Review

Clinical and pharmacological evaluation of buprenorphine and naloxone combinations: why the 4:1 ratio for treatment?

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Abstract

Although only a partial μ-opiate agonist, buprenorphine can be abused and diverted from medical therapy to the illicit drug market. A combination of buprenorphine and naloxone for sublingual administration may discourage diversion and abuse by precipitating opiate withdrawal when taken parenterally. Because opiate-abusing populations are not homogeneous and have varying levels of opiate dependence, the efficacy of buprenorphine and naloxone in precipitating opiate withdrawal or in attenuating the pleasurable effects of buprenorphine may vary. This chapter describes the effects of sublingual and parenteral buprenorphine and naloxone combinations in several populations of opiate-dependent people. We conclude that buprenorphine and naloxone combinations should not diminish the efficacy of sublingual buprenorphine, but should have lower abuse liability than buprenorphine alone.

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1. Introduction

Initial reports suggested that buprenorphine would have a low abuse potential (Jasinski et al., 1978; Jasinski, 1979). However, like all potent μ-opiates, parenteral abuse and illicit diversion of buprenorphine has been reported worldwide (O’Connor et al., 1988; Singh et al., 1992; Robinson et al., 1993). The majority of the reported abuse occurs in heroin addicts who intravenously administer extracts of crushed tablets (Segui et al., 1991; Lavelle et al., 1991; San et al., 1993; Nigam et al., 1994). Injection drug abusers are at risk for serious bacterial and viral diseases, including HIV. Strategies which diminish the parenteral abuse liability of treatment medications will decrease transmission of infections between injection drug abusers; hence, the development of a formulation of buprenorphine less abusable by injection.

The efficacy of buprenorphine, alone or in combination with naloxone, for the treatment of opiate dependence is described in other chapters. Here we review the rationale for selecting a 4:1 ratio of buprenorphine to naloxone for marketed formulation and how the combination was assessed for safety and efficacy. We discuss the effects of both buprenorphine and naloxine in different populations of opiate abusers and nonabusers and use these findings to estimate abuse liability.

2. Requirements for a buprenorphine and naloxone combination

Buprenorphine and naloxone dose combinations should diminish the parenteral abuse liability of buprenorphine in opiate-dependent individuals by precipitating opiate withdrawal when taken parenterally but not sublingually. Naloxone in solution has a relatively low sublingual absorption of 8–10% (Weinberg et al., 1988; Preston et al., 1990; Harris et al., 2000), whereas buprenorphine in solution is better absorbed (≈ 30–50%) and has significant pharmacologic activity when
given sublingually (Olley and Tiong, 1988; Weinberg et al., 1988; Jasinski et al., 1989; Mendelson et al., 1997a,b). The rapid and unpleasant effects of naloxone when administered intravenously to opiate-dependent people (O’Brien et al., 1978; Gilman et al., 1990; Mendelson et al., 1997a,b) suggested that it would be an ideal candidate for a combination formulation. The optimal combination formulation of buprenorphine and naloxone would preserve the therapeutic effects of buprenorphine and minimize opiate antagonist effects of naloxone when given sublingually. However, if the same combination was taken illicitly by a parenteral route, it would have the opposite effects, precipitating substantial opiate withdrawal.

This was an unusual requirement for a new drug formulation. In general, successful medications do not produce unpleasant effects and exhibit minimal interindividual variability. However, the buprenorphine and naloxone combination needed to be aversive when administered parenterally but well tolerated when given sublingually. In addition, interindividual variability was desirable, with rapidly precipitated withdrawal in parenteral abusers but suppression of withdrawal (and illicit opiate use) in treated patients. Precipitated withdrawal can produce substantial sympathetic activation, with marked elevations in heart rate and blood pressure. Therefore, the combination should be as safe as possible. Because naloxone produces both desired aversive effects and potentially dangerous sympathetic activation, determining the lowest effective dose of naloxone required for precipitated withdrawal was important.

Precedents for combination agonist and antagonist opioid formulations include pentazocine and naloxone mixtures, which significantly reduced parenteral pentazocine abuse (Ghodsie, 1987). A methadone and naloxone oral dose combination was tested but not widely prescribed (Nutt and Jasinski, 1974; Loimer et al., 1991). A survey of New Zealand opiate abusers suggested that a buprenorphine and naloxone combination marketed in that country appeared to decrease abuse liability for lower, analgesic buprenorphine doses (0.3–0.6 mg) (Robinson et al., 1993). However, sublingual buprenorphine doses in solution in the range of 4–32 mg per day are needed for opiate addiction treatment in most patients (Johnson et al., 1995; Ling et al., 1996; Strain et al., 1996; Schottenfeld et al., 1997; Eder et al., 1998; Ling et al., 1998), and the lowest effective dose is 2 mg (Johnson et al., 1992). Buprenorphine combinations with naloxone in this dose range had not been studied.

