Executive Summary

Federal statute, the Drug Addiction Treatment Act of 2000 (DATA 2000), has established a new paradigm for the medication-assisted treatment of opioid addiction in the United States (Drug Addiction Treatment Act of 2000). Prior to the enactment of DATA 2000, the use of opioid medications to treat opioid addiction was permissible only in federally approved Opioid Treatment Programs (OTPs) (i.e., methadone clinics), and only with the Schedule II opioid medications methadone and levo-alpha-acetyl-methadol (LAAM), which could only be dispensed, not prescribed.* Now, under the provisions of DATA 2000, qualifying physicians in the medical office and other appropriate settings outside the OTP system may prescribe and/or dispense Schedule III, IV, and V opioid medications for the treatment of opioid addiction if such medications have been specifically approved by the Food and Drug Administration (FDA) for that indication. (The text of DATA 2000 can be viewed at http://www.buprenorphine.samhsa.gov/fulllaw.html.)

In October 2002, FDA approved two sublingual formulations of the Schedule III opioid partial agonist medication buprenorphine for the treatment of opioid addiction. These medications, Subutex® (buprenorphine) and Suboxone® (buprenorphine/naloxone), are the first and, as of this writing, the only Schedule III, IV, or V medications to have received such FDA approval and, thus, to be eligible for use under DATA 2000. Office-based treatment with buprenorphine promises to bring opioid addiction care into the mainstream of medical practice, thereby greatly expanding access to treatment and bringing new hope to thousands.

DATA 2000 directs the Substance Abuse and Mental Health Services Administration (SAMHSA) to develop a Treatment Improvement

*Due to a number of factors, including the association of LAAM with cardiac arrhythmias in some patients, as of January 1, 2004, the sole manufacturer has ceased production of the drug.
Protocol (TIP) containing best practice guidelines for the treatment and maintenance of opioid-dependent patients. This TIP, Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction, is the product of that mandate. The TIP was developed by SAMHSA and a team of independent substance abuse treatment professionals, in consultation with the National Institute on Drug Abuse, the Drug Enforcement Administration (DEA), and FDA. The purpose of this TIP is to provide physicians with science-based clinical practice guidelines on the use of buprenorphine in the treatment of opioid addiction. The primary audience of this TIP is physicians who are interested in providing buprenorphine for the treatment of opioid addiction.

In developing this TIP, the consensus panel, made up of research and clinical experts in the field of opioid addiction treatment, recognized that while buprenorphine offers new hope to many individuals, pharmacotherapy alone is rarely sufficient for the long-term successful treatment of opioid addiction. As a result, these guidelines emphasize that optimally effective and comprehensive opioid addiction care is achieved when attention is provided to all of an individual’s medical and psychosocial comorbidities.

This TIP is composed of 6 chapters and 10 appendices, including a complete list of references (Appendix A, Bibliography). Chapter 1, Introduction, describes the basic facts regarding opioid addiction, the traditional approaches to its treatment, and the new DATA 2000 treatment paradigm.

Chapter 2, Pharmacology, addresses, in-depth, the physiology and pharmacology of opioids in general, and of buprenorphine in particular. The chapter also provides a review of the research literature regarding the safety and effectiveness of buprenorphine for the treatment of opioid addiction.

Chapter 3, Patient Assessment, summarizes an approach to screening and assessment of individuals who are addicted to opioids and who may be candidates for treatment with buprenorphine.

Chapter 4, Treatment Protocols, provides detailed protocols on the use of buprenorphine for the treatment of opioid addiction, including both maintenance and withdrawal treatment approaches.

Chapter 5, Special Populations, discusses several special populations whose circumstances require careful consideration as they begin buprenorphine treatment. Treating these special populations requires an understanding of available resources and often involves collaboration with specialists in other areas of care.

Chapter 6, Policies and Procedures, discusses legal and regulatory issues pertaining to the provision of opioid addiction treatment, including the procedures and physician qualifications necessary to obtain the required waiver under DATA 2000 to provide office-based opioid addiction treatment, recommended office practice policies and procedures, the security and confidentiality of opioid addiction care information, and the use of buprenorphine in OTPs.

The following sections summarize the content of this TIP and are grouped by chapter.

Chapter 1, Introduction

Chapter 1 provides an overview of opioid addiction in the United States today, including the historical context of the current treatment environment, the scope of the opioid addiction problem, the traditional approaches to treatment, and an introduction to buprenorphine as an opioid addiction treatment.

Opioid addiction includes not only misuse and abuse of heroin, but also the less commonly recognized issue of misuse and abuse of prescription opioid pain medications, such as hydrocodone, oxycodone, and meperidine.
Rates of addiction to prescription opioids have been increasing. The incidence of emergency department visits related to prescription opioid pain medications has more than doubled between 1994 and 2001. Recent data show that in at least 15 metropolitan areas, two or more narcotic pain medications—primarily oxycodone, hydrocodone, and codeine—were ranked among the 10 most common drugs involved in drug abuse deaths (SAMHSA 2002b).

The prevalence of heroin addiction in the United States also has been increasing and currently is believed to be the highest it has been since the 1970s. According to the Office of National Drug Control Policy (ONDCP), an estimated 810,000 to 1,000,000 individuals in the United States were addicted to heroin in the year 2000 (ONDCP 2003).

Well-run methadone maintenance programs (with programming that includes counseling services, vocational resources, referrals, and appropriate drug monitoring) have been shown to decrease opioid use and related crime, increase employment, and decrease the incidence of human immunodeficiency virus (HIV) related to needle sharing. In addition, treatment in such programs improves physical and mental health and decreases overall mortality from opioid addiction. Unfortunately, despite these results, methadone maintenance treatment system capacity has not kept pace with the rise in the prevalence of opioid addiction.

More than 20 years ago, buprenorphine was identified as a viable option for the maintenance treatment of individuals addicted to opioids. Research conducted over the past two decades has documented the safety and effectiveness of buprenorphine for this indication. The enactment of DATA 2000 has now enabled physicians in the United States to offer specifically approved forms of buprenorphine for the treatment of opioid addiction.

Chapter 2, Pharmacology

Buprenorphine has unique pharmacological properties that make it an effective and well-tolerated addition to the available pharmacological treatments for opioid addiction. This chapter reviews the general pharmacology of opioid agonists and antagonists, as well as the opioid partial agonist properties of buprenorphine.

Drugs that activate opioid receptors on neurons are termed opioid agonists. Heroin and methadone are opioid agonists. The repeated administration of opioid agonists results in dose-dependent physical dependence and tolerance. Physical dependence is manifested as a characteristic set of withdrawal signs and symptoms upon reduction, cessation, or loss of an active compound at its receptors. Addiction, conversely, is a behavioral syndrome characterized by the repeated, compulsive seeking or use of a substance, despite adverse social, psychological, and/or physical consequences. Opioid addiction often, but not always, is accompanied by tolerance, physical dependence, and opioid withdrawal symptoms.

Opioids that bind to opioid receptors but block them, rather than activating them, are termed opioid antagonists. Examples of opioid antagonists are naltrexone and naloxone.

Opioid partial agonists are drugs that activate receptors, but not to the same degree as full agonists. Increasing the dose of a partial agonist does not produce as great an effect as does increasing the dose of a full agonist. The agonist effects of a partial agonist reach a ceiling at moderate doses and do not increase from that point, even with increases in dosage. Buprenorphine is an opioid partial agonist. It is the partial agonist properties of buprenorphine that make it a safe and an effective option for the treatment of opioid addiction. Buprenorphine has sufficient agonist properties such that when it is administered to individuals who are not opioid dependent but
who are familiar with the effects of opioids, they experience subjectively positive opioid effects. These subjective effects aid in maintaining compliance with buprenorphine dosing in patients who are opioid dependent.

Buprenorphine occupies opioid receptors with great affinity and thus blocks opioid full agonists from exerting their effects. Buprenorphine dissociates from opioid receptors at a slow rate. This enables daily or less frequent dosing of buprenorphine, as infrequently as three times per week in some studies.

Buprenorphine is abusable, consistent with its agonist action at opioid receptors. Its abuse potential, however, is lower in comparison with that of opioid full agonists. A formulation containing buprenorphine in combination with naloxone has been developed to decrease the potential for abuse via the injection route. Physicians who prescribe or dispense buprenorphine or buprenorphine/naloxone should monitor for diversion of the medications.

Due to the potential for serious drug-drug interactions, buprenorphine must be used cautiously with certain other types of medications, particularly benzodiazepines, other sedative drugs, opioid antagonists, medications metabolized by the cytochrome P450 3A4 system, and opioid agonists.

Chapter 3, Patient Assessment

This chapter provides an approach to the screening, assessment, and diagnosis of opioid addiction problems, and for determining when buprenorphine is an appropriate option for treatment. The necessary first steps in the medical management of opioid addiction are (1) the use of validated screening tools to identify patients who may have an opioid use problem and (2) further assessment to clearly delineate the scope of an opioid addiction problem when one is identified. When treatment is indicated, consideration must be given to the appropriate treatment approach, treatment setting, and level of treatment intensity, based on a patient’s preferences, addiction history, presence of medical or psychiatric comorbidities, and readiness to change. Buprenorphine is a treatment option for many, but not for all.

Screening

The Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction Consensus Panel recommends that physicians periodically and regularly screen all patients for substance use and substance-related problems, not just those patients who fit the stereotypical picture of addiction. Several validated addiction screening instruments are discussed. The full text of selected screening instruments is provided in Appendix B, Assessment and Screening Instruments.

Assessment

If screening indicates the presence of an opioid use disorder, further assessment is indicated to thoroughly delineate the patient’s problem, to identify comorbid or complicating medical or emotional conditions, and to determine the appropriate treatment setting and level of treatment intensity for the patient. Complete assessment may require several office visits, but initial treatment should not be delayed during this period.

The Guidelines document provides recommendations on effective interviewing techniques and on the components of the complete history, physical examination, and recommended initial laboratory evaluation of patients with opioid addiction.

