Practical Considerations for the Clinical Use of Buprenorphine

Buprenorphine is a new and attractive medication option for many opioid-addicted adults and their physicians. Before initiating buprenorphine treatment, providers must be aware of such critical factors as how the medication works, its efficacy and safety profile, how it is used in opioid withdrawal as well as maintenance treatment, and how patients can best be selected, educated about buprenorphine, and monitored throughout treatment. This article reviews these important issues as well as requirements for physician and staff training and needs for additional research on this unique medication.

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Buprenorphine was approved by the U.S. Food and Drug Administration (FDA) in October 2002 as a Schedule III narcotic for use in treating opioid-dependent men and opioid-dependent women who are not pregnant. The new medication's unique pharmacological characteristics provide for less respiratory depression or overdose risk than opioids such as morphine, heroin, methadone, and oxycodone, as well as milder manifestations of withdrawal upon cessation. This wide safety margin makes buprenorphine suitable for use in new treatment settings, such as office practices, as well as more traditional opioid treatment programs. Further supporting this versatility, buprenorphine can be effective when taken every other day or less frequently, and it is supplied in a combined formulation with naloxone that is designed to reduce its potential for abuse. The medication is therefore a welcome addition to a restricted treatment armamentarium, especially now that LAAM (levo-alpha-acetylmethadol hydrochloride), another widely used medication, is being discontinued by the manufacturer because of safety concerns (U.S. Food and Drug Administration, 2003). This article reviews buprenorphine's pharmacology and clinical use, including appropriate dosing; patient selection, education, and monitoring; and physician and staff training; and it identifies important questions for research.

PHARMACOLOGY AND CLINICAL TRIALS

Buprenorphine's Effects

Buprenorphine is chemically an opioid. Like other opioids, it produces most of its important effects by interacting with a structure on nerve cells called the mu opioid receptor (see "Heroin, Buprenorphine, and Naloxone Effects at the Mu Opioid Receptor"). The special characteristics that distinguish buprenorphine from other opioids and make it useful for helping people overcome opioid addiction result from the unique ways it interacts with this receptor (e.g., Bickel and Amass, 1995; Jasinski, Pevnick, and Griffith, 1978; Martin et al., 1976):

- **Buprenorphine is a partial agonist at (i.e., stimulator of) the mu receptor.** When the mu receptor is stimulated, it sets in motion a chain of nerve cell activities that underlies most of the familiar opioid effects, for example, pain reduction, feelings of well-being or pleasure, and respiratory suppression. By stimulating the receptor only partially, buprenorphine yields those same effects, but with less intensity than heroin, morphine, or methadone, all of which stimulate the receptor fully (Johnson and Strain, 1999). Whereas those drugs can cause powerful euphoria, motivating continued abuse, buprenorphine provides a positive but moderate psychoactive effect that reduces craving and helps patients comply with their medication regimens (Jasinski, Pevnick, and Griffith, 1978; Walsh et al., 1994).
- **Buprenorphine has high affinity for the mu receptor.** That is, buprenorphine binds tightly to mu receptors, more so than abused opioids and methadone do. Consequently, if a patient takes an abused opioid on top of buprenorphine, the medication will block it from reaching the receptors and producing the desired strong effects. Moreover, if buprenorphine is given to an individual who has already taken another opioid, it displaces the other opioid from the receptors. This effect necessitates care when a clinician initiates buprenorphine therapy; depending on the dosage of buprenorphine, the patient's level of physical dependence, and when he or she last administered an abused opioid, the abrupt stripping of the other opioid from the mu receptor can precipitate withdrawal.
- **Buprenorphine disassociates (detaches) from the mu opioid receptor slowly.** This characteristic probably accounts for buprenorphine's long duration of action in the treatment of opioid dependence.

While buprenorphine's manner of interacting with the mu receptor gives rise to its most important attributes and advantages in addiction treatment, the medication also has a significant action at a second receptor:

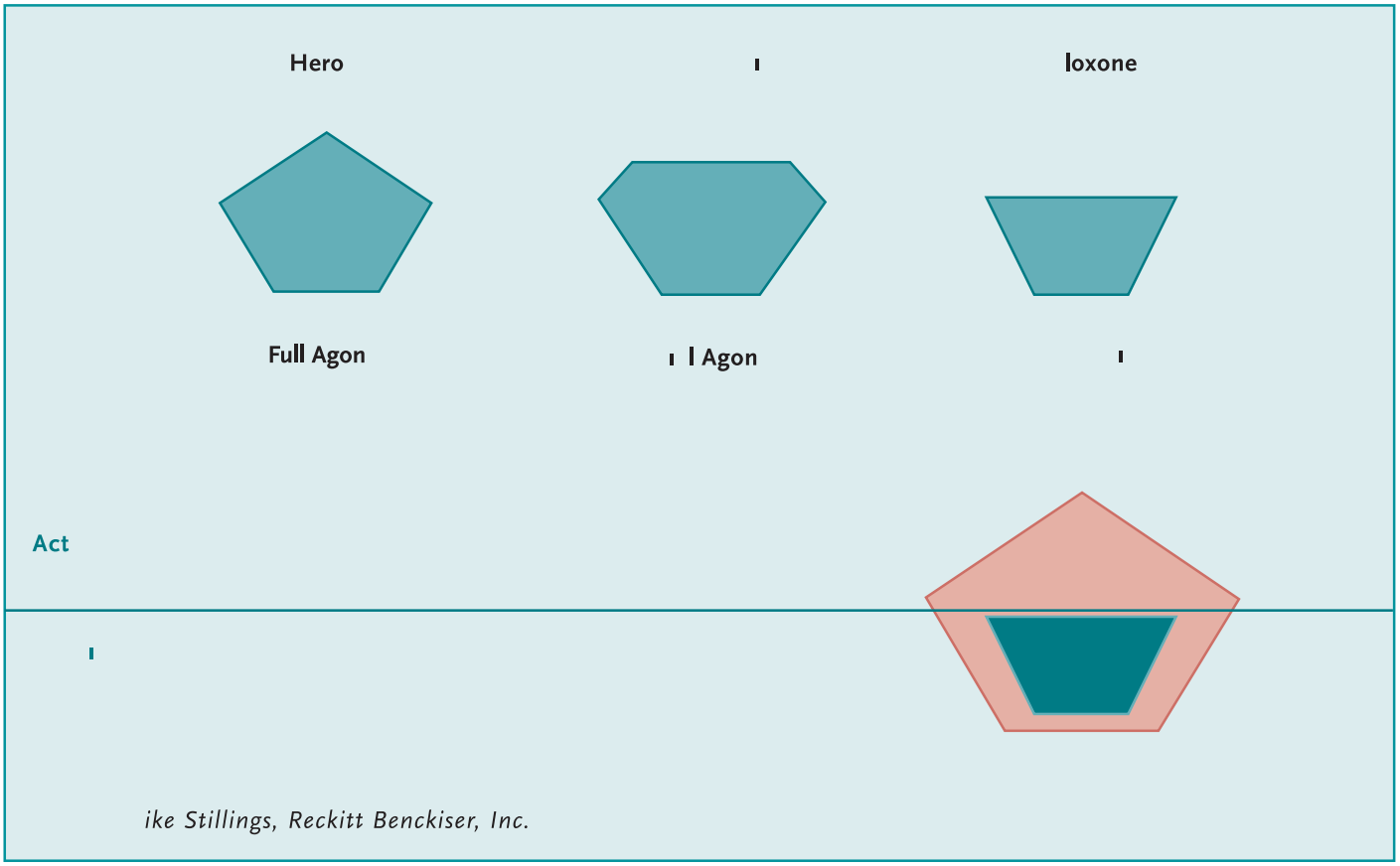
- **Buprenorphine is an antagonist (i.e., prevents stimulation) of the kappa opioid receptor** (Cowan, Lewis, and Macfarlane, 1977). Stimulation of the kappa opioid receptor plays a role in producing some of the major symptoms associated with opioid withdrawal, such as chronic depression. By attaching to the kappa receptor and slowing its activity, buprenorphine may induce positive mood and feelings of well-being (Rothman et al., 2000).

