Office-Based Buprenorphine for Patients with Opioid Dependence

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Abstract

The profile of opioid dependence in the United States is changing. Abuse of prescription opioids is more common than that of illicit opioids. Recent data indicate that there are approximately 1.6 million individuals with prescription opioid abuse or dependence and 323,000 with heroin abuse or dependence. Despite this prevalence, nearly 80% of these individuals go untreated. One option for expanding treatment is the use of buprenorphine and the buprenorphine/naloxone combination. Buprenorphine is a partial opioid agonist that can be prescribed by trained Internists and dispensed at pharmacies.

The case-based discussion in this paper addresses the clinical presentation of a patient with opioid dependence and describes the relatively new practice of office-based treatment with buprenorphine/naloxone. It examines the different components of treatment, the role of the Internist in providing this treatment, and the logistics of treating this growing and multi-faceted patient population.

Clinical presentation of opioid dependence

A 35-year-old patient returns for the management of her diabetes mellitus and depression. In reviewing her chart, you notice that she has received prescriptions for oxycodone from your colleagues for the past six months. She has requested early refills on her oxycodone. You originally prescribed oxycodone for a wrist fracture last year, but there is no indication that she continues to require this medication.

She appears uncomfortable when you express concern. She admits to excessive use of oxycodone despite the healing of her fracture. She feels pain “all over” once the oxycodone wears off, and notes that opiates give her energy. She has visited different doctors and emergency departments in the past six months to obtain opioids and has stolen morphine from her mother.

Is this patient opioid dependent? How common is addiction to prescription opioids?

Diagnosing opioid dependence can be challenging, especially in patients who take prescription opioids and report pain (1). There are behaviors that may alert the clinician to potential misuse of controlled substances, although none have been validated. These include...
lost, stolen, or adulterated prescriptions, use of other sources (for example, obtaining prescriptions from other physicians, purchases from non-medical professionals) to obtain medications, requests for early refills, and urine toxicology testing that is inconsistent with prescriptions (2, 3). Anxiety symptoms, fair/poor health, misuse of another class of prescription medications, heroin use, and initiation of substance use before age 13 are more common in patients who misuse prescription opioids and have a diagnoses of opioid abuse or dependence (4).

The criteria for diagnosing opioid dependence in the Diagnostic and Statistical Manual, Fourth Edition, Text Revised (5) include physical dependence and behaviors that constitute addiction (Table 1). Physical dependence occurs after short periods of opioid use and is characterized by tolerance and withdrawal (6, 7). Opioid dependence (addiction) is a chronic and relapsing disease that is characterized by impaired control over drug use that persists despite harms (5).

There are neurobiologic changes that occur in the development of opioid dependence. Opioid use leads to neuronal adaptations in various regions of the brain. Adaptations in G protein-coupled receptors, up-regulation of cyclic adenosine monophosphate second messenger pathways, and changes in transcription and translation (8), result in tolerance, withdrawal, and craving.

The profile of opioid dependence in the United States is dominated by prescription opioids. From the 2006 National Survey on Drug Use and Health, a federally-administered sample that may under-report the prevalence, due to under-sampling, of marginalized populations, 3.7 million persons reported lifetime and over half a million reported past-year heroin use (9). Approximately 323,000 individuals met criteria for heroin abuse or dependence. Over 12 million reported non-medical use of prescription opioids (9). Of these, 1.6 million met criteria for prescription opioid abuse or dependence. Demographically, 73% were employed, 77% completed high school, 41% had an annual income of greater than $40,000, and 61% were insured (4). Most patients do not receive treatment. In 2005 only 331,000 individuals entered treatment for opioid dependence (10). The discrepancy between the scope of the problem and the number receiving treatment creates a need to expand access.

She becomes teary and admits to snorting heroin to relieve withdrawal symptoms. She has injected heroin once, last New Years Eve. You refer her to a local clinic for methadone. She states that she knows too many people and can not afford to be seen in a drug treatment clinic. She requests a referral for “detox” so she can “be off of everything”.