The consensus panel recommends that initial and ongoing drug screening should be used to detect or confirm the recent use of drugs (e.g., alcohol, benzodiazepines, barbiturates), which could complicate patient management. Urine screening is the most commonly used and generally most cost-effective testing method.
Diagnosis of Opioid-Related Disorders

After a thorough assessment of a patient has been conducted, a formal diagnosis can be made. As a general rule, to be considered for buprenorphine maintenance, patients should have a diagnosis of opioid dependence, as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association 2000). This diagnosis is based not merely on physical dependence on opioids but rather on opioid addiction with compulsive use despite harm. (See DSM-IV-TR diagnostic criteria in Appendix C, DSM-IV-TR Material.)

Determining Appropriateness for Buprenorphine Treatment

A detailed approach to determining the suitability of buprenorphine as a treatment option for patients with opioid addiction is included in the Guidelines. The evaluation includes determining if appropriate patient motivation exists and ruling out contraindicating medical and psychiatric comorbidities.

Patients for whom buprenorphine may be an appropriate treatment option are those who

- Are interested in treatment for opioid addiction
- Have no contraindications to buprenorphine treatment
- Can be expected to be reasonably compliant with such treatment
- Understand the benefits and risks of buprenorphine treatment
- Are willing to follow safety precautions for buprenorphine treatment
- Agree to buprenorphine treatment after a review of treatment options

Patients less likely to be appropriate candidates for buprenorphine treatment of opioid addiction in an office-based setting are individuals whose circumstances or conditions include

- Comorbid dependence on high doses of benzodiazepines or other central nervous system depressants (including alcohol)
- Significant untreated psychiatric comorbidity
- Active or chronic suicidal or homicidal ideation or attempts
- Multiple previous treatments for drug abuse with frequent relapses (except that multiple previous detoxification attempts followed by relapse are a strong indication for long-term maintenance treatment)
- Poor response to previous treatment attempts with buprenorphine
- Significant medical complications

Chapter 4, Treatment Protocols

This chapter provides detailed protocols for the use of buprenorphine in the treatment of opioid addiction. A variety of clinical scenarios are addressed, including whether patients are addicted to long- versus short-acting opioids, and whether the approach selected is maintenance treatment or medically supervised withdrawal (which must be followed by long-term drug-free or naltrexone treatment to be useful to the patient).

Maintenance Treatment

Maintenance treatment with buprenorphine for opioid addiction consists of three phases: (1) induction, (2) stabilization, and (3) maintenance. Induction is the first stage of buprenorphine treatment and involves helping patients begin the process of switching from the opioid of abuse to buprenorphine. The goal of the induction phase is to find the minimum dose of buprenorphine at which the patient discontinues or markedly diminishes use of other opioids and experiences no
Executive Summary

withdrawal symptoms, minimal or no side effects, and no craving for the drug of abuse. The consensus panel recommends that the buprenorphine/naloxone combination be used for induction treatment (and for stabilization and maintenance) for most patients. The consensus panel further recommends that initial induction doses be administered as observed treatment; further doses may be provided via prescription thereafter.

To minimize the chances of precipitated withdrawal, patients who are transferring from long-acting opioids (e.g., methadone, sustained release morphine, sustained release oxycodone) to buprenorphine should be inducted using buprenorphine monotherapy, but switched to buprenorphine/naloxone soon thereafter. Because of the potential for naloxone to precipitate withdrawal in both mother and fetus, pregnant women who are deemed to be appropriate candidates for buprenorphine treatment should be inducted and maintained on buprenorphine monotherapy.

The stabilization phase has begun when a patient is experiencing no withdrawal symptoms, is experiencing minimal or no side effects, and no longer has uncontrollable cravings for opioid agonists. Dosage adjustments may be necessary during early stabilization, and frequent contact with the patient increases the likelihood of compliance.

The longest period that a patient is on buprenorphine is the maintenance phase. This period may be indefinite. During the maintenance phase, attention must be focused on the psychosocial and family issues that have been identified during the course of treatment as contributing to a patient’s addiction.

Medically Supervised Withdrawal (“Detoxification”) Buprenorphine can be used for the medically supervised withdrawal of patients from both self-administered opioids and from opioid agonist treatment with methadone or LAAM. The goal of using buprenorphine for medically supervised withdrawal from opioids is to provide a transition from the state of physical dependence on opioids to an opioid-free state, while minimizing withdrawal symptoms (and avoiding side effects of buprenorphine).

Medically supervised withdrawal with buprenorphine consists of an induction phase and a dose-reduction phase. The consensus panel recommends that patients dependent on short-acting opioids (e.g., hydromorphone, oxycodone, heroin) who will be receiving medically supervised withdrawal be inducted directly onto buprenorphine/naloxone tablets. The use of buprenorphine (either as buprenorphine monotherapy or buprenorphine/naloxone combination treatment) to taper off long-acting opioids should be considered only for those patients who have evidence of sustained medical and psychosocial stability, and should be undertaken in conjunction and in coordination with patients’ OTPs.

Nonpharmacological Interventions Pharmacotherapy alone is rarely sufficient treatment for drug addiction. For most patients, drug abuse counseling—individual or group—and participation in self-help programs are necessary components of comprehensive addiction care. As part of training in the treatment of opioid addiction, physicians should at a minimum obtain some knowledge about the basic principles of brief intervention in case of relapse. Physicians considering providing opioid addiction care should ensure that they are capable of providing psychosocial services, either in their own practices or through referrals to reputable behavioral health practitioners in their communities. In fact, DATA 2000 stipulates that when physicians submit notification to SAMHSA to obtain the required waiver to practice opioid addiction treatment outside the OTP setting, they must attest to their capacity to refer such patients for appropriate counseling and other nonpharmacological therapies.
Treatment Monitoring

Patients and their physicians together need to reach agreement on the goals of treatment and develop a treatment plan based on the patient's particular problems and needs. During the stabilization phase, patients receiving maintenance treatment should be seen on at least a weekly basis. Once a stable buprenorphine dose is reached and toxicologic samples are free of illicit opioids, the physician may determine that less frequent visits (biweekly or longer, up to 30 days) are acceptable. During opioid addiction treatment with buprenorphine, toxicology tests for relevant illicit drugs should be administered at least monthly.

Chapter 5, Special Populations

This chapter discusses the approach to patients who have certain life circumstances or comorbid medical or behavioral conditions that warrant special consideration during the assessment and treatment of opioid addiction.

Patients With Medical Comorbidities

Patients who are addicted to opioids often have other medical comorbid problems as a consequence of both high-risk behaviors and of direct toxic effects of the active and inert ingredients in illicit drugs. In patients being treated with buprenorphine for opioid addiction, it is important to screen for and manage common comorbid medical conditions and to anticipate known and potential drug interactions.

Pregnant Women and Neonates

The scant evidence available does not show any causal adverse effects on pregnancy or neonatal outcomes from buprenorphine treatment, but this evidence is from case series, not from controlled studies. Methadone is currently the standard of care in the United States for the treatment of opioid addiction in pregnant women. Pregnant women who present for treatment of opioid addiction should be referred to specialized services in methadone maintenance treatment programs. If such specialized services are refused by a patient or are unavailable in the community, maintenance treatment with buprenorphine may be considered as an alternative.

Adolescents/Young Adults

Buprenorphine can be a useful option for the treatment of adolescents with opioid addiction problems. The treatment of addiction in adolescents, however, is complicated by a number of medical, legal, and ethical considerations. Physicians intending to treat addiction in adolescents should be thoroughly familiar with the laws in their States regarding parental consent. Physicians who do not specialize in the treatment of opioid addiction should strongly consider consulting with, or referring adolescent patients to, addiction specialists. Additionally, State child protection agencies can be a valuable resource when determining the proper disposition for adolescent patients addicted to opioids.

Geriatric Patients

Literature on the use of buprenorphine in geriatric patients is extremely limited. Due to potential differences in rates of metabolism and absorption compared to younger individuals, care should be exercised in the use of buprenorphine in geriatric patients.

Patients With Significant Psychiatric Comorbidity

The presence and severity of comorbid psychiatric conditions must be assessed prior to initiating buprenorphine treatment, and a
determination made whether referral to specialized behavioral health services is necessary. The psychiatric disorders most commonly encountered in patients addicted to opioids are other substance abuse disorders, depressive disorders, posttraumatic stress disorder, substance-induced psychiatric disorders, and antisocial and borderline personality disorder.

As with medical comorbidities, it is important to explore the medications used to treat the other psychiatric conditions. Assessing for drug interactions is a critical part of the process.

**Polysubstance Abuse**

Abuse of multiple drugs (polysubstance abuse) by individuals addicted to opioids is common. Pharmacotherapy with buprenorphine for opioid addiction will not necessarily have a beneficial effect on an individual’s use of other drugs. Care in the prescribing of buprenorphine for patients who abuse alcohol and for those who abuse sedative/hypnotic drugs (especially benzodiazepines) must be exercised because of the documented potential for fatal interactions.

**Patients With Pain**

Physicians may encounter particular complexities with regard to abuse and addiction in the use of opioids to treat patients with pain. Some patients move from needing prescription opioids for the treatment of pain to abusing them. Physicians concerned about this changing diagnostic picture now may legally use an opioid—buprenorphine—to help facilitate a controlled detoxification in order to manage the physical dependence of the patient who no longer has pain that requires an opioid, but who continues to take the opioid for its mood-altering effects.

Patients who need treatment for pain but not for addiction should be treated within the context of a medical or surgical setting. They should not be transferred to an opioid maintenance treatment program simply because they have become physically dependent on prescribed opioids in the course of medical treatment.

Patients who are being treated for addiction also may experience pain due to illness or injury unrelated to drug use. Pain in patients receiving buprenorphine treatment for opioid addiction should be treated initially with nonopioid analgesics when appropriate.

Patients maintained on buprenorphine whose acute pain is not relieved by nonopioid medications should receive the usual aggressive pain management, which may include the use of short-acting opioid pain relievers. While patients are taking opioid pain medications, the administration of buprenorphine generally should be discontinued. When restarting buprenorphine, to prevent acutely precipitating withdrawal, administration generally should not begin until sufficient time has elapsed for the opioid pain medication to have cleared from the patient’s system, as demonstrated by the onset of early withdrawal symptoms. Patients who are receiving long-acting opioids for chronic severe pain may not be good candidates for buprenorphine treatment because of the ceiling effect on buprenorphine’s analgesic properties.

