

Office-Based Treatment of Opiate-Dependent Patients with Buprenorphine: *It's About Time*

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ABSTRACT

Buprenorphine, a partial agonist with numerous unique properties, has been available in the United States in an injectable form for the past 2 decades. However, with the exception of physicians at specialized methadone clinics, it had been illegal for anyone to prescribe opiate replacement therapy for opiate dependence in the US since 1914. In 2000, the amendment to the Controlled Substance Abuse Act ensured that individuals who take a sanctioned course are now able to prescribe buprenorphine for up to 30 patients at a given time. There are several clinical advantages associated with the use of buprenorphine. First, overdose is much less likely to occur with buprenorphine than with other opiates. Second, buprenorphine doses >32 mg are clinically ineffective, therefore discouraging increased and endlessly escalating use. Third, buprenorphine blocks the effects of other opiates; those who have a lapse do not experience any opiate high, therefore relapse with this drug is much less likely. Buprenorphine has unique pharmacologic properties and unique regulatory features as well. From a regulatory standpoint, buprenorphine allows the patient to be treated for opiate dependence in an office setting, thus enabling increased freedom for both patient and physician.

INTRODUCTION

In 2000, with the introduction of the amendment to the Controlled Substance Act, regulatory bodies of the United States government ushered in a revolutionary period in the treatment of opiate dependence. For the first time in >80 years, physicians in the US were able to prescribe opiate replacement therapy for opiate-dependent patients.¹

Needs Assessment: Opiate dependence is increasing among a wide variety of populations. An oral form of buprenorphine is newly available. It has a number of unique pharmacologic advantages over other treatments, as well as regulatory advantages for physicians. This article offers an introductory primer to the medication and the best strategies for using it.

Learning Objectives:

- Identify the regulations involved in obtaining permission to prescribe buprenorphine and using it clinically.
- Review the pharmacology and clinical use of buprenorphine.
- Recognize the role of adjuvant therapies, as well as additional medications, to be used in conjunction with buprenorphine.

Target Audience: Primary care physicians and psychiatrists.

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The long and torturous history of opiate misuse, abuse, and dependence, is beyond the scope of this article. However, briefly, the federal regulation concerning prescribing opiates in the US began with the Harrison Act of 1914. This act was in response to widespread abuse of opiates, largely by a middle class population. While the Harrison Act did not actually prohibit physicians from prescribing opiates for addicted patients within a legitimate medical context, regulatory agencies ensured that such use was, in effect, prohibited. Thus, from 1914 until the 1960s, opiate-dependence treatment with substitution was essentially prohibited in the US.

The need for additional treatment of opiate dependence was recognized in response to widespread use of opiates by US soldiers in Vietnam. Given the high prevalence of opiate addiction in war veterans, it was deemed necessary that methadone be made available as a therapeutic tool. Since the late 1960s, methadone has been available in the US in specially regulated clinics with strict rules and controls.² Many professionals believe that while methadone maintenance is quite effective and certainly indicated for many patients, the current regulations can act as barriers to treatment for numerous people.³ That there are far fewer slots at methadone treatment clinics than there are opiate-dependent people also creates a barrier to treatment.

Congress enacted an amendment to the Substance Abuse Act in 2000, calling for the availability of special training for physicians to prescribe opiates that were Schedule III or below. Buprenorphine, a partial opiate agonist, was approved as a Schedule III drug and would be available for treatment in the outpatient setting. Some specific caveats were put in place from a logistical standpoint. Most notably, if physicians were to prescribe, maintain, or detoxify patients on this medication outside of a hospital setting, they would be required to complete additional training. This eventually became an 8-hour course developed in a collaborative manner and offered by a variety of professional addiction organizations and government agencies.⁴

Taking the course and completing an exam allows a clinician to obtain a special Drug Enforcement Administration (DEA) certification administered by the state regulatory agency. A cap of 30 patients at a time is stipulated for individual clinicians in an effort to prevent very large and therefore possibly ill-managed treatment practices.⁵ Recently, that cap has come under scrutiny and criticism. Several professionals believe that it is a hindrance, especially in areas of the country where the availability of physicians certified to prescribe buprenorphine is limited. Sensibly, the cap for

group practices has recently been eliminated, but the 30-person cap remains for individual physicians.