3. Efficacy of buprenorphine and naloxone in precipitating opiate withdrawal

Some buprenorphine likely will be diverted from therapeutic to illicit use. Effective deterrence will depend to some extent on the magnitude and likelihood of adverse events. Because people already dependent on opiates are most likely to abuse an opiate drug, several studies have evaluated the efficacy of buprenorphine and naloxone combinations in precipitating opiate withdrawal. Complicating matters, opiate-abusing and dependent populations are not homogeneous. The varying levels of tolerance and dependence between infrequent users of opiates and patients on methadone maintenance mandated assessment of buprenorphine and naloxone combinations in a range of defined opiate-abusing and dependent populations. We and others have studied the effects of buprenorphine and naloxone in populations spanning a range of opiate abuse and dependence. Tables 1 and 2 summarize the results of human studies using various buprenorphine and naloxone combinations.

4. Buprenorphine and naloxone effects in opiate-dependent people

Quantification of the degree of opiate dependence can be difficult. No agreed upon definition exists distinguishing low, moderate, and high levels of opiate dependence. Substitution trials have used daily doses as large as 240 mg morphine (Fraser and Isbell, 1960) given in equal doses (60 mg s.c. doses every 6 h) to suppress withdrawal in highly dependent subjects. More recent substitution and challenge studies of partial agonists of morphine were conducted with volunteers dependent on 60 mg morphine sulfate given in four daily 15 mg s.c. or i.m. doses. At this dose, sufficient effects were produced to reliably suppress measured signs and symptoms of opiate withdrawal (Jasinski, 1977; Schuh et al., 1996). This dose of morphine was approximately equivalent to a 30 mg daily oral methadone dose, and is generally associated with moderate dependence.

Parenterally administered buprenorphine and naloxone reliably precipitate opiate withdrawal in people with high to moderate levels of opiate dependence. In two studies (Preston et al., 1988; Mendelson et al., 1997a,b), patients taking 30 mg or more of methadone per day had substantial precipitated withdrawal following fixed ratio (2:1, 1.5:1 and 1:1) low dose buprenorphine (0.2–0.3 mg) and naloxone (0.1–0.2 mg) combinations. These buprenorphine doses are in the analgesic dose range for opiate-naïve patients. The very small doses of naloxone required to precipitate substantial withdrawal (and a clear dislike for this combination) suggests a low abuse liability in people with moderate to high levels of opiate dependence.

In opiate-dependent daily heroin users, an i.v. dose of a 1:1 ratio of buprenorphine to naloxone (2 mg) produced opiate withdrawal and decreased the estimated illicit street value of the combination (Mendelson...
Table 1  
Effects of buprenorphine (B) and naloxone (B:N) combinations in opiate-naive, experienced, or dependent populations

