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Buprenorphine maintenance: A new treatment for opioid dependence

ABSTRACT

Buprenorphine (Subutex) is a safe and effective treatment for opioid dependence, and has very low potential for abuse, especially when it is combined with naloxone (Narcan) in a single sublingual tablet (Suboxone). New regulations allow physicians who are certified in buprenorphine therapy to offer it in their offices, a development that can substantially increase patient access to treatment.

KEY POINTS

The most effective treatment for opioid dependence is the combination of maintenance therapy (ie, with medically prescribed opioids) and psychological counseling.

Buprenorphine and combined buprenorphine and naloxone are the only agents approved by the US Food and Drug Administration for office-based treatment of opioid dependence.

Most patients being treated for opioid addiction should be maintained on combined buprenorphine and naloxone, which is less likely than buprenorphine alone to be inappropriately used or sold.

Physicians can easily obtain training and certification to provide buprenorphine therapy in their offices.

THERE IS SOMETHING NEW in the treatment of opioid dependence: buprenorphine (Subutex, Suboxone) maintenance therapy in the physician's office. Traditionally, only methadone has been used for maintenance therapy, and only in highly regulated special clinics. But now that a safe, effective drug with low potential for abuse is available, new legislation allows physicians to offer it in their offices, thereby expanding patient access.

This article discusses the problem of opioid abuse in the United States and the principles of buprenorphine therapy.

OPIOID ADDICTION IS GROWING

Illicit use of opioids is a growing health problem in the United States. According to the 2004 National Survey on Drug Use and Health, 31.8 million Americans had used narcotic pain relievers for nonmedical purposes in their lifetime, and 3.1 million had used heroin.[1] In 2003, federally funded treatment centers saw more than 270,000 admissions for heroin addiction and more than 48,000 admissions for prescription opioid addiction,[2] the latter being nearly twice as many as in 2000. Between 750,000 and 1 million people in the United States are addicted to heroin, according to estimates from the Office of National Drug Control Policy.[3] This would mean that only about one fourth of heroin addicts are receiving treatment for it.

Opioid abuse often leads to addiction with physical dependence, manifested by tolerance and withdrawal. Addiction also entails behavioral dependence, characterized by the inability to control use, continued use despite the adverse consequences, and social dysfunction.[4]

The costs to the patient, family, and society are high in terms of sickness, death, crime, lost productivity, and family disruption.[5,6]

MAINTENANCE WORKS BETTER THAN DETOXIFICATION

There are two approaches to the pharmacologic treatment of opioid dependence: detoxification and maintenance therapy.

Detoxification is the short-term management of opioid withdrawal and is designed to bring the patient into an opioid-free state while he or she starts to undergo counseling to prevent relapses.

Symptoms of opioid withdrawal can be quite severe and include muscle and joint pains, restlessness, irritability, nausea, vomiting, diarrhea, and insomnia. Physical signs of withdrawal include diaphoresis, rhinorrhea, piloerection, tachycardia, and hypertension. Avoiding this unpleasant complex is a compelling motivation for addicts to continue to use illicit opioids.

Withdrawal symptoms can be managed by substituting a long-acting opioid agonist such as methadone and slowly tapering it, which typically causes less severe withdrawal symptoms than abruptly stopping heroin or prescription opioids.

Regardless of how abstinence is achieved, relatively few patients manage to stay in treatment and off drugs after detoxification.[7,8] Reasons cited: opioid dependence is by nature chronic and relapsing, most detoxification centers cannot provide ongoing support, and few effective strategies to prevent relapse are available.

Maintenance (substitution) therapy involves replacing abused opioids with medically prescribed opioids that are slow in onset, long-acting, and less likely to be abused. Maintenance medications prevent withdrawal and compete for opioid receptor binding sites, blocking the effects of any self-administered illicit opioids such as heroin.

Unlike detoxification approaches, maintenance therapy involves no immediate attempt to wean patients off medication once they are stabilized. Treatment is continued as long as the patient benefits, is at risk for relapse, has no serious side effects, and the clinician believes maintenance treatment is still required.

