Buprenorphine for Office-Based Treatment of Patients With Opioid Addiction

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The Drug Addiction Treatment Act of 2000 (DATA 2000) was established to create a new paradigm for medication-assisted treatment of opiate addiction in the United States. Before enactment of DATA 2000, the use of opioid medications to treat opioid addiction was permissible only in federally approved treatment programs, ie, methadone clinics. The only medications permitted were Schedule II drugs (eg, methadone and L-a-acetylmethadol [LAAM]), which could only be dispensed, not prescribed. Under provisions of DATA 2000, qualified physicians in a medical office and other appropriate settings outside the opioid treatment program system may prescribe or dispense (or both), Schedule III, IV, and V opioid medications for treatment of opioid addiction if such medications have been specifically approved by the US Food and Drug Administration for that indication. Opioid addiction treatment programs were commonly known as methadone clinics. They now may also dispense buprenorphine hydrochloride and the buprenorphine hydrochloride–naloxone combination.


In October 2002, the US Food and Drug Administration (FDA) approved two sublingual formulations of buprenorphine, a Schedule III opioid partial agonist, for treatment of opioid addiction. These medications, buprenorphine and buprenorphine and naloxone in combination are the first, and as of this publication, the only Schedule III, IV, or V medications to have received FDA approval for use under the Drug Addiction Treatment Act of 2000 (DATA 2000). The intent is that office-based treatment with buprenorphine will bring addiction care into the mainstream of medicine by greatly expanding access and providing hope to thousands of drug abusers.

Opioid addiction includes not only heroin-related problems, but also the increasingly recognized abuse of prescription pain medications such as hydrocodone, oxycodone hydrochloride, meperidine hydrochloride, and hydromorphone hydrochloride. Rates of addiction to these analgesics have been increasing rapidly. The incidence of emergency department visits related to prescription opioid pain medications has more than doubled between 1994 and 2001. The prevalence of heroin addiction in the United States has also 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, an estimated 810,000 to 1 million individuals in the United States were addicted to heroin in the year 2000.

Opioid Treatment Programs

Opioid treatment programs (OTPs), which are methadone maintenance programs that embrace interventions that include counseling services, vocational resources, referrals, and appropriate drug monitoring, have been shown to reduce opioid use and related crime, increase employment, and decrease the incidence of human immunodeficiency virus (HIV) related to needle sharing. In addition, abusers enrolled in such programs gain improved physical and mental health and decreased overall mortality for opioid addiction. Unfortunately, despite these results, the capacity of the methadone maintenance treatment system has not kept pace with the rise in opioid addiction.

Buprenorphine as Option in Opioid Treatment Programs

Buprenorphine was identified as a viable option for maintenance treatment of indi-
viduals addicted to opioids more than 20 years ago. Research during the past two decades has documented the safety and effectiveness of buprenorphine for this indication, and the enactment of DATA 2000 has now enabled physicians in the United States to offer specifically improved forms of buprenorphine for treating patients with opioid addiction.

In this regard, it was recently reported that buprenorphine and methadone had similar safety and side effect profiles, and there was no evidence that buprenorphine was selectively associated with abnormal liver function compared with methadone.

Buprenorphine has unique pharmacologic properties that make it an effective and well-tolerated addition to available pharmacologic treatment modalities for addiction. Drugs that activate opiate receptors or neurons are termed opioid agonists (eg, heroin and methadone). Repeated administration of opioid agonists produces physical dependence and tolerance.

Physical dependence is manifested as a characteristic set of withdrawal signs and symptoms that emerge on reduction or complete cessation of use of an active compound.

Addiction is a behavioral syndrome characterized by repeated compulsive seeking or use of a substance despite adverse social, psychological, or physical consequences either singly or in combination. Opioid addiction often, but not always, is accompanied by tolerance, physical dependence, and opioid withdrawal syndromes (Table). Drugs that bind to, but do not activate, opioid receptors are opioid antagonists (eg, naltrexone and naloxone). Opioid partial agonists are drugs that activate receptors, but to a lesser degree than full agonists. Increasing the dose of a partial agonist does not produce as strong an effect as does increasing that of a full agonist. The therapeutic effects of a partial agonist reach a ceiling at moderate doses and does not increase from that point, even with higher doses.

The partial agonist properties of buprenorphine make it a safe and effective option for treatment of patients for opioid addiction. Buprenorphine has sufficient agonist properties such that when it is administered to individuals who are not opioid dependent but are familiar with the effects of opioids, they experience subjectively positive opioid effects. These subjective effects aid in maintaining compliance with buprenorphine during patients who are opioid dependent. Buprenorphine also occupies opioid receptors with strong affinity and thus blocks opioid full agonists from exerting effects. Buprenorphine dissociates from opioid receptors at a slow rate. This enables daily—or less frequent—dosing (eg, three times per week).

