The Pharmacology of Opioids
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Chapter Outline

- Definition of Drugs in the Class
- Substances Included in the Class
- Epidemiology of Opioid Abuse and Addiction
- Pharmacokinetics of Specific Drugs
- Pharmacodynamics
- Tolerance Development
- Toxicity States and Their Medical Management
- Medical Complications of Opioids
- Conclusions and Future Research Directions

Definition of Drugs in the Class

Three distinct types of opioid receptors are found in the nervous system: mu, kappa, and delta. Classic clinically used opioid analgesics act primarily as agonists or partial agonists at mu receptors. Heroin or illicit prescription opioids also act primarily as mu opioid receptor (MOP-r) agonists. Compounds in this class include the natural opiates (drugs derived from opium) and their man-made congeners which are agonists or antagonists, as well as the endogenous opioid neuropeptide agonists, products of three separate genes (1). The genes for each of these three receptors and each of these three classes of opioid peptides have been cloned from humans (2,3). These opioid receptors are members of the Gi-protein–coupled, 7-transmembrane domain superfamily. The three main families of endogenous opioid peptides—beta-endorphin, enkephalins, and dynorphins—have a degree of selectivity for the three receptor types. For example, beta-endorphin and the enkephalins have relatively high affinity at mu and delta receptors and much lower at kappa. The dynorphins, by contrast, have relative selectivity for kappa receptors over the mu and delta. These receptors mediate a complex, partially overlapping array of physiologic and neurobiologic functions (4). For the purposes of this chapter, we will concentrate on the mu receptor as most of the clinically used opioids are active at this receptor. However, the entire endogenous opioid system plays an important role in responses to addictive opiates, including morphine, codeine, and heroin, as well as to synthetic opioids (3).

Beta-endorphin is a product of proopiomelanocortin, which is produced primarily in the anterior pituitary of humans. It is also produced in the central nervous system (CNS) and in the periphery. The mu receptors mediate both the analgesic and rewarding effects of opioid compounds (be they heroin or prescription opioids) as well as their effects on many systems in the body, such as in the hypothalamic–pituitary–adrenal (HPA) axis, immune, gastrointestinal (GI), and pulmonary function.

The term “opioids” refers to all compounds, natural and synthetic, functionally related to opium derived from poppies and endogenous opioid neuropeptides. Opium is a naturally occurring mixture directly derived from the juice of the opium poppy (Papaver somniferum). Morphine (the prototypical MOP-r agonist) is the main active alkaloid in opium, whereas thebaine can be used as a starting point for production of semisynthetic MOP-r ligands. This chapter reviews the pharmacology of several exogenous opioids that are significant in the area of opioid addiction and its treatment, that is, heroin, morphine, oxycodone, codeine, meperidine, pentazocine, hydromorphone, and hydrocodone, as well as methadone, levo-alpha-acetylmethadol (LAAM), and buprenorphine.

Substances Included in the Class

Heroin

Heroin is synthetically derived from the natural opioid alkaloid morphine. Largely owing to its very rapid onset of action and very short half-life, heroin is a popular drug of abuse. Heroin is classified in Schedule I (i.e., not available for any therapeutic use in the United States), although it is available in a few countries as a medication for treatment of heroin addiction (5,6). Heroin is a prodrug that
is not itself active. It is most effective when used intravenously, but increasingly is used intranasally and, sometimes, smoked in the free base form (7). Intranasal and smoked routes may have increased in popularity because of the wider availability of high-purity heroin in recent years, and also as a means to reduce the risk of human immunodeficiency virus (HIV-1) transmission from intravenous use. Heroin is rapidly deacetylated to 6-monoacetyl morphine and morphine, both of which are active at the mu opioid receptor.

**Morphine and Synthetic Compounds**

Morphine is a natural product of the poppy plant, *Papaver somniferum*. Chemically, morphine is an alkaloid that belongs to the class of phenanthrenes. This class also includes codeine and thebaine. Modifications of the latter result in synthetic compounds discussed below (4). Morphine is prescribed primarily as a high-potency analgesic. Biotransformations or synthetic modifications of the chemical structure of the morphine molecule at the 3, 6, and 17 positions produce other compounds, including morphine-6-glucuronide (M6G), a major pharmacologically active metabolite of morphine in humans. Related compounds include hydrocodone (Vicodin), oxycodone (OxyContin), hydromorphone (Dilaudid), and heroin. Synthetic compounds also include antagonists such as naloxone (Narcan), naltrexone (Trexan or ReVia or Vivitrol), and nalnafene (Revix), as well as partial agonists such as buprenorphine alone (Subutex) or, when combined with naloxone, (Suboxone) (4).

**Oxycodone**

Oxycodone has been used clinically since the early 1900s. It is combined with aspirin or acetaminophen for the treatment of moderate pain and is available orally without coadministration. It is a semisynthetic compound derived from thebaine, with agonist activity primarily at mu receptors. Although structurally similar to codeine, it is pharmacodynamically comparable to morphine and has a 1:2 equivalence with morphine (10).

**Codeine**

French pharmacist Pierre-Jean Robiquet first discovered several natural products including codeine (11). Codeine is methyl morphine, with a methyl substitution on the phenolic hydroxyl group of morphine. It is more lipophilic than morphine and thus crosses the blood–brain barrier faster. It also has less first-pass metabolism in the liver, therefore, greater oral bioavailability than morphine, although it is less potent than morphine. A small part of codeine is metabolized to morphine via cytochrome 2D6 (4).

**Meperidine**

Meperidine is a phenylpiperidine and has a number of congeners. It is mostly effective in the CNS and bowel; however, it is no longer used for treatment of chronic pain owing to concerns regarding toxicity of its major metabolite and should not be used for greater than 48 hours or at doses greater than 600 mg/d. It has serotonergic activity when combined with monoamine oxidase inhibitors, which can produce serotonin toxicity (clonus, hyperreflexia, hyperthermia, and agitation) (12).

**Pentazocine**

Both parenteral and oral formulations of pentazocine were approved for marketing in the late 1960s. It is one of the initial “agonist–antagonist” medications. Pentazocine is a weak antagonist or partial agonist (it has a “ceiling effect,” plateau in maximal effect, contrasted with a full agonist) at the mu receptor and is also a kappa receptor partial agonist. In 1983, in order to block the euphorogenic effects of appropriately injected pentazocine, pentazocine was manufactured in combination with naloxone (Talwin NX). Thus, if injected, this formulation would actually precipitate withdrawal in those with opioid dependence. Some data from the DAWN (Drug Abuse Warning Network) database indicated that abuse declined after this reformulation (13).

**Hydromorphone**

Hydromorphone is a more potent opioid analgesic than morphine. It is used for the treatment of moderate to severe pain and is excreted, along with its metabolites, by the kidney. It can be given intravenously, by infusion, orally, and per rectum, with low oral bioavailability. On a milligram basis, it is five times more potent than morphine when given orally, and 8.5 times as potent when given intravenously (14). A minor pathway for the metabolism of morphine to hydromorphone has been identified (15).

