National Institute on Drug Abuse

RESEARCH

MONOGRAPH SERIES

Buprenorphine: An Alternative Treatment for Opioid Dependence

121

U.S. Department of Health and Human Services • Public Health Service • National Institutes of Health

Buprenorphine: An Alternative Treatment for Opioid Dependence

Editor:

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Research Monograph 121
1992

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Alcohol, Drug Abuse, and Mental Health Administration

National Institute on Drug Abuse
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ACKNOWLEDGMENT

This monograph is based on the papers and discussions from a technical review on "Buprenorphine: An Alternative Treatment for Opioid Dependence" held on March 16-17, 1989, in Rockville, MD. The technical review was sponsored by the National Institute on Drug Abuse (NIDA).

NIDA Research Monographs are indexed in the "Index Medicus." They are selectively included in the coverage of "American Statistics Index," "BioSciences Information Service," "Chemical Abstracts," "Current Contents," "Psychological Abstracts," and "Psychopharmacology Abstracts."

DHHS publication number (ADM)92-1912
Printed 1992

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Introduction

Jack D. Blaine

Buprenorphine is a partial μ-opioid agonist and κ-antagonist marketed in the United States as an injectable analgesic by Reckitt & Colman Pharmaceutical Division. Recent studies performed in large part by the National Institute on Drug Abuse (NIDA) Addiction Research Center and by NIDA grantees indicate that buprenorphine possesses an interesting and unique mixed partial μ-agonist-antagonist profile, which should make it useful therapeutically for detoxification and maintenance treatment of heroin- and methadone-dependent persons. Thus, buprenorphine combines the characteristics of methadone and naltrexone, having both agonist and antagonist actions depending on the circumstances of its use. Buprenorphine potentially has important clinical significance because it offers the possibility of being acceptable to opiate-abusing patients seeking treatment; it decreases their heroin use, has a better safety profile than pure agonists (e.g., methadone), and does not produce a clinically significant level of physical dependence; thus, discontinuation from buprenorphine is easier than detoxification from methadone.

Buprenorphine from the scientific viewpoint illustrates the potential promise offered by various novel opioid compounds that were developed following recent advances in understanding the neuropharmacology of opioids. In humans, buprenorphine has less intrinsic agonist activity than morphine and should have a low abuse potential compared with other opioid agonists. In the initial and limited clinical studies, buprenorphine treatment by the sublingual route appears to be acceptable to narcotic addicts. These clinical studies demonstrate that buprenorphine can be substituted for reasonable doses of heroin or methadone in dependent persons and can be subsequently withdrawn without undue discomfort and with excellent safety. Therefore, buprenorphine appears to be a promising alternative to the currently available treatments for opioid dependence. More recently, scientists have also been exploring its potential for the treatment of cocaine addiction.

NIDA is the Federal agency with primary responsibility for research on the health effects of abused drugs, the nature of the addictive process, and the effects of drugs on our society. NIDA's research enhances the effectiveness

of drug abuse treatment and prevention efforts by expanding the knowledge resources on which these efforts are based. After careful review and priority setting, NIDA concentrates its research resources on areas of drug abuse that most seriously challenge the Nation's public health. In line with this research direction, a NIDA technical review meeting was held March 16-17, 1989, in Rockville, MD, sponsored by the Treatment Research Branch of the Division of Clinical Research, NIDA.

The NIDA research monograph series, including this one published by the Institute's Community and Professional Education Branch, is an established vehicle for dissemination of scientific information in the drug abuse field. Geared to researchers, the series is designed to cover the full range of basic, applied, and developmental research supported by NIDA. The monographs constitute an essential step in the process of developing and carrying forward NIDA's research objectives.

This publication seeks to gather together most of what is known about buprenorphine-its metabolism and kinetics, clinical efficacy and safety, behavioral pharmacology, and effects in animals and humans. There are considerable data from clinical and animal studies to demonstrate the acute safety of the drug when used as an analgesic. Clinical studies reviewed in this monograph as well as others conducted since the technical review indicate that buprenorphine shows promise as a treatment for heroin addiction.

One of the major advantages of using buprenorphine as a treatment drug is that addicts are willing to take it. Buprenorphine is somewhat reinforcing but does not produce the "rush" effect so familiar to opiate addicts. A daily sublingual dose of 8 mg has been shown to be effective in suppressing heroin self-administration and does not produce clinically significant physical dependence based on the mild nature of abstinence symptoms noted after abrupt discontinuation of the medication. Buprenorphine appears to be a safe drug; the potential for lethal overdose is remote even at 10 times the therapeutic dose. That it may be administered sublingually removes association with injection apparatus, which in itself may be reinforcing to some intravenous drug users. Finally, buprenorphine may even have an effect on cocaine as well as heroin self-administration. This is especially important since many serious heroin addicts use both heroin and cocaine when available.

However, there are problems yet to be solved. One of these is the formulation of the drug for a practical treatment regimen. Buprenorphine has low bioavailability when administered orally. The preferred route of administration is sublingual, but this presents problems for take-home medication programs

because the sublingual formulation would be vulnerable to diversion and abuse by injection. However, if the product is not available for home dosing, its usefulness for long-term maintenance is limited. Some creative solutions have been proposed for the problem in Lewis and Walter's chapter, such as incorporating naloxone or naltrexone, both of which have low bioavailability sublingually but would antagonize the effect of the agonist if the capsule were dissolved and injected. Combination formulations would not discourage use by nondependent opiate users or subjects maintained on buprenorphine but would contain sufficient antagonist to precipitate the abstinence syndrome in an opiate-dependent individual if the buprenorphine-antagonist combination product were injected. Lewis and Walter also believe that combination products could be made less attractive to nondependent users if sufficient naltrexone were present to attenuate the agonist effects of buprenorphine.

The abuse potential of any treatment drug must be balanced against its safety and efficacy relative to other pharmacotherapies currently available. Considering all the data currently available, it would appear that buprenorphine is a promising treatment drug for opiate addiction and may even be useful when that addiction is combined with occasional-to-frequent cocaine use. Buprenorphine appears to be as effective as methadone for detoxification of heroin addicts but does not induce significant physical dependence in humans and can be discontinued without severe withdrawal symptoms.

Although some preliminary studies seem to indicate that buprenorphine has a modulating, therapeutic effect on cocaine usage, contradictory data have also been reported recently. NIDA must evaluate, in larger, well-controlled clinical trials, how buprenorphine affects the practice of speedballing (intravenous use of heroin combined with cocaine), methadone plus cocaine usage, and solo cocaine usage in various forms and with varying frequencies.

Since this technical review, several buprenorphine-methadone comparison trials have been completed by Dr. Thomas Kosten and Dr. Rolley E. Johnson, and Dr. Walter Ling is conducting another. Drs. George Bigelow and Jack Mendelson have also continued their studies of buprenorphine. NIDA is, at the time of this writing, almost ready to undertake a large, multicenter clinical trial of sublingual buprenorphine at 12 sites, assessing four doses of the drug (1,4,8, and 16 mg) in 480 to 720 street heroin addicts. This will be a 16-week safety and efficacy study. NIDA hopes to use the results as a final pivotal study toward a buprenorphine new drug application.

NIDA views buprenotphine as a safer, more acceptable maintenance or detoxification option for many opiate-dependent addicts. It also envisions

buprenorphine as an intermediary drug (i.e., between methadone and being drug-free) for those patients who wish detoxification from methadone.

The Institute is preparing a buprenorphine combination product, incorporating the antagonist naloxone. NIDA expects that this preparation will be ready by fall 1992 and will be tested in clinical trials with a view toward take-home dosing.

Although buprenorphine appears to be a bright new tool in the treatment of heroin addiction, it is important to refrain from viewing it as a chemical panacea. Drug addiction has multiple causes and is a complicated disorder. NIDA anticipates that buprenorphine and its successor pharmacotherapies will attenuate drug addiction, but it is unlikely that any single drug will eliminate it.

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Buprenorphine—Background to Its Development as a Treatment for Opiate Dependence

John W. Lewis and Donald Walter

INTRODUCTION

Buprenorphine was developed by Reckitt & Colman Products as an analgesic following the interest generated in the mixed agonist-antagonist class of opioids. These were seen as offering clinically useful analgesia with greater safety and lower liability to abuse than the opiate agonists (Lewis 1982). Buprenorphine is now known to be a partial agonist at p-receptors and an antagonist at κ-receptors (Leander 1988). At these receptor subtypes, it has high and almost equal affinity. The kinetics of buprenorphine's opiate-receptor interactions are slow, giving it a very long duration of action. This can be related to the results of direct dependence studies in animals and humans, when naloxone failed to precipitate abstinence and abrupt withdrawal produced only mild and often delayed effects (Lewis et al. 1988).

These characteristics, though not fully established at the time, suggested to D.R. Jasinski that buprenorphine could be a useful treatment for opiate dependence because it had some of the characteristics of methadone and other characteristics more akin to the pure opiate antagonist naltrexone. In their definitive study, Jasinski and colleagues (1978) confirmed the above characteristics and in addition showed that buprenorphine produced a limited level of morphine-like subjective effects that made it acceptable to addicts and on repeated administration blocked the effects of large single doses of morphine for at least 24 hours.

Thus, the potential utility of buprenorphine in the treatment of opiate dependence has been recognized for more than 10 years, and clinical studies to evaluate this potential have been undertaken during this period. Most of the significant studies are reviewed in this volume. This chapter discusses (1) the potential contribution of the package of data assembled for the registration of buprenorphine as an analgesic to the obtaining of a new drug application for

the drug as a treatment for opiate dependence; (2) human pharmacokinetic studies with the analgesic product; and (3) the formulation of buprenorphine for detoxification and maintenance indications.

REGULATORY STATUS

In many countries, buprenorphine is approved as an analgesic for injection (0.3 mg) and sublingual (0.2-mg tablet) use. Buprenorphine was first marketed in the United Kingdom in 1978 for injection and was marketed in 1981 and 1982 as a sublingual tablet. In the United States, only the injection is available; the ampule was launched in 1986. Buprenorphine is controlled internationally in Schedule III of the Psychotropic Convention of 1989. In the United States, it is listed in Schedule V of the Controlled Substances Act, with a narcotic drug designation.

PACKAGE OF SAFETY DATA

Preclinical Safety

Buprenorphine has a full preclinical safety package that comprises data on chronic toxicity in four species and from acute toxicity and mutagenicity studies, carcinogenicity studies in two species, and a full range of reproduction studies in two species. Absorption, distribution, metabolism, and excretion studies have been carried out in five animal species.

Clinical Safety

A comprehensive number of clinical studies have been carried out to determine the safety and analgesic efficacy of buprenorphine by the sublingual route, with data available from more than 10,000 patients. The majority of these patients received doses of up to 1.2 mg per day; however, approximately 1,200 patients have received doses greater than 1.2 mg per day, with more than 200 of these receiving sublingual buprenorphine for periods greater than 1 month.

HUMAN PHARMACOKINETICS

Buprenorphine is a very potent drug, and only low doses are needed in the treatment of pain. A consequence of this is that blood levels of the drug are also low and difficult to assay. Most of the human pharmacokinetic studies have been carried out using a sensitive radioimmunoassay (RIA) (Bartlett et al. 1980); however, the antibody used in the assay cross-reacts to the *N*-dealkyl metabolite. A method in which buprenorphine is extracted prior to RIA (Hand et al. 1986) has proved difficult to validate. Soon after dosing, most of the

immunoreactivity in plasma is buprenorphine, whereas later, a mixture of buprenorphine and metabolites is present. These observations should be taken into account when pharmacokinetic data are interpreted.

Oral

Early clinical studies showed that, as in animal studies, orally administered buprenorphine was extensively metabolized by the intestine and liver during its absorption. The low oral bioavailability makes this route of administration impractical and costly. Three other routes of administration have been studied in detail: intravenous (IV), intramuscular (IM), and sublingual.

Intravenous

Buprenorphine is readily distributed into tissues, giving a large volume of distribution of the order of 10 L/kg. The elimination profile is multiexponential (Bullingham et al. 1980, 1982) but can be simplified as a rapid distribution phase ($T_{1/2}\approx$ 2 minutes) and a slower elimination phase with a plasma half-life of 3 to 5 hours. A further very slow phase of elimination of immunoreactivity ($t_{1/2}$>24 hours) is apparent from studies using longer observation periods. Buprenorphine is cleared from plasma predominantly by biliary excretion following conjugation with glucuronic acid or Ndealkylation and conjugation. A small amount of drug and metabolites is cleared slowly by the kidney (Cone et al. 1984). Some enterohepatic circulation of drug and metabolite occurs, and this, coupled with the slow urinary excretion, probably accounts for the protracted terminal elimination phase.

Intramuscular

Buprenorphine is rapidly absorbed by the IM route (T_{max}=5-15 minutes), and the bioavailability is good, ranging between 40 and 90 percent relative to an IV dose (Bullingham et al. 1980). The elimination profile is similar to that following IV administration, comprising two elimination phases.

Sublingual

The rate of absorption of buprenorphine is slower by the sublingual route, giving a mean T_{max} at approximately 200 minutes. Sublingual bioavailability is of the order of 55 percent (range 16 to 94 percent) (Bullingham et al. 1982). Other studies indicate good dose proportionality over the analgesic dose range, but no data are available for the higher sublingual doses used in the treatment of opioid dependence. The elimination profile is similar to that observed for the other routes, comprising two phases of elimination of immunoreactivity, with plasma half-lives of 3 to 5 hours and >24 hours.

Following three-timesdaily chronic sublingual dosing of 0.4 mg, steady-state levels of buprenorphine were achieved at about 4 days. The elimination profile following chronic dosing was similar to that following a single dose.

A study of the excretion of buprenorphine and its metabolites following 1 and 2 mg of sublingual buprenorphine showed that buprenorphine was excreted predominantly via the feces, whereas a small amount of conjugated buprenorphine and *N-d*ealkyl buprenorphine and its conjugate were slowly excreted via the urine (Cone et al. 1984).

FORMULATION

For a product to be used in the treatment of addiction, an oral dosage form is preferred over parenteral unless the "injection" is in depot form requiring infrequent administration. Buprenorphine has good sublingual bioavailability but poor availability by the oral route. In the analgesic dose range, 10 mg of IM morphine is equivalent to 0.4 to 0.6 mg buprenorphine sublingually and to 2 to 3 mg orally. From the studies of Jasinski and colleagues (1978), Johnson and Fudala (this volume), and Bigelow and Preston (this volume), it can now be estimated that for treatment of opiate dependence, approximately 4 mg of sublingual buprenorphine is the equivalent of a daily dose of 40 mg of oral methadone. The equivalent oral dose of buprenorphine (about 20 mg) would have an adverse effect on the daily cost of treatment. Moreover, the considerable amount of clinical safety data available from sublingual analgesic studies makes sublingual the route of choice for the addiction-treatment product. Most of the reported clinical studies of opioiddependent subjects have used this route.

The problem with use of the sublingual route for a treatment product is that the drug, for it to be absorbed, must be readily soluble in water. This means that an insoluble, sublingual formulation designed to be noninjectable also would not be absorbed. Thus, a sublingual buprenorphine product given as take-home medication in maintenance programs would be vulnerable to diversion and abuse by injection. Such diversion would negate a major objective of the proposed development of buprenorphine: the reduction of IV drug abuse and the spread of acquired immunodeficiency syndrome.

Of course there will be no problem if the product is not available for take-home use. A product used for detoxification and maintenance for up to 3 months can be administered daily at the drug treatment clinic. To ensure that such a product is rapidly absorbed by the intended route (not swallowed) and cannot be sequestered in the mouth, a solution of buprenorphine is the preferred presentation.

The limitation imposed by disallowing a take-home product would not be practicable for maintenance because nearly all methadone programs allow take-home after 3 months of satisfactory participation. A buprenorphine maintenance product would have to be either protected against diversion in the take-home situation or presented at a dose level and in a formulation that would allow three-times-a-week dosing similar to that used for naltrexone. This would require a product with a 48- to 72-hour duration. Data obtained at the Addiction Research Center on every-other-day dosing do not encourage the belief that sublingual buprenorphine at reasonable doses possesses sufficient duration of opiate-blocking effect for such a regime to be viable.

At present the only available method of protecting against diversion of take-home sublingual buprenorphine is the incorporation of a pure antagonist, either naloxone or naltrexone. Several products incorporating naloxone (but not naltrexone) into oral formulations of opiates have been developed, including a methadone-maintenance product (Gordon et al. 1974). The rationale for these products is that naloxone has very low oral bioavailability, considerably lower than that of the oral opiates. Thus, an amount of naloxone can be introduced into the opiate preparations that will have no effect when taken orally but will antagonize the effect of the opiate if the oral product is dissolved in water and injected.

