Medication-Assisted Treatment
For Opioid Addiction in Opioid Treatment Programs

A Treatment Improvement Protocol

TIP 43

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Substance Abuse and Mental Health Services Administration
Center for Substance Abuse Treatment
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MEDICATION-ASSISTED TREATMENT

1 Introduction

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Opioid addiction is a problem with high costs to individuals, families, and society. Injection drug use-associated exposure accounts for approximately one-third of all AIDS cases diagnosed in the United States through 2003 (National Center for HIV, STD and TB Prevention 2005) and for many cases of hepatitis C (National Institute on Drug Abuse 2000; Thomas 2001). In the criminal justice system, people who use heroin account for an estimated one-third of the $17 billion spent each year for legal responses to drug-related crime. Indirect costs from lost productivity and overdose also are high (Mark et al. 2001), and people with opioid addictions and their families experience severe reductions in their quality of life. The increasing abuse of prescription opioids is another major concern, both for their damaging effects and as gateway drugs to other substance use (see chapter 2).

Purpose of This TIP

This Treatment Improvement Protocol (TIP) is a guide to medication-assisted treatment for opioid addiction (MAT) in opioid treatment programs (OTPs). Compared with MAT in other settings, such as physicians' offices or detoxification centers, treatment in OTPs provides a more comprehensive, individually tailored program of medication therapy integrated with psychosocial and medical treatment and support services that address most factors affecting each patient. Treatment in OTPs also can include detoxification from illicit opioids and medically supervised withdrawal from maintenance medications.

This TIP combines and updates TIP 1 (*State Methadone Treatment Guidelines*, published in 1993), TIP 10 (*Assessment and Treatment of Cocaine-Abusing Methadone-Maintained Patients*, published in 1994), TIP 20 (*Matching Treatment to Patient Needs in Opioid Substitution Therapy*, published in 1995), and TIP 22 (*LAAM in the Treatment of Opiate Addiction*, published in 1995). It incorporates the many changes in MAT that have occurred since the publication of TIP 1, primarily as they are reflected in OTPs, and discusses the challenges that remain.

Key Definitions

The glossary (Appendix C) and list of acronyms (Appendix B) at the back of the book provide definitions of key words, terms, acronyms, and abbreviations. Particularly important distinctions among selected terms and phrases are discussed below.

Distinctions between dependence and addiction vary across treatment fields. This TIP uses the term "dependence" to refer to physiological effects of substance abuse and "addiction" for physical dependence on and subjective need and craving for a psychoactive substance either to experience its positive effects or to avoid negative effects associated with withdrawal from that substance.

The intended audience for this TIP is treatment providers and administrators working in OTPs.

MAT is any treatment for opioid addiction that includes a medication (e.g., methadone, buprenorphine, levo-alpha acetyl methadol [LAAM], naltrexone) approved by the U.S. Food and Drug Administration (FDA) for opioid addiction detoxification or maintenance treatment. MAT may be provided in an OTP or an OTP medication unit (e.g., pharmacy, physician's office) or, for buprenorphine, a physician's office or other health care setting. Comprehensive maintenance, medical maintenance, interim maintenance, detoxification, and medically supervised withdrawal (defined under "Treatment Options" below and individually in the glossary) are types of MAT.

An OTP is any treatment program certified by the Substance Abuse and Mental Health Services Administration (SAMHSA) in conformance with 42 Code of Federal Regulations (CFR), Part 8, to provide supervised assessment and medication-assisted treatment for patients who are opioid addicted. An OTP can exist in a number of settings, including, but not limited to, intensive outpatient, residential, and hospital settings. Types of treatment can include medical maintenance, medically supervised withdrawal, and detoxification, either with or without various levels of medical, psychosocial, and other types of care.

The term "abstinence" in this TIP refers to nonuse of alcohol or illicit drugs (drugs not approved by FDA), as well as nonabuse of prescription drugs. Abstinence does not refer to withdrawal from legally prescribed maintenance medications for addiction treatment (for which "medically supervised withdrawal" is the preferred term).

Terminology continues to evolve for describing the combination of substance use and mental disorders. In this TIP, "co-occurring" is the preferred term, but others use "coexisting," "dual diagnosis," and "comorbid" to describe the combination of current or former substance use disorders and any other Axis I or any Axis II mental disorders recognized by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* (American Psychiatric Association 2000). (See also TIP 42, *Substance Abuse Treatment for Persons With Co-Occurring Disorders* [CSAT 2005*b*].)

Audience for This TIP

The intended audience for this TIP is treatment providers and administrators working in OTPs. Other groups that want to understand the principles and procedures followed in MAT also will benefit.

A Decade of Change

Several forces are transforming the MAT field. The implementation of an accreditation system (*Federal Register* 64:39814) is standardizing and improving opioid addiction treatment (for

details, see 42 CFR, Part 8). Choices of medication, including methadone, buprenorphine, LAAM, and naltrexone (see chapter 3), now are available to treat opioid addiction. Each has its own benefits and limitations. Continued research on opioid addiction and treatment is clarifying what works to improve treatment outcomes, with an emphasis on accelerating the incorporation of evidence-based methods into treatment. Changes in the health care system nationwide (e.g., the growth of managed care and effects of the Health Insurance Portability and Accountability Act) are having an effect on OTPs and other types of health care programs. Understanding and acceptance of opioid addiction as a medical disorder by patients, health care providers, the media, and the public have increased since the publication of TIP 1.

MAT—A More Accepted Form of Treatment

Opioid addiction as a medical disorder

Discussions about whether addiction is a medical disorder or a moral problem have a long history. For decades, studies have supported the view that opioid addiction is a medical disorder that can be treated effectively with medications administered under conditions consistent with their pharmacological efficacy, when treatment includes comprehensive services, such as psychosocial counseling, treatment for co-occurring disorders, medical services, vocational rehabilitation services, and case management services (e.g., Dole and Nyswander 1967; McLellan et al. 1993).

Dole (1988, p. 3025) described the medical basis of methadone maintenance as follows:

> The treatment is corrective, normalizing neurological and endocrinologic processes in patients whose endogenous ligand-receptor function has been deranged by long-term use of powerful narcotic drugs. Why some persons who are exposed to narcotics are more susceptible than others to this derangement and whether long-term addicts can recover normal function without maintenance therapy are questions for the future. At present, the most that can be said is that there seems to be a specific neurological basis for the compulsive use of heroin by addicts and that methadone taken in optimal doses can correct the disorder.

Similarities to other medical disorders

McLellan and colleagues (2000) compared basic aspects of substance addiction with those of three disorders—asthma, hypertension, and diabetes—which universally are considered "medical" and usually chronic and relapsing and for which behavioral change is an important part of treatment. They found that genetic, personal-choice, and environmental factors played comparable roles in the etiology and course for these disorders and that rates of relapse and adherence to medication were similar, although substance addiction often was treated as an acute, not chronic, illness. Their review of outcome literature showed that, as with the other disorders, substance addiction has no reliable cure but that patients who comply with treatment regimens have more favorable outcomes. Fewer than 30 percent of patients with asthma, hypertension, or diabetes adhered to their medication regimens, prescribed diets, or other changes to increase their functional status and reduce their risk of symptom recurrence. As a result, 50 to 70 percent experienced recurrent symptoms each year to the point of requiring additional medical care to reestablish remission.

Another similarity found between opioid addiction and these medical disorders was their outcome predictors (McLellan et al. 2000). For example, patients who were older and employed with stable families and marriages were found to be more likely to comply with treatment and have positive treatment results than were younger, unemployed patients with less stable family support.

The concept of opioid addiction as a medical disorder was supported further by other treatment followup studies showing that opioid addiction has a reasonably predictable course, similar to such conditions as diabetes, hypertension, and asthma. For example, Woody and Cacciola (1994) found that the risk of relapse for a person who was opioid addicted was highest during the first 3 to 6 months after cessation of opioid use. This risk declined for the first 12 months after cessation and continued to decrease but at a much slower rate. Results from other posttreatment studies indicated that roughly 80 percent of patients who are opioid addicted but leave MAT resume daily opioid use within 1 year after leaving treatment (e.g., Magura and Rosenblum 2001).