<table>
<thead>
<tr>
<th>Study</th>
<th>Goal</th>
<th>N</th>
<th>Population</th>
<th>B:N Dose route</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rolly et al., 1986</td>
<td>Examine efficacy and safety of B and B:N combo in post-surgical pain</td>
<td>30 B (9 M)</td>
<td>Post-orthopedic or gynecological surgery</td>
<td>0.3 mg B and 0.2 mg N i.m. (3:2 B:N)</td>
<td>No difference in analgesic efficacy between B and B:N</td>
</tr>
<tr>
<td>Vanacker et al., 1986</td>
<td>Compare B and B:N combo efficacy in post-surgical pain</td>
<td>34 B (13 M)</td>
<td>Abdominal surgery</td>
<td>0.3 mg B and 0.2 mg N i.m. (3:2 B:N)</td>
<td>No difference in analgesic efficacy between B and B:N</td>
</tr>
<tr>
<td>Preston et al., 1988</td>
<td>Determine abuse liability of B:N combo</td>
<td>6 M</td>
<td>Opiate-dependent, methadone maint (30 mg/day)</td>
<td>B:N precipitated w/d less than N alone (using subjective, behavioral, and physiological measures)</td>
<td></td>
</tr>
<tr>
<td>Mendelson et al., 1989</td>
<td>Measure effects of non-B-induced prolactin release</td>
<td>6 M</td>
<td>Opiate-naive</td>
<td>N suppressed B-induced prolactin release in a dose-dependent manner</td>
<td></td>
</tr>
<tr>
<td>Weinhold et al., 1992</td>
<td>Evaluate agonist effects of B:N combo</td>
<td>7 M</td>
<td>Opiate experienced, nondependent</td>
<td>N attenuated agonist effects of B</td>
<td></td>
</tr>
<tr>
<td>Mendelson et al., 1996</td>
<td>Compare effects of B, N, B:N combo</td>
<td>8 M</td>
<td>Opiate-dependent (confirmed by N-induced w/d)</td>
<td>B:N induced substantial w/d; N diminished B agonist effects; B diminished N antagonist effects</td>
<td></td>
</tr>
<tr>
<td>Mendelson et al., 1997a,b</td>
<td>Evaluate effects of B:N combo</td>
<td>6 (5 M)</td>
<td>Opiate-dependent, methadone maint (49–60 mg/day)</td>
<td>B:N induced w/d using physiological and subjective measures</td>
<td></td>
</tr>
<tr>
<td>Fudala et al., 1998</td>
<td>Evaluate effects of B:N combo</td>
<td>10 M</td>
<td>Opiate-dependent morphine maint. (15 mg i.m. q.i.d.)</td>
<td>B:N precipitated w/d using subjective and observed measures</td>
<td></td>
</tr>
<tr>
<td>Mendelson et al., 1999</td>
<td>Evaluate effects of B:N combo</td>
<td>12 (11 M)</td>
<td>Opiate-dependent morphine maint. (15 mg i.m. q.i.d.)</td>
<td>N precipitated w/d, increased HR, BP, RR (8:1 only increased self-reported w/d; 2:1, 4:1 produced w/d using self-reported, observed and physiological measures)</td>
<td></td>
</tr>
<tr>
<td>Strain et al., 2000</td>
<td>Evaluate abuse potential of sublingual B and B:N in non-dependent opiate abusers</td>
<td>7 M</td>
<td>Opiate abusers who were not physically dependent</td>
<td>B:N induced w/d, increased HR, BP, RR (8:1 only increased self-reported w/d; 2:1, 4:1 produced w/d using self-reported, observed and physiological measures)</td>
<td></td>
</tr>
<tr>
<td>Stoller et al., 2001</td>
<td>Assess abuse liability of B:N doses in the therapeutic range</td>
<td>10 (gender not specified)</td>
<td>Heroin addicts stabilized on oral hydromorphone 40 mg daily</td>
<td>B:N induced w/d, increased HR, BP, RR (8:1 only increased self-reported w/d; 2:1, 4:1 produced w/d using self-reported, observed and physiological measures)</td>
<td></td>
</tr>
<tr>
<td>Comer and Collins, 2002</td>
<td>Assess the reinforcing effects of B and B:N combinations in recently withdrawn heroin addicts</td>
<td>6 (5 M)</td>
<td>Heroin addicts withdrawn from heroin for 1–6 weeks</td>
<td>B:N induced w/d, increased HR, BP, RR (8:1 only increased self-reported w/d; 2:1, 4:1 produced w/d using self-reported, observed and physiological measures)</td>
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B, Buprenorphine; N, Naloxone; w/d, withdrawal; i.v., intravenous; i.m., intramuscular; s.c., subcutaneous; s.l., sublingual; M, male.
Table 2
Effects of buprenorphine (B) and naloxone (B:N) combinations in buprenorphine maintained or abusing populations