Is detoxification the right treatment option for some patients?

Patients may voice a desire to be “off of everything”. Studies on detoxification are often limited by lack of long-term follow-up (11). There is good quality evidence (12) that outcomes with detoxification, compared to ongoing medication treatment (maintenance) with the opioid agonist methadone or the partial agonist buprenorphine, are worse. A meta-analysis revealed that methadone, as compared to detoxification, more effectively retained patients in treatment (Relative Risk (RR) = 3.05; 95% Confidence Intervals (CI): 1.75–5.35) and decreased heroin use (RR=0.32; 95% CI: 0.23–0.44) (13). Good quality evidence reveals that buprenorphine detoxification outcomes are similar. A study of patients randomized to individual counseling and either buprenorphine maintenance or a six-day buprenorphine detoxification found that 75% of the maintenance group, compared to 0% of the detoxification group, were in treatment at one year (P<0.001) (14). Four detoxified patient died during follow-up and none remained in treatment after 50 days. In another study.
of buprenorphine detoxification only 5/37 (14%) patients produced two or fewer opioid positive urines and were retained in treatment for 12 weeks (15).

Some studies demonstrate reasonable short-term treatment retention with detoxification (16, 17) and a trial of detoxification, along with counseling, may be appropriate for patients with a short period and low level of dependence (16, 18). Patients attempting detoxification should be warned that they will lose tolerance and risk overdose and death if they resume opioid use at their pre-detoxification levels (19).

The patient undergoes a 14-day detoxification. One week later she reports that she is abusing oxycodone. She wants to know if you can provide treatment from your office. You indicate that you received training and have begun providing a new medication, buprenorphine/naloxone, for opioid dependence.

What are the important differences between buprenorphine/naloxone and methadone treatment?

Buprenorphine is a partial agonist at the mu opioid receptor (Table 2). It has low abuse and diversion potential (25), especially when combined with the antagonist naloxone, and has a low risk for respiratory depression or overdose (26). It is a sublingual tablet usually taken daily. While there is good evidence demonstrating reduced treatment retention (RR=0.79; 95% CI: 0.62–1.01) and reduced ability to suppress illicit opioid use (Standardized Mean Difference=0.27; 95% CI: 0.05–0.50) in trials comparing buprenorphine with methadone (27), buprenorphine and buprenorphine/naloxone may be prescribed by physicians and dispensed at pharmacies while methadone must be dispensed from opioid treatment programs (28).

In the United States, the buprenorphine/naloxone tablet comes in a 4:1 ratio (29–34). This combination may reduce the abuse potential in contrast to buprenorphine alone (35, 36). Buprenorphine is well-absorbed sublingually, and naloxone is absorption is limited (37, 38). When injected naloxone, however, is rapidly bioavailable and can precipitate withdrawal in opioid-tolerant patients (39). Physicians should use the buprenorphine/naloxone combination instead of the buprenorphine monotherapy except for directly observed treatment or during pregnancy (40).

Women receiving buprenorphine/naloxone who become pregnant should switch to buprenorphine alone or methadone (40). Current data indicates that buprenorphine may be safe in pregnancy (41). Studies on naloxone’s safety in pregnancy do not exist (42).

What is required for a physician to prescribe buprenorphine/naloxone for opioid dependence? What training and support are needed?

The Drug Addiction Treatment Act or DATA 2000 (43) allows qualifying physicians to use approved medications to treat opioid dependence (Table 3). Most physicians will qualify by completing an eight-hour course on the treatment of opioid dependence. Information about training is available at http://www.buprenorphine.samhsa.gov. In 2005, 56% of physicians eligible to prescribe were non-addiction specialists (25). As of January 2008, 13,095 U.S. physicians were trained.

