence, dysphoria, and respiratory depression [4]. **Delta receptors** (found using delta-alanine-delta-leucine-enkephalin) are located largely in the brain itself and are thought to be responsible for psychotomimetic and dysphoric effects [4], as well as the development of tolerance.

Mechanism of Action in Pain Relief

Opioid receptors are found throughout the body, but primarily in the brain, spinal cord, and intestinal tract. These receptors are complex structures made up of 7 amino acid chains, each of which bridges the membrane, forming a channel which can allow calcium ions to pass in or out of the neuron. Opioid receptors are G-linked proteins within the membranes of cells; when activated, the receptor releases a protein, which migrates within the cell, activating Na/K channels or influencing enzymes within the cell, or influencing nuclear gene transcription

(Fig. 4.1) [6]. These opioid receptors can be presynaptic or postsynaptic. Presynaptic opioid receptors inhibit neurotransmitter release of compounds such as acetylcholine, norepinephrine, serotonin, and substance P. It is important to remember that the inhibition of an inhibitory neuron may then result in excitation [6].

The natural reward centers of the brain reside in the dopaminergic system of the ventral tegmental area (VTA), and GABA neurons usually inhibit these dopaminergic systems. Opioids inhibit the presynaptic receptors on the GABA neurons, which increases the release of dopamine, which is intensely pleasurable. Other drugs of abuse such as alcohol, nicotine, and benzodiazepines have their activity in the same areas of the brain [7] (Fig. 4.2).

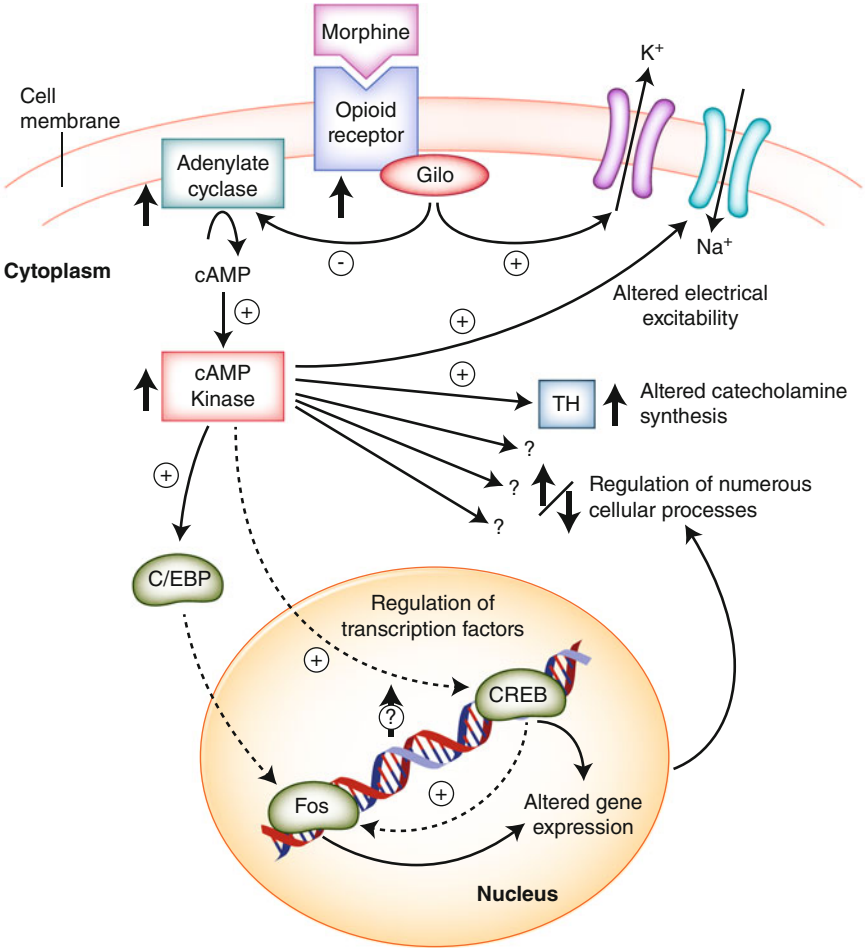

Fig. 4.1 Opioid actions. With permission from Trescot et al. [1]