Multiple controlled studies show that maintenance therapy is more effective than detoxification: patients are more likely to stay in the program[9] and less likely to engage in illicit opioid use or criminal activity or to acquire human immunodeficiency virus (measured by seroconversion) if they are in maintenance programs.[10,11] Maintenance therapy is so much more effective than detoxification that it has become the first-line treatment for chronic opioid abuse, even though it is at odds with the traditional philosophy of substance abuse treatment, which is grounded in abstinence and "12-step" approaches.[12]

Nevertheless, some patients prefer to pursue complete abstinence after withdrawal. Patients undergoing detoxification who want to stay off opioids completely should be provided with options to help prevent relapse, including residential therapeutic communities, psychosocial counseling, or self-help groups. Another strategy, naltrexone (ReVia, Depade) maintenance therapy, would seem attractive for preventing relapse by blocking opioid receptors, but patients tend to stop taking it, and outcomes are poor.[13]

Psychosocial counseling is a necessary adjunct to pharmacologic therapy. Often, it begins during detoxification, in which case permanent abstinence is strongly encouraged. However, psychosocial therapy has also been shown to improve the success rate of replacement treatments.[14] Counseling focuses on behavior modification, motivation, coping skills, interpersonal relationships, and social reintegration. It can be one-on-one or in groups; participation in a 12-step group is usually recommended.

After opiate detoxification, few addicts stay in treatment and off drugs

FEDERAL REGULATIONS HAVE BEEN EASED

Although opioid maintenance therapy is effective, most physicians have not been allowed to offer it until recently.

Methadone maintenance therapy began to be widely accepted in the mid-1960s after Dole and Nyswander,[15] in a landmark study,

proved that it was effective. However, federal regulations passed in 1973 imposed many restrictions on methadone therapy. Patients had to meet certain criteria to receive it, and since it could be dispensed only at approved facilities, most patients had to go to the clinic almost every day to get their dose. Treatment centers and providers had to provide rehabilitative services with treatment and needed to re-register every year with the US Drug Enforcement Agency.[16]

Federal regulations were eventually changed somewhat after a 1995 Institute of Medicine review[17] faulted the 1973 regulations as being overly concerned with procedures and restricting clinical judgment, but the reforms did little to improve the process or increase patient access. Additional practitioner accreditation requirements were even imposed, further limiting physicians' willingness to provide maintenance therapy.

Fortunately, the arduous regulatory system has been substantially improved recently in response to increased rates of abuse of heroin and prescription opioids, high rates of viral transmission from needle-sharing, the discrepancy between the number of opioid-dependent people and those receiving treatment, and recognition that opioid dependence is a chronic medical condition and that opioid substitution therapy is effective.[16] New initiatives have made treatment more accessible and convenient for patients and have increased physician involvement in care.

New regulations increase access to treatment

The Drug Addiction Treatment Act of October 2000 (DATA) allows qualified physicians to prescribe schedule III, IV, and V narcotics that are approved by the US Food and Drug Administration (FDA) for addiction. A licensed physician can become qualified to treat opioid dependence by obtaining addiction-related training and certification from one of various medical societies (eg, the American Board of Medical Specialties, the American Society of Addiction Medicine, the American Osteopathic Association, the American Academy of Addiction Psychiatry, the American Medical Association, or the American Psychiatric Association).

The Drug Addiction Treatment Act also requires that doctors who wish to provide maintenance treatment notify the US Substance Abuse and Mental Health Services Administration of their intention, that they limit maintenance therapy to 100 patients, and that they can refer patients for counseling or other ancillary services. Physicians who meet these requirements can prescribe approved opioids in an office-based setting.

It is hoped that the expansion of maintenance treatment from specialized clinics to physician offices will bring the treatment of opioid dependence into mainstream medicine and encourage general practitioners and internists to become competent and comfortable in managing this disease.[18] Office-based treatment may help eliminate the social stigma associated with methadone programs and may help expand patient access.