**Patients Recently Discharged From Controlled Environments**

A number of issues should be considered in determining the most appropriate treatment modalities for patients with addiction who are recently released from controlled environments (e.g., prison). Intensive buprenorphine monitoring activities are required, and treating physicians may be called upon to verify and explain treatment regimens (e.g., to parole and probation officers); to document patient compliance; and to interact with the legal system, employers, and others. If an OTP alternative is available, physicians
should determine if any patient factors preclude referral.

Healthcare Professionals Who Are Addicted to Opioids

There is a substantial problem of addiction to prescription opioids among physicians and other health professionals, especially within certain specialties. Prescription opioid addiction in health professionals should be viewed as an occupational hazard of the practice of medicine. Health professionals with substance abuse disorders often require specialized, extended care.

Chapter 6, Policies and Procedures

This chapter presents information on a number of administrative and regulatory issues pertaining to the use of controlled substances in the treatment of opioid addiction that are beyond the general medico-legal responsibilities that govern most other types of medical practice. Physicians should become thoroughly familiar with these issues prior to undertaking the treatment of opioid addiction.

The DATA 2000 Waiver

To practice office-based treatment of opioid addiction under the auspices of DATA 2000, physicians must first obtain a waiver from the special registration requirements established in the Narcotic Addict Treatment Act of 1974 and its enabling regulations. To obtain a DATA 2000 waiver, a physician must submit notification to SAMHSA of his or her intent to begin dispensing and/or prescribing this treatment. The Notification of Intent form must contain information on the physician’s qualifying credentials and must contain additional certifications, including that the physician (or the physician’s group practice) will not treat more than 30 patients for addiction at any one time. Notification of Intent forms can be filled out and submitted online at the SAMHSA Buprenorphine Web site at http://www.buprenorphine.samhsa.gov. Alternatively, the form can be printed out from the site and submitted via ground mail or fax. (The site contains detailed information about buprenorphine, the DATA 2000 paradigm, and the physician waiver process.) Physicians who meet the qualifications defined in DATA 2000 are issued a waiver by SAMHSA and a special identification number by DEA.

To qualify for a DATA 2000 waiver, physicians must have completed at least 8 hours of approved training in the treatment of opioid addiction or have certain other qualifications as defined in the legislation (e.g., clinical research experience with the treatment medication, certification in addiction medicine) and must attest that they can provide or refer patients to the necessary, concurrent psychosocial services. The consensus panel recommends that all physicians who plan to practice opioid addiction treatment with buprenorphine attend a DATA 2000-qualifying 8-hour training program on buprenorphine. SAMHSA maintains a list of upcoming DATA 2000-qualifying buprenorphine training sessions on the SAMHSA Buprenorphine Web site. Additional information about DATA 2000 and buprenorphine also can be obtained by contacting the SAMHSA Buprenorphine Information Center by phone at 866-BUP-CSAT (866-287-2728) or via e-mail at info@buprenorphine.samhsa.gov.

Preparing for Office-Based Opioid Treatment

Prior to embarking on the provision of office-based addiction treatment services, medical practices that will be new to this form of care should undertake certain preparations to ensure the highest quality experience for patients, providers, and staff. Providers and practice staff should have an appropriate level of training, experience, and comfort with opioid addiction treatment. Linkages with other medical and mental health professionals
should be established to ensure continuity of
treatment and the availability of comprehen-
sive, community-based, psychosocial services.

Privacy and Confidentiality
The privacy and confidentiality of individ-
ually identifiable drug or alcohol treatment
information is protected by SAMHSA confi-
dentiality regulation Title 42, Part 2 of the
Code of Federal Regulations (42 C.F.R. Part
2). This regulation mandates that addiction
treatment information in the possession of
substance abuse treatment providers be
handled with a greater degree of confiden-
tiality than general medical information.
Among other stipulations, regulation
42 C.F.R. Part 2 requires that physicians
providing opioid addiction treatment obtain
signed patient consent before disclosing
individually identifiable addiction treat-
ment information to any third party. The
requirement for signed patient consent
extends to activities such as telephoning or
faxing addiction treatment prescriptions to
pharmacies, as this information constitutes
disclosure of the patient’s addiction treat-
ment. A sample consent form with all the
elements required by 42 C.F.R. Part 2 is
included as Appendix D, Consent to Release

Buprenorphine Use in OTPs
In May 2003, the Federal OTP regulations
(42 C.F.R. Part 8) were amended to add
Subutex® and Suboxone® to the list of
approved opioid medications that may be used
in federally certified and registered OTPs
(i.e., methadone clinics). OTPs that choose to
use Subutex® and Suboxone® in the treatment
of opioid addiction must adhere to the same
Federal treatment standards established for
all medications under 42 C.F.R. Part 8.
1 Introduction

Practical Guidelines for Physicians

Physicians are invited to use the Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction to make practical and informed decisions about the treatment of opioid addiction with buprenorphine. This document provides step-by-step guidance through the opioid addiction treatment decisionmaking process. Using the materials provided in these guidelines, physicians should be able to (1) perform initial screening and assessment of patients with opioid addiction, (2) determine the appropriateness of buprenorphine treatment for patients with opioid addiction, (3) provide treatment of opioid addiction with buprenorphine according to established protocols, (4) assess for the presence of and arrange appropriate treatment services for comorbid medical and psychosocial conditions, and (5) determine when to seek specialty addiction treatment referral or consultation.

The history of opioid addiction treatment forms an important backdrop for the decisions that physicians will make regarding their use of buprenorphine. Developing informed decisions about care should take into account the state of the art of opioid addiction treatment and ancillary services that exist to support both the patient and physician.

Historical Context

A significant breakthrough in the treatment of opioid addiction occurred with the introduction of methadone in the 1960s. Methadone maintenance proved safe and effective and enabled patients to lead functional lives—something that was often not possible using only drug-free approaches. Within a few years of its introduction, however, new laws and regulations in the United States, including the Methadone Regulations in 1972 and the Narcotic Addict Treatment Act of 1974, effectively limited methadone maintenance treatment to the context of the Opioid Treatment Program (OTP) (i.e., methadone clinic) setting. These laws and regulations established a closed distribution system for
methadone that required special licensing by both Federal and State authorities. The new system made it very difficult for physicians to use methadone to treat opioid addiction in an office setting or even in a general drug rehabilitation program. To receive methadone maintenance, patients were required to attend an OTP, usually on a daily basis. The stigma and inconvenience associated with receiving methadone maintenance in the OTP setting led, in part, to the current situation in the United States in which it is estimated that fewer than 25 percent of the individuals with opioid addiction receive any form of treatment for it (NIH Consensus Statement 1997). Another result of the closed distribution system was that most U.S. physicians were prevented from gaining experience and expertise in the treatment of opioid addiction. The Food and Drug Administration (FDA) approval of the longer acting opioid agonist levo-alpha-acetyl-methadol (LAAM) in the 1990s did little to change the situation.\(^*\)


Efforts to return opioid addiction treatment to the mainstream of medical care began to take shape and gain momentum in the 1990s. In October 2000, the Children’s Health Act of 2000 (P.L. 106-310) was enacted into law. Title XXXV of the Act provides a “Waiver Authority for Physicians Who Dispense or Prescribe Certain Narcotic Drugs for Maintenance Treatment or Detoxification Treatment of Opioid-Dependent Patients.” This part of the law is known as the Drug Addiction Treatment Act of 2000 (DATA 2000; Clark 2003).

Under the provisions of DATA 2000, qualifying physicians may now obtain a waiver from the special registration requirements in the Narcotic Addict Treatment Act of 1974, and its enabling regulations, to treat opioid addiction with Schedule III, IV, and V opioid medications that have been specifically approved by FDA for that indication, and to prescribe and/or dispense these medications in treatment settings other than licensed OTPs, including in office-based settings. On October 8, 2002, two new sublingual formulations of the opioid partial agonist buprenorphine, Subutex\(^*\) (buprenorphine) and Suboxone\(^*\) (buprenorphine/naloxone), became the first and, as of this writing, the only Schedule III, IV, or V medications to have received this FDA approval.

To qualify for a DATA 2000 waiver, physicians must have completed at least 8 hours of approved training in the treatment of opioid addiction or have certain other qualifications defined in the legislation (e.g., clinical research experience with the treatment medication, certification in addiction medicine) and must attest that they can provide or refer patients to necessary, concurrent psychosocial services. (Chapter 6 provides a detailed discussion of the qualifying criteria defined in DATA 2000 and of the procedure for obtaining a waiver.)

Physicians who obtain DATA 2000 waivers may treat opioid addiction with Subutex\(^*\) or Suboxone\(^*\) in any appropriate clinical settings in which they are credentialed to practice medicine. The promise of DATA 2000 is to help destigmatize opioid addiction treatment and to enable qualified physicians to manage

---

\(^*\) Due to a number of factors, including the association of LAAM with cardiac arrhythmias in some patients, as of January 1, 2004, the sole manufacturer has ceased production of the drug.
opioid addiction in their own practices, thus greatly expanding currently available treatment options and increasing the overall availability of treatment.

**New Guidelines**

The new guidelines provide information about the medical use of buprenorphine, based on (1) the evidence available from buprenorphine studies and (2) clinical experience using buprenorphine in the treatment of opioid addiction. The guidelines are as complete as the expert members of the Consensus Panel on Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction could make them and should provide a reasonable basis for current best practices in the area. Physicians should note that the guidelines are not intended to fully address all possible issues that can arise in the treatment of patients who are addicted to opioids. Some issues cannot be substantively addressed in the guidelines because of the lack of controlled studies and the limited U.S. experience using buprenorphine in office-based settings. Physicians are urged to seek the advice of knowledgeable addiction specialists if their questions are not answered fully by the guidelines, and should keep themselves aware of training and information on the use of buprenorphine that becomes available after the publication of this document. Such information will be posted regularly on the SAMHSA Buprenorphine Web site at http://www.buprenorphine.samhsa.gov.