There are two formulations of buprenorphine for treating opioid dependence, a buprenorphine hydrochloride (HCl) tablet (Subutex) and a combination tablet (Suboxone) containing buprenorphine HCl plus naloxone HCl in a ratio of 4:1 (Fudala et al., 1998; Mendelson and Jones, 2003; Mendelson et al., 1996, 1997*b*, 1999; Preston, Bigelow, and Liebson, 1988). Both tablets produce similar clinical effects when administered sublingually (Stoller et al., 2001). Suboxone was developed because buprenorphine alone has potential for abuse (e.g., Pickworth et al., 1993; Strain et al., 1997) and has been abused in other countries (O'Connor et al., 1988; Singh et al., 1992; Varescon et al., 2002). Unlike buprenorphine, naloxone is poorly absorbed and has little effect when taken sublingually (Chiang and Hawks, 2003; Preston, Bigelow, and Liebson, 1990); however, when injected by an opioid-addicted person, naloxone can precipitate an opioid withdrawal syndrome—a strong deterrent to diversion of Suboxone and its abuse by injection (O'Brien et al., 1978).

Research on Safety and Efficacy

Initial research showed that buprenorphine produced signs and symptoms similar to those of morphine use (for example, constricted pupils, sleepiness, and itchy skin), yet, unlike morphine, it produced little physical dependence or respiratory depression and only mild withdrawal symptoms, even when withdrawn abruptly (Fudala et al., 1990; Jasinski, Pevnick, and Griffith, 1978). In early efficacy studies, chronic buprenorphine-treated subjects did not self-administer heroin to the same extent as placebo-treated subjects (Mello and Mendelson, 1980; Mello, Mendelson, and Kuehnle, 1982). Given its positive psychoactive

Heroin, Buprenorphine, and Naloxone Effects at the Mu Opioid Receptor



Heroin, buprenorphine, and naloxone (represented above by blue polygons) produce contrasting effects because they interact differently with the brain's mu opioid receptors (red pentagons).

First, the chemicals differ in how much each stimulates the receptors (represented above by the percentage of receptor "activity zone" each fills). The stronger the stimulation, the more pronounced will be the opioid effects of pain relief, feelings of well-being, respiratory depression, and so on. Heroin, classified as a full receptor agonist (stimulator), nearly fills the activity zone. Buprenorphine, a partial receptor agonist, fills a smaller portion of it. Naloxone does not stimulate the receptor at all.

Second, each chemical binds to the receptors more or less strongly (represented above by the percentage of receptor "affinity zone" it fills). A chemical that forms a tighter bond can push one with a weaker bond off the receptors and take its place. Thus, buprenorphine can push heroin off the receptors, and in doing so replace heroin's full receptor stimulation with its own partial stimulation. Buprenorphine also binds more tightly than naloxone.

Naloxone can compete with heroin for the receptors. Because naloxone can block heroin and other opioids from stimulating the receptors while not itself stimulating them, it can precipitate opioid withdrawal and is classified as an opioid receptor "antagonist."

effects, buprenorphine seemed likely to be accepted by patients (Mello and Mendelson, 1995), while its improved safety profile (Jasinski and Preston, 1995) would provide treatment practitioners with a unique medication for treating opioid dependence.

Subsequently, numerous studies examined the safety and efficacy of buprenorphine maintenance treatment (Ahmadi, 2002; Amass, Kamien, and Mikulich, 2000; Fischer et al., 1999; Fudala and Johnson, 1995; Fudala et al., 2003; Johnson, Jaffe, and Fudala, 1992; Johnson et al., 1995*a*, 1995*b*, 2000; Kosten et al., 1993; Ling et al., 1996; Mattick et al., 2003; Pani et al., 2000; Perez de los Cobos et al., 2000; Petitjean et al., 2001; Schottenfeld et al., 1997, 2000; Strain et al., 1994; Uehlinger et al., 1998). The only study to compare buprenorphine, LAAM, and high-dose methadone found that all three produced similar reductions in illicit opioid use and were superior to low-dose methadone (Johnson et al., 2000).

Many of the randomized controlled clinical trials conducted with buprenorphine have limitations. Most of the trials were conducted with men only, in

monitored outpatient settings as opposed to office settings, over periods of less than a year, and with fixed doses (whereas flexible doses would be expected to produce better outcomes). Most studies used the liquid form of buprenorphine, so a dose conversion from liquid to tablet is necessary for proper interpretation of the results. In addition, most studies with tablets used Subutex, whereas Suboxone is the intended first-line form of buprenorphine.

Some studies have reported similar patient retention rates for buprenorphine and methadone (Johnson, Jaffe, and Fudala,1992; Johnson et al., 2000; Pani et al., 2000; Strain et al., 1994). Where differences in retention were observed, buprenorphine treatment was associated with greater dropout rates. Although the reason for this difference is not known, it is possible that:

- The buprenorphine induction was too slow (Fischer et al., 1999; Mattick et al., 2003; Petitjean et al., 2001);
- The maximum buprenorphine dose was too low (Fischer et al., 1999; Kosten et al., 1993; Ling et al., 1996; Mattick et al., 2003; Petitjean et al., 2001; Schottenfeld et al., 1997); or
- Patients were able to terminate buprenoprhine treatment more comfortably than methadone treatment because of buprenorphine's milder withdrawal effects (Mattick et al., 2003).

Despite its limitations, this research, in sum, demonstrates that buprenorphine has efficacy similar to methadone over a broad dose range. Trials that used larger maintenance doses of the medications produced greater decreases in illicit opioid use, a dose-response relationship that confirms the medication's causal contributions to the desired outcome. (See "The Response to Buprenorphine Is Dose Related and Comparable to Methadone.") There is a great deal of variation in individuals' responses to medication; consequently, patients should receive dosage tailored to their individual responses.

Though buprenorphine and methadone have shown similar efficacy in controlled trials, the comparative mildness of buprenorphine's positive psychoactive effects has raised questions about its effectiveness for highly dependent patients (Walsh et al., 1994). Although there are reports of effective treatment of highly dependent patients with Subutex doses higher than 32 mg (personal communication, Rolley E. Johnson, Reckitt Benckiser Pharmaceuticals, Inc., September 6, 2003), buprenorphine's limitations in this population of patients warrant further study.

