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Chapter 3. Pharmacology of Medications Used To Treat Opioid Addiction

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This chapter reviews the pharmacology and clinical applications of the principal medications used to treat opioid addiction in opioid treatment programs (OTPs), including the opioid agonists methadone and levo-alpha acetyl methadol (LAAM), the partial opioid agonist buprenorphine, and the opioid antagonist naltrexone. Coverage of LAAM is brief because its future availability is uncertain. Coverage of buprenorphine is short because TIP 40, *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction* (CSAT 2004*a*), discusses its pharmacology in more detail. Coverage of naltrexone is short because its use in the United States generally has been limited to easing withdrawal symptoms for a small portion of patients undergoing medically supervised withdrawal after maintenance treatment. Exhibit 3-1 provides information about these and other medications for opioid addiction treatment, including the year of their U.S. Food and Drug Administration (FDA) approval and their U.S. Drug Enforcement Administration (DEA) drug schedule assignment.

Exhibit 3-1. Pharmacotherapeutic Medications for Opioid Addiction Treatment

Product	Formulations	Receptor Pharmacology	FDA Approval	DEA Schedule	Treatment Settings
Methadone	Oral solution, liquid concentrate, tablet/diskette, and powder	Full mu opioid agonist	Never formally approved by FDA	II	OTP
LAAM	Oral solution	Full mu opioid agonist	1993	II	OTP
Buprenorphine (Subutex®)	Sublingual tablet	Partial mu opioid agonist	2002	III	Physician's office, OTP, or other health care setting
Buprenorphine-naloxone (Suboxone®)	Sublingual tablet	Partial mu opioid agonist/mu antagonist	2002	III	Physician's office, OTP, or other health care setting
Naltrexone	Oral tablet	Mu opioid antagonist	1984	Not scheduled	Physician's office, OTP, any substance abuse treatment program

The most frequently used medication for opioid addiction treatment in OTPs is methadone, and much of this chapter focuses on methadone pharmacology. LAAM always has been used much less than methadone, and its use was reduced further in 2001, after it was associated with cardiac arrhythmia in some patients. That

association led FDA to warn that LAAM be used only for patients not responding well to methadone. That warning and other factors led the manufacturer to cease production of LAAM on January 1, 2004 (Schobelock 2003), making its continued availability uncertain after depletion of existing stocks. Programs were encouraged to transfer patients using LAAM to other treatments. Another pharmaceutical company may manufacture and distribute LAAM in the future.

FDA approved buprenorphine on October 8, 2002, for use in medical maintenance treatment and medically supervised withdrawal. It is the first partial opioid agonist in recent U.S. history available for use by certified physicians outside the traditional opioid treatment delivery system and the strict requirements of the Narcotic Addict Treatment Act of 1974 (see chapter 2). In addition, on May 22, 2003, an interim rule change made buprenorphine available for use in OTPs that receive certification from the Substance Abuse and Mental Health Services Administration (SAMHSA) to dispense buprenorphine. Physicians working in medical offices or other appropriate settings must obtain a waiver from SAMHSA to use buprenorphine to treat opioid addiction (see Exhibit 3-2). Qualified physicians may dispense or prescribe buprenorphine products for up to 30 patients at a time under the provisions of the Drug Addiction Treatment Act of 2000 (DATA). (More information about DATA and waivers can be found at www.buprenorphine.samhsa.gov; also see Boatwright 2002.)

Exhibit 3-2. Requirements for Physicians' Waivers To Dispense or Prescribe Buprenorphine and Buprenorphine-Naloxone to Patients Who Are Opioid Addicted

"To qualify for a waiver under DATA 2000 a licensed physician (MD or DO) must meet any one or more of the following criteria:
• The physician holds a subspecialty board certification in addiction psychiatry from the American Board of Medical Specialties.
• The physician holds an addiction certification from the American Society of Addiction Medicine.
• The physician holds a subspecialty board certification in addiction medicine from the American Osteopathic Association.
• The physician has, with respect to the treatment and management of opioid-addicted patients, completed not less than eight hours of training (through classroom situations, seminars at professional society meetings, electronic communications, or otherwise) that is provided by the American Society of Addiction Medicine, the American Academy of Addiction Psychiatry, the American Medical Association, the American Osteopathic Association, the American Psychiatric Association, or any other organization that the Secretary [of Health and Human Services] determines is appropriate for purposes of this subclause.
• The physician has participated as an investigator in one or more clinical trials leading to the approval of a narcotic drug in schedule III, IV, or V for maintenance or detoxification treatment, as demonstrated by a statement submitted to the Secretary by the sponsor of such approved drug.
• The physician has such other training or experience as the State medical licensing board (of the State in which the physician will provide maintenance or detoxification treatment) considers to demonstrate the ability of the physician to treat and manage opioid-addicted patients.
• The physician has such other training or experience as the Secretary considers to demonstrate the ability of the physician to treat and manage opioid-addicted patients. Any criteria of the Secretary under this subclause shall be established by regulation. Any such criteria are effective only for 3 years after the date on which the criteria are promulgated, but may be extended for such additional discrete 3-year periods as the Secretary considers appropriate for purposes of this subclause. Such an extension of criteria may only be effectuated through a statement published in the *Federal Register* by the Secretary during the 30-day period preceding the end of the 3-year period involved."

Source: www.buprenorphine.samhsa.gov/waiver_qualifications.html.

The consensus panel for this TIP expects that the availability of buprenorphine in multiple settings will increase the number of patients in treatment and that its availability in physicians' offices and other medical and health care settings should help move medical maintenance treatment of opioid addiction into mainstream medical practice.