**Opioid Addiction Today in the United States**

**Opioid Addiction**

Opioid addiction is a neurobehavioral syndrome characterized by the repeated, compulsive seeking or use of an opioid despite adverse social, psychological, and/or physical consequences.

Addiction is often (but not always) accompanied by physical dependence, a withdrawal syndrome, and tolerance. Physical dependence is defined as a physiological state of adaptation to a substance, the absence of which produces symptoms and signs of withdrawal. Withdrawal syndrome consists of a predictable group of signs and symptoms resulting from abrupt removal of, or a rapid decrease in the regular dosage of, a psychoactive substance. The syndrome is often characterized by overactivity of the physiological functions that were suppressed by the drug and/or depression of the functions that were stimulated by the drug. Tolerance is a state in which a drug produces a diminishing biological or behavioral response; in other words, higher doses are needed to produce the same effect that the user experienced initially.

It is possible to be physically dependent on a drug without being addicted to it, and conversely, it is possible to be addicted without being physically dependent (Nelson et al. 1982). An example of physical dependence on opioids without addiction is a patient with cancer who becomes tolerant of and physically dependent on opioids prescribed to control pain. Such a patient may experience withdrawal symptoms with discontinuation of the usual dose but will not experience social, psychological, or physical harm from using the drug and would not seek out the drug if it were no longer needed for analgesia (Jacox et al. 1994). An example of addiction to opioids without physical dependence is a patient addicted to oxycodone who has been recently detoxified from the drug. In this situation, the patient may no longer be suffering from withdrawal symptoms or tolerance but may continue to crave an opioid high and will invariably relapse to active opioid abuse without further treatment.

Factors contributing to the development of opioid addiction include the reinforcing properties and availability of opioids, family and peer influences, sociocultural environment, personality, and existing psychiatric disorders. Genetic heritage appears to
influence susceptibility to alcohol addiction and, possibly, addiction to tobacco and other drugs as well (Goldstein 1994).

Addiction Rates

According to the January 2003 Drug Abuse Warning Network (DAWN) Report published by SAMHSA’s OAS, the incidence of abuse of prescription opioid pain medications (also known as narcotic analgesics), such as hydrocodone, oxycodone, meperidine, and propoxyphene, has risen markedly in recent years (Crane 2003). The incidence of emergency department (ED) visits related to these medications has been increasing since the 1990s and has more than doubled between 1994 and 2001 (Crane 2003). In 2001, there were an estimated 90,232 ED visits related to opioid analgesic abuse, a 117 percent increase since 1994. Nationally, opioid analgesics were involved in 14 percent of all drug-abuse-related ED visits in 2001 (SAMHSA 2002b). According to the DAWN Mortality Data Report for 2002 (SAMHSA 2002c), hydrocodone ranked among the 10 most common drugs related to deaths in 18 cities, including Detroit (63), Las Vegas (46), Dallas (36), New Orleans (33), and Oklahoma City (31). Oxycodone ranked among the 10 most common drugs related to deaths in 19 cities, including Philadelphia (88), Baltimore (34), Boston (34), Phoenix (34), and Miami (28).

The rise of heroin use appears to be a nationwide phenomenon in the United States. Historically, heroin purity has been less than 10 percent. By the late 1990s, however, purity was between 50 and 80 percent. The increase in purity has made heroin easier to use by noninjection routes, such as snorting and smoking. Because individuals can become addicted to or overdose from heroin taken via any route, the increase in the type and number of routes used has led to a rise in new cases of heroin addiction across all sociodemographic categories.

Many addicted individuals may switch to the injection route as their heroin use continues to increase, or if heroin purity should decrease again. An increase in rates of injection drug use would have a significant effect on the incidence of human immunodeficiency virus (HIV) infection, hepatitis B and C, and other infectious diseases.

The rise of heroin use appears to be a nationwide phenomenon in the United States. Heroin overdose deaths have risen sharply, as have ED admissions involving heroin. The most recent data on such ED admissions come from SAMHSA’s DAWN reports, which can be accessed via the Web at the following sites: http://dawninfo.samhsa.gov/ or http://www.nida.nih.gov/CEWG/DAWN.html.

Current State of Opioid Addiction Treatment

There are two main modalities for the treatment of opioid addiction: pharmacotherapy and psychosocial therapy. Pharmacotherapies now available for opioid addiction include (1) agonist maintenance with methadone; (2) partial-agonist maintenance with buprenorphine or buprenorphine plus naloxone; (3) antagonist maintenance using naltrexone; and (4) the use of antiwithdrawal (“detoxification”) agents (e.g., methadone, buprenorphine, and/or clonidine) for brief periods, and in tapering doses, to facilitate entry into drug-free or antagonist treatment.
Psychosocial approaches (e.g., residential therapeutic communities), mutual-help programs (e.g., Narcotics Anonymous), and 12-Step- or abstinence-based treatment programs are important modalities in the treatment of addiction to heroin and other opioids, either as stand-alone interventions or in combination with pharmacotherapy.

In 2003, more than 200,000 individuals in the United States were maintained on methadone or LAAM (SAMHSA 2002a). Although precise data are difficult to obtain, it is estimated that fewer than 5,000 individuals are maintained on naltrexone for opioid addiction. The number of individuals in 12-Step programs is unknown because of the undisclosed nature of the programs and their assurance of anonymity. The number of patients in residential therapeutic community treatment who identify opioids as their primary drugs of abuse is conservatively estimated at 3,000-4,000. (This estimate is derived from various sources, both published, such as Drug Abuse Treatment Outcome Studies [DATOS], and unpublished, such as Therapeutic Communities of America reports, found at http://www.drugabuse.gov/about/organization/despr/DATOS.html and http://www.therapeuticcommunitiesofamerica.org.)

Current Pharmacotherapy Treatment Options for Opioid Addiction

Three traditional types of pharmacotherapy for opioid addiction are described briefly in this section: (1) agonist treatment (e.g., methadone pharmacotherapy), (2) antagonist treatment (e.g., naltrexone), and (3) the use of these and other agents (e.g., clonidine) to help withdrawal from opioid drugs as a means of entry into treatment. A discussion of the new treatment option using buprenorphine follows.

Agonist Pharmacotherapy

Methadone is the most commonly used medication for opioid addiction treatment in the United States. Well-run OTPs—with appropriate drug monitoring, counseling services (individual, group, family), and vocational resources and referrals—have been demonstrated to decrease heroin use and related crime, increase employment, improve physical and mental health (McLellan et al. 1993), and markedly reduce mortality (see the forthcoming TIP Medication-Assisted Treatment for Opioid Addiction [CSAT in development†]), as well as the incidence of needle sharing (Metzger et al. 1991) and HIV transmission (Metzger et al. 1993). Methadone suppresses opioid withdrawal, blocks the effects of other opioids, and decreases craving for opioids.

Antagonist Pharmacotherapy

Naltrexone is an opioid antagonist that blocks the effects of heroin and most other opioids. It does not have addictive properties or produce physical dependence, and tolerance does not develop. It has a long half-life, and its therapeutic effects can last up to 3 days. Naltrexone is not a stigmatized treatment. It also decreases the likelihood of alcohol relapse when used to treat alcohol dependence.

From a purely pharmacological point of view, naltrexone would appear to have the properties of a useful medication for the treatment of opioid addiction. Its usefulness in the treatment of opioid addiction, however, has been limited because of certain disadvantages. First, many addicted patients are not interested in taking naltrexone because, unlike methadone and LAAM, it has no opioid

---

1Some TIPs are available online at http://www.kap.samhsa.gov/products/manuals/index.htm. Others can be ordered from the National Clearinghouse for Alcohol and Drug Information (NCADI) by accessing its electronic catalog http://store.health.org/catalog/ or by calling 1-800-729-6686. Up to five free hard copies may be ordered using the NCADI order number.
agonist effects; patients continue to experience cravings and are thereby not motivated to maintain adherence to the medication regimen. Second, a patient addicted to opioids must be fully withdrawn for up to 2 weeks from all opioids before beginning naltrexone treatment. Unfortunately, during this withdrawal period, many patients relapse to use of opioids and are unable to start on naltrexone. Furthermore, once patients have started on naltrexone, it may increase the risk for overdose death if relapse does occur.

Naltrexone has demonstrated some utility among subgroups of addicted patients with strong motivation and psychosocial support for treatment and medication adherence (e.g., healthcare professionals, business executives, younger patients, patients involved in the criminal justice system). Because most addicted patients will not voluntarily take naltrexone, however, the number of individuals maintained on it continues to be low. Research is under way on a number of sustained-release, injectable forms of naltrexone in an effort to increase adherence, particularly in the early stages of treatment.

Agents Used To Assist With Withdrawal From Opioid Drugs

Medically supervised withdrawal (detoxification) from opioids is an initial component of certain treatment programs but, by itself, does not constitute treatment of addiction. A variety of agents and methods are available for medically supervised withdrawal from opioids. These include methadone dose-reduction, the use of clonidine and other alpha-adrenergic agonists to suppress withdrawal signs and symptoms, and rapid detoxification procedures (e.g., with a combination of naltrexone or naloxone and clonidine and, more recently, buprenorphine). Each of these methods has strengths and weaknesses. When used properly, various pharmacological agents can produce safe and less uncomfortable opioid withdrawal. As a result of the increasing purity of street heroin, however, physicians are reporting more difficulty managing patients with the use of clonidine and other alpha-adrenergic agonists during withdrawal.

Unfortunately, the majority of individuals addicted to opioids relapse to opioid use after withdrawal, regardless of the withdrawal method used. Too often, physicians and facilities use dose-reduction and withdrawal in isolation without adequate arrangements for the appropriate treatment and support services that decrease the likelihood of relapse and that are usually necessary for long-term recovery. (For more information about agents used to assist with withdrawal, see the forthcoming TIP Medication-Assisted Treatment for Opioid Addiction [CSAT in development].)