Once qualified, a physician must notify the Center for Substance Abuse Treatment of their intent to practice under DATA 2000. Notification forms are available at http://www.buprenorphine.samhsa.gov. Subsequently, the Drug Enforcement Administration will issue a second registration which is needed on all prescriptions for buprenorphine/naloxone for opioid dependence.
To assist physicians who are not accustomed to providing treatment for addiction, the Center for Substance Abuse Treatment has provided a practice guideline (40) and funds the Physician Clinical Support System (http://www.pcssmentor.org/) to provide mentoring services via email, telephone, and/or onsite visits to buprenorphine/naloxone-prescribing physicians’ offices.

You discuss with her that opioid dependence is a medical condition. You note that it is a chronic and relapsing disorder that may need treatment with medication, counseling and lifestyle modification. She agrees to try buprenorphine/naloxone.

What are the features of office-based buprenorphine/naloxone treatment? What does a physician need to provide this care?

Office-based treatment emphasizes a medical approach to opioid dependence. The important features of office-based buprenorphine treatment are outlined (Table 4). Not all patients will be appropriate for receiving treatment from an Internist. Research demonstrates that patients who lack significant and untreated psychiatric (for example psychosis) or substance use comorbidity can do well in this setting (44–47). Patients who have previously failed office-based treatment, or who have severe psychiatric illness or comorbid substance use, high levels of physical dependence, or who are unable to comply with office guidelines may do poorly (40).

A history and physical exam aids patient selection. The history should confirm the diagnosis of opioid dependence. Documentation should include the effect of dependence on daily function, a substance use history, past treatments, psychiatric history and injection-related diseases. Appropriate testing and vaccinations should be provided (48–50). Laboratory assessments should include liver function tests (51) and a complete blood count and standard chemistries as indicated. Buprenorphine/naloxone appears to possess minimal risks of liver toxicity when taken sublingually. Liver function tests should be conducted at baseline and periodically if indicated. (52).

Urine toxicology monitoring is important because patients may deny drug use. Once a patient has entered maintenance treatment, urine testing can be conducted weekly to monthly (40). Urine immunoassay testing can infrequently give false positive and false negative results resulting from interference from contaminants (53, 54). Gas chromatography/mass spectroscopy can be used for further analysis. Repeat urine samples can increase accuracy. Standard urine analyses detect naturally occurring opioids and their metabolites (for example, morphine, heroin). Testing for synthetic or semi-synthetic opioids (oxycodone, methadone, hydrocodone), should be requested. Standard urine assays detect recent use of heroin/morphine (1–3 days), some benzodiazepines (up to 30 days), cocaine (1–3 days), methadone (2–4 days), marijuana (chronic use, up to 30 days; occasional use, 1–3 days), and oxycodone (1–2 days) (55). The response to positive urine tests should take into account the overall clinical picture, type of drug found, and stage in treatment. Responses include increasing the frequency of visits, a dose change, the initiation of or an increasing level of counseling, or a transfer to another form of care (methadone, in-patient).

The patient and provider should agree upon the terms of treatment before the first prescription is written. There are resources to assist physicians in discussing buprenorphine/naloxone induction and maintenance, medication adherence, and examples of patient/provider agreements (http://www.csam-asam.org/resources-buprenorphine_info.vp.html). Information for patients and their families about buprenorphine/naloxone treatment is also available (56).
Are there medication interactions to consider?

Buprenorphine is metabolized to norbuprenorphine by the cytochrome CYP3A4 isoenzyme. Theoretically, CYP 3A4 inhibitors may increase and CYP3A4 inducers may decrease plasma concentrations of buprenorphine and providers should consider adjusting the buprenorphine/naloxone dose accordingly. Clinical experience suggests otherwise. Reports of interactions are lacking. Empiric studies focus on protease inhibitor medications (57). This data indicate that while some pharmacokinetic changes may lead to sedation in a small proportion of patients receiving atazanavir and buprenorphine, most medication interactions do not appear to be of clinical significance (58–60).

What instructions should be given to patients prior to their first dose of buprenorphine/naloxone?