<table>
<thead>
<tr>
<th>Study</th>
<th>N Population</th>
<th>B:N Dose ratio</th>
<th>Results</th>
</tr>
</thead>
</table>
| Koster et al., 1994                        | Opiate-dependent B-maint (21 mg or 0.1 mg i.v. solution) | 8 mg B s.l. (n = 5) | N precipitated w/d using subjective and observed measures. The buprenorphine and naloxone combination effects and was considered liable to abuse by these subjects. The buprenorphine and naloxone combination was very aversive and not substantially different from naloxone alone. Following the combination dose, opiate agonist effects did eventually emerge but they were always delayed and attenuated when compared to buprenorphine alone. Although some degree of opiate withdrawal was usually precipitated by parenteral administration of this buprenorphine and naloxone combination, there was considerable between-subject variability in withdrawal intensity. Some of this variability was probably due to differing self-administered opiate doses and resulting levels of dependence inherent in any group of untreated heroin injectors. In subjects maintained on 40 mg/day of oral hydromorphone, parenteral doses of 1.0–16 mg of buprenorphine combined with 0.25–4 mg of naloxone (always in a 4:1 ratio) produced reliable dose-dependent precipitated withdrawal. Similar doses of sublingual buprenorphine and naloxone or buprenorphine alone did not precipitate withdrawal. Maximal cardiovascular responses in this highly dependent population were not excessive, suggesting that precipitated withdrawal will be relatively safe in typical heroin addicts (Stoller et al., 2001).

5. Comparisons of three different buprenorphine and naloxone dose ratios

Empirical evaluation of a range of dose combinations guided optimal formulation of a s.l. medication with low abuse liability for the treatment of opiate dependence. We tested the effects of three buprenorphine and naloxone combinations in opiate-dependent subjects where controlled doses of morphine were substituted for illicit heroin (Mendelson et al., 1999). The primary goals of this study were to determine the dose range over which i.v. naloxone, in combination with i.v. buprenorphine, would precipitate opiate withdrawal signs and symptoms and attenuate the pleasurable effects of buprenorphine in subjects with a moderate level of opiate dependence. To minimize variability due to differing degrees of opiate dependence, subjects were stabilized on parenteral morphine. With this paradigm, volunteers physically dependent on variable but always uncertain self-administered doses of illicit opiates are given known doses of morphine to achieve a stable level of dependence. Thus, when the experimental medication is substituted for morphine, opiate agonist and antagonist effects can be measured under controlled laboratory conditions. After stabilization for 5 days on a 60 mg daily dose of morphine given as four 15 mg i.m. doses,
Subjects were challenged, under double-blind conditions, with a 2 mg i.v. dose of buprenorphine alone and in combination with 1, 0.5 and 0.25 mg naloxone (ratios of 2:1, 4:1 and 8:1). We knew naloxone at doses similar to those used in the study reliably precipitates opiate withdrawal in subjects maintained on 60 mg/day i.m. morphine (Schuh et al., 1996).

All three buprenorphine and naloxone combinations produced opiate antagonist effects when given intravenously. The naloxone in the combination dose produced dose-dependent precipitated withdrawal, with the 2:1 ratio (1 mg naloxone) producing the greatest and the 8:1 ratio (0.25 mg naloxone) the least opiate withdrawal (Fig. 2). All indices of opiate withdrawal were increased by the 2:1 and 4:1 ratios. With the 8:1 ratio, only self-reports of ‘global’ withdrawal were increased. Both subjective and physiologic withdrawal effects peaked within 5 min after injection of naloxone plus buprenorphine, then dissipated within 45 min for all combinations. The duration of withdrawal effects also depended on naloxone dose and lasted 30 min after the 2:1 ratio and 15 min after the 4:1 and 8:1 combinations. Buprenorphine-induced pupil constriction was significantly attenuated by the 2:1 and 4:1 buprenorphine and naloxone combinations, but not by the 8:1 ratio. In general, the 8:1 combination had a more variable between-subject response and less overall effect. The 2:1 and 4:1 ratios were generally similar in the profile of antagonist effects. Although the 2:1 ratio could be distinguished from the 4:1 ratio on some withdrawal measures, both the 2:1 and 4:1 precipitated substantial withdrawal.

If buprenorphine was diverted from therapeutic to illicit use, our volunteer subjects would be typical potential purchasers. All subjects were regularly purchasing illicit heroin. They were qualified to judge the potential illicit street value of buprenorphine and naloxone combinations. They judged i.v. buprenorphine and morphine equivalent in dollar value ($10 and 8, respectively). The estimated monetary value of all combination ratios was substantially less than buprenorphine or morphine. Although some subjects would be willing to pay small amounts for the 4:1 and 8:1 combination ratios ($4), no one expressed any desire to pay for the 2:1 dose.