Although buprenorphine can be misused (consistent with agonist action at opioid receptors), its abuse potential is lower in comparison with a full opioid agonist. A new 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 the buprenorphine and naloxone combination should monitor for diversion. Because of the potential for serious drug-drug interaction, buprenorphine must be used with caution with certain other types of medications, particularly benzodiazepines, other sedative drugs, opioid agonists and antagonists, and drugs metabolized by cytochrome P450 3A4.

### Medical Management of Opioid Addiction

The necessary first steps of the medical management of opioid addiction are:

- use of validated screening tools for identifying patients who may be abusing these drugs, and
- further assessment to clearly delineate the scope of the disorder.

When treatment is indicated, consideration must be given to the appropriate type, setting, and level of intensity based on patient preferences, addiction history, presence of medical...
or psychiatric comorbidities, and readiness to change. Buprenorphine is a treatment option for many such patients. Screening instruments are available for establishing substance abuse and related problems. It is recommended that physicians evaluate all patients for such problems.

Screening for Addiction
Available validated instruments included the drug abuse screening tests, CAGE questionnaire (focuses on “Cutting down, Annoyance by criticism, Guilty feeling, and Eye-openers”),7 CAGE-Aid (CAGE questions adapted to include drugs), Tweak questionnaire, and Audit Michigan Alcoholism Screening Test. These screening instruments can be found listed in numerous Substance Abuse and Mental Health Services Administration (SAMHSA) publications.8

If screening indicates the presence of an opioid use disorder, further assessment is indicated to thoroughly delineate the patient’s problem, identify comorbid or complicating medical or emotional problems, and determine appropriate setting and level of treatment. Complete assessment may require several office visits, but initial treatment should not be delayed. It is recommended that initial and on-going drug screening should be done to detect or confirm recent use of drugs such as alcohol, benzodiazepines, and barbiturates, which could complicate management of a patient’s addiction. Urine screening is the most commonly used and generally most cost-effective testing method to identify use, but it is not a scientifically valid method to establish impairment.

Diagnosis of Opioid Dependence and Patient Selection
After a thorough assessment 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 by the Desk Reference to the Diagnostic Criteria From DSM-IV-TR.9 This diagnosis is based not merely on physical dependence on opioids which many patients exhibit (eg, those suffering from cancer), but also on an addiction process (ie, compulsive use despite harm).

It is important to determine during evaluation if the patient is appropriately motivated and to rule out contraindicating medical and psychiatric comorbidities. Buprenorphine may be an appropriate option for the following:

- patients who are willing to follow safety precautions for buprenorphine therapy; and
- patients who agree to buprenorphine administration after review of other options.

Patients who are less likely to be appropriate candidates for buprenorphine treatment in an office-based setting are those whose circumstances or conditions include:

- comorbid dependence on high doses of benzodiazepines or other central nervous system depressants (including alcohol);
- significant psychiatric comorbidity;
active or chronic suicidal or homicidal ideation or intents;
- multiple previous treatments for drug abuse with frequent relapses (except when previous detoxification followed by relapse are strong indication for long-term maintenance);
- poor response to previous treatment with buprenorphine; and
- significant medical complications.

**Treatment Protocols**

Protocols for treatment with buprenorphine for opioid addiction consist of three phases: induction, stabilization, and maintenance (Figure).

Induction involves helping patients begin the process of switching from the opioid of abuse to buprenorphine. The goal is to find the minimum dose of buprenorphine at which the patient discontinues or markedly diminishes use of opioids and has no withdrawal symptoms, minimal or no side effects, and no craving for the drug of abuse. It is recommended that the buprenorphine and naloxone combination be used for the induction, stabilization, and maintenance for most patients and that the initial induction doses be administered as observed treatment with further doses provided by prescription, ie, one or two times a week initially, then once at week 2, then once every 3 to 4 weeks.

To minimize chances of precipitating withdrawal, patients who are transitioning from long-acting opioids (eg, methadone, sustained-release morphine, or sustained-release oxycodone) to buprenorphine should undergo induction using buprenorphine monotherapy, but be switched to the buprenorphine and naloxone combination soon after. 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 undergo induction and maintenance solely on this drug.

Stabilization is begun when a patient is having no withdrawal symptoms, minimal or no side effects, and no longer has uncontrolled cravings for opiate agonists. Dosage adjustments may be necessary during early stabilization, and frequent contact with the patient increases the likelihood of compliance: four or five times a month the first month, then once every 2 weeks thereafter. The longer period during which the patient is on buprenorphine therapy is the maintenance phase. This period may be indefinite. During the maintenance phase, attention must be focused on social family issues that have been identified during the course of treatment as contributing to a patient’s addiction.

**Medically Supervised Withdrawal or Detoxification**

Buprenorphine can be used for medically supervised withdrawal of patients from both self-administered opioids and from prescribed opioid agonist treatment with methadone. The goal is to provide a transition from physical dependence on opioids to a drug-free state while minimizing withdrawal symptoms and avoiding side effects.

Medically supervised withdrawal with buprenorphine consists of an induction phase and a dose-reduction phase. Using buprenorphine to taper off long-acting opiates should be considered only for those patients who have evidence of sustained medical and psychosocial stability, and should be undertaken in conjunction and coordination with patient’s opioid treatment programs.