While most physicians who prescribe buprenorphine are deeply impressed with its clinical efficacy and ease of use, the medical community at large has been slow to accept the medication.⁶ This is based on a variety of reasons. First, there remains a large stigma to opiate dependence in the US, which is transferred to the professionals who choose to treat these addicted patients.⁷ Second, the long history of draconian attempts to regulate physicians has created a climate of fear in the medical community in terms of dealing with both addicted patients and those venturing into the area of opiate dependence. Third, the pharmacology of buprenorphine, if not unique then at least complicated, makes it somewhat difficult to understand. This article provides a basic description, but because the drug is still a complicated pharmacology, many physicians have been reluctant to treat patients with it. Fourth, while maintaining a patient on buprenorphine is usually quite simple, the induction phase, in which it is necessary for the patient to be in a state of withdrawal, is sometimes difficult to manage from a logistic point of view.⁸ Lastly, early efforts at educating clinicians, in an effort to prevent misuse, may have had the unintended consequence of inducing fear into the clinicians, rather than instilling a sense of the safety of the medication.

PHARMACOLOGY OF BUPRENORPHINE

Buprenorphine is a partial μ -receptor agonist. It binds very tightly to the μ -opiate receptor. However, unlike traditional opiates, buprenorphine occupies approximately 70% of the receptor. Buprenorphine differs from other opiates in that it lacks the almost infinite capacity for the development of tolerance. It is quite common in practice to come across patients who started out with one bag of heroin or a couple of typical opiate tablets, who are now consuming ten times that amount just to feel normal. This is not the case with buprenorphine. An average maintenance dose of buprenorphine is approximately 16 mg. The highest dose is approximately 32 mg, with some variation. Increasing doses >32 mg tend to have no increased clinical efficacy, and increased doses significantly >32 mg can actually induce autoantagonism. Thus, the clinician does not have to worry about the patient using increased amounts or infinitely increased amounts of buprenorphine.

Buprenorphine has a relatively safe profile in terms of the possibility of overdose.⁹ There is a consensus that most opiate overdoses are accidental, or quasi-accidental, per-

haps resulting from carelessness, lack of understanding of the potency of the opiate being taken, and being unaware of decreased tolerance. For example, an individual who is imprisoned and then released may not realize that his or her tolerance has greatly reduced. Returning to the previous dosage may result in fatal consequences. The pharmacology of buprenorphine does not make overdose impossible, but it does make it much less likely.¹⁰

Because of the high binding capacity of buprenorphine, it has the overall effect of acting as an opiate blocker. This is extremely useful because if a patient on buprenorphine relapses, there is no experienced high or reinforcement. The practical effect is that the person who impulsively uses an opiate while on buprenorphine quickly realizes the futility of taking the drug and therefore ceases.¹¹ Furthermore, patients accustomed to buprenorphine may experience this as a sort of chemical “safety net,” as it reduces anxiety and, indirectly, cravings and urges.¹²

Unlike buprenorphine, full μ -agonists can migrate into the brain slowly or quickly. When they migrate quickly, they tend to be very reinforcing, and when they migrate slowly, they might be less reinforcing. Once they occupy the opiate receptors they provide the full panoply of opiate effects, including decreased pain, euphoria, changes in temperature sensation, and pinpoint pupils. Higher doses may cause decreased respiratory rate, and very high doses may cause respiratory arrest and death.

Buprenorphine, on the other hand, binds tightly, filling the opiate receptors such that even if another opiate is introduced, they could not occupy their usual space in the receptor. Hence, an individual who is treated with buprenorphine and then attempts to relapse (eg, by taking heroin, a combination of acetaminophen and oxycodone, or any other opiate), will fail.¹³

BUPRENORPHINE PREPARATIONS

In addition to the injectable form, which has been available in the US for many years under the brand name Buprenex, the medication is also available in two oral forms. Each of these forms is available in doses of 8 mg and 2 mg. The brand Subutex contains only buprenorphine. The brand Suboxone contains buprenorphine and naloxone in a 4:1 ratio. From a practical standpoint, oral naloxone has no appreciable bioavailability.¹⁴ The purpose of its addition was to make it less likely that an individual would try and pulverize the medication and inject it. Injected naloxone does have bioavailability, and results in immediate withdrawal. This is therefore a public health measure, in order to prevent

diversion of the medication. In the experience of the authors of this article, despite misconceptions about Suboxone, patients can be reassured that it is the choice favored by public health authorities, and that it has no physiological effect unless illicitly ground up and injected.¹⁵ Anecdotally, this preparation supposedly has a slightly better taste.