**Hydrocodone**

Hydrocodone is a prescription drug frequently prescribed for a relatively minor (such as dental) pain. It is often used in combination with acetaminophen; thus, there can be hepatotoxicity associated with its abuse (8).

**Methadone**

Methadone is a synthetic long-acting full mu opioid agonist, active by parenteral and oral routes. It was first synthesized as a potential analgesic in Germany in the late 1930s and first studied for human use in the 1950s in the United States. It has been used primarily as a maintenance treatment for heroin addiction since the first research done in 1964 (16), and it was approved by the U.S. Food and Drug Administration (FDA) in 1972. Methadone is also used and is very effective in the treatment of chronic pain; however, it should not be used in opioid-naïve patients, due to the risk of respiratory depression. The (R)-methadone enantiomer has up to 50 times more analgesic activity and also the potential to produce more respiratory depression than the (S)-enantiomer. Both enantiomers have
modest N-methyl-D-aspartate (NMDA) receptor antagonism. Methadone has a diphenylethylamine chemical structure and consists of a racemic mixture of \(d(S)\)– and \(l(R)\)-methadone. Again, the \(l(R)\)-enantiomer is responsible for the majority of opioid effects as it is up to 50 times more potent than the \(d(S)\)-enantiomer (17).

**Levo-alpha-acetylmethadol**

LAAM is a synthetic, longer-acting (48-hour) congener of methadone that is also orally effective. LAAM was first studied in the 1970s for the treatment of heroin addiction (18) and approved in 1993 by the FDA (19) after a large multicenter safety trial. Postmarketing, after reports of prolonged QTc intervals on electrocardiogram, which can lead to torsade de pointes that may have been caused by LAAM, a black-box warning was added to the product label (20,21). LAAM remains approved for humans in the United States. However, no company is manufacturing LAAM at this time. As the new drug application for LAAM has not been withdrawn, LAAM could once again be made available in the United States (22).

**Buprenorphine**

Buprenorphine alone, and in combination with naloxone, was approved in 2002 by the FDA as an office-based sublingual treatment for heroin and opioid addiction (23–25) at the same time; buprenorphine was reclassified by the Drug Enforcement Administration from a Schedule V to a Schedule III drug (13). Buprenorphine alone, or when combined with naloxone, is a primarily MOP-r–directed partial agonist and is also a kappa partial agonist. The structure of buprenorphine is that of an oripavine with a C7 side chain, which contains a tert-butyl group. Norbuprenorphine is a major metabolite of buprenorphine in humans, with activity at the MOP-r as well (25).

The formulations of specific drugs are shown in Table 9-1.

### Clinical Uses

Clinically used opioids (i.e., primarily MOP-r agonists) are used for pain control, and as maintenance medications for opioid addiction (i.e., methadone and buprenorphine). For minor pain, such as post–dental procedures, opioids such as hydrocodone are used. For more chronic or severe pain, opioids such as morphine may be used. There is the risk of iatrogenic addiction, respiratory depression, and also diversion of these medications. As a result, they must be dispensed cautiously. This caution, however, must be carefully balanced against the risk of undermedicating pain for each individual patient. When there is addiction to opioids, the approved long-acting opioid pharmacotherapies are available by prescription for detoxification and for maintenance, the latter having a well-proven long-term beneficial effect on patient health. Depot naltrexone (Vivitrol) was recently (October 2010) approved as a monthly IM injection for prevention of relapse following detoxification from opioid addiction.

### Table 9-1 Formulations and Their Methods of Use/Abuse

<table>
<thead>
<tr>
<th>DRUG</th>
<th>FORMULATION</th>
<th>METHOD OF USE/ABUSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heroin</td>
<td>Powder</td>
<td>IV, intranasal, smoked, SC</td>
</tr>
<tr>
<td></td>
<td>Free base</td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>Oral, injectable solution</td>
<td>Oral, SC, IV</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Tablet: can be With aspirin or With acetaminophen (potentially hepatotoxic) IR or CR</td>
<td>PO, abused when crushed and then snorted or injected IV, SC</td>
</tr>
<tr>
<td>Codeine</td>
<td>Tablet</td>
<td>Oral, SC, IV</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>Tablet NX formulation: combined with naloxone</td>
<td>Oral, SC, IV</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>Oral</td>
<td>PO (low oral bioavailability), IV, PR (per rectum)</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>Tablet With acetaminophen</td>
<td>PO</td>
</tr>
<tr>
<td>Methadone</td>
<td>Tablet, liquid</td>
<td>PO, IV</td>
</tr>
<tr>
<td>LAAM</td>
<td>Tablet</td>
<td>PO</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Tablet With naloxone Film (sublingual)</td>
<td>SL, IV, SC</td>
</tr>
</tbody>
</table>

### Nonmedical Uses

Opioids are abused initially for their euphoria-inducing effects. There are patients who are prescribed opioids for pain treatment who go on to abuse and/or become dependent upon the medication, due to physiologic and/or psychological factors. Heroin, as mentioned, is not available for medical indications in the United States. Methadone and buprenorphine are sometimes diverted by those for whom it is prescribed, generally not for euphoria-inducing effects, but to prevent withdrawal.

### Historical Features

Sumerian clay tablets (3000 BC.) refer to the poppy; Sumerians named opium “gil” (“happiness”). The ancient Egyptians also cultivated poppies. Opium use was initially restricted and later became widely used. “Thebaine” is derived from the name for the Egyptian city “Thebes.” “Opium” may be a Greek-derived word (“opion” = poppy juice). Opium figures prominently in Greek mythology and was also mentioned in Hippocrates’ writings (460–377 BC). The ancient Roman author Pliny warned of the dangers of addiction to opium. In 1804, a young German pharmacist, Friedrich Sertüner, isolated morphine (which he named
after Morpheus, the Greek god of dreams) (26). As a major development in opioid use and abuse, the hypodermic needle was perfected in 1853, which allowed for rapid analgesia, but also greater abuse morbidity. Diacetylmorphine was first synthesized as a semisynthetic analog in the 1870s by the Bayer company and marketed under the name “heroin.”

**EPIDEMIOLOGY OF OPIOID ABUSE AND ADDICTION**

The pharmacology of opioids is of particular relevance to the treatment of addictive disorders, given reports of increases in the abuse of illicit opioids, as well as illicit use of prescribed opioid medications (27). More than 100,000 people aged 12 to 25 initiated use annually between 1995 and 2002 (3). According to the Office of National Drug Control Policy publication of January 2008, more than 2.1 million teenagers in 2006 abused prescription drugs, and one-third of new abusers of prescription drugs in 2006 were 12- to 17-year-olds. Among 12- to 13-year-olds, prescription drugs are the drug of choice (28). According to the Substance Abuse and Mental Health Services Administration (SAMHSA) Treatment Episode Data Set, annual admissions to substance abuse treatment for primary heroin abuse increased from 228,000 in 1995 to 254,000 in 2005, with the percentage of primary heroin admissions remaining steady at about 14% to 15% of all substance abuse treatment admissions (7).