**Nonpharmacologic Therapy**

Pharmacologic therapy 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 the training in the treatment of patients with opioid addiction, physicians should obtain knowledge about basic principles of brief intervention in case of relapse.

Physicians who decide to care for opioid addicts should ensure that they are capable of providing psychosocial services, either in their own practices or through referral to reputable behavioral health practitioners in their community. In fact, DATA 2000 stipulates that when physicians submit notification to SAMHSA to obtain the required waiver to initiate practice of opioid addiction treatment outside the OTP setting, they must attest to their capacity to refer such patients for appropriate counseling and other nonpharmacologic therapy. The physician should reach agreement with the patient when involved in treatment and develop an individualized treatment plan based on the patient’s particular problems and needs.

During stabilization, patients receiving maintenance treatment should be seen on at least a weekly basis. Once a stable buprenorphine dose is reached and toxicologic screens (eg, the enzyme multiplied immunoassay test [EMIT]) are free of illicit opioids, amphetamines, benzodiazepines, methamphetamine, marijuana, and PCP, physicians may determine that less frequent visits are acceptable. During opioid addiction treatment with buprenorphine, such toxicology tests should be administered at least monthly.

Buprenorphine is a drug that will lend itself to special populations (eg, adolescents with opioid addiction). Treatment of these patients for such abuse is complicated by a number of medical, legal, and ethical considerations. Physicians intending to care for adolescents should be thoroughly familiar with the laws in their state regarding parental consent. Physicians who do not specialize in treatment of opioid abuse should strongly consider referring adolescent patients to an addiction specialist. Additionally, state child protection agencies can be a valuable resource when determining the proper disposition for these young patients.

Another population in which buprenorphine has been valuable is those recently discharged from controlled environments such as prison and residential living programs. Intensive buprenorphine monitoring activities are required, and treating physicians may be called on to verify and explain treatment regimens to parole or probation officers, and to document the patient’s compliance to interact with legal system inquiries and others when treatment is mandated by the court. If an opiate treatment program is available, physicians should determine if any patient factors preclude referral. For patients to qualify to receive methadone treatment for addiction, they must have a urine drug screen positive for opiate.
Required Qualifications and Training

To practice office-based treatment of patients with opioid addiction under the auspices of DATA 2000, physicians must first obtain a waiver from the special registration requirements established in the Narcotic Treatment Act of 1974 and its enabling regulations. To obtain a DATA 2000 waiver, physicians submit a notification to SAMHSA of their intent to begin dispensing and/or prescribing this medication. A notification of Intent form must contain information on the physician’s qualifying credentials, as well as additional certifications including a statement that the physician (or physician’s group practice) will not treat more than 30 patients for addiction at any time. Notification of Intent forms can be filled out and submitted online at the SAMHSA buprenorphine Web site. Alternatively, this form can be printed from the site and submitted via ground mail or fax.

To qualify for a DATA 2000 waiver, physicians must have completed at least 8 hours of approved training in the treatment of patients with opioid addiction or have certain other qualifications as defined in the legislation (e.g., clinical research experience with certification in addiction medicine; statement that they can provide patients with 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.

Before embarking on the provision of office-based addiction treatment services, 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 comprehensive community-based psychosocial services.

Maintaining Privacy and Confidentiality

The privacy and confidentiality of individually identifiable drug or alcohol treatment information is protected by SAMHSA confidentiality regulation (Title 42 Part 2 of the Code of Federal Regulations [42CFR Part 2]). This regulation mandates that addiction treatment information in the possession of the substance abuse treatment providers be handled with a greater degree of confidentiality than general medical information.

Among other stipulations, 42CFR Part 2 requires that physicians providing opioid addiction treatment obtain signed patient consent before disclosing such individually identifiable information to any third party. The requirement for signed patient consent extends to activity such as telephoning or faxing addiction treatment prescriptions to pharmacies, as this information constitutes disclosure of the patient’s addiction treatment. In May 2003, the Federal Opioid Treatment Program Regulations were amended to add buprenorphine and buprenorphine-naloxone to the list of approved opioid medications that may be used in federally certified and registered opioid treatment programs, that is, methadone clinics. Any OTP that decides to administer these two agents must adhere to the same federal treatment standards established for all medications under 42CFR Part 8.

Comment

Buprenorphine, available alone and in combination with naloxone as sublingual tablets, provides a feasible alternative to treatment of patients with opioid addiction in the outpatient setting. It is a safe and convenient drug that can be provided on a prescription basis for patients who meet treatment criteria. Buprenorphine is a viable pharmacologic tool in the therapy for addiction because it provides a level of comfort to patients without euphoric effects. It also blocks the effect of other opioids. The office practice with buprenorphine, when used according to guidelines with monitoring and available psychosocial support, should permit many people who have either willingly or unwillingly become dependent on opioids to gain freedom from this addiction and maintain a normal and viable lifestyle.

References


Bibliography