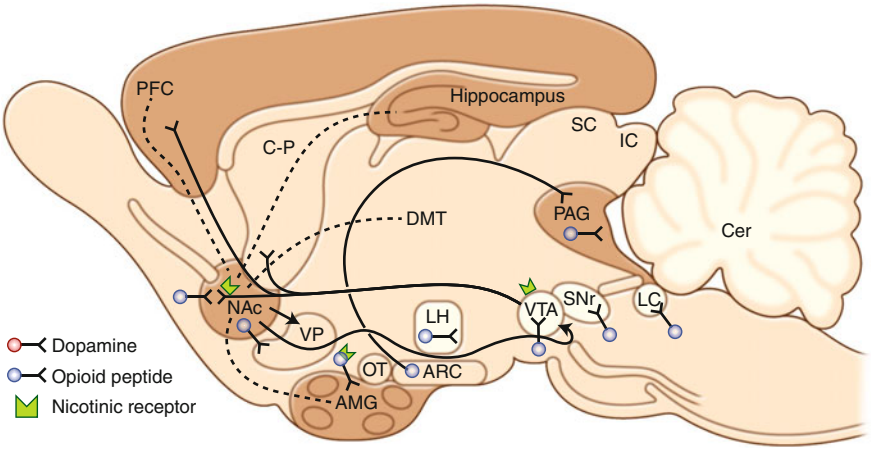

Fig. 4.2 Site of action of opioids and other drugs of abuse. *AMG* amydala; *ARC* arcuate nucleus; *CER* cerebellum; *C-P* caudate putamen; *DMT* dorsomedial thalamus; *IC* inferior colliculus; *LC* locus coeruleus; *LH* lateral hypothalamus; *Nac* nucleus accumbens; *OT* olfactory tubercle; *PAG* periaqueductal gray; *PFC* frontal cortex; *SC* superior colliculus; *SNr* substantia nigra; *VP* ventral pallidum; *VTA* ventral tegmental area. With permission from Trescot et al. [1]

Opioid Routes of Administration

Major advances in the pharmacotherapy of chronic pain have led to the development of extended-release opioid delivery systems, thereby allowing less frequent dosing than the classic short-acting formulas. It is the patterns in serum drug levels that define the difference between short-acting opioids (SAO) and long-acting opioids (LAO); with SAOs, serum opioid levels rise rapidly following administration and then decline rapidly, while LAO administration allows for less fluctuation in serum opioid levels and an extended period within the therapeutic range [8]. The assumption that plasma levels of opioids correspond to analgesia has led to the additional concept of minimum effective concentration (MEC), the plasma level of an opioid below which there is ineffective analgesia. Long-acting opioids can have a true intrinsic long-acting effect (i.e., methadone) or could be made in a sustained-release preparation. For the purposes of this discussion, we are including short-acting opiates prepared in a sustained-release preparation as "long-acting opioids."

There are many proposed advantages of the long-acting opioid formulas compared to the short-acting formulas. Because of the longer duration of action, there is a lessening of the frequency and severity of end-of-dose pain [9]. Furthermore, it has been suggested that less frequent dosing leads to increased compliance and improved efficacy [10]. Sustained analgesia and uninterrupted sleep are other potential advantages of the extended-release formulation compared to the short-acting variety. However, in a recent systematic review of long-acting versus short-acting opioids, Rauck [11] noted that, while it was clear that long-acting opioids achieved more stable drug levels, there was no clear evidence from

appropriately designed comparative trials to make a case for the use of one type of formulation over the other on the basis of clinical efficacy.

Opioid Formulations

Oral

The standard and mainstay route of opioid administration, especially for chronic pain, is the oral route. Short- and long-acting opioids (see above) are available for many of the opioids described below, with and without adjuvant medications such as acetaminophen or NSAIDs. Oral absorption and onset of action depend on stomach pH, GI motility, and formulation.

Transmucosal

Oral transmucosal fentanyl citrate (OTFC) has become a mainstay in the treatment of breakthrough cancer pain, because it provides faster absorption of the lipophilic fentanyl than any other oral opioid formulation [12]. This "fentanyl lollipop" consists of medication on the end of a stick, which is applied to the buccal membrane. A newer formulation of fentanyl, the fentanyl buccal tablet (FBT), was designed to provide an even faster relief. Additional delivery systems for intranasal [13, 14] and inhaled fentanyl [15] have been developed.

Intravenous

Intravenous delivery of opioids allows for rapid and reliable delivery of medicine, but accessing a vein for administration of drugs is not always viable. In general, the IV dose is approximately 1/3rd of the oral dose, since IV medications do not have a first pass effect. Opioids can be delivered intermittently or continuously; patient-controlled analgesia (PCA) is now available for outpatient use, so that small doses of opioid are delivered when the patient pushes a button, with or without a continuous infusion of opioid.