Similar to patients with other chronic disorders, many who are opioid addicted have been found to respond best to treatment that combines pharmacological and behavioral interventions. As detailed throughout this TIP, treatment of opioid addiction with maintenance medication, along with other treatment services for related problems that affect patients' motivation and treatment compliance, increases the likelihood of cessation of opioid abuse. Conversely, discontinuation of maintenance medication often results in dropout from other services and a return to previous levels of opioid abuse, with its accompanying adverse medical and psychosocial consequences (Ball and Ross 1991). Entry into comprehensive maintenance treatment provides an opportunity to prevent, screen for, and treat diseases such as HIV/AIDS, hepatitis B and C, and tuberculosis (see chapter 10) and to increase compliance with medical, psychiatric, and prenatal care (Chaulk et al. 1995; Umbricht-Schneiter et al. 1994). Recent data on buprenorphine indicate that treatment with this medication, like methadone, has similar positive outcomes (CSAT 2004*a*; Johnson et al. 2000; Kakko et al. 2003).

Viewing opioid addiction as a medical disorder is consistent with the idea that treatment of even severe cases improves outcomes, just as in other chronic and relapsing medical disorders, even before abstinence is achieved. For example, Metzger and colleagues (1998) found that substance abuse treatment was associated with a significantly lower risk of HIV infection than was nontreatment. Treatment also was associated with a significant reduction, but not necessarily cessation, of drug use for many individuals. Similar findings on the positive health outcomes associated with maintenance treatment of opioid addiction, regardless of whether abstinence was attained, were seen in studies finding that methadone maintenance decreases overdose death. Data on benefits of partial responses to maintenance treatment resemble the benefits of treatment for other chronic medical disorders in terms of symptom alleviation. An analogy with MAT would be the desirability of reducing the risk of HIV infection, overdose, and the many psychosocial complications of addiction, which is not as desirable as the benefits of attaining complete abstinence from opioids but is associated with significantly improved patient health and well-being. The goal is always reducing or eliminating the use of illicit opioids and other illicit drugs and the problematic use of prescription drugs.

The medical community recognizes that opioid addiction is a chronic medical disorder that can be treated effectively with a combination of medication and psychosocial services. An important development in MAT during the 1990s was the 1997 publication of recommendations by a National Institutes of Health consensus panel on effective medical treatment of opiate addiction. After hearing from experts and the public and examining the literature, the panel concluded that "[opioid addiction] is a medical disorder that can be effectively treated with significant benefits for the patient and society" (National Institutes of Health 1997*b*, p. 18). That panel explicitly rejected the notion "that [addiction] is self-induced or a failure of willpower and that efforts to treat it inevitably fail" (p. 18). It called for "a commitment to offer effective treatment for [opioid addiction] to all who need it" (p. 2). The panel also called for Federal and State efforts to reduce the stigma attached to MAT and to expand MAT through increased funding, less restrictive

regulation, and efforts to make treatment available in all States (p. 24). The consensus panel for this TIP further recommends that access to treatment with methadone and other FDA-approved medications for opioid addiction be increased for people who are incarcerated, on parole, or on probation.

The trend toward greater acceptance of MAT as an effective treatment for opioid addiction has resulted in fewer State-mandated restrictions for treatment. For example, many States have removed restrictions on the length of time that patients may remain in treatment.

More Treatment Programs and More Patients in Treatment

In 1993, when TIP 1 was published, approximately 750 registered OTPs were treating some 115,000 patients in 40 States, the District of Columbia, Puerto Rico, and the Virgin Islands (CSAT 1993*b*, p. 1). At this writing, more than 1,100 OTPs operating in 44 States, the District of Columbia, Puerto Rico, and the Virgin Islands are treating more than 200,000 patients (Substance Abuse and Mental Health Services Administration n.d.*b*; Nicholas Reuter, personal communication, June 2004). As of this writing, methadone treatment is not available in six States: Idaho, Mississippi, Montana, North Dakota, South Dakota, and Wyoming.

Most expansion in the treatment system in the past 10 years has occurred in the proprietary sector. Historically, most OTPs were funded publicly, whereas proprietary programs were in the minority. In the 1980s, public funding for methadone treatment began to be reduced, along with State, Federal, and local budgets, and increasingly was replaced by private fee-for-service treatment programs in which patients bore more of the costs (Knight et al. 1996*a*, 1996*b*; Magura and Rosenblum 2001).

Choices of Medications

The National Institute on Drug Abuse (NIDA) has been working to broaden the array of effective treatment medications for chronic opioid addiction. Just after the publication of TIP 1, FDA approved the use of LAAM, although its use has been curtailed substantially since then (see chapter 3). In October 2002, FDA approved two new formulations containing buprenorphine for treatment of opioid addiction. Buprenorphine is used to treat individuals who have been opioid addicted for less than 1 year, as well as patients for whom buprenorphine's unique properties are beneficial (CSAT 2004*a*). The opioid antagonist naltrexone is available to treat people who are opioid addicted and have undergone medically supervised withdrawal. These medications are discussed in chapter 3.

> The medical community recognizes that opioid addiction is a chronic medical disorder that can be treated effectively…

Treatment Options

OTPs can provide several treatment options:

- Maintenance treatment combines pharmacotherapy with a full program of assessment, psychosocial intervention, and support services; it is the approach with the greatest likelihood of long-term success for many patients.
- Medical maintenance treatment is provided to stabilize patients and may include long-term provision of methadone, buprenorphine, LAAM, or naltrexone, with a reduction in clinic attendance and other services. A patient can receive medical maintenance at an OTP, after he or she is stabilized fully. The patient usually must complete a comprehensive treatment program first. The decision about whether to provide medical maintenance must be made by a licensed practitioner. A designated medication unit

(e.g., physician's office, pharmacy, long-term care facility) affiliated with an OTP can provide some medical maintenance services. To reduce clinic attendance—a key feature of medical maintenance—patients must qualify, subject to variations in State regulations (which may be more stringent than Federal regulations), to receive 7- to 14-day supplies of methadone for take-home dosing after 1 year of continuous treatment and 15- to 30-day supplies after 2 years of continuous treatment in an OTP (if additional criteria are satisfied [see chapter 5]) (42 CFR, Part 8 § 12(h); *Federal Register* 66:4079).

- Detoxification from short-acting opioids involves medication and, perhaps, counseling or other assistance to stabilize patients who are opioid addicted by withdrawing them in a controlled manner from the illicit opioids.
- Medically supervised withdrawal treatment involves the controlled tapering of treatment medication for patients who want to remain abstinent from opioids without the assistance of medication.

Based on the framework provided by the Drug Addiction Treatment Act of 2000 (21 United States Code 823(g)), qualified practitioners are authorized to use Subutex® and Suboxone® (see chapter 3) to treat chronic opioid addiction in an office-based opioid treatment (OBOT) or other health care setting.

Dosage decisions should be appropriate and tailored to each patient.

These alternatives are increasing access to care as OTPs broaden their range of treatment options, more physicians offer OBOT and become better trained in MAT principles and methods, and individuals with opioid addiction seek new points of treatment entry. At this writing, the availability of these options varies, often because of individual State regulations.

Changes in the Federal Regulatory System

On May 18, 2001, SAMHSA promulgated a new accreditation oversight system. Its goal is to "reduce the variability in the quality of opioid treatment services, and reform the treatment system to provide for expanded treatment capacity" (*Federal Register* 64:39814). As OTPs meet these national standards, treatment improvement is expected to continue along with increased attention to program evaluation and quality improvement mechanisms. The consensus panel hopes that this TIP will contribute to the movement toward quality-driven treatment standards.

Remaining Challenges

Although important strides have been made, much remains to be done to improve and expand treatment and to address the stigma that affects patients and programs.

Administering Appropriate Dose Levels

The consensus panel believes that programs should monitor and adjust patients' dose levels of methadone and other opioid treatment medications to ensure that they receive therapeutic dosages without regard to arbitrary dose-level ceilings that are unsupported by research evidence. Dosage decisions should be appropriate and tailored to each patient. Progress has been made to ensure that patients receive the therapeutic dosage levels they need to remain stabilized; however, the panel finds it troubling that some OTPs still fail to prescribe medication in adequate doses (D'Aunno and Pollack 2002).

