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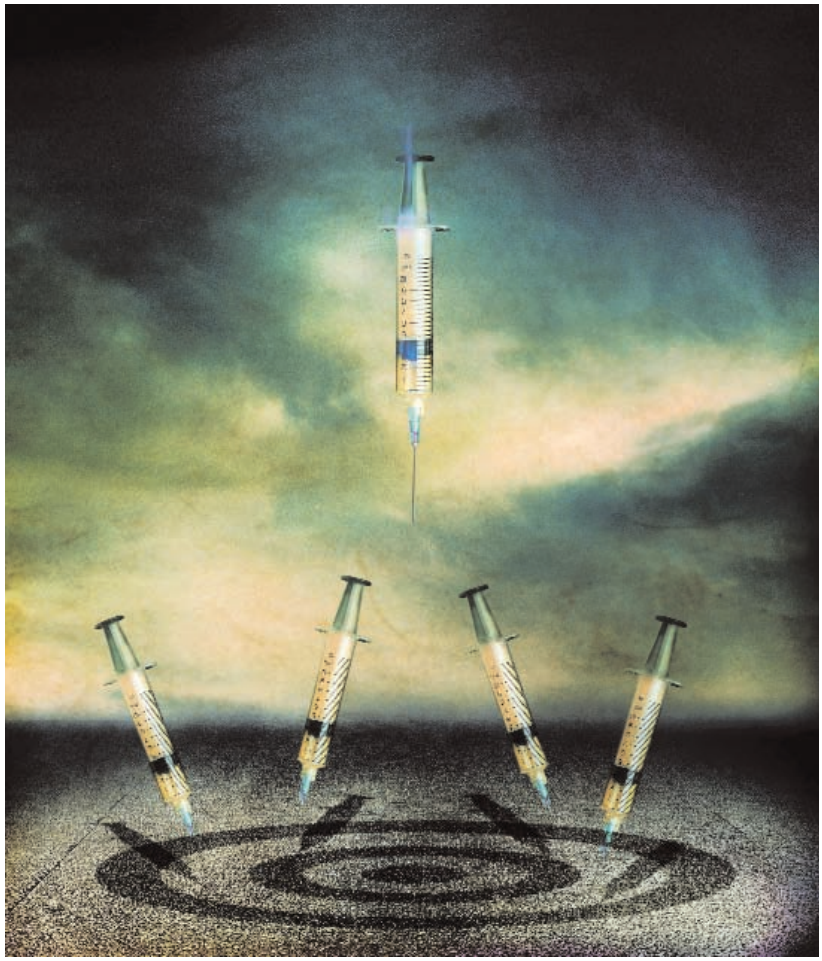
Buprenorphine:

A (Relatively) New Treatment For Opioid Dependence

ABSTRACT

Opioid dependence is a significant and growing problem in the United States. For nearly a century, federal regulations have made it illegal for psychiatrists and other physicians to pharmacologically manage this condition in an office-based setting using opioids. The passage of the Drug Addiction Treatment Act of 2000 has made it possible for all physicians to prescribe buprenorphine to patients in such a setting. Buprenorphine, a partial *mu*-opoid receptor agonist, has unique pharmacologic properties that distinguish it from methadone and other medications used in the treatment of opioid dependence. It has been shown to be as effective as methadone and is generally safe and well-tolerated. It is available in two sublingual formulations: Subutex, which contains only buprenorphine, and Suboxone, which also contains naloxone. Physicians who wish to prescribe either must obtain a special waiver from the federal government and are currently limited to prescribing it for 30 patients at a time.



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INTRODUCTION

Opioid dependence (addiction) is a serious problem in the United States. It is characterized by physiologic dependence (the development of tolerance and withdrawal) as well as a maladaptive pattern of opioid use with impaired control over use, compulsive use, continued use despite harm, and craving (Table 1). According to the National Survey on Drug Use and Health, the incidence of abuse of prescription opioid pain medications (products containing codeine, dilaudid, fentanyl, hydrocodone, hydromorphone, meperidine morphine, oxycodone, oxymorphone, propoxyphene) has risen markedly in recent years with 4.4 million people reporting non-medical use in 2004 (up from 2.8 million in 2000).[1] The same survey found that in 2004, 118,000 individuals in the US used heroin for the first time. In 2003, the Drug Abuse Warning Network reported an estimated 17 percent of drug-related emergency department visits were related to opioid analgesic abuse (36% of the cases specifically seeking detoxification) with eight percent related to heroin use.[2] According to the Office of National Drug Control Policy (ONDCP), there were an estimated 810,000 to 1,000,000 individuals addicted to heroin in the United States in the year 2000.[3] It is believed that a rise in the purity of heroin (from less than 10 percent in the 1970s to between 50 and 90 percent in the 1990s), increased cultivation of poppies in Mexico, and a resultant reduction in price have given rise to new populations of heroin users (including many from the middle and upper classes) as heroin is now easier to use by noninjection routes, such as snorting and smoking.

