Buprenorphine Treatment of Opioid Dependence: A Review

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Buprenorphine, a partial mu-agonist opioid, is a promising pharmacotherapy for the treatment of opioid dependence. One hundred and eight papers are organized according to 3 components essential to buprenorphine's use as a pharmacotherapy for opioid dependence: inducting patients onto buprenorphine, maintaining patients on buprenorphine, and discontinuing patients from buprenorphine treatment. The research suggests that inducting patients onto buprenorphine should lead to limited discomfort if appropriate procedures are followed. As a maintenance treatment, buprenorphine is as efficacious as methadone, blocks the effects of exogenously administered opioids, promotes treatment compliance, and, importantly, can support an alternate-day dosing regimen by doubling the daily dose. Discontinuing buprenorphine treatment appears to result in a mild-to-moderate opioid withdrawal syndrome that is less severe than that observed with full- efficacy agonists.

Heroin and other opioid dependencies are an enduring public health problem and, unfortunately, the prevalence of that problem has been increasing. For example, between the second and third quarters of 1991, heroin- and morphine-related cases increased 10% across 500 hospital emergency rooms in 21 U.S. cities (Swan, 1992). Decreased price and increased purity of street heroin may have, in part, fueled this resurgence. Given the association between intravenous heroin use and AIDS, the drug abuse treatment and public health community would be wise not to underestimate the severity of this increased heroin problem.

Fortunately, the National Institute on Drug Abuse (NIDA) has been actively developing a new medication, buprenorphine, for the treatment of opioid dependence. NIDA anticipates Food and Drug Administration (FDA) approval of buprenorphine for this indication in the near future (D. Segal, personal communication, December 8, 1994). Buprenorphine, a low-efficacy, partial agonist of the morphine-type, exhibits a unique profile of effects, including (a) a ceiling on agonist activity that decreases the possibility of overdose and may limit abuse liability (Walsh, Preston, Stitzer, Cone, & Bigelow, 1994), (b) opioid-antagonist activity that blocks the effects of exogenously administered opioids (Bickel et al., 1988b), (c) a high affinity for the mu-opioid receptor that decreases the magnitude of withdrawal signs and symptoms (Rance & Dickens, 1978), and (d) opioid-agonist activity that promotes treatment compliance (Jasinski, Pevnick, & Griffith, 1978).

Although more work is necessary to identify and characterize buprenorphine's unique clinical pharmacology, results to date suggest that it is a viable and useful pharmacotherapy for opioid dependence. Given that buprenorphine may soon be available for widespread clinical use, reviewing the literature available to guide practitioners in the use of buprenorphine for opioid dependence treatment is both practical and timely. Thus, in this review we address three main topic areas: (a) transferring opioid-dependent patients onto buprenorphine; (b) maintaining patients on buprenorphine; and (c) discontinuing patients from buprenorphine treatment. We also review additional research elucidating buprenorphine's therapeutic potential and make recommendations for integrating buprenorphine into existing treatment programs. Before doing this, we briefly review buprenorphine's pharmacology and side effects profile.

Buprenorphine's Pharmacology and Side Effects

Buprenorphine hydrochloride, a derivative of the morphine alkaloid thebaine, is a partial agonist opioid at the mu receptor and an opioid antagonist at the kappa receptor (Lewis, 1985). Buprenorphine's partial agonist effects at, and its unusually high affinity for, the mu receptor have been proposed as the principal determinants of its pharmacological profile (Lewis, 1985).

Partial agonists can be defined as agents whose maximal response is below the maximum possible for that system (Kenakin, 1987). For example, the prototypical full agonist morphine produced dose-related decreases in respiration rate, while buprenorphine produced effects less than that of morphine and reached a "ceiling" above which further increases in dose had no further effect (Cowan, Doxey, & Harry, 1977). This ceiling on buprenorphine's agonist activity limits the possibility of overdose and provides a wide margin of safety.

The other determinant of buprenorphine's pharmacological profile is its unusually high affinity for the mu receptor. This affinity has been characterized as irreversible and is demonstrated by the inability of the prototypical opioid antagonist naloxone to fully antagonize buprenorphine's effects (Woods, France, Bertalmio, Gmerek, & Winger, 1985). For example,
naloxone doses that are 10- to 30-fold those required to reverse morphine's effects are necessary to partially reverse the effects of buprenorphine (Heel, Brogden, Speight, & Avery, 1979; Woods et al., 1985). Buprenorphine's irreversibility will therefore allow it to block other opioid agonists in a fashion not dissimilar from opioid antagonists. This irreversibility of buprenorphine once bound to the receptor is also the mechanism that extends its duration of action beyond its plasma half-life of 3 hr (Jaffe & Martin, 1990).

The medical side effects of acute buprenorphine administration are similar to those of opioid agonists and include constipation, dizziness, drowsiness, headache, miosis, nausea, respiratory depression, sweating, and vomiting (Heel et al., 1979). Opioid-dependent individuals show tolerance to many of these effects (Lange et al., 1990). Moreover, researchers obtained similar profiles of self-reported adverse effects for opioid-dependent individuals receiving either buprenorphine or methadone (Johnson, Jaffe, & Fudala, 1992). One study reported increased serum amino-transferase levels in opioid-dependent individuals receiving buprenorphine (Lange et al., 1990). This finding suggests that buprenorphine induced hepatic dysfunction. Given the high prevalence of hepatic disease in parenteral drug abusers, these results should be considered seriously (Lange et al., 1990). However, the authors provided several plausible alternative hypotheses for these results and concluded that further research will be needed to discern buprenorphine's effect on hepatic function.

For more detailed reviews of buprenorphine's basic, behavioral, and clinical pharmacology, consult Heel et al. (1979), Lewis, Rance, and Sanger (1983), and Mello and Mendelson (1985).

Transferring Patients Onto Buprenorphine

When the FDA approves buprenorphine for the treatment of opioid dependence, opioid-dependent individuals using illicit opioids or receiving treatment with methadone may be transferred to buprenorphine. The transfer of opioid-dependent individuals to buprenorphine raises the important clinical issue of whether patients may initially experience withdrawal discomfort from buprenorphine. Because withdrawal discomfort could adversely affect treatment retention and abstinence rates, understanding how withdrawal occurs and how to avoid it will be important when transferring patients onto buprenorphine.