Just as with methadone (Ernst et al., 2002), a number of overdose deaths have been reported with intravenous use or very high doses of the combination of buprenorphine and benzodiazepines (Kintz, 2002; Reynaud et al., 1998; Singh et al., 1992). The interaction mechanism is unclear, but it appears not to be related to the drugs' absorption, distribution, metabolism, or elimination from the body (Kilicarslan and Sellers, 2000). The interaction potential of sublingual buprenorphine and oral benzodiazepines is unclear. In controlled clinical trials in the United States, one death has been reported of a patient using oral benzodiazepine in conjunction with buprenorphine.

Suboxone, the buprenorphine-naloxone combination, has been shown to effectively treat opioid dependence or block the effects of illicit opioids without noticeable negative effects of naloxone (Amass, Kamien, and Mikulich, 2000, 2001; Comer and Collins, 2002; Harris et al., 2000; Strain et al., 2000, 2002). Given buprenorphine's (particularly Suboxone's) lower potential for abuse and strong safety profile—its plateau of subjective effects with increasing doses and the fact that it causes little respiratory depression—it is considered a first-line medication option for beginning opioid-dependence treatment (Fudala et al., 2003; Ling and Compton, 1997).

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THERAPEUTIC GOALS

Federal Requirements

As a medication that private physicians can prescribe under the Drug Addiction Treatment Act of 2000 (Public Law 106-310, referred to as "DATA 2000"), buprenorphine provides an alternative for patients who do not have access to methadone clinics or do not meet criteria for treatment in an opioid treatment program. For example, admission criteria for methadone treatment clinics often include opioid dependence for 1 year or more (Leshner, 2003). Patients are potential candidates for buprenorphine treatment through physicians' offices if they meet the American Psychiatric Association's current opioid dependence criteria (American Psychiatric Association, 2000). However, if buprenorphine treatment is given in an opioid treatment program, such as a methadone clinic, patients must meet the same Federal guideline criteria for admission that apply to methadone therapy

The Response to Buprenorphine Is Dose Related and Comparable to Methadone

These four studies clearly illustrate two key conclusions that emerged from the large body of clinical studies on buprenorphine conducted to date. The medication's effects are dose related and comparable to those of methadone. The dosages of buprenorphine and methadone used in these four studies mostly were low relative to current guidelines for optimal dosing, which may account, among other possible reasons, for the low rates of opioid-negative urine samples among patients in some of the study arms.

Medication	Dose (mg/d)	Number of Subjects (M/F)	Days of Treatment (all groups)	Subjects Completing Study %	Opioid-Negative Urine Samples %[a]	Reference
Studies showing a dose-response relationship						
Buprenorphine Methadone	4 12 20 65	23/6 20/9 21/9 16/12	168	35 55 47 64	23 42 28 55	Schottenfeld et al., 1997
Buprenorphine	1 4 8 16	736 total; ≈1/3 F	112	40 51 52 61	19 29 33 38	Ling et al., 1998
Studies showing efficacy comparable to methadone						
Buprenorphine + naloxone Methadone	8:2 16:4 45 90	162 total across both medication groups	118	34 total across both medication groups	64 64 36 52	Amass, Kamien, and Mikulich, 2000
Buprenorphine Methadone	2-32 (avg. 10.9 week 6, 11.2 week 13) 20-150 (avg. 52.6 week 6, 57.3 week 13)	139/61 142/63	91	50 59	≈51[b] ≈49[b]	Mattick et al., 2003

[a] For all patients enrolled in treatment, except, in the study by Amass and colleagues, for patients who completed treatment.
[b] Urine samples that were scheduled but not provided by patients were counted as positive.

Buprenorphine, while effective for eliminating illicit opioid use, is not a cure for opioid dependence: No medication has been found to change the behaviors associated with illicit drug use.

(U.S. Department of Health and Human Services, 2001).

Under DATA 2000, physicians can apply to the Center for Substance Abuse Treatment, a component of the Substance Abuse and Mental Health Services Administration (SAMHSA), for a waiver of the Controlled Substance Act that will enable them to treat up to 30 patients (O'Connor, 2000). Physicians may be eligible for the waiver if they meet at least one of the following criteria (SAMHSA, 2003):

- Certification in addiction medicine through the American Board of Medical Specialties, American Society of Addiction Medicine, or American Osteopathic Association;
- Completion of at least 8 hours of approved training in the treatment or management of patients dependent on opioids;
- Other training or experience that demonstrates their ability to treat and manage opioid-dependent patients.

Physicians also must certify that they can provide or refer patients to needed ancillary services, such as behavioral counseling, mental health care, and case management (Clark, 2001).

Treatment Objectives

The objectives of buprenorphine therapy are identical to those of treatment with methadone (Fudala and Johnson, 1995):

- To prevent opioid withdrawal signs and symptoms,
- To provide a comfortable induction onto the medication, and
- To then attenuate the motivations (such as craving) to use illicit opioids.

By eliminating illicit drug use, patients dependent on opioids can begin to focus on repairing family and social relationships, finding positive social support networks, obtaining fulfilling employment, and engaging in new forms of recreation and other activities that contribute to healthy, balanced living.

Buprenorphine, while effective for eliminating illicit opioid use, is not a cure for opioid dependence: No medication has been found to change the behaviors associated with illicit drug use. Like all other medications for drug dependence, buprenorphine will more successfully promote and sustain abstinence when prescribed as one component of a complete treatment regimen that also includes behavioral interventions (Montoya et al., 2003; National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction, 1998).

On a societal level, treatment that includes buprenorphine has been shown to reduce the harmful effects of opioid dependence by reducing drug use severity, increasing social status, and impeding the spread of HIV/AIDS and other infectious diseases (Fhima et al., 2001; Kakko et al., 2003; Mattick et al., 2003). It may also provide a net economic advantage, with increased costs for the medication and for physician and nursing services offset by reductions in dispensing, counseling, and administrative costs as well as some of the costs patients must incur to obtain treatment (Rosenheck and Kosten, 2001). (See "Costs of Buprenorphine and Access to Care.")

MEDICATION MANAGEMENT

Patient Selection

To date, few studies have examined which type of patient is best treated with buprenorphine rather than methadone. One study comparing buprenorphine- and methadone-maintained patients observed that, unique to buprenorphine patients, those with histories of sedative dependence stayed in treatment longer and used less cocaine (Schottenfeld, Pakes, and Kosten, 1998). Other research has reported differential responses to buprenorphine between men and women, with women showing greater (Johnson et al., 1995*a*) or lesser drug use (Schottenfeld, Pakes, and Kosten, 1998) than did men or methadone-maintained women (Jones et al., 2001).

The clinician should consider a number of factors prior to starting a patient on buprenorphine. First: The patient may be taking other medications that might make buprenorphine a more, or less, attractive option. Buprenorphine's interactions with other medications tend to be similar to methadone's but with some notable differences (see "Alcohol and Medication Interactions With Buprenorphine and Methadone"). In general, buprenorphine appears to have few significant drug interactions. When interactions occur, they appear to increase the effects of buprenorphine by decreasing its metabolism. Such interactions can easily be mitigated by a reduced buprenorphine dose.