Patients should be instructed to abstain from opioids for 12–24 hours (with short-acting opioids such as heroin or oxycodone) or 24–36 hours (with long-acting opioids such as methadone or sustained release oxycodone) prior to their first dose of buprenorphine/naloxone. This will help to ensure that they are experiencing mild to moderate opioid withdrawal as they take their first dose. Scheduling the induction appointment early in the day can decrease the risk of prior opioid use. Starting treatment prior to the end of the week allows for weekday follow-up.

The patient should present for induction in mild to moderate withdrawal. Formal opioid withdrawal scales are available to assess the severity of a patient’s withdrawal (40). Buprenorphine has high affinity for the mu opioid receptor but partial agonist activity. It can cause opioid withdrawal by displacing full opioid agonists. The overall decrease in agonist activity that accompanies the abrupt transition from a full agonist to buprenorphine is referred to as precipitated withdrawal (61–63).

Transferring patients from methadone to buprenorphine can be difficult since methadone is a relatively long-acting opioid agonist and can have stores in the liver and adipose tissue that can be released leading to ongoing agonist activity (64). The data on the optimal dose of methadone for a patient to be on as they transfer to buprenorphine/naloxone are limited. One guideline recommends <30 mg per day of methadone (64). Recent clinical experience suggests that patients should decrease the dose to <40 mg per day (65, 66). In addition, the appropriate dose of buprenorphine/naloxone for patients who are transferring from methadone is not clear. One study found that lower doses of buprenorphine/naloxone produced less withdrawal compared to larger doses in patients stabilized on methadone (67). Induction should be initiated 24–48 hours after the last dose of methadone and when the patient is manifesting opioid withdrawal.

Clinicians have developed induction techniques that are compatible with primary care and office-based practice (20, 44–47, 68, 69). One detail to address is how patients will obtain their first medication dose. The physician can keep a supply of medication in the office for administration on the induction day (storage must be consistent with regulations for Class III controlled substances), they can have the patient fill a prescription for the first day’s dose and bring it to the office, or they can fax a prescription to a pharmacy and have the medication delivered. Home inductions have demonstrated feasibility in select populations (44).

Once the patient is documented to be in withdrawal, a reasonable first dose of buprenorphine/naloxone is 2/0.5–4/1 mg. Typically the maximum first day dose ranges from 8/2 mg to 12/3 mg. During the induction and stabilization period, the patient should be seen at least weekly. Biweekly or monthly visits can be initiated once the patient has a stable medication dose and is making progress towards abstinence. Key components of these visits
include discussion of ongoing drug use, identification of triggers, discussion of urine toxicology results, and potential modifications in medication dosing.

**What type of counseling should be provided?**

Pharmacologic treatment of addiction can be enhanced by counseling. Opioid dependent patients benefit from education and counseling similar to how patients with diabetes and hypertension benefit from education and counseling (70). Some patients will have ongoing opioid use due to the psychological aspects of their addiction or may develop or manifest use of other substances (for example, alcohol, benzodiazepines, cocaine). Concomitant drug and alcohol use can be addressed with specific counseling techniques (71, 72). One study of treatment program-based methadone-maintained patients demonstrated improved abstinence and treatment retention in patients receiving more intensive services (73). A systematic review of studies in patients receiving treatment program-based methadone demonstrated that counseling was associated with decreased heroin use but non-significant improvements in treatment retention (18). Trials with differing intensities of counseling for patients receiving either buprenorphine or buprenorphine/naloxone are contradictory (45, 74). An observational study of buprenorphine/naloxone in primary care found a positive association between counseling attendance and treatment retention (47). In another study, approximately half of the patients sought out counseling and a quarter attended self-help groups (44). A trial of three levels of counseling and visit frequency was unable to detect decreased drug use or improved retention in patients who received 40 minutes of weekly counseling compared with those receiving 20 minutes (45). Less intensive counseling was associated with greater patient satisfaction (75).