The majority of persons in treatment for heroin addiction are in methadone maintenance treatment. Also, currently, there are approximately 24,000 US physicians eligible to prescribe buprenorphine as office-based treatment to patients for treatment of opioid dependence (personal communication, Reckitt-Colman Co.). Eligibility requirements for physicians to use buprenorphine in treatment of addiction are as follows (as established by the SAMHSA Data 2000; Drug Addiction Treatment Act 2000): completion of an 8-hour continuing medical education course; notification of the government of the intent to use buprenorphine for treatment of opioid-dependent patients; and having both the capacity to provide or refer patients for ancillary services and, as of December 2006, being in agreement to treat no more than 100 patients (increased from the original 30 maximum) at any one time in an individual or group practice (29,30).

Two cross-sectional studies conducted in New York City from 2000 to 2004 found that among new admissions to drug treatment, of those patients who had stopped injecting heroin as of 6 months prior to the study, the most common reasons for cessation included concerns about health and preference for the intranasal route (31).

The recent and major problem of opioid abuse and addiction is the illicit (nonprescription) use of prescription opioids, obtained illicitly or from family members or friends. As of 2007, 8th, 10th, and 12th grade students nationwide continued to show a decline in the proportions reporting illicit drug use. Less than 1% of students in these grades reported any use of heroin in 2007. However, the prevalence of other narcotic drug use reported for twelfth graders was 9.2% (32). In a National Institutes of Health: National Institute of Drug Abuse Research Report, published in 2001 and revised in 2005, it was reported that benzodiazepines and opioid pain relievers were the two most frequently reported prescription medications in drug abuse–related cases (33). In 2005, 30.1% of persons addicted to heroin sought treatment with methadone or buprenorphine maintenance, whereas only 19.9% of those addicted to illicitly used prescription opioids sought such pharmacotherapy (7).

**Neurobiology, Mechanisms of Action, and Relationship to Abuse Liability**

Abused opioids have primarily agonist effects at MOP- receptors (encoded by the mu opioid receptor gene [OPRM1]) (17,34). MOP- receptors are members of the G-protein–coupled 7-transmembrane domain superfamily; they are coupled to G and G proteins, and thus MOP- agonists typically acutely result in a downstream decrease in adenylate cyclase activity (35).

**Distribution in CNS and mediation of different functions**

MOP- are widely distributed in the CNS, and the constellation of their in vivo effects is mediated in different CNS areas (36–38). Thus, therapeutically desirable analgesic effects can be mediated in different sites including dorsal spinal cord and thalamus, whereas undesirable effects, such as respiratory depression, are thought to be mediated in the brainstem (39). Other regions involved in the classic processes of physiologic dependence/withdrawal to MOP- agonists are thought to include the locus ceruleus and related centers (40,41). Classic rewarding effects of MOP- agonists, of relevance to abuse and addiction, are likely mediated to a substantial degree in ventral and dorsal striatal areas and can depend (although not exclusively) (42) on downstream activation of the dopaminergic mesocorticolimbic and nigrostriatal systems (43,44).

**MOP- Signaling Properties and Addiction/Abuse Potential**

A major underlying concept in the abuse potential of MOP- agonists is their pharmacodynamic efficacy (i.e., their relative ability to stimulate downstream second messenger systems). In general, compounds with progressively greater efficacy (e.g., morphine or fentanyl-like compounds) have greater analgesic effects but also have greater abuse potential than partial agonists such as buprenorphine (35,45). Furthermore, other downstream effects of MOP- agonist exposure are now postulated to be of relevance to the relative balance of therapeutic and undesirable effects.
of MOP-r agonists, including propensity to cause tolerance, or abuse potential. Major mechanisms of current interest are the relative propensity of compounds to cause MOP-r desensitization, and internalization, potentially related to their ability to stimulate the β-arrestin signaling pathways (46,47). For example, the main active heroin metabolite, morphine, results in lesser desensitization and internalization of receptors, compared to the endogenous neuropeptide ligands, or methadone (48). Thus, methadone maintenance can be used effectively for extended periods without the development of further tolerance (or progressively greater methadone dose requirements) (49). By contrast, abused heroin (through its main metabolite, morphine), or abused prescription opioids, may result in progressive cycles of dependence and tolerance, secondary to a lesser recruitment of endogenous MOP-r desensitization/internalization mechanisms (50).

PHARMACOKINETICS OF SPECIFIC DRUGS

It is beyond the scope of this chapter to provide a comprehensive table of dosing equivalents. There are a number of excellent reviews on this topic (4,8,51).

Heroin (Diacetylmorphine) Pharmacokinetics

Heroin is a very efficient prodrug that is more water soluble and more potent than morphine (52). It is synthesized from morphine by acetylation at both the 3 and 6 positions and metabolized in humans to active opioid compounds first by deacetylation to the active 6-monoacetylmorphine (6-MAM), and then by further deacetylation to morphine (52). Well-designed studies of heroin pharmacokinetics in humans have been performed (53–56). Heroin has an average half-life in blood of 3 minutes after intravenous administration; the half-life of 6-acetylmorphine in humans appears to be 30 minutes (53).

The use of intranasal, intramuscular, and subcutaneous heroin all produce peak blood levels of heroin or 6-acetyl-morphine within 5 minutes; however, intranasal use has about half the relative potency of parenteral routes (54). Further research needs to be carried out on the role of 6-acetylmorphine (administered directly) in relation to the pharmacokinetics of parenteral heroin, particularly its onset of action and potency as compared with morphine. Most of the enzymes involved in the metabolism of opioids are part of the P450 microsomal enzyme system, though heroin and morphine are also biotransformed outside this system.

Morphine Pharmacokinetics

Morphine is largely selective for MOP-r and is considered by most physicians in the United States the drug of choice for the treatment of cancer pain. Morphine is biotransformed mainly by hepatic glucuronidation to the major but inactive metabolite morphine-3-glucuronide (M3G) and the biologically active M6G compound (57).

Oxycodone Pharmacokinetics

The onset of action of oxycodone begins after 1 hour of PO (oral) administration, and in the CR form lasts for approximately 12 hours, with a plasma half-life of 3 to 4 hours for the immediate release (IR). Stable plasma levels are achieved within 24 hours. Oral bioavailability ranges from 60% to 87%, with 45% protein bound. Oxycodone is mostly metabolized in the liver, with the remainder as well as the metabolites metabolized in the kidneys. The two main metabolites are oxymorphone, which is also a potent analgesic, and the weaker analgesic noroxycodone, which is its major metabolite (10,61). In terms of protein binding and lipophilicity, oxycodone is similar to morphine, with slightly longer half-life and greater bioavailability. Unlike morphine, oxycodone is metabolized mostly by the cytochrome enzyme CYP2D6, while morphine in humans is primarily glucuronidated (62).