Second: Some co-occurring medical conditions can be contraindications for buprenorphine use. These could include difficult breathing or lung problems, kidney or gallbladder problems, head injury, severe mental disorders, adrenal or thyroid dysfunction, urination problems, or enlarged prostate. Patients taking buprenorphine who have hepatitis or impaired liver function should be routinely monitored, especially when taking high doses, because the medication's potential to increase liver damage has not been fully evaluated (Petry et al., 2000).

Some co-occurring medical conditions can be contraindications for buprenorphine use.

The FDA has not approved methadone or buprenorphine for use during pregnancy. Buprenorphine is in FDA's category C, a mid-level risk category within the range A (low risk)-B-C-D-X. Methadone is in category B. Category C drugs have shown adverse effects on fetuses in animal studies and have not been adequately studied in humans.

Thousands of women have continued methadone maintenance throughout pregnancy with no

Costs of Buprenorphine And Access to Care

Buprenorphine is expected to increase the availability of addiction treatment for an estimated 166,000 illicit opioid users and 1.5 million problem users of prescription opioids (Substance Abuse and Mental Health Services Administration, 2002). But because buprenorphine can be dispensed in office settings and is more expensive than methadone, some providers are concerned that only highly motivated, more affluent patients with access to social supports will be able to receive it.

In fact, however, buprenorphine costs less than most newly FDA-approved medications (about $10 per 16-mg dose) and has been estimated to be cost-effective (Barnett et al., 2001). That buprenorphine may be attracting new patients into treatment can also be viewed as a benefit. A recent study comparing patients treated with buprenorphine in a physician's office to others treated with the new medication in an opioid treatment program showed that the former were different in several respects: They had fewer years of opioid use, less injection drug use, and greater rates of current prescription opioid use (Sullivan et al., 2003).

Alcohol and Medication Interactions With Buprenorphine and Methadone

Medication	Use	Buprenorphine Effect	Methadone Effect	References
Alcohol	No medical use	Increased effect due to decreased buprenorphine metabolism; can be fatal	Increased effect due to decreased methadone metabolism	White and Irvine, 1999
Amantidine	Treatment for Parkinson's disease	No change in effect	No change in effect	Kosten et al., 1992; Oliveto et al., 1995
Benzodiazepines	Treatment for anxiety, sleep difficulty	Increased effect can be fatal	Increased effect; potentially fatal	Ernst et al., 2002; Kilicarslan and Sellers, 2000; Kintz, 2002; Reynaud et al., 1998; Singh et al., 1992;
Carbamazepine	Anticonvulsant	No change in effect	Decreased effect	Eap et al., 2002; Paetzold et al., 2000; Schlatter et al., 1999
Desipramine	Antidepressant	No change in effect	Higher desipramine serum levels	Kosten et al., 1992; Maany et al., 1989; Oliveto, 1995
Disulfiram	Alcohol abuse treatment	No change in effect	No change in effect	George et al., 2000; Kreek, 1981; Tong et al., 1980
Fluoxetine	Antidepressant	No change in effect	No change in effect	Iribarne et al., 1998; Oliveto et al., 1995
Fluvoxamine	Antidepressant	Increased effect due to decreased buprenorphine metabolism	Increased effect due to decreased methadone metabolism	Bertschy et al., 1996; DeMaria and Serota, 1999; Iribarne et al., 1998
HAART (highly active antiretroviral therapy)	HIV treatment	No change in effect	Decreased effect	Carrieri et al., 2000; McCance-Katz et al., 2002
Indinavir	HIV/AIDS treatment	Increased effect due to decreased buprenorphine metabolism	Increased effect due to decreased methadone metabolism	Fornataro, 1999; Iribarne et al., 1998
Ketoconazole	Antifungal agent	Increased effect due to decreased buprenorphine metabolism	Higher ketoconazole doses not tolerated	Ibrahim et al., 2000; Kosten et al., 2002
Naltrexone	Alcohol abuse treatment	Risk of opioid withdrawal	Increased effect due to decreased methadone metabolism	Eissenberg et al., 1996; Johnson, 2001; Kosten et al., 1990
Nevirapine	HIV treatment	Increased effect due to decreased buprenorphine metabolism	Decreased effect	Heelon and Meade, 1999
Omeprazole	Gastrointestinal treatment	No change in effect	Increased effect reduces respiration in rats	de Castro et al., 1996; Kilicarslan and Sellers, 2000

Alcohol and Medication Interactions With Buprenorphine and Methadone *(continued)*

Medication	Use	Buprenorphine Effect	Methadone Effect	References
Partial opioid agonists	Treatment of pain	Risk of opioid withdrawal	Risk of opioid withdrawal	Strain et al., 1993
Ritonavir	HIV treatment	Increased effect due to decreased buprenorphine metabolism		Clarke et al., 2002;[a] Iribarne et al., 1998; McCance-Katz et al., 2003;[b] Stevens et al., 2003[a]
Saquinavir	HIV treatment	Increased effect due to decreased buprenorphine metabolism	Increased effect due to decreased methadone metabolism	Iribarne et al., 1998
Zidovudine	HIV treatment		Increased zidovudine toxicity In combination with lamivudine and abdavir, increased methadone metabolism and withdrawal No methadone dose change required for lamivudine-zidovudine combination	McCance-Katz et al., 1998 Pardo Lopez et al., 2003 Rainey et al., 2002

[a] In combination lopinavir-ritonavir, Clarke et al. (2002) and Stevens et al. (2003) showed increased methadone metabolism but no withdrawal or need for dose adjustment.

[b] McCance-Katz and colleagues (2003) showed ritonavir alone had no significant effect on methadone metabolism, but the lopinavir-ritonavir combination produced withdrawal and required dose adjustments.

apparent significant adverse fetal effects (Kaltenbach, Berghella, and Finnegan, 1998; Kandall et al., 1999; Wang, 1999). FDA acknowledges that the potential benefits of methadone during pregnancy may outweigh possible hazards, and both SAMHSA and NIDA endorse methadone treatment for opioid-dependent women, regardless of pregnancy. However, because experience with buprenorphine is more limited and further studies are pending, current guidelines exclude the use of buprenorphine during pregnancy. They also recommend that women who become pregnant while receiving maintenance therapy with buprenorphine switch to methadone. Women initiating opioid agonist treatment therefore require appropriate information to help them make informed decisions about each medication's risks and benefits in case of pregnancy, including what they might experience should they become pregnant and change medications during pregnancy. (See Johnson, Jones, and Fischer, 2003, for a review of buprenorphine and pregnancy.)

Currently, buprenorphine is recommended for use only by patients aged 16 and older because safety and effectiveness data for younger adolescents are lacking. However, the use of heroin by American adolescents is at its highest level since the 1960s (U.S. Department of Justice, 1999), and results of an ongoing study at five sites in NIDA's National Drug Abuse Treatment Clinical Trials Network (CTN) may prove illuminating. The CTN study is comparing the effectiveness, for 14- to 21-year-olds, of Suboxone solely for detoxification (7 to 14 days) versus Suboxone detoxification plus maintenance therapy (3 months), when each is supplemented by twice-weekly psychosocial support for 3 months (Woody, 2003). This study may confirm the reported finding of Marsch and colleagues (2003) that in a 28-day outpatient setting under double-blind conditions,

buprenorphine was superior to clonidine—an antihypertensive medication often used to alleviate opioid withdrawal symptoms—in retaining patients in treatment and reducing their opioid use.