Physicians prescribing buprenorphine/naloxone must be able to access counseling for their patients (43). The actual use of counseling, however, appears to be infrequent. In a report of patient experience, 41% reported no counseling in their first month of treatment (76). The options for counseling in office-based practice vary by setting. Some practices provide on-site counseling services via allied health professionals, nurses and/or social workers. Most settings need to refer to local services. Physicians can cultivate relationships with nurses, social workers, mental health counselors, treatment facilities, or local self-help groups. It is useful to review local addiction treatment providers (http://findtreatment.samhsa.gov) and those covered by a patient’s insurance. Patients with significant psychiatric comorbidity may need co-management with a psychiatrist or may need to be transferred to the care of an addiction psychiatrist.

**How does one bill for office-based buprenorphine/naloxone?**

Office-based buprenorphine treatment is new and the reimbursement system is evolving (77). Private and public insurers have variable coverage. Some insurers cover all services provided by an Internist and others do not. Items that need to be covered include office visits (typically weekly during stabilization and biweekly or monthly once patient is stable), medication, counseling (typically weekly or biweekly during stabilization and monthly once patient is stable), urine testing conducted weekly to monthly), and blood tests (at baseline and repeated when clinically indicated) (40). Urine toxicology analyses range between $5 and $55 depending on the type of assay and the number of tests performed. Daily medication doses generally fall within 8 and 24 milligrams and can cost $4 to $19 per day (78). Some patients may need to pay out of pocket for certain items. Physicians should determine how the expenses will be covered prior to initiating treatment. The International Classification of Diseases, Ninth Revision code for opioid dependence is 304.0. Providers can use Current Procedural Terminology codes such as outpatient new patient (99201–05), outpatient consultation (99241–45), and outpatient established patient revisit (99211–15) for office visits.
How should one educate their office staff and their colleagues providing coverage?

It is useful to educate office staff to facilitate a positive experience for the patients, providers, and staff (79). Training for office staff should include general education about addiction and the rationale for medication treatment (45, 70). It may be necessary to educate staff about using a non-judgmental attitude (80, 81). Staff should be aware of guidelines regarding confidentiality (82).

Buprenorphine/naloxone providers must assure cross-coverage for their patients. The covering physician only needs a special Drug Enforcement Administration registration if prescribing the medication. General medical and psychiatric conditions can be covered without this specific registration.

The patient does well with buprenorphine/naloxone and attends monthly appointments with you and a social worker. Her hemoglobin A1C has improved due to better medication compliance. Her depression improves with abstinence yet ultimately only fully responds to a selective serotonin reuptake inhibitor. After several months your service pages you. The patient is in the emergency room with a kidney stone. She is worried about receiving opioids for pain and is not sure if she should take her buprenorphine/naloxone.

What happens if a patient requires pain medication while receiving buprenorphine/naloxone?

It is appropriate to use opioids to manage pain in opioid dependent patients. Clinicians should be cautious to avoid precipitating a relapse to uncontrolled use. One strategy is to discuss this concern with the patient and limit the number of pills and duration of opioid use. Opioid dependent patients often require higher doses than non-dependent patients because of tolerance.

Buprenorphine has high affinity and slow dissociation at the mu opioid receptor. This means that it can be difficult to obtain analgesia in a patient receiving buprenorphine/naloxone. Acute pain management in patients receiving methadone and buprenorphine has been reviewed recently (1). Briefly, acute moderate pain can be managed by continuing the buprenorphine/naloxone and adding non-steroidal anti-inflammatory agents. If a painful condition is anticipated (for example, elective surgery) the last dose of buprenorphine/naloxone should occur approximately 24 hours before the need for analgesia. For brief pain (for example, 8 to 12 hours), short-acting full opioid agonists can be titrated. Alternatively, a case report described the benefits of a temporary increase of buprenorphine/naloxone for analgesia (83).

For severe pain of more than 12 to 24 hours, buprenorphine/naloxone should be discontinued and replaced with a full agonist analgesic. Initial doses may be higher than needed on subsequent days to overcome buprenorphine’s partial blockade of the opioid receptors. Once the pain no longer requires opioids, the patient should discontinue their opioid medication, be allowed to experience withdrawal, and be inducted back onto buprenorphine/naloxone.