REGULATION

The regulation of buprenorphine is unique for clinicians. Upon completing specialized training, which can be obtained online through various professional organizations or in courses given throughout the country, the physician is able to apply for and receive a special DEA registration number allowing active prescription of buprenorphine in the office at a 30-patient limit. This allows a patient to receive care from a clinician of choice and takes away the cumbersome bureaucracy associated with other clinically administered opiate maintenance treatments.¹⁶

OTHER TREATMENTS FOR OPIATE DEPENDENCE

Some strategies may be employed in an effort to better engage and retain patients in treatment.⁵ Patients seeking treatment for addiction, even when voluntary, often are experiencing some ambivalence about this decision. It is important for the provider to distinguish between ambivalence and resistance, and to recognize that ambivalence is to be expected. Expectations should reflect the recognition of ambivalence so that patients are not refused treatment if they are not fully committed and fully engaged in the process. By practicing adjuvant therapeutic strategies, the provider may be able to guide the patient toward self-assured dedication to the process of treatment.⁵

One such technique is the practice of motivational enhancement therapy.² Assuming the patient is capable of change, but unsure of whether he or she wants to do so, motivational enhancement therapy is employed to resolve ambivalence and tap into the patient's inherent motivation and inner resources so that the patient may initiate and maintain behavioral changes. The provider empathizes with the patient and assists the patient in recognizing the discrepancy between his or her current lifestyle and how he or she wants to continue living. This is accomplished without argumentation or aggressive confrontation. Instead, the provider expects resistance and moves with it rather than against it.

This process aides the provider in fostering and supporting the patient's self-efficacy so that the patient learns that he or she is capable of changing.² Being supportive of the patient's decision to try buprenorphine and acknowledging his or her ambiguity can strengthen and sustain patient commitment. Because of the many advantages of buprenorphine, the clinician is at a relative advantage in advocating treatment.

As the patient demonstrates positive behavioral changes, it is important to provide the means to sustain such improvements.⁵ Relapse-prevention therapy has been shown to be effective in teaching patients how to recognize and maintain these positive changes.¹⁷ Relapse-prevention therapy is a cognitive-behavioral intervention designed to educate the individual about the process of relapse and to develop strategies that can be used to prevent the return to substance abuse.¹⁷ The first step is to explain to the patient that relapse is a process rather than an event. This process can be initiated when the individual finds himself in a high-risk situation. Training the patient to identify such situations and cope with them responsibly will help to prevent relapse. If a lapse occurs, the provider can assist the patient in addressing the situation in order to minimize negative consequences by resuming engagement in treatment.² If the provider is not able to provide therapy to the patient, a referral network should be established in order to assist the patient in finding adjuvant treatment. These adjuvant treatments, as well as many others, are particularly helpful when used in conjunction with buprenorphine, which offers an excellent safety profile as well as pharmacologic "safety nets."

Maintenance therapy is controversial in some clinical settings with a 12-step orientation. It is likely that such programs and or meetings will be highly beneficial to patients seeking treatment. Clinicians and patients may be reminded that the official policy of 12-step organizations is that medication issues are, and ought to be, between a patient and his or her physician. Buprenorphine is an approved medical treatment and its use is therefore sanctioned.

Psychiatric comorbidity is extremely high in opiate-dependent patients, estimated from 47% to 78%, depending upon the study. Most experienced clinicians believe that thorough evaluation of a patient before prescribing buprenorphine is important, in order to determine that the patient is indeed opiate dependent and to determine what other forms of treatment might be beneficial to this individual after initiating buprenorphine treatment.¹⁸ This is both a requirement of the regulations and is clinically responsible. While some clinicians will want to have a ready supply of potential therapies and professionals at hand, it may be as simple as

knowing the local social services helpline. These additional treatments might be as varied as family therapy to deal with the disruption of family harmony; additional pharmacologic therapy for other psychiatric disorders; the evaluation of a medical problems associated with opiate dependence, especially hepatitis B and C which has a very high prevalence in this population⁸; or any number of other treatments.