Exploring patients' expectations for buprenorphine treatment is important. New medications often generate unrealistic hopes. Explaining to the patient what buprenorphine can do (block illicit opioid effects, decrease craving) and what it cannot do (prevent him or her from ever using drugs again) may help enhance treatment outcomes. Conversely, some patients may expect buprenorphine treatment to fail. Unless addressed, such an expectation can become self-fulfilling.

Explaining to the patient what buprenorphine can do and what it cannot do may help enhance treatment outcomes.

The decision to use buprenorphine is not irreversible. Should a patient have intolerable side effects or fail to respond to buprenorphine—that is, continue illicit opioid use after dose adjustments and stabilization on a maintenance dose—he or she can easily be switched to methadone.

Initiating Therapy

The initial goals of buprenorphine therapy are to quickly minimize opioid withdrawal signs and symptoms, maximize patient comfort, and achieve an appropriate maintenance dose. When an opioid-dependent patient presents for treatment and buprenorphine is selected as the appropriate medication, the clinician must make several decisions:

- Which buprenorphine tablet (Suboxone or Subutex) should be used for induction into therapy and for maintenance?
- When should the first buprenorphine dose be administered?
- What are the optimal induction dose and schedule to achieve stabilized maintenance?

Tablet Selection

For a patient who is dependent on a short-acting opioid like heroin, Suboxone will probably be appropriate for both induction and maintenance. Suboxone is also likely to be preferred in cases where medication is dispensed to be taken away from the office or clinic. Although some research suggests that patients on long-acting opioid agonists such as OxyContin (oxycodone) or methadone may experience less severe withdrawal symptoms if initially given Subutex (Amass, Kamien, and Mikulich, 2000, 2001), a recent report documents safe induction of therapy with Suboxone for more than 900 patients (Cunningham-Rathner et al., 2003). The induction was accomplished over 3 days with minimal withdrawal effects, similar to the 3 to 4 days of mild withdrawal symptoms observed with induction of buprenorphine alone (Fudala and Johnson, 1995).

When To Administer Buprenorphine

Both theory (Martin et al., 1976) and early clinical experience (personal communication, Rolley E. Johnson, Reckitt Benckiser Pharmaceuticals, Inc., September 6, 2003) support a recommendation that clinicians initiate buprenorphine therapy only after clear and objective signs of opioid withdrawal are present. The reason is that, as discussed, buprenorphine will displace other opioids from the patient's mu opioid receptors. This effect may propel a patient who is not already in withdrawal into withdrawal if buprenorphine does not also provide enough mu opioid receptor stimulation to compensate for what the other opioid was providing. Because buprenorphine stimulates the receptor less strongly than other opioids, it will more likely achieve this compensation if the concentration of other opioids in the patient's system is low.

Waiting to initiate buprenorphine therapy until the patient enters withdrawal from the other opioids entails some mild discomfort for the patient, but it provides a good indication that the concentration of other opioids is probably low enough that buprenorphine can be administered safely. For some patients, the period for transition to buprenorphine may be as little as 4 to 6 hours if they have been using short-acting opioids or as much as 24 to 96 hours for long-acting opioids (Amass, Kamien, and Mikulich, 2000, 2001; Bouchez, Beauverie, and Touzeau, 1998; Johnson, Strain, and Amass, 2003; Law et al., 1997; Levin et al., 1997; Lintzeris, 2000; Lintzeris et al., 2001; Strain et al., 1995; Walsh et al., 1995).

The recommendation to initiate buprenorphine treatment after withdrawal commences applies to patients on both long- and short-acting opioids. The potential persistence in the system of long-acting opioids such as MS Contin (morphine), oxycodone, and methadone, however, together with variations in patients' rates of metabolism and in their sublingual absorption of buprenorphine, necessitate an additional consideration in the timing of buprenorphine initiation. Particularly if a patient has been taking a high dose of a long-acting opioid, the

concentration remaining in his or her body at the start of withdrawal may be higher than buprenorphine can compensate for. If this is the case, the patient may experience an intensification of withdrawal when the medication replaces the other opioid on the mu opioid receptors. An illustration of these effects is the observation that patients maintained on lower doses of methadone (for example, 20 to 40 mg) appear to have a smoother transition when buprenorphine is introduced 20 hours after the last methadone dose than do patients maintained at higher doses (60 mg or more) and given buprenorphine 40 hours after the last methadone dose (Strain et al., 1992; Walsh et al., 1995).

One option for easing the transition from a long-acting opioid to buprenorphine is to reduce the dose to 30 mg methadone or its equivalent while providing ancillary support to prevent relapse to illicit opioid use; such supports could include non-opioid medications to alleviate withdrawal symptoms and intensive counseling or case management (Jasinski et al., 1984; Johnson and Strain, 1999; Johnson, Strain, and Amass, 2003; Strain et al., 1992, 1995; Walsh et al., 1995). For some patients, a dose reduction to 30 mg methadone may not be possible or may entail significant risk of relapse. Thus, for patients on higher methadone doses, increasing the time between the last long-acting opioid dose and the initial buprenorphine dose, so that objective signs of withdrawal are present and maximal tolerable withdrawal is achieved, should help avoid a buprenorphine-precipitated withdrawal (Bouchez, Beauveries, and Touzeau, 1998; Lintzeris et al., 2003). For patients on more than 60 mg methadone who are unable to decrease the dose, transfer to buprenorphine in a closely monitored inpatient setting is suggested (Lintzeris et al., 2001).

Optimal Induction Dosing and Schedule

The initial daily buprenorphine dose currently recommended is 4 to 8 mg, although higher doses have been given. Clinicians generally start with 4 mg Suboxone, and if withdrawal signs do not worsen, give a second 4-mg dose in 2 to 4 hours. Some clinicians provide an additional dose (2 to 4 mg) for the patient to take at home if withdrawal symptoms reemerge during the first 24 hours.

Practitioners should monitor for indications of buprenorphine-precipitated withdrawal, including sweating, anxiety, cravings, and gastrointestinal symptoms such as abdominal cramps, diarrhea, and/or nausea. Such symptoms may appear within 1 1/2 hours after buprenorphine dosing, peak within 1 1/2 to 3 hours, and diminish thereafter (Lintzeris et al., 2001). This differs from withdrawal caused by underdosing of buprenorphine, which can occur during the latter part of a 24-hour dosing interval.

Clinicians can achieve the maintenance dose of buprenorphine by doubling the dose each day up to a maximum of 24 to 32 mg (Ling et al., 1998; Ling and Smith, 2002). If induction occurs too slowly, patients might terminate their treatment (Mattick et al., 2003; Petitjean et al., 2001). A number of studies have shown that a target dose of 16 mg can be reached in 2 to 3 days (Johnson, Strain, and Amass, 2003) with minimal withdrawal effects (Johnson et al., 1989; Kuhlman et al., 1998). To manage the patient's transition from Subutex to Suboxone therapy, the clinician needs simply to replace the dose of Subutex with Suboxone containing the same amount of buprenorphine.

Buprenorphine blood concentrations stabilize after approximately 7 days of consistent dosing (Chiang and Hawks, 2003). If withdrawal symptoms subsequently emerge during any 24-hour dosing interval, the dose is too low and should be increased.