BUPRENORPHINE: A PARTIAL OPIOID AGONIST

Buprenorphine and combined buprenorphine and naloxone are currently the only agents approved by the FDA for the office-based treatment of opioid dependence. Buprenorphine is a schedule III narcotic that was originally marketed for parenteral treatment of acute pain. Two sublingual tablet formulations have been developed for detoxification and maintenance treatment of opioid dependence, and these preparations were approved by the FDA in October 2002.

Buprenorphine binds with high affinity to both the mu opioid receptor (as a partial agonist) and the kappa receptor (as an antagonist). The drug's actions at the mu receptor are thought to be responsible for its usefulness in treating opioid addiction. Heroin and other opioids also bind the mu receptor, but as full agonists. Buprenorphine displaces these drugs but does not fully activate the receptor. Therefore, it causes only limited subjective and physiologic agonist effects and has a lower potential for abuse.[19]

Furthermore, although buprenorphine produces a subjective sense of well-being, it has a ceiling effect due to its partial agonist activity: higher doses do not produce more euphoria or respiratory depression.[20] Thus, it

is much safer than full agonists such as methadone, which do cause more euphoria in higher doses, are more likely to be abused, cause more intense withdrawal symptoms, and pose a higher risk of respiratory depression and death by overdose.

Thus, buprenorphine's pharmacologic properties combine the benefits of full opioid agonists and antagonists.[21] Like the full agonist methadone, buprenorphine elicits positive reinforcing effects due to its agonist activity at the opioid receptor, which reduces the desire to abuse opioids and facilitates treatment compliance. Like the antagonist naltrexone, buprenorphine has a high affinity for the receptor and dissociates from it slowly, so it has a long duration of action, allowing for less-than-daily dosing and enhancing treatment ease and compliance. Like both types of drugs, buprenorphine blocks the effects of illicit opioids, deterring their abuse.

Combination tablet deters abuse

On the other hand, like methadone, buprenorphine can be abused, particularly if taken intravenously.[22] To deter abuse, a combination tablet (Suboxone) was developed that contains buprenorphine and naloxone (Narcan) in a 4-to-1 ratio.

The naloxone in this formulation discourages patients from pulverizing and injecting the tablets but does not affect its efficacy if taken sublingually, as directed. Naloxone has poor bioavailability when taken sublingually and so has little effect, but if the combination tablets are injected, the effect of naloxone predominates, precipitating withdrawal symptoms in opioid-dependent patients or producing no subjective effect in patients who have never taken opiods.[23]

Taken orally, buprenorphine and naloxone are broken down by extensive first-pass hepatic metabolism that limits their bioavailability.

The combination product's reduced potential for abuse has made its use acceptable outside of highly regulated methadone clinics. Proper maintenance therapy with buprenorphine or buprenorphine-naloxone suppresses withdrawal symptoms in patients dependent on opioids and replaces tolerance to parenterally administered opioids.[21]

Doubling or tripling the maintenance dose can safely prolong the suppression of withdrawal symptoms. However, in some cases, high doses precipitate withdrawal, a phenomenon more likely to occur if high-dose buprenorphine is started in patients soon after being taken off high doses of illicit or maintenance opioids.[24]

CLINICAL USE OF BUPRENORPHINE

Buprenorphine is indicated for both detoxification and maintenance therapy, and can be used for starting treatment or for transferring from methadone maintenance.

Of importance: buprenorphine should be started when patients are experiencing mild to moderate withdrawal symptoms.[25] This can be as soon as 4 hours after the last use of a short-acting opioid such as heroin or as late as 48 hours or more after a taking long-acting opioid such as methadone or slow-release oxycodone (OxyContin).