She successfully passes her kidney stone and starts back on the buprenorphine/naloxone. She returns to your office two weeks later and when asked about her drug use, she hesitates and then admits that over the weekend, after drinking with friends, she took some oxycodone. She denied feeling any euphoria or withdrawal, only guilt.
How should episodic drug use be handled?

Episodic illicit opioid use in previously abstinent patients is common in patients receiving buprenorphine/naloxone. In one trial, only 27% of patients achieved continuous abstinence from opioids for 13 weeks (84). Another study reported 26% of patients obtaining greater than or equal to 12 weeks of consecutive abstinence (85). In patients followed for at least two years, 9% of urines had evidence of illicit opioid use (86). This episodic use does not represent a treatment failure but needs to be addressed to prevent a complete relapse. The clinician should ensure that the patient is taking their full dose of medication and allowing adequate time for it to dissolve. The patient should be asked about the circumstances regarding illicit opioid use (for example, concomitant alcohol use or psychosocial stressors) and symptoms of opioid withdrawal or craving. The dose of medication can be increased in 2–4 mg intervals to ameliorate craving or withdrawal. The clinician can increase the frequency of urine testing and/or counseling (for example, every four or seven days) and shorten the duration of prescriptions (for example, seven or fourteen days).

You increase the frequency of urine testing to weekly for four weeks and the patient experiences no further relapses and continues to see you on a monthly basis.

The patient has now been in office-based treatment with you for over a year and is asking about the option of discontinuing buprenorphine/naloxone.

How should buprenorphine/naloxone be tapered? How should one educate patients who would like to discontinue pharmacotherapy for opioid dependence?

Most literature supports the efficacy of maintenance treatment over that of detoxification. In some cases, detoxification is the endpoint of long-term opioid agonist treatment with either buprenorphine or methadone. Withdrawal from buprenorphine may be milder than withdrawal from other opioids because of its partial agonist properties. Longer tapers, often over months, are more successful than more rapid tapers. Data from a small study that examined two detoxification schedules over 12 days versus 36 days showed that gradual reduction in buprenorphine produced less subject-rated opioid withdrawal, illicit opioid use, and greater treatment retention than the more rapid detoxification (87).

Physicians should consider ancillary medications to assist with opioid withdrawal symptoms in patients who choose detoxification. One trial of buprenorphine/naloxone detoxification showed that approximately 80% of patients received at least one ancillary medication for insomnia (62%), anxiety and restlessness (52%), and arthralgias (54%) (16).

Counseling improves outcomes in detoxification. A systematic review found that counseling increased the number of patients who completed treatment (RR=1.7; 95% CI: 1.11–2.55), who were abstinent from drugs (RR= 2.4; 95% CI: 1.61–3.66), and decreased the number of patients who failed to follow-up (RR=0.48; 95% CI: 0.38–0.59) (18).

Patients considering buprenorphine/naloxone detoxification should know the risk of relapse to drug use and overdose once off maintenance treatment. In addition, the provider should highlight the potential need to increase counseling and/or increase the monitoring of urine toxicologies during and after the period of tapering.

After discussing the various treatment options with you, she decides to continue treatment but states that she would like to consider the option of slowly tapering off buprenorphine/naloxone in the future.

Internists are often involved with many of their patients’ clinical issues that historically have been delegated to other specialties (for example, depression treatment, end-of-life care). Office-based buprenorphine/naloxone treatment affords the opportunity for Internists to
participate in the care and treatment of their patients who have developed opioid
dependence. It also provides the opportunity for opioid dependent patients to experience
their addiction as a chronic medical condition that responds to treatment and can be
addressed by a physician. The new option afforded by buprenorphine/naloxone can result in
dramatic changes in a patient’s life and satisfaction for their provider.