Combinations of buprenorphine with naloxone for analgesic use by injection and as a sublingual tablet have been developed (Reckitt & Colman Products). The principle behind the injection product is that in nontolerant/nondependent patients the combination behaves like buprenorphine, with very little attenuation of the agonist effect due to the very different pharmacokinetics and kinetics of the drug-receptor interaction of the two drugs. In tolerant/dependent subjects, the combination behaves like naloxone, and abstinence is precipitated. Thus, diversion in a population of dependent opiate users would be strongly discouraged. The sublingual combination of buprenorphine and naloxone also benefits from the superior sublingual bioavailability of buprenorphine over naloxone in a manner similar to that of the oral naloxone combinations.

The analgesic combinations are:

Injection: buprenorphine 0.3 mg+naloxone 0.2 mg
Sublingual: buprenorphine 0.2 mg+naloxone 0.2 mg

Combinations with these ratios would not discourage injection by nontolerant/nondependent opiate users or by subjects maintained on buprenorphine and, in this regard, would be unsatisfactory as maintenance products. To be injection-proof, a combination product would need to contain sufficient antagonist to

attenuate substantially the agonist effect of buprenorphine when injected. The agonist effect by sublingual administration would be largely dependent on the superior sublingual bioavailability of buprenorphine over the antagonist.

Naltrexone, which is approved for maintenance as an oral product, is preferred to naloxone for incorporation into a sublingual buprenorphine product for take-home use. Its duration of action is significantly longer than that of natoxone, more evenly matching that of buprenorphine. Naloxone's short duration of action means that, even if present in substantial dose in the combination, it would only delay the onset of buprenorphine's agonist effects.

Because naltrexone is more potent than naloxone, it is estimated that the ratio of sublingual naltrexone to buprenorphine to prevent injection by opiate-dependent abusers is between 1:6 and 1:4. To be injection-proof, the proportion of naltrexone would need to be increased to between 1:2 and 1:1. Assuming a unit dose of buprenorphine between 4 and 8 mg, the naltrexone present (minimum of 1 mg, for example) is likely also to precipitate abstinence in opiate-dependent subjects by the sublingual route. As a result, such a product could not be used for detoxification, since transfer to it from a state of dependence on street opiates or methadone would be extremely uncomfortable. The procedure would therefore be to stabilize subjects on the buprenorphine-alone detoxification product before transfer to the combination.

The buprenorphine/naltrexone combination product, which for convenience could be a sublingual tablet, should permit greater flexibility in the use of naltrexone as an opiate-blocking drug because transfer between the combination and the antagonist in both directions should be readily achieved.

CONCLUSION

Development of buprenorphine for the treatment of opiate addiction should be directed to a sublingual buprenorphine-alone product for detoxification/short-term maintenance, for which a considerable amount of supporting clinical safety data from analgesic studies is available. To prevent diversion and injection of a sublingual buprenorphine maintenance product, incorporation of naltrexone should be explored.

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Behavioral Pharmacology of Buprenorphine: Issues Relevant to Its Potential in Treating Drug Abuse

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INTRODUCTION

Buprenorphine is a partial opioid agonist that, because of its long duration of antagonist action and unusual profile of agonist action, has considerable promise for the treatment of narcotic drug abuse. This chapter reviews the effects of buprenorphine in animal preparations that have been useful in elucidating the mechanisms of action of opioid drugs and advances the concept that buprenorphine activates p-type central receptors as a partial agonist with noncompetitive actions. Evidence for this is drawn from in vitro and in vivo preparations sensitive to a variety of opiate actions. This view of buprenorphine's central actions provides a conceptual framework for the interpretation of its behavioral and physiological actions.

The effects of chronically administered buprenorphine, although critical when the drug is considered in a treatment setting, unfortunately have not received much experimental attention. It is hoped that the framework developed in this chapter will anticipate some of the issues associated with buprenorphine's action during chronic administration. The actions of buprenorphine in a variety of preparations are described, beginning with a consideration of its binding characteristics and its actions in smooth-muscle preparations, progressing to a consideration of its behavioral actions, including its ability to produce analgesia, respiratory depression, discriminative stimulus (i.e., subjective) effects, and reinforcing stimulus effects, and ending with its capacity to produce and alter dependence.

BINDING CHARACTERISTICS

Opioids bind in the central nervous system to recognition sites that can be differentiated into three major types: the so-called μ-receptors, κ-receptors, and &receptors. Buprenorphine has been shown by a variety of investigators

to displace tritiated ligands that have selective affinities for each of the three receptor types (Sadee et al. 1982). Many investigators, using in vitro rhesus monkey brain techniques, have found that buprenorphine has no marked selectivity for any of the three types of opiate receptor sites. The authors' work, carried out in vitro (F. Medzihradsky, unpublished observations), suggests that buprenorphine has a slightly higher affinity at the μ-receptor binding site as compared with that at the κ-binding site. Using in vivo receptor binding techniques to examine opioid receptor types, Sadee and coworkers (1982) found that at small doses buprenorphine has selective affinity in rat brain for μ-receptor sites and at larger doses has affinity for other opioid receptor sites. Richards and Sadee (1985) using in vivo receptor binding procedures in rats, report that buprenorphine has similar affinity for μ- and κ-sites and less affinity for δ-sites.

Buprenorphine dissociates from opioid receptor binding sites very slowly (Hambrook and Rance 1976). As will be seen later when buprenorphine's in vivo actions are considered, this facet of the drug's action is extremely helpful in interpreting some of the actions of buprenorphine that are quite novel in comparison with other opioid p-partial agonists. Evidence for slow dissociation is reported by Rance and Dickens (1978), who have found that the opioid antagonist diprenorphine, if given prior to or at the same time as buprenorphine, is far more effective in preventing buprenorphine's attachment to opioid receptors than if the antagonist is given after buprenorphine has had an opportunity to attach to opioid receptor sites.

SMOOTH-MUSCLE PREPARATIONS

As do other opioid agonists, buprenorphine exerts an inhibitory action on electrically stimulated smooth-muscle preparations that have opioid receptors. Buprenorphine's concentration-related inhibitory actions reach their maxima relatively slowly and are not as complete as are those of prototypic opioid agonists. This partial inhibitory effect is consistent with a partial agonist action at opioid receptors, and it can be prevented by prior administration of narcotic antagonists. There is evidence that buprenorphine exerts inhibitory effects through actions on both μ- and κ-opioid receptors in various smooth-muscle preparations (Kajiwara et al. 1986). Once an inhibitory effect has been obtained with buprenorphine, in contrast to that produced by most other opioid agonists, it is resistant to reversal by narcotic antagonists or by washing; this resistance is indicative of an irreversible phase of action on opioid receptors (Schulz and Herz 1976).

ANALGESIA

Buprenorphine has complex analgesic actions that differ across analgesic assays and species. Rance (1979) has reported that buprenorphine has analgesic activity in the mouse writhing assay and the rat tail-pressure assay but not in the rat tail-flick assay; buprenorphine acts as an antagonist of the analgesic effect of morphine in the rat and mouse tail-flick assays. This pattern of activity is not unlike other partial agonist opioid analgesics. Generally, in assays that are sensitive to the effects of analgesics, that is, assays that demonstrate analgesia following administration of relatively small doses of full agonists, buprenorphine exerts maximum levels of analgesia. In less sensitive assays, those requiring relatively large doses of full agonists to produce analgesia, buprenorphine is less likely to have an analgesic action.

In some analgesic assays, buprenorphine produces peak analgesic action at relatively small doses; at larger doses, the analgesic effect is attenuated (Rance 1979). This unusual inverted-U-shaped dose/effect curve of buprenorphine has provoked much discussion and is most frequently thought to reflect some form of autoinhibition. Rance and associates (1980) found that naloxone produced a symmetrical rightward shift of both limbs of the buprenorphine dose/response curve.

At small doses, lower than those at which it produces analgesia, buprenorphine acts as antagonist of the analgesic actions of full opioid agonists. The authors and other researchers have observed that it antagonizes the analgesia produced by μ- and κ-agonists in a variety of species (Negus and Dykstra 1988; the authors, unpublished observations). The larger the dose, the longer is the duration of antagonist action. Cowan and colleagues (1977) were the first to point out that buprenorphine has a long duration of antagonist action in comparison with other standard opioid antagonists. Under appropriate conditions, buprenorphine can be used to produce a noncompetitive antagonism of the analgesic actions of morphine. Tallarida and Cowan (1992) capitalized on this noncompetitive antagonism of morphine to make the first calculation of an association constant for morphine's analgesic effect in the rat.

In the rhesus monkey warm-water tail-withdrawal assay, a modification of Dykstra and Woods (1986), it was found that buprenorphine produces a temperature-dependent analgesia of modest magnitude compared with that produced by full opioid analgesics of either the μ- or κ-type (Dykstra et al. 1987). A comparison of alfentanil and buprenorphine analgesic effects is shown in figure 1; it can be seen that, whereas alfentanil can produce a full analgesic action at both 50 and 55 °C, buprenorphine produces an incomplete

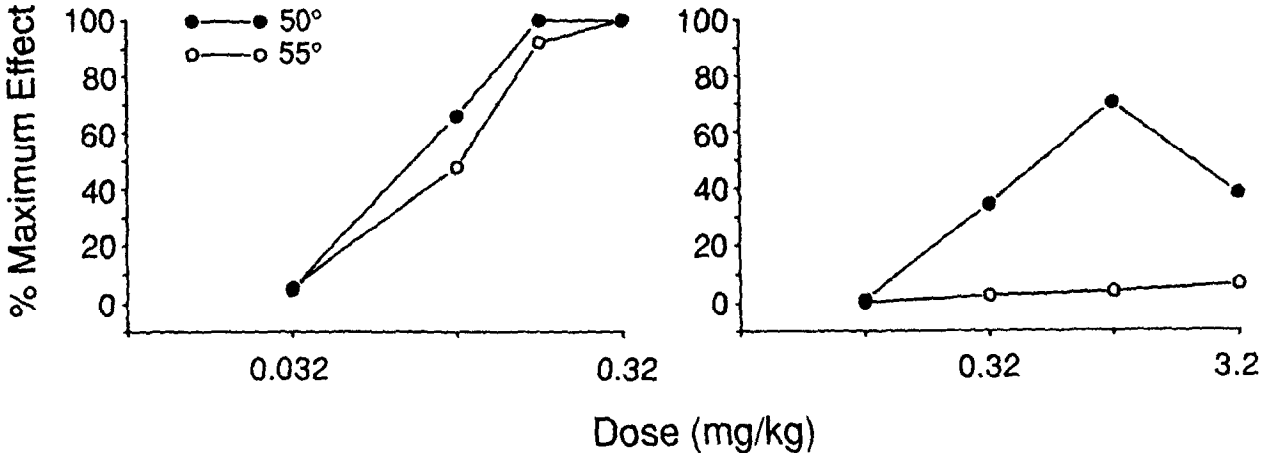

FIGURE 1. *Comparison of alfentanil (left) and buprenorphine (right) analgesic effects*

analgesia at 50 °C and has no analgesic action at 55 °C. At 50 °C, one can also see the inverted-U-shaped dose/response curve that was noted above in rodents. Similar to what was shown by Rance and coworkers (1960) in rodents, both the ascending and descending limbs of this curve are shifted to a comparable extent to the right by prior administration of the opioid antagonist quadazocine (figure 2).

Figure 3 demonstrates the antagonist effects of buprenotphine in analgesia assays: Buprenorphine at a dose of 0.1 mg/kg produces a rightward shift in the analgesia dose/effect curves for the μ-receptor agonist alfentanil and the κ-receptor agonist U-50,466. Thus, buprenorphine's antagonist actions are clearly observed at μ- and κ-receptors.

In summary, the analgesic actions of buprenorphine are apparently quite complex, depending as they do on the particular assay system, animal species, and dose conditions used. It is necessary to use the concept of μ-partial agonist with irreversible actions to account for this pattern of activity.

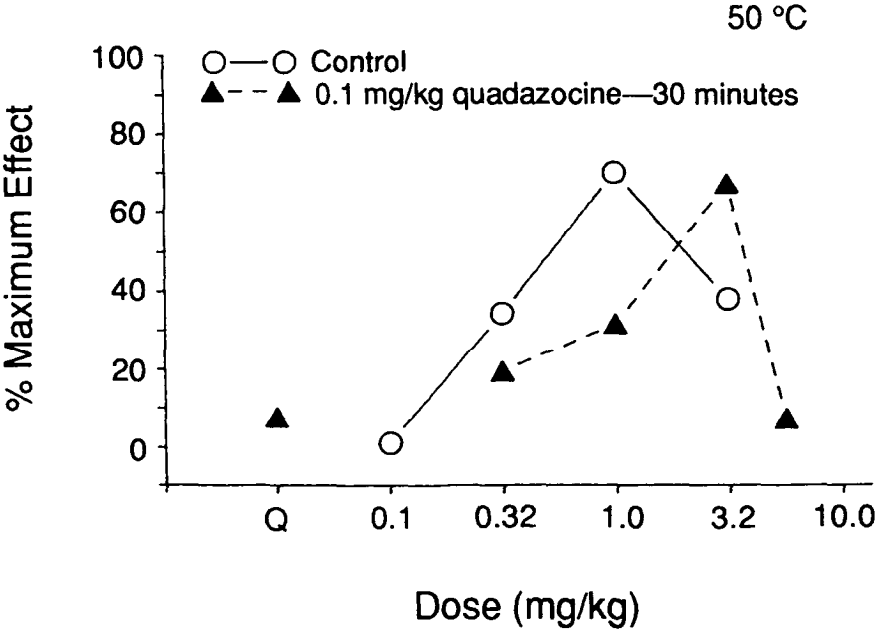

FIGURE 2. *Buprenorphine analgesic effects after administration of quadazocine*

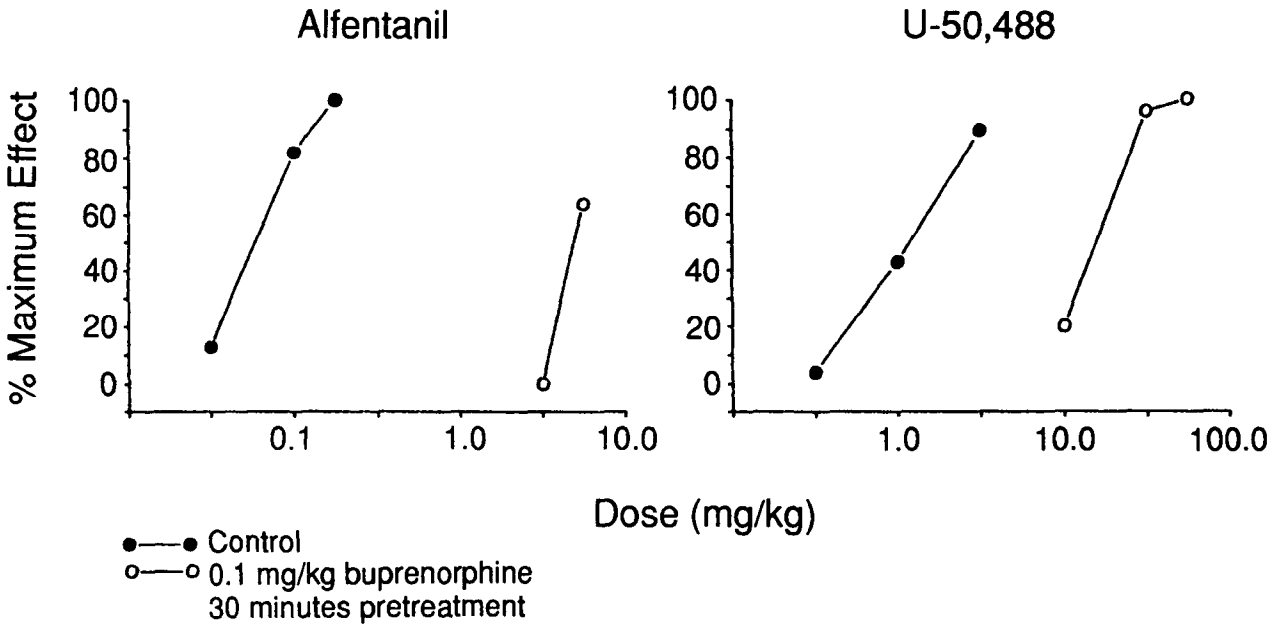

FIGURE 3. *Antagonist effects of buprenorphine in analgesia assays*

RESPIRATORY EFFECTS

Doxey and coworkers (1977) compared the effects of intra-arterial buprenorphine and morphine on arterial pCO_2, in conscious rats. Whereas morphine produces a dose-related increase in pCO_2, buprenorphine again produces an inverted-U-shaped dose/effect curve with a maximum increment of pCO_2 much less than that produced by morphine. In rhesus monkeys, the authors have compared buprenorphine to other partial agonists, such as nalbuphine, with respect to the respiratory stimulation produced by increasing concentrations of CO_2. Compared with full agonists, such as alfentanil, buprenorphine and nalbuphine have shallow dose/response curves and produce limited suppression of respiration. Doses of nalbuphine and buprenorphine that cause a modest decrement in CO_2-stimulated respiration act as antagonists of respiratory depression produced by alfentanil. Thus, buprenorphine has a partial agonist action in respiratory systems similar to that shown in other opioid-sensitive biological systems.