Codeine Pharmacokinetics

Codeine has a high oral-parenteral effect, owing to low first-pass metabolism in the liver. Metabolites are mostly inactive and excreted in the urine, with about 10% demethylated via CYP2D6 to morphine, which is mostly responsible for the analgesic effect of codeine, as codeine itself has very low affinity for opioid receptors. Genetic variations in this enzyme system may result in lower production of M6G. The allelic variants have different frequency in different ethnic groups, and can affect the depth of analgesia. Repeated doses of codeine may result in the accumulation of the active metabolite M6G in patients with renal disease.
Meperidine Pharmacokinetics

Onset of analgesia begins with the oral route after 15 minutes, with peak in 1 to 2 hours, which is close to peak level in plasma, with duration of about 1.5 to 3 hours (4). It is absorbed by all routes, but intramuscular administration results in a less reliable peak plasma level after 45 minutes, with wide range of plasma concentrations. After oral administration, about 50% of meperidine enters circulation without first-pass metabolism, with peak at 1 to 2 hours. Meperidine is mostly metabolized in the liver, with half-life of about 3 hours. Cirrhosis leads to increased bioavailability and half-life of both meperidine and normeperidine. Sixty percent of meperidine is protein bound and little is excreted unmetabolized (12).

Pentazocine Pharmacokinetics

Pentazocine is a mixed agonist–antagonist (with intermediate efficacy effects at both MOP-r and KOP-r) that can be given intramuscularly or orally, but is not currently available in the oral formulation. It can cause psychotomimetic effects (likely due to its KOP-r actions) and therefore has a very limited role in the treatment of chronic pain. Its duration of action is 3 to 6 hours. Its peak effect is at 0.5 to 1 hour when given intramuscularly and 1 to 2 hours when given orally (8). Sixty percent of the drug is bound to protein. Pentazocine is metabolized by the liver via oxidative and glucuronide conjugation with an extensive first-pass effect. When administered orally, the bioavailability of pentazocine is about 10%, except in patients with cirrhosis, which increases bioavailability to 60% to 70%. The drug half-life is 2 to 3 hours. Small amounts of unchanged pentazocine are excreted with urine (8).

Hydromorphone Pharmacokinetics

Hydromorphone is shorter acting than morphine. It is derived from morphine, although it may also be produced in the body in small amounts by N-demethylation of hydrocodone. It has an oral bioavailability of 30% to 40%, with an analgesic onset after 10 to 20 minutes, which peaks at about 30 to 60 minutes and persists for about 3 to 5 hours. The oral–parenteral ratio is about 5:1, with an equivalency of 1.5 mg of hydrocodone to 10 mg morphine (63).

Hydrocodone Pharmacokinetics

Hydrocodone has a half-life of 2 to 4 hours, with a peak effect at 0.5 to 1 hour. Its duration of action is 3 to 4 hours (8). Codeine may show up as trace quantities of hydrocodone in urine testing as up to 11% of codeine is metabolized to hydrocodone (64), which could be misinterpreted as hydrocodone abuse.

Methadone Pharmacokinetics

Methadone, as used in the United States, is a racemic compound; the l(R)-enantiomer is the active enantiomer and the other d(S)-enantiomer is the inactive enantiomer. Both enantiomers are weak NMDA receptor antagonists; therefore, racemic methadone, retards and attenuates the development of opioid tolerance (65). Methadone meets the two important criteria for a medication for the treatment of addiction: high systemic bioavailability (>90%) with oral administration and long apparent half-life with long-term administration in humans (66). The medical safety of long-term methadone maintenance treatment has been well studied (67).

Oral methadone has a rapid absorption but a delayed onset of action, with peak plasma levels achieved by 2 to 4 hours and sustained over a 24-hour dosing period (36,66,68,69). Moreover, the mean plasma apparent terminal half-life of racemic d,l-methadone in human subjects is around 24 hours (66). The l-enantiomer has a half-life of 36 hours (65,70,71). Biotransformation of methadone is accelerated in the third trimester; therefore, methadone dose may need to be increased in the final stages of pregnancy (72).

When taken on a chronic basis, methadone is stored and accumulated mostly in the liver (68,73). Methadone plasma levels are relatively constant because of slow release of unmetabolized methadone into the blood, which extends the apparent terminal half-life. Methadone is more than 90% plasma protein bound both to albumin and globulins (72,74). These properties help explain why methadone maintenance treatment is effective as a once-daily, orally administered pharmacotherapy for heroin addiction (16), unlike heroin and morphine, both of which have a relatively rapid onset and offset of effect and short duration of action.

Owing to the long half-life of methadone, when beginning long-term methadone maintenance treatment (usually starting with a 20- to 40-mg daily dose), escalation of dose exceeding the rate of development of tolerance can result in accumulation, with sedation and even respiratory depression. Thus, dosages must be increased slowly, usually by 10 mg every 4 to 7 days. In some patients, doses in the appropriate range (e.g., 80 to 150 mg/d) do not result in either clinical improvement or in apparent therapeutic plasma levels of 250 to 400 ng/mL, and this may be due to “rapid metabolism” related to individual genetic differences of the cytochrome P450–enzyme or p-glycoprotein–related transporter systems (69,75,76), the latter also potentially related to blood–brain barrier passage of methadone. Methadone levels in the cerebrospinal fluid peak 3 to 8 hours after methadone dosing (77,78).

Methadone is biotransformed in the liver by the cytochrome P450–related enzymes (primarily by the CYP3A4 and, to a lesser extent, the CYP2B6, CYP2D6, and CYP1A2 systems) to two N-demethylated biologically inactive metabolites, which undergo additional oxidative metabolism (17,65). Methadone and its metabolites are excreted in nearly equal amounts in urine and in feces (78–82). In patients with renal disease, methadone can be cleared almost entirely by the GI tract, reducing potential toxicity by preventing accumulation (80–82). Patients with severe
long-standing liver disease have decreased methadone metabolism and thus slower metabolic clearance of methadone, yet lower than expected plasma methadone levels as a result of lower hepatic reservoirs of methadone because of reduced liver size. Methadone disposition is relatively normal in patients with mild to moderate liver impairment (78,83,84).

Other drugs can interact with methadone because of their effects on hepatic enzymes in the cytochrome P450–related enzyme system (74): see chart. The drug–drug interactions with methadone are complex and must be considered on a case-by-case basis in individual patients (74). The major categories of drugs potentially interacting with methadone include both inducers and inhibitors of CYP3A4, (as well as inhibitors of CYP2D6, such as paroxetine) (84). CYP3A4 inducers include rifampin (85), rifabutin (86), carbamazepine (87), phenytoin (88), and phenobarbital (63), some of which have been shown to have a documented effect (85), (87), (88). Although CYP3A4 inhibitors, which include fluconazole (89), fluvoxamine (90), fluoxetine (91), paroxetine (84), and possibly erythromycin and ketoconazole, have been hypothesized to result in significant drug interactions (17,65,74), very few of these medications have been shown to have a documented effect, either pharmacokinetic or pharmacodynamic, in humans at the doses used in methadone treatment, and some have been shown to have little or no effect, such as rifabutin (86) and fluoxetine (91).

