**C. Methadone**

Methadone [METH-a-done] is a synthetic, orally eff ective opioid which has variable equianalgesic potency compared to that of morphine and the conversion between the two products is not linear. Methadone induces less euphoria and has a somewhat longer duration of action.

**1. Mechanism of action:** The actions of methadone are mediated by µ receptors. In addition, methadone is an antagonist of the N-methyl- D-aspartate (NMDA) receptor, which is useful in the treatment of neurogenic pain.

**2. Actions:** Methadone is well absorbed when administered orally, unlike morphine, which is only partially absorbed from the GI tract. Like morphine, methadone increases biliary pressure and is also con- stipating (but less so than morphine).

3**. Therapeutic uses**: Methadone is used as an analgesic in nocicep- tive and neurogenic pain as well as in the controlled withdrawal of dependent abusers from heroin and morphine. Orally administered, methadone is substituted for the injected opioid. The patient is then slowly weaned from methadone. Methadone causes a withdrawal syndrome that is milder but more protracted (days to weeks) than that of other opioids (Figure 14.8).

**4. Pharmacokinetics**: Methadone is readily absorbed following oral administration. The drug is biotransformed in the liver and is excreted almost exclusively in feces. It is important to understand the phar- macokinetics of methadone when using this medication, due to mul- tiple variables associated with it. Methadone is very lipophilic, lead- ing to accumulation in the fat tissues. The slow release from these fat tissues causes the half-life to range from 12 to 40 hours and has been reported to extend up to 150 hours. The actual duration of analgesia ranges from 4 to 8 hours. Upon repetitive dosing, methadone levels can accumulate due to this long terminal half-life, thereby leading to toxicity. The metabolism is variable because it relies on multiple cytochrome P450 (CYP450) enzymes, some of which are aff ected by known genetic polymorphisms and are susceptible to many drug- drug interactions.

**5. Adverse effects**: Methadone can produce physical dependence like that of morphine but has less neurotoxicity than what is seen with morphine due to the lack of active metabolites. Methadone can cause torsades de pointes in certain situations. Overdosing is pos- sible when prescribers are not aware of the incomplete cross-toler- ance between methadone and other opioids, the long half-life asso- ciated with methadone and the proper titration guidelines to avoid its accumulation, and the multiple drug-drug interactions that can occur with this agent.

**D. Fentanyl**

Fentanyl [FEN-ta-nil], which is chemically related to meperidine, has 100-fold the analgesic potency of morphine and is used in anesthe- sia. The drug is highly lipophilic and has a rapid onset and short dura- tion of action (15–30 minutes). It is usually administered IV, epidurally, or intrathecally. Epidural fentanyl is used to induce anesthesia (see p. 145) and for analgesia postoperatively and during labor. An oral trans- mucosal preparation and a transdermal patch are also available. The transmucosal preparation is used in the treatment of cancer patients with breakthrough pain who are tolerant to opioids (Figure 14.9). The transdermal patch must be used with caution, because death resulting from hypoventilation has been known to occur. [Note: The transdermal patch creates a reservoir of the drug in the skin. Hence, the onset is delayed 12 hours, and the offset is prolonged.] Fentanyl is often used during cardiac surgery because of its negligible effects on myocardial contractility. Muscular rigidity, primarily of the abdomen and chest wall, is often observed with fentanyl use in anesthesia. Fentanyl is metabo- lized to inactive metabolites by the CYP450 3A4 system, and drugs that inhibit this isozyme can potentiate the effect of fentanyl. Most of the drug and metabolites are eliminated through the urine. Adverse effects of fentanyl are similar to those of other µ-receptor agonists. Because of life-threatening hypoventilation, the fentanyl patch is contraindicated in the management of acute and postoperative pain and in pain that can be ameliorated with other analgesics. Unlike meperidine, it causes pupillary constriction.

**E. Sufentanil, alfentanil, and remifentanil**

Three drugs related to fentanyl, sufentanil [soo-FEN-ta-nil], alfentanil [al- FEN-ta-nil], and remifentanil [rem-ih-FEN-ta-nil], differ in their potency and metabolic disposition. Sufentanil is even more potent than fentanyl, whereas the other two are less potent and shorter acting.