Pharmacology and Pharmacotherapy

Methadone and LAAM

The synthetic opioids methadone and LAAM are the only long-acting full opioid agonists approved for opioid pharmacotherapy at this writing. Opioid agonists bind to the mu opiate receptors on the surfaces of brain cells, which mediate the analgesic and other effects of opioids. Methadone and LAAM produce a range of mu agonist effects similar to those of short-acting opioids. Therapeutically appropriate doses of these agonist medications produce cross-tolerance for short-acting opioids such as morphine and heroin, thereby suppressing withdrawal symptoms and opioid craving as a short-acting opioid is eliminated from the body. The dose needed to produce cross-tolerance depends on a patient's level of tolerance for short-acting opioids.

LAAM is longer acting than methadone. Unlike methadone, it cannot be administered daily because its longer duration of action would lead to accumulation of toxic levels in the body that could result in death (Roxane Laboratories, Inc., 2001). Articles by Oda and Kharasch (2001) and Walsh and colleagues (1998), as well as the manufacturer's package insert for ORLAAM ® (Roxane Laboratories, Inc., 2001), provide more information on LAAM's pharmacology.

When given intramuscularly or orally, methadone suppresses pain for 4 to 6 hours. Intramuscular methadone is used only for patients who cannot take oral methadone, for example, patients in medication-assisted treatment for opioid addiction (MAT) who are admitted to a hospital for emergency medical procedures. Methadone should not be given parenterally in an OTP.

Because of its extensive bioavailability and longer half-life, an adequate daily oral dose of methadone suppresses withdrawal and drug craving for 24 to 36 hours in most patients who are opioid addicted. Patients with special needs may require split methadone doses given more than once daily. Methadone is metabolized chiefly by the cytochrome P3A4 (CYP3A4) enzyme system (Oda and Kharasch 2001), which is significant when methadone is coadministered with other medications that also operate along this metabolic pathway (see “Interactions With Other Therapeutic Medications” below).

After patient induction into methadone pharmacotherapy, a steady-state concentration (i.e., the level at which the amount of drug entering the body equals the amount being excreted) of methadone usually is achieved in 5 to 7.5 days (four to five half-lives of the drug). Methadone's pharmacological profile supports sustained activity at the mu opiate receptors, which allows substantial normalization of many physiological disturbances resulting from the repeated cycles of intoxication and withdrawal associated with addiction to short-acting opioids. Therapeutically appropriate doses of methadone also attenuate or block the euphoric effects of heroin and other opioids. *Goodman and Gilman's Pharmacological Basis of Therapeutics* (Hardman et al. 2001) provides a comprehensive description of methadone's pharmacological effects.

Methadone is up to 80 percent orally bioavailable, and its elimination half-life ranges from 24 to 36 hours. When methadone is administered daily in steady oral doses, its level in blood should maintain a 24-hour asymptomatic state, without episodes of overmedication or withdrawal (Payte and Zweben 1998). Methadone's body clearance rate varies considerably between individuals. The serum methadone level (SML) and elimination half-life are influenced by several factors including pregnancy and a patient's absorption, metabolism and protein binding, changes in urinary pH, use of other medications, diet, physical condition, age, and use of vitamin and herbal products (Payte and Zweben 1998).

Measuring methadone via SMLs helps determine how much is circulating in patients' systems. In a typical 24-hour period after dosing, SMLs should peak after about 2 to 4 hours and decline gradually to trough levels thereafter (Payte and Zweben 1998). Although researchers have noted a strong correlation between methadone dosage and serum concentrations in some patients, the relationship is not necessarily linear, and a high degree of variation exists among patients (reviewed by Leavitt et al. 2000). The rate-of-change ratio between peak and trough SMLs can be useful clinically; Payte and Zweben (1998) suggested that peak SMLs should not exceed twice the trough levels.

Researchers have found that trough SMLs of 150 to 600 ng/mL are necessary to suppress drug craving (reviewed in Leavitt et al. 2000). Many treatment providers consider that trough SMLs of ≥400 ng/mL provide adequate opioid cross-tolerance, thereby controlling patients' opioid abuse; however, Eap and colleagues (2002) found no studies that validated these minimum trough levels.

Methadone has two enantiomeric forms, “(*R*)-” (also called *levo*- or L-) methadone and “(*S*)-” (*dextro*- or D-) methadone, which have the same chemical formula but different spatial arrangements. OTPs in the United States use a 50:50 racemic mixture of these two enantiomers. Only (*R*)-methadone has clinically significant mu receptor agonist activity, and its potency as an analgesic is 50 times greater than that of (*S*)-methadone (Eap et al. 2002). (*R*)-methadone also has a significantly higher mean clearance rate than (*S*)-methadone (Eap et al. 1999).

Methadone is metabolized into inactive metabolites, mainly in the liver by CYP450 enzymes, but probably also by

enzymes in the intestines. These metabolites are then excreted. Drugs that induce or inhibit this enzyme activity can affect methadone metabolism. If these enzymes are stimulated by other medications, the duration of methadone's effect and SMLs may be lowered, precipitating withdrawal symptoms. If these enzymes are inhibited by other medications, methadone metabolism may be slowed, and the SMLs and duration of methadone's effect in patients may be increased (Eap et al. 2002; Leavitt et al. 2000; Payte and Zweben 1998).