Subcutaneous

Subcutaneous opioid injections can be an option for the patient unable to tolerate oral medications but without IV access. The medication is administered through a

butterfly needle and can be given intermittently or continuously. Onset is slower and lower peak effect than IV, but this may be a better option for acute or escalating pain than transdermal fentanyl, which has an even slower onset and prolonged effect [16]. Subcutaneous infusions up to 10 cc/h can be usually absorbed, but patients are usually more comfortable with 2–3 cc/h.

Rectal

The rectal mucosa absorbs many medications easily, including most opioids, and the blood flow from the rectum bypasses the liver, so that rectal morphine results in blood levels that are almost 90 % of the oral dose [17]. A double-blind, double-dummy, crossover study in 1995 compared oral versus rectal morphine, which was shown to be effective, easy to manage, and inexpensive, with a rapid onset of action [18].

Transdermal

The skin is the largest organ in the body, with a surface area of one to two square meters. It can be used to deliver typically lipophilic medications, which makes it appealing as a drug absorbtion modality. However, the skin functions as a barrier to the elements, and those same properties limit its effectiveness as a drug delivery site. Medications must have a small molecular weight with high lipid solubility to pass across the skin barrier, and fentanyl is one of the most effective opioids for transdermal delivery [19]. Although all opioids have similar side effects (see opioid side effects), transdermal fentanyl appears to have less constipation, but did show skin reactions in 1–3 % of the 153 cancer pain patients studied [20].

Intrathecal/Epidural

Oral and parenteral opioids work by dulling the brain so that it does not recognize the pain signals as easily. Intrathecal and epidural opioids attach to opioid receptors at the spinal level, blocking pain signals from reaching the brain. The medications are more potent when administered intrathecally as opposed to systemically. There are several conversion tables that have been suggested, but one needs to use great caution in moving from a systemic to intrathecal administration. As an example, in the past, 300 mg of morphine orally (systemically) has been felt to be equivalent to 5 mg in the epidural space or 1 mg in the spinal fluid (intrathecal space). However, there is significant variability in patients' response, and one needs to use significant caution in using these kinds of conversion tables. These dramatically lower doses

result in less sedation and mental clouding. Single-dose administration of intrathecal opioids has been used for acute pain, such as post postoperative pain. Continuous infusions for cancer pain and chronic noncancer pain utilized implanted subcutaneous pumps connected to intrathecal catheters. However, because these systems require specialist's placement and care, they are often not considered until very late in the course of the cancer, and hematologic abnormalities such as chemotherapy-induced thrombocytopenia may severely limit the ability to safely access the spinal canal. Although intrathecal opioid pain relief can be dramatic, procedural complications remain high, including infection, pump and catheter failures, drug errors, and post-dural puncture headaches [21]. Pruritus is seen more commonly with neural axial opioids than systemic opioids, with an incidence between 30 and 100 %, effectively reversed by opioid antagonists. Although respiratory depression is the dreaded complication of intrathecal opioids, its incidence is low (0.09–0.4 %) [22].

Common Opiates in Clinical Practice

Codeine

It is believed that the analgesic activity from codeine occurs from metabolism of codeine to morphine by CYP2D6. Because of the great heterogeneity in the CYP2D6 enzyme, with both fast metabolizers and slow metabolizers, codeine may not be an effective drug in all populations. In 2007, the FDA issued a Public Health Advisory [23] regarding a serious side effect in nursing infants whose mothers are apparent CYP2D6 ultra-rapid metabolizers, who, while taking codeine, had rapid and higher levels of morphine in the breast milk, with subsequent potentially fatal neonate respiratory depression.

Although codeine is often referred to as a "weak" analgesic, in a cancer pain study comparing 25 mg of hydrocodone (a "strong" analgesic) to 150 mg of codeine (a "weak" analgesic), 58 % of the codeine patients obtained relief compared to 57 % of the hydrocodone patients [24].

Hydrocodone

Hydrocodone is similar in structure to codeine and is a weak mu receptor agonist, but the CYP2D6 enzyme demethylates it into hydromorphone (see below), which has much stronger mu binding and therefore stronger opioid activity [25]. Like codeine, it has been proposed that hydrocodone is a pro-drug. In other words, patients who are CYP2D6 deficient, or patients who are on CYP2D6 inhibitors, may not produce the hydromorphone metabolites and therefore may have less than expected analgesia.