A number of studies have examined specific antiretroviral medications used in the treatment of HIV-1 and their interaction with methadone. There are reported pharmacokinetic interactions, usually through the CYP3A4 system, affecting either methadone or the antiretroviral medication, which sometimes have clinical manifestations (92,93).

Methadone levels are significantly affected by the regular consumption of more than four alcoholic drinks per day (94). Lowered methadone biotransformation secondary to hepatic enzyme competition occurs during excessive ethanol use, with resultant increases in levels of methadone (95). When chronic use of alcohol is no longer present, the metabolism may be accelerated owing to the enhancement of the P450 enzymes (95), resulting in lower than expected plasma methadone levels.

St. John’s wort (a dietary supplement sometimes self-administered by patients for depression) and grapefruit juice (via the CYP3A4 isoenzyme system) may affect the plasma concentration of methadone (96,97) and are not recommended during methadone maintenance treatment (97).

**Levo-alpha-acetylmethadol Pharmacokinetics**

LAAM, a congener of methadone, shares with methadone the properties of long duration of effect (48 vs. 24 hours for methadone, in part owing to its active metabolites norLAAM and dinorLAAM, as well as its steady-state perfusion of mu opioid receptors), oral effectiveness (18), and function as a pure opioid agonist, active mostly at the mu opioid receptor. NorLAAM and dinorLAAM accumulate with chronic administration. In addition, LAAM and its metabolites bind to tissue proteins (18).

The clearance of norLAAM and LAAM is similar, whereas the clearance of dinorLAAM is more prolonged than that of its parent compound (18). The peak pharmacologic effect of LAAM as measured by amount of pupillary constriction occurred at 8 hours and then diminished at a rate most like that of norLAAM metabolism (18).

Because of the metabolism of LAAM by the cytochrome P450 3A4 system–related microsomal enzymes to norLAAM and dinorLAAM, drug interactions can occur (e.g., rifampin and long-term alcohol abuse tend to induce this enzyme system). In their presence, increased biotransformation of LAAM could accelerate the production of norLAAM and dinorLAAM. LAAM metabolism theoretically could be retarded if hepatic drug metabolism is diminished, as occurs in the presence of very large quantities of either ethanol, or perhaps with large doses of benzodiazepines, or with intake of cimetidine (18).

**Buprenorphine Pharmacokinetics**

Buprenorphine is metabolized to norbuprenorphine, due to dealkylation in the cytochrome P450–related enzyme 3A4 system, of which buprenorphine itself is a weak inhibitor (98). Buprenorphine undergoes extensive first pass in the liver; thus, it is administered sublingually with 50% to 60% bioavailability. Despite the ceiling effect of buprenorphine as previously described, there have been a number of reported cases of deaths in Europe with concurrent benzodiazepine abuse (99). There have been many reports of the intravenous abuse of the sublingual preparation of buprenorphine in many countries. A second formulation of sublingual buprenorphine (combined with naloxone), was developed in 1984, and modeled after our early well-studied formulation of methadone/naloxone, is now increasingly used in the United States and worldwide (67). In this formulation, naloxone will not precipitate withdrawal when taken sublingually because of its limited oral bioavailability; however, it may block the initial euphoric effects of buprenorphine if abused by the intravenous route and may also then precipitate acute opioid withdrawal (100,101). However, naloxone apparently cannot effectively displace buprenorphine in overdose situations, particularly when benzodiazepines are present. With acute buprenorphine intoxication, there may be mild mental status changes, mild to minimal respiratory effects, small but not pinpoint pupils, and essentially stable vital signs. In some situations, naloxone apparently can improve the respiratory depression but with limited effect on the other symptoms (101). Patients should be observed for 24 to 48 hours.

Initially developed as an analgesic, buprenorphine has been shown in most studies to be as effective as morphine
in many situations. Buprenorphine has some modest kappa opioid receptor (KOP-r) activity, as a partial agonist (102). Owing to its ceiling effect, increasing buprenorphine doses in humans beyond 32 mg sublingually has no greater MOP-r agonist effect (103). Sixteen milligrams sublingual buprenorphine is the most commonly used dose in the treatment of opioid addiction, which is similar in efficacy to around 60 mg of methadone (104).

Buprenorphine has a long duration of action (24 to 48 hours) when administered on a chronic basis, not because of its pharmacokinetic profile, but because of its very slow dissociation from MOP-r. Two important properties of buprenorphine are (a) its apparent lower severity of withdrawal signs and symptoms on cessation, compared with heroin, and, possibly, with methadone and LAAM and (b) its reduced potential to produce lethal overdose when used alone in opiate-naïve or nontolerant persons, because of its partial agonist properties. Given intravenously, buprenorphine has an apparent beta-terminal plasma half-life of about 3 to 5 hours. When given orally, it is relatively ineffective because of its first-pass metabolism (18), that is, rapid biotransformation, probably by the intestinal mucosa and, especially, by the liver. Sublingual preparations of buprenorphine can be liquid or tablet, both of which require about 120 minutes for time to peak. However, peak plasma concentrations of the sublingual tablet and mean area under the plasma concentration time curve are lower than that of the liquid at equivalent doses (103,105–107).

In two positron emission tomography (PET) studies of MOP-r with buprenorphine, studies initiated in volunteers (13 initiated, 5 completing), who were treated with buprenorphine for up to 10 weeks maximum, at dosages of 2 mg, 16 mg, and 32 mg sublingually, it was found that buprenorphine induced dose-dependent reductions in MOP-r availability occupation far greater than that seen during moderate to high dose methadone maintenance treatment (36,108,109). This is consistent with high receptor occupancy by buprenorphine as a partial agonist, at therapeutic doses.

The mechanism by which buprenorphine blocks the effects of heroin or morphine is probably similar to those observed with methadone in maintenance treatment, which blocks moderate to high doses of heroin or morphine, principally by tolerance and cross-tolerance (16). This may be in addition to relative blockade due to buprenorphine’s partial agonist profile.

**PHARMACODYNAMICS**

The pharmacodynamics of the clinically important MOP-r agonists are wide ranging, with the most pronounced effects produced in the CNS and GI tract.

The mechanism of action for all of the clinically relevant opioids described here is at the MOP-r, in which they act preferentially as agonists, except for buprenorphine, which is a partial mu opioid agonist (109), and a low efficacy ligand (antagonist or partial agonist) at kappa receptors (102).