Several CYP450 isoforms help metabolize methadone, including CYP3A4 (the most abundant), CYP2B6, CYP2D6, and possibly, but to a smaller extent, CYP1A2, CYP2C9, and CYP2C19 (Cozza and Armstrong 2001; Eap et al. 2002; Gerber et al. 2004). Different enzymes metabolize (*R*)- and (*S*)-methadone differently. Numerous genetic and environmental factors affect these enzymes and account for variations in methadone metabolism among individuals. Some enzymes also play a part in metabolizing other medications, such as benzodiazepines, antidepressants, anticonvulsants, antibiotics, and antiviral agents (e.g., HIV protease inhibitors). Through their effects on these enzymes, some medications can raise or lower patients' SMLs. Especially during initiation of methadone maintenance, methadone can increase CYP3A4 activity, thereby accelerating its own metabolism in some individuals (Eap et al. 2002; Leavitt et al. 2000).

CYP2D6 selectively metabolizes the (*R*)-methadone enantiomer. Production of this enzyme is affected by genetic factors. A small portion of the population does not produce much CYP2D6, whereas others have very high CYP2D6 activity. The latter group may require much higher methadone doses to compensate for their high rate of (*R*)-methadone metabolism (Eap et al. 2002; Leavitt et al. 2000). Individuals also differ considerably in CYP3A4 and CYP1A2 activity, accounting in part for the wide variations in methadone metabolism (Eap et al. 2002).

Buprenorphine

Buprenorphine, a derivative of the opium alkaloid thebaine, is a synthetic opioid and generally is described as a partial agonist at the mu opiate receptor and an antagonist at the kappa receptor. Research has demonstrated that buprenorphine's partial agonist effects at mu receptors, its unusually high affinity for these receptors, and its slow dissociation from them are principal determinants of its pharmacological profile (Cowan 2003).

In the 1990s, researchers determined that, as a partial mu agonist, buprenorphine does not activate mu receptors fully (i.e., it has low intrinsic activity), resulting in a ceiling effect that prevents larger doses of buprenorphine from producing greater agonist effects (Walsh et al. 1994). As a result, there is a greater margin of safety from death by respiratory depression when increased doses of buprenorphine are used, compared with increased doses of full opioid agonists. Buprenorphine overdose is uncommon, although it has been reported in France, and it is associated almost always with injection of buprenorphine coupled with ingestion of high doses of benzodiazepines, alcohol, or other sedative-type substances (Kintz 2001, 2002). Another feature of buprenorphine is that it can be used on a daily or less-than-daily basis. Typically, the interdosing interval is extended by doubling or tripling the daily dose to permit alternate-day or thrice weekly dosing (Amass et al. 2000, 2001), which is possible because, although larger doses do not increase buprenorphine's agonist activity, they do lengthen its duration of action (Chawarski et al. 1999).

Buprenorphine also may be an excellent agent to facilitate detoxification from illicit opioids and abused prescription opioids. Although it has a relatively short plasma half-life (about 4 to 6 hours), buprenorphine has a long duration of action resulting from its high affinity for and correspondingly slow dissociation from the mu receptor (Cowan 2003). This slow dissociation likely reduces the magnitude of withdrawal symptoms during detoxification (Johnson et al. 2003*b*). Some evidence supports a short-term course of buprenorphine-naloxone therapy for detoxification from opioids.

Buprenorphine is metabolized in the liver by the CYP3A4 subgroup of CYP450 enzymes (Kobayashi et al. 1998), and, like methadone and LAAM, its rate of metabolism is affected by coadministration of other medications metabolized along this pathway.

Depending on the dosage, buprenorphine activity can be viewed as falling between that of full agonists, such as methadone and LAAM, and antagonists, such as naltrexone (Exhibit 3-3) (Johnson et al. 2003*b*). Because it is a partial agonist at higher doses, buprenorphine also can precipitate opioidlike withdrawal symptoms in patients with high levels of physical dependence on opioids, making it appear to function more like an antagonist under these conditions (see “Induction” in chapter 5).

Naltrexone

Naltrexone is a highly effective opioid antagonist that tightly binds to mu opiate receptors. Because it has a higher affinity for these receptors than has heroin, morphine, or methadone, naltrexone displaces those drugs from receptors and blocks their effects. It can, therefore, precipitate withdrawal in patients who have not been abstinent

from short-acting opioids for at least 7 days and have not been abstinent from long-acting ones, such as methadone, for at least 10 days (O'Connor and Fiellin 2000). Naltrexone displaces buprenorphine to a lesser degree, but, in high enough doses, it overrides buprenorphine's activity as well.

Because naltrexone has no narcotic effect, there are no withdrawal symptoms when a patient stops using naltrexone, nor does naltrexone have abuse potential. Early research concluded that tolerance does not develop for naltrexone's antagonist properties, even after many months of regular use (Kleber et al. 1985). A 50 mg tablet markedly attenuates or blocks opioid effects for 24 hours, and a 100 to 150 mg dose can block opioid effects for up to 72 hours (O'Brien et al. 1975).

The FDA approved naltrexone for maintenance treatment in 1984 based on its pharmacological effects, without requiring proof of its efficacy in clinical trials for opioid addiction treatment. Despite its potential advantages, it has had little impact on the treatment of opioid addiction in the United States, primarily because of poor patient compliance (O'Connor and Fiellin 2000).

Dosage Forms

Methadone

Methadone is provided in various forms, including diskettes, tablets, oral solution, liquid concentrate, and powder. In the United States, methadone used in MAT almost always is administered orally in liquid form. Parenteral administration is prohibited in OTPs. Parenteral abuse of methadone is not widespread, and people rarely inject the methadone dispensed in U.S. OTPs because it is mixed with substances (e.g., flavored drinks) that make injection unattractive.