While opioid use itself can lead to serious medical problems, such as overdose, many of the consequences of opioid use are due to the intravenous route of administration. Common consequences include infection with human immunodeficiency virus (HIV), hepatitis B and hepatitis C, bacterial endocarditis, abscesses, emboli, and septicemia. Additionally, individuals with opioid addiction tend to suffer a progressive deterioration of quality of life. Loss of savings, loss of employment, estrangement from family and friends, and incarceration are frequent social consequences.

Individuals addicted to opioids face many challenges as they battle this disease. Sudden discontinuation of opioids in a dependent patient typically results in an extremely uncomfortable withdrawal syndrome (Table 2). Some of these symptoms, in addition to craving for opioids, may persist for weeks and months after the last use of an opioid. It has been demonstrated that treating all addictions as chronic disorders leads to improved outcomes for patients.[4] Opioid maintenance therapy has been demonstrated to be an effective means to decrease illicit opioid use in addicted patients.[5] In the US, the primary pharmacologic treatment has been methadone. However, access to methadone treatment has been restricted by federal law (The Narcotic Addict Treatment Act of 1974) to highly regulated treatment programs variously referred to as Methadone Programs, Methadone Maintenance

TABLE 1: DSM-IV-TR diagnostic criteria for substance dependence

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12 month period:

1. **Tolerance, as defined by either of the following:**
   a) a need for markedly increased amounts of the substance to achieve intoxication or desired effect
   b) markedly diminished effect with continued use of the same amount of the substance
2. **Withdrawal, as manifested by either of the following:**
   a) the characteristic withdrawal syndrome for the substance
   b) the same (or closely related) substance is taken to relieve or avoid withdrawal symptoms
3. **The substance is often taken in larger amounts or over a longer period than was intended**
4. **There is a persistent desire or unsuccessful efforts to cut down or control substance use**
5. **A great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects**
6. **important social, occupational, or recreational activities are given up or reduced because of substance use**
7. **The substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.**

TABLE 2: Signs and symptoms of opioid withdrawal

Abdominal Cramping
Anorexia
Anxiety
Diarrhea
Dysphoria
Elevated Blood Pressure
Fatigue
Fever
Headache
Insomnia
Lacrimation
Muscle Spasms
Mydriasis
Myalgia
Nausea
Piloerection
Restlessness
Rhinorrhea
Tachypnea
Tachycardia
Vomitting
Yawning

Programs, Narcotic Replacement Programs, and Opioid Treatment Programs (OTP). These programs typically have stringent entrance criteria and long waiting lists. They are often located in urban areas, and public opposition often makes it difficult for new programs to open. Several states do not have maintenance programs. The combination of the under-availability (approximately 1100 programs nationally), the stigma (with the general public, patients, and healthcare practitioners), and the inconvenience (patients are required to attend a clinic on a daily basis) associated with receiving methadone in the OTP has contributed to the low rate of treatment among patients with opioid addiction. The National Survey on Drug Use and Health found that 283,000 people in the US had received any treatment for heroin dependence in 2004.[1]

Since the Harrison Narcotics Act of 1914, office based-treatment of opioid addiction has not been available in the United States (Table 3). Most physicians have become accustomed to treating the disorders related to opioid addiction (infectious diseases, abscesses, psychiatric sequelae, etc.) but not the addiction itself. The Drug Addiction Treatment Act of 2000 (DATA)[6] has made it possible for physicians to manage opioid-dependent patients with opioid maintenance in an outpatient setting. This act states that a physician can prescribe and a pharmacist can dispense Schedule III, IV, or V "narcotic" medications approved by the Food and Drug Administration (FDA) for the treatment of narcotic-use disorders. In October, 2002, the FDA approved buprenorphine (Subutex®) and a combined formulation of buprenorphine plus naloxone (Suboxone®) for use in the treatment of opioid dependence.