Withdrawal discomfort could result from three separate processes (Johnson, Cone, Henningfield, & Fudala, 1989). First, the buprenorphine dose may be too low and, therefore, possess insufficient agonist effects to substitute for another opioid agonist. In this case, a higher dose of buprenorphine would suppress withdrawal. Second, buprenorphine, as a partial agonist, may not fully substitute for full opioid agonists. In this case, buprenorphine at any dose would fail to suppress withdrawal completely (i.e., withdrawal would occur but to a lesser degree than that obtained without buprenorphine administration). Third, buprenorphine, as a partial agonist, may directly precipitate withdrawal. In this case, higher doses of buprenorphine would produce more withdrawal than lower doses. The first and second sources of withdrawal would result in greatest withdrawal discomfort during the typical time-course of withdrawal expected with the maintenance opioid used. The third source of withdrawal discomfort (direct precipitation of withdrawal) would result in peak withdrawal discomfort during buprenorphine's acute effects and could pose the greatest difficulty in transferring opioid-dependent patients to buprenorphine.

Both precipitation and suppression of opioid withdrawal by buprenorphine have been demonstrated in preclinical studies. In those studies, withdrawal intensity was directly related to the dose of the maintenance drug (e.g., morphine) and the dose of buprenorphine (Cowen, 1974; Martin, Gilbert, Eades, Thompson, & Huppler, 1975; Martin, Eades, Thompson, Huppler, & Gilbert, 1976). Importantly, whether buprenorphine precipitates or suppresses withdrawal seems to be determined by the interval between agonist and buprenorphine administration. Buprenorphine precipitated withdrawal in a dose-related fashion when it was administered to morphine-dependent monkeys 1 hr after the last morphine administration, when morphine's effects were still evident (Aceto, 1984). In contrast, buprenorphine suppressed withdrawal in a dose-related fashion when it was administered 15 hr after the last morphine administration; that is, when morphine's agonist effects had dissipated and withdrawal signs and symptoms were present (Aceto, 1984). These findings suggest that buprenorphine's withdrawal-precipitating or withdrawal-attenuating effects are critically determined by the activity at the receptor at the time of buprenorphine administration. When receptor activity is high (i.e., when a µ agonist is present), buprenorphine will displace opioid agonists from the receptor. This displacement will result in reduced receptor activity because buprenorphine is less efficacious than full µ agonists. The reduced receptor activity will in turn result in opioid withdrawal. However, when receptor activity is low (i.e., when there is no µ agonist activity for some time), buprenorphine will occupy the receptor, increase receptor activity, and consequently suppress opioid withdrawal.

Buprenorphine's withdrawal-producing effects have also been observed in opioid-dependent patients and are related to the level of opioid dependence (i.e., level of use of street opioids, maintenance dose of methadone, or both), the buprenorphine substitution dose, and the temporal interval between agonist administration and buprenorphine. For example, opioid withdrawal has been observed when methadone maintenance patients were transferred abruptly to buprenorphine. Three patients maintained on 25, 58, or 60 mg orally (PO) methadone per day were abruptly transferred to 2 mg subcutaneously (SC) buprenorphine per day and experienced a mild transient opioid withdrawal (Lukas, Jasinski, & Johnson, 1984). However, whether the withdrawal was precipitated by buprenorphine or was due to buprenorphine failing to substitute fully for methadone is unclear. Similarly, withdrawal symptoms emerged when heroin-dependent and methadone-maintained patients (25 mg PO) were transferred to 2, 4, or 8 mg sublingually (SL) buprenorphine in an open trial (Kosten & Kleber, 1988). Although patients transferred to the 4-mg buprenorphine dose experienced only transient increases in withdrawal scores, withdrawal symptoms emerged in patients...
transferred to the 2- or 8-mg dose. Whereas the 2-mg dose may have had insufficient agonist activity to suppress withdrawal symptomology (i.e., the normally occurring withdrawal), the 8-mg dose may have directly precipitated opioid withdrawal (Johnson et al., 1989). Finally, two laboratory studies support the role of level of opioid dependence (i.e., maintenance dose of methadone) in buprenorphine-precipitated withdrawal (June, Preston, Bigelow, & Stitzer, 1993; Strain, Preston, Liebson, & Bigelow, 1992). Acute buprenorphine (2, 4, and 8 mg SL) precipitated withdrawal dose-dependently in patients maintained on high-dose (60 mg PO) methadone (June et al., 1993); however, acute buprenorphine (0.5–8.0 mg intramuscularly, IM) did not precipitate withdrawal in patients maintained on low-dose (30 mg PO) methadone (Strain et al., 1992).

Clinical reports indicate that when equipotent doses of buprenorphine and methadone are used, buprenorphine appears as effective as methadone in suppressing opioid withdrawal symptomology (Bickel et al., 1988a; Johnson et al., 1992). This information has helped determine adequate buprenorphine substitution doses for patients transferring from methadone or street opioids to buprenorphine. Double-blind clinical observations indicate that opioid-dependent patients randomized to receive either outpatient methadone (30 mg PO) or buprenorphine (2 mg SL) treatment do not experience significantly different withdrawal (Bickel et al., 1988a). Similarly, methadone (20 or 60 mg PO) and buprenorphine (8 mg SL) were equally effective at suppressing withdrawal in opioid-dependent patients in a double-blind, double-dummy outpatient comparison (Johnson et al., 1992). However, withdrawal scores of patients receiving 20 mg methadone were suspect due to the increased illicit opioid use in that group (Johnson et al., 1992). The data to date suggest that 8 mg SL buprenorphine appears to suppress withdrawal symptomology as effectively as 60 mg PO methadone.

On the basis of the aforementioned clinical reports, dose equivalencies between commonly used street opioids, methadone, and buprenorphine can be constructed and used to guide clinicians in the determination of the appropriate buprenorphine substitution dose (see Table 1). The guide presented in Table 1 has been used successfully in outpatient studies at the University of Vermont's Outpatient Buprenorphine Treatment Program to determine the buprenorphine maintenance dose (Amass, Bickel, Crean, & Higgins, 1995; Amass, Bickel, Higgins, & Badger, 1994; Amass, Bickel, Higgins, & Hughes, 1994; Amass, Bickel, Hughes, & Peterson, 1993; Bickel, Amass, Crean, & Higgins, 1995). On the basis of the patients' treatment records, self-reports of opioid use, or both, the patients' buprenorphine maintenance dose is determined during the first week of treatment. For example, if a patient reported being maintained on 60 mg of oral methadone or injecting more than three bags of heroin per day, the patient's sublingual buprenorphine maintenance dose would be 8 mg. To decrease the likelihood of precipitated withdrawal by buprenorphine, we would recommend that the patients report for induction in the beginning stages of withdrawal. We would ask them to accomplish this by either abstaining or reducing the amount of the maintenance drug they use in the 24 to 72 hr before induction. We would then