Approved forms of methadone for oral administration are supplied in various doses and concentrations, allowing OTPs to choose which to dispense on the basis of clinic and patient preferences, convenience, and cost. The diskette form comprises scored tablets, which are dissolved in water, mixed with a flavored liquid, and taken orally. Advantages are easy inventory and the ability for patients to see what they are taking before water is added. The diskette is not suited, however, for small dose increments and decrements. Methadone tablets, which dissolve in water, can be used in conjunction with diskettes for small dose changes; however, tablets normally are used only for analgesic applications; OTPs favor forms less subject to diversion. The liquid concentrate form offers complete dosing flexibility, particularly with a computer-assisted dispensing pump system. The powder form can be mixed with water into a solution.

LAAM

LAAM is supplied to OTPs as a colorless liquid to be taken orally. When LAAM was approved, Federal regulations required OTPs to ensure that “dosage forms of LAAM and methadone are easily distinguished” (21 Code of Federal Regulations, Part 291 § 505). Therefore, OTPs color LAAM to distinguish it from methadone.

Buprenorphine

Buprenorphine is available in sublingual tablets containing either buprenorphine alone (sometimes called monotherapy tablets and marketed under the name Subutex) or combined with naloxone (called combination therapy tablets with the trade name Suboxone). For the combination therapy tablet, the ratio of buprenorphine to naloxone is 4 mg of buprenorphine to 1 mg of naloxone. The combination tablet was developed because of problems with injection abuse of buprenorphine reported outside the United States, where injection of buprenorphine is not permitted for treatment. Injected alone, buprenorphine precipitates withdrawal symptoms in most patients who are opioid addicted, and the addition of naloxone increases this likelihood. The combination tablet may precipitate acute withdrawal. Withdrawal also may be precipitated if too much or too little buprenorphine is given or if it is administered while the opioid receptors are highly occupied by an opioid agonist. Therefore, physicians need to be careful when timing the initiation of buprenorphine induction.

Naltrexone

Naltrexone was first produced by DuPont under the trade name Revia®. However, it is now produced by Mallinckrodt under the trade name Depade® and is supplied in 25, 50, and 100 mg tablets.

Efficacy

Methadone

Methadone maintenance has been demonstrated repeatedly to be safe and effective when used with appropriate safeguards and psychosocial services (O'Connor and Fiellin 2000). Maintenance treatment typically leads to reduction or cessation of illicit opioid use and its adverse consequences, including cellulitis, hepatitis, and HIV infection from use of nonsterile injection equipment, as well as criminal behavior associated with obtaining drugs. Methadone pharmacotherapy has been shown to lead to improved overall adjustment, including reductions in psychiatric symptoms, unemployment, and family or social problems. Mattick and colleagues (2003) provide complete reviews of the effectiveness of methadone.

LAAM

Controlled clinical trials generally have established that LAAM is as effective as methadone and buprenorphine in reducing illicit-opioid use and retaining patients in treatment when equipotent doses are compared (e.g., Johnson et al. 2000; White et al. 2002). Appel and colleagues (2001) provide more information on LAAM's efficacy.

Buprenorphine

The primary efficacy of buprenorphine in clinical trials was demonstrated via patient retention and elimination of illicit-opioid-positive drug tests. Compared with equipotent doses of both methadone and LAAM, buprenorphine produced similar rates of treatment retention and abstinence from illicit opioids. In a controlled, randomized study comparing the efficacy of LAAM (75 to 115 mg), buprenorphine sublingual solution (16 to 32 mg), and methadone (60 to 100 mg), all three medications substantially reduced illicit opioid use (Johnson et al. 2000).

Johnson and colleagues (2003*b*) reviewed numerous studies evaluating the efficacy of buprenorphine for maintenance treatment lasting up to 1 year. These studies have shown that daily doses of 8 mg of sublingual solution or 8 to 16 mg of the buprenorphine tablet are safe and well tolerated. Most studies comparing buprenorphine and methadone have shown that 8 mg of sublingual buprenorphine or 16 mg of the tablet per day is equivalent to approximately 60 mg of oral methadone per day. A study by Fudala and colleagues (2003) demonstrated the efficacy and safety of the buprenorphine-naloxone combination tablet in office-based settings.

Naltrexone

Naltrexone is highly effective in preventing relapse when used as directed. However, most studies have indicated very high (70 to 80 percent) dropout rates from naltrexone therapy (Stine et al. 2003). A study by Rothenberg and colleagues (2002) found especially poor retention levels for patients who had received methadone before naltrexone treatment (none of them completed 6 months of treatment, compared with 31 percent of patients who had not received methadone before naltrexone therapy). Other studies have demonstrated better compliance when naltrexone therapy is supported with payment scheduling and vouchers (e.g., Preston et al. 1999*b*).

Side Effects

Long-term methadone, LAAM, or buprenorphine therapy is associated with few side effects. Although patients typically have high levels of medical and mental disorders, most result from preexisting problems or the consequences of addiction, not from the treatment medication (Institute of Medicine 1995). Chapter 10 provides a review of related medical problems in patients who are opioid addicted.

The most common adverse effects reported by patients receiving methadone or LAAM are constipation, which is caused by slowed gastric motility, and sweating; a similar side effect profile is seen for buprenorphine. Other side effects include insomnia or early awakening and decreased libido or sexual performance (Hardman et al. 2001). Possible side effects reported after regular use of these medications are listed in Exhibit 3-4.