Buprenorphine: A New Treatment Option for Opioid Addiction

Buprenorphine’s pharmacological and safety profile (see chapter 2) makes it an attractive treatment for patients addicted to opioids as well as for the medical professionals treating them. Buprenorphine is a partial agonist at the mu opioid receptor and an antagonist at the kappa receptor. It has very high affinity and low intrinsic activity at the mu receptor and will displace morphine, methadone, and other opioid full agonists from the receptor. Its partial agonist effects imbue buprenorphine with several clinically desirable pharmacological properties: lower abuse potential, lower level of physical dependence (less withdrawal discomfort), a ceiling effect at higher doses, and greater safety in overdose compared with opioid full agonists.

At analgesic doses, buprenorphine is 20–50 times more potent than morphine. Because of its low intrinsic activity at the mu receptor, however, at increasing doses, unlike a full opioid agonist, the agonist effects of buprenorphine reach a maximum and do not continue to increase linearly with increasing doses of
the drug—the ceiling effect. One consequence of the ceiling effect is that an overdose of buprenorphine is less likely to cause fatal respiratory depression than is an overdose of a full mu opioid agonist.

In the pharmacotherapy of opioid addiction, buprenorphine, as a partial opioid agonist, can be thought of as occupying a midpoint between opioid full agonists (e.g., methadone, LAAM) and opioid antagonists (e.g., naltrexone, nalmefene). It has sufficient agonist properties such that individuals addicted to opioids perceive a reinforcing subjective effect from the medication, often described in terms of “feeling normal.” In higher doses, and under certain circumstances, its antagonist properties can cause the precipitation of acute withdrawal if administered to an individual who is physically dependent on opioids and maintained on a sufficient dose of a full agonist. In this scenario, buprenorphine can displace the full agonist from the mu receptors, yet not provide the equivalent degree of receptor activation, thereby leading to a net decrease in agonist effect and the onset of withdrawal. (See chapter 2 for more details on such effects.) Furthermore, because of the high affinity of buprenorphine for the opioid receptor, this precipitated abstinence syndrome may be difficult to reverse. Buprenorphine produces a blockade to subsequently administered opioid agonists in a dose-responsive manner. This effect makes the drug particularly appealing to well-motivated patients, as it provides an additional disincentive to continued opioid use.

Buprenorphine can produce euphoria, especially if it is injected. Buprenorphine does produce physical dependence, although it appears to do so to a lesser degree than do full opioid agonists, and it appears to be easier to discontinue at the end of medication treatment.

Buprenorphine has several pharmaceutical uses. It is a potent analgesic, available in many countries as a 0.3–0.4 mg sublingual tablet (Temgesic®). Until 2002, the only form of buprenorphine approved and marketed in the United States was the parenteral form for treatment of pain (Buprenex®). In 2002, two sublingual tablet formulations of buprenorphine were approved by FDA as opioid addiction treatment medications: buprenorphine alone (Subutex®) and a combination tablet containing buprenorphine plus naloxone in a 4:1 ratio (Suboxone®). Both of these tablets are Schedule III opioids and therefore eligible for use in the treatment of opioid addiction under DATA 2000. Figure 1–1 shows the dosage forms of buprenorphine currently available in the United States. Note that, as of the date of this publication, Subutex® and Suboxone® are the only forms of buprenorphine that are indicated and can be legally used for the treatment of opioid addiction in the United States—neither Buprenex® nor its generic equivalent can be used legally to treat opioid addiction.

Many of the large clinical studies of buprenorphine in the treatment of opioid addiction in the United States have been conducted under the joint sponsorship of the National Institute on Drug Abuse (NIDA) and Reckitt Benckiser, the company holding the buprenorphine patent. The most extensive clinical experience with buprenorphine used for treatment of opioid addiction is in France, where the medication has been available for office-based treatment of opioid addiction since February 1996. In France, buprenorphine can be prescribed for...
maintenance treatment by both addiction specialists and general practitioners. It is estimated that close to 70,000 patients are currently receiving maintenance treatment with buprenorphine in France.

Buprenorphine doses studied for opioid addiction treatment have ranged from 1–2 mg to 16–32 mg, depending upon the formulation (solution versus tablet), with duration of treatment lasting from a few weeks to years. Using the outcome measures of illicit opioid use, retention in treatment, and assessment for adverse events, studies have shown that buprenorphine treatment reduces opioid use, retains patients in treatment, has few side effects, and is acceptable to most patients (Johnson 1992; Johnson 2000; Ling 1996; Ling 1998; O’Connor 2000).

Although buprenorphine has been abused and injected by individuals addicted to opioids in countries where the sublingual tablet is available as an analgesic, its abuse potential appears substantially less than that of full opioid agonists. To reduce the potential for abuse even further, the sublingual tablet dosage form combining buprenorphine with naloxone was developed by NIDA and Reckitt Benckiser.

The buprenorphine/naloxone combination tablet appears to have reduced abuse potential compared with buprenorphine alone when studied in opioid-dependent populations. It works on the principle that naloxone is approximately 10–20 times more potent by injection than by the sublingual route. Therefore, if the combination is taken sublingually,

<table>
<thead>
<tr>
<th>Medication</th>
<th>Trade Name</th>
<th>Dosage Form(s)</th>
<th>Indication</th>
<th>Company</th>
<th>FDA-Approved for Opioid Addiction Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>Subutex®</td>
<td>2- or 8-mg sublingual tablets</td>
<td>Opioid addiction</td>
<td>Reckitt Benckiser</td>
<td>Yes</td>
</tr>
<tr>
<td>Buprenorphine/naloxone</td>
<td>Suboxone®</td>
<td>2- or 8-mg sublingual tablets with buprenorphine/naloxone in 4:1 ratio</td>
<td>Opioid addiction</td>
<td>Reckitt Benckiser</td>
<td>Yes</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Buprenex®</td>
<td>Injectable ampules</td>
<td>Moderate-to-severe pain</td>
<td>Reckitt Benckiser</td>
<td>No</td>
</tr>
<tr>
<td>Buprenorphine injectable</td>
<td>Buprenorphine Injectable ampules (generic)</td>
<td>Injectable ampules</td>
<td>Moderate-to-severe pain</td>
<td>Abbott Laboratories</td>
<td>No</td>
</tr>
</tbody>
</table>
as directed, the small amount of naloxone available should not interfere with the desired effects of buprenorphine. If the combination form is dissolved and injected by an individual physically dependent on opioids, however, the increased bioavailability of naloxone via the parenteral route should precipitate an opioid withdrawal syndrome.

Summary and Overview of the Guidelines

Buprenorphine as a medication, and the circumstances under which it can be used, together provide a new means to treat opioid addiction in the United States. Buprenorphine’s usefulness stems from its unique pharmacological and safety profile, which encourages treatment adherence and reduces the possibilities for both abuse and overdose. Because buprenorphine has unusual pharmacological properties, physicians may want to consult with addiction specialists to understand more fully the partial opioid agonist effects of buprenorphine and how these properties are useful in opioid addiction treatment. Although buprenorphine offers special advantages to many patients, it is not for everyone. Care must be taken to assess each patient fully and to develop a realistic treatment plan for each patient accepted for buprenorphine treatment.

Chapter 2 provides additional information on the pharmacological properties of opioids in general and of buprenorphine in particular, along with safety considerations (especially drug interactions). Chapter 3 provides important screening guidelines and specific tools for initially assessing patients. Chapter 4 provides a step-by-step guide for initiating and maintaining treatment and developing a treatment plan. Chapter 5 provides guidelines on the use of buprenorphine with special populations, including, for example, pregnant women, adolescents, individuals leaving controlled environments (e.g., prison), and healthcare professionals who are addicted. Chapter 6 provides important information on policies and procedures relevant to opioid addiction treatment under the DATA 2000 paradigm. References (see appendix A) are provided so that physicians can consult them to develop the best fit for each patient’s treatment plan.

As of the date of this publication, Subutex® (buprenorphine) and Suboxone® (buprenorphine/naloxone) are the only forms of buprenorphine that have received FDA approval for use in opioid addiction treatment. Throughout the remainder of this document, use of the term buprenorphine will apply to both sublingual formulations of buprenorphine and to any similarly formulated generic products that may receive FDA approval in the future. When information is presented that is specific to either the buprenorphine monotherapy formulation or to the buprenorphine/naloxone combination, the specific designation will be employed, either by the trade name of the currently approved products (which will be meant to include any similar generic equivalents that may be approved in the future) or by the full formula designation.

The consensus panel notes that these guidelines represent one approach, but not necessarily the only approach, to the treatment of opioid addiction with buprenorphine. The panel considers these guidelines not as inflexible rules that must be applied in every instance, but rather as guidance to be considered in the evaluation and treatment of individual patients. Because each patient is unique, and because scientific knowledge and clinical best practices change over time, the application of these guidelines to the treatment of an individual patient must be informed by the needs of the patient, the changing body of scientific and clinical knowledge, and the clinical judgment of the physician.
2 Pharmacology

Overview

Five topics related to the general pharmacology of opioids are reviewed in the first part of this chapter: (1) opioid receptors; (2) functions of opioids at receptors; (3) consequences of repeated administration and withdrawal of opioids; (4) the affinity, intrinsic activity, and dissociation of opioids from receptors; and (5) general characteristics of abused opioids. These topics are followed by a detailed review of the general and applied pharmacology of buprenorphine.

General Opioid Pharmacology

Opioid Receptors

Opioid receptors are molecules on the surfaces of cells to which opioid compounds attach and through which they exert their effects. Different types of opioid receptors are present in the brain. The receptor most relevant to opioid abuse and treatment is the mu receptor. It is through activation of the mu receptor that opioids exert their analgesic, euphorogenic, and addictive effects. The roles of other types of opioid receptors in the brain (that is, non-mu opioid receptors) in the addictive process are not well defined.

The Functions of Opioids at Receptors

Opioids can interact with receptors in different ways. For purposes of this discussion, three types of drug/receptor interactions are described: agonists (or full agonists), antagonists, and partial agonists.

Full Agonists

Drugs that activate receptors in the brain are termed agonists. Agonists bind to receptors and turn them on—they produce an effect
in the organism. Full mu opioid agonists activate mu receptors. Increasing doses of full agonists produce increasing effects until a maximum effect is reached or the receptor is fully activated. Opioids with the greatest abuse potential are full agonists (e.g., morphine, heroin, methadone, oxycodone, hydromorphone).