DISCRIMINATIVE STIMULUS EFFECTS

In animals trained to discriminate between the stimulus effects of μ-receptor agonists, such as codeine or etorphine and saline, buprenorphine produces a full μ-agonist-like action. This effect is attained with small doses of buprenorphine in rats, pigeons, and primates. For example, in rhesus monkeys trained to discriminate etorphine from saline, buprenorphine will produce etorphine-appropriate responding in doses of 0.03 to 0.1 mg/kg (Young et al. 1984). In pigeons trained to discriminate morphine from saline, doses of naltrexone that prevent morphine from producing a discriminative stimulus effect also prevent buprenorphine from producing morphine-appropriate responding (figure 4). On the other hand, if buprenorphine is allowed to produce its discriminative stimulus effect, naltrexone, even in doses far above those necessary to reverse the discriminative stimulus effects of morphine, fails to reverse this effect of buprenorphine. Thus, in drug-discrimination assays, buprenorphine produces an irreversible p-agonist action, just as it does in other behavioral assays such as analgesia (figure 5).

In pigeons, buprenorphine produces a discriminative stimulus effect that is of strikingly long duration. A dose of 5.6 mg/kg evokes a morphine-like discriminative effect for as long as 5 days (France et al. 1984).

REINFORCING STIMULUS EFFECTS

Rhesus monkeys, given the opportunity to self-administer buprenorphine, readily do so. In fact, many partial p-agonist analgesics will maintain responding in rhesus monkeys (Young et al. 1964). On the other hand,

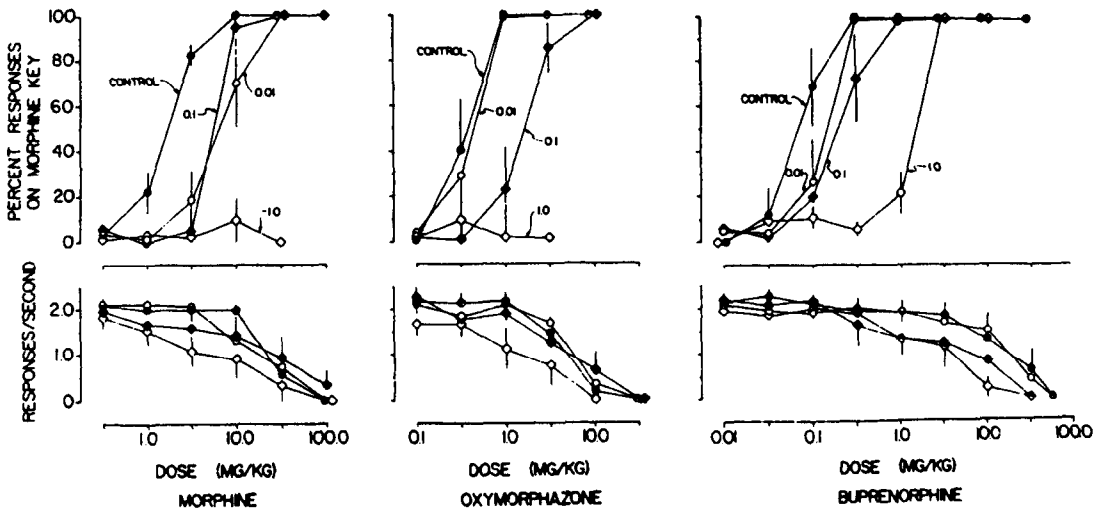

FIGURE 4. *Dose/effect curves showing naltrexone antagonism of the discriminative stimulus effects of morphine (left panel), oxymorphazone (middle panel), and buprenorphine (right panel) in pigeons trained* to *discriminate 5.6 mg/kg of morphine from saline (n=5)*

KEY: ●, no pretreatment; ○, 0.01 mg/kg of naltrexone; ◆, 0.1 mg/kg of naltrexone; ◇, 1.0 mg/kg of naltrexone

NOTE: Naltrexone was administered 10 minutes before the first dose of each test drug.

SOURCE: France, C.P.; Jacobson, A.E.; and Woods, J.H. Discriminative stimulus effects of reversible and irreversible opiate agonists: Morphine, oxymorphazone and buprenorphine. *J Pharmacol Exp Ther* 230:652-657, 1964. Copyright 1964 by American Society for Pharmacology and Experimental Therapeutics.

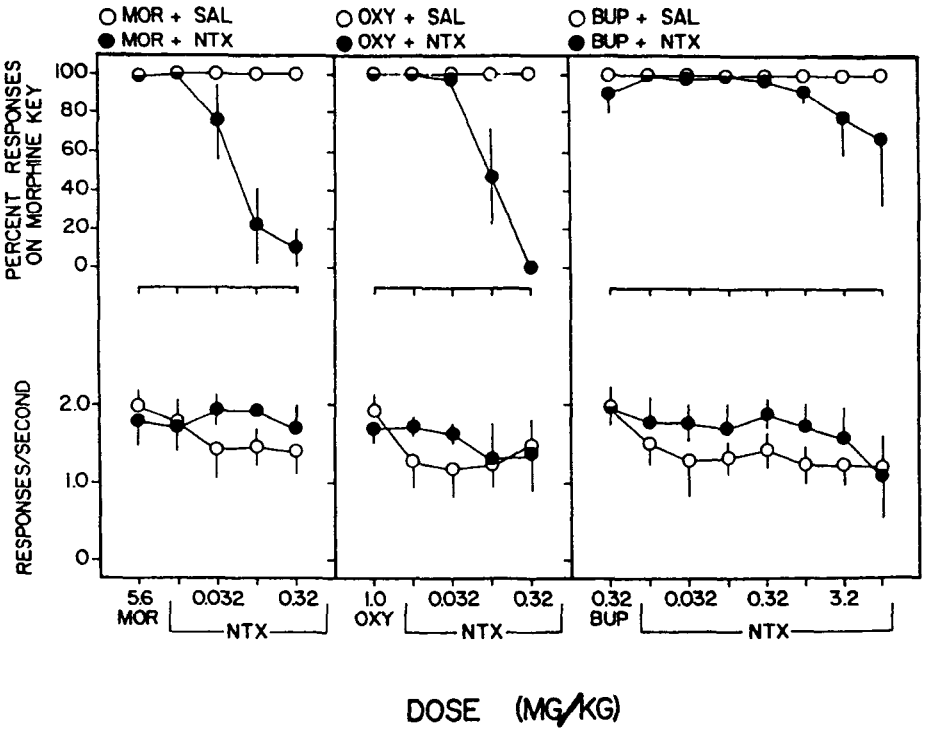

FIGURE 5. *Dose/effect curves showing the relative reversibility of the discriminative stimulus effects of morphine (left panel), oxymorphazone (middle panel), and buprenorphine (right panel) in pigeons trained to discriminate 5.6 mg/kg of morphine from saline (n=5)*

Key: ○, single injection of each agonist followed by saline injections; ●, tests in which each agonist (doses given on abscissae) was followed by increasing doses of naltrexone

SOURCE: France, C.P.; Jacobson, A.E.; and Woods, J.H. Discriminative stimulus effects of reversible and irreversible opiate agonists: Morphine, oxymorphazone and buprenorphine. *J Pharmacol Exp Ther* 230:652-657, 1994. Copyright 1984 by American Society for Pharmacology and Experimental Therapeutics.

buprenorphine maintains low rates of responding in the baboon, compared with other narcotics such as butorphanol, pentazocine, and nalbuphine (Lukas et al. 1983). In progressive ratio assessments, buprenorphine and nalbuphine both maintain lower breakpoints than do full agonists such as codeine or alfentanil (G.D. Winger, unpublished observations). These data may reflect a reduced reinforcing stimulus efficacy of some partial μ-agonists.

TOLERANCE AND DEPENDENCE

From the first descriptions of the effects of buprenorphine in rodents (Cowan et al. 1977), it has been clear that, when buprenorphine is given chronically to mice, tolerance to its analgesic actions is observed.

Subsequently, other investigators have noted tolerance development to analgesic effects of buprenorphine in rats (Berthold and Moerschbaecher 1988). Tolerance to other behavioral effects of buprenorphine also is observed, including effects on food-maintained, schedule-controlled behavior in rodents and primates (Berthold and Moerschbaecher 1988; Dykstra 1989). Tolerance that develops to buprenorphine has not been characterized pharmacologically to any great extent; this is an area of research in need of extensive investigation.

In morphine-dependent rodents (Cowan et al. 1977) and in morphine-dependent monkeys (Gmerek 1984), buprenorphine precipitates a withdrawal syndrome comparable with that produced by competitive antagonists such as naltrexone or quadazocine. The potential irreversibility of the antagonist actions of buprenorphine (figure 6) is indicated by the fact that much larger amounts of morphine are required to reverse the withdrawal precipitated by buprenorphine than to reverse the withdrawal syndrome precipitated by naltrexone or quadazocine (Gmerek 1984; Gmerek and Woods 1985).

Attempts to produce physiological dependence on buprenorphine in animals generally have been negative; both deprivation-induced withdrawal and antagonist-induced withdrawal are difficult to demonstrate following chronic administration of buprenorphine (Woods and Gmerek 1985). A smaller number of studies have shown a modest withdrawal syndrome that develops quite a while after chronic administration of buprenorphine has been terminated. In a particularly intriguing experiment by Dum and associates (1981) a chronic regimen of buprenorphine, which does not produce dependence, was shown to enhance the capacity of morphine to produce dependence. It is only with this indirect procedure that buprenorphine can clearly be shown to augment dependence. The absence of a withdrawal syndrome on termination of buprenorphine chronic administration has been attributed to the slow dissociation of buprenorphine from the μ-opioid receptor (Rance 1979).

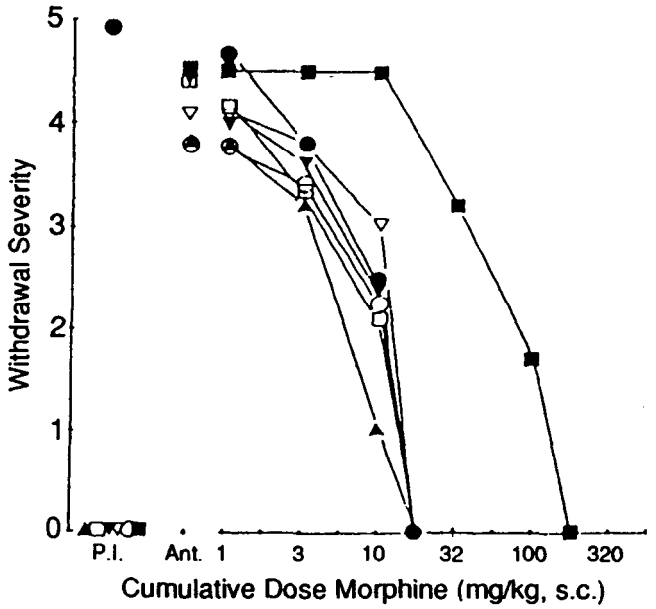

FIGURE 6. *Morphine suppression of 14-hour deprivation-induced abstinence (●) and withdrawal precipitated by naloxone (▲), naltrexone (□), MR 2266 (▼), cycazocine (▽), Win 44,441 (○), and buprenorphine (H) in morphine-dependent rhesus monkeys (mean of 6)*

NOTE: P.I.=preinjection; Ant.=antagonist administration

SOURCE: Gmerek 1984. Copyright 1984 by Churchill Livingstone (Edinburgh).

CONCLUSIONS

To develop a reasonable descriptive framework for understanding the physiological and behavioral effects of buprenorphine, it is helpful to refer to principles of receptor theory (Kenakin 1987) that cannot be elaborated here in any great detail. First, it is important to appreciate that all the agonist actions of buprenorphine at behavioral levels of description can be reasonably attributed to p-receptor activation. In support of this notion, increasing doses of the full μ-agonist alfentanil first produce discriminative and reinforcing stimulus effects, followed by analgesia and eventually respiratory depressant effects. These effects occur through a common receptor, as demonstrated by pA_2, analysis

using quadazocine (Dykstra et al. 1987; the authors, unpublished observations), and they may be assumed to require increasing amounts of receptor occupancy, as indicated by the increase in dose required to evoke them. This is schematically indicated in figure 7. It might be supposed that k-agonists with low efficacy would be able to mimic the effects produced by low doses of a full agonist, that is, those effects that occur with the occupation and activation of a few receptors. Such a low-efficacy agonist would be unable, however, to mimic the effects produced by a high dose of the full agonist, effects requiring occupation and activation of many receptors. In fact, a compound of low efficacy would be expected to antagonize the effects of large doses of a high-efficacy compound because the former drug would occupy the receptors but would produce no effect. Buprenorphine fits this conceptual scheme by readily producing discriminative effects in a variety of preparations and producing a full analgesic effect in assay systems that require little receptor occupation and activation. In analgesia assay systems in which more receptor occupation and activation is required, or in measures of respiratory depression, buprenorphine produces limited effects and, indeed, acts as an antagonist of a full agonist (the authors, unpublished observations).

It should be possible, based on various behavioral assays, to order μ-opioid agonists based on their apparent efficacy. One potential ordering of these compounds is shown in the middle portion of figure 7. Nalbuphine appears to exert its discriminative stimulus, reinforcing stimulus, and analgesic actions through a common μ-receptor (the authors, unpublished observations). Along with buprenorphine, it produces a limited respiratory depressant action in the rhesus monkey but produces a greater degree of analgesia than does buprenorphine. These data are consistent with the ordering of nalbuphine, in efficacy, between buprenorphine and alfentanil.

Finally, after demonstrating how buprenorphine's agonist effects can be related to those of other μ-agonists, it is important to point out how buprenorphine is distinct from other partial μ-agonists Buprenorphine's uniquely slow receptor dissociation kinetics are probably responsible for the noncompetitive antagonist effects of buprenorphine that are not observed with other p-partial agonists described to date. These kinetics account for the rightward and downward shifts of the effects of full agonists produced by buprenorphine, initially described by Tallarida and Cowan (1982). The authors have made similar observations in rhesus monkeys. The unusual receptor kinetics of buprenorphine also might account for the prolonged nature of the antagonist effects of buprenorphine when administered in moderate and high doses. Since the agonist actions of buprenorphine are not observed at this time, it is probably also necessary to invoke the notion that acute tolerance to the agonist actions of buprenorphine occurs with a single administration of the drug.

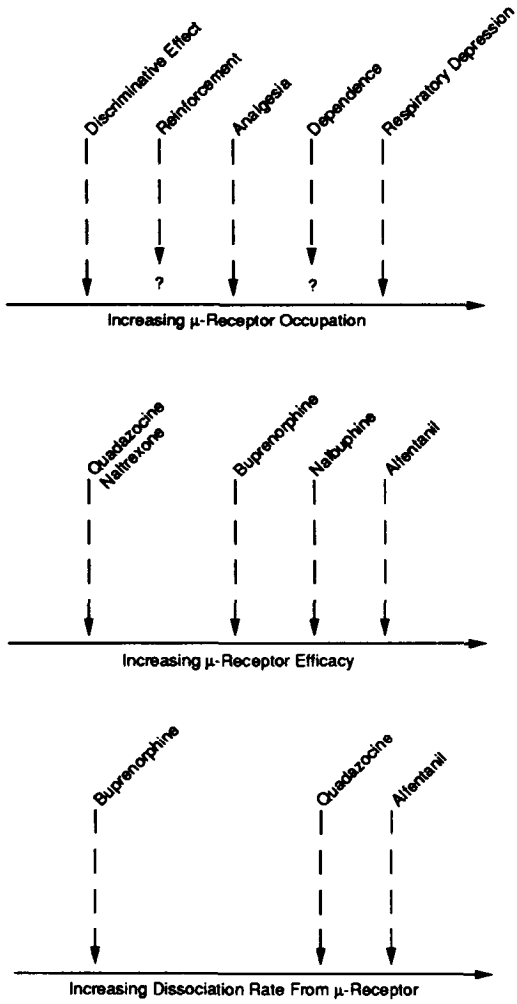

FIGURE 7. *Top: hypothetical ordering of receptor-occupation requirements of various behavioral tests. Discriminative stimulus effects develop with the fewest number of receptors occupied, and respiratory depression requires the most. Middle: relative apparent efficacy in rhesus monkeys of several drugs that bind to the μ-receptor. Quadazocine and naltrexone have no apparent efficacy, whereas alfentanil has greater apparent efficacy than buprenorphine or nalbuphine. Bottom: order of dissociation of three opioids from the μ-receptor. Buprenorphine dissociates most slowly and alfentanil most rapidly with quadazocine being intermediate.*

The studies that will be extremely important for the development of buprenorphine as a drug for the treatment of narcotic drug abuse are those that involve a careful description of agonist and antagonist actions on behavior during chronic administration. It is important to characterize these agonist/antagonist actions of buprenorphine in comparison with the actions of competitive antagonists and short-acting reversible agonists such as alfentanil. When these data are in hand for animals, it will be far easier to develop a rational clinical pharmacology of buprenorphine that will be appropriate to drug abuse treatment situations.