Exhibit 3-4. Possible Side Effects of Opioid Agonist and Partial Agonist Therapy

Whole Body Effects
• Weakness, loss of energy (asthenia)
• Back pain, chills
• Fluid accumulation (edema)
• Hot flashes
• Flu syndrome and malaise

• Weight gain
Gastrointestinal Effects
• Constipation
• Dry mouth
• Nausea and vomitin
• Abdominal pain
Musculoskeletal Effects
• Joint pain (arthralgia)
• Muscle pain (myalgia)
Nervous System Effects
• Abnormal dreams
• Anxiety
• Decreased sex drive
• Depression
• Euphoria
• Headache
• Decreased sensitivity to tactile stimulation (hypesthesia)
• Insomnia
• Nervousness
• Somnolence
Respiratory Effects
• Cough
• Rhinitis
• Yawning
Cardiac Effects
• Electrocardiogram changes (possible QT prolongation with LAAM or high doses of methadone)
• Postural hypotension
• Yawning
Cardiac Effects
• Electrocardiogram changes (possible QT prolongation with LAAM or high doses of methadone)
• Postural hypotension
• Slowed heart rate (bradycardia)
Hepatic Effects
• Abnormal liver function tests
Endocrine Effects
• Hyperprolactinemia
• Absence of menstrual periods (amenorrhea)
Skin and Appendage Effects
• Sweating
• Rash
Special Sensory Effects
• Blurred vision

Urogenital Effects
• Difficult ejaculation
• Impotence

Cardiovascular Effects

Methadone

Methadone has been shown to increase QT intervals in at least two studies (i.e., Krantz et al. 2003; Martell et al. 2003). A QT interval is that part of a patient's electrocardiogram reading that begins at the onset of the QRS complex and extends to the end of the T wave. The QT interval represents the time between the start of ventricular depolarization and the end of ventricular repolarization. The QT interval normally varies depending on heart rate, age, and gender. The QT interval may be influenced by electrolyte balance, medications, and ischemia. A prolonged QT interval increases the risk of developing a cardiac arrhythmia called torsade de pointes.

Cases of torsade de pointes have been reported in patients taking high doses of methadone (mean daily doses of approximately 400 mg). Although information about this effect is limited, 6 of 17 patients who developed torsade de pointes in one study had an increase in their methadone dose during the month preceding arrhythmia (Krantz et al. 2003). This finding supported the possibility that methadone contributed to the development of arrhythmia. Furthermore, Martell and colleagues (2003) showed that, regardless of dose, a statistically significant increase occurred in QT intervals during the first 2 months of treatment. Practitioners should be aware of potential QT-prolonging effects of methadone, especially at high doses, and should be aware of interactions with other medications that also have QT-prolonging properties or with medications that slow the elimination of methadone.

LAAM

LAAM has been associated with prolonged QT interval in some patients and, in rare cases, with death from torsade de pointes arrhythmia. As a result, it has been taken off the market in Europe, and it has been given a “black box” warning (i.e., a required warning on the package insert and other product-related materials) in the United States by FDA. These findings have led to discontinuation of LAAM therapy for new patients by most American OTPs. Currently, it is labeled for use only when no other treatment option exists or for continuing use in patients who already have demonstrated tolerability for the medication (Roxane Laboratories, Inc., 2001).

Before a patient is started on LAAM, providers must follow informed-consent procedures about QT interval prolongation and provide information about the possibility of arrhythmia and sudden death (CSAT 1999*b*). Patients should be screened for cardiac risk factors, including preexisting prolonged QT intervals or other cardiac problems (Food and Drug Administration 2001; Schwetz 2001). More information about LAAM is available from Roxane Laboratories Technical Product Information at 800-962-8364 and in chapter 2.

Side Effects of Naltrexone

Approximately 10 percent of patients receiving naltrexone have gastrointestinal side effects (e.g., nausea and vomiting) that may necessitate stopping the medication. Most patients, however, experience only mild, transient stomach upset (Stine et al. 2003). Naltrexone also can cause anxiety, nervousness, insomnia, headache, joint or muscle pain, and tiredness in some patients (National Library of Medicine 1997).

Effects on the Immune System

Short-acting opioids such as heroin and morphine interfere with the normal activity of the immune system, perhaps through stress hormones such as cortisol, which are known to suppress immune function. These effects are not seen with methadone, which does not appear to affect natural killer cell activity, immunoglobulin, or T or B cells (Novick et al. 1989).

Effects on the Liver

Methadone, LAAM, and buprenorphine are metabolized by the liver, but no evidence exists that they are hepatotoxic (Joseph et al. 2000). Because the liver is a major storage site for these medications, patients with liver disease should be expected to metabolize opioid-based medications more slowly, which might raise blood levels of these medications but lower their stores and shorten their duration of action. Abnormal liver functions among patients maintained on these drugs usually are caused by viral infections, most commonly hepatitis C

acquired from contaminated needles, or by cirrhosis secondary to alcoholism (Marray 1992). Chapter 10 provides information on medical conditions commonly seen in patients who are opioid addicted.

Although the presence of liver disease is not a reason to exclude patients from MAT, severe persistent liver disease in these patients indicates the need to monitor liver functions regularly and to use caution in dosage adjustment. Severe liver impairment might result in toxic serum levels of an opioid medication. Symptoms of toxic levels include poor concentration, drowsiness, dizziness when standing, and excessive anxiety (sometimes called feeling “wired”). These effects usually can be managed by dose reduction. The consensus panel and the FDA labels on Subutex and Suboxone recommend baseline and periodic liver function testing for patients receiving buprenorphine.

In evaluating naltrexone to treat alcoholism, a Center for Substance Abuse Treatment consensus panel (CSAT 1998*a*) recommended caution in using naltrexone for patients who have high (three times normal) serum transaminase levels. OTPs should perform liver function tests before naltrexone therapy and periodically thereafter to ensure healthy liver function. For the relatively few cases in which liver toxicity occurs, treatment should be discontinued after determining that the liver problem has no other cause.