Until recently, hydrocodone was only available in a short-acting medication, containing either ibuprofen or acetaminophen; however, hydrocodone is now available as an extended release.

Hydromorphone

Hydromorphone is a hydrogenated ketone of morphine [26]. Like morphine, it acts primarily on mu-opioid receptors and to a lesser degree on delta receptors. While hydromorphone is 7–10 times more potent than morphine in single-dose studies [27], the oral and parenteral steady-state equivalence is 1:5, while the equivalence of chronic infusions may be as little as 1:3:5 [28]. It is highly water-soluble, which allows for very concentrated formulations, and in patients with renal failure, it may be preferred over morphine. Hydromorphone is metabolized primarily to hydromorphone-3-glucuronide (H3G), which, similar to the corresponding M3G, is not only devoid of analgesic activity but also evokes a range of dose-dependent excited behaviors including allodynia, myoclonus, and seizures in animal models [29]. Hydromorphone is available in an immediate-release as well as extended-release formulation [30].

Oxycodone

Oxycodone has activity at multiple opiate receptors including the kappa receptor, which gives it a unique antisedative effect ("perky Percocet"). It undergoes extensive hepatic metabolism, by glucuronidation to noroxycodone (which has less than 1 % of the analgesia potency of oxycodone), and by CYP2D6 to oxymorphone [31], which is about 50 % more potent [32]. Because oxycodone is dependent on the CYP2D6 pathway for clearance, it is possible that drug–drug interactions can occur with 2D6 inhibitors, and genetic issues may also interfere with metabolism. Oxycodone is available as a combination product with acetaminophen, in a short-acting formulation without acetaminophen, and in an extended-release formulation without acetaminophen.

Morphine

Morphine is metabolized by glucuronidation, producing morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G) in a ratio of 6:1. M6G is believed to be responsible for some additional analgesic effects of morphine [33]. M3G, on the other hand, is believed to potentially lead to hyperalgesia [34], with increased pain,

agitation, and myoclonus. Morphine is also metabolized in small amounts to codeine and hydromorphone. For instance, in one study, hydromorphone was present in 66 % of morphine consumers without aberrant drug behavior [35]; this usually occurs with doses higher than 100 mg/day.

Methadone

Methadone is a synthetic mu-agonist medication. It is a racemic mixture of 2 enantiomers; the R-methadone form is more potent, with a 10-fold higher affinity for opioid receptors (which accounts for virtually all of its analgesic effect), while S-methadone is the NMDA antagonist. The NMDA antagonistic effect makes it potentially useful in neuropathic and "opioid-resistant" pain conditions. The S-isomer also inhibits reuptake of serotonin and norepinephrine, which should be recognized when using methadone in combination with SSRIs and TCAs. Although it has traditionally been used to treat heroin addicts, its flexibility in dosing, use in neuropathic pain, and cheap price have led to a recent increase in its use. Unfortunately, a lack of awareness of its metabolism and potential drug interactions, its cardiac effects, and its long half-life has led to a dramatic increase in the deaths associated with this medication [36].

Methadone is unrelated to standard opioids, leading to its usefulness in patients with "true" morphine allergies. Methadone is metabolized in the liver and intestines and excreted almost exclusively in feces, an advantage in patients with renal insufficiency or failure.

The metabolism of methadone is always variable [37]. Methadone is metabolized by CYP3A4 primarily and CYP2D6 secondarily; CYP2D6 preferentially metabolizes the R-methadone, while CYP3A4 and CYP1A2 metabolize both enantiomers. CYP1B2 and CYP2C19 are possibly involved, and a newly proposed enzyme CYP2B6 may be emerging as an important intermediary metabolic transformation [38]. CYP3A4 expression can vary up to 30-fold, and there can be genetic polymorphism of CYP2D6, ranging from poor to rapid metabolism. The initiation of methadone therapy can induce the CYP3A4 enzyme for 5–7 days, leading to low blood levels initially, but unexpectedly high levels may follow about a week later if the medication has been rapidly titrated upward. A wide variety of substances can also induce or inhibit these enzymes [39]. The potential differences in enzymatic metabolic conversion of methadone may explain the inconsistency of observed half-life.

Methadone has no active metabolites and therefore may result in less hyperalgesia, myoclonus, and neurotoxicity than morphine. It may be unique in its lack of profound euphoria, but its analgesic action (4–8 h) is significantly shorter than its elimination

half-life (up to 150 h), and patient's self-directed redosing and a long half-life may lead to the potential of respiratory depression and death.