**F. Heroin**

Heroin [HAIR-o-in] does not occur naturally. It is produced by diacetyla- tion of morphine, which leads to a threefold increase in its potency. Its greater lipid solubility allows it to cross the blood-brain barrier more rapidly than morphine, causing a more exaggerated euphoria when the drug is injected. Heroin is converted to morphine in the body, but its effects last about half as long. It has no accepted medical use in the United States but is used therapeutically in other countries for the severe pain of cancer. G. Oxycodone and oxymorphone Oxycodone [ok-see-KOE-done] is a semisynthetic derivative of morphine. It is orally active and is sometimes formulated with aspirin or acetamin- ophen. It is used to treat moderate to severe pain and has many prop- erties in common with morphine. Its oral analgesic eff ect is approxi- mately twice that of morphine. Oxycodone is metabolized via CYP450 2D6 and 3A4 enzyme systems. Excretion is via the kidney. Abuse of the sustained-release preparation (ingestion of crushed tablets) has been implicated in many deaths. It is important that the higher-dosage forms of the latter preparation be used only by patients who are tolerant to opioids. Oxymorphone [ox-ee-MOR-fone] is a narcotic analgesic with a potency similar to that of hydromorphone (see below). It is available in both immediate-acting and extended-release formulations. There are not any clinically relevant drug-drug interactions associated with the CYP450 enzyme system compared to oxycodone. H. Hydromorphone and hydrocodone Hydromorphone [hye-droe-MORE-fone] and hydrocodone [hye-droe- KOE-done] are orally active, semisynthetic analogues of morphine and codeine, respectively. Oral hydromorphone is approximately eight to ten times more potent than oral morphine as an analgesic and is used most often to treat severe pain. Hydromorphone is preferred over morphine in patients with renal dysfunction due to less accumulation of active metabolites compared to morphine. Hydrocodone is the methyl ether of hydromorphone, but is much weaker an analgesic than hydromorphone. The analgesic potency of oral hydrocodone is approximately that of morphine. Hydrocodone is often combined with acetaminophen or ibu- profen to treat moderate-to-severe pain. It is also used as an antitussive. Hydrocodone is metabolized in the liver to several metabolites, one of which is hydromorphone via the actions of CYP450 2D6, which can be aff ected by drug-drug interactions.

**IV. MODERATE/LOW AGONIST**

1. **Codeine**

The analgesic actions of codeine [KOE-deen] derive from its conversion to morphine by the CYP450 2D6 enzyme system, whereas the drug’s antitussive eff ects are due to codeine itself. Thus, codeine is a much less potent analgesic than morphine. Codeine’s analgesic potency is approxi- mately 30 percent that of morphine. Codeine shows good antitussive activity at doses that do not cause analgesia. At commonly used doses, the drug has a lower potential for abuse than morphine. Codeine is often used in combination with aspirin or acetaminophen. [Note: In most non- prescription cough preparations, codeine has been replaced by drugs such as dextromethorphan, a synthetic cough depressant that has rel- atively no analgesic action and a relatively low potential for abuse in usual antitussive doses.] Figure 14.10 shows some of the actions of codeine.

**V. MIXED AGONIST-ANTAGONISTS AND PARTIAL AGONISTS**

Drugs that stimulate one receptor but block another are termed mixed agonist-antagonists. The eff ects of these drugs depend on previous expo- sure to opioids. In individuals who have not recently received opioids (naïve patients), mixed agonist-antagonists show agonist activity and are used to relieve pain. In the patient with opioid dependence, the agonist-antagonist drugs may show primarily blocking effects (that is, produce withdrawal symptoms)

**. A. Pentazocine**

Pentazocine [pen-TAZ-oh-seen] acts as an agonist on κ receptors and is a weak antagonist at µ and δ receptors. Pentazocine promotes anal- gesia by activating receptors in the spinal cord, and it is used to relieve moderate pain. It may be administered either orally or parenterally. Pentazocine produces less euphoria compared to morphine. In higher doses, the drug causes respiratory depression and decreases the activ- ity of the GI tract. High doses increase blood pressure and can cause hallucinations, nightmares, dysphoria, tachycardia, and dizziness. The latter properties have led to its decreased use. In angina, pentazocine increases the mean aortic pressure and pulmonary arterial pressure and, thus, increases the work of the heart. The drug decreases renal plasma flow. Despite its antagonist action, pentazocine does not antag- onize the respiratory depression of morphine, but it can precipitate a withdrawal syndrome in a morphine abuser. Tolerance and dependence develop on repeated use.

1. **Buprenorphine**

Buprenorphine [byoo-pre-NOR-feen] is classified as a partial agonist, acting at the µ receptor. It acts like morphine in naïve patients, but it can also precipitate withdrawal in morphine users. A major use is in opi- ate detoxification, because it has a less severe and shorter duration of withdrawal symptoms compared to methadone (see Figures 14.8 and 14.11). It causes little sedation, respiratory depression, and hypoten- sion, even at high doses. In contrast to methadone, which is available only at specialized clinics, buprenorphine is approved for office-based detoxification or maintenance. Buprenorphine is administered sublin- gually, parenterally, or transdermally and has a long duration of action because of its tight binding to the μ receptor. The tablets are indicated for the treatment of opioid dependence and are available in buprenor- phine alone (Subutex) and also in a combination product contain- ing buprenorphine and naloxone (Suboxone). Naloxone was added to buprenorphine to prevent the abuse of buprenorphine via IV adminis- tration. There is no clinical effect seen with oral naloxone, but, upon IV administration, opioid antagonism will occur, and the patient will experience withdrawal. The injectable form and the once weekly trans- dermal patch are indicated for the relief of moderate to severe pain. It is metabolized by the liver and excreted in bile and urine. Adverse effects include respiratory depression that cannot easily be reversed by naloxone and decreased (or, rarely, increased) blood pressure, nau- sea, and dizziness.