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Self-reported use</th>
<th>Methadone equivalent (mg PO)</th>
<th>Buprenorphine equivalent (mg SL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone</td>
<td>5–7 pills</td>
<td>20–30</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>10–14 pills</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>&gt; 20 pills</td>
<td>50–60</td>
<td>8</td>
</tr>
<tr>
<td>Hydrocodone</td>
<td>7–10 pills</td>
<td>20–30</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>14–20 pills</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>&gt; 20 pills</td>
<td>50–60</td>
<td>8</td>
</tr>
<tr>
<td>Codeine</td>
<td>7–10 pills</td>
<td>20–30</td>
<td>2</td>
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<tr>
<td></td>
<td>14–20 pills</td>
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<td>4</td>
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<tr>
<td></td>
<td>&gt; 20 pills</td>
<td>50–60</td>
<td>8</td>
</tr>
<tr>
<td>Meperidine</td>
<td>4 pills (300 mg)</td>
<td>20–30</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>8 pills per 600 mg</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>&gt; 8 pills per 600 mg</td>
<td></td>
<td>50–60</td>
</tr>
<tr>
<td>Hydro-</td>
<td>2–3 4-mg pills</td>
<td>20–30</td>
<td>2</td>
</tr>
<tr>
<td>morphine</td>
<td>4–7 4-mg pills</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>&gt; 8 4-mg pills</td>
<td>50–60</td>
<td>8</td>
</tr>
<tr>
<td>Heroin</td>
<td>1 bag</td>
<td>20–30</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>2–3 bags</td>
<td>40</td>
<td>4</td>
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<tr>
<td></td>
<td>&gt; 3 bags</td>
<td>50–60</td>
<td>8</td>
</tr>
<tr>
<td>Morphine</td>
<td>1–2 pills</td>
<td>20–30</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3–4 pills</td>
<td>40</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>&gt; 5 pills (60 mg)</td>
<td>50–60</td>
<td>8</td>
</tr>
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</table>

Note. PO = orally; SL = sublingually; IV = intravenous.
whether these induction procedures were more effective or necessary relative to any other procedure. Thus, research is warranted to determine the efficacy of different induction procedures.

In conclusion, comfortably transferring patients from methadone or other opioids to buprenorphine requires four steps:

1. Instruct patients to abstain or lower maintenance dose of methadone or other opioids for 24 to 72 hr before buprenorphine induction.

2. Select the appropriate buprenorphine substitution dose (see Table 1).

3. Start the patient on a dose of buprenorphine lower than the recommended substitution dose and increment the buprenorphine dose to the final substitution dose over the first several days of treatment.

4. Impose a temporal interval of at least 12 hr between prior agonist and buprenorphine administration. The presence of mild withdrawal symptoms at the time of buprenorphine administration is desirable.

Use of these procedures will permit patients to be placed on doses of buprenorphine that will likely suppress withdrawal signs and symptoms but not precipitate withdrawal.

Maintaining Patients on Buprenorphine

We will consider buprenorphine’s utility as a maintenance treatment by evaluating its similarity to other opioids, the opioid blockade it engenders, and its efficacy in clinical outcome trials. By doing so, buprenorphine’s impact on the clinical status of opioid-dependent individuals is elucidated and the outcome of treatment studies may be more easily interpreted.

Agonist Effects

Agonist activity as used here refers to the extent to which buprenorphine, a partial μ-opioid agonist, exhibits actions similar to full μ-opioid agonists such as morphine and methadone. Such actions are relevant to the clinical issues of substitution, abuse liability, compliance, and duration of action. Agents similar to full efficacy agonists are more likely to be accepted by patients, to maintain medication compliance, and hence to be substitutable; however, the more similar an agent is to morphine or methadone, the greater the liability for abuse. Moreover, the duration of buprenorphine’s agonist actions is essential in determining optimal interdosing intervals.

Discriminative stimulus and self-reported effects. The extent to which discriminative stimulus and self-reported effects of buprenorphine are similar to full opioid agonists can elucidate how well buprenorphine will substitute for other treatment agents such as methadone. The drug discrimination procedure is one of the most rigorous laboratory procedures for assessing substitutability of psychoactive drugs (Schuster & Johnson, 1988). The drug discrimination procedure trains a discrimination based on the interoceptive drug effects between a drug (such as morphine) and placebo. The resulting discrimination is typically highly specific. Thus, if a discrimination were trained between morphine and placebo, then generally only morphineline drugs would substitute for morphine (i.e., produce morphine-appropriate responses) and all other drugs, such as secobarbital or d-amphetamine, would produce placebo-appropriate responses. The utility of this procedure is derived from the concordance of results between animal and human opioid drug discrimination studies (Kamien, Bickel, Hughes, Higgins, & Smith, 1993) and measures of drug discrimination and self-reports in human opioid drug discrimination studies (Preston, Bigelow, Bickel, Liebson, 1987, 1989; Bickel, Bigelow, Preston, & Liebson, 1989).

Buprenorphine generally substitutes for other morphinelike opioids in drug discrimination studies across several species, including humans. For example, in nondependent rhesus monkeys trained to discriminate codeine (5 mg/kg) from saline, buprenorphine produced codeine-appropriate responding; that is, buprenorphine was identified as “codeine-like” (Hoffmeister, 1988). Humans show a similar profile of results. For example, when nondependent humans were trained to discriminate hydromorphone from saline, buprenorphine produced hydromorphone-appropriate responding and was rated as being subjectively similar to hydromorphone (Preston, Liebson, & Bigelow, 1992). However, buprenorphine partially generalized to both hydromorphone and pentazocine in post-addict volunteers trained to discriminate between saline, hydromorphone, and pentazocine, while producing effects unlike either drug on measures of self-report (Preston et al., 1989). In other human studies, buprenorphine produced a profile of subjective effects similar to those effects produced by morphine in dependent and nondependent opiate abusers (Jasinski et al., 1978; Johnson et al., 1989; Mello & Mendelson, 1980) as well as in healthy volunteers (Blom, Bondesson, & Gunne, 1987; Fullerton, Timm, Kolski, & Bertino, 1991; Gal, 1989). Overall, these studies, with one exception, indicate that buprenorphine and full efficacy morphinelike agonists generally share a common profile of discriminative stimulus and self-reported agonist effects, suggesting that buprenorphine should substitute well for other treatment agents such as methadone.