Methadone also has the potential to cause cardiac arrhythmias, specifically prolonged QTc intervals and/or torsade de pointes under certain circumstances [40–44]. Congenital QT prolongation, high methadone levels (usually over 60 mg per day), drug–drug interaction (such as some antidepressants, antiarrhythmics, chloroquine, quinolone, macrolide antibiotics), and conditions that increase QT prolongation (such as hypokalemia and hypomagnesemia) or IV methadone [45] (because it contains chlorobutanol, which prolongs QTc intervals) may increase that risk [46]. Combining methadone with a CYP3A4 inhibitor such as ciprofloxacin [47] potentially can increase that risk. Therefore, several experts recommend that pretreatment and possibly periodic cardiograms be obtained in patients starting or increasing methadone [48, 49].

It is recommended that a switch to methadone from another opioid be accompanied by a large (50–90 %) decrease in the calculated equipotent dose [50]. It cannot be too strongly emphasized that the dosing of methadone can be potentially lethal and must be done with knowledge and caution.

In addition, there have been several tragic deaths, when patients were identified with respiratory depression and then treated with naloxone; unfortunately, because methadone has such a long half-life, these patients were discharged from the ER, only to die from respiratory depression when the naloxone wore off before the methadone sedation resolved [51].

Fentanyl

Fentanyl is approximately 80 times more potent than morphine, is highly lipophilic, and binds strongly to plasma proteins. Fentanyl undergoes extensive metabolism in the liver. Fentanyl is metabolized by CYP3A4, but to inactive and nontoxic metabolites [52]; however, CYP3A4 inhibitors may lead to increased fentanyl blood levels. It is available in an intravenous formulation, and is commonly used for anesthesia and procedure analgesia. The transdermal formulation has a lag time of 6–12 h to onset of action after application and typically reaches steady state in 3–6 days. When a patch is removed, a subcutaneous reservoir remains, and drug clearance may take up to 24 h. Because fentanyl is highly lipophilic, it can also be absorbed sublingually/transbuccally as well intranasally or inhaled.

The usual recommendation for calculating the equipotent dose of different opioids involves calculating the 24-hour dose as "morphine equivalents." However, Hanks and Fallon [53] instead suggest relating the starting doses to 4-hour doses of morphine rather than 24-hour doses. For example, in patients receiving 5–20 mg oral morphine every 4 hours (or the equivalent in controlled-release morphine), start with 25 mcg/hour fentanyl patches that are changed every 72 hours; patients on 25–35 mg oral morphine every 4 hours would start with 50 mcg/hour fentanyl patches; 40–50 mg oral morphine every 4 hours would be equivalent to 75 mcg/hour

fentanyl patches, and 55–65 mg oral morphine every 4 hours would convert to 100 mcg/hour fentanyl patches. They feel that the controversies over appropriate morphine to fentanyl potency ratio calculations miss the point that fentanyl transdermally behaves differently and cannot be equated with oral routes when calculating relative potency.

Buprenorphine

Buprenorphine is a mu-opioid partial agonist with strong affinity but low efficacy at the mu receptor as well as kappa-antagonist activity [54]. It has been used for acute pain for many years and more recently has been used as well for treatment of opioid dependence and now for chronic pain. It is metabolized via CYP3A4 to an active metabolite and also by CYP2C8. Both the drug and its metabolite are also metabolized by glucuronidation, which reduces the risk of clinically significant medication interaction [55].

As a partial agonist, buprenorphine can be used to treat withdrawal, stimulating the opioid receptors without significant euphoria. Because buprenorphine has such a strong affinity for the mu receptor, it prevents the activity of illicit mu-receptor agonists such as heroin, which makes it an excellent medication for opioid maintenance therapy. However, it is also a useful medication for acute and chronic pain, particularly as an initial medication before escalating to full mu agonists, as well as treatment for opioid hyperalgesia (OIH). OIH is a condition where the opioid appears to cause more pain, which results in an escalation in opioid use without improvement in analgesia. Spinal dynorphin (a known kappa agonist) increases during opioid administration [56], and the kappa-antagonist effect of buprenorphine appears to be related to its positive effect on OIH. Buprenorphine is available for intravenous, transdermal, and sublingual use.