As of the first quarter of 2005, more than 4,500 physicians had obtained the waiver required to prescribe buprenorphine. Approximately two-thirds of these physicians reported that they had actually prescribed the medication.[7]

BUPRENORPHINE

Buprenorphine is a semi-synthetic opioid derived from thebaine, a naturally occuring alkaloid of the opium poppy, *Papaver somniferum*. Buprenorphine is a partial mu receptor agonist originally developed as analgesic but its potential utility for the management of opioid dependence has been discussed since early research in the 1970s.[8] Due to its partial agonist properties, buprenorphine offers some potential pharmacologic advantages over methadone in the management of opioid addiction, such as decreased respiratory depression, less sedation, less withdrawal symptoms, lower risk of toxicity at higher doses, and decreased risk of diversion. There is also the potential for better acceptance by the general public, patients, and healthcare professionals, as well as the ability for physicians to provide more integrated treatment for all medical/psychiatric conditions.

Buprenorphine has three FDA indications: opioid detoxification, opioid maintenance, and pain management. Opioid detoxification describes the process in which a physically dependent individual is gradually tapered off all opioids. Opioid maintenance, on the other hand, is the long-term substitution with a regulated opioid with the goal of decreasing illicit drug use.

Buprenorphine is a DEA Schedule III medication. Under federal law, buprenorphine (Suboxone and Subutex) can only be prescribed for opioid addiction by "qualified physicians" (Table 4). The physician is required to have an active DEA registration and a waiver to prescribe buprenorphine. Buprenex (the parenteral formulation) is not FDA-approved for the treatment of opioid dependence, and its use for that purpose is illegal and may be punishable by law.

Additionally a "qualified physician" must have the capacity to refer patients for appropriate addiction counseling and ancillary services and must certify that he or she will treat no more than 30 patients at one time with buprenorphine. For further information on locations of the required eight-hour course or its online equivalent, see Table 5.

Pharmacology. Buprenorphine exerts the majority of its effects at the mu

TABLE 3: Select history of pharmacologic treatments for opioid dependence	
1860s	Various "cures" for morphine and opium addiction began to appear
1870s	Use of cocaine to treat morphine addiction began
1874	Diacetyl-morphine (Heroin) was synthesized
1898	Heroin was marketed by Bayer for cough; also used to treat morphine addiction
1912	Morphine maintenance clinics began in Jacksonville, Florida
1914	Harrison Narcotics Act: used federal taxation to limit sale/transfer of "narcotics"
1923	Opioid maintenance was outlawed by the US government.
1965	Article published in JAMA describing success of methadone maintenance.
1971	First FDA regulations for Methadone Maintenance
1972	Revision of FDA regulations
1973	Methadone Diversion Control Act
1974	Narcotic Addict Treatment Act (Gave DEA power over storage, licensing, etc.)
1970s	Research with LAAM was conducted; heroin clinics started in UK; first use of clonidine for detoxification
1985	Naltrexone approved in US to treat opioid dependence
1990s	Buprenorphine used for detoxification from opioids; further trials with morphine and heroin maintenance
1993	LAAM approved in the US to treat opioid dependence
1995	IOM report recommending reduced regulations for methadone maintenance
2000	Drug Abuse Treatment Act (Section 3502 of The Children's Health Act of 2000)
2002	FDA approved Subutex and Suboxone
2003	Subutex and Suboxone available in pharmacies
2005	DATA amended: 30 patient per group practice limit lifted

opioid receptor where it acts as a partial agonist. Because of the relatively decreased activation (compared to a full agonist), there is a plateau of receptor activation with no further effect from further increase in dose. This is in contrast with full opioid agonists, such as methadone and heroin, which exert greater opioid receptor activity as the dose is increased (Figure 1). Buprenorphine also has a high affinity for and slow dissociation from mu opioid receptors. This allows buprenorphine to block the effects of other opioids taken after buprenorphine. It also allows the clinical effects of buprenorphine to last significantly longer than would be expected based solely on its elimination half-life.

Buprenorphine is readily absorbed through the gastrointestinal and mucosal membranes. However, due to extensive first-pass metabolism, buprenorphine has very poor oral bioavailability (10% of the intravenous route) if swallowed. Its availability is significantly increased with sublingual administration (30–50% of the intravenous route),[9,10] making this a feasible route of administration for the treatment of opioid dependence. The mean time to maximum plasma concentration following sublingual administration is one hour, ranging from 30 minutes to 3.5 hours. Buprenorphine has a large volume of distribution and is highly protein bound (96%). It is metabolized primarily in the liver via the cytochrome P-450 3A4. The primary products of this metabolism are norbuprenorphine and its conjugate. Norbuprenorphine has little ability to cross the blood brain barrier and so its effects are negligible. The terminal half-life ranges from three hours after intravenous administration to 28 to 37 hours after sublingual administration.[10] It is unclear why there is such a difference in half life depending on the route of administration but this may be related to sequestring of buprenorphine in the oral mucosa. Most of the buprenorphine is eliminated in the feces, with approximately 10 to 30 percent excreted in urine.[11]