In a study similar to ours, opiate addicts were stabilized on the same daily dose of i.m. morphine sulfate (60 mg/day) and a single 4:1 dose ratio of buprenorphine and naloxone was evaluated (Fudala et al., 1998). Significant opiate withdrawal effects were produced by the i.v. dose of buprenorphine 2 mg and naloxone 0.5 mg, suggesting a decreased abuse potential.
subjects, maximal opioid agonist effects were always smaller and delayed (for up to 3 h) following buprenorphine and naloxone combinations when compared with buprenorphine alone (Mendelson et al., 1996). The time course of effects was biphasic on self-ratings of global intoxication, with opiate antagonist-like effects dominating in the first 90 min and opioid agonist-like effects emerging only later in the second hour (Fig. 1). Comer and Collins (2002) also found that combinations of buprenorphine and naloxone (2 mg buprenorphine with 0.5 mg naloxone and 8 mg buprenorphine with 2 mg naloxone i.v.) attenuated the positive subjective effects of buprenorphine (2 and 8 mg, respectively) in recently detoxified heroin addicts. However, in this population of addicts who had only been off heroin for 1–6 weeks, both buprenorphine and the combination had similar reinforcing properties. Therefore, in people not currently in treatment, the combination of attenuated pleasurable effects (in both dependent and nondependent abusers) and precipitated opiate withdrawal (in dependent abusers) should decrease the illicit market value of buprenorphine.

In our study of three dose ratios of buprenorphine and naloxone, we assessed the ability of these combinations to attenuate opioid agonist effects. The opiate agonist effects of buprenorphine remained substantial following 5 days exposure to 60 mg/day of morphine. Buprenorphine 2 mg was equivalent to 15 mg of morphine on all opiate agonist measures (Mendelson et al., 1999). All three of the buprenorphine and naloxone combinations we tested diminished the opiate agonist effects of buprenorphine, with the 2:1 ratio decreasing all opiate agonist measures (Mendelson et al., 1999). The 4:1 and 8:1 ratios decreased global intoxication and opiate agonist scale indices but did not alter drug liking. All subjects rated all the intravenous buprenorphine and naloxone challenges as dysphoric, not euphoric. Our results are in agreement with reports from opiate abusers who were not physically dependent. Opiate agonist effects of lower buprenorphine doses were attenuated by concurrent naloxone at dose ratios of 1:2, 1:1 and 2:1 (Weinhold et al., 1992). Although not tested in this experiment, diminished pleasurable effects would be expected in nondependent opiate abusers administered buprenorphine and naloxone combinations similar to the ones we tested.

Strain evaluated the effects of sublingual buprenorphine and naloxone tablets (1/0.25, 2/0.5, 4/1, 8/2, 16/4 mg) in opiate abusers with a low level of physical dependence. When compared to intramuscular hydromorphone (2 and 4 mg), the opiate agonist effects of buprenorphine doses greater than 4 mg were similar to hydromorphone. None of the sublingual buprenorphine and naloxone doses produced opiate withdrawal (Strain et al., 2000). These authors concluded that sublingual

6. What about buprenorphine and naloxone in less dependent populations?

A substantial percentage of individuals abusing heroin or other opiates do not experience precipitated withdrawal after naloxone challenge (Kanof et al., 1991). Combination formulations might not be aversive in these individuals because naloxone-preficitated withdrawal would not occur. Therefore, in nondependent abusers an important additional feature of a combination would be attenuation of pleasurable and reinforcing effects of buprenorphine if the combination dose is taken parenterally. In our study of heroin-dependent

Fig. 2. Observer rating on the Clinical Institute Narcotic Assessment (CINA) Scale in opiate-dependent subjects stabilized on 60 mg/day i.m. morphine and challenged with three dose ratios of buprenorphine and naloxone. Change scores (mean ± S.D., n = 12) from baseline at 15 min postdose are shown. *, Significantly different from buprenorphine, morphine, and placebo (P ≤ 0.01). Bup (buprenorphine, 2 mg), MS (morphine sulfate, 15 mg); 8:1 (buprenorphine, 2 mg; naloxone, 0.25 mg); 4:1 (buprenorphine, 2 mg; Naloxone, 0.5 mg); 2:1 (buprenorphine, 2 mg; naloxone, 1 mg); Plac (placebo). (Mendelson et al., 1996) Reproduced with permission from the publisher.
buprenorphine and naloxone had a relatively low abuse liability in nondependent opiate abusers.