Treating Patients Who Have More Complex Problems

Complex problems can complicate patients' diagnosis and treatment. When TIP 1 was published, the opioid addiction treatment system faced two major challenges—the spread of HIV/AIDS and the problem of untreated co-occurring disorders. The consensus panel believes that the provision of psychiatric services at or through OTPs has not kept pace with best practices. It is critical that OTPs be prepared to diagnose and treat co-occurring disorders aggressively, either directly or by referral. This issue is discussed in chapter 12.

The treatment system is grappling with the implications of hepatitis C virus (HCV) infection among people who inject drugs, with estimates of HCV infection in this group ranging from 60 percent on average nationwide (National Institute on Drug Abuse 2000) to 90 percent in some regions (Thomas 2001). OTPs face the challenge of how to provide patient education and HCV testing for people who inject drugs.

Patterns of opioid abuse have changed in the past decade. For example, in some areas of the country, patients are presenting with addiction to pain management medications as a primary admission indication (CSAT 2001*a*; Office of National Drug Control Policy 2002). OTPs report that patients addicted to pain management medications require higher therapeutic methadone levels than other patients. Since the mid-1990s, the prevalence of lifetime heroin use has increased for both youth and young adults. From 1995 to 2002, the rate among youth ages 12 to 17 increased from 0.1 to 0.4 percent; among young adults ages 18 to 25, the rate rose from 0.8 to 1.6 percent (Substance Abuse and Mental Health Services Administration 2003*c*).

Promoting Evidence-Based Treatment Services

Throughout this TIP are many examples of types of interventions—comprehensive MAT, medical maintenance, psychosocial interventions, and more—and program characteristics that have been demonstrated to improve retention and outcomes for patients. The consensus panel recommends that program administrators and treatment providers compare their practices with these evidence-based practices and make necessary changes where appropriate. Moreover, OTPs should measure their outcomes continuously, using appropriate program evaluation tools, to improve treatment quality (see chapter 14). Finally, OTPs may want to partner with the research community to investigate and adopt new interventions for improving outcomes.

In addition, SAMHSA has established and funded the Addiction Technology Transfer Center (ATTC) Network, which is dedicated to improving the skills and knowledge of substance abuse treatment providers and increasing their awareness of research findings. Regional centers in the ATTC Network seek to accomplish this goal by identifying and advancing opportunities to improve addiction treatment through the dissemination of new information in response to emerging needs and developments in the treatment field. (For more information, visit the ATTC Web site at www.nattc.org.)

Expanding the Treatment System

Although the number of patients enrolled in OTPs for addiction treatment has almost doubled since 1993, an estimated 898,000 people chronically or occasionally use heroin in the United States (Office of National Drug Control Policy 2003). Only about 20 percent of people who use heroin are being treated. For people who abuse opioid medications normally obtained by prescription, the percentage in treatment is even lower.

Lack of funding for services remains a significant barrier to treatment. In many States, Medicaid does not reimburse MAT services; accordingly, patients, many of whom

have limited financial resources, are compelled to finance their treatment.

Making Treatment Available to Criminal Justice Populations

Criminal justice populations are in critical need of opioid addiction treatment, yet most do not have access to MAT (National Center on Addiction and Substance Abuse 1998; National Drug Court Institute 2002; U.S. Department of Justice 1999). Resistance to MAT by many in the criminal justice system may be rooted in the traditional view that medical maintenance treatment is substitution of one drug for another (National Center on Addiction and Substance Abuse 1998). The Rikers Island jail facility in New York City has been providing inmates access to methadone treatment since 1987 (National Drug Court Institute 2002). Rhode Island jail facilities offer a 30-day dose-tapering program. The consensus panel understands that few other correctional institutions have provided MAT services.

Promoting Comprehensive Treatment

In its 1999 publication, *Principles of Drug Addiction Treatment: A Research-Based Guide*, NIDA stressed the importance of comprehensive treatment services by devoting 3 of the 13 principles of effective drug addiction treatment to comprehensive care (see Exhibit 1-1) (National Institute on Drug Abuse 1999).

The consensus panel believes that it is critical to emphasize the central importance of comprehensive care as more physicians begin to use buprenorphine to treat chronic opioid addiction in their private offices. Ideally, a full continuum of care should integrate the services of primary care physicians who dispense opioid treatment medications in private offices and other medication units with the services provided by counselors, case managers, and other essential staff in OTPs.

Combating Stigma

For almost a century, the predominant view of opioid addiction has been that it is a self-induced or self-inflicted condition resulting from a character disorder or moral failing and that this condition is best handled as a criminal matter (see chapter 2). Use of methadone and other therapeutic medications has been viewed traditionally as substitute therapy—merely replacing one addiction with another and the treatment of choice for those too weak to overcome temptation. The stigma associated with

Exhibit 1-1

NIDA Comprehensive Care-Related Principles of Effective Drug Addiction Treatment

- Effective treatment attends to multiple needs of the individual, not just his or her drug use.
- Counseling (individual and/or group) and other behavioral therapies are critical components of effective treatment for addiction.
- Medications are an important element of treatment for many patients, especially when combined with counseling and other behavioral therapies.

Source: National Institute on Drug Abuse 1999.

MAT has been unique in its permeation of community institutions, affecting the attitudes of medical and health care professionals; social services agencies and workers; paraprofessionals; employers, families, and friends of persons who are opioid addicted; and other people who formerly abused substances, as well as influencing criminal justice policies, creating political opposition, and limiting funding and space for OTPs.

Although diversion control is an important part of MAT, public policy sometimes has seemed to place greater emphasis on protecting society from methadone than on the addiction, violence, and infectious diseases that these medications help alleviate (Institute of Medicine 1995; Joseph et al. 2000; Nadelmann and McNeeley 1996). The cost-effectiveness of MAT often has been overlooked (see chapter 2).

Stigma affects patients in various ways. It discourages them from entering treatment and prompts them to leave treatment early. It creates a barrier for those trying to access other parts of the health care system. A striking example is the failure of many medical practitioners to medicate pain adequately in this group. In addition, the refusal of some organ transplant programs to provide liver transplants to patients maintained on methadone may be a result of stigma, as well as a lack of convincing data on outcomes for methadone patients who receive transplants.

Stigma affects programs too. It prevents new programs from opening when community opposition develops. It can affect a program's internal operations. Staff members who work in OTPs sometimes absorb society's antipathy toward patients in MAT and may deliver program services with a punitive or countertherapeutic demeanor. OTPs must guard against these attitudes through supervision, education, and leadership efforts (see chapter 14).

Several factors have made the destructive force of stigma particularly intractable, including the isolation of MAT from mainstream medicine, negative media reports about treatment, and the public impressions made by poorly run programs. Fortunately, positive changes are occurring in each area.

Positive stories about MAT in the media are sometimes overshadowed by highly charged negative accounts, for example, stories about patients loitering outside OTPs or diversion of take-home doses. SAMHSA, recognizing that "[s]ignificant reduction in stigma and changes in attitudes will require a concerted effort based on systematic research" (CSAT 2000*b*, p. 4), has undertaken a national educational campaign, titled Partners for Recovery. Many OTP managers and staff members have isolated themselves from their communities, which contributes to negative stereotypes and media stories. Managers and staff members should develop effective skills for working with the media. The consensus panel believes that the patient advocacy movement also can advance a national educational campaign about MAT.

Managers and staff members should develop effective skills for working with the media.

Strong efforts are needed to eliminate stigma within OTPs as well. Staff members should treat patients with respect and pay attention to the terms they use. The term "substitution treatment" should be avoided because it incorrectly implies that long-acting opioid medications act like heroin and other short-acting opioids. Terms such as "dirty" and "clean" in reference to drug-test specimens should be replaced by more clinically useful terms such as "positive" and "negative," respectively. The use of criminal justice terms such as "probationary treatment" should be replaced with clinically appropriate language (see chapter 14).

Finally, programs should become better neighbors. Idle, perhaps intoxicated, patients who

remain near an OTP can become, by default, the program's public representatives and easy targets for complaints from the community. Frequently, patient loitering is a result of insufficient program management. Patient conduct in and around OTPs should be considered both a treatment and a community relations concern.