DETOXIFICATION VERSUS MAINTENANCE

Unlike other opiate treatments, buprenorphine may be utilized for maintenance or detoxification.¹⁹ The clinician has, in collaboration with his patient, the option of deciding how long the patient wishes to be on the medication: 2 weeks, 1 month, 6 months, or perhaps indefinitely. This will be subject to revision and evaluation by government regulations in the coming years. The outlook is promising for long-term buprenorphine treatment in individuals who require it.

An inverse relation exists between the duration of opiate use and dosage, and the likelihood of a successful detoxification versus the need for maintenance. There are no hard and fast rules about this, but there is a correlation. An individual who has been on a high dose of opiates for many years will likely do better with maintenance, whereas an individual who has a relatively short course with a low dose of either illicit or non-illicit opiates is much more likely to be successfully detoxified.

If detoxification is chosen, it can be spread out over time, thus eliminating many of the symptoms associated with a protracted withdrawal syndrome. Adjuvant medications may be used, such as anxiolytics or somnolents. Other medications, such as clonidine or lofexidine (which lessen withdrawal), as well as other non-opiate analgesics, may be employed.²⁰ The physician has the option to determine the duration of treatment with the patient. Regarding detoxification, it is a principal in pharmacology that the brain experiences the effects of many mood-altering medications in terms of a percentage of receptor occupancy, and not in terms of dosage. In determining the treatment regimen, this means the dose depends upon the percentage of reduction, not the absolute dosage. Therefore, the reduction of buprenorphine from 32 mg to 16 mg is experienced by the patient in a manner similar to 16 mg to 8 mg. Once the individual receives 8 mg and decides to go below the pharmacokinetics, the situation becomes somewhat different. Above 8 mg, both the half-life and the steady state are extremely long compared to other opiates, and in higher doses buprenorphine may be administered as infrequently as every 3 days.

Below 8 mg, the pharmacokinetics become shorter acting. Prolonged use of buprenorphine at doses below 8 mg may be problematic from a clinical standpoint, and the patient may experience some mild symptoms of withdrawal, particularly anxiety. For this reason, the authors of this article advocate allowing the patient who wishes to withdraw to “drift down” from doses higher than 8 mg/day at a very slow pace (weeks or months). Once at 8 mg, a definitive plan and timetable should be established. It is particularly helpful to pick a time for this last phase, when the patient’s life is relatively free from stress, when access to opiates is minimal, and when the patient is sufficiently prepared to avoid hazardous situations. Other nonpharmacologic treatments may be employed as well. These may include relaxation techniques, warm baths, or anything else that makes the patient feel physically better. Additionally, supportive psychotherapy, 12-step meeting attendance, or other adjunct treatments may be highly beneficial.

The authors of this article strongly advocate that individuals have a supply of low-dose buprenorphine available so that if they do relapse, they can choose to relapse on buprenorphine.¹⁷

INDUCTION OF BUPRENORPHINE

Buprenorphine is an easy medication for clinicians to maintain. It is somewhat more difficult for the individual undergoing induction.²¹ With the exception of methadone, (which needs to be in doses <40 mg, and is preferred at ≤20 mg), most of the short-acting opiates may be approached similarly. Interestingly, in clinical experience of the authors of this article, the dosage that an individual is on has little to do with the success of the induction.²² The only variable is the amount of buprenorphine needed on the first day of induction, and the subsequent stabilized amount. A rough guide to the doses needed is available elsewhere.²³

In order to be started on buprenorphine, the patient must be in partial withdrawal. A documented clinical opiate withdrawal scale score of ≥8 is recommended before starting, unless there are other factors involved wherein a lower dose might be acceptable.²⁴ An example is an individual who has taken substantial doses of anti-withdrawal medications. In general, while small doses of these may be helpful, they may also cloud the clinical picture and make recognition of a precipitated withdrawal more difficult. For this reason, and because the withdrawal phase before induction is relatively short, the use of only small amounts of these medications during the induction phase is advocated. A clinician can explain to the patient that because buprenorphine is a par-

tial agonist and binds more tightly than other opiates, it can displace the agonists inhabiting a receptor and cause that particular receptor to go from 100% occupancy to approximately 70% occupancy almost instantaneously. This would precipitate an unpleasant, severe, and difficult withdrawal. Precipitated withdrawal is usually not a medical emergency, nor is it particularly dangerous in an individual who is not otherwise medically compromised. However, it is highly unpleasant.²⁵ Therefore, there is a need for individuals who wish to undergo induction to present to the clinician with mild to moderate withdrawal. The authors of this article advocate using objective scales. Unless there are other factors involved, the individual should have a score of ≥10.²⁶