Side Effects of Buprenorphine

Johnson and colleagues (2003*b*) reported that buprenorphine in solution or tablet and the combination buprenorphine-naloxone tablet were well tolerated. Few serious side effects have been reported in studies involving more than 5,000 patients, although, like other opioids, buprenorphine can produce constipation, headache, nausea and vomiting, and dizziness (Fudala et al. 2003; Ling et al. 1998). Increases in liver enzymes (aspartate aminotransferase and alanine aminotransferase) were observed in individuals receiving buprenorphine who also were positive for hepatitis C (Petry et al. 2000). At this writing, 53 cases of buprenorphine-associated hepatitis have been reported in France since 1996 (Auriacombe et al. 2003). One report suggested an association between injection buprenorphine misuse and liver toxicity, possibly from buprenorphine's increased bioavailability when administered parenterally (Berson et al. 2001). The direct role of buprenorphine in these abnormalities is unclear because many individuals in these studies might have had hepatitis B or C. Additional studies are needed to clarify this issue.

Interactions With Other Therapeutic Medications

Because methadone, LAAM, and buprenorphine are metabolized chiefly by the CYP3A4 enzyme system (a part of the CYP450 system), drugs that inhibit or induce the CYP450 system can alter the pharmacokinetic properties of these medications. Drugs that inhibit or induce this system can cause clinically significant increases or decreases, respectively, in serum and tissue levels of opioid medications.

Drugs that induce the CYP450 enzyme system can precipitate withdrawal in patients receiving methadone, LAAM, or buprenorphine. Most notable are certain medications used to treat HIV infection, such as nelfinavir (McCance-Katz et al. 2000), efavirenz (Clarke, S.M., et al. 2001*b*), and nevirapine (Clarke, S.M., et al. 2001*a* ; Otero et al. 1999). Other common inducers are carbamazepine, phenytoin, and phenobarbital (Michalets 1998).

Psychiatric medications sharing the same metabolic pathways as methadone and LAAM include some selective serotonin reuptake inhibitors (SSRIs), which inhibit the isoenzymes that metabolize methadone and might increase SMLs (Nemeroff et al. 1996). Hamilton and colleagues (2000), who examined SMLs in patients who were depressed, receiving the SSRI sertraline, and undergoing methadone pharmacotherapy, found that sertraline produced modest increases in SMLs during the first 6 weeks of treatment. They concluded that patients who are methadone maintained and receiving SSRIs should be monitored for altered SMLs. However, because clinical experience with patients in MAT who take SSRIs has not indicated that these alterations are clinically significant, the consensus panel recommends careful monitoring of these patients but not routine testing of their SMLs. Of all the SSRIs, fluvoxamine likely has the most potential to cause excessive SMLs while patients are receiving it and decreased SMLs after patients discontinue it (Alderman and Frith 1999). Fluvoxamine has been implicated in oversedation and respiratory depression when combined with methadone (Alderman and Frith 1999).

Earlier studies showed that methadone increased serum levels of tricyclic antidepressants, indicating that the oral doses required for a therapeutic response to tricyclics might be lower than those needed for a positive response in patients not addicted to opioids (Maany et al. 1989).

Finally, rifampin, carbamazepine, phenobarbital (used occasionally for the treatment of seizure disorders), and some medications to treat HIV infection (see chapter 10) also may induce liver enzymes that speed the body's transformation of methadone. Patients taking these medications might need increases in their methadone dosage

or split doses to maintain stability.

Exhibit 3-5 summarizes other reported drug interactions with methadone.

Exhibit 3-5. Reported Drug Interactions With Methadone

Agent	Effect on Methadone	Possible Mechanism	Remarks
Amitriptyline	Decreased clearance	Inhibition of one or several CYP isozymes (1A2, 2C9, 2C19, 2D6, 3A4)	Clinical relevance unclear
Amprenavir	Decreased serum levels; possible decreased opioid effects	Induction of CYP3A	Median 65% decrease of SMLs in five patients; association of amprenavir and abacavir, with amprenavir the likeliest inducing agent
Amylobarbitone	Increased clearance	Induction of CYP3A	Clearance determined in patients receiving methadone for cancer pain
Ciprofloxacin	Increased opioid effects	Inhibition of CYP1A2 and/or CYP3A4	One case report of sedation, confusion, and respiratory depression
Diazepam	Increased opioid effects	Mechanism unclear; probably not a pharmacokinetic interaction	Clinical relevance unclear
Efavirenz	Decreased plasma levels and opioid effects	Induction of CYP3A	Mean 57% decrease of AUC* in 11 patients; 1 case report of reduction of both enantiomers of methadone
Ethanol	Increased opioid effects and added sedation	Mechanism unclear	Clinical relevance unclear
Fluconazole	Decreased methadone clearance and increased SMLs	Inhibition of CYP3A4	Increased AUC by 35% in 13 patients after 200 mg/day for 14 days
Fluoxetine	Increased SMLs	Inhibition of CYP2D6 (stereoselectivity for (*R*)-methadone)	Increased plasma levels (mean increase 32%) for (*R*)- but not (*S*)-methadone in seven patients
Fluvoxamine	Increased SMLs and increased opioid effects	Inhibition of one or several CYP isozymes (1A2, 2C19, 3A4, 2C9)	One case report of hypoventilation, severe hypoxemia, and hypercapnia; two case reports of withdrawal symptoms when fluvoxamine stopped; one case report of fluvoxamine use to decrease methadone metabolism induced by barbiturate
Fusidic acid	Decreased opioid effects	Induction of CYP3A and CYP2C	Reports of withdrawal symptoms after 4-week therapy
Moclobemide	Increased opioid effects	Inhibition of CYP2D6 and/or CYP1A2	One case report of withdrawal symptoms when moclobemide stopped
Nelfinavir	Decreased SMLs	Induction of CYP3A; possible induction of P-glycoprotein	Mean decrease about 55% in two patients