**Antagonists**

Antagonists also bind to opioid receptors, but instead of activating receptors, they effectively block them. Antagonists do not activate receptors, and they prevent receptors from being activated by agonist compounds. An antagonist is like a key that fits in a lock but does not open it and prevents another key from being inserted to open the lock. Examples of opioid antagonists are naltrexone and naloxone.

**Partial Agonists**

Partial agonists possess some of the properties of both antagonists and full agonists. Partial agonists bind to receptors and activate them, but not to the same degree as do full agonists. At lower doses and in individuals who are not dependent on opioids, full agonists and partial agonists produce effects that are indistinguishable. As doses are increased, both full and partial agonists produce increasing effects. At a certain point, however, as illustrated in figure 2–1, the increasing effects of partial agonists reach maximum levels and do not increase further, even if doses continue to rise—the ceiling effect. The figure represents any effect mediated by mu opioid receptors (e.g., analgesia, euphoria, respiratory depression). As higher doses are reached, partial agonists can act like antagonists—occupying receptors but not activating them (or only partially activating them), while at the same time displacing or blocking full agonists from receptors. Buprenorphine is an example of a mu opioid partial agonist, and its properties as such are discussed in detail below.

**Consequences of Repeated Administration and Withdrawal of Opioid Drugs**

The repeated administration of a mu opioid agonist results in tolerance and dose-dependent physical dependence. Tolerance is characterized by a decreased subjective and objective response to the same amount of opioids used over time or by the need to keep increasing the amount used to achieve the desired effect. In the case of abuse or addiction, the desired effect typically is euphoria. Physical dependence is manifested as a characteristic set of withdrawal signs and symptoms in response to reduction, cessation, or loss of the active compound at receptors (withdrawal syndrome).

Typical signs and symptoms of the opioid withdrawal syndrome include lacrimation, diarrhea, rhinorrhea, piloerection, yawning, cramps and aches, pupillary dilation, and sweating. Not all of these signs and symptoms are necessarily present in any single individual experiencing the opioid withdrawal syndrome. Withdrawal, characterized by marked distress, may include drug craving and drug seeking and is frequently associated with relapse to drug use in a patient with opioid addiction. In an individual who otherwise is in good general health (e.g., with no history of significant cardiovascular disease), opioid withdrawal is not life threatening. Patients with cardiovascular disease or other severe conditions will need comanagement involving the appropriate specialist, as well as consultation with an addiction specialist.

Two types of withdrawal are associated with mu opioid agonists: spontaneous withdrawal and precipitated withdrawal.

**Spontaneous Withdrawal**

Spontaneous withdrawal can occur when an individual who is physically dependent on mu agonist opioids (e.g., has been using...
opioids on a daily basis) suddenly discontinues that opioid use. It also can occur if an individual who is physically dependent markedly decreases his or her daily opioid use.

In an individual who is physically dependent on heroin, spontaneous withdrawal usually begins 6–12 hours after the last dose and peaks in intensity 36–72 hours after the last use. The spontaneous withdrawal syndrome from heroin lasts approximately 5 days, although a milder, protracted withdrawal may last longer. Other short-acting opioids, such as oxycodone and hydrocodone, have kinetic profiles that are similar to heroin, and the time course of spontaneous withdrawal for these agents should be similar to that documented for heroin. Opioids with longer half-lives have a longer period before the onset of spontaneous withdrawal (e.g., 24–72 hours for methadone) and a longer period before peak withdrawal is experienced.

**Precipitated Withdrawal**

Precipitated withdrawal also occurs in individuals who are physically dependent on mu agonist opioids. Precipitated withdrawal usually occurs when an individual physically dependent on opioids is administered an opioid antagonist. In an individual who is not physically dependent upon opioids, the acute administration of an antagonist typically produces no effects. In an individual who is physically dependent on opioids, however, an antagonist produces a syndrome of withdrawal.
that is qualitatively similar to that seen with spontaneous withdrawal (although the onset is faster and the syndrome is shorter, depending on the half-life of the antagonist). One way to conceptualize precipitated withdrawal is that the antagonist displaces agonists from receptors, but because the antagonist does not activate the receptor, there is a net decrease in agonist effect, resulting in withdrawal.

It is also possible for partial agonists to precipitate withdrawal. If an individual who is physically dependent on opioids receives an acute dose of a partial agonist, the partial agonist can displace the full agonist from the receptors yet not activate the receptors as much as the full agonist had. The net effect would be a decrease in agonist effect and a precipitated withdrawal syndrome. Precipitated withdrawal with a partial agonist is more likely to occur in an individual who has a high level of physical dependence (e.g., high use of opioids each day), who takes the partial agonist soon after a dose of full agonist, and/or who takes a high dose of the partial agonist. These points, discussed in more detail below, are directly relevant to the initiation of buprenorphine treatment.

Affinity, Intrinsic Activity, and Dissociation

The strength with which a drug binds to its receptor is termed its affinity. The degree to which a drug activates its receptors is termed its intrinsic activity. Affinity for a receptor and activation of the receptor are two different qualities of a drug. A drug can have high affinity for a receptor but not activate the receptor (e.g., an antagonist). Mu opioid agonists, partial agonists, and antagonists can vary in their affinity.

In addition to variations in affinity and intrinsic activity, drugs also vary in their rate of dissociation from receptors. Dissociation is a measure of the disengagement or uncoupling of the drug from the receptor. Dissociation is not the same as affinity—a drug can have high affinity for a receptor (it is difficult to displace it from the receptor with another drug once the first drug is present), but it still dissociates or uncouples from the receptor with some regularity. Buprenorphine’s slow dissociation contributes to its long duration of action.

Characteristics of Abused Drugs

The rate of onset of the pharmacological effects of a drug, and thereby its abuse potential, is determined by a number of factors. Important among these are the drug’s route of administration, its half-life, and its lipophilicity (which determines how fast the drug reaches the brain). A faster route of drug administration (e.g., injection, smoking), a shorter half-life, and a faster onset of action all are associated with a higher abuse potential of a drug. With all classes of drugs of abuse, it has been shown that the likelihood of abuse is related to the ease of administration, the cost of the drug, and how fast the user experiences the desired results after the drug’s administration. In this respect, heroin is highly abusable, as it currently is inexpensive; can be snorted, smoked, or injected; and produces a rapid euphoricogenic response.

Pharmacology of Buprenorphine

Overview

Buprenorphine is a thebaine derivative that is legally classified as a narcotic. It is available in numerous countries for use as an analgesic. When used as an analgesic, buprenorphine is
usually given by injection, via a sublingual tablet, or as a transdermal patch, and doses are relatively low (compared with doses used in the treatment of opioid addiction). The typical analgesic dose of buprenorphine is 0.3–0.6 mg (intramuscular or intravenous), and its analgesic effects last about 6 hours.

Buprenorphine is a partial agonist that exerts significant actions at the mu opioid receptor. As reviewed in the previous section, however, its maximal opioid effects are less than that of full agonists, and reach a ceiling where higher doses do not result in increasing effect. Because it is a partial agonist, higher doses of buprenorphine can be given with fewer adverse effects (e.g., respiratory depression) than are seen with higher doses of full agonist opioids. Past a certain point, dose increases of buprenorphine do not further increase the pharmacological effects of the drug but do increase its duration of withdrawal suppression and opioid blockade.

At low doses, buprenorphine is many times more potent than morphine. Individuals who are not dependent on opioids but who are familiar with the effects of opioids experience a subjectively positive opioid effect when they receive an acute dose of buprenorphine. These subjective effects aid in maintaining compliance with buprenorphine dosing in patients who are addicted to opioids.

**Affinity, Intrinsic Activity, and Dissociation**

Buprenorphine has high affinity for, but low intrinsic activity at, mu receptors. Buprenorphine displaces morphine, methadone, and other full opioid agonists from receptors. It also can block the effects of other opioids (Bickel et al. 1988; Rosen et al. 1994; Strain et al. 2002). Because of buprenorphine’s higher affinity for the mu receptor, full agonists cannot displace it and therefore will not exert an opioid effect on receptors already occupied by buprenorphine. This effect is dose related, as shown by Comer et al. (2001) in a study demonstrating that the 16-mg dose of the sublingual buprenorphine-alone tablet was more effective than the 8-mg dose in blocking the reinforcing effects of heroin. Similarly, it is difficult for opioid antagonists (e.g., naloxone) to displace buprenorphine and precipitate withdrawal.

Buprenorphine has a slow dissociation rate from the mu opioid receptor, which gives rise to its prolonged suppression of opioid withdrawal and blockade of exogenous opioids. This enables buprenorphine dosing to occur on a less frequent basis than full opioid agonists (Amass et al. 1994a,b, 1998, 2000, 2001). Buprenorphine can be given as infrequently as three times per week (Amass et al. 2001; Perez de los Cobos et al. 2000; and Schottenfeld et al. 2000). Buprenorphine’s effectiveness as a medication for the treatment of opioid addiction on a daily or less-than-daily basis contrasts with its relatively short duration of action as an analgesic.