Precipitated withdrawal in general is dramatic and is usually not subtle. It includes severe withdrawal symptoms, including increased heart rate and blood pressure. In general, the patient is given adequate education, adequate preparation, and perhaps small doses of medications to deal with anxiety and/or withdrawal symptoms.²⁷ Precipitated withdrawal is and ought to be rare. While induction may be done at home or in a doctor’s office, it is the feeling of the authors of this article that specialized clinics or specialized induction centers are highly useful. These specialized settings can educate the patient in an authoritative manner, as well as relieve the anxiety of clinicians who may not be as familiar with buprenorphine as some of their colleagues.²⁸

CLINICAL EXPERIENCE

The Columbia University buprenorphine program opened in October 2003. Since that time, the program has evaluated approximately 500 patients and induced approximately 340 of them. A typical procedure includes an evaluation of a patient prior to induction. At that time, a history is obtained and a physical evaluation is performed. If the patient does not have a private physician, the entire procedure and medication are explained. This way the clinicians get to know their patients and the patients are relieved of some of their anxiety associated with the new medication. Typically, patients are seen the next day or, depending on the patient’s schedule, in the following days or weeks. In the morning or afternoon they arrive for the induction, in mild to moderate withdrawal and some discomfort. It is usually requested that they bring a chaperone or at least arrange for transportation in advance.

The patient is evaluated to make sure that he or she is indeed showing signs of objective withdrawal, depending upon the dose of the opiates the patient is on. The patient

is then given either 2 mg or 4 mg of buprenorphine, sublingually. Based on the degree of dependency reported, the clinicians usually have a good idea what dosages are needed, and each hour or so the patients are given an additional 2–4 mg until they feel comfortable. For example, a patient who uses six bags of heroin a day will most likely need 12 mg of buprenorphine. The patient is then sent home with a chaperone, and usually a future appointment is made within the same week. A few sessions of relapse prevention therapy is routinely offered as well.

CONCLUSION

Buprenorphine is a unique compound with a number of pharmacologic advantages. These include, but are not limited to, difficulty (but not impossibility) in overdosing; a ceiling effect, which prevents the need for patients to take steadily increasing amounts; and antagonism of the effects of other opiates, so clinically a lapse is much less likely to result in a relapse. In terms of regulations, it is now permissible to be prescribed buprenorphine by a physician for the purpose of relieving opiate dependence and/or withdrawal. Furthermore, the patient has the freedom of selecting a clinician that he or she prefers. *PP*