Agent	Effect on Methadone	Possible Mechanism	Remarks
Nevirapine	Decreased SMLs and opioid effects	Induction of CYP3A	Case reports of very important decrease in SMLs and severe withdrawal symptoms
Paroxetine	Increased SMLs	Inhibition of CYP2D6 (stereoselectivity for (*R*)-methadone)	Increased (*R*)-methadone plasma levels in eight CYP2C6 extensive metabolizers (32%) but not in poor metabolizers (3%)
Phenobarbital	Decreased SMLs and opioid effects	Induction of CYP3A	One case report with a 31% reduction of trough SMLs
Phenytoin	Decreased SMLs and opioid effects	Induction of CYP3A	Mean 2.4-fold decrease of SMLs with moderately severe opioid withdrawal symptoms
Rifampin	Decreased SMLs and opioid effects	Induction of CYP3A	Cases of severe withdrawal symptoms
Ritonavir	Decreased SMLs and opioid effects	Induction of CYP3A, possible induction of P-glycoprotein; induction of CYP2C19 and/or CYP2B6 suggested to explain greater induction of metabolism of (*S*)- than (*R*)-methadone	Mean 36% decrease of the AUC in 11 patients after a 14-day treatment; high interindividual variability of decrease in SMLs
Sertraline	Increased SMLs	Inhibition of one or several CYP isozymes (3A4, 2D6, 1A2, 2C9, 2C19)	No side effects from excess dosage recorded
Spironolactone	Increased clearance	Induction of CYP3A	Clearance determined in patients receiving methadone for cancer pain

* Area under the concentration-time curve.

Adapted from Eap et al. 2002, by permission of Adis International.

Exhibit 3-6 provides a list of other substances that are known to induce or inhibit CYP3A4 and potentially could affect levels of methadone, LAAM, and buprenorphine.

Exhibit 3-6. Other Inducers and Inhibitors of CYP450 and CYP3A4

CYP3A4 Inducers Expected To Reduce Opioid Medication Levels
Carbamazepine
Dexamethasone
Ethosuximide
Primidone
Rifabutin
Troglitazone
CYP3A4 Inhibitors Expected To Increase Opioid Medication Levels*
Amiodarone

Cannabinoids
Clarithromycin
Erythromycin
Grapefruit juice
Indinavir
Itraconazole
Ketoconazole
Metronidazole
Mibefradil
Miconazole
Nefazodone
Norfloxacin
Omeprazole (slight)
Quinine
Saquinavir
Troleandomycin
Zafirlukast

* Although clarithromycin and erythromycin are CYP3A4 inhibitors, azithromycin does not inhibit CYP3A4.

Adapted from Michalets 1998, from *Pharmacotherapy* with permission; with additional information from Gourevitch and Friedland 2000 and McCance-Katz et al. 2000

Little information is available on the interaction of naltrexone with other medications. Lethargy and somnolence have been reported when naltrexone is used along with Thorazine® (chlorpromazine) or Mellaril® (thioridazine), and caution should be taken when naltrexone is used with other antipsychotic drugs. Patients taking naltrexone experience significant blockade of opioid effects from medications taken for analgesia. However, this blockade is present only when naltrexone is taken regularly; it will cease 24 to 72 hours after naltrexone is discontinued (O'Connor and Fiellin 2000).

Strategies To Prevent or Minimize Harmful Drug Interactions in MAT

To control patients' vulnerability to adverse cardiac and other harmful effects of drug interactions with methadone or LAAM, the consensus panel recommends obtaining a thorough drug and medication history, including results of drug and other laboratory tests. In some cases, particularly when patients are treated in multiple settings, consolidating this information can be a challenge.

Treatment providers should rely on their experience, intuition, and common sense to anticipate and circumvent negative drug interactions. The traditional advice when adding drugs to a therapeutic regimen is to start with low doses, increase slowly, and monitor closely. In many cases, medication dosages lower than those recommended by the manufacturer may be sufficient for the desired therapeutic effect (Cohen 1999). This is especially prudent for patients receiving agonist medications who have a positive diagnosis for cardiac risk factors.

Educating patients about the risks of drug interaction is essential. The following information should be emphasized:

- During any agonist-based pharmacotherapy, abusing drugs or medications that are respiratory depressants (e.g., alcohol, other opioid agonists, benzodiazepines) may be fatal.
- Current or potential cardiovascular risk factors may be aggravated by opioid agonist pharmacotherapy, but certain treatment strategies reduce cardiovascular risk (and should be included as needed in patients' treatment plans).
- Other drugs—illicit, prescribed, or over the counter—have potential to interact with opioid agonist medications (specific, relevant information should be provided).

- Patients should know the symptoms of arrhythmia, such as palpitations, dizziness, lightheadedness, syncope, or seizures, and should seek immediate medical attention when they occur.
- Maintaining and not exceeding dosage schedules, amounts, and other medication regimens are important to avoid adverse drug interactions.