Opioids in general affect heat regulation mechanisms in the hypothalamus. Body temperature decreases slightly, except with chronic high doses where temperature may be increased (4). Opioids also act in the hypothalamus to inhibit the release of gonadotropin-releasing hormone and corticotropin-releasing hormone, producing a reduction in luteinizing hormone, follicle-stimulating hormone, adrenocorticotropic hormone (ACTH), and beta-endorphin (110). With decrease in these hormones, plasma concentrations of testosterone and cortisol are lowered. Mu agonists increase the amount of prolactin in plasma by decreasing dopaminergic inhibition. Given chronically, there is tolerance to the effects of morphine on the neuroendocrine system. Mu opioid agonists also tend to have antidiuretic effects (111–114).

Morphine also causes constriction of the pupil (4). Opioids can cause seizures at doses much higher than used for analgesia. Naloxone is less potent in antagonizing seizures due to meperidine versus other opioids such as morphine or methadone, possibly due to convulsant metabolites (normeperidine). Therefore, meperidine is no longer used for chronic pain, and is not to be used for greater than 48 hours or greater than 600 mg/d dose (12).

All opioids must be used cautiously in patients with impaired respiratory function. Also, opioids have the potential to elevate intracranial pressure (115) (e.g., in the setting of head injury, they can produce an exaggerated respiratory depression, as well as mental status changes that can confuse the clinical picture). Typical side effects of all opioids include drowsiness, nausea, and constipation, while vomiting, pruritus, and dizziness are less common; however, all of these tend to lessen in intensity over time.

Codeine is commonly used to suppress cough at doses lower than used for analgesia (starting with 10 to 20 mg given orally) and can increase to higher doses for chronic (lower airway) cough. Codeine reduces cough via a central mechanism, with doses greater than 65 mg not indicated, owing to little increased therapeutic effect with increasing side effects (4).

Pentazocine as a mixed agonist–antagonist drug has a “ceiling effect,” like buprenorphine, which limits the degree of analgesia. Pentazocine can lead to the development of psychotomimetic side effects, not reversible with naloxone; therefore, these may not be mediated through MOPr. Pentazocine has affinity for kappa receptors (116). Pentazocine can also produce withdrawal in opioid-tolerant patients, due to its weak antagonist effects.

Methadone, like all mu opioid agonists, affects multiple organ systems, with tolerance developing at different rates to each effect. In the treatment of illicit opioid dependence or pain with prescribed opiates, proper dosing (titrated to the tolerance of the individual patient) is essential to avoid CNS depression. The precise neuronal and molecular mechanisms of physical tolerance have not been fully elucidated (112). However, it has been shown in studies of the d(R)-enantiomer of methadone (which is relatively inactive at
the MOP-r) that this isomer has modest NMDA antagonist activity, which attenuates the development of morphine tolerance in rodents, but does not affect physical dependence (117). Tolerance to the different effects of methadone occurs at different time points, with persistence (after at least 3 years of chronic treatment) of increased sweating and constipation (67) as well as a persistence of the pulsatile increase in prolactin entrained to the peak level of methadone, which occurs approximately 2 to 4 hours after daily administration (110,113,114).

With the use of oral methadone, analgesia occurs at 30 to 60 minutes. The analgesic effect of a single methadone dose given intramuscularly is equivalent to morphine, but its cumulative effects occur over time (8). It is recommended that methadone not be used for analgesia in mu agonist-naive patients due to the risk of accumulation. Rather, it should be used only in patients who have already been exposed to mu agonists and have gained a degree of tolerance.

Any euphoria produced by any opioid agonist, primarily short-acting opioids, apparently is mediated in part by the ventral tegmentum, where opioid agonist–mediated inhibition of GABAergic neurons results in disinhibition and thus activation of dopamine neurons extending to the nucleus accumbens. Norepinephrine-secreting cells in the locus ceruleus appear to play an important role in opioid withdrawal, whereas both serotonin and dopamine exert effects on dependence and craving (112,114).

Chronic administration of long-acting opioids (such as methadone) leads to the gradual development of tolerance to the effects on hypothalamic-releasing factors, with resumption of normal menses and return of plasma levels of testosterone to normal within 1 year as well as return to normal levels and activity of anterior pituitary-derived ACTH and beta-endorphin and normal ACTH stimulation in approximately 3 months (67,110). In humans, prolactin release is under tonic inhibition by tuberoinfundibular dopaminergic tone. With the use of short-acting opiates, there is a prompt increase in the release of prolactin because of an abrupt lowering of dopamine levels in the tuberoinfundibular dopaminergic system. With chronic methadone treatment, there is partial, but not complete, tolerance to this response (see below) (67,110,113,118,119).

The metyrapone test blocks 11-beta-hydroxylation of cortisol in the adrenal cortex. Heroin reduces the normal stress response to this test. However, a normal response is restored during chronic methadone maintenance treatment (67,110,120,121). With heroin use, thyroid levels may be elevated because of raised thyroid-binding globulin; thus, there are increased measures without abnormal function (67,110). The hypothalamic and pituitary effects of opioids can produce antidiuretic effects by the release of vasopressin (4,110).

Acutely, short-acting opiates can cause many effects. During chronic methadone maintenance treatment, many of these effects may diminish or present with a different time course. In the cardiovascular system, acute administration of opioids may cause peripheral vasodilatation, decreased peripheral resistance, reduced baroreceptor reflexes, histamine release, and decreased reflex vasoconstriction caused by raised PCO₂ (4). In the stomach, hydrochloric acid secretion may be inhibited, and somatostatin release from the pancreas may be elevated (4). Acetylcholine release from the GI tract is inhibited, and motility is slowed, as is absorption of drugs. The presence of increased appetite has also been noted. Biliary, pancreatic, and intestinal secretions may be reduced and digestion in the small intestine slowed. In the large intestine, there are reduced propulsion and higher tone (4,67,110,111). Tolerance develops to each of these effects. The short-acting opioids such as heroin or morphine, administered on an acute or chronic basis, reduce rosettes formed by human T lymphocytes (110,111). Morphine reduces cytotoxic activity of natural killer cells and increases growth of implanted tumors in experimental models (110,111). In contrast, with the chronic use of the long-acting opioid methadone, absolute numbers of T cells, T-cell subsets, B cells, and quantitative immunoglobulins are gradually restored to normal over 3 to 10 years, along with restoration of normal natural killer cell activity (122). During the chronic use of short-acting narcotics, these immunologic indices are abnormal (e.g., with the use of heroin), possibly in part by mediation through the neuroendocrine system, since cortisol suppresses many parameters of immune function and cortisol levels increase in opioid withdrawal. Normalization of most of these immunologic indices may gradually occur with methadone maintenance treatment (67,110,111). Thus, during methadone maintenance treatment, no daily withdrawal episodes occur.