REFERENCES

1. Drug Addiction Treatment Act of 2000. Public Law No. 106-310. XXXV-Waiver authority for physicians who dispense or prescribe certain narcotic drugs for maintenance treatment or detoxification treatment. Available at: <http://www.buprenorphine.samhsa.gov/fullaw.html>. Accessed January 3, 2006.
2. Center for Substance Abuse Treatment. *Medication-Assisted Treatment for Opioid Addiction in Opioid Treatment Programs*. Treatment Improvement Protocol (TIP) Series 43. DHHS Publication No. (SMA) 05-4048. Rockville, MD: Substance Abuse and Mental Health Services Administration; 2005.
3. Johnson RE, Chutuape MA, Strain EC, Walsh SL, Stitzer ML, Bigelow GE. A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. *N Engl J Med*. 2000;343(18):1290-1297.
4. Center for Substance Abuse Treatment. *A Guide to Substance Abuse Services for Primary Care Clinicians*. Treatment Improvement Protocol (TIP) Series, Number 24. DHHS Pub. No. (SMA) 97-3139. Washington, DC: US Government Printing Office; 1997.
5. Center for Substance Abuse Treatment. *Brief Interventions and Brief Therapies for Substance Abuse*. Treatment Improvement Protocol (TIP) Series. DHHS Pub. No. (SMA) 99-3353. Washington, DC: US Government Printing Office; 1999.
6. Clark HW. Office-based practice and opioid-use disorders. *N Engl J Med*. 2003;349(10):928-930.
7. Brown RL, Rounds LA. Conjoint Screening questionnaires for alcohol and other drug abuse: criterion validity in a primary care practice. *Wis Med J*. 1995;94(3):135-140.
8. Petry NM, Bickel WK, Piasecki D, Marsch LA, Badger GJ. Elevated liver enzyme levels in opioid-dependent patients with hepatitis treated with buprenorphine. *Am J Addict*. 2000;9(3):265-269.
9. Gaulier JM, Marquet P, Lacassie E, Dupuy JL, Lachatre G. Fatal Intoxication following self-administration of a massive dose of buprenorphine. *J Forensic Sci*. 2000;45(1):226-228.
10. Reynaud M, Tracqui A, Petit G, Potard D, Courty P. Six deaths linked to misuse of buprenorphine-benzodiazepine combinations. *Am J Psychiatry*. 1998;155(3):448-449.
11. Comer SD, Collins ED, Fischman MW. Buprenorphine sublingual tablets: effects on IV heroin self-administration by humans. *Psychopharmacology (Berl)*. 2001;154(1):28-37.
12. Schottenfeld RS, Pakes JR, Oliveto A, Ziedonis D, Kosten TR. Buprenorphine vs methadone maintenance treatment for concurrent opioid dependence and cocaine abuse. *Arch Gen Psychiatry*. 1997;54(8):713-720.
13. O'Connor PG, Fiellin DA. Pharmacologic treatment of heroin-dependent patients. *Ann Intern Med*. 2000;133(1):40-54.
14. Preston KL, Bigelow GE, Liebson IA. Effects of sublingually given naloxone in opioid-dependent human volunteers. *Drug Alcohol Depend*. 1990;25(1):27-34.
15. Strain EC, Preston KL, Liebson IA, Bigelow GE. Acute effects of buprenorphine, hydromorphone and naloxone in methadone-maintained volunteers. *J Pharmacol Exp Ther*. 1992;261(3):985-993.
16. O'Connor PG, Oliveto AH, Shi JM, et al. A randomized trial of buprenorphine maintenance for heroin dependence in a primary care clinic for substance users versus a methadone clinic. *Am J Med*. 1998;105(2):100-105.
17. Marlatt GA, Gordon JR, eds. *Relapse Prevention: Maintenance Strategies in the Treatment of Addictive Behaviors*. New York, NY: Guilford Press; 1985.
18. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed rev. Washington, DC: American Psychiatric Association; 2000.
19. Ling W, Charuvastra C, Collins JF, et al. Buprenorphine maintenance treatment of opioid dependence: a multicenter, randomized clinical trial. *Addiction*. 1998;93(4):475-486.
20. Cheskin LJ, Fudala PJ, Johnson RE. A controlled comparison of buprenorphine and clonidine for acute detoxification from opioids. *Drug Alcohol Depend*. 1994;36(2):115-121.
21. Johnson RE, Cone EJ, Henningfield JE, Fudala PJ. Use of buprenorphine in the treatment of opiate addiction. I. Physiologic and behavioral effects during a rapid dose induction. *Clin Pharmacol Ther*. 1989;46(3):335-343.
22. Amass L, Bickel WK, Crean JP, Blake J, Higgins ST. Alternate-day buprenorphine dosing is preferred to daily dosing by opioid-dependent humans. *Psychopharmacology (Berl)*. 1998;136(3):217-225.
23. Johnson RE, Strain EC, Amass L. Buprenorphine: how to use it right. *Drug Alcohol Depend*. 2003;70(2 suppl):S59-S77.
24. Bradley BP, Gossop M, Phillips GT, Legarda JJ. The development of an opiate withdrawal scale (OWS). *Br J Addict*. 1987;82(10):1139-1142.
25. Bickel WK, Amass L, Crean JP, Badger GJ. Buprenorphine dosing every 1, 2 or 3 days in opioid-dependent patients. *Psychopharmacology (Berl)*. 1999;146(2):111-118.
26. Handelsman L, Cochrane KJ, Aronson MJ, Ness R, Rubinstein KJ, Kanof PD. Two new rating scales for opiate withdrawal. *Am J Drug Alcohol Abuse*. 1987;13(3):293-308.
27. Banys P, Clark HW, Tusel DJ, et al. An open trial of low dose buprenorphine in treating methadone withdrawal. *J Subst Abuse Treat*. 1994;11(1):9-15.
28. Johnson RE, Jones HE, Fischer G. Use of buprenorphine in pregnancy: patient management and effects on the neonate. *Drug Alcohol Depend*. 2003;70(2 suppl):S87-S101.

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