The Future of MAT

This is an exciting and challenging time for the MAT field, as positive changes accelerate and reinforce one another. The consensus panel hopes that this publication will advance high-quality care in OTPs by providing up-to-date information on science-based, best-treatment practices and by highlighting sound ethical principles of treatment. Equipped with this TIP, the accreditation standards, and a developing alliance with the general medical community, OTPs should be able to improve and expand effective opioid addiction treatment throughout the country.

2 History of Medication-Assisted Treatment for Opioid Addiction

In This Chapter...

Emergence of Opioid Addiction as a Significant Problem and the Roots of Controversy

Origins of Opioid Maintenance Therapy

Regulatory History

This chapter describes the history of opioid use and addiction in the United States; changes in the population groups affected by opioid addiction disorders; and this country's social, political, legal, and medical responses. The chapter emphasizes factors affecting the development and course of medication-assisted treatment for opioid addiction (MAT) in opioid treatment programs (OTPs).

Opioid addiction has affected different population groups and socioeconomic classes in the United States at different times. Society's response has changed along with changes in the groups or classes most affected, shifts in social and political attitudes toward opioid addiction, and the accumulation of more and better information about its causes and treatments (Musto 1999). The consensus panel for this TIP believes that an appreciation for the roots of opioid addiction and treatment is important because attitudes and beliefs about opioid use and addiction that are rooted in U.S. history over the past 150 years continue to influence policies governing MAT.

Emergence of Opioid Addiction as a Significant Problem and the Roots of Controversy

Many of today's substances of abuse including the opioids—primarily opium, morphine, heroin, and some prescription opioids—gained their early popularity as curatives provided by physicians, pharmacists, and others in the healing professions or as ingredients in commercial products ranging from pain elixirs and cough suppressants to beverages. These products usually delivered the benefits for which they were used, at least initially, such as pain relief, increased physical and mental energy (or "refreshment"), and reduced anxiety. For example, opioids were often the best available substances to relieve pain on Civil War battlefields. Unfortunately, the uncontrolled use of opioids either for prescribed and advertised benefits or for nonmedicinal effects leads to

increased tolerance and addiction. Tolerance increases the need for larger quantities of opioids, more frequent use, or combination with other substances to sustain their effects; it also increases the severity of withdrawal when addiction is not satisfied. Recognition of this problem has spurred a long-running debate among patients and people who use opioids, their families, physicians, researchers, community leaders, patient advocates, and government officials. This debate centers on two different views: (1) opioid addiction is a generally incurable disease that requires long-term maintenance with medication; or (2) opioid addiction stems from weak will, lack of morals, other psychodynamic factors, or an environmentally determined predilection that is rectified by criminalization of uncontrolled use and distribution and measures promoting abstinence.

[O]pioids were prescribed widely to alleviate acute and chronic pain, other types of discomfort, and stress.

The Changing Face of Opioid Addiction

Opioid addiction first emerged as a serious problem in this country during and after the Civil War, when opioids were prescribed widely to alleviate acute and chronic pain, other types of discomfort, and stress. Although a smaller pattern of nonmedical opioid use continued as well, mainly opium smoking among Chinese immigrants and members of the Caucasian "underground" (e.g., prostitutes, gamblers, petty criminals), iatrogenic addiction was much more common (White 1998). By the late 19th century, probably two-thirds of those addicted to opioids (including opium, morphine, and laudanum) were middle- and upper-class White women, a fact Brecher and the Editors of Consumer Reports (1972, p. 17) attribute to "the widespread medical custom of prescribing opiates for menstrual and menopausal discomfort, and the many proprietary opiates prescribed for 'female troubles.'" Civil War veterans who were addicted by medical procedures composed another group, but their numbers were dwindling. By 1900, an estimated 300,000 persons were opioid addicted in the United States (Brecher and Editors 1972; Courtwright 2001; Courtwright et al. 1989).

During the late 19th and early 20th centuries, U.S. society generally viewed iatrogenic addiction among women and disabled war veterans sympathetically—as an unfortunate medical condition—and treated these groups with tolerance and empathy, particularly because neither group presented major social problems (Courtwright 2001). Doctors usually prescribed more opioids for these patients, and sanatoriums were established for questionable "cures" of the resulting addictions. The chronic nature of opioid addiction soon became evident, however, because many people who entered sanatoriums for a cure relapsed to addictive opioid use after discharge. In Eugene O'Neill's autobiographical drama "Long Day's Journey Into Night," for example, his father refuses to return O'Neill's mother, who is addicted, to a sanatorium because he is aware of the addictive qualities of morphine and is resigned to the inevitability of relapse (Courtwright 2001).

By the end of the 19th century, doctors became more cautious in prescribing morphine and other opioids, and the prevalence of opioid addiction decreased. Small groups still practiced opium smoking, but most Americans regarded it as socially irresponsible and immoral. It is noteworthy, however, that heroin, introduced in 1898 as a cough suppressant, also began to be misused for its euphoric qualities, gradually attracting new types of users. This development, along with diffusion of the hypodermic technique of drug administration, which gained popularity between 1910 and 1920, had a profound effect on opioid use and addiction in the 20th century and beyond (Courtwright 2001).

The size and composition of the U.S. opioid-addicted population began to change in the early 20th century with the arrival of waves of European immigrants. Courtwright (2001) portrays most users of opioids of this period as young men in their 20s: "down-and-outs" of recent-immigrant European stock who were crowded into tenements and ghettos and acquired their addiction during adolescence or early adulthood. They often resorted to illegal means to obtain their opioids, usually from nonmedical sources and specifically for the euphoric effects. "Gone was the stereotype of the addicted matron; in its place stood that of the street criminal" (Courtwright 2001, p. 1).

The initial treatment response in the early 20th century continued to involve the prescriptive administration of short-acting opioids. By the 1920s, morphine was prescribed or dispensed in numerous municipal treatment programs (Courtwright et al. 1989).

Addictive use of opium, cocaine, and heroin, along with drug-related crime, especially in poor urban communities, increasingly concerned social, religious, and political leaders. The tolerance and empathy shown toward Civil War veterans and middle-aged women evaporated; negative attitudes toward and discrimination against new immigrants probably colored views of addiction. Immigrants and others who trafficked in and abused drugs were viewed as a threat. As detailed below, society's response was to turn from rudimentary forms of treatment to law enforcement (Brecher and Editors 1972; Courtwright 2001; Courtwright et al. 1989). For more on trends in the 1920s and 1930s, see "Early treatment efforts" below.

McCoy (n.d.) refers to a forced decline in opioid addiction during World War II, brought about by restrictions on shipping and strict port security, which produced a marked hiatus in global opium trafficking and caused the U.S. opioid-addicted population to drop to a historic low of about 20,000. Once smuggling resumed after the war, the population that had used opioids resumed the habit.

Another major change in the U.S. opioid-addicted population occurred after World War II. As many European immigrants moved from crowded cities, Hispanics and African-Americans moved into areas with preexisting opioid abuse problems, and the more susceptible people in these groups acquired the disorder (Courtwright 2001; Courtwright et al. 1989).

The post-World War II shift in the composition of opioid-addicted groups coincided with hardening attitudes toward these groups, leading some researchers to conclude that stigmatization of people with addiction disorders and their substances of abuse reflected, at least in part, class and ethnic biases. A portion of U.S. society appeared to view with disdain and fear the poor White, Asian, African-American, and Hispanic people with addiction disorders who lived in the inner-city ghettos (Courtwright et al. 1989).

Brecher and the Editors of Consumer Reports (1972) point out that, by the mid-1960s, the number of middle-class young White Americans using heroin was on the rise, as was addiction-related crime. By the 1970s, U.S. military involvement in Vietnam also was having an effect. From one-fourth (Brecher and Editors 1972) to one-half (Courtwright 2001) of American enlisted men in Vietnam were believed to have used or become addicted to heroin; however, White (1998) points out that the feared epidemic of heroin addiction among returning veterans did not materialize fully. He concludes, "Vietnam demonstrated that a pattern of drug use could emerge in response to a particular environment and that spontaneous remission could occur when the environment was changed" (p. 303).

By the 1980s, an estimated 500,000 Americans used illicit opioids (mainly heroin), mostly poor young minority men and women in the inner cities. Although this number represented a 66-percent increase over the estimated number of late 19th-century Americans with opioid addiction, the per capita rate was much less than in the late 19th century because the population had more than doubled

(Courtwright et al. 1989). Nevertheless, addiction became not only a major medical problem but also an explosive social issue (Courtwright 2001; Courtwright et al. 1989).