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ACKNOWLEDGEMENT

Research and preparation of the manuscript were supported by U.S. Public Health Service grant DA-00254.

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Assessment of Buprenorphine in a Drug Discrimination Procedure in Humans

George E. Bigelow and Kenzie L. Preston

INTRODUCTION

Drug discrimination testing is a behavioral procedure that is widely used to characterize and classify the pharmacological effects of psychoactive drugs. In this procedure subjects are given explicit behavioral training in identifying specific training drugs and are then tested with novel drugs or doses to determine if they are identified as being similar to the training drugs. Drug discrimination training proceeds by providing controlled experimental exposures to the training drugs and by providing contingent reinforcement (reward) for correct identification responses. When subjects successfully learn the drug discrimination, the stimulus effects of the training drugs serve as cues for which identification response will be reinforced on that trial. When a novel drug or dose is identified as being similar to a training drug, this presumably indicates a similarity in the stimulus effects produced by those two drug/dose conditions.

The drug discrimination paradigm is illustrated schematically in figure 1, which represents a three-choice drug discrimination procedure. In this illustration, each of three training drugs is associated with a different identification response; each of these three responses leads to reinforcement only in the presence of its own associated drug stimulus condition.

The drug discrimination methodology was developed in the animal laboratory, where it has received extensive application as a tool for characterizing and classifying the nature of psychopharmacological drug effects. Procedurally, the drug discrimination procedure is designed to assess the stimulus effects of drugs (i.e., the extent to which test drugs' stimulus effects are similar to those of training drugs). For drugs in the opioid class, it appears that the drug discrimination procedure also can provide information about the underlying neuropharmacological mechanisms of drug action. In particular, it appears that opioids acting as agonists at μ- vs. κ-opioid receptor sites have different

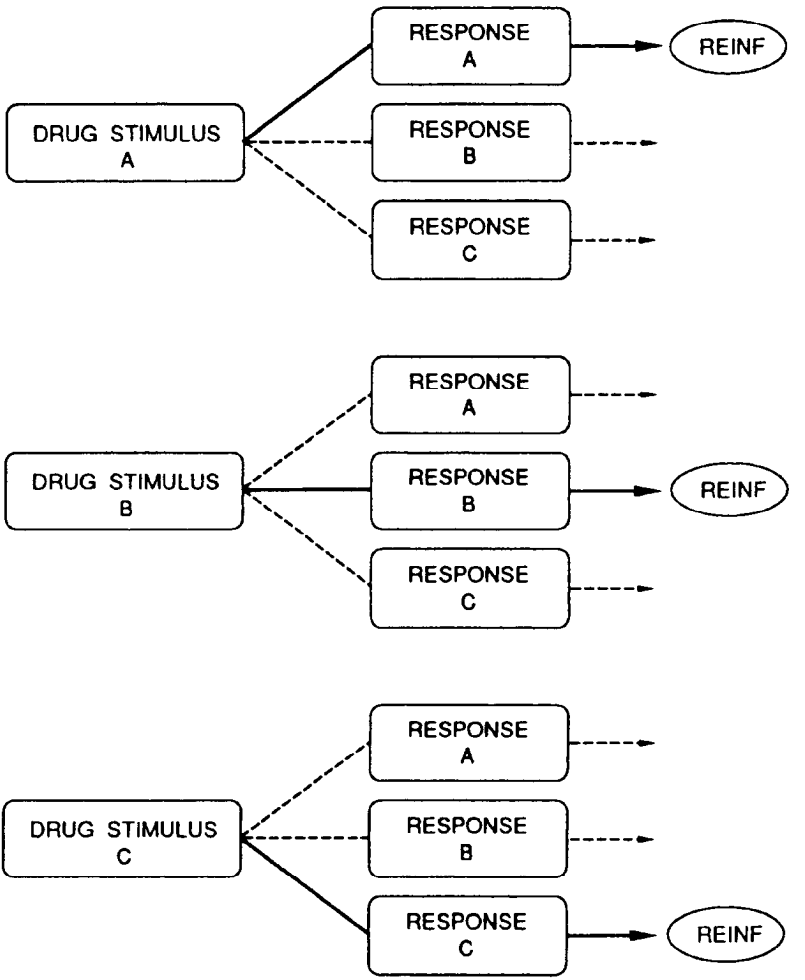

FIGURE 1. *Schematic representation of a three-choice drug discrimination procedure, showing the association of contingent reinforcement with different specific responses under each of several* different *drug stimulus conditions*

stimulus effects and that drug discrimination behavior may be used to infer probable opioid receptor activity (Holtzman 1993).

Drugs' stimulus effects may be related to their subjective effects. There is substantial face validity to the notion that drugs that produce similar subjective

effects might be behaviorally discriminated as similar also. There is less face validity to the reverse relationship (that drugs with similar stimulus effects might produce similar subjective effects), perhaps because of our uncertainty about the nature or locus of the stimulus effects upon which discriminations might be based. Nevertheless, it is commonly speculated that drug discrimination behavior may provide an index of drugs' subjective effects. Such speculation has been inherently untestable in the animal laboratory. Human subjects, however, uniquely provide the opportunity to assess both stimulus effects and subjective effects simultaneously.

This chapter provides a summary of several studies from the authors' laboratory in which buprenorphine has been tested using the drug discrimination procedure in human volunteers to assess concurrently the similarity of its stimulus effects to those of other opioids and its effects on self-reported subjective experience (Bigelow and Preston 1989).

OPIOID DRUG DISCRIMINATION IN HUMANS: GENERAL METHODS

Participants

Participants in these studies were healthy adult male volunteers with substantial histories of illicit opioid drug abuse who continued to abuse opioids intermittently but who were currently not physically dependent. Volunteers received medical examination, including urinalysis for drugs of abuse, provided a medical and drug use history, and were monitored in the residential unit for several days to ensure they were drug-free and nondependent prior to study initiation. Volunteers provided written informed consent and were paid for their research participation.

Setting

The studies were conducted in a residential laboratory, where participants resided throughout the study duration. Study durations were approximately 7 weeks. A variety of recreational activities was available within the laboratory. Urinalysis monitoring of volunteers was conducted intermittently throughout each study to ensure subjects' abstinence from drugs other than those administered as part of the study.

Experimental Sessions

Experimental sessions were conducted daily, 7 days per week. The sequence of events was: predrug data were collected; drug was administered; 20 minutes were allowed for drug absorption; and then the assessment session began.

The assessment session was of approximately 100 minutes in duration and included assessment both of drug discrimination behavior and of self-reports of subjective drug effects.

Drug Administration

Drugs were administered by intramuscular (IM) injection to the deltoid muscle of the arm by research nursing staff. All procedures were double blind and randomized. The training drugs were designated only by randomly determined arbitrary letter codes (e.g., A, B, C or J, K, L). Drug doses were adjusted for body weight and expressed on a per 70 kg basis. Hydromorphone has served as a standard morphine-like pure p-receptor agonist. The other drugs studied have been the opioid mixed agonist-antagonists currently marketed in the United States—pentazocine, butorphanol, nalbuphine, and buprenorphine.

Discrimination Procedures

Training and testing of the drug discrimination proceeded in three phases. In the first phase, designated the "training" phase, each subject received two exposures to each of the training drugs; they were told the arbitrary letter code of the drug at the time of injection and were told to attend carefully to the drug's effects and to try to learn to recognize the effects of each training drug and to discriminate among them. In the second phase, designated the "test of acquisition" phase, each subject again received two exposures to each of the training drugs, but they were not told the letter code until after the assessment session. In each of these two phases the amount of money the subject earned in the session was determined by his accuracy during the assessment session in identifying the correct letter code of the drug administered. In the third phase, designated the "test" phase, each subject received exposures to a range of doses of the drugs being tested. Since these drugs/doses were usually different from the training drug conditions, there was no "correct" response to be rewarded; the subject was informed at the end of the assessment session that this had been a test session, that the identity of the drug given in that session could not be revealed, and that his earnings for that session were determined by the accuracy of discrimination performance in prior test of acquisition sessions. To provide continued training and incentive for correct discrimination performance, test of acquisition sessions were randomly distributed throughout the test phase.

During each assessment session the subject could indicate his drug discrimination response by pressing keys labeled with each of the arbitrary drug letter codes associated with the training drugs. There were two such discrimination performance opportunities, each of 8.5minute duration. During

each of these the subject could earn points later exchangeable for money by pressing the correct key. Points could be earned at a maximum rate of one per second (i.e., a fixed-interval 1-second schedule of reinforcement).

Subjective Effect Measures

During each assessment session the subject also completed a standard battery of subjective effect self-report questions. These included adjective rating scales of items describing effects associated with opioids, visual analog scales (VAS) of global aspects of drug effects, and a short form of the Addiction Research Center Inventory (ARCI). The VAS provided ratings on a 100-point scale of the extent to which the subject experienced "Any Drug Effect," "Liking" for the drug effect, "Good Effects," "Bad Effects," "High," and "Sick." The ARCI included the Morphine-Benzedrine Group (MBG) scale, which is empirically derived as sensitive to opioid agonist effects and is commonly characterized as providing an index of drug-induced "euphoria."

EVALUATION OF BUPRENORPHINE IN A THREE-CHOICE HYDROMORPHONE-PENTAZOCINE-PLACEBO DISCRIMINATION

Four nondependent postaddict volunteers were tested with a range of doses of buprenorphine (0.11-0.9 mg/70 kg) after having been first trained on a three-choice discrimination between IM saline, 3 mg/70 kg hydromorphone, and 45 mg/70 kg pentazocine (Preston et al. 1989). Also tested was a range of doses of hydromorphone and of the opioid mixed agonist-antagonists-pentazocine, butorphanol, and nalbuphine.

Drug discrimination results for buprenorphine and the two training drugs are shown in figure 2. Saline was discriminated as being saline-like. Hydromorphone showed a dose-related increase in being discriminated as like the hydromorphone training dose. Similarly, pentazocine showed a dose-related increase in being discriminated as like the pentazocine training dose. Buprenorphine, however, was not reliably discriminated as being like either of the training drugs. Subjects' discrimination responses were divided evenly between hydromorphone-appropriate and pentazocine-appropriate.

Not shown are the data for butorphanol and nalbuphine, which indicated that butorphanol at high doses (6 mg/70 kg) generalized completely to the pentazocine training condition, whereas nalbuphine (in doses up to 24 mg/70 kg) generalized partially to pentazocine and partially to hydromorphone.

Selected subjective effect results for buprenorphine and the two training drugs are shown in figure 3. Only hydromorphone and buprenorphine produced

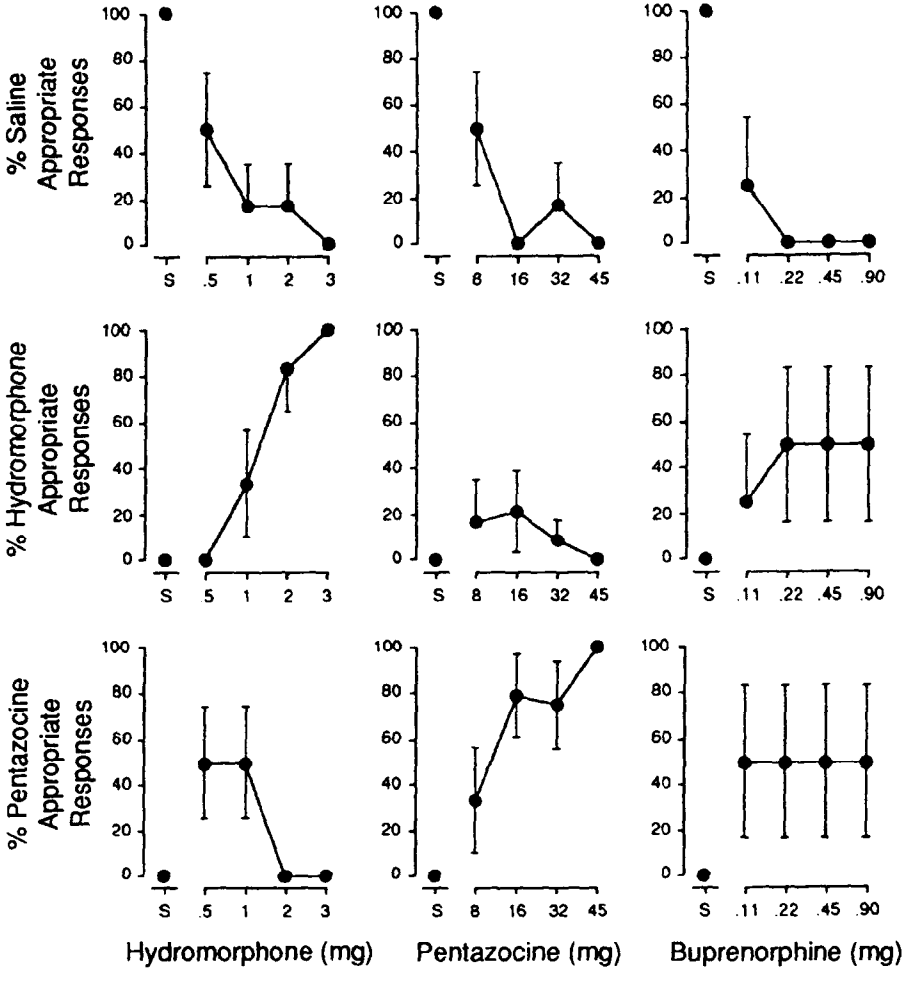

FIGURE 2. *Drug discrimination results are shown for a range of doses of hydromorphone, pentazocine, and buprenorphine for subjects trained to discriminate among saline, hydromotphone, and pentazocine. The buprenotphine data are based on four subjects, the hydromorphone and pentazocine data on six subjects.*

significant elevations on the MBG scale score of the ARCI. On the "Good Effects" VAS, both hydromorphone and buprenorphine produced similar dose-related elevations.

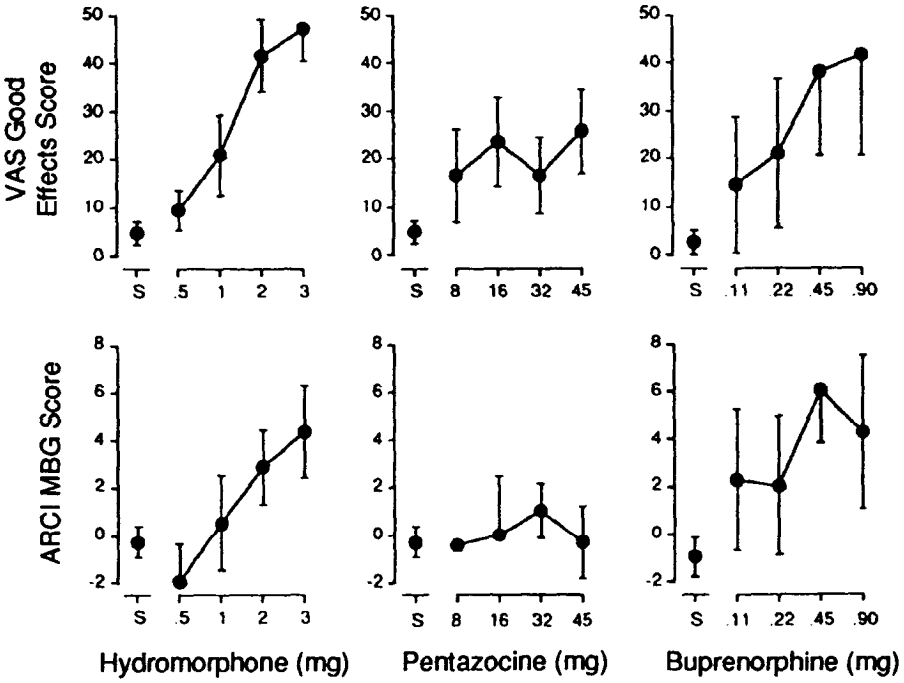

FIGURE 3. *Selected subjected effects data are shown for a range of doses of hydromotphone, pentazocine, and buprenorphine. The data were collected concurrently with the behavioral drug discrimination data shown in figure 2 and are based on the same sample sizes. Brackets are standard errors of the mean.*

Subsequent Drug Discrimination Studies

Subsequent to the study described above, the authors have evaluated buprenorphine in two other drug discrimination procedures, the reports of which have not yet been published. These are described here only rather generally, for the purpose of characterizing the additional information they provide concerning the overall profile of pharmacological activity of buprenorphine.