TOLERANCE DEVELOPMENT

Tolerance may be defined as a loss of any effect after repeated use, leading to the need for higher doses to get the desired equivalent effect (112,123). Physical dependence is now known to be molecularly and clinically different from tolerance (112,123). All opiate and opioid medications lead to development of tolerance and physical dependence, though the rate of development of tolerance varies from one medication to another. Tolerance may develop at different rates for any side effects of any opioid medication and can occur over days, weeks, or years. Development of tolerance to opiates and opioids does not involve drug disposition and metabolism. There appears to be a complex interplay at both the single-cell and neuronal system levels (112).

Two unique characteristics distinguish methadone from almost all other therapeutic opiates and opioids. First, after binding to MOP-r, the methadone–opioid receptor complex undergoes rapid endocytosis, exactly like endogenous opioids (e.g., beta-endorphin or met-enkephalin) (112,123). Second, it has been shown that both enantiomers of methadone, present in equal amounts in a racemic mixture, have modest NMDA antagonist action and that NMDA antagonist attenuates or prevents tolerance to opiates and opioids
Patients maintained on methadone rapidly develop partial or full tolerance to most of methadone’s side effects (e.g., nausea and vomiting, miosis, sedation). However, tolerance develops at a slower rate to the neuroendocrine effects of the HPA and hypothalamic–pituitary–gonadal axes. Tolerance develops even more slowly to the constipating effects of opioids (67). The only side effect to which tolerance does not develop is sweating (67), which is not excessive and does not interfere with extreme physical activities in heat or in sunlight. Tolerance develops more rapidly to the “on-off” effects of short-acting narcotics (e.g., heroin, morphine, and even extended-release preparations of short-acting narcotics, such as oxycodone [OxyContin]). Therefore, the GI and neuroendocrine side effects of short-acting opioids tend to persist (66).

TOXICITY STATES AND THEIR MEDICAL MANAGEMENT

Acute opioid overdose is characterized by the triad of stupor or coma, respiratory depression, and “pinpoint” pupils. Needle marks may be noted.

Individualized dosing and reliance on regular clinical assessments are important, as diminished respiration occurs with opioids until tolerance develops. When any opioid is used beyond the degree of tolerance that is developed, reduced response to carbon dioxide centers in the pons and medulla can lead to CO₂ retention. Initially there is depressed cough (which is mediated by the medulla) as well as nausea and vomiting, which may be mediated by the area postrema of the medulla, and which disappear rapidly with the development of tolerance. Constriction of the pupil is the result of parasympathetic nerve excitation. In opioid overdose, convulsions have been reported, probably because of inhibition of the release of GABA in the CNS (4).

Mydriasis or normal pupils may be observed in patients with an overdose of meperidine, propoxyphene, dextromethorphan, pentazocine, and diphenoxylate with atropine (i.e., Lomotil) (4, 124, 125).

A full opioid overdose can be effectively treated with an opioid antagonist. However, the pharmacokinetic profile of the opioid must be considered. Since naloxone has a half-life of only 30 minutes, more than one dose may be needed for management of any opioid overdose. When overdose occurs owing to excessive use of methadone in an opioid-naïve or weakly tolerant person, repeated intravenous doses or intravenous constant infusion of naloxone may be needed for up to 24 hours or longer. Most opioids have a half-life of 4 hours or longer; therefore, repeated naloxone administration is usually needed. Otherwise, the overdose may be only transiently reversed, and the patient may lapse back into the comatose overdose situation (94).

**MEDICAL COMPLICATIONS OF OPIOIDS**

**Central Nervous System**

Effects of opioids on the CNS are minimal in therapeutic doses. The two main effects of opioid overdose on the CNS are depression of the mental status and depression of respiratory activity. Depending on the dose ingested, mental status may vary from mild sedation to stupor and coma. Significant depression of mental status is accompanied by a suppressed gag reflex, which predisposes the patient to aspiration of gastric contents into the lungs in the setting of centrally mediated nausea and vomiting. A few opioids may cause generalized seizures (e.g., high-dose meperidine). Respiratory depression manifests itself as low respiratory rate, hypoxia, and hypercarbia; it is the most frequent cause of death owing to opioid overdose (4).

**Pulmonary**

Effects of opioids on the pulmonary system are minimal in therapeutic doses. In addition to causing centrally mediated respiratory depression, overdose of opioids may affect the respiratory system directly by causing noncardiogenic pulmonary edema (NCPE) and bronchospasm. NCPE typically presents with frothy, pink bronchial secretions, cyanosis, and rales accompanying respiratory depression in a stuporous or comatose patient. NCPE is particularly associated with intravenous and inhalational use of heroin and occurs in 48% to 80% of patients hospitalized with heroin overdose. Heroin may also induce acute bronchospasm (4).

**Cardiovascular**

Effects of opioids on the cardiovascular system are minimal in therapeutic doses. In overdose, cardiovascular dysfunction occurs mostly owing to hypoxia caused by respiratory depression. Opioids may cause a release of histamine leading to vasodilatation that, in turn, results in orthostatic hypotension. Morphine directly reduces peripheral vascular tone, an effect that is used therapeutically in pulmonary edema and myocardial infarction.

The effect of opioids on heart rate is variable: Nausea and vomiting may stimulate vasovagal tone, leading to brachycardia; however, orthostatic hypotension may reflexively cause mild tachycardia. Overdose of propoxyphene may lead to direct myocardial toxicity. Cardiovascular problems associated with an intravenous route of opioid abuse include bacterial endocarditis, venous thrombosis, septic pulmonary emboli, emboli of cornstarch and talc (additives) to the retina, lungs, kidney, and liver, pseudoaneurysms, and mycotic aneurysms (125).

High (>300 mg/d) doses of methadone have been associated with prolongation of QT interval and with torsades de pointes (126). Many patients receiving high doses of methadone were receiving other medications as well, such as antiretrovirals, which are known to prolong QT₉ (127). Chlorobutanol, the preservative used in the only commercial formulation of parenteral methadone, potentiates...
methadone's ability to block ionic current through cardiac potassium channels, thus contributing to QTc prolongation (128). A prospective cohort study (129) of methadone treatment showed a statistically significant (mean of 10.8 ms) prolongation of QTc interval regardless of methadone dose during the first 2 months of methadone treatment; however, this prolongation did not appear to be clinically significant. The mean QTc value in this study was 428 ms; a QTc value of greater than 500 ms is considered to be a potential risk for torsades de pointes (129). The degree of QTc prolongation correlates with both the trough and peak serum methadone concentrations (130). In 2005, another study showed that methadone modestly increased both QTc (by 14.1 ms) and QTc dispersion (from 32.9 ± 12 to 42.4 ± 15 ms) after 6 months of therapy. The effect was not thought to be clinically significant (131). A 2006 cross-sectional study in Tel Aviv, Israel, showed that methadone maintenance therapy was safe, but that QTc interval must be measured before and during therapy with high doses (>120 mg/d) of methadone (132).