By the end of the 1990s, an estimated 898,000 people in the United States chronically or occasionally used heroin (Office of National Drug Control Policy 2003), and the number seeking treatment was approximately 200,000 (almost double the number during the 1980s). The abuse of opioids that normally were obtained by prescription was a growing concern because of both their damaging effects and their potential as gateway drugs to other substance use. Treatment admission rates for addiction to opioid analgesics more than doubled between 1992 and 2001 (Substance Abuse and Mental Health Services Administration 2004), and visits to emergency rooms related to opioid analgesic abuse increased 117 percent between 1994 and 2001 (Substance Abuse and Mental Health Services Administration 2003*b*).

Society's Changing Response

The Harrison Narcotic Act of 1914

The Pure Food and Drug Act of 1906, which required medicines containing opioids to say so on their labels, was the first national response to the changing image of people with addictions (Brecher and Editors 1972). The Harrison Narcotic Act of 1914 was the earliest significant Federal attempt to place strict controls on opioids and other substances (Brecher and Editors 1972). Although U.S. mercantile and trade interests were also at stake, the widely held perception that people with addictions generally were members of a White criminal underclass or a Chinese minority has been portrayed as an underlying motivation for the statute (Courtwright 2001; Courtwright et al. 1989). The Harrison Act was conceived not as a prohibition law but as a measure to regulate the manufacture, distribution, and prescription of opioids, coca, and their derivatives. Under the act's provisions, manufacturers, pharmacists, and physicians had to be licensed, keep records for inspection, and pay modest fees to the U.S. Department of the Treasury, referred to hereafter as Treasury.

The act permitted physicians and dentists to dispense or distribute opioids "to a patient . . . in the course of [the physician's] professional practice only" (38 Stat. 786 [1914]). Although this provision permitted physicians to prescribe or dispense opioids so long as they kept the required records, Treasury interpreted the act as a prohibition on physicians' prescribing opioids to persons with addictions to maintain their addictions. (Treasury was the agency responsible for enforcing the Harrison Act as well as prohibition laws.) Treasury's position appeared to be that addiction is not a disease and the person with an addiction, therefore, was not a patient. It followed that any physician prescribing or dispensing opioids to such individuals was not doing so in the "course of his professional practice" (White 1998). In 1919, the United States Supreme Court upheld Treasury's interpretation. This interpretation and enforcement of the Harrison Act effectively ended, until well into the 1960s, any legitimate role for the general medical profession in medication-assisted treatment for Americans who had drug addictions (White 1998).

Early treatment efforts

Until the 1919 Supreme Court decision upholding Treasury's interpretation of the Harrison Act, numerous municipalities with large numbers of residents who were opioid addicted were operating treatment clinics in which morphine was prescribed or dispensed. Some clinics prescribed heroin and cocaine (Courtwright et al. 1989). These early OTPs varied in how they functioned; some provided detoxification treatment and others adopted a maintenance policy (Courtwright 2001; Gewirtz 1969). Perhaps the best known of these early OTPs were the Department of Health program in New York City, where those with addictions were detoxified with decreasing doses of heroin and morphine, and the program established by Dr. Willis Butler in Shreveport, Louisiana,

which not only detoxified patients but also maintained some of them on morphine (Courtwright et al. 1989).

Courtwright and others state that Treasury regarded these clinics as a threat to its anti-maintenance philosophy. By the early 1920s, it had succeeded in closing them through legal pressure, critical inspections, and threats. The last program to be closed was Dr. Butler's in Shreveport (Courtwright 2001; Courtwright et al. 1989).

In the 1920s, an increase in crime related to the acquisition of illicit opioids was reported in cities throughout the country. In 1929, Congress appropriated funds to establish two new treatment facilities, initially called "narcotics farms" (White 1998), in Fort Worth, Texas, and Lexington, Kentucky. The Lexington facility, which opened to patients in 1935, was renamed the U.S. Public Health Service Narcotics Hospital in 1936. These institutions detoxified patients with opioid addiction who entered voluntarily, and they also served as hospitals for prison inmates who had opioid addictions and were legally committed through a Federal court. The prescribed stay was about 6 months, although some patients stayed longer. Prisoners could stay for up to 10 years. These hospitals offered social, medical, psychological, and psychiatric services in addition to detoxification and had a low patient-to-staff ratio (about 2 to 1), but the atmosphere was described as prisonlike, especially at the Lexington facility (White 1998). Two major followup studies showed the program to be a failure. One reported a relapse rate of 93 percent in 1,881 former patients over a 1.0- to 4.5-year followup period (Hunt and Odoroff 1962). The second found a relapse rate of 97 percent in 453 former patients over followup periods of 6 months to 5 years (Duvall et al. 1963). The Lexington hospital facility was turned over to the Bureau of Prisons in 1974 (Courtwright et al. 1989). Despite the failure of these programs, White credits the research conducted there with providing "much of the foundation upon which modern treatment advances were built" (White 1998, p. 126).

The increase in heroin addiction in New York City after World War II led, in 1952, to the establishment of Riverside Hospital for adolescents with addiction disorders. This program also proved to be a failure. A followup study in 1956 showed a high posttreatment relapse rate (e.g., at least 86 percent of patients admitted in 1955), and the Riverside facility was closed in 1961 (Brecher and Editors 1972).

Experiment in civil commitment

Civil commitment is portrayed by Brecher and the Editors of Consumer Reports (1972) and White (1998) as legislation enabling those with substance addiction and those "in imminent danger of becoming addicted" (White 1998, p. 250) to be confined in rehabilitation centers without having first committed or been convicted of a crime. Civil commitment was instituted in California and New York in the 1960s to allay fears about addiction-related crimes against people and property in the inner cities. People with addictions could be committed to facilities through a voluntary process that included a medical examination to validate the presence of an addiction, or they could be committed for 3 years when arrested on a misdemeanor charge, as an alternative to a jail sentence. The civil commitment program instituted in New York in 1966 turned out to be exceedingly expensive, and the positive results were minimal (Brecher and Editors 1972; Inciardi 1988). The great majority of those admitted, treated, and paroled to aftercare programs dropped out of these programs, and they usually could not be located. A review of California's civil commitment experience in the

> Treasury's position appeared to be that addiction is not a disease… and the person… not a patient.

1960s showed that five of every six patients committed for addictions and subsequently placed on aftercare relapsed, were rearrested, dropped out of treatment, died, or were removed from the program by writs of habeas corpus (Joseph 1988; Joseph and Dole 1970).

Although statutes permitting involuntary commitment might remain on the books in some States, such laws rarely have been used to commit people who abuse substances and who are not under criminal justice jurisdiction (Anglin 1988). Court decisions after the 1960s generally have required that an individual be a danger to himself or herself or others before the legal system can use involuntary commitment (e.g., *O'Connor* v. *Donaldson*, 422 U.S. 563, 1975).

The search for alternatives

In New York, death rates associated with the injection of heroin increased from 7.2 to 35.8 per 10,000 deaths between 1950 and 1961 (Frank 2000; Joseph et al. 2000). In the 1960s and 1970s, more than 150,000 names were added to the Narcotics Register in New York City. (The Narcotics Register, active from 1967 to 1974, was a list of known or suspected persons with addictions.)

Support for opioid maintenance grew, especially because no effective psychosocial alternative existed to treat the large number of people with opioid addictions.

By the middle to late 1960s, illicit–opioid-related mortality had become the leading cause of death for young adults from ages 15 to 35 in New York City. The number of serum hepatitis (now called hepatitis B) cases related to contaminated needles also was increasing. Record numbers of people with opioid addictions were arrested for drug-related crimes (e.g., possession, sales, robbery, burglary), and overcrowded jails had no effective method to ease detoxification (Inciardi 1988; Joseph and Dole 1970). By 1968, the Manhattan County Jail for Men (also known as the Tombs) had been wracked by riots blamed on poor living conditions, severe overcrowding, and lack of medical care for inmates with drug addictions.