Maintenance

The optimal maintenance dose of buprenorphine is one that suppresses withdrawal signs and symptoms and enables the patient to cease illicit opioid use. The amount of medication needed to accomplish these goals will vary from patient to patient, in part because individuals differ with respect to sublingual absorption (Chiang and Hawks, 2003; Mendelson et al., 1997*a*), metabolism, and response to the medication. A dose of between 4 and 24 mg per day has been suggested as likely to be efficacious for many patients. Although doses of 32 mg and higher are being used and have been reported in the literature, going beyond 32 mg may not always enhance the medication's efficacy (Strain et al., 2002).

Once a maintenance dose is achieved, it should not routinely require adjustments, as patients maintained on buprenorphine have not clearly demonstrated tolerance for the medication. However, much research has investigated dosing schedules (Amass et al., 1994, 1998; Amass, Kamien, and Mikulich, 2000, 2001; Bickel et al., 1999; Greenwald et al.,

2002; Petry et al., 2000; Petry, Bickel, and Badger, 2001). In general, once a stable buprenorphine dose is achieved, the medication can be administered every other day or, in some cases, three times weekly (such as Monday, Wednesday, and Friday) (Johnson et al., 2000; Mattick et al., 2003), which can improve medication compliance and patient satisfaction (Amass et al., 1998; Amass, Kamien, and Mikulich, 2001). Extending the dosing interval to once every 4 days increases withdrawal symptoms (Amass, Kamien, and Mikulich, 2001; Gross et al., 2001; Petry, Bickel, and Badger, 2001). If alternate-day dosing is desired, the dose must be increased to the equivalent daily dose; for instance, if the daily dose is 12 mg, then the every-other-day dose should be 24 mg (Amass et al., 1994, 1998; Amass, Kamien, and Mikulich, 2000). If thrice-weekly dosing is used, the Monday and Wednesday doses should be twice the daily maintenance dose, and the Friday dose 50 percent greater than the Wednesday dose (Johnson et al., 2000). Dosing less often than daily will be advantageous in opioid treatment programs where take-home doses are prohibited by government regulations or program polcies.

Medical Withdrawal

The safety and efficacy of buprenorphine have been clearly demonstrated in the context of medically assisted withdrawal from opioids, and it appears that buprenorphine is associated with fewer opioid withdrawal signs and symptoms than would be expected with methadone or LAAM (Lintzeris et al., 2003). This characteristic may help clinicians retain patients during medically assisted withdrawal, but sustained abstinence is not expected to be any greater with buprenorphine than with methadone.

As more patients are treated with buprenorphine, physicians and managed care organizations will seek standardized withdrawal protocols, but no one protocol is appropriate for all patients. Protocols should be tailored to patient needs and the inpatient or outpatient setting (Lintzeris et al., 2001). Several reviews have examined buprenorphine-assisted medical withdrawal (Gowing, Ali, and White, 2002; Rosen and Kosten, 1995); a thorough review of this topic is beyond the scope of this article.

Because DATA 2000 specifies that physicians can treat only 30 patients at a time with buprenorphine, some may feel compelled to use buprenorphine primarily for medical withdrawal in order to meet the demand for treatment. Hopefully physicians will obtain certification for buprenorphine use in sufficient numbers to fully exploit the medication's potential to reduce the current unmet demand for treatment (Vastag, 2003).

As always, withdrawal of illicit opioids is only a first step in the complete treatment process. Patients need a specific psychosocial treatment plan to help them maintain drug abstinence after completion of withdrawal.

Patient Monitoring

It is important to monitor patients, using best practice guidelines, to ensure that they are responding positively to buprenorphine and other aspects of treatment. SAMHSA is preparing practice guidelines for buprenorphine and anticipates publishing them as a Treatment Improvement Protocol (TIP 40) later in 2004. Urinalysis is an important tool for patient monitoring and can help determine whether patients are reducing their use of illicit opioids.

If patients are continuing to use opioids, they may need an increased buprenorphine dose. However, if the dose appears adequate, environmental factors should be examined for situations associated with continued drug use (for example, when a partner is using) and appropriate interventions employed. Buprenorphine is not detected in onsite or spot-testing urinalysis drug screens. If compliance with the medication is a concern, more sophisticated tests can be ordered to detect buprenorphine metabolites in the urine or other biological material, but such tests are expensive and require more time. Faster and cheaper buprenorphine detection kits should become available in the near future.

EDUCATING PATIENTS AND CAREGIVERS

Patient Education

Basic information about buprenorphine should be conveyed at the outset and reinforced throughout the course of treatment. Face-to-face conversations, supplemented by written fact sheets, are helpful. Important instructions for patients include:

- Let Subutex or Suboxone tablets dissolve under your tongue; they are much less effective if swallowed.
- Take no more than two tablets at a time; otherwise you may swallow them by mistake.
- Wetting the mouth before placing the tablets under your tongue can help the tablets dissolve faster.

- Don't smoke for 10 to 15 minutes before you take your medication. Not smoking seems to help the tablets dissolve faster.
- Be sure to tell your doctor or other health care professional about any discomfort you feel. He or she may be able to give you medication that will help.
- Before you have any medical or dental treatment that involves anesthesia or pain-relieving medication, be sure to tell your physician or dentist that you are taking buprenorphine. The medications may interfere with one another.
- Do not drive a car or operate machinery until you are sure you can do so safely.

Preparing patients for the possibility of some temporary discomfort during the transition process and developing a trusting patient-doctor relationship are extremely important. It is especially important to encourage patients to tell their health care provider about any effects they feel, because temporary side effects can often be alleviated with over-the-counter medications like Tylenol for headache or Benadryl for sleep or anxiety.

Warn patients that if they continue to use illicit opioids, they may have difficulty stabilizing on buprenorphine, and that if they take their buprenorphine dose shortly after use of an illicit opioid, they may experience transient withdrawal symptoms. Because of buprenorphine's potential to block the effects of other opioids, it is critical to advise patients to alert other treatment providers (such as dentists and emergency room personnel) that they are taking buprenorphine before undergoing any medical procedure or receiving treatment for injury or illness that involves the use of opioids to control pain (see SAMHSA's Web site at *www.buprenorphine.samhsa.gov* or the manufacturer for guidance).

In addition, patients should be cautioned against using buprenorphine in combination with other central nervous system depressants such as alcohol and benzodiazepines. And they should be counseled that the side effects of buprenorphine are similar to those of other opioid agonists; the most common are headache, withdrawal syndrome, nonspecific pain, nausea, and constipation. These side effects are not unexpected, are generally mild and manageable, and often resolve within 3 weeks (Mello and Mendelson, 1995).

Patients need to be made aware that misuse of buprenorphine can have serious results. Just as with methadone (Ernst et al., 2002), injecting buprenorphine or using larger doses than those prescribed in combination with benzodiazepines can cause death (Kintz, 2002; Reynaud et al., 1998; Singh et al., 1992).

Patients who have a history of liver disease need to be informed about the need for routine monitoring, as increased liver enzyme levels have been reported during buprenorphine maintenance therapy (Lange et al., 1990; Petry et al., 2000*b*). And finally, warn all patients that injecting Subutex may cause liver damage (Berson et al., 2001*a*, 2001*b*).