Hydromorphone vs. Saline Discrimination

Four nondependent postaddict volunteers were tested with a range of doses of buprenorphine after having been first trained on a two-choice discrimination between IM saline and 3 mg/70 kg hydromorphone (described briefly in Bigelow

and Preston 1969). Also tested were a range of doses of hydromorphone and of the other opioid mixed agonist-antagonists-pentazocine, butorphanol, and nalbuphine. In this two-choice procedure all the active opioids were discriminated as being more similar to hydromotphone than to saline. Subjective effect data showed buprenorphine to be the only one of the mixed agonist-antagonists to produce significant score elevations on the MBG scale of the ARCI, as did hydromorphone.

Hydromorphone-Butorphanol-Saline Discrimination

Six nondependent postaddict volunteers were tested with a range of doses of buprenorphine after first having been trained on a three-choice discrimination between IM saline, 3 mg/70 kg hydromorphone, and 6 mg/70 kg butorphanol. Also tested were a range of doses of hydromorphone, pentazocine, butorphanol, and nalbuphine. Only hydromorphone and buprenorphine were discriminated as having stimulus effects similar to the hydromorphone training dose. Nalbuphine and butorphanol were discriminated as being butotphanoi-like. Pentazocine generalized partially to both hydromorphone and butorphanol, but completely to neither. Subjective effect data again showed similarities in the effects of hydromorphone and buprenorphine in contrast to those of butorphanol.

SUMMARY AND CONCLUSIONS

These studies indicate that buprenorphine shares stimulus effects with other opioid drugs and that in overall profile of effects buprenorphine is more similar to hydromorphone than are the other opioid mixed agonist-antagonists tested-pentazocine, butorphanol, and nalbuphine. This characterization is supported by the behavioral drug discrimination results and by the subjective effect self-report results.

In the drug discrimination assessments buprenorphine showed a pattern of generalization that was different from that of the other opioid-mixed agonist-antagonists. It did not generalize completely to either pentazocine or butorphanol, but it did generalize to hydromorphone in two studies and partially in a third. Both nalbuphine and pentazocine showed at least partial generalization to butorphanol, but buprenorphine did not. Butorphanol showed little generalization to hydromorphone except in the two-choice hydromorphone vs. saline discrimination in which all the tested mixed agonist-antagonists generalized to hydromorphone.

The subjective effect self-report data also revealed a pattern of response to buprenorphine that was different from that to the other mixed agonist-

antagonists. In particular, buprenorphine's profile of acute subjective effects was similar to that of hydromorphone. There were dose-related increases on various scales reflecting positive subjective effects, with little evidence of the dysphoric effects that are characteristic of high doses of the other mixed agonist-antagonists.

These data are compatible with the view that buprenorphine is a partial agonist at the μ-receptor Although they do not demonstrate the ceiling on magnitude of pharmacological effects that would be characteristic of a partial agonist, they do demonstrate that buprenorphine's profile of activity—both stimulus effects and subjective effects-is similar to that of the pure μ-agonist hydromorphone.

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ACKNOWLEDGEMENT

The work described in this chapter was supported by National Institute on Drug Abuse grants DA-00050, DA-04089, and DA-06120.

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Human Laboratory Studies of Buprenorphine

Jack H. Mendelson and Nancy K. Mello

INTRODUCTION

During 1978, Jasinski and associates (1978) reported their initial studies of the human pharmacology and abuse potential of buprenorphine. They found that buprenorphine (8 mg/day) blocked the subjective and miotic effects of high doses of morphine (60/120 mg/day) for up to 29.5 hours. They also concluded that buprenorphine maintenance, unlike other opiate agonists, does not induce significant physical dependence in humans. These studies stimulated the authors' evaluation of the effectiveness of buprenorphine for suppressing heroin self-administration by heroin-dependent men (Mello and Mendelson 1980; Mello et al. 1982). In this chapter, data obtained in those studies are reexamined, with special emphasis on both safety and effectiveness of the drug for treatment of opioid and perhaps cocaine abuse. Findings obtained in studies of buprenorphine and cocaine effects on anterior pituitary function (Mendelson et al. 1982, 1988) also are presented. These data are relevant for use of buprenorphine as a pharmacotherapeutic adjunct for reducing risk for infectious disease, induding acquired immunodefiiiency syndrome (AIDS), by persons who abuse both opiates and cocaine. Finally, new data concerning a buprenorphine preparation that includes the opioid antagonist naloxone (Mendelson et al. 1989) are presented. These studies highlight findings that may be relevant to reducing illicit diversion of buprenorphine in clinical treatment settings as well as to increasing the safety of new programs invoking buprenorphine maintenance for intravenous (IV) heroin abuse.

BUPRENORPHINE EFFECTS ON HEROIN SELF-ADMINISTRATION BY HEROIN-DEPENDENT MEN

During 1980 and 1982, the authors described a series of studies designed to determine the effectiveness of buprenorphine for suppressing heroin self-administration by heroin-dependent men (Mello and Mendelson 1980; Mello et al. 1982).

Methods

Ten adult male volunteers with a history of heroin abuse gave informed consent for participation in studies to evaluate the effects of buprenorphine on heroin self-administration in an inpatient clinical research study. No subject was under any legal constraint. Subjects were selected from volunteers who had failed in conventional treatment programs.

Subjects were in good health, as determined by clinical and laboratory examination. Each subject was given a complete physical examination, mental status assessment, chest x-ray, electrocardiogram, and the following laboratory assessments: albumin, alkaline phosphatase, bilirubin, total blood urea nitrogen, calcium, chloride, cholesterol, creatinine, glucose, iron, lactic acid dehydrogenase. phosphorus, potassium, serum glutamic oxaloacetic transaminase, sodium, total protein, triglycerides, uric acid, routine urinalysis, hematocrit, hemoglobin, white blood count differential, and Australian antigen and serology. Urine screens for opiate and other drug use by the subjects were performed upon their admission to the research ward.

These subjects had abused heroin for an average of 10.4 years (range 1 to 19 years). The average age was 28.6 years (range 24 to 32 years). Most subjects had grown up in communities near Boston and had an average of 12.4 years of formal education (range 11 to 16 years). At the time of selection for the study, seven subjects were unemployed, and three had recently worked at semiskilled jobs.

Six subjects participated in a single study in which three subjects were assigned to buprenorphine and three to its placebo. Four subjects participated in two separate studies and received both buprenorphine and placebo in a counterbalanced order (i.e., two received buprenorphine first and two received placebo first), Consequently, final data are reported for seven subjects assigned to buprenorphine and seven subjects to placebo under double-blind conditions. Two other volunteers left the study on days 6 and 10, respectively. One subject assigned to buprenorphine was discharged for illicit drug use (diazepam), and one subject assigned to placebo left for personal reasons.

Subjects were recruited in groups of four and lived on the clinical research ward throughout the 40-day study. The research ward contained two semiprivate bedrooms, a nursing station, a kitchen and lavatories, examining and testing rooms, an operant equipment room, and a spacious day room comfortably furnished with television, high fidelity equipment, and other recreational materials. The clinical nursing staff was present 24 hours each day.

Subjects were fully informed about the duration and sequence of the experimental conditions, and each procedure was carefully explained. Buprenorphine was described as an experimental drug that may "block the heroin high" and eventually may be used like methadone for long-term maintenance treatment. Subjects were told they would receive either buprenorphine or its placebo but neither they nor the nursing staff would be told which. Subjects were asked to report any discomfort or unusual effects experienced during buprenorphine (or placebo) administration. Subjects were told that minimal side effects, such as fatigue or nausea, and some pleasurable subjective effects were reported during previous buprenorphine evaluations.

Upon discharge, subjects were offered an opportunity for outpatient maintenance on the long-acting antagonist naltrexone. Naltrexone was available for 1 year after discharge. Staff attempted to maintain contact with subjects after discharge. An aftercare program was developed for each subject at an outpatient-treatment program near his home. Subjects who left the program early also were given referrals to a drug-treatment program.

Sequence of Drug Conditions. The successive drug conditions for the buprenorphine and placebo groups are shown in table 1. The buprenorphine induction, maintenance, and withdrawal schedules were identical to those used by Jasinski and coworkers (1978). After a 5-day, drug-free baseline, subjects were given ascending doses of buprenorphine (or its placebo) for 14 days. An ascending dose schedule was used to assess the physiological and behavioral effects of various doses of buprenorphine and to ensure patient safety. An initial buprenorphine dose of 0.5 mg/day subcutaneous (SC) was gradually increased in 0.5-mg increments for 12 days and 1-mg increments for 2 days to a final dose of 8 mg/day SC. The volumes of buprenorphine and placebo injections were equivalent at each dose level.

Subjects were maintained on 8 mg/day of buprenorphine (or placebo) for 10 days, during which they could work at a simple operant task for IV heroin. Six subjects were maintained on 8 mg/day of buprenorphine for 10 days. One subject developed hypotension, a side effect typical of opioid agonists, and was maintained on 4 mg/day of buprenorphine.

Subsequently, subjects were gradually withdrawn from buprenorphine over 5 days. The dose-reduction sequence was as follows: 7, 6, 5, 3, and 1 mg/day. Subjects who were assigned to placebo buprenorphine and used heroin were detoxified with methadone in progressively decreasing doses (25 to 5 mg/day) over 5 days.

TABLE 1. *Sequence of drug conditions*

Buprenorphine Group (n=7)	Buprenorphine Placebo Group (n=7)	Condition Duration* (days)
Drug-free baseline	Drug-free baseline	5
Buprenorphine (0.5-8 mg/day SC)	Buprenorphine placebo (=volume x.c.)	14
Heroin (21 or 40.5 mg/day IV)+ buprenorphone (8 mg/day SC)	Heroin (21 or 40.5 mg/day IV)+ buprenorphine placebo	10
Buprenorphine detoxification (7-1 mg/day)	Methadone detoxification (25-5 mg/day)	5
Drug-free baseline	Drug-free baseline	3
Naltrexone (10-50 mg/day)	Naltrexone (10-50 mg/day)	3

*Total days=40

SOURCE: Adapted from Mello et al. 1982. Copyright 1982 by the American Society for Pharmacology and Experimental Therapeutics.

A 3-day, drug-free period preceded exposure to naltrexone to reduce the possibility that naltrexone might precipitate withdrawal from the opiate agonist effects of buprenorphine. Buprenorphine is highly lipophilic and has been shown to dissociate very slowly from tissue (Rance and Dickens 1978; Hambrook and Rance 1976). Although the protocol specified a gradual increase in naltrexone dosage from 10 to 50 mg/day over 3 days before discharge, only one subject elected to be discharged on naltrexone. Two other subjects left before the naltrexone condition, on days 30 and 34, respectively.

Heroin Self-Administration Procedures. Medical and ethical considerations preclude study of spontaneous patterns of unrestricted heroin self-administration as has been possible for marijuana (Mendelson et al. 1974, 1976) alcohol (Mello and Mendelson 1965, 1972) sedatives (Griffiths et al. 1976; Pickens et al. 1977), and some forms of polydrug use (Mello et al. 1978). Subjects were limited to a total of three heroin injections each day, once every 8 hours (at 9 a.m., 5 p.m., and 1 a.m.). The effects of buprenorphine on self-administration of both low and high doses of heroin were examined. A total of 21 mg/day of heroin was available for the first 5 days and 40.5 mg/day for the second 5 days. Subjects could refuse to take any heroin dose earned, but they

were not allowed to take fractional doses (e.g., 3 mg instead of 7 mg). Subjects were not told that the heroin dose would be increased on day 6.

Drugs. Heroin (98 to 99 percent pure) was obtained from the National Institute on Drug Abuse (NIDA), Rockville, MD, in 8-mg sterile vials. Heroin was diluted with saline immediately before injection. Subjects injected heroin intravenously under the supervision of a physician. During the 10 days of heroin availability, 24-hour physician coverage was provided, and the nursing staff was trained in the use of emergency medical equipment. Heroin in a total daily dose range of 40 to 60 mg has proven to be safe, and the IV self-administration procedure has not been associated with any medical complications (Meyer and Mirin 1979; Mello et al. 1981).

Buprenorphine hydrochloride was provided by Reckitt & Colman, Ltd., Hull, England, through NIDA. Buprenorphine was diluted with sterile water adjusted to pH 4 with HCl. The buprenorphine solution (4 mg/mL) was passed through a Millipore filter to remove pyrogens before SC administration. Equal volumes of sterile water adjusted to pH 4 were used as a vehicle control.

Heroin and Money-Acquisition Procedures. Operant procedures were used to evaluate the effects of buprenorphine on heroin self-administration. Operant performances for heroin and money were compared, and the effects of heroin use on operant work patterns were examined.

Subjects could work for money at a simple operant task throughout the study. This provided a measure of buprenorphine (or placebo) and heroin effects on performance. The opportunity to work for money also was intended to encourage subjects to remain in the study, inasmuch as heroin was available for only 10 of the 40 study days. This procedure previously has been proven effective in minimizing patient attrition (Mello et al. 1981).

Subjects could work for points for heroin on the last day (day 14) of the buprenorphine induction period and each day of heroin availability. Heroin points could be accumulated and spent throughout the 10-day heroin availability period. Operant points earned for money and for heroin were not interchangeable. Subjects chose whether to work for money or for heroin each time they turned on their operant instruments by pressing the appropriate button on a panel in the day room (Mello et al. 1981). Subjects could work at the operant task at any time for as long as they wished. A 5-minute pause in responding required reactivation of the operant instrument.

To earn points for money or heroin, subjects were required to press the button on a portable operant manipulandum on a second-order fixed ratio (FR) 300,

fixed interval (FI) 1-second schedule of reinforcement (FR 300 [FI 1 second: S]). Only the first response after 1 second had elapsed was recorded as an effective response by the programing circuitry. Responses emitted at a rate faster than once per second had no programed consequence. Each effective response was followed by a brief stimulus light flash on the operant panel. Three hundred effective responses on the FI 1-second schedule of reinforcement earned one purchase point in about 5 minutes. Each heroin injection cost 18 purchase points. Approximately 90 minutes of sustained performance were required to earn enough purchase points to buy one heroin injection (7 to 13.5 mg) or to acquire $1.50 in cash paid upon completion of the study. Subjects had to work about 4.5 hours each day to earn the 54 purchase points necessary to buy all three heroin injections available daily.

A record of points earned for heroin and for money was available continuously on counters located on the operant panel on the day room wall. Whenever a subject accumulated 18 purchase points, he could press a drug request button to inform staff that he wished to take the next available heroin dose. The requisite number of purchase points then was subtracted from his total points. Additional details of the operant manipulandum and apparatus have been described previously (Mello et al. 1981).

Points earned for heroin that were not spent during the period of heroin availability could not be exchanged for money. To avoid penalizing subjects who were assigned to buprenorphine maintenance and elected not to use heroin, however, points earned for heroin on the last day of the baseline period could be exchanged for money at the end of the study.

In addition to money earned by working at the operant task, subjects also could earn money for cooperation with various procedures. For example, subjects could earn about $144 by cooperating with routine medical assessments and completing the various self-report forms. An additional $80 was paid for participation in blood collection procedures. Consequently, subjects could earn about $224 for cooperation. If a subject damaged the operant equipment or other laboratory equipment, he was fined accordingly. This simple schedule of compensation has been effective in maintaining cooperation and retaining subjects in the study (Mello et al. 1981).

Data Recording and Analysis. The pattern, rate, and duration of operant responding for heroin and money were automatically recorded by the programing circuitry. Cumulative recorders provided an analog record of operant response patterns. The number of purchase points earned and the number of heroin purchases also were automatically recorded. Time (minutes) spent working at the operant task for money or for heroin was recorded on

running time meters. Individual patterns of operant performance and heroin use are presented graphically. Group data and within-subject comparisons of operant performance across drug conditions were evaluated with *t* tests.

Medical Status and Related Measures. A physician examined each subject daily to assess possible drug side effects. Clinical interviews and mental-status exams were combined with physical and neurological examinations. Vital signs were taken three times each day, and clinical laboratory assessments were completed once each week.