As the incidence of addiction and related criminal activity rose dramatically in urban areas, concern grew in the legal and medical communities because increased incarceration had failed to stem the tide. The legal and medical professions were perturbed by the post-World War II rise in opioid addiction in the United States and the ineffectiveness of Federal regulatory policy. In 1958, a joint committee of the American Bar Association and the American Medical Association (AMA) issued a report recommending that an outpatient facility prescribing opioids to treat addiction be established on a controlled experimental basis (Brecher and Editors 1972).

Other groups voiced support for the concept of opioid maintenance programs. The New York Academy of Medicine recommended, in 1955 and again in 1963, that clinics be established in affiliation with hospitals to dispense opioids in a controlled manner to patients addicted to illicit opioids. In 1956, the AMA advocated a research project to investigate the feasibility of dispensing opioids in an OTP. In 1963, the Kennedy administration's Advisory Commission on Narcotic and Drug Abuse also recommended research to determine the effectiveness of outpatient OTPs' dispensing of opioids to people addicted to opioids (Brecher and Editors 1972). In the early 1970s, faced with increased opioid-related drug use and crimes, the Nixon administration greatly increased funding to stem the supply of illicit opioids, primarily heroin, entering the United States. It also greatly increased funding for methadone maintenance, and the number of patients receiving methadone increased from 9,000 in 1971 to 73,000 in 1973 (Courtwright 2001). Support for opioid

maintenance grew, especially because no effective psychosocial alternative existed to treat the large number of people with opioid addictions.

Origins of Opioid Maintenance Therapy

Development of Medications To Treat Opioid Addiction

Early rationale for methadone maintenance treatment

In 1962, Dr. Vincent P. Dole, a specialist in metabolism at The Rockefeller University, became chair of the Narcotics Committee of the Health Research Council of New York City. After studying the scientific, public health, and social ramifications of addiction in the city, he received a grant to establish a research unit to investigate the feasibility of opioid maintenance. In preparing for this research, he read *The Drug Addict as a Patient* by Dr. Marie E. Nyswander (Nyswander 1956), a psychiatrist with extensive experience treating patients who were addicted to opioids. She was convinced that these individuals could be treated within general medical practice. She also believed that many would have to be maintained on opioids for extended periods to function because a significant number of people who attempted abstinence without medication relapsed, in spite of detoxifications, hospitalizations, and psychotherapy (Brecher and Editors 1972; Courtwright et al. 1989). Dr. Nyswander joined Dr. Dole's research staff in 1964. Among others joining the team was clinical investigator Dr. Mary Jeanne Kreek.

These researchers realized that morphine, which is related to heroin, was not a good choice as an opioid maintenance drug because patients' social functioning was impaired by morphine's sedating effects (White 1998). Also, the short half-life of morphine required several injections per day, and, as tolerance developed, increasing amounts were needed over a short time for patients to remain stable (Brecher and Editors 1972). Other short-acting opioids, such as heroin, codeine, oxycodone, and meperidine (Demerol®), showed similar results (Dole 1980, 1988).

Development of methadone

With short-acting opioids eliminated as options for maintenance therapy, research focused on methadone. Methadone appeared to be longer acting and effective when administered orally. It also was selected on the basis of observations of its use in patients withdrawing from heroin and as an analgesic in the experimental treatment of pain (Dole 1980, 1988). In 1964, technology was not available to measure blood levels of heroin, morphine, or methadone to assess duration of action. Proof of the efficacy of methadone maintenance treatment depended on observation and recognition by researchers.

In an initial study, methadone was administered to two patients previously maintained on morphine. Once tolerance for daily doses of 50 to 120 mg was established, patients could function normally without the anxiety associated with drug craving (White 1998). During this research, the following important findings about methadone maintenance were noted, all supporting its efficacy and benefits (Dole 1980, 1988):

- Patients did not experience euphoric, tranquilizing, or analgesic effects. Their affect and consciousness were normal. Therefore, they could socialize and work normally without the incapacitating effects of short-acting opioids such as morphine or heroin.
- A therapeutic, appropriate dose of methadone reduced or blocked the euphoric and tranquilizing effects of all opioid drugs examined (e.g., morphine, heroin, meperidine, and opium), regardless of whether a patient injected or smoked the drugs.
- No change usually occurred in tolerance levels for methadone over time, unlike for morphine and other opioids; therefore, a dose could be held constant for extended periods (more than 20 years in some cases).

- Methadone was effective when administered orally. Because it has a half-life of 24 to 36 hours, patients could take it once a day without using a syringe.
- Methadone relieved the opioid craving or hunger that patients with addiction described as a major factor in relapse and continued illegal use.
- Methadone, like most opioid-class drugs, caused what were considered minimal side effects, and research indicated that methadone was medically safe and nontoxic.

Expansion of methadone maintenance from research project to public health program

In 1965, the initial research project on methadone safety and efficacy was transferred to Manhattan General Hospital in New York City (Brecher and Editors 1972). Because Dole and his colleagues knew that an independent evaluation of this new treatment would be necessary, a team headed by Dr. Frances Rowe Gearing was formed at Columbia University School of Public Health to evaluate patient progress as this treatment expanded. In general, the team found that patients' social functioning improved with time in treatment, as measured by elimination of illicit-opioid use and better outcomes in employment, school attendance, and homemaking. Most patients were stabilized on methadone doses of 80 to 120 mg/day. Most patients who remained in treatment subsequently eliminated illicit-opioid use. However, 20 percent or more of these patients also had entered treatment with alcohol and polysubstance abuse problems, despite intake screening that attempted to eliminate these patients from treatment (Gearing and Schweitzer 1974). Methadone treatment was continued for these patients, along with attempts to treat their alcoholism and polysubstance abuse. Further evaluation, research, and expansion of the program ultimately were recommended (Joseph and Dole 1970) and instituted. Methadone maintenance became a major public health initiative to treat opioid addiction under the leadership of Dr. Jerome Jaffe, who headed the Special Action Office for Drug Abuse Prevention in the Executive Office of the White House in the early 1970s. Dr. Jaffe's office oversaw the creation of a nationwide, publicly funded system of treatment programs for opioid addiction.

Development of LAAM

Like methadone, levo-alpha acetyl methadol (LAAM) was classified as a U.S. Drug Enforcement Administration (DEA) schedule II controlled substance (i.e., having a high potential for abuse but also a currently accepted medical use) that creates a pharmacologic cross-tolerance for other opioids and therefore blocks their euphoric effects while controlling opioid craving. Whereas methadone suppressed opioid withdrawal symptoms for 24 hours or longer, LAAM achieved this effect for 48 to 72 hours or longer.

LAAM was first developed in 1948 by German chemists as an analgesic (Finn and Wilcock 1997). By the late 1960s, interest arose in LAAM as an alternative to methadone (American Association for the Treatment of Opioid Dependence n.d.). Between 1969 and 1981, 27 separate studies of more than 6,000 patients established LAAM's safety and efficacy (National Institute on Drug Abuse 1993*a*). The U.S. Food and Drug Administration (FDA) approved LAAM for use in OTPs in July 1993 (National Institute on Drug Abuse 1993*a*).

Later studies continued to confirm that LAAM was an effective alternative to methadone and was preferred by some patients (Glanz et al. 1997). However, in April 2001, based on reported LAAM-related disturbances in cardiac function, FDA and Roxane Laboratories, Inc., manufacturer of ORLAAM®, strengthened the warnings in LAAM product labeling (Haehl 2001). The American Association for the Treatment of Opioid Dependence has issued clinical guidelines for LAAM (American Association for the Treatment of Opioid Dependence n.d.). At this writing, only 3

percent of patients enrolled in maintenance programs in the United States are receiving LAAM (Substance Abuse and Mental Health Services Administration 2002*a*).

In 2003, Roxane Laboratories announced that it would stop producing LAAM on January 1, 2004 (Schobelock 2003), making LAAM's continued availability doubtful. This TIP continues to include basic, limited coverage of LAAM in discussions of opioid medications because of its clinical significance and relevance in MAT.

Development of buprenorphine

Information on the development of the latest successful maintenance medication, buprenorphine, is in "DEA classification of buprenorphine" below and TIP 40, *Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction* (CSAT 2004*a*).