**Bioavailability**

Buprenorphine has poor gastrointestinal (GI) bioavailability (Brewster et al. 1981; Walter and Inturrisi 1995), and fair sublingual bioavailability. (See figure 2–2.) FDA-approved formulations of the drug for treatment of opioid addiction are in the form of sublingual tablets that are held under the tongue and absorbed through the sublingual mucosa. Studies of sublingually administered buprenorphine have employed either an alcohol-based solution or a tablet formulation of the drug. Confusion may result when reviewing the literature on the effectiveness of buprenorphine at various doses because most early trials and clinical studies of buprenorphine were performed with a sublingually administered liquid preparation, whereas the oral formulations marketed in the United States are sublingual tablets. Studies have shown that the bioavailability of buprenorphine in sublingual tablet form is significantly less than via sublingual liquid solution—about 50–70 percent that of the liquid form (Nath et al. 1999; Schuh and Johanson 1999), so the dosages of buprenorphine sublingual tablets
Bioavailability of Buprenorphine

<table>
<thead>
<tr>
<th>Route of Administration</th>
<th>Buprenorphine Bioavailability Relative to Intravenous Route of Administration</th>
<th>Buprenorphine Bioavailability Relative to Intramuscular Route of Administration</th>
<th>Buprenorphine Bioavailability Relative to Sublingual Solution Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravenous</td>
<td>100%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Intramuscular</td>
<td>70%</td>
<td>100%</td>
<td>—</td>
</tr>
<tr>
<td>Sublingual Solution</td>
<td>49%</td>
<td>70%</td>
<td>100%</td>
</tr>
<tr>
<td>Sublingual Tablet</td>
<td>29%</td>
<td>42%</td>
<td>50–70%</td>
</tr>
</tbody>
</table>

Abuse Potential

Abuse of buprenorphine has been reported to occur via the sublingual and intranasal routes but primarily via diversion of sublingual tablets to the injection route. In a study from France (Obadia et al. 2001), sublingual, buprenorphine-only tablets (Subutex®), marketed for the treatment of opioid addiction, were diverted to the injection route.

Laboratory studies with inpatient subjects have examined the effects of buprenorphine relevant to abuse potential in two populations: (1) subjects who have a history of opioid abuse but are not physically dependent on opioids, and (2) subjects who are physically dependent on opioids.

Abuse Potential in Nonphysically Dependent Opioid Users

In nonphysically dependent opioid users, acute parenteral doses of buprenorphine produce typical mu agonist opioid effects (e.g., pupillary constriction, mild euphoria), suggesting that this population could abuse...
buprenorphine (Jasinski et al. 1978, 1989; Pickworth et al. 1993). Similar effects can occur in this population when buprenorphine is administered via other routes, including the sublingual route (Jasinski et al. 1989; Johnson et al. 1989; Walsh et al. 1994). Strain et al. (2000) recently reconfirmed the opioid-like effects of sublingually administered buprenorphine in this population. These researchers further found that, in nondependent subjects, the addition of naloxone (in the buprenorphine/naloxone combination tablet) did not attenuate buprenorphine's opioid effects via the sublingual route. The onset of effects via the sublingual route is slower than that seen with parenteral administration, suggesting that the abuse potential by this route is lower than via the parenteral route.

Abuse Potential in Physically Dependent Opioid Users

The abuse potential of buprenorphine in individuals who are physically dependent on opioids varies as a function of three factors: (1) level of physical dependence, (2) time interval between administration of the full agonist and of buprenorphine, and (3) the dose of buprenorphine administered.

Level of Physical Dependence. In individuals with a high level of physical dependence (e.g., those using substantial amounts of opioids on a daily basis), buprenorphine may precipitate withdrawal when taken during the time of opioid intoxication or receptor occupancy. The relationship between level of physical dependence and buprenorphine-related precipitated withdrawal has been investigated primarily in subjects maintained on methadone. For example, patients maintained on 60 mg of methadone daily can experience precipitated withdrawal from acute doses of sublingual buprenorphine (Walsh et al. 1995). Conversely, in individuals with a low level of physical dependence (e.g., patients maintained on <30 mg per day of methadone), buprenorphine could produce opioid agonist effects, thus suggesting a potential for abuse.

Time Interval. The abuse potential of buprenorphine in opioid-dependent individuals also varies as a function of the time interval between the dose of agonist and the dose of buprenorphine. At relatively short time intervals (e.g., 2 hours after a dose of methadone), buprenorphine can precipitate withdrawal— even when the level of physical dependence is relatively low (Strain et al. 1995). At longer time intervals, it becomes more likely that buprenorphine will exhibit either no effects (i.e., similar to placebo [Strain et al. 1992]) or effects similar to opioid agonists.

Acute Dose of Buprenorphine. Finally, the dose of buprenorphine administered also can influence its abuse potential. Low doses of injected buprenorphine (e.g., <2 mg) produce minimal effects in opioid-dependent patients and are primarily identified as similar to placebo (Strain et al. 1992) although there has been at least one report of more precipitated abstinence (Banys et al. 1994).

Higher doses can be identified as opioid agonist-like, especially as the time interval since the dose of agonist increases (e.g., 24 or more hours) and if the individual has a lower level of physical dependence (e.g., 30 mg per day of methadone or the equivalent).

Although buprenorphine can precipitate withdrawal under certain circumstances, it is worth noting that it does not usually produce severe precipitated withdrawal symptoms.

Potential for Physical Dependence

Repeated administration of buprenorphine produces or maintains opioid physical dependence; however, because buprenorphine is a partial agonist, the level of physical dependence appears to be less than that produced by full agonists (Eissenberg et al. 1996). Furthermore, the withdrawal syndrome associated with buprenorphine discontinuation may be significantly milder in intensity, and the onset of withdrawal signs
and symptoms slower, than that seen with full mu agonists (Eissenberg et al. 1997; Jasinski et al. 1978; Mello et al. 1982; San et al. 1992). The reason for the slower onset of withdrawal symptoms is not completely understood but is likely related to buprenorphine's slow dissociation from the mu receptor. Gradual dose reduction of buprenorphine results in an even milder withdrawal syndrome.

Metabolism and Excretion
A high percentage of buprenorphine is bound to plasma protein and is metabolized in the liver by the cytochrome P450 3A4 enzyme system into norbuprenorphine and other products (Iribarne et al. 1997; Kobayashi et al. 1998). First-pass effects account for its relatively low GI bioavailability and its short plasma half-life. (See the buprenorphine package inserts for a more detailed explanation of its metabolism and excretion.)

Side Effects
The primary side effects of buprenorphine are similar to other mu opioid agonists (e.g., nausea, vomiting, constipation), but the intensity of these side effects may be less than that produced by full agonist opioids.

Buprenorphine Safety, Adverse Reactions, and Drug Interactions

Accidental Ingestion and Overdose
Because of buprenorphine's poor GI bioavailability, swallowing the tablets will result in a milder effect compared with administering them sublingually. (By extrapolation, buprenorphine tablets are approximately one-fifth as potent when swallowed versus when taken sublingually.) Buprenorphine's ceiling effect also adds to its safety in accidental or intentional overdose.

Preclinical studies suggest that high acute doses of buprenorphine (analogous to an overdose) produce no significant respiratory depression or other life-threatening sequelae (e.g., circulatory collapse). Overdose of buprenorphine combined with other medications, however, may increase morbidity and mortality, as described further below.

Respiratory Depression
In contrast to full mu agonists, overdose of buprenorphine (by itself) does not appear to cause lethal respiratory depression in non-compromised individuals. Consistent with this clinical observation, a preclinical study of buprenorphine showed initial dose-related increases in pCO₂ (arterial carbon dioxide level) followed by decreases in pCO₂ compatible with buprenorphine's bell-shaped dose-response curve (Cowan et al. 1977). However, although none of the outpatient clinical trials comparing buprenorphine to methadone or placebo reported adverse events of respiratory depression, some cases have been reported of respiratory depression induced by buprenorphine in individuals not physically dependent on opioids (Gal 1989; Thörn et al. 1988). In addition, buprenorphine, in combination with other sedative drugs, has been reported to produce respiratory depression. (See “Drug Interactions” below.)

Cognitive and Psychomotor Effects
Available evidence in patients maintained on buprenorphine indicates no clinically significant disruption in cognitive and psychomotor performance (Walsh et al. 1994).

Hepatic Effects
Elevation in liver enzymes (AST and ALT) has been reported in individuals receiving buprenorphine (Lange et al. 1990; Petry et al. 2000). There also appears to be a possible
association between intravenous buprenorphine misuse and liver toxicity (Berson et al. 2001). See Johnson et al. 2003b for further details. Mild elevations in liver enzymes have been noted in patients with hepatitis who received long-term buprenorphine dosing (Petry 2000).

Perinatal Effects
There is limited clinical experience with buprenorphine maintenance in pregnant women who are addicted to opioids. The literature in this area is limited to case reports, prospective studies, and open-labeled controlled studies; however, no randomized controlled studies have been reported (Johnson et al. 2003b). See “Pregnant Women and Neonates” in chapter 5 for a detailed discussion of the available clinical and research evidence.

Buprenorphine-Induced Precipitated Withdrawal
Administration of buprenorphine can precipitate an opioid withdrawal syndrome. Although there is much variability in response to buprenorphine, precipitated withdrawal symptoms tend to be milder than those produced by antagonist-precipitated withdrawal, and intervention is rarely required. In controlled studies in which buprenorphine was given to individuals who were physically dependent on opioids, the precipitated withdrawal syndrome was both mild in intensity and easily tolerated (Strain et al. 1995). However, at least one open-label small-sample trial of low-dose buprenorphine caused a patient to experience pronounced, precipitated, and poorly tolerated withdrawal of severe intensity (Banys et al. 1994). The probability of precipitating a withdrawal syndrome is minimized by reducing the dose of mu agonist before buprenorphine treatment is initiated, by allowing a longer elapsed interval between last agonist dose and first buprenorphine dose, and by starting treatment with a lower buprenorphine dose.

Drug Interactions
Benzodiazepines and Other Sedative Drugs
There have been case reports of deaths apparently associated with injections of buprenorphine combined with benzodiazepines and/or other central nervous system (CNS) depressants (e.g., alcohol) (Reynaud et al. 1998a,b). Gaulier et al. (2000) reported a case of fatal overdose in which buprenorphine and its metabolites, as well as the metabolites of flunitrazepam, were very high at the time of death. Although it is not known if this is a pharmacodynamic interaction, Ibrahim et al. (2000) and Kılıçaslan and Sellers (2000) suggest that, because of buprenorphine’s weak ability to inhibit the cytochrome P 450 3A4 system, the effect is more likely pharmacodynamic. This interaction, however, underscores the importance for physicians to be cautious in prescribing buprenorphine in conjunction with benzodiazepines, as well as in prescribing buprenorphine to patients who are addicted to opioids and also are abusing or are addicted to benzodiazepines. It is prudent to assume that these cautions also should be applied to buprenorphine combined with other CNS depressants, including alcohol and barbiturates.