A series of multidisciplinary studies of the behavioral and biological effects of buprenorphine and heroin was conducted concurrently with the behavioral studies described in this report. The effects of buprenorphine on prolactin and luteinizing hormone levels also were studied (Mendelson et al. 1982). Samples for measurement of buprenorphine levels in plasma were collected periodically for analysis at the NIDA Intramural Research Program. A Profile of Mood States was completed daily and before and after each heroin injection. The duration and latency of the heroin 'rush" were assessed after each heroin injection. The effects of buprenorphine and heroin on cigarette smoking also were studied (Mello et al. 1985).

Results

Subjective and Physiological Effects of Buprenorphine. The mixed agonist-antagonist buprenorphine produced somatic and sedative effects similar to those previously reported for opiate agonists (Mansky 1978). Constipation was the most frequent and persistent opioid-like effect of buprenorphine. Half the subjects developed tolerance to this side effect by the 21st day of buprenorphine exposure. Only three subjects reported feeling drowsy during buprenorphine induction, and tolerance developed rapidly to this sedative effect. Decreased libido was reported by most subjects at high doses of buprenorphine (7 to 8 mg/day). Although decreased libido was reported at low doses of buprenorphine during induction, similar changes in libido were not reported during detoxification, when buprenorphine doses were reduced to 3.0 mg/day. Other somatic effects (e.g., itching, headache, dizziness, tinnitus, dry mouth, and urinary hesitancy) were reported only occasionally during the early phase of buprenorphine induction. Reports of changes in appetite and sleep patterns were infrequent and transient. Other transient side effects included development of a mild erythematous blotchy rash on the arms and trunk within 2 hours of buprenorphine injection (0.5 mg/kg) in one subject. The rash did not persist or recur. At buprenorphine doses of 6.5 to 8.0 mg/day, one subject developed muscle twitching at the injection site, which disappeared after 4 days at 8.0 mg/day.

Five of the seven subjects tolerated buprenorphine well and had no persistent debilitating side effects. Two subjects developed sufficiently severe idiosyncratic reactions to buprenorphine to require modification of the protocol. One subject developed hypotension after 2.0 mg/day of buprenotphine. Blood pressure fell to 100 systolic/60 diastolic and remained low as buprenorphine doses were increased to 4.0 mg/day. The hypotension was associated with feelings of panic, and the subject reported being "scared, terrified, paranoid, and lonely." Similar panic reactions were not reported by other subjects. Buprenorphine doses for this subject were not increased above 4.0 mg/day because his blood pressure remained in the range of 90 to 100 systolic and 50 to 70 diastolic throughout the study.

A second subject developed severe nausea and vomiting after 0.5 mg/kg of buprenorphine. This subject reported frequent severe nausea and vomiting after using opiates. The severity of his reaction, however, dictated a slower progression of buprenorphine dose increases over the first 7 days of buprenorphine induction. This subject developed tolerance to the buprenorphine-induced nausea and vomiting within 8 days and was able to tolerate high doses of buprenorphine comfortably without recurrence of the nausea. No other clinically significant side effects were reported.

All subjects reported that buprenorphine had opiate-like effects on mood, characterized by a generalized feeling of contentment. No sensation of a "rush" or "high" was reported after SC buprenorphine injection. Although this study was conducted under double-blind conditions, it is likely that the buprenorphine group correctly surmised that they were receiving an active drug. On the first day that subjects could work for points for heroin (day 14 of the induction period), the buprenorphine group earned significantly fewer heroin points than did the placebo group ($p < .01$). Several placebo subjects said they thought they were receiving buprenorphine, but this expectancy did not appear to influence heroin self-administration. The placebo-maintained subjects did not report side effects during the induction or maintenance phase.

BUPRENORPHINE EFFECTS ON HEROIN SELF-ADMINISTRATION AND OPERANT PERFORMANCE

Effects of buprenorphine and placebo maintenance on heroin self-administration are shown in figure 1. Three subjects, maintained on placebo only, administered 100 percent of all available heroin each day. In contrast, three subjects who received only buprenorphine self-administered only 2 to 4 percent of all heroin available. Three other subjects who were maintained on placebo and buprenorphine in a crossover study self-administered 93 to 100 percent of all heroin available during the placebo condition; however, on

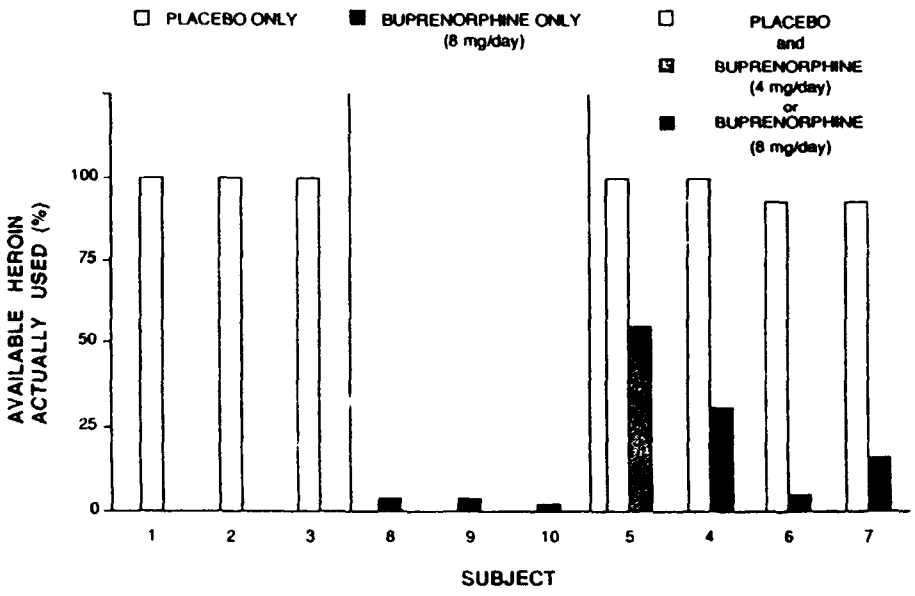

FIGURE 1. *Available heroin self-administration during buprenorphine and placebo conditions*

SOURCE: Mello, N.K., and Mendelson, J.H. Buprenorphine suppresses heroin use by heroin addicts. *Science* 207:657-659,1960. Copyright 1980 by American Association for the Advancement of Science.

buprenorphine maintenance, heroin self-administration was significantly suppressed to 69 to 96 percent of levels administered during placebo maintenance. One subject (number 5) maintained on 4 mg of buprenorphine per day, reduced heroin self-administration to 55 percent of the dosage administered during the placebo condition.

Buprenorphine maintenance did not have significant effects on operant performance. Comparisons of the total number of operant points earned by the placebo maintenance group and the buprenorphine maintenance group during each condition (baseline, induction, maintenance, and detoxification) showed no statistically significant differences.

OPIATE AND COCAINE EFFECTS ON PROLACTIN SECRETION: POSSIBLE COMORBIDITY FOR INFECTIOUS DISEASE, INCLUDING AIDS

The effects of opiate agonists on prolactin secretion appear to be similar in all species. As has been demonstrated by many investigators, plasma prolactin levels are increased by opiates in rats (Clemens and Sawyer 1974; Dobrin and Mares 1974; Ojeda et al. 1974; Zimmerman et al. 1974; Bruni et al. 1977; Cocchi et al. 1977) and in humans (Tolis et al. 1975, 1978; Ellingboe et al. 1980).

Cocaine abuse also affects prolactin secretion. Gawin and Kleber (1985) found decreased prolactin levels in men and women who were studied in outpatient clinic settings for the treatment of cocaine abuse. Dackis and Gold (1985) found that plasma prolactin levels increased in men treated in inpatient facilities for cocaine abuse and that these increased levels were significantly higher than those in age-matched normal men. Cocores and colleagues (1986) reported occurrence of hyperprolactinemia as well as self-reports of sexual dysfunction in 7 of 10 cocaine abusers.

The authors recently have determined plasma luteinizing hormone, prolactin, testosterone, and cortisol levels in 16 patients after hospital admission for cocaine abuse during the course of 4 weeks of hospitalization and before discharge (Mendelson et al. 1988). Significant hyperprolactinemia was detected when the patients were admitted to the hospital, and elevated prolactin levels persisted until the time of discharge. The authors have concluded that persistent elevation of plasma prolactin levels following cocaine withdrawal may reflect a chronic cocaine-induced derangement in neural dopaminergic regulatory systems.

The authors have studied the effects of buprenorphine on plasma prolactin levels during maintenance and withdrawal (Mendelson et al. 1982). The sequence of drug conditions for these studies is shown in table 1. Although a significant increase in plasma prolactin levels during buprenorphine induction was observed, plasma prolactin values were not in the hyperprolactinemic range. The increments in prolactin levels during buprenorphine induction and maintenance were relatively small (when contrasted with the drug-free period) and were within the normal range of adult male values.

Figure 2 shows plasma prolactin levels in patients who were cocaine abusers. Hyperprolactinemia observed on admission persisted until the patient's discharge from the hospital. In contrast, plasma prolactin levels obtained from patients during induction and maintenance on buprenorphine were within the range for normal adult males.

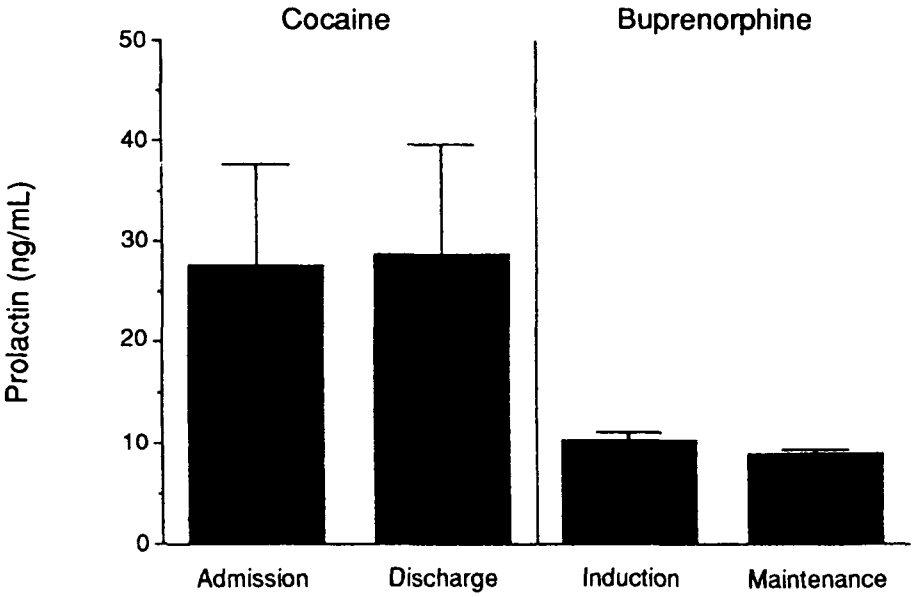

FIGURE 2. *Plasma prolactin levels for cocaine abusers on admission and discharge from hospital treatment and in heroin-dependent subjects during buprenorphine induction and maintenance*

There is increasing evidence that prolactin may be an important neuroendocrine modulator of immune function. A recent report in Science noted that "several lines of evidence indicate that prolactin may be an important immunoregulatory hormone" as a function of "the critical influence of pituitary prolactin release on maintenance of lymphocyte function and on lymphokind-dependent macrophage activation" (Bernton et al. 1999). The authors of this chapter postulate that cocaine-induced hyperprolactinemia may be an important factor in the comorbidity of cocaine abuse for AIDS risk. Therefore, if buprenorphine pharmacotherapy will be effective in suppressing cocaine self-administration by cocaine abusers, as suggested by the findings of Mello and Mendelson (this volume), buprenorphine maintenance may help reduce risk for infectious disease, including AIDS.

A NALOXONE-BUPRENORPHINE PREPARATION FOR ENHANCING SAFETY OF BUPRENORPHINE MAINTENANCE THERAPY

Although the abuse potential of buprenorphine appears to be low, and lethal overdose of the drug is precluded by the antagonist component of the drug

(Lewis et al. 1983; Banks 1979) there is a potential for illicit buprenorphine use. One pharmacologic strategy for reducing abuse liability of opioid agonist drugs prepared for oral administration is the addition of a short-acting opioid antagonist such as naloxone to the pharmaceutical preparation. For example, 0.5 mg of naloxone hydrochloride has been added to capsules containing 50 mg of pentazocine hydrochloride (Talwin Nx) (Legros et al. 1984). Naloxone has no pharmacologic activity in dosages of 0.5 mg when administered orally because of its low oral bioavailability (1 percent) (Gordon et al. 1974). If pentazocine is administered parenterally, however, naloxone inhibits the effects of pentazocine, and this has resulted in a decrease in reports of pentazocine abuse (Poklis 1984).

The efficacy of naloxone for reducing parenteral abuse of buprenorphine is difficult to predict, because buprenorphine alone is equivalent to naltrexone, a potent opiate antagonist, in blocking subjective and miotic effects of high doses of morphine (Jasinski et al. 1978; Martin et al. 1973). Mendelson and colleagues (1989) recently have reported findings from a study to determine if the opioid agonist effects of buprenorphine on prolactin stimulation could be inhibited by concomitant parenteral administration of naloxone. Since plasma prolactin levels increase following administration of most morphine-like opioid agonist drugs, the effect of naloxone on the prolactin response may be of help in predicting efficacy of opioid antagonists for inhibiting the potential abuse of buprenorphine.

Methods

Six healthy adult males between the ages of 18 and 39 (mean age 26.71±7.5 years) provided informed consent for participation in this study. All subjects had normal physical examinations, including an electrocardiogram; they also had normal blood chemistry and blood hemogram studies. Subjects did not have any past or current history of alcohol or drug abuse. No subject was receiving any medication, and none had consumed alcohol for at least 48 hours prior to each study.

Each subject was studied on six occasions ranging from 7 to 27 days (x=10, SD=±8) apart. On each study day an IV catheter was inserted into the subjects arm vein. At zero time the subject received a simultaneous intramuscular (IM) injection within 30 seconds of either buprenorphine (0.3 mg) and saline or buprenorphine (0.3 mg) and naloxone (0.15-0.6 mg). Each subject also received two simultaneous injections of saline.

Blood samples for determination of plasma prolactin, plasma naloxone, and plasma buprenorphine levels were obtained immediately before and at 10, 30,

and 55 minutes following simultaneous injections. Plasma prolactin levels were measured in duplicate, using a double antibody radioimmunoassay similar to that described for human gonadotropins (Midgley 1966). Radioiodinated prolactin was purchased from Cambridge Medical Diagnostics, Billerica, MA. Antiprolactin serum (NIAMDD-anti-hPRL-2, also known as AFP-C11580) and human prolactin reference preparation (NIAMDD-hPRL-RP-1, also designated AFP-231C), prepared by Dr. A.F. Parlow, were obtained from the National Hormone and Pituitary Program at the National Institutes of Health. Results are expressed as nanograms of hPRL-RP-1 standard per milliliter of plasma. Intra-assay and interassay coefficients of variance (CV) were 4.6 percent and 10.2 percent, respectively. Assay sensitivity was 2.3 ng/mL.

Plasma naloxone levels were measured by radioimmunoassay using a specific antisera provided by Dr. C.E. Inturrisi following a procedure described by Hahn and colleagues (1983). Tritiated naloxone at a specific activity of 50 Ci/mmol was purchased from Amersham International Plc., United Kingdom. The mean interassay CV over a sample concentration range of 0.1 to 5.0 ng/mL was 6.5 percent. Assay sensitivity was 0.1 ng/mL.

Plasma buprenorphine levels were measured by a previously described radioimmunoassay procedure (Bartlett et al. 1980). Tritiated buprenorphine was provided at a specific activity of 2.6 Ci/mmol by Reckitt & Colman. The mean interassay CV over a sample concentration range of 0.1 to 1.0 ng/mL was 4.6 percent. Assay sensitivity was 0.1 ng/mL.

Data analysis for determining significant differences was carried out with a two-way analysis of variance for repeated measures.

Results

The mean baseline prolactin levels for the six subjects prior to injection of saline, buprenorphine, or naloxone were within the range of normal values for adult males (x=13.2 ng/mL, SE=0.7). Figure 3 shows plasma prolactin levels following concurrent administration of two doses of saline or concurrent administration of saline and 0.3 mg buprenorphine intramuscularly (top panel). Following saline injections, there was a small decrease in plasma prolactin levels at 30 and 55 minutes. Following buprenorphine administration (0.3 mg) and saline, there was a progressive increase in plasma prolactin levels. The mean increase in plasma prolactin levels at 30 and 55 minutes was approximately 10 and 25 ng/mL, respectively. The buprenorphine-induced stimulation of plasma prolactin levels at these times was statistically significant when compared with baseline values (time 30-Dunnett t=3.103, df=15, p <.01; time 55-Dunnett t=6.916, df=15, p<.01).