Development of naltrexone

Naltrexone is the only pure opioid antagonist of the medications described here (see chapter 3). In the early 1980s, the National Institute on Drug Abuse (NIDA) completed initial testing of naltrexone to treat opioid addiction, and FDA approved naltrexone for this use in 1984. In 1995, naltrexone also received FDA approval as a preventive treatment for relapse to alcohol use among patients dependent on alcohol. Some opioid treatment providers have found that naltrexone is most useful for highly motivated patients who have undergone detoxification from opioids and need additional support to avoid relapse or who desire an expedited detoxification schedule because of external circumstances. Naltrexone also may benefit some patients in the beginning stages of opioid use and addiction. Other patient groups frequently have demonstrated poor compliance with long-term naltrexone therapy, mainly because naltrexone neither eases craving for the effects of illicit opioids when used as directed nor produces withdrawal symptoms when discontinued (Tai et al. 2001).

Public Policy Studies and Reports Since 1993

Analyses since the publication of TIP 1 have shown that maintenance treatment for opioid addiction is effective in both treatment outcomes and costs.

California Drug and Alcohol Treatment Assessment

In 1994, the California Department of Alcohol and Drug Programs published the results of a pioneering large-scale study of the effectiveness, benefits, and costs of substance abuse treatment in California. Using State databases, provider records, and followup interviews with treatment participants, the study detailed the effects of treatment on participant behavior including drug and alcohol use, criminal activity, health, health care use, and income; the costs of treatment; and the economic value of treatment to society (Gerstein et al. 1994).

Analyses…have shown that maintenance treatment for opioid addiction is effective in both treatment outcomes and costs.

Among the California Drug and Alcohol Treatment Assessment's findings were the following:

- Treatment was cost beneficial to taxpayers, with the cost averaging $7 returned for every dollar invested (Gerstein et al. 1994). "Each day of treatment paid for itself (the benefits to taxpaying citizens equaled or exceeded the costs) on the day it was received, primarily through an avoidance of crime" (Gerstein et al. 1994, p. iv). "Regardless of the modality of care, treatment-related economic savings outweighed costs by at least 4 to 1" (Gerstein et al. 1994, p. 90).

- Methadone treatment was among the most cost-effective treatments, yielding savings of $3 to $4 for every dollar spent. This was true for each major methadone treatment modality, but costs were lower in an outpatient OTP than in a residential or social modality (Gerstein et al. 1994).
- Patients in methadone maintenance showed the greatest reduction in intensity of heroin use, down by two-thirds, of any type of opioid addiction treatment studied.
- Patients in methadone maintenance showed the greatest reductions in criminal activity and drug selling, down 84 percent and 86 percent, respectively, of any type of opioid addiction treatment studied.
- Health care use decreased for all treatment modalities; participants in methadone maintenance treatment showed the greatest reduction in the number of days of hospitalization, down 57.6 percent, of any modality.

Institute of Medicine

In 1995, the Institute of Medicine (IOM) produced a study titled *Federal Regulation of Methadone Treatment* (Institute of Medicine 1995). This study concluded that FDA regulations were inhibiting physicians from exercising their professional judgment; isolating methadone treatment from mainstream medicine, thereby depriving patients of important ancillary services; and discouraging research into new medications. This IOM study recommended that the Federal regulatory process be modified to

- Encourage programs to provide comprehensive services, such as individual and group counseling and medical care
- Emphasize the need for continuing clinical assessment throughout treatment
- End arbitrary restrictions on OTP practices.

National Institutes of Health

In 1997, a National Institutes of Health (NIH) consensus panel called for expansion of methadone maintenance treatment. It identified such barriers as the public's misperception of persons who are opioid addicted not as individuals with a disease but as "other" or "different," the misperception "that [addiction] is self-induced or a failure of willpower and that efforts to treat it inevitably fail," and overregulation of methadone treatment that limits the flexibility and responsiveness of treatment programs (National Institutes of Health 1997*b*). That panel called for the following:

- Federal leadership to inform the public that opioid addiction is a medical disorder that can be treated effectively, with significant benefits for the patient and society
- Access to methadone treatment for persons under legal supervision (e.g., probation, parole, incarceration)
- Increase in funding for methadone maintenance treatment
- Reduction in unnecessary regulation of MAT, including
  - Replacement of FDA regulation and oversight of MAT with more effective, less expensive measures, such as accreditation, to improve the quality of methadone treatment
  - Revision of DEA regulations to eliminate the extra level of regulation placed on methadone compared with other schedule II opioids, thereby encouraging more physicians and pharmacies to prescribe and dispense methadone and making maintenance treatment available in more locations

For more than three decades, methadone's use to treat addiction has been subjected to extensive Federal, State, and local regulation.

- Faster approval of new medications for MAT by FDA and the States
- Expansion of the availability of maintenance pharmacotherapy to States and programs where it is currently unavailable.

Regulatory History

For more than three decades, methadone's use to treat addiction has been subjected to extensive Federal, State, and local regulation. (For a detailed history of Federal regulation of methadone treatment, see chapter 5 in the IOM report [1995] edited by Rettig and Yarmolinsky.)

Laws Related to Controlled Substances as Addiction Treatment Medications

Congress has enacted several significant statutes since 1970 to limit and control the availability of psychoactive drugs and their use to treat addiction.

Controlled Substances Act (1970)

The Controlled Substances Act of 1970 (Public Law [P.L.] 91–513) requires all manufacturers, distributors, and practitioners who prescribe, dispense, or administer controlled substances to register with DEA. A physician seeking registration must meet certain standards established by the Secretary of Health and Human Services and must comply with regulations established by the U.S. Attorney General regarding security of opioid stocks and maintenance of records.

Narcotic Addict Treatment Act (1974)

In passing the Narcotic Addict Treatment Act of 1974 (P.L. 93–281), which amended the Controlled Substances Act, Congress recognized the use of an opioid drug to treat opioid addiction as critical and, for the first time in Federal law, defined "maintenance treatment." To promote closer monitoring of programs that use opioids for maintenance treatment, the law required separate DEA registration by medical practitioners who dispense opioid drugs in the treatment of opioid addiction. Previously, any physician with a DEA registration could prescribe methadone for pain management or addiction treatment. This act also increased coordination between the U.S. Department of Health and Human Services (DHHS) and DEA. Under its provisions, before a practitioner can obtain registration from DEA, DHHS must determine that the practitioner is qualified according to established treatment standards.

The Narcotic Addict Treatment Act also established NIDA as an institute independent of the National Institute of Mental Health. Authority to regulate the treatment of opioid addiction was split between NIDA and FDA. NIDA became responsible for determining appropriate standards for medical, scientific, and public health aspects of drug abuse treatment. FDA received the authority to determine the safety and effectiveness of drugs and approve new drugs for opioid addiction treatment.

Drug Addiction Treatment Act (2000)

The Drug Addiction Treatment Act of 2000 (DATA [P.L. 106–310 div. B]) amended that portion of the Controlled Substances Act mandating separate registration for practitioners who dispense opioids in addiction treatment. It allows practitioners who meet certain qualifying criteria to dispense or prescribe schedule III, IV, or V controlled substances specifically approved by FDA for MAT. Chapter 3 describes the specific requirements that physicians must satisfy under DATA provisions, including the requirement that physicians must

have the capacity to refer patients for needed counseling and other ancillary services.

DEA classification of buprenorphine

On October 8, 2002, DEA completed its evaluation of buprenorphine, classifying it as a schedule III drug (i.e., having potential for abuse and a currently accepted medical use in treatment but less potential for addiction than schedule II drugs). FDA made buprenorphine the first drug approved for treatment of opioid addiction in physicians' offices (CSAT 2004*a*; Substance Abuse and Mental Health Services Administration 2003*a*; see also chapter 3).

History of Methadone Regulation

Federal regulation

In 1972, FDA issued regulations governing eligibility, evaluation procedures, dosages, take-home medications, frequency of patient visits, medical and psychiatric services, counseling, support services, and related details for methadone treatment programs. Several modifications were made to these regulations during the 1980s. Until 2001, FDA was responsible for approving these programs and ensuring compliance with FDA regulations.

The new regulations acknowledged that addiction is a medical disorder not amenable to one-size-fits-all treatment.

As experience with the effectiveness of methadone grew, criticism of the 1972 FDA regulations increased from physicians, who complained that the regulations placed burdens on their practice of medicine, and from addiction treatment specialists, who pointed out that proscriptive regulations failed to leave room for treatment innovation. (See comments on the new rules in their proposed form [*Federal Register* 64:39812–39814].)