Reinforcing effects: Abuse liability and treatment compliance. The reinforcing effects of morphinelike drugs are important clinically because they play a large role in the agent’s potential for abuse and maintenance of treatment compliance. Generally, reinforcing effects are inferred when a drug is self-administered at rates greater than placebo. However, reinforcing effects may also be inferred by examining an agents’ abuse at the societal level, given that self-administered drugs are also those drugs abused by humans (Schuster & Thompson, 1969). Finally, treatment compliance can be considered to reflect, in part, reinforcing effects of the agent and, thus, examining compliance can also reflect on buprenorphine’s reinforcing effects. Concordance across these three dimensions would provide confirming evidence of buprenorphine’s reinforcing effects. Although no buprenorphine self-administration studies on humans have been reported to date, nonhuman primate self-administration studies have demonstrated that buprenorphine functions as a reinforcer and, therefore, has potential for abuse. Buprenorphine has been demonstrated to function as a reinforcer in rhesus monkeys, maintaining responding above
that maintained by saline (Hoffmeister, 1988; Mello, Bree, & Mendelson, 1981; Winger, Skjoldager, & Woods, 1992; Woods, 1977; Yanagita, Katoh, Wakasa, & Onimura, 1982; Young, Stephens, Hein, & Woods, 1984), but it did so in only 1 of 4 baboons in another study (Lukas, Brady, & Griffiths, 1986). Although buprenorphine has been reported to exhibit lower reinforcing efficacy than morphine and other full efficacy μ agonists (Lukas et al., 1986; Mello, Lukas, Bree, & Mendelson, 1988; Woods, 1977), these cross-drug comparisons of reinforcing efficacy must be interpreted with care (Katz, 1990).

A lower abuse liability for buprenorphine relative to a full efficacy agonist is supported by the dose-related plateau on subjective and physiological effects observed with buprenorphine in humans (Amass et al., 1993; Bigelow, 1991; Walsh et al., 1994). Finally, buprenorphine, because of the risk of precipitated withdrawal, may have a lower abuse potential than other opioids in highly dependent individuals (Johnson et al., 1989), but it still may be abused by individuals with lower levels of dependence (e.g., Strang, 1985).

Clinical reports do indicate, however, that buprenorphine clearly has potential for abuse. Numerous reports exist of buprenorphine abuse in countries where its availability has been largely unrestricted including Ireland (O’Connor, Moloney, Travers, & Campbell, 1988), England (Strang, 1985), Scotland (Gray, Ferry, & Jauhar, 1989; Hamerseley, Lavelle, & Forsyth, 1990; Robertson & Bucknall, 1986; Sakol, Stark, & Sykes, 1989), India (Chowdhury & Chowdhury, 1990; Singh, Mattoo, Malhotra, & Varma, 1992), Australia (Quigley, Brede-meyer, & Seow, 1984), New Zealand (Harper, 1983; Rainey, 1986; Robinson, Dukes, Robinson, Cooke, & Mahoney, 1993), and Spain (San, Tremoleda, Ollé, Serra, & de la Torre, 1989; Torrens, San, & Camí, 1993). Moreover, buprenorphine dependence has been reported in Germany by individuals not previously dependent on opiates (Richert, Strauss, Arnim, Vogel, & Zech, 1983) and was purportedly the drug of choice in Edinburgh, Scotland (Lavelle, Hammerseley, Forsyth, & Bain, 1991). Not surprisingly, restrictions on prescribing have been introduced in some of these countries (O’Connor et al., 1988; Strang, 1991). General practitioners and scientists from abroad have noted that buprenorphine is purer, cheaper, and easier to obtain than black market heroin. These qualities make buprenorphine a popular and economic alternative to heroin, perhaps even more so when heroin supplies are low.

Buprenorphine is also active by several different routes of administration. For example, a large rise in intravenous use of sublingual preparations has been reported (Sakol et al., 1989), consistent with a human laboratory investigation demonstrating that intravenous buprenorphine has substantial potential for abuse (Pickworth, Johnson, Holicky, & Cone, 1993). The intravenous use of the crushed tablet formulation is prompting additional concern over increased risk for spreading the HIV infection and AIDS (O’Connor et al., 1988; Robertson, Roberts, Black, Davitt, & Stewart, 1987; Strang, 1985, 1991). In the United States, alternative routes of administration have been explored as a way of limiting buprenorphine’s abuse potential. Although the subcutaneous preparation was investigated in early clinical studies (Jasinski et al., 1978; Mello, Mendelson, & Kuehnle, 1982), noninjectable sublingual formulations are now advocated as a better drug delivery system because they are more convenient to administer, will minimize illicit diversion relative to the injectable formulation, and may be more economical to manufacture (Jasinski, Fudala, & Johnson, 1989). However, 6 out of 8 heroin-dependent individuals on long-term buprenorphine maintenance in New York who received sublingual buprenorphine (range 0.6-3.9 mg) for self-administration at home administered the solution intranally, as this route reportedly produced a stronger drug effect; the other 2 individuals receiving the highest doses claimed that the drug volume precluded sublingual administration and continued to self-administer their buprenorphine subcutaneously (Resnick, Resnick, & Galanter, 1991). Interestingly, the pharmacokinetic profile of intranasal buprenorphine (Eriksen et al., 1989) resembles that of intramuscular administration (Bullingham, McQuay, Moore, & Bennett, 1980), a route which is approximately twice as potent as sublingually administered buprenorphine (Wallenstein, Kaiko, Rogers, & Houde, 1986). Thus, the formulation used is important in mitigating buprenorphine’s abuse potential, and caution is recommended with the use of take-home medication.

Finally, buprenorphine’s reinforcing effects are reflected by its ability to maintain compliance rates comparable to methadone across several outpatient maintenance treatment studies. Retention rates of 72% were reported for 39 patients receiving between 2 and 6 mg SL buprenorphine daily for 1 month (Kosten, Morgan, & Kleber, 1991). These findings extend those of an earlier report with 16 patients maintained on daily sublingual buprenorphine (2, 4, or 8 mg), where retention rates of 81% over the 1-month maintenance period were reported (Kosten & Kleber, 1988). Higher retention rates (i.e., 96%) have been observed in patients maintained for 28 days on 8 mg SL buprenorphine, when continued participation was contingent on an individual never missing more than two consecutive clinic visits (Amass, Bickel, Higgins, & Hughes, 1994). Direct, controlled comparisons of sublingual buprenorphine with oral methadone (2 mg buprenorphine versus 30 mg methadone and 8 mg buprenorphine versus 60 mg methadone) have demonstrated comparable retention rates during maintenance and detoxification treatment for periods up to 25 weeks (Bickel et al., 1988a; Johnson et al., 1992).