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References

1. Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance
2. Ives TJ, Chelminski PR, Hammett-Stabler CA, et al. Predictors of opioid misuse in patients with
3. Reid MC, Engles-Horton LL, Weber MB, Kerns RD, Rogers EL, O’Connor PG. Use of opioid
medications for chronic noncancer pain syndromes in primary care.[see comment]. Journal of
4. Becker WC, Sullivan LE, Tetrault JM, Desai RA, Fiellin DA. Non-medical use, abuse and
dependence on prescription opioids among U.S. adults: Psychiatric, medical and substance use
correlates. Drug Alcohol Depend. 10.1016/j.drugalcdep.2007.09.018
6. American Academy of Pain Medicine, American Pain Society, American Society of Addiction
Accessed at http://www.ampainsoc.org/advocacy/opioids2.htm on
7. O’Brien CP, Volkow N, Li TK. What’s in a word? Addiction versus dependence in DSM-V.
9. Office Applied Studies, Substance Abuse and Mental Health Services Administration. (Research
Triangle Institute). Overview of Findings from the 2006 National Survey on Drug Use and Health.
2007.
10. Substance Abuse and Mental Health Services Administration (SAMHSA). [September 19, 2007]
TEDSAd2k3Index.htm on
Updates, 2000–2003. Agency for Healthcare Research and Quality; Rockville, MD: Ratings:
3rduspsfl/ratings.htm on [January 14, 2008]
13. Mattick RP, Breen C, Kimber J, Davoli M. Methadone maintenance therapy versus no opioid
replacement therapy for opioid dependence. Cochrane Database System Review. 2003
14. Kakko J, Svanborg KD, Kreek MJ, Heilig M. 1-year retention and social function after
buprenorphine-assisted relapse prevention treatment for heroin dependence in Sweden: a
15. Collins ED, Kleber HD, Whittington RA, Heitler NE. Anesthesia-assisted vs buprenorphine-or
clonidine-assisted heroin detoxification and naltrexone induction: A randomized trial. JAMA.


42. DuPont Pharmaceuticals-U.S. Narcan [package insert]. Newark, DE: Rev 2/95


78. Jones, ES.; Moore, BA.; Sindelar, JL.; O’Connor, PG.; Schottenfeld, RS.; Fiellin, DA. Drug Alcohol Depend. Cost Analysis of Clinic and Office-based Treatment of Opioid Dependence: Results with Methadone and Buprenorphine in Clinically Stable Patients. Under revision


Buprenorphine/naloxone, a medication used to treat opioid dependence, can be prescribed by a trained Internist and provides increased access to treatment.

Buprenorphine/naloxone is less effective than methadone in retaining patients in treatment and decreasing illicit opioid use, yet is able to be prescribed by office-based physicians and dispensed at pharmacies.

Patients who lack significant and untreated psychiatric or substance use comorbidity, who have not failed office-based treatment in the past, and who are able to comply with office guidelines are likely good candidates for office-based buprenorphine/naloxone treatment.

Physicians can qualify to prescribe buprenorphine/naloxone by completing an eight-hour course on the treatment of opioid dependence and then will receive a new registration from the Drug Enforcement Administration which is needed on all prescriptions written for buprenorphine/naloxone.

Office-based treatment of opioid dependence affords the opportunity for Internists to care for and treat their opioid dependent patients and allows patients to view their addiction as a manageable medical condition.
Table 1

A maladaptive pattern of opioid 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 opioids to achieve intoxication or desired effect
   b. Markedly diminished effect with continued use of the same amount of opioids

2 Withdrawal, as manifested by either of the following:
   a. The characteristic withdrawal syndrome for opioids
   b. Opioids (or a closely related substance) is taken to relieve or avoid withdrawal symptoms

3 Opioids are 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 opioid use

5 A great deal of time is spent in activities necessary to obtain opioids (for example, visiting multiple doctors or driving long distances), use of opioids, or recover from its effects

6 Important social, occupational, or recreational activities are given up or reduced because of opioid use

7 Opioid 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 opioids (for example, current opioid use despite recognition of opioid-induced depression)
### Table 2

Comparison of Buprenorphine, Buprenorphine/naloxone and Methadone for the Treatment of Opioid Dependence