In addition to the primary effects on the mu opioid receptor, buprenorphine also appears to act as an antagonist at the kappa opioid receptor (possibly involved with spinal analgesia and antidysphoric effects), as an

agonist at the delta receptor (clinical significance uncertain), and as a partial agonist at the opioid-receptor-like 1 (ORL-1).[12]

Clinical trials. Several meta-analyses of studies comparing buprenorphine to placebo and methadone for the maintenance treatment of opioid addiction indicate buprenorphine is more effective than placebo and as effective as methadone with both drugs being more effective at higher doses.[13–16] Some studies appear to show that buprenorphine may not be as effective as methadone for patients requiring higher doses of methadone (See Table 5 for a summary of some of the key controlled trials). When reviewing the literature of clinical trials with buprenorphine, it is important to remember that the majority of earlier studies were conducted with a sublingual liquid solution. Because the absorption of this solution is different than absorption of the FDA-approved tablet, exact dosing comparisons cannot be made.

Fewer studies have been conducted on short-term detoxification with buprenorphine. One large, multicenter study with both inpatients and outpatients demonstrated that buprenorphine was clearly superior to clonidine in measures of completion of detoxification and negative urine samples at the end of the detoxification (77% vs 22% in the inpatient condition; 29% vs 5% in the outpatient condition).[25] However, a large proportion of both groups did not complete the out-patient detoxification. Further research is needed to determine the longer-term outcomes of patients detoxified from opioids versus those who remain on buprenorphine maintenance.

Safety. It is estimated that buprenorphine has been prescribed to over 100,000 people in the United States[7] and close to 200,000 worldwide.[26] It is very well tolerated with side effects similar to other opioids though tending to be less severe and seen less often. The most common side effects include constipation, headache, nausea, urinary retention, and sedation.[27] Although a decrease in respiratory rate may be observed, this is generally not clinically significant.[28] There are reports of fatal overdose involving buprenorphine and benzodiazepines.[29,30,31] These reports have all come from Europe (where the buprenorphine/naloxone combination is not used) and generally involved individuals who appear to have injected benzodiazepines with dissolved buprenorphine tablets. Although there are no reports of significant buprenorphine overdoses when taken orally or sublingually, buprenorphine should be used with caution in individuals who have a history of benzodiazepine misuse.

Mild elevation in liver enzymes (AST and ALT) has been reported in patients receiving buprenorphine,[27,32] though the clinical significance of this is uncertain. There is also a report of hepatitis following intravenous misuse of buprenorphine.[33] Because of this potential effect on liver enzymes, it is recommended that liver function tests be monitored periodically during the course of treatment with buprenorphine.

Since buprenorphine is metabolized primarily via the cytochrome p450 3A4 system, there is potential for interaction with medications that induce or inhibit this pathway. Common inducers of this enzyme include phenytoin, phenobarbital, carbamazepine, rifampin, afavirenz, and nevirapine. Common inhibitors include fluconazole, erythromycin, indinavir, ketoconazole, metronidazole, ritonavir, and saquinavir. With the exception of a few studies with protease inhibitors (see "Patients with HIV infection" in the "SPECIAL POPULATIONS" section below), very little research has been done to formally assess the extent of drug-drug interactions with buprenorphine. Clinicians should be aware of the potential for interactions with other medications metabolized by the

TABLE 4: Requirements to become qualified to prescribe buprenorphine

The physician has the capacity to refer patients for counseling and ancillary services. The physician is licensed under state law and meets at least one of the following requirements:

1. **Board certification in addiction psychiatry**
2. **Certification in addiction medicine from the American Society of Addiction Medicine (ASAM)**
3. **Board certification in addiction medicine from the American Osteopathic Association (AOA)**
4. **Completion of at least eight hours in the treatment and management that is provided by the ASAM, AOA, the American Medical Association, the American Academy of Addiction Psychiatry, or the American Psychiatric Association.**
5. **Participation in the clinical trials leading to the approval of buprenorphine**
6. **Training or experience deemed sufficient by the physician's state licensing board**
7. **Training or experience deemed sufficient by the Secretary of Health and Human Services.**

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