Induction therapy

The goal of induction therapy is to suppress opioid withdrawal as quickly and safely as possible, with adequate doses of buprenorphine. Undertreated patients are at extremely high risk of relapsing and dropping out of treatment because of withdrawal symptoms breaking through.[25]

The initial dose is typically buprenorphine 4 mg sublingually. After a period of clinical assessment (usually 4–12 hours), an additional 2 to 4 mg of buprenorphine is often needed to ameliorate withdrawal symptoms. Brief, objective scales are available to assess the severity of withdrawal symptoms and aid in dosing.[26] Subsequent dosing should be increased over 3 or 4 days to achieve a total maintenance dosage of buprenorphine of 8 to 32 mg daily, usually in divided doses given twice a day or four times a day. In our experience, this induction is best performed in a hospital area with trained, experienced staff, for 1 to 3 days, for optimal dosage titration, psychological support, and medical assessment of comorbidities.

If patients inject buprenorphine-naloxone, they get mostly the effect of naloxone

Maintenance therapy

Maintenance treatment with buprenorphine is designed to reduce or eliminate cravings for

opioids, prevent withdrawal symptoms from emerging, and deter the use of other opioids by blocking their effects.

The optimal dosage is determined by clinical judgment based on side effects, intoxication or withdrawal, illicit opioid use or cravings, and patient satisfaction. More than 32 mg per day is rarely required. Dosing less often than once daily is feasible but is rarely preferred[27]: the dose of each tablet should be adjusted to account for the interval between dosing.[21] In an every-other-day schedule, the dose is doubled.

Unless a significant contraindication exists (eg, pregnancy or hypersensitivity to naloxone) all patients should be maintained on the combination product to reduce the likelihood of abuse or of diversion (ie, theft or sale of the product to others).[25] If buprenorphine alone was used for induction, the same dosage of buprenorphine should be used when switching to the combination product. Typically, induction is carried out with buprenorphine alone, then an equal dose of buprenorphine-naloxone is substituted when the patient is stable.

Baseline and periodic liver function tests are advised when starting buprenorphine

Discontinuing therapy

Some patients wish to discontinue maintenance therapy to achieve an opioid-free lifestyle. Although symptoms that arise after abruptly stopping buprenorphine therapy are typically less severe than after stopping full opioid agonists, gradually reducing the dosage is recommended, either by "equal reduction" (ie, reducing the daily dose by 2 mg every week) or "50% reduction" (ie, cutting the daily dose in half every week).[21] Severely dependent patients may require very gradual reduction.

Buprenorphine for detoxification

Many of these same principles also apply to the use of buprenorphine in detoxification in patients who desire complete abstinence at the onset of treatment. However, with opiate dependence, all detoxification approaches more commonly result in relapse, and maintenance is often the preferred treatment approach. Nonetheless, detoxification with buprenorphine has been accomplished in both inpatient and outpatient populations.[28]

As with substitution therapy, buprenorphine 4 to 8 mg should be started when the patient is experiencing moderate withdrawal symptoms. Daily doses should be increased until withdrawal symptoms are controlled, and then doses should be tapered over 3 to 10 days,[19] or longer if needed. Fixed and flexible dosing schedules are available, but clinical judgment and patient response should ultimately guide therapy. If naltrexone maintenance is chosen following detoxification or weaning from buprenorphine maintenance, the first dose of naltrexone should be given at least 7 days after the last dose of buprenorphine.

SIDE EFFECTS, ABUSE, AND OVERDOSE

Side effects of buprenorphine therapy include those associated with full opioid agonists (eg, constipation, nausea, vomiting) but tend to be less severe. Because buprenorphine is metabolized by the liver, effects can be prolonged in patients who have impaired hepatic function or who are taking medications that inhibit the cytochrome P450 3A4 system.

Serious side effects are extremely rare, but hepatic abnormalities may develop,[29] especially in patients with viral hepatitis or other hepatic disease, or in those who misuse the drug intravenously. Baseline liver enzymes and bilirubin tests, with repeat testing every 3 to 12 months, are a good idea, especially with a history of hepatic compromise. Buprenorphine is well tolerated in patients with renal disease.