<table>
<thead>
<tr>
<th>Pharmacologic action at mu opioid receptor</th>
<th>Buprenorphine or Buprenorphine/naloxone</th>
<th>Methadone</th>
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<tr>
<td>Buprenorphine: Partial agonist; Naloxone: Full antagonist</td>
<td>Pharmacological withdrawal, maintenance therapy</td>
<td>Pharmacological withdrawal, maintenance therapy</td>
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<tr>
<td>Full agonist</td>
<td>Oral</td>
<td>20–120 milligrams **</td>
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<th>Route of administration</th>
<th>Sublingual *</th>
<th>Oral</th>
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<td>Buprenorphine: 2–32 milligrams ** (20); Naloxone: 0.5–8 milligrams</td>
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<td>20–120 milligrams **</td>
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<th>Dose</th>
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<th>Frequency of administration</th>
<th>Daily or thrice weekly</th>
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<td>Headache, nausea, sweating, constipation, rhinitis (21–23)</td>
<td>Cardiac dysthymia, hypotension, diaphoresis, constipation, nausea, vomiting, asthma, dizziness, lightheadedness (24), sedation, constipation</td>
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<th>Primary side effects (not related to withdrawal syndrome)</th>
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<td>Contraindications</td>
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<td>Use in pregnancy</td>
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<td>Location of prescribing/dispensing in treatment of opioid dependence</td>
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<td>Regulations on prescribing and dispensing</td>
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<tr>
<td>Methadone cannot be prescribed for the care of opioid dependent patients by physicians except for up to 72 hours as a bridge to treatment entry. It can be dispensed only from licensed opioid treatment programs; Federal regulations govern frequency of medication dispensing (for example, daily, thrice weekly, weekly)</td>
</tr>
</tbody>
</table>

| Insurance coverage | Variable, depending on plan | Variable, depending on plan |

* Naloxone not well absorbed sublingually resulting in primary buprenorphine effect. Naloxone added to discourage injection misuse.

** Lower doses typically reflect dose initiation or dose taper in stabilized patients.
Table 3
Criteria for Qualifying to Prescribe Under Drug Addiction Treatment Act of 2000

<table>
<thead>
<tr>
<th>Licensed physician</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meet one of the following:</td>
</tr>
<tr>
<td>1 Completion of an eight-hour course provided by the American Society of Addiction Medicine, the American Academy of Addiction Psychiatry, the American Osteopathic Association, the American Psychiatric Association, or the American Medical Association</td>
</tr>
<tr>
<td>2 Board certification in Addiction Psychiatry</td>
</tr>
<tr>
<td>3 Certification in Addiction Medicine by the American Society of Addiction Medicine of the American Osteopathic Association</td>
</tr>
<tr>
<td>4 Serve as an investigator in a buprenorphine clinical trial leading to the Food and Drug Administration approval</td>
</tr>
<tr>
<td>5 Training/experience as determined by state medical licensing board</td>
</tr>
<tr>
<td>6 Other criteria established through regulation by the Secretary of Health and Human Services</td>
</tr>
</tbody>
</table>
Table 4
Requirements for Physicians to Provide Buprenorphine or Buprenorphine/naloxone Treatment

<table>
<thead>
<tr>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certification in Addiction Medicine, Psychiatry or completion of a Drug Addiction Treatment Act (DATA 2000)-qualifying eight-hour training course</td>
</tr>
<tr>
<td>Receipt of a second registration from the Drug Enforcement Administration allowing the prescription of buprenorphine and buprenorphine/naloxone Ability to assess diagnosis of opioid dependence</td>
</tr>
<tr>
<td>Ability to conduct urine toxicology testing (on-site or referral to outside laboratory)</td>
</tr>
<tr>
<td>Ability to conduct basic laboratory assessments</td>
</tr>
<tr>
<td>Capacity to establish linkages to mental health professionals and substance abuse treatment programs</td>
</tr>
</tbody>
</table>