Physician and Staff Training

In response to the requirements of DATA 2000, training curricula have been developed to educate physicians about buprenorphine (including its pharmacology, treatment goals and duration, side effects, and drug interactions), appropriate induction and maintenance dosing for patients entering treatment, addressing individual patient problems, and guidelines for professional conduct in delivering opioid-agonist treatment (Lintzeris et al., 2002; Strain, 2001). Physicians can obtain the required training through professional organizations, including the American Society of Addiction Medicine, American Psychiatric Association, American Academy of Addiction Psychiatry, and American Osteopathic Association.

Members of the physician's office staff who are not familiar with treatment of opioid-dependent patients will need explicit training. A staff orientation program should include:

- A basic introduction to addiction medicine.
- A description of buprenorphine's unique pharmacology, the protocols for treatment induction and maintenance, and potential side effects or adverse reactions.
- Principles regarding appropriate interactions with patients—basic respect, a positive, nonjudgmental attitude, and maintenance of consistent interpersonal boundaries. Guidelines for staff and patient conduct will minimize manipulation by patients and adverse staff-patient interactions.
- Principles of patient confidentiality.
- Rules for the storing, distribution, and administration of medication, including policies with respect to lost prescriptions. Consistent and therapeutic responses must be developed, because the staff may discover that some patients are misusing or diverting their medication.

- An overview of the typical psychosocial issues that opioid-dependent patients face.
- Guidance in responding to requests for information or obvious patient needs. Identifying and establishing linkages with community resources prior to treating patients will maximize positive treatment experiences for both staff members and patients (Strain et al., 2001).
- Protocols to handle disclosure of suicide risk, child abuse, communicable diseases, and domestic violence.

A number of Internet resources exist to help physicians and their staffs address these issues (see "Web of Support").

Web of Support

Among the many useful Web sites to visit:

- *www.hipaa.samhsa.gov* for guidance on patient confidentiality
- *www.suboxone.com* for manufacturer's information on buprenorphine treatment for physicians, patients, and families
- *www.samhsa.gov* for Federal requirements and other information on medication-assisted treatment.

RESEARCH NEEDS

Much has been learned about buprenorphine through the 25 years' research that culminated in FDA's approval of the medication. As buprenorphine enters into widespread use in established opioid treatment settings and general medical practices, new research issues come to the fore. Among them are:

- Buprenorphine's efficacy in special populations, such as incarcerated people and adolescents;
- Its safety during pregnancy—potential effects of buprenorphine treatment on the developing fetus, including possibly long-term consequences;
- Clinical determination of which patients are best treated with buprenorphine and which with other opioid-dependence treatments;
- Suboxone's potential for abuse by means of inhaling or smoking (since buprenorphine is bioavailable through intranasal administration) (Lindhardt et al., 2001);
- The transition from methadone or other long-acting mu opioids (such as morphine and oxycodone) in outpatient settings, where any withdrawal discomfort may make the patient especially vulnerable to relapse;
- The effects of buprenorphine on cognitive function, psychomotor performance, and immune function; and
- The potential interactions of buprenorphine with medications prescribed to treat other chronic illnesses (for example, HIV, hepatitis, and depression) and to manage pain.

CONCLUSION

Buprenorphine is a safe and effective treatment for opioid-dependent men and opioid-dependent women who are not pregnant. Several unique features enhance buprenorphine's appropriateness for some patients and treatment settings. First, its partial mu opioid-agonist properties provide a wide safety margin, with relatively slim chances for severe overdose effects. Second, buprenorphine's long duration of action allows for flexible, patient-tailored dose administration multiple times daily, daily, or at longer intervals. Third, when injected by an opioid-dependent person who is not buprenorphine-maintained, the combination of buprenorphine plus naloxone (Suboxone) precipitates immediate and significant withdrawal syndrome, a deterrent to abuse.

The availability of a safe, effective medication that physicians can use to treat opioid-dependent patients in an office practice is an important advance. Now patients with the illness of opioid addiction can be helped in private with a medical treatment option similar to that for other chronic illnesses. Buprenorphine tremendously expands opportunities for delivering addiction treatment in settings and geographical areas where established treatment programs are scarce or nonexistent, and for matching treatment to individual patients' needs in all settings.

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Response: Integrating Buprenorphine Therapy into Clinical Practice

Martin C. Doot, M.D., J. Thomas Payte, M.D., and Arthur Van Zee, M.D.

Arthur Van Zee: Dr. Jones's paper is very informative. I found much that was new to me even after 7 months' experience with buprenorphine. I wish I had it when we were starting out.

We're looking at buprenorphine as a means to incorporate more flexibility into our abstinence-based treatment model.

Martin Doot: The information in this article is consistent with other reviews of buprenorphine therapy I've seen. I wish it had more on the psychosocial aspects of drug treatment, though.

J. Thomas Payte: If I had only one source, this article is the one I would want to have. When it is published, I want all the physicians in our programs to have it as background reading. I particularly liked the explanations of how partial agonists work and how they differ from full agonists and antagonists.

Programs and strategies

Van Zee: We are looking to buprenorphine as a possible solution to a very difficult situation. Our clinic is in the heart of Appalachia, in the southwestern corner of Virginia. Until about 3 years ago we had no large-scale opioid addiction, but the OxyContin epidemic changed that. There are now tens of thousands of new opioid addicts in our region. Methadone treatment programs may be 2 hours away by car. Try to imagine a 23-year-old single mother getting her daughter up at 4:30 every morning to drive to Tennessee to get a methadone dose. Because of these difficulties, prior to buprenorphine, I would just detox patients and set them up with our local counseling team. Now, I can offer them comprehensive treatment with an effective medication.

We've had some wonderful success stories already—people who started induction 7 months ago and who have come very far, not just in terms of abstinence, but also in terms of real personal growth. We've also had many lapses. I think I've initiated 46 patients on buprenorphine; 23 are still in the program, and about 15 to 17 are doing well.

Doot: I work in a multispecialty, office-based group practice affiliated with a large teaching hospital near Chicago. We're looking at buprenorphine as a means to incorporate more flexibility into our abstinence-based treatment model. We intend to offer it for maintenance as well as to improve outcomes with abstinence-based treatment.

Our group participated in the buprenorphine clinical trials because our State agency wanted an abstinence-based perspective on the medication. Patients chose buprenorphine or traditional abstinence-based therapy. Our counselors found that after a while they had a group of patients they were encouraging to use 12-step facilitation and relapse prevention techniques, who were well past detox but still using buprenorphine. What came out of this was a new model, in which we meet patients where they are, accept some of the goals they set for themselves, and then move them along the continuum of change.

Our counselors are comfortable with this model. I've had some say to me, 'I really think this patient

would do better on maintenance.' That never happened before.

Payte: I have been in addiction medicine full-time since the 1960s and was involved in one of the last clinical trials of buprenorphine. Now I work for Colonial Management Group, which operates 43 methadone treatment programs in 14 States. The physicians in our organization have shown intense interest in buprenorphine, and we are now gearing up to use it. For me, buprenorphine is particularly promising because of its safety and flexibility. It's not as strong as methadone, and has long-lasting action, so you don't see significant problems if a patient misses one or two doses, as you do with methadone.

Which patients?