Abuse potential of combination product low

In theory, buprenorphine is unlikely to be intravenously abused because of its partial agonist activity, slow onset, and potential for precipitating withdrawal. Few data to confirm this assumption are available for the United States, but a preliminary report suggests very little abuse occurs compared with full agonist drugs such as methadone or oxycodone.[30]

Intravenous misuse of buprenorphine tablets has been reported in France, where buprenorphine monotherapy has been used with minimal regulatory restriction since 1996.[29] The use of the combination product in the United States should deter this problem.

Overdose rarely a problem

Accidental ingestion or overdose of buprenorphine rarely presents a clinical problem, due to its poor oral bioavailability and its partial agonist activity causing a ceiling effect. In contrast to full opioid agonists, buprenorphine does not appear to cause significant respiratory depression in noncompromised patients.[25]

However, deaths have been reported from intravenous abuse of buprenorphine combined with benzodiazepines.[31] Physicians should use caution when prescribing central nervous system depressants to patients maintained on buprenorphine. Moreover, because of buprenorphine's high affinity for the opioid receptor and its slow dissociation, standard naloxone reversal may not be effective to treat respiratory depression caused by buprenorphine. Full respiratory support, including mechanical ventilation, may be needed until the effects of buprenorphine dissipate.

BUPRENORPHINE IN OFFICE-BASED TREATMENT

Clinical trials show that buprenorphine is about as effective as methadone in maintenance therapy,[32,33] but it offers several advantages: overdose is less likely, the buprenorphine-naloxone combination is unlikely to be abused, and fewer restrictions regulate its use, making it available as an office-based treatment.

Several studies support the efficacy and safety of office-based buprenorphine therapy and show that it can be successfully implemented by physicians without experience in treating opioid-dependent patients.[34–37]

Detailed clinical guidelines for using buprenorphine in the office-based management of opioid-dependent patients are available from the Substance Abuse and Mental Health Services Administration at **http://buprenorphine.samhsa.gov/**.[25]

Interested primary care physicians should consult the proceedings of the 2003 American Academy of Addiction Psychiatry consensus conference on office-based buprenorphine therapy.[38] Several issues should be considered:

- Although supervised dosing is not mandated by federal regulations or even by safety considerations, close clinical observation during the first week of therapy may lead to better treatment retention and outcomes.
- Many patients with opioid dependence have other psychiatric diagnoses, and concurrent psychosocial counseling is vital to treatment success. By law, physicians providing buprenorphine therapy must be able to provide this counseling or refer patients for it.
- Additional medical services may be required, including on-site urine toxicology testing. Physicians should be prepared to respond rapidly to illicit drug use in previously stabilized patients by adjusting the buprenorphine dose, testing the urine toxicology more frequently, or providing more intensive psychosocial services.
- The 8 hours of training required for primary care physicians to provide office-based buprenorphine therapy are usually adequate. Additional competence may be gained by consulting or observing an experienced colleague.
- A strong working relationship with a pharmacy where patients can regularly obtain their medication can be extremely helpful.

Office-based treatment increases access

Office-based treatment is achieving the objectives behind the major impetus for the Drug Addiction Treatment Act of 2000 and the approval of buprenorphine: more patients have access to treatment, and the base of physicians providing therapy has expanded.

Office-based treatment may attract a different type of patient who is earlier in the progression of opioid dependence, thereby possibly preventing virus transmission from intravenous drug use. A recent study found that patients entering office-based buprenorphine treatment are more likely than patients entering a methadone clinic to be male, employed full-time, have no history of methadone treatment, have fewer years of opioid dependence, and have a lower rate of intravenous drug abuse.[39]

The number of physicians who have received the waiver to prescribe buprenorphine has increased dramatically over the past few years. In 2003, only 1,185 physicians could prescribe buprenorphine in an office-based setting[40]; there are now more than 8,000.[41] ■

Intravenous abuse of buprenorphine combined with benzodiazepines can be fatal

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