Gastrointestinal

In addition to causing nausea and vomiting, short-acting opioids (and also early maintenance treatment with long-acting opioids) slows GI motility, leading to constipation and possible fecal impaction. This centrally and peripherally mediated effect may lead to changes in intestinal absorption. Morphine may cause spasms of the sphincter of Oddi; hence, it should not be used in biliary colic. However, clinical studies have not shown a significant difference between sphincter effects of morphine and meperidine, which are often recommended for biliary colic. Prospective studies determined that tolerance to the constipating effect of chronic methadone maintenance treatment develops within 3 years (67).

Renal

Heroin, illicit methadone, and propoxyphene have been rarely associated with rhabdomyolysis, which may cause renal failure. However, there is considerable evidence that this is owing to admixtures of other chemicals with illicit drugs. Rhabdomyolysis has never been seen in methadone treatment. Heroin, morphine, and pentazocine may cause nephropathy when used intravenously, leading to glomerulonephritis (125).

Musculoskeletal

Very high doses of opioids may induce centrally mediated muscle rigidity of the chest and abdominal wall. Intravenously abused opioids may cause osteomyelitis, septic arthritis, polymyositis, and fibrous myopathy (4).

Infectious Diseases

Injection routes (intravenous, subcutaneous) of opioid abuse, due to the use of shared unclean needles, may lead to transmission of HIV-1 infection, hepatitis B, hepatitis C, as well as bacteria causing cellulitis, skin and neck abscesses, endocarditis, and botulism (125).

CONCLUSIONS AND FUTURE RESEARCH DIRECTIONS

The specific neuronal and molecular basis of opioid tolerance and dependence, which may differ between different end points (e.g., analgesia, vs. respiratory depression, vs. mediaton of reward), has not been fully elucidated.

Physiogenetics and Pharmacogenetics of MOP-r Function

Five single nucleotide polymorphisms have been identified in the coding region of the human OPRM1 (132). Three of these five single nucleotide polymorphisms lead to amino acid changes, and two (the A118G and the C17T variants) have high allelic frequencies: 2% to more than 40%, in different cultural and ethnic groups. The C17T variant may have some association with opiate dependence (132). Binding studies have shown that exogenous ligands, including methadone and morphine, bind similarly to the A118G variant and to the prototype receptor; however, the endogenous opioid beta-endorphin has greater affinity and potency in activating the receptor, in certain constructs (132). Genetic factors, such as the presence of this functional A118G variant, which regulates pharmacodynamics, may contribute to intersubject variability with response to opioid ligands, or especially the opioid antagonists (132–134).

Stress Responsivity

Atypical response to stress and stressors, as demonstrated by changes in HPA axis function, has been shown in heroin addicts. These responses tend to normalize after stabilization on a steady dose of methadone. During cycles of heroin addiction, abstinence, and relapse, there is a flattened circadian rhythm of glucocorticoid levels, with increased levels during opiate withdrawal. With steady-state methadone treatment, both circadian rhythms and plasma levels of the HPA axis normalize, as do responses of the HPA axis to chemically induced stress (120). One imaging study using PET showed only 19% to 32% greater occupancy of opioid receptors in specific brain areas related to pain and analgesia, as well as addiction (caudate, putamen, amygdala, anterior cingulate cortex, and thalamus) during steady-dose methadone maintenance volunteers compared with normal volunteers (36). The presence of these unoccupied receptors may be followed up as a research direction, to potentially explain how physiologic systems disrupted during cycles of heroin abuse, can become normalized during methadone maintenance treatment.

The effects of another MOP-r partial agonist widely used in the treatment of opioid addiction, buprenorphine (or buprenorphine/naloxone), on specific indices of neuroendocrine function have not been extensively studied. The effects of buprenorphine on other aspects of physiology
known to be disrupted during cycles of opiate addiction have also not been studied extensively. In the area of opioid agonist treatment pharmacology, more rigorous studies of complex drug interactions with methadone and other medications are needed, including studies of medications for patients with comorbid conditions, such as HIV-1, hepatitis C virus, and psychiatric illnesses. From a broader perspective, basic science information at the molecular and animal level should be integrated with clinical research and observation (3). This research should include further elucidation of the differences in the stress-responsive HPA axis in persons maintained on other long-acting opioid agonist pharmacotherapy, such as buprenorphine versus methadone, including possible gender differences.

**Evolutions in Medical Maintenance**

Studies conducted since the mid-1980s have demonstrated the effectiveness of “medical maintenance,” which involves transferring patients in a conventional methadone maintenance treatment program to a monthly office-based treatment with methadone. In order to qualify in the early studies, methadone-maintained patients have to be abstinent from illicit substances for months to years, employed, and adhere to conventional treatment before they can be admitted to office-based methadone treatment (135–137).

Federal Guidelines governing methadone maintenance treatment were rigorously reanalyzed by all three branches of the government, and the new interpretations of the guidelines published in the Federal Register, and were finally approved in early 2001 (21). Now, in accordance with Federal Guidelines, any patient may be transferred from a methadone maintenance clinic, constituted according to the old and new guidelines, to an individual physician’s office-based practice at any time, based solely on the clinical assessment of the medical staff of the clinic and the physician who is accepting the patient. There is no constraint on length of time in a methadone clinic before moving to an office-based practice, dose of methadone being used, or length of time of abstinence from illicit use of substances (21). There are no further requirements other than the fact that the physicians offering office-based treatment will refer the patient back to the original methadone clinic or another methadone clinic with which a referral has been arranged, if any significant problems ensue. However, individual states may impose more rigid regulations.

The guidelines governing entrance into methadone maintenance treatment remain very strict and far beyond the establishment of a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis of opiate addiction. Requirements include multiple daily self-administrations of heroin or any short-acting opiate for 1 year or more. To appropriately conduct a study of office-based induction to methadone maintenance treatment, the individual physicians involved each create a setting to adhere to the guidelines of a “methadone clinic.” One study reported outstanding success in office-based induction into methadone maintenance treatment (138).

To enter buprenorphine or buprenorphine/naloxone treatment, it is necessary only that a patient meet the DSM-IV criteria for “opioid dependence” (i.e., opioid addiction). Each physician administering buprenorphine (or buprenorphine/naloxone) maintenance treatment must take an 8-hour training course and should offer access to behavioral therapy. Office-based buprenorphine treatment has been found to be effective in many patients (139,140).

Patients with high levels of tolerance to an opioid may not be able to be effectively treated with the partial agonist buprenorphine or with buprenorphine/naloxone, since the maximal effective dose of buprenorphine is around 24 or 32 mg sublingually, approximately equivalent to 60 or 70 mg of methadone (relatively low doses) (141). Patients may be transferred with ease from buprenorphine to methadone maintenance treatment. The converse is not as simple, as the addition of buprenorphine will produce opioid withdrawal in patients who are being maintained on usual doses of methadone. Thus, significant dose reduction of methadone to suboptimal treatment levels (e.g., 30 to 40 mg/d) must be used prior to starting buprenorphine treatment.

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CHAPTER 9 • THE PHARMACOLOGY OF OPIOIDS