Doot: The new medication will be particularly useful for patients who cannot achieve recovery through traditional abstinence-based programs. Some people drop out of these programs because the biological dimension of their addiction is so powerful they can't get past it to begin to address the other tasks of treatment—healing their family, healing the way they think, entering a spiritual recovery program. Buprenorphine is going to play a tremendous role in keeping these individuals in therapy.

A patient who abuses multiple drugs is likely to have a difficult time sticking with buprenorphine. With these patients, you're likely to get into 12-step, abstinence-oriented kinds of interventions anyway, because we don't have medications for cocaine and those for alcohol don't work terribly well. You ask yourself, 'Should this be a patient we gradually taper off the buprenorphine as they learn how to use the 12-step recovery program?' I think there is going to be a role for the gradual buprenorphine taper.

My partners and I are particularly interested in using buprenorphine to help impaired health care professionals. At present, however, I don't consider buprenorphine a first-line option for most of these patients. First, opioid-dependent physicians generally do well in abstinence-based programs, which are more acceptable in the eyes of society. Second, the article makes an excellent point: We need more research on whether buprenorphine impairs cognitive functioning and psychomotor performance. I suspect it doesn't, but until I know, I can't go before a licensing board and say, 'This doctor can continue to do surgery while taking this medication.'

Payte: If it weren't for its relatively high cost, I would see buprenorphine as a trial entry drug for virtually every new patient coming to our methadone clinics. But if I were asked to choose among patients, I would be tempted to give a preferential nod to the younger patients with shorter abuse histories and less severity, in consideration of the safety factor. Actually, I would be prone to refer adolescents for treatment in a physician's office rather than expose them to the atmosphere of a methadone clinic.

Some established methadone patients also can gain advantages from switching to buprenorphine, particularly greater safety. Some want to get away from the 'M' word—the stigma associated with methadone. Our long-term, stabilized patients now have once-monthly attendance at many of our clinics, so the attraction of buprenorphine's less frequent clinic visits is somewhat attenuated.

Generally, patients will let you know if they are not doing well on buprenorphine. If their drug craving persists on what should be an adequate dose—24 to 32 mg, you may have to switch to the stronger agonist. But it's easier to go from buprenorphine to methadone than the other way around.

If it weren't for its relatively high cost, I would see buprenorphine as a trial entry drug for virtually every new patient coming to our methadone clinics.

Van Zee: I've found that I can't predict very well who's going to do well and who isn't. I've seen people do well who I thought wouldn't have much of a chance. And I've been disappointed with people who had much more social and emotional support but didn't succeed. I would probably exclude the individual who is obviously psychiatrically unstable and anyone with impending legal problems—that is, anyone facing a stay in prison in the near future. Most often, though not always, it's impractical to induce buprenorphine and maintain a patient on it in jail.

What I like to see happen is that an individual is seen by the counselors, starts 12-step meetings, and then comes to me. I also believe that putting a patient on buprenorphine should be a decision made by the entire treatment team.

Doot: Ideally, you'd like the candidate for buprenorphine to have psychosocial stability, be willing to sign a contract, have adequate resources to follow through, and have family support. However, we have adjunct treatments that can overcome many of the problems that would disqualify patients. If you can supply the proper psychosocial support—get a patient into a

halfway house, for example—you have a much better chance of success.

It's important to keep asking, 'What are we missing?' Often there are other treatable conditions that are standing in the way of recovery from addiction.

Dosing schedules and diversion

It's about half as costly to take one-and-a-half 8-mg tablets as it is to take an 8 and two 2s.

Doot: Some of the early guidelines for buprenorphine recommended Subutex [buprenorphine alone] for initiating therapy. In the clinical trial I participated in, we used Suboxone [buprenorphine combined with naloxone] for induction, with no problems. I haven't seen a need for Subutex in the clinic, and I was pleased that Dr. Jones clarified that in her paper.

In most situations, I think daily dosing is best. My patients remember easier to take something once in the morning than to try to recall if it's Monday, Tuesday, or Wednesday. Missing doses could potentially raise the risk for relapse by reducing protection against craving.

Payte: I agree wholeheartedly. In my brief experience with buprenorphine, patients have sometimes forgotten to take their tablets for a day or two before finally remembering. Even at that point, they were fairly comfortable. Buprenorphine just doesn't give as strong a reminder as methadone. Also, because of blood level fluctuations over the dosing intervals, I expect we will obtain the smoothest and best medication effect by not going to every-other-day dosing. The rationale for wider dosing intervals would come into play in clinics whose patients aren't allowed take-home doses but who can't attend every day.

Doot: Some patients actually need the structure of clinic dispensing. The patients who come to me for office-based treatment tell me they don't want to come every day, but some don't do well coming in only once a week.

Van Zee: That's been our experience. In midsummer, before we tightened up our program, a lot of our buprenorphine was getting out on the street. Now we have a minority of patients who don't get take-home medication, but instead come to the clinic every day or every 2 or 3 days. For some, this has been a real help in getting to clean urines, faithful attendance at meetings, and so on.

I do feel good about the fact that when buprenorphine is diverted onto the street, its downside in terms of inadvertent overdose is small compared to methadone.

Payte: Methadone diversion is something I've been living with for years. I participated on an Institute of Medicine panel that tried to determine its impact. We concluded that the negative effects were difficult to pinpoint and probably overemphasized as a reason to deter take-homes. Buprenorphine particularly reduces the risk even more.

Doot: I have found that patients on higher buprenorphine doses often split their doses. Rather than taking the full 24 mg in the morning, they will come back and say, 'Well, Doc, I took one in the morning and two at night.' As long as they take the total daily dose, those who split it seem to benefit just as well as those who didn't.

Van Zee: A small minority of my patients had nausea if they took the whole dose at once. They did better splitting the dose.

To save our people money, we only prescribe the 8-mg tablet, not the 2 mg. If someone is on 12 mg a day, it's about half as costly to take one-and-a-half 8-mg tablets as it is to take an 8 and two 2s. Also, the bigger the quantity purchased at one time, the lower the price. We have patients buy a whole month's supply. If we don't think a patient should have that much on hand, we have them buy a month's supply and store it at the clinic for dispensing 8 or 10 days at a time.

The learning curve

Van Zee: I've learned some things the hard way; in fact, my program is probably being salvaged by the nurses and counselors who are making it work in spite of my mistakes. We have learned two basic lessons: One, it is a mistake to overstate the value of medication in recovery; and two, you need a tight structure to have a successful program.

We assumed early on that if the medication took away the craving and the patients didn't wake up every morning sick and thinking about where to get pills, and their urines were clean, they should do all right. We underestimated the psychosocial adjustments needed for recovery, and so set ourselves up for disappointment when people who seemed to be doing well would relapse after 3 or 4 months. And we

were forced to add structure. Now each patient signs a contract upon entering the program, promising to attend 12-step meetings 3 times a week and meet with a counselor once a week. In addition, we do random pill counts and urine testing. We have found that people do better when the requirements are clear.

Doot: I expect it will continue to be difficult to motivate primary care physicians to 'hang out their shingle' and announce that they intend to take care of the addicts among their patients. This has been the disappointment with all the medications developed so far to treat substance use disorders. Physicians have tended not to diagnose the problem, perhaps because they do not have much hope of helping. Buprenorphine may change that situation. &