Researchers (e.g., Cohen 1999; Levy et al. 2000; Piscitelli and Rodvold 2001) have provided other suggestions for treatment providers to minimize harmful drug interactions in MAT:

- When possible, substitute alternative medications that do not interact with opioid treatment medications (e.g., azithromycin for erythromycin [because the latter is a strong CYP3A4 inhibitor] or divalproex for carbamazepine [because the latter is a potent CYP3A4 inducer]).
- When other medications must be coadministered with opioid treatment medications, select those that have the least potential for interaction.
- Consider whether significant adverse drug interactions might be ameliorated by administering a medication with or without food or by altering dosing schedules.
- Be aware that, the more complicated the medication regimen, the less likely patients will adhere to it, necessitating increased vigilance on the part of treatment providers as the complexity of medication treatment increases.
- When potentially interactive medications are coadministered, adjust the agonist or partial agonist dosage based on patient response, rather than prophylactically basing the dosage on expected interaction, because degrees of interaction vary dramatically; prejudging the amount of a necessary dosage adjustment is unlikely to work.
- When opioid medication dosage must be adjusted to compensate for the effects of interacting drugs, observe patients for signs or symptoms of opioid withdrawal or sedation to determine whether they are undermedicated or overmedicated.
- When a potentially interactive drug combination must be used and concerns exist about adverse effects if opioid medication is increased, for example, in patients with preexisting cardiovascular conditions, closely monitor drug serum concentrations or increase testing frequency. Advise patients of the physical signs or symptoms of adverse interactions, and tell them what to do if these indicators occur.
- Be aware of concomitant preexisting diseases (e.g., diseases that decrease renal or hepatic function) and preexisting cardiovascular conditions that might influence the potential for adverse drug interactions.

Knowledge about medication interactions with methadone and other medications used in the treatment of opioid addiction is changing constantly. The reader is advised to check for the most current information on a regular basis. A useful Web site is medicine.iupui.edu/flockhart.

Safety

Methadone and LAAM

The safety profiles of methadone and LAAM are excellent when these drugs are taken as directed by the manufacturer and, for LAAM, when patients are screened carefully for any cardiac risk factors. However, because both methadone and LAAM are full mu opioid agonists, overdose and death can occur if they are taken in larger amounts than directed and in amounts exceeding patients' tolerance levels. Unintended, possibly lethal respiratory depressant effects also can occur if these medications are used in combination with substances that depress the central nervous system, such as alcohol and benzodiazepines.

Buprenorphine

Like methadone, buprenorphine generally is safe and well tolerated when used as recommended by the manufacturer, and buprenorphine's partial agonist characteristics reduce the risk of respiratory depression from overdose.

Buprenorphine overdose deaths reported in France generally have been attributed to the concurrent parenteral abuse of buprenorphine and benzodiazepines (Kintz 2001; Reynaud et al. 1998; Tracqui et al. 1998*a* , 1998*b*). Only two overdose deaths have been attributed to buprenorphine alone (Kintz 2002). The potential for injection abuse with buprenorphine is believed lower than with full agonists because, as a partial agonist, buprenorphine can precipitate withdrawal in individuals who are opioid addicted. Moreover, use of combination buprenorphine-

naloxone tablets in the United States should mitigate further the risk of abuse. As with any agonist-based pharmacotherapy, however, it is extremely important to educate patients about the potential lethality of abusing treatment medication alone or in combination with respiratory depressants, especially benzodiazepines.

Naltrexone

Naltrexone generally is safe when used according to the manufacturer's directions. Hall and Wodak (1999) cautioned that overdose rates for patients on naltrexone who relapse to heroin use might be higher than among patients receiving other treatments for opioid addiction. Further investigation is needed to validate this concern.

Figures

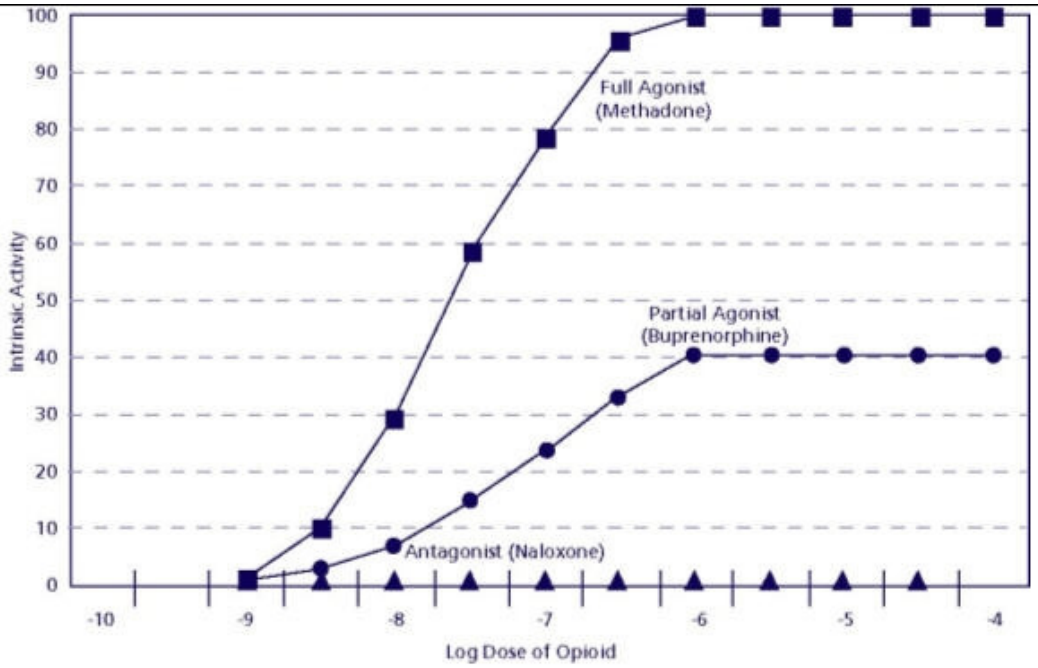

Exhibit 3-3. Intrinsic Activity of Full Agonist (Methadone), Partial Agonist (Buprenorphine), and Antagonist (Naloxone) Therapy

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