**C. Nalbuphine and butorphanol**

Nalbuphine [NAL-byoo-feen] and butorphanol [byoo-TOR-fa-nole], like pentazocine, play a limited role in the treatment of chronic pain. Neither is available for oral use. Their propensity to cause psychotomimetic (actions mimicking the symptoms of psychosis) effects is less than that of pentazocine. Nalbuphine does not affect the heart or increase blood pressure, in contrast to pentazocine and butorphanol. A benefit of all three medications is that they exhibit a ceiling effect for respiratory depression.

**VI. OTHER ANALGESICS**

1. **Tramadol**

Tramadol (TRA-ma-dole) is a centrally acting analgesic that binds to the µ-opioid receptor. The drug undergoes extensive metabolism via CYP450 2D6, leading to an active metabolite that has a much higher affi nity for the µ receptor than the parent compound. In addition, it weakly inhibits reuptake of norepinephrine and serotonin. It is used to manage moderate to moderately severe pain. Its respiratory-depressant activity is less than that of morphine. Naloxone (see below) can only par- tially reverse the analgesia produced by tramadol or its active metab- olite. Anaphylactoid reactions have been reported. Toxicity through drug-drug interactions with medications, such as selective serotonin reuptake inhibitors and tricyclic antidepressants, or in overdose, leads to CNS excitation and seizures. Tramadol should also be avoided in patients taking MAOIs.

1. **Tapentadol**

Tapentadol (ta-PEN-ta-dol) is a centrally acting analgesic that binds the µ-opioid receptor and is also a norepinephrine reuptake inhibitor that is believed to create an additive eff ect to the opioid actions. It has been used to manage moderate to severe pain, both chronic and acute. Limited drug-drug interactions have been seen with tapentadol due to the pharmacokinetic profi le. Tapentadol does not appear to inhib- it or induce the CYP450 enzyme system because it is mainly metabo- lized by glucuronidation. Because tapentadol does not produce active metabolites, dosing adjustment is not necessary in mild to moderate renal impairment. Tapentadol should be avoided in patients currently taking MAOIs and those who have taken MAOIs within the last 14 days. Tapentadol is currently available in an immediate-release formulation.

**VII. ANTAGONISTS**

The opioid antagonists bind with high affi nity to opioid receptors but fail to activate the receptor-mediated response. Administration of opioid antagonists produces no profound eff ects in normal individuals. However, in patients dependent on opioids, antagonists rapidly reverse the eff ect of agonists, such as morphine or any full µ-agonist, and precipitate the symp- toms of opiate withdrawal.

1. **Naloxone**

Naloxone [nal-OX-own] is used to reverse the coma and respiratory depression of opioid overdose. It rapidly displaces all receptor-bound opioid molecules and, therefore, is able to reverse the eff ect of a mor- phine overdose (Figure 14.12). Within 30 seconds of IV injection of nalox- one, the respiratory depression and coma characteristic of high doses of morphine are reversed, causing the patient to be revived and alert. Naloxone has a half-life of 30 to 81 minutes. [Note: Because of its rela- tively short duration of action, a depressed patient who has been treat- ed and recovered may lapse back into respiratory depression.] Naloxone is a competitive antagonist at µ, κ, and δ, receptors, with a tenfold higher affi nity for µ than for κ receptors. This may explain why nalox- one readily reverses respiratory depression with only minimal reversal of the analgesia that results from agonist stimulation of κ receptors in the spinal cord. Naloxone produces no pharmacologic eff ects in normal individuals, but it precipitates withdrawal symptoms in opioid abus- ers. Figure 14.13 summarizes some of the signs and symptoms of opi- ate withdrawal. There is no clinical eff ect seen with oral naloxone, but, upon IV administration, opioid antagonism will occur, and the patient will experience withdrawal. This is why naloxone has been combined with oral opioids to deter IV drug abuse.

1. **Naltrexone**

Naltrexone [nal-TREX-own] has actions similar to those of naloxone. It has a longer duration of action than naloxone, and a single oral dose of naltrexone blocks the eff ect of injected heroin for up to 48 hours. Naltrexone in combination with clonidine (and, sometimes, with buprenorphine) is used for rapid opioid detoxifi cation. Although it may also be benefi cial in treating chronic alcoholism by an unknown mecha- nism, benzodiazepines and clonidine are preferred. Naltrexone can lead to hepatotoxicity