In conclusion, buprenorphine has reinforcing effects that have been exhibited in studies with nonhumans, are evidenced by abuse patterns of buprenorphine by humans in a variety of countries, and are consistent with the retention data obtained with buprenorphine when compared with methadone. Buprenorphine’s abuse liability highlights the need to exercise caution and maintain regulatory control over this compound, but it also indicates buprenorphine’s acceptability as a treatment agent for opioid-dependent patients.

**Duration of agonist effects and dosing schedules.** Identifying the range of buprenorphine doses and interdosing intervals that maintain agonist activity may significantly increase the options available to clinics providing buprenorphine treatment. Currently, methadone must be administered at least once daily to suppress withdrawal signs and symptoms. Take-home doses must be provided to patients when they cannot attend the clinic on a daily basis, which in turn increases the risk for medication diversion (e.g., Goldman & Thistel, 1978; Kirn, 1988). Alternatively, i-alpha-acetylmethadol (LAAM), a
long-acting full efficacy μ agonist recently approved by the FDA for the treatment of heroin dependence, permits dosing three times a week without increased withdrawal signs and symptoms and thereby obviates the problems inherent with take-home medication (Bigelow & Preston, 1995). Although initial tests of longer interdosing intervals with buprenorphine did not support its feasibility for this use (Fudala et al., 1990), more recent information suggests that buprenorphine is closer to LAAM than may have originally been thought (Amass, Bickel, Higgins, & Badger, 1994).

The first study examining whether addicts could be maintained on buprenorphine less frequently than once daily studied 19 heroin-dependent males residing on a residential treatment unit (Fudala et al., 1990). Patients were assigned randomly to receive an 8-mg SL buprenorphine dose either daily or every 48 hr for 18 days using a double-blind, placebo-controlled design. Self-reported drug and withdrawal effects and physiologic responses (except pupil diameter) did not differ significantly between the 2 groups, but clinically relevant behavioral effects were present between drug and nondrug days for patients receiving buprenorphine on alternate days. These individuals reported greater “urge for opioid” and significantly higher ratings on the LSD (dysphoria) subscale of the Addiction Research Center Inventory short form (Jasinski, 1977; Martin, Sloan, Sapiro, & Jasinski, 1971) during placebo as compared with buprenorphine days and correctly identified placebo doses 70% of the time. Moreover, self-reported opioid withdrawal effects and pupil responses oscillated as a function of drug and nondrug days, such that increased withdrawal rating scores and pupil dilation covaried with placebo administration. This profile of withdrawal effects on nondrug days for individuals receiving buprenorphine on alternate days might increase susceptibility to illicit opioid use (Fudala et al., 1990). Therefore, the more stable withdrawal scores obtained with once daily dosing supported using daily dosing in clinical settings.

However, another and perhaps more effective approach to using buprenorphine in an alternate-day dosing schedule was suggested in a recent clinical pharmacology study. In that report, the acute substitution of 16 mg per 70 kg of sublingual buprenorphine was more effective than the 8 mg per 70 kg maintenance dose at suppressing withdrawal symptoms for 24 hr (Amass et al., 1993). These data suggest that administering double the maintenance dose of buprenorphine may extend withdrawal suppression beyond 24 hr and thereby support a report, the acute substitution of 16 mg per 70 kg of sublingual once daily dosing supported using daily dosing in clinical settings. Participation was contingent on daily attendance and opioid abstinence. Opioid abstinence was verified by on-site urinalysis testing conducted under observation three times per week. Seventy-seven percent of the participants (10 out of 13) completed the study (n = 6, 4 mg per 70 kg; n = 4, 8 mg per 70 kg). No differences were observed between alternate-day and daily dosing in terms of opioid intoxication, opioid withdrawal, the ability to discriminate placebo doses, retention, or positive urinalysis results for nonopioid drugs. The only significant difference observed was in participant-rated agonist effects, which were lower during alternate-day than daily administration. These data suggest that buprenorphine can be administered safely and effectively every 48 hr by doubling the maintenance dose. Moreover, this dosing schedule may be cost-effective for programs and be useful in settings (e.g., rural areas) where travel is a barrier to treatment. This observation was extended in subsequent studies showing that this alternate-day dosing procedure functions as a reinforcer (Amass et al., 1995). Perhaps most significantly, the maintenance dose can also be tripled, permitting patients to attend the clinic every third day without risk of overdose or withdrawal (Bickel et al., 1995). Thus, like LAAM, buprenorphine has the potential to be dispensed three times per week by administering double doses Monday and Wednesday and a triple dose on Friday. Data from a current outpatient clinical trial indicate this 3-day a week dosing procedure is acceptable to patients and is preferred to a 4-day a week regimen (Bickel & Amass, 1994).

Although a large-scale clinical trial to assess carefully the efficacy of alternate-day dosing with buprenorphine is warranted, these findings illustrate that buprenorphine has some similarities to LAAM and represent an advance over methadone in the treatment of opioid dependence. Double maintenance doses every 48 hr allow patients to attend the clinic less frequently without the use of take-home doses and the consequent risk for diversion of medication, a risk which is particularly relevant given the numerous reports of buprenorphine abuse. This procedure may also enhance compliance in patients whose work, parental responsibilities, or commute time to the clinic make daily attendance difficult.

**Antagonist Properties and Duration of Opioid Blockade**

One of buprenorphine’s most desirable clinical actions is its ability to block the effects of opioid agonists such as heroin. Buprenorphine (16 mg SC) blocked the self-reported and physiological effects of 120 mg SC morphine administered 1.5 hr after buprenorphine administration (Jasinski et al., 1978). Buprenorphine (2, 4, 8, and 16 mg SL) has also produced a dose-related blockade of the effects of hydromorphone (18 mg SC) 24 hr after the last buprenorphine administration (Bickel et al., 1988b). Buprenorphine blockade of self-reports at 24 hr was greater than its blockade of physiological measures of opioid-agonist effects. This selective blockade is similar to that observed during the dissipation of naltrexone blockade (Vereby, Volavka, Mule, & Resnick, 1977). Thus, these data suggest the blockade produced by the maintenance dose of buprenorphine may be dissipating at the end of the 24-hr period.