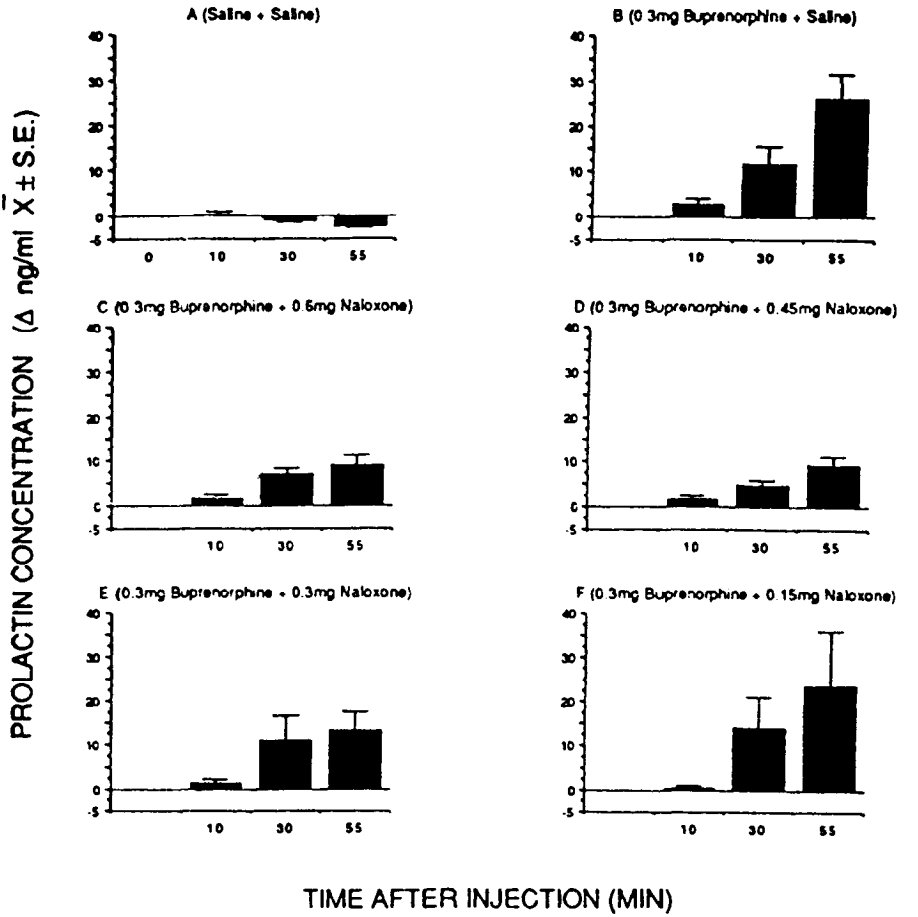

FIGURE 3. *Plasma prolactin concentration (Δ ng/mL X±SE) following simultaneous administration of 0.3 mg buprenorphine plus saline (B) or 0.3 mg buprenorphine plus 0.6 (C), 0.45 (D), 0.3 (E), and 0.15 (F) mg naloxone*

NOTE: B vs. C, at time 55 ($p < .05$). B vs. D, at time 55 ($p < .05$). B vs. E, nonsignificant. B vs. F, nonsignificant.

SOURCE: Mendelson, J.H.; Mello, N.K.; Teoh, S.K.; Lloyd-Jones, J.G.; and Clifford, J.M. Naloxone suppresses buprenorphine stimulation of plasma prolactin. *J Clin Psychopharmacol* 9(2):105-109, 1989.

Figure 3 shows that peak prolactin levels that were observed after 0.3 mg of buprenorphine plus 0.6 mg naloxone (55 minutes) were significantly less than those found 55 minutes after administration of 0.3 mg buprenorphine and saline (Dunnett t=2.032, df=35, p <.05). Plasma prolactin values after administration of 0.3 mg buprenorphine plus 0.45 mg naloxone were not significantly different from prolactin values following administration of 0.3 mg buprenorphine and 0.6 mg naloxone (figure 3). Simultaneous injection of 0.3 mg buprenorphine and 0.45 mg naloxone also resulted in a significant attenuation of buprenorphine-stimulated prolactin levels at 55 minutes (Dunnett t=2.02, df=35, p <.05). When 0.3 mg buprenorphine was administered with 0.3 mg naloxone, plasma prolactin levels were increased slightly, but not significantly, over values observed when 0.3 mg buprenorphine was administered with 0.45 mg naloxone. When 0.3 mg buprenorphine was administered with 0.3 mg or 0.115 mg naloxone, the increase in plasma prolactin levels was not significantly different from prolactin levels following administration of 0.3 rng buprenorphine plus saline. Taken together, data in figure 3 demonstrate a dose/effect relationship between naloxone dose and suppression of the increase in plasma prolactin levels produced by administration of 0.3 mg buprenorphine.

Figure 4 shows plasma naloxone concentrations following IM injection of 0.3 mg buprenorphine and concurrent IM naloxone administration in doses of 0.6, 0.45, 0.3, and 0.15 mg. A linear relationship was found between the dose of naloxone administered and the concentration of naloxone in plasma.

Figure 5 shows plasma buprenorphine levels following IM administration of buprenorphine (0.3 mg) plus saline and buprenorphine (0.3 mg) plus 0.6, 0.45, 0.3, and 0.15 mg naloxone. Plasma buprenorphine levels were not affected significantly by concomitant IM administration of naloxone.

DISCUSSION

Increased plasma prolactin levels found in this study are consistent with previous reports of increased plasma concentrations of prolactin following buprenorphine administration to humans (Mendelson et al. 1982; McQuay et al. 1980; Bullingham et al. 1993; Rolandi et al. 1993). The magnitude of prolactin stimulation following buprenorphine administration (0.3 mg) observed in this study indicates that buprenorphine is approximately two and one-half times more potent than an equianalgesic (10 mg) dose of morphine administered parenterally (Zis et al. 1964). The finding that naloxone significantly inhibited the prolactin-stimulating effects of buprenorphine in a dose-dependent manner is consistent with previous reports that concomitant administration of an opiate antagonist and buprenorphine results in a significant reduction or total blockade

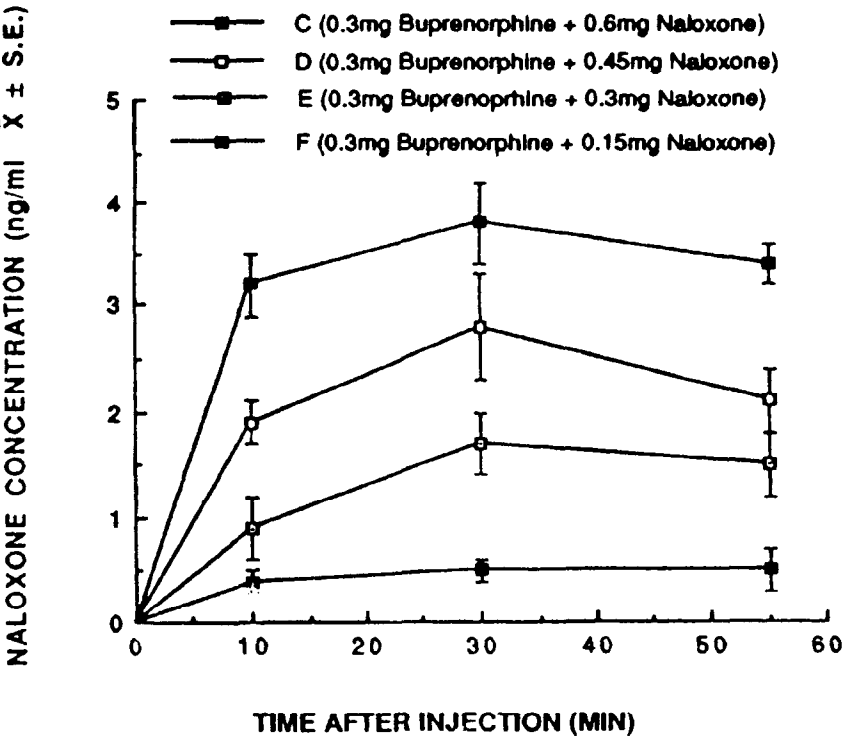

FIGURE 4. *Plasma naloxone concentration (ng/mL X±SE) following simultaneous administration of 0.3 mg buprenorphine plus 0.6 (C), 0.45 (D), 0.3 (E), and 0.15 (F) mg naloxone*

NOTE: C vs. D, at all times ($p < .01$). C vs. E, at all times ($p < .01$). C vs. F, at all times ($p < .01$).

SOURCE: Mendelson, J.H.; Mello, N.K.; Teoh, S.K.; Lloyd-Jones, J.G.; and Clifford, J.M. Naloxone suppresses buprenorphine stimulation of plasma prolactin. *J Clin Psychopharmacol* 9(2):105-109, 1989.

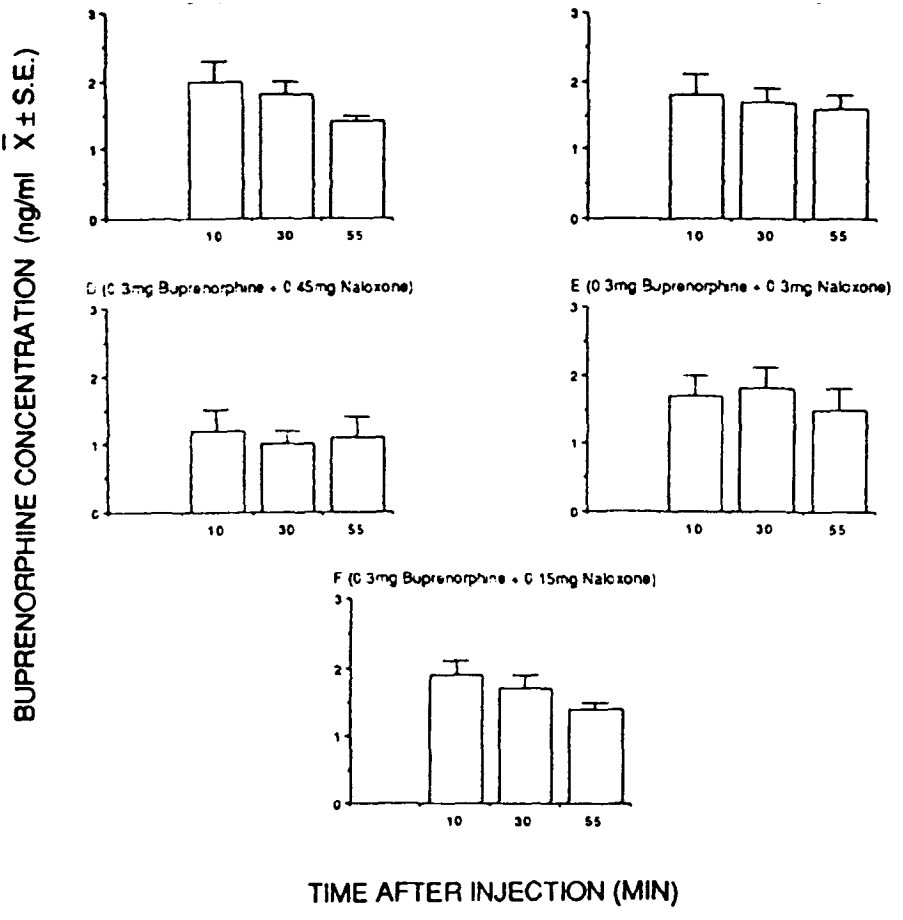

FIGURE 5. *Plasma buprenorphine concentration (ng/mL X±S.E.) following simultaneous administration of 0.3 mg buprenorphine* plus *saline (B) or 0.3 mg buprenorphine plus 0.6 (C), 0.45 (D), 0.3 (E), and 0.15 (F) mg naloxone*

NOTE: No significant difference between treatments

SOURCE: Mendelson, J.H.; Mello, N.K.; Teoh, S.K.; Lloyd-Jones, J.G.; and Clifford, J.M. Naloxone suppresses buprenorphine stimulation of plasma prolactin. *J Clin Psychopharmacol* 9(2):105-109,1989.

of buprenorphine-induced opiate-agonist activity (Lewis et al. 1963; Cowan et al. 1977a, 1977b; Heel et al. 1979; Kubicki and Azcona 1979; Budd 1963).

The efficacy of naloxone for blocking buprenorphine stimulation of prolactin probably is related to the rate of buprenorphine and naloxone binding in the central nervous system. Naloxone rapidly binds with the F-opiate receptor, but buprenorphine has been shown to bind slowly with p-receptors (Budd 1963; Norwich Eaton Pharmaceuticals, Inc., 1985; Boas and Villiger 1965).

Data obtained in this study indicate that concomitant parenteral administration of naloxone and buprenorphine inhibits the prolactin stimulation observed when buprenorphine is administered alone. Since prolactin stimulation occurs rapidly following opioid-agonist administration and is concordant with the rapid induction of the pharmacologic reinforcing properties associated with opioid abuse, the authors postulate that naloxone added to buprenorphine parenteral preparations would reduce the abuse potential of buprenorphine. This would be particularly important for diminishing the abuse liability of buprenorphine by persons whose drug-seeking and drug-use behavior is highly motivated by the prompt, predictable onset of "the rush" following IV drug self-administration (Mello and Mendelson 1980).

Bigelow and associates (1987) have reported that in "subjects maintained on a low dose of methadone (30 mg), clinically useful doses of buprenorphine plus naloxone 0.2 mg produced significant abstinence syndromes which were similar to those produced by naloxone 0.2 mg alone and which were perceived by subjects as being quite unpleasant." Based on these studies, Bigelow and coworkers (1987) concluded that "combinations of buprenorphine and naloxone have a low potential for abuse in an opioid-dependent population." There are also recent reports that administration of an IM combination of buprenorphine (0.3 mg) and naloxone (0.2 mg) was as safe and effective in relieving moderate to severe pain in patients following surgery as 0.3 mg buprenorphine alone (Vanacker et al. 1986; Rolly et al. 1986). These observations (Bigelow et al. 1987; Vanacker et al. 1986; Rolly et al. 1986) are consistent with data showing that buprenorphine binds slowly to the p-receptor (Budd 1963; Norwich Eaton Pharmaceuticals, Inc., 1985; Boas and Villiger 1985). Naloxone binds rapidly to the p-receptor but has a relatively short duration of action. Thus, the abuse potential of buprenorphine may be diminished by the addition of naloxone to buprenorphine preparations.

CONCLUSIONS

The authors conclude that buprenorphine may be an effective and safe pharmacotherapy for heroin abuse and concurrent heroin and cocaine abuse for the following reasons:

1. Buprenorphine effectively suppresses heroin self-administration.

2. Buprenorphine is reinforcing but does not produce “rush”-like effects.

3. Buprenorphine does not induce significant physical dependence.

4. The possibility of buprenorphine lethal overdose is remote.

5. Buprenorphine does not induce disorders of hormone function that would increase risk for infectious disease.

6. Buprenorphine may be administered sublingually.

7. Buprenorphine may be combined with naloxone to reduce illicit diversion for IV use.

8. Buprenorphine may suppress both opiate and cocaine self-administration.

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ACKNOWLEDGMENTS

This research was supported in part by NIDA grants DA-04059, DA-00064, DA-00101, and DA-02519.

Portions of this report were originally published in "Science," "American Journal of Psychiatry," "Journal of Pharmacology and Experimental Therapeutics," and "Journal of Clinical Psychopharmacology" and are reprinted with permission of the editors.

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Primate Studies of the Behavioral Pharmacology of Buprenorphine

Nancy K. Mello and Jack H. Mendelson

INTRODUCTION

Buprenorphine, an opioid mixed agonist-antagonist, is a powerful analgesic with minimal capacity to induce physical dependence (Houde 1979; Jaffe and Martin 1985; Martin 1979). Clinical studies suggest that buprenorphine is potentially useful for the treatment of opioid dependence (Mello and Mendelson 1980; Mello et al. 1982; Jasinski et al. 1982, 1983). Buprenorphine, an oripavine derivative of thebaine, is a congener of etorphine, a potent opioid agonist, and diprenorphine, an opioid antagonist (Lewis 1974). The basic pharmacology of buprenorphine has been described elsewhere (Lewis et al. 1983; Cowan et al. 1977a, 1977b; Jacob et al. 1979; Martin et al. 1976). This chapter summarizes some studies of the behavioral pharmacology of buprenorphine in the primate model and discusses recent studies that suggest that buprenorphine may be useful as a pharmacotherapy for the treatment of cocaine abuse as well as opioid dependence.