The movement away from a compliance orientation and toward an accreditation model was supported by a number of reviews, including the 1997 NIH consensus development conference on Effective Treatment of Opiate Addiction and the review of 1972 FDA regulations by IOM (Institute of Medicine 1995). Interest in accreditation grew because of its emphasis on self-assessment and improvement and on integration of quality assurance and performance elements developed by expert accreditation organizations. In addition, trends in national health care fueled movement toward accreditation. Many managed care organizations require all accredited health care practitioners to demonstrate quality care. Several States grant exemptions from State licensing requirements (called "deemed status") to accredited health care facilities.

Final regulations issued by DHHS and the Substance Abuse and Mental Health Services Administration (SAMHSA) on January 17, 2001, effective May 18, 2001, govern the use of methadone and LAAM in both maintenance and detoxification treatments for opioid addiction. The 1972 FDA regulations were repealed, and a new accreditation-based regulatory system was created. The new system shifted administration and oversight from FDA to SAMHSA. The new regulations acknowledged that addiction is a medical disorder not amenable to one-size-fits-all treatment. They recognized that different patients, at different times, could need vastly different services.

Accreditation itself is a peer-review process that evaluates a treatment program against SAMHSA's opioid treatment standards and accreditation standards of SAMHSA-approved accrediting bodies (42 Code of Federal Regulations, Part 8). It includes site visits by

specialists with experience in opioid pharmacotherapy and related activities.

The new regulations establish an entirely different regulatory and oversight structure for MAT. The DEA role remains the same, but FDA's authority to approve and monitor programs has been transferred to SAMHSA. Instead of detailed proscriptive rules, the new regulations set forth general certification requirements and Federal opioid treatment standards. These are elaborated in best-practice guidelines and in accreditation "elements" (or standards) developed by the SAMHSA-approved accreditation bodies. SAMHSA has employed a series of expert panels to develop guidelines for an accreditation-based certification system. Placing detailed practice criteria in accreditation standards rather than in regulations permits SAMHSA and the accreditation bodies to update the standards as needed.

The new regulations provide that, once a program is accredited, SAMHSA uses accreditation results along with other data to determine whether the program is qualified to carry out treatment under the standards in the regulations. SAMHSA maintains oversight of accreditation elements in its review of accreditation bodies' initial and renewal applications.

The consensus panel for this TIP expects the accreditation process to result in an integrated and individualized approach to services, increased patient satisfaction, better staff recruitment, enhanced community confidence and outcomes, and improvements in quality of care. The shift to accreditation enables SAMHSA to focus its oversight efforts on improving treatment rather than ensuring that programs are meeting regulatory criteria.

States

The new Federal regulations preserve States' authority to regulate OTPs. Oversight of treatment medications remains a tripartite system involving States, DHHS/SAMHSA, and the U.S. Department of Justice/DEA.

States can monitor the same areas as Federal agencies, but State rules do not always echo Federal regulations. Some States have established medical recertification requirements for continuation of comprehensive, long-term MAT after a specified period. Other State and local requirements, such as certificates of need, zoning, and licensure, can affect the number, size, and location of OTPs. These regulations are not affected by the change in Federal regulations.

3 Pharmacology of Medications Used To Treat Opioid Addiction

In This Chapter...

Pharmacology and Pharmacotherapy

Dosage Forms

Efficacy

Side Effects

Interactions With Other Therapeutic Medications

Safety

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.

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

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

(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.)

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.

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.

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 co-administered 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 over-medication 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).

> [A]n adequate daily oral dose of methadone suppresses withdrawal and drug craving for 24 to 36 hours…

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).

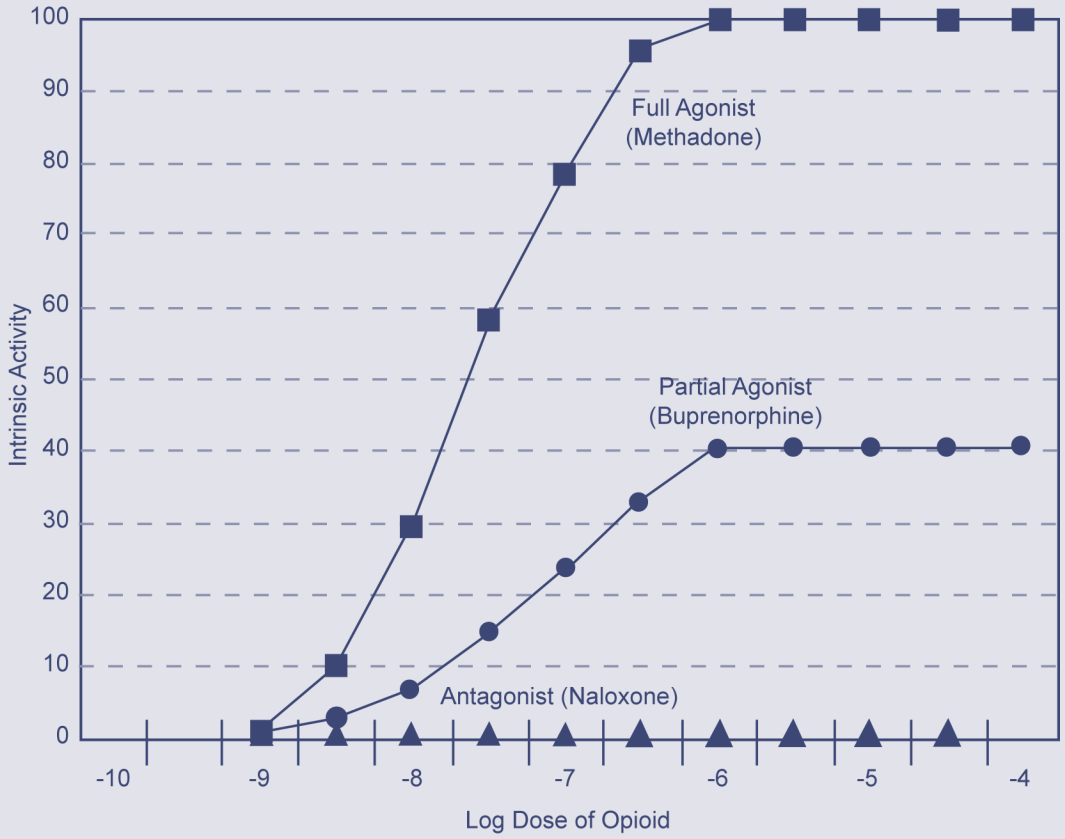
Naltrexone

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).

Exhibit 3-3

Intrinsic Activity of Full Agonist (Methadone), Partial Agonist (Buprenorphine), and Antagonist (Naloxone) Therapy



Source: Reprinted from *Drug and Alcohol Dependence* 70(Suppl.) Johnson et al. Buprenorphine: How to use it right. S59–S77, 2003*b*, with permission from Elsevier.

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.

In a…study comparing the efficacy of LAAM…, buprenorphine…, and methadone…, all three medications substantially reduced illicit opioid use.

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 vomiting
- 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
- 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

(continued on following page)

Exhibit 3-5

Reported Drug Interactions With Methadone (continued)

Agent	Effect on Methadone	Possible Mechanism	Remarks
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

*Area under the concentration-time curve.

Exhibit 3-5

Reported Drug Interactions With Methadone (continued)

Agent	Effect on Methadone	Possible Mechanism	Remarks
Nelfinavir	Decreased SMLs	Induction of CYP3A; possible induction of P-glycoprotein	Mean decrease about 55% in two patients
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

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.

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

Exhibit 3-6

Other Inducers and Inhibitors of CYP450 and CYP3A4

CYP3A4 Inducers Expected To Reduce Opioid Medication Levels		
Carbamazepine	Ethosuximide	Rifabutin
Dexamethasone	Primidone	Troglitazone
CYP3A4 Inhibitors Expected To Increase Opioid Medication Levels*		
Amiodarone	Itraconazole	Norfloxacin
Cannabinoids	Ketoconazole	Omeprazole (slight)
Clarithromycin	Metronidazole	Quinine
Erythromycin	Mibefradil	Saquinavir
Grapefruit juice	Miconazole	Troleandomycin
Indinavir	Nefazodone	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.

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.