The extent to which that blockade will extend beyond 24 hr...
when double the maintenance dose has been administered
remains to be determined and may impact on how alternate-
day dosing regimens are implemented into treatment pro-
grams. For example, if blockade extends for the entire interdos-
ing interval, then these dosing schedules could be applicable to
most patients. However, if these dosing schedules fail to
provide blockade throughout the dosing interval, then such
dosing schedules may need to be restricted to patients who
have achieved appreciable periods of abstinence from street
opioids.

Efficacy as a Treatment Agent

Buprenorphine appears as efficacious as methadone in
suppressing opioid intake across both nonhumans and hu-
mans. Chronic intravenous buprenorphine and methadone, at
roughly equivalent doses according to potency estimates (i.e., 1
mg/kg/day buprenorphine and 24 mg/kg/day methadone,
Jaffe & Martin, 1990), suppressed similar levels of morphine
and heroin self-administration to the same degree in rhesus
monkeys (Harrigan & Downs, 1981). However, another pre-
clinical report of the effects of buprenorphine and methadone
on opiate self-administration in rhesus monkeys found bu-
prenorphine more effective than methadone (Mello, Bree, &
Mendelson, 1983). The reason for the different outcomes is
unknown.

Laboratory studies in humans have shown that buprenor-
phine produces a 69% to 98% suppression of heroin self-
administration in opioid-dependent humans receiving daily
subcutaneous doses of 8 mg (Mello & Mendelson, 1980; Mello
et al., 1982). Dose-dependent decreases in illicit opioid use
have also been reported with sublingual buprenorphine main-
tenance in a small sample. Approximately 30% of urine
collected during 2-mg maintenance was opiate-positive com-
pared with only 10% during 16-mg maintenance (Bickel et al.,
1988b).

Similar results were reported in several controlled, outpa-
tient studies. Patients maintained for 17 weeks on either
buprenorphine (8 mg SL) or methadone (60 mg PO) had
comparable rates of illicit opiate use (47% and 56%, respec-
tively; Johnson et al., 1992). In another study, patients main-
tained for 16 weeks on either buprenorphine (average daily
dose 8.9 mg SL) or methadone (average daily dose 54 mg PO)
also had comparable rates of illicit opiate use (55% and 47%,
respectively; Strain, Stitzer, Liebson, & Bigelow, 1994). In
patients completing 1 month of outpatient treatment with
buprenorphine (2 and 6 mg SL daily), illicit opioid use
decreased by 50%, although not dose-dependently (Kosten
et al., 1991). When opioid abstinence was reinforced with vouch-
ers exchangeable for retail items, 87.5% of urine samples were
opioid-negative in outpatients maintained on daily 8 mg SL
buprenorphine (Amass, Bickel, Higgins, & Hughes, 1994).
Thus, buprenorphine appears to be at least as effective as
methadone at suppressing illicit opioid use in both laboratory
settings and during outpatient treatment.

Discontinuing Buprenorphine Treatment

If buprenorphine becomes widely available as an opioid
treatment agent, knowledge of the extent of withdrawal
occurring following abrupt and gradual discontinuation with
buprenorphine will be important for patient management.
Further, because of its unique pharmacology, buprenorphine
may permit patients to transition directly from buprenorphine
to naltrexone (an opioid antagonist) treatment. Such a transi-
tion would be beneficial since naltrexone greatly reduces the
risk for relapse in this population (Kleber, 1985).

Abrupt Discontinuation

Buprenorphine can induce physical dependence (Fudala et
al., 1990; Jasinski et al., 1978). Therefore, knowledge of the
degree of physical dependence resulting from abrupt discontin-
uation of chronic buprenorphine treatment will dictate the
type of dose taper regimens used for both inpatient and
ambulatory detoxification of opioid-dependent patients.

A withdrawal syndrome of a mild-to-moderate magnitude
has been reported following abrupt discontinuation of bu-
prenorphine in opioid-dependent humans. This result suggests
that physical dependence develops to some limited degree
during chronic treatment (Fudala et al., 1990; Jasinski et al.,
1978; Kosten & Kleber, 1988; Lukas et al., 1984). Mild,
antagonist-precipitated withdrawal signs have also occurred in
response to high-dose naltrexone challenge following main-
tenance with 3 mg SL buprenorphine (Kosten et al., 1990).

In contrast, withdrawal signs were not observed when
buprenorphine was discontinued over a 5-day period in heroin
addicts who were maintained on an 8 mg SC dose for 10 days
(Mello & Mendelson, 1980; Mello et al., 1982). Similarly,
abstinence signs have not been documented in preclinical
studies with patas (Cowan, 1974) and macaque (Lukas, Mello,
Bree, & Mendelson, 1988) monkeys when buprenorphine was
discontinued following a month of chronic treatment (see also
Mello et al., 1981).

These inconsistent findings must be evaluated carefully with
the recognition that increased withdrawal symptoms may be
associated with higher buprenorphine doses and longer treat-
ment regimens. For example, in an outpatient study, buprenor-
phine was abruptly discontinued in opioid-dependent patients
following 1 month of 2, 4, or 8 mg SL buprenorphine (Kosten
& Kleber, 1988). In the 24-hr following discontinuation,
withdrawal symptoms increased in a dose-dependent fashion
with minimal withdrawal observed in patients receiving either
the 2- or 4-mg dose, while withdrawal scores doubled, increas-
ing from mild to moderate, in patients maintained on 8 mg
buprenorphine. Observations were not reported beyond the
24-hr period following discontinuation. Unfortunately,
because of the brief duration of the observations, this study may
have failed to measure peak withdrawal symptoms. In another
study, mild withdrawal symptoms were observed during a
10-day period of saline treatment in opioid-dependent patients
previously maintained for 45 days on 2 mg SC buprenorphine
(Lukas et al., 1984), a dose that is equivalent to approximately
3 mg SL (Jasinski et al., 1989). This 10-day assessment period
was consistent with the typical 10-day observation period used
to characterize withdrawal from prototypic opiates (Fraser,
Van Horn, Martin, Wolbach, & Isbell, 1961).

Withdrawal signs were sufficient to warrant therapeutic
intervention in 53% of 15 participants withdrawn from bu-
Detoxification Scheduling

The decreased magnitude of opioid withdrawal observed following abrupt discontinuation of buprenorphine relative to full efficacy agonists may result from buprenorphine's slow dissociation from opiate receptors and long duration of action. These qualities may impact positively on detoxification outcomes by permitting accelerated buprenorphine detoxifications to be used without inducing significant withdrawal distress. In designing a buprenorphine detoxification program, three main objectives should be met. First, patient compliance should be maintained. Second, opioid abstinence should be achieved. Third, minimal abstinence symptomatology should result from the dose reduction schedule to minimize the risk for relapse.