There are multiple opioid conversion tables that have been used to rotate the patient from one opioid to another. Unfortunately, most of these tables were developed based on acute levels of opioid dosing, not chronic usage, which can lead to relative overdose. Similarly, morphine to methadone conversions need to take into account the effect of opioid-induced hyperalgia from morphine, so that the

Table 4.2 Oral morphine to methadone conversion

Oral morphine dose (mg)	MS: methadone ratio
30–90	4:1
90–300	8:1
300–800	12:1
800–1000	15:1
>1000	20:1

Modified from Ripamonti et al. [77]

higher the dose of morphine, the smaller the equivalent methadone dose (see Table 4.2). Webster and Fine [57] have recently suggested that standard opioid conversion tables have contributed to fatal and near-fatal opioid overdoses.

Opioid Side Effects

Opioids are well known to cause a variety of side effects, most commonly nausea and vomiting, constipation, sedation, and respiratory depression [58]. These side effects can be significant, and some patients avoid opioids even in the face of significant pain, in an effect to limit such side effects, which may act as a significant barrier to adequate pain relief [59].

Constipation

Constipation is the most common adverse effect from opioids, occurring in 40–95 % of patients treated with opioids [60], and is caused by opioid receptor stimulation in the gut. The subsequent decrease in GI motility results in increased fecal fluid absorption, decreased peristalsis, as well as increased pyloric and anal sphincter tone, all resulting in hard, dry stools and reduced spontaneous bowel movements. It is essential that prophylactic treatment be instituted on the initiation of opioid treatment, since this, of all the side effects of opioids, does not resolve over time.

Nausea

Nausea has been reported to occur in up to 25 % of patients treated with opioids [61]. Mechanism for this nausea may include direct stimulation of the chemotactic trigger zone (CTZ), reduced gastrointestinal motility leading to gastric distention, and increased vestibular sensitivity [62].

Pruritus

Two to ten percent of patients on opioids will develop pruritus [63], which results from a direct release of histamine, and not usually an antigen/antibody reaction. It is

therefore better considered an adverse reaction than an allergic reaction and is usually treated symptomatically with antihistamines such as diphenhydramine.

Sedation and Cognitive Dysfunction

The incidence of sedation can vary from 20 to 60 % [64], is usually associated with an initiation or increase in opioids, and is usually transient. Cognitive dysfunction can be compounded by the presence of infection, dehydration, metabolic abnormalities, or advanced disease [65].

Respiratory Depression and Sleep Apnea

A significant proportion of patients taking long-term opioids develop central apnea during sleep. Teichtahl and colleagues [66] examined 10 patients in a methadone maintenance program and performed a clinical assessment and overnight polysomnography. They found that all 10 patients had evidence of central sleep apnea, with 6 patients having a central apnea index (CAI) [the number of central apnea events per hour] [67] greater than 5 and 4 patients with a CAI greater than 10. In a larger follow-up study of 50 patients taking long-term methadone, 30 % of the patients had a CAI greater than 5, and 20 % had a CAI greater than 10 [68].

Endocrine Effects

Endorphins appear to be primarily involved in the regulation of gonadotropins and ACTH release [69]. Amenorrhea developed in the 52 % female patients on opioids for chronic pain [70], while the testosterone levels were subnormal in 74 % of males on sustained-release oral opioids [71]. These effects are more profound with IV or intrathecal opioids than oral opioids [72].

Immunologic Effects

Acute and chronic opioid administration can cause inhibitory effects on antibody and cellular immune responses, natural killer cell activity, cytokine expression, and phagocytic activity. Chronic administration of opioids decreases the proliferative capacity of macrophage progenitor cells and lymphocytes [73].

Relationship Between Side Effects and Sex or Ethnicity

Several studies suggest that sex and ethnic differences exist to explain the differences seen in side effect profiles. Women have, for instance, been found to be more sensitive to the respiratory effects of morphine [74] and more often have nausea and emesis with opioids [75, 76].

Future Directions

Opioids of lower addictive potential, such as tamper resistant extended-release opioids, are coming on the market, in an effort to expand the use of opioids while decreasing the addiction and diversion potential. Opioid abuse screening tools (such as the Opioid Risk Tool—ORT), genetic testing, and fMRIs to look at brain areas associated with addiction and pain perception may also help identify those patients at risk for opioid abuse, while maintaining access for those patients in whom opioids are appropriate management for their painful condition.

Conclusion

Opioids are broad-spectrum analgesics, with multiple effects and side effects. When used wisely and with appropriate caution and knowledge of metabolism and interactions, opioids can offer significant relief from soul-draining pain.

> Few things a doctor does are more important than relieving pain…Pain is soul destroying. No patient should have to endure intense pain unnecessarily. The quality of mercy is essential to the practice of medicine; here, of all places, it should not be strained.
>
> Marcia Angell, MD

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