7. Buprenorphine and naloxone effects in buprenorphine-stabilized opiate addicts

Would the combination dose present a problem for patients taking buprenorphine regularly? In opiate-dependent subjects stabilized for 7 days on 8 mg/day of s.l. buprenorphine solution (Harris et al., 2000), s.l. 8 mg buprenorphine with 4 or 8 mg naloxone (2:1 and 1:1 ratios) did not precipitate opiate withdrawal. Buprenorphine abuse in patients treated with s.l. buprenorphine may also be limited by the partial agonist properties of buprenorphine with ceiling effects at higher doses (Walsh et al., 1994). Parenteral naloxone precipitates withdrawal in patients maintained on s.l. buprenorphine, but relatively large doses of naloxone are needed. For example, in patients taking 2–3 mg/day of s.l. buprenorphine solution, i.m. naloxone 35 mg (0.5 mg/kg) precipitated withdrawal (Kosten et al., 1990). Similarly, i.m. naloxone 3 mg/70 kg precipitated withdrawal in patients maintained on s.l. buprenorphine solution (Eisenberg et al., 1996). In buprenorphine abusers injecting an average of 1.3 mg per day, naloxone 1.2 mg i.v. also precipitated withdrawal (Nigam et al., 1994). In contrast, patients maintained for 45–52 days on 8 mg of s.c. buprenorphine did not experience opiate withdrawal following 4 mg of s.c. naloxone (Jasinski et al., 1978).

8. Safety of buprenorphine and naloxone combinations

Buprenorphine and naloxone combinations appeared safe in our opiate-dependent subjects. Naloxone produced an expected dose-dependent sympathetic activation with statistically significant (but clinically and functionally insignificant) increases in heart rate, blood pressure, and respiratory rate. No subject developed unstable cardiovascular changes despite substantial subjective withdrawal. Therefore, although unpleasant, combination formulations are probably safe in otherwise healthy opiate-dependent individuals. Because most heroin overdose deaths are due to respiratory depression (Gilman et al., 1990), illicit administration of buprenorphine formulations containing naloxone are probably safer than continued heroin abuse. In non-opiate abusers, lower doses of buprenorphine and naloxone combinations retain analgesic efficacy (Rolly et al., 1986; Vanacker et al., 1986) and suppress buprenorphine-induced stimulation of prolactin (Mendelson et al., 1989).

9. Effects of buprenorphine on opiate withdrawal

Because buprenorphine is a partial μ-agonist and could displace full μ-agonists from receptor sites, in theory μ-opiate-dependent people could experience precipitated withdrawal after buprenorphine. Precipitated withdrawal was evident in morphine-dependent laboratory animals (Martin et al., 1976) and in methadone-maintained volunteers challenged with i.m. injections of 1 and 2 mg buprenorphine (but not 0.5, 4 or 8 mg) 20 h after the last methadone dose (Strain et al., 1995). In our studies, opiate withdrawal did not occur after buprenorphine given alone, consistent with the reports of others (Strain et al., 1992; Walsh et al., 1995; Schuh et al., 1996).

10. Conclusions

The abuse liability of buprenorphine in μ-opiate-dependent individuals can safely and effectively be diminished by the use of buprenorphine and naloxone combination formulations. Intravenous administration of buprenorphine and naloxone combinations containing more than 0.5 mg naloxone in a 2:1 or 4:1 ratio of buprenorphine to naloxone reliably precipitates opiate withdrawal. The combination dose is judged to have low illicit street value by parenteral opiate abusers. In addition to precipitating withdrawal, these combinations substantially diminish the rewarding effects of buprenorphine. At the doses of buprenorphine needed to treat opiate dependence, combination formulations with 2:1 or 4:1 ratios of buprenorphine to naloxone should have lower abuse liability than buprenorphine alone. The 4:1 ratio of buprenorphine to naloxone appears preferable to the 2:1 ratio because it provides a lower naloxone dose.

Several factors limit extrapolation of the data to all populations of opiate abusers. First, there are almost no data on the effects of buprenorphine and naloxone combinations in women. Buprenorphine is safe and effective for treatment of pregnant heroin addicts (Fischer et al., 2000; Johnson et al., 2001) and may become the standard pharmacotherapy in this group. Therefore, studies in this group are clearly needed. Second, although most abusers inject buprenorphine, some nonparenteral abuse occurs (San et al., 1993; Cracowski et al., 1999). The effects of intranasal buprenorphine and naloxone combinations in highly opiate-dependent people are not yet well defined (for example, we could find no reports of smoked buprenorphine). However, these alternate routes of administration are relatively uncommon. In the populations of opiate addicts most likely to abuse buprenorphine, the addition of naloxone should decrease abuse liability and illicit diversion.
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