Some insight as to whether withdrawal from buprenorphine can be best achieved by a gradual or rapid dose-reduction schedule can be gleaned from two controlled studies. A random assignment 90-day outpatient study compared sublingual buprenorphine (2 mg) to oral methadone (30 mg) in 45 heroin dependent individuals by using double-blind, double-dummy procedures (Bickel et al., 1988a). Following 3 weeks of maintenance at the 2-mg dose, the dose was reduced (1.34, 0.67, 0.34, and 0.17 mg) at weekly intervals over 4 weeks followed by 6 weeks of placebo medication. There were no significant differences between methadone and buprenorphine on retention, illicit drug use, or withdrawal symptoms. The percentage of patients continuing in both treatments after Week 6 declined rapidly, and illicit opiate use steadily increased through the detoxification, suggesting that this rapid taper schedule was not optimal.

A random-assignment 66-day outpatient study demonstrated that a 36-day gradual buprenorphine dose reduction was superior to a 12-day rapid buprenorphine dose reduction when incentives for opioid-negative urine samples were offered and counseling was mandated (Amass, Bickel, Higgins, & Hughes, 1994). Participant retention was lower, and opioid use and participant-rated withdrawal increased to a greater extent during rapid buprenorphine detoxification. For the gradual and rapid dose reductions, respectively, 100% versus 0% of patients were retained in treatment for the entire 9 weeks, and 33.3% versus 61.3% of urine was positive for opioids during detoxification. Participant-rated withdrawal increased at a rate 6 times higher during rapid as opposed to gradual detoxification. Taking both studies together, the available data indicate that rapid buprenorphine dose reduction is associated with poorer treatment outcome. Nonetheless, more studies are necessary to understand how to best use buprenorphine as a detoxification agent.

Buprenorphine–Naltrexone Interactions

The literature published to date suggests that buprenorphine is not antagonized by opioid antagonists except at high doses of the antagonist, differentiating it from full efficacy agonists. This characteristic may benefit three treatment areas. First, it may be possible to transfer patients directly from buprenorphine to naltrexone, thereby eliminating the need for detoxification before naltrexone treatment. Second, a combination buprenorphine–naltrexone product might be developed to extend buprenorphine's duration of blockade and further limit its abuse liability. Third, by developing a range of combination mixtures in which the buprenorphine:naltrexone ratio is gradually adjusted, a seamless transition to naltrexone treatment may be possible.

Preclinical data suggest that opioid antagonists do not displace buprenorphine from receptors and therefore do not precipitate withdrawal (Woods et al., 1985). For example, when naloxone (0.3 mg/kg) was administered before buprenorphine, the effects of buprenorphine were completely blocked (i.e., buprenorphine did not displace naloxone). However, when buprenorphine was administered first, naloxone doses...
up to 100 mg/kg did not reverse buprenorphine’s effects (i.e., naloxone did not displace buprenorphine; Shannon, Cone, & Gorodetzky, 1984). Thus, the dose of an opioid antagonist necessary to reverse the actions of buprenorphine is substantially greater than the dose necessary to block the effects of this compound (France, Jacobson, & Woods, 1984; Rance & Dickens, 1978). Buprenorphine’s high affinity for opioid receptors undoubtedly prevents naloxone from displacing buprenorphine already bound to these sites (Hambrook & Ranee, 1976), while also limiting the intensity of antagonist-precipitated withdrawal.

Clinical reports further confirm that very large doses of naloxone are required to antagonize the effects of buprenorphine. For example, 4 mg SC naloxone administered 3.5 hr after buprenorphine failed to precipitate withdrawal in 3 participants maintained on 8 mg SC buprenorphine for 38 days (Jasinski et al., 1978). In fact, precipitating withdrawal from buprenorphine when naloxone is administered 24 hr after the last buprenorphine dose requires at least 25 times the intravenous naloxone dose (i.e., 0.4 mg) necessary to precipitate marked or severe withdrawal from full agonists such as morphine (Kosten et al., 1988, 1989, 1990; Quigley et al., 1984). Only a remarkable dose of naloxone (35 mg IV) produced a mild withdrawal response in patients maintained on 3 mg SL buprenorphine (Kosten et al., 1990). In healthy volunteers, reversal of buprenorphine-induced (0.3 mg IV) respiratory depression by naloxone was dose-dependent and had gradual onset, with maximal reversal effects taking 3 hr following a 10-mg IV dose (Gal, 1989). The lack of the abrupt reversal effect, typical of most naloxone-opioid interactions, again underscores naloxone’s difficulty in displacing buprenorphine already bound to opioid receptors (Hambrook & Rance, 1976).

The previous observations suggest that buprenorphine may result in an easier and more expedient transition to naltrexone than is currently possible with methadone. Such a transition may improve patients’ compliance with naltrexone treatment. The question of how to most effectively transfer patients from buprenorphine to naltrexone must await more research, but the possibilities could vary across a broad range. At one extreme, detoxification with buprenorphine may decrease the number of days required without medication before starting naltrexone. The transition from methadone to naltrexone requires patients to be completely detoxified from methadone, to cope with the methadone withdrawal syndrome, and to remain abstinent from opioids for up to 10 days before receiving naltrexone (Kleber, 1989). This delay between agonist and antagonist therapy substantially increases an individual’s susceptibility to relapse (Kleber, 1989). Other techniques have been developed to shorten the period between agonist and antagonist therapy, but these procedures require hospitalization and the coadministration of other agents such as clonidine and benzodiazepines (Brewer, Rezac, & Bailey, 1988; Charney, Hening, & Kleber, 1986; Kosten et al., 1990, 1991; Loimer, Lenz, Schmid, & Presslich, 1991; Vining, Kosten, & Kleber, 1988). However, because buprenorphine is not easily antagonized by opioid antagonists, the transition from buprenorphine to naltrexone may be easier. Thus, perhaps naltrexone could be administered at the end of a detoxification with a limited delay.