Opioid Antagonists
Buprenorphine treatment should not be combined with opioid antagonists (e.g.,
naltrexone). It is common for individuals who are addicted to opioids to be concurrently dependent on alcohol. Although naltrexone may decrease the likelihood of relapse to drinking, patients maintained on opioids should not be given naltrexone to prevent alcohol relapse since the naltrexone can precipitate an opioid withdrawal syndrome in buprenorphine-maintained patients. Thus, physicians should not prescribe naltrexone for patients being treated with buprenorphine for opioid addiction.

Medications Metabolized by Cytochrome P450 3A4
Buprenorphine is metabolized by the cytochrome P450 3A4 enzyme system. Other medications that interact with this enzyme system should be used with caution in patients taking buprenorphine. No controlled studies, however, have examined these pharmacokinetic interactions. Figure 2–3 lists some of the drugs known to be metabolized by cytochrome P 450 3A 4. In some cases, these drugs may either enhance or decrease buprenorphine’s effects through actions on the cytochrome P 450 3A 4 system.¹

Opioid Agonists
Clinical situations may arise in which a full agonist may be required for patients who currently are being treated with buprenorphine, such as in the treatment of acute pain. Although this medication interaction has not been studied systematically, the pharmacological characteristics of buprenorphine suggest that it may be difficult to obtain adequate analgesia with full agonists in patients stabilized on maintenance buprenorphine.

Data nonspecific to buprenorphine suggest that, in patients maintained chronically on methadone, the acute administration of full mu agonists for analgesia can be effective. If the necessity should arise for the use of a full mu agonist for pain relief in a patient maintained on buprenorphine, the buprenorphine should be discontinued until the pain can be controlled without the use of opioid pain medications. It must be recognized that treatment with full mu agonists for pain relief will produce increased opioid tolerance and a higher degree of physical dependence. See “Patients With Pain” in chapter 5 for a detailed discussion of the treatment of pain in patients maintained on buprenorphine.

Effectiveness of Buprenorphine Treatment
Buprenorphine can be used for either long-term maintenance or for medically supervised withdrawal (detoxification) from opioids. The preponderance of research evidence and clinical experience, however, indicates that opioid maintenance treatments have a much higher likelihood of long-term success than do any forms of withdrawal treatment. In any event, the immediate goals in starting buprenorphine should be stabilization of the patient and abstinence from illicit opioids, rather than any arbitrary or predetermined schedule of withdrawal from the prescribed medication.

Maintenance Treatment
A number of clinical trials have established the effectiveness of buprenorphine for the maintenance treatment of opioid addiction. These have included studies that compared buprenorphine to placebo (Johnson et al. 1995; Ling et al. 1998; Fudala et al. 2003), as well as comparisons to methadone (e.g., Johnson et al. 1992; Ling et al. 1996; Pani et al. 2000; Petitjean et al. 2001; Schottenfeld et al. 1997; Strain et al. 1994a, 1994b) and to

¹It is important to understand that in vitro findings may not be predictive of what occurs in humans, underscoring the need for clinicians to monitor patients for potential drug interactions and associated adverse events.
Partial List of Medications Metabolized by Cytochrome P450 3A4

<table>
<thead>
<tr>
<th>Inhibitors (potentially increasing blood levels of buprenorphine)</th>
<th>Substrates</th>
<th>Inducers (potentially decreasing blood levels of buprenorphine)</th>
</tr>
</thead>
</table>

For a continuously updated list of cytochrome P450 3A4 drug interactions, visit http://medicine.iupui.edu/flockhart/table.htm.

methadone and levo-alpha-acetyl-methadol (LAAM) (Johnson et al. 2000). Results from these studies suggest that buprenorphine in a dose range of 8–16 mg a day sublingually is as clinically effective as approximately 60 mg a day of oral methadone, although it is unlikely to be as effective as full therapeutic doses of methadone (e.g., 120 mg per day) in patients requiring higher levels of full agonist activity for effective treatment.

A meta-analysis comparing buprenorphine to methadone (Barnett et al. 2001) concluded that buprenorphine was more effective than 20–35 mg of methadone but did not have as robust an effect as 50–80 mg methadone—much the same effects as the individual studies have concluded.

Buprenorphine’s partial mu agonist properties make it mildly reinforcing, thus
The safety and efficacy profile of sublingual buprenorphine/naloxone appears to be equivalent to that of buprenorphine alone. Encouraging patient compliance with regular administration. This is in contrast to medications such as naltrexone, which also blocks the effects of opioid agonists but lacks any agonist effects. Because a medication such as naltrexone is not reinforcing, adherence in therapeutic use is poor. Naltrexone also may increase the risk for overdose death in the event of relapse following its discontinuation.

**Medically Supervised Withdrawal**

Although controlled clinical studies of the use of buprenorphine as an agent for treating opioid withdrawal (detoxification) are scarce, some clinical research on its use for this indication has been conducted (Parran et al. 1994). In general, buprenorphine has been used in three ways for withdrawal from opioids: long-period withdrawal (>30 days), usually on an outpatient basis; moderate-period withdrawal (>3 days but <30 days), again on an outpatient basis; and short-period withdrawal (<3 days), which often has been conducted on an inpatient basis. The available evidence from buprenorphine and methadone research suggests that long-period buprenorphine withdrawal probably would be more effective than moderate- or short-period withdrawals but that all forms of withdrawal are less effective compared with ongoing opioid maintenance (Amass et al. 1994a,b; Sees et al. 2000).

Long-Period Withdrawal. Although few data are available on the use of buprenorphine for gradual withdrawal over a period of months, the literature on opioid withdrawal can be used to guide recommendations in this regard. This literature suggests that using buprenorphine for gradual detoxification is more effective than its use for rapid detoxification in terms of patient compliance and relapse to opioid use. These findings are analogous to those seen with methadone which show that patients undergoing a 10-week methadone dose reduction (i.e., 10 percent per week) had a higher rate of opioid-positive urine samples than those receiving a 30-week dose reduction (i.e., 3 percent per week) and asked for more schedule interruptions (Senay et al. 1977).

Moderate-Period Withdrawal. Few studies of withdrawal from illicit opioids have been conducted using buprenorphine for moderate periods (>3 days, but <30 days). Moderate-period withdrawal using buprenorphine suppresses signs and symptoms of withdrawal, is tolerated by patients, and is safe. For example, a study comparing 10 days of buprenorphine versus clonidine for the inpatient treatment of opioid withdrawal found buprenorphine superior to clonidine in relieving withdrawal signs and symptoms (Nigam et al. 1993). Outcomes with moderate-period withdrawal, however, are unlikely to be as positive as those seen with long-period withdrawal (Amass et al. 1994a,b).

Short-Period Withdrawal. The liquid form of buprenorphine has been studied for the withdrawal from opioids over short periods (e.g., 3 days) (Armenian et al. 1999). In these studies, the doses of buprenorphine administered were low (compared to maintenance doses) and typically were administered two or three times per day, either by injection or by having the patient hold the liquid under his or her tongue. (Note that this off-label use of the liquid form of buprenorphine is unlawful outside an approved study setting and is now unnecessary due to the FDA approval of Subutex® and Suboxone®.)

Reports have indicated that buprenorphine is well accepted by patients for short-period withdrawal and that opioid withdrawal signs and symptoms are suppressed (DiPaula et al.
When compared with clonidine for the treatment of short-period withdrawal, buprenorphine is better accepted by patients and more effective in relieving withdrawal symptoms (Cheskin et al. 1994). Long-term outcomes from short-period opioid withdrawal using buprenorphine have not been reported, however, and studies of other withdrawal modalities have shown that brief withdrawal periods do not produce measurable long-term benefits (Simpson and Sells 1989); patients usually relapse to opioid use.

**The Buprenorphine/Naloxone Combination**

There have been reports from several countries of abuse of buprenorphine by injection. Because of this buprenorphine abuse, a sublingual tablet form containing naloxone has been developed for the U.S. market to decrease the potential for abuse of the combination product via the injection route. Sublingual naloxone has relatively low bioavailability (Preston et al. 1990), while sublingual buprenorphine has good bioavailability. (Both naloxone and buprenorphine have poor GI bioavailability.) Thus, if a tablet containing buprenorphine plus naloxone is taken as directed—sublingually—the patient will experience a predominant buprenorphine effect. However, if an opioid-dependent individual dissolves and injects the combination tablet, the potential for abuse of the combination via injection increases. Four types of individuals might attempt to abuse buprenorphine or buprenorphine/naloxone tablets parenterally:

1. Those using diverted tablets who are physically dependent on illicit opioids (e.g., heroin). Parenteral use of the combination buprenorphine/naloxone tablet by these individuals would result in precipitated withdrawal more reliably than injection of buprenorphine alone.

2. Those using diverted tablets who are taking therapeutic full agonist opioids (e.g., oxycodone, methadone). Parenteral use of the combination buprenorphine/naloxone tablet by these individuals also would result in a precipitated withdrawal syndrome more reliably than injection of buprenorphine alone.

3. Those receiving prescription buprenorphine or buprenorphine/naloxone tablets who dissolve and inject their own medication. This population would experience an agonist effect from buprenorphine but no antagonist effect from naloxone, as large doses of opioid antagonists are needed to precipitate withdrawal in buprenorphine-maintained subjects.
(Eissenberg et al. 1996). Although some of the agonist effects of buprenorphine may be attenuated by the simultaneous injection of naloxone, acute agonist effects will still be experienced whether the combination or the monotherapy product is injected.

4. Those who abuse opioids but who are not physically dependent on them. In this group, neither naloxone nor buprenorphine will produce precipitated withdrawal. Sublingual or injected use of either buprenorphine product will produce opioid agonist effects; however, the euphoric effects would be mild.

**Summary**

An understanding of both the general pharmacology of opioids and the specific pharmacological properties of buprenorphine is essential for physicians who intend to treat opioid addiction with buprenorphine. Buprenorphine has unique qualities that make it an effective and safe addition to the available pharmacological treatments for opioid addiction. The combination of buprenorphine with the opioid antagonist naloxone further increases its safety and decreases—but does not eliminate—the likelihood of diversion and misuse.