At the other extreme, buprenorphine and naltrexone could be coadministered at certain doses and permit a seamless transition from buprenorphine to buprenorphine–naltrexone to naltrexone. For example, perhaps a series of mixtures varying in net agonist effect could be used to gradually taper the agonist actions over time, while slowly fading patients into naltrexone treatment. Moreover, a combination buprenorphine–naloxone or buprenorphine–naltrexone mixture may limit buprenorphine’s abuse potential and may be one strategy for mitigating against illicit diversion (Preston, Bigelow, & Liebson, 1988; Weinhold, Preston, Farre, Liebson, & Bigelow, 1992). Of course, the alternate-day dosing schedules, discussed earlier, may minimize many concerns about diversion via take-home doses. However, there still may be occasions where such a combination mixture is useful, such as for travel or emergencies that extend beyond the limits of the alternate-day dosing effect.

A sublingual buprenorphine–naloxone combination tablet is in fact being developed by NIDA (D. Segal, personal communication, December 8, 1994). This sublingual combination tablet may be particularly useful because of the different parenteral to sublingual potency profiles for buprenorphine and naloxone. While buprenorphine has an approximately 2:1 parenteral to sublingual potency ratio (McQuay, Moore, & Bullingham, 1986), studies with opioid-dependent participants indicate a parenteral to sublingual potency ratio of approximately 10:1 to 20:1 for naloxone (Preston, Bigelow, & Liebson, 1990). Sublingual naloxone doses up to 5 times the intravenous dose that reverses toxic opioid overdose can be administered safely to opioid abusers without precipitating withdrawal (Preston et al., 1990). Thus, the possibility exists that a combination mixture could be developed that would permit buprenorphine’s agonist actions to operate when administered sublingually but would precipitate withdrawal in opioid-dependent individuals when administered parenterally and hence help mitigate against unauthorized use of buprenorphine. This strategy for limiting abuse has been successfully achieved with pentazocine–naloxone combinations (Legros, Khalili-Varasteh, & Margetts, 1984), and initial studies with buprenorphine are encouraging. For example, the concurrent administration of buprenorphine and naloxone to nondependent postaddicts produced less agonist effects than buprenorphine alone (Weinhold et al., 1992). In participants maintained on 50 mg/day of oral methadone, naloxone (0.2 mg IM) alone and in combination with buprenorphine (0.2 and 0.3 mg IM) precipitated withdrawal (Preston et al., 1988). Although the combination product was identified as an opioid antagonist, buprenorphine somewhat “blunted” naloxone’s effects on withdrawal scores. Importantly, this buprenorphine–naloxone mixture (i.e., 0.3/0.2 IM) did not compromise the analgesic efficacy or safety of buprenorphine when administered for the treatment of postoperative pain (Rolly, Poelaert, Mungroup, & Paelinck, 1986; Vanacker, Vandermeersch, & Tomasson, 1986). More research is necessary to determine the extent to which a sublingual combination mixture can mitigate against parenteral abuse of buprenorphine. Although prior research suggests that a combination mixture would precipitate with-
drawal in methadone-maintained individuals, studies are needed to assess directly the effects of a combination mixture in those populations most likely to abuse buprenorphine once it is available for widespread clinical use: buprenorphine-maintained individuals, opioid-dependent individuals not seeking treatment, and nondependent opioid abusers. The degree to which a combination mixture limits buprenorphine abuse will most likely depend on the extent to which naltrexone either antagonizes opioids or blunts buprenorphine’s effects when doses of buprenorphine indicated for opioid dependence treatment are used.

Finally, a combination product, assuming there is a compatible formulation, may enhance the acceptability of naltrexone. Naltrexone’s limited acceptability among patients is reflected by the fact that few individuals suitable for naltrexone treatment ever receive the first dose (Kleber, 1989). One factor contributing to this limited acceptability is the absence of agonist effects. If buprenorphine and naltrexone could be coadministered at certain doses, then the agonist effects of buprenorphine might support self-administration, while naltrexone would blunt the effects of illicit opioids. Of course, dose selection of the two agents would be very important. Ideally, the buprenorphine dose would need to be sufficiently low so that it did not produce any clinically significant physical dependence, but it would need to be sufficiently high for agonist effects to be experienced. The naltrexone dose would need to be sufficiently low so as to not block buprenorphine’s effects but sufficiently high so as to blunt the effect of any illicit opioid. This raises the important question of whether blockade needs to be total to produce clinically important results (cf. Bickel et al., 1988b). Nonetheless, if successful, the combination product would promote treatment compliance via buprenorphine’s agonist effects, while naltrexone’s antagonist effects could enhance blockade and permit smaller buprenorphine doses to be used (i.e., to block other opioids with buprenorphine alone is expensive, requiring doses 25- to 50-fold greater than the analgesic dose).

We do not know where along this range of potential outcomes the results of research will point. Nonetheless, any of these outcomes should minimize the likelihood of relapse following buprenorphine before the initiation of naltrexone treatment. Issues in transitioning patients from buprenorphine to naltrexone and the feasibility of the combination product also raise numerous questions about the clinical pharmacology of these two compounds. Significant questions include identifying doses of naltrexone that would permit the expression of buprenorphine’s agonist effects, assessing the efficacy and duration of the blockade produced by the combination product, and evaluating the effects of the combination product on treatment compliance. Such information is essential to determine the feasibility of the combination mixture.

**Summary and Future Directions**

Buprenorphine is a promising alternative for the treatment of opioid dependence, and it appears to compare favorably to methadone for both maintenance and detoxification treatment. Buprenorphine can antagonize the effects of μ opioids, is less likely to be associated with toxic overdoses, results in milder withdrawal symptomology during gradual detoxification, and can support less than daily dosing regimens. However, several clinical issues remain to be resolved before buprenorphine is accepted for widespread clinical use. Issues that await further research include developing protocols for transferring patients from methadone to buprenorphine, determining the proper buprenorphine maintenance dose, assessing the feasibility of a combination buprenorphine–naltrexone product, determining the most effective detoxification schedule, and evaluating buprenorphine’s safety for long-term maintenance. Although the lack of behavioral and physiological toxicity associated with large buprenorphine doses may support a longer interdosing interval, the extent to which blockade of exogenous opioids is maintained over intervals greater than 24 hr also remains to be determined. Finally, although buprenorphine has a wider margin of safety than methadone, it still has the potential for abuse. Therefore, regulatory control should be maintained once buprenorphine is approved as a treatment agent. Ultimately, controlled outpatient investigations designed to determine how buprenorphine and other rehabilitative services can be combined to yield better treatment outcomes are necessary.

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Received November 13, 1994
Revision received April 17, 1995
Accepted May 24, 1995