Both opiate agonists and opiate antagonists have been used to treat opiate addiction, and each approach is based on a different rationale (Jaffe 1985). Opioid *agonists* such as methadone and its long-acting derivative levo-alpha-acetylmethadol (LAAM) produce subjective effects that are similar to heroin's and induce cross-tolerance to opioids, attenuating the euphorigenic response to other opioid drugs (Blaine et al. 1978, 1981; Dole and Nyswander 1965; Jaffe 1985). Opioid *antagonists* such as naltrexone antagonize the subjective and physiological effects of opioids for 24 hours or more (Martin et al. 1973a; Verebey et al. 1976; Julius and Renault 1976). Clinical research has shown that naltrexone effectively suppresses heroin self-administration by heroin addicts (Meyer and Mirin 1979; Mello et al. 1981). Unlike methadone, naltrexone can be discontinued abruptly without discomfort if a patient wishes to resume drug use. Naltrexone, however, has no opioid-like agonist effects, and this probably contributes to the poor patient acceptance of narcotic antagonist treatment (Meyer and Mirin 1979; Mello et al. 1981). Outpatient evaluations of naltrexone treatment have shown that most patients tend to

discontinue naltrexone within days or weeks (Meyer and Mirin 1979; O'Brien et al. 1975; Resnick and Washton 1978; Schecter 1980; Crabtree 1984).

Buprenorphine combines the characteristics of both opioid agonist and antagonist pharmacotherapies for heroin addiction and offers some advantages over either opioid agonists or antagonists used alone (Mello and Mendelson 1985). For example, unlike methadone, buprenorphine does not produce severe and protracted withdrawal signs and symptoms in humans (Jasinski et al. 1978; Mello et al. 1982; Lukas et al. 1984; Fudala et al. 1989). Buprenorphine is also safer than opioid agonists, since its antagonist component appears to prevent lethal overdose even at approximately 10 times the analgesic therapeutic dose (Banks 1979). This characteristic reduces the possibility of opiate overdose deaths so often associated with illicit methadone use (Kreek 1978).

The first inpatient clinical studies of subcutaneous (SC) buprenorphine administration by Jasinski and coworkers (1978) showed that it was equivalent to naltrexone in the duration of opiate *antagonist* action (Martin et al. 1973a). Suprenorphine (8 mg/day SC) blocked the subjective and miotic effects of high doses of morphine (60 to 120 mg/day) for up to 29.5 hours. More recently, sublingual buprenorphine maintenance (2, 4, 8, and 16 mg) administration has been shown to produce a dose-related blockade of a hydromorphone challenge (Bickel et al. 1988a). Moreover, the buprenorphine blockade of hydromorphone's subjective effects persisted for 24 hours (Bickel et al. 1988a). Buprenorphine also is effective for opiate detoxification (Jasinski et al. 1982, 1983; Bickel et al. 1988b; Kosten and Kleber 1988), and the availability of a sublingual preparation of buprenorphine further enhances its potential clinical utility.

Although the pharmacological profile of buprenorphine would predict that it should be effective in the treatment of opioid dependence, it was important to determine whether buprenorphine in fact attenuated heroin self-administration by heroin addicts. The first inpatient evaluation of buprenorphine effects on heroin self-administration was conducted in the Clinical Behavior Laboratory of the Harvard-McLean Alcohol and Drug Abuse Research Center (Mello and Mendelson 1980; Mello et al. 1982). Operant techniques were used to provide an objective and quantifiable measure of drug-seeking behavior. The operant paradigm used was similar to that previously employed in a clinical evaluation of naltrexone (Mello et al. 1981).

Buprenorphine maintenance reduced heroin self-administration by experienced heroin abusers by 69 to 98 percent. Seven subjects maintained on buprenorphine treatment (8 mg/day) took significantly less heroin than did

seven subjects maintained on buprenorphine placebo ($p < .001$). A lower dose of buprenorphine (4 mg/day) also significantly reduced heroin self-administration in comparison to placebo maintenance ($p < .02$) and suppressed overall heroin use by 45 percent. In contrast, placebo buprenorphine subjects took between 98 and 100 percent of all the heroin available over the 10-day period of heroin availability. Only two subjects used less than the daily maximum amount of heroin available and on only two occasions. Buprenorphine was accepted by the subjects, and tolerance to its opiate-agonist side effects developed gradually. Buprenorphine did not suppress these subjects' ability to perform an operant task for money. These data suggest that buprenotphine should be an effective pharmacotherapy for the treatment of heroin addiction (Mello and Mendelson 1980; Mello et al. 1982). A more complete description of these clinical studies appears in Mendelson and Mello (this volume).

BUPRENORPHINE'S EFFECTS ON OPIATE SELF-ADMINISTRATION: PRIMATE STUDIES

One question of important clinical relevance is the comparative effectiveness of buprenorphine and methadone for the treatment of opiate dependence. The authors used a primate drug self-administration model to compare the effectiveness of buprenorphine and methadone in suppressing the intravenous (IV) self-administration of two commonly abused opiates, heroin and hydromorphone (Mello et al. 1988).

Six male macaque monkeys were surgically implanted with chronic indwelling double-lumen catheters to permit IV drug self-administration. All surgical procedures were performed under aseptic conditions. One catheter lumen was used for opiate drug self-administration, and the second lumen was used for administration of the maintenance treatment drugs, buprenorphine or methadone. Monkeys were maintained in accordance with Department of Health and Human Services "Guidelines for the Care and Use of Laboratory Animals," and their health status was periodically monitored by a veterinarian.

After a treatment-free baseline of 60 sessions of stable opiate self-administration, the effects of IV saline control treatment on food and opiate self-administration were studied for 20 sessions. Subsequently, monkeys were assigned to treatment with either buprenorphine or methadone. Animals in each treatment group were equated for drug history insofar as possible. Two monkeys were studied under both buprenorphine and methadone maintenance conditions in a single crossover design. However, the toxic effects of high doses of methadone in the methadone-first group precluded use of a single crossover design in all subjects (Mello et al. 1988).

The effects of methadone and buprenorphine treatment on opiate and food self-administration were studied over an ascending and a descending dose series. Doses of each drug were extrapolated from the clinically effective dose range. However, it was necessary to exceed the clinical dose range of both buprenorphine and methadone to affect significantly opiate self-administration by primates. Buprenorphine was studied over a dose range of 0.014 to 0.789 mg/kg/day (equivalent to 1 to 56 mg/day in humans), and each dose was studied for 20 consecutive sessions. Methadone was studied over a dose range of 0.179 to 11.86 mg/kg/day (equivalent to 12.5 to 800 mg/day in humans). Each methadone dose also was studied for 20 sessions each unless adverse reactions required terminating a high toxic dose of methadone after 1 or 2 days. The severity of adverse reactions to methadone limited the maximum dose studied in individual monkeys.

Food (1 g banana pellet) and IV drug self-administration, heroin (0.01 and 0.02 mg/kg/injection) or hydromorphone (0.02 mg/kg/injection), were maintained on a fixed ratio (FR) second-order schedule of reinforcement (FR 4 [VR 16:S]). An average of 64 responses was required for delivery of each food pellet or drug injection. Food sessions began at 11 a.m., 3 p.m., 7 p.m., and 11 p.m. each day, and drug sessions began 1 hour later at 12 noon, 4 p.m., 8 p.m., and 12 p.m. Each drug or food session lasted for 1 hour or until 20 drug injections or 65 food pellets were delivered. Operant drug and food sessions were run every day, 7 days a week.

Maintenance drug or saline control solutions were delivered 9 hours after termination of the last opiate drug session at midnight. This time was chosen to reduce the possibility that buprenorphine, a mixed agonist-antagonist, would precipitate opiate withdrawal and discomfort in monkeys that self-administered high doses of opiates. Buprenorphine, methadone, and saline-control solutions were administered at 9:30 a.m., 1.5 hours before the first morning opiate self-administration session at 12 noon The four daily opiate and food sessions were 1.5 to 15 hours after methadone or buprenorphine administration. Treatment drugs were given at a rate of 1 mL solution every 2 minutes and flushed through with sterile saline in a volume that exceeded the estimated catheter dead space. Additional details of the apparatus and procedures have been published (Mello et al. 1983).

Opiate Self-Administration During Buprenorphine and Methadone Maintenance Treatment

Buprenorphine significantly suppressed opiate self-administration by macaque monkeys at doses between 0.282 and 0.675 mg/kg/day, equivalent to 20 to 48 mg/day in humans. Significant suppression of opiate self-administration ($p<.05$-

.001) required 2.5 to 7 times the buprenorphine dose shown to be effective in human opiate abusers (Mello et al. 1982). In contrast, methadone over a dose range of 1.43 to 11.86 mg/kg/day failed to suppress opiate self-administration in four of five monkeys studied. This methadone dose range is equivalent to 100 to 800 mg/day in humans. Illustrative data showing the effects of buprenorphine and methadone on opiate self-administration in monkeys (A389, B205) used in a single crossover design appear in figures 1 and 2. Monkeys took 43 percent of their total daily opiate injections during the first daily drug sessions, 2.5 hours after methadone administration. Consequently, the distribution of opiate self-administration across drug sessions did not account for the absence of methadone suppression. The authors conclude that buprenorphine is more effective than methadone in suppressing heroin administration in the primate model (Mello et al. 1983). These data demonstrate the feasibility of using the primate drug self-administration model for the evaluation of new pharmacotherapies for the treatment of opiate addiction.

Although a controlled clinical study comparing buprenorphine and methadone has not yet been conducted, these primate data are consistent with clinical evaluations of buprenorphine (Mello and Mendelson 1980; Mello et al. 1982) and with previous studies of the effects of methadone on opiate self-administration by opiate addicts (Martin et al. 1973b; Jones and Prada 1977). Inpatient studies showed that some heroin addicts maintained on 50 to 100 mg/day of methadone continued to work for hydromorphone (4 mg IV) by riding an exercycle for 10 miles within 1 hour for approximately 2.5 months (Martin et al. 1973b; Jones and Prada 1975). Martin and coworkers (1973b) concluded that even at 100 mg/day of methadone, “cross-tolerance is not complete enough to completely abolish the reinforcing properties of 4 mg of hydromorphone hydrochloride, which would be equieuphorigenic to approximately 10 mg of heroin” (p. 294). Outpatient clinical studies also have shown that methadone is not uniformly effective with all patients and some methadone maintenance patients continue to use heroin, albeit at a lower level (Chambers and Taylor 1973; Chambers et al. 1973). A diverse pattern of polydrug abuse among methadone maintenance patients has been well documented (Langrod 1970; Bourne 1975; Maddox and Elliot 1975; Stimmel et al. 1978).

Methadone has been shown to block heroin self-administration in rhesus monkeys, but only at doses associated with severe debilitation, depression, and death (Harrigan and Downs 1981). A methadone dose of 12 to 24 mg/kg/day suppressed heroin self-administration in one monkey (Harrigan and Downs 1981). However, for lower methadone treatment doses, most investigators have reported continued opiate self-administration. For example, persistent opiate self-administration during methadone maintenance was observed in the

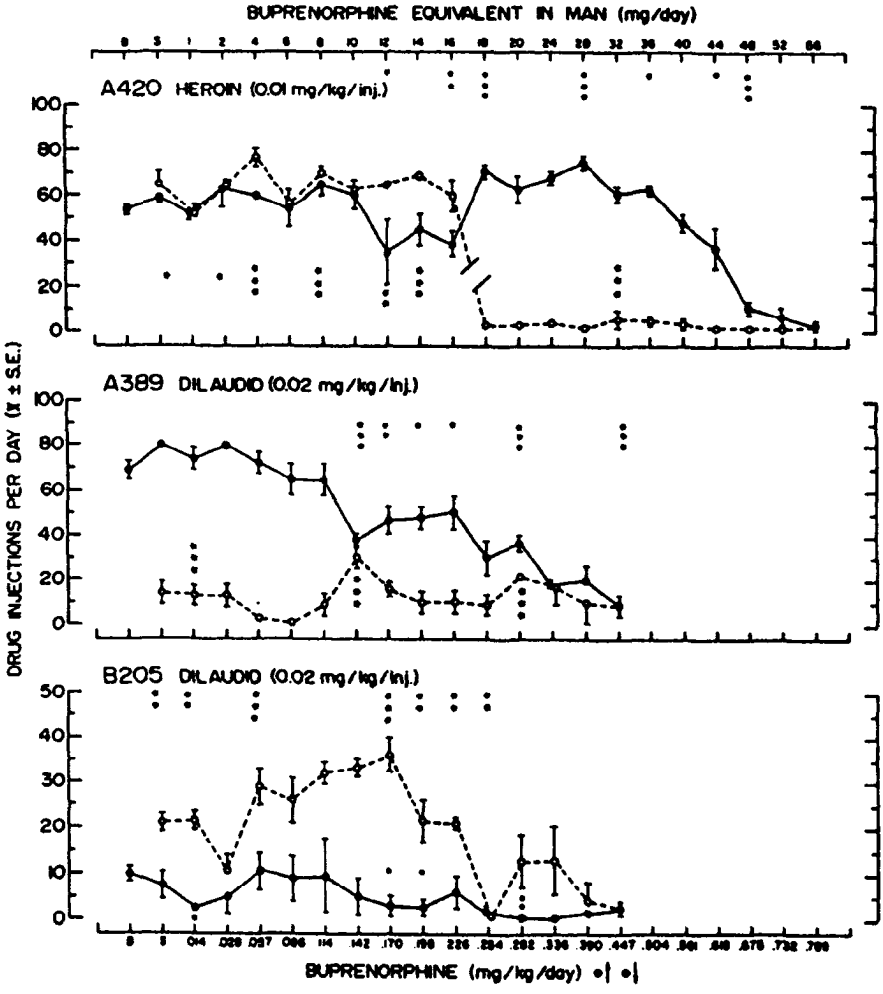


FIGURE 1. *Opiate self-administration during buprenorphine maintenance*

*p<.05
**p<.01
***p<.001

NOTE: After a treatment-free baseline (B) of 60 sessions, saline control treatment (S) was followed by buprenorphine treatment over an ascending (●) then a descending (○) dose series. Buprenorphine

doses (milligrams per kilogram per day) are shown on the lower abscissa, and the equivalent dose in humans (milligrams per day) is shown on the top abscissa. Total drug injections (inj) per day for 20 sessions over 5 days (mean±S.E.) are shown on the left ordinate. Statistically significant changes from the baseline during drug self-administration are indicated by black stars for the ascending dose series and open stars for the descending dose series. Significance levels are shown for the first value or midpoint of a series of similar values. Monkey A420 lost his catheter (//) during descending buprenorphine dose 0.226 mg/kg/day and was reimplanted, and after a 28-day interval, the 0.226 mg/kg/day dose was repeated.

SOURCE: Mello, N.K.; Bree, M.P.; and Mendelson, J.H. Comparison of buprenorphine and methadone effects on opiate self-administration in primates. *J Pharmacol Exp Ther* 225(2):378-386, 1983. Copyright 1983 by American Society for Pharmacology and Experimental Therapeutics.

dog (Jones and Prada 1977). Methadone maintenance resulted in an initial suppression of morphine self-administration (1 mg/kg/injection), which gradually returned to control levels over 2 weeks and subsequently increased significantly above premaintenance control levels (Jones and Prada 1977). In the baboon, a continuous infusion of methadone (8.3 mg/kg/hour) reduced, but did not eliminate, choices of heroin (0.3-0.96 mg/kg) over food during 10 consecutive days of observation (Griffiths et al. 1976). Thus, it appears that although sufficient doses of opiate agonists can temporarily decrease opiate self-administration (Griffiths et al. 1976; Wurster et al. 1977), extended observations have shown that opiate self-administration returns to baseline levels through time (Jones and Prada 1977; Mello et al. 1983).

The buprenorphine dose-related suppression of opiate intake observed is not consistent with previous studies of the effects of continuous buprenorphine infusions. For example, Harrigan and Downs (1981) reported that continuous infusion of 0.020 or 0.040 mg/kg/hour of buprenorphine did not significantly change morphine self-administration (2, 10, 50,250, and 625 mg/kg/injection) during 15-minute access periods once every 4 hours. It is difficult to equate continuous infusions with a single daily bolus drug administration. However, a continuous buprenorphine infusion of 0.020 to 0.040 mg/kg/hour would be equivalent to bolus administration of 0.48 to 0.96 mg/kg/day. Significant suppression of opiate self-administration at lower doses of buprenorphine (0.336-0.447 mg/kg/day) was observed. Several other procedural differences limit comparisons between the present study and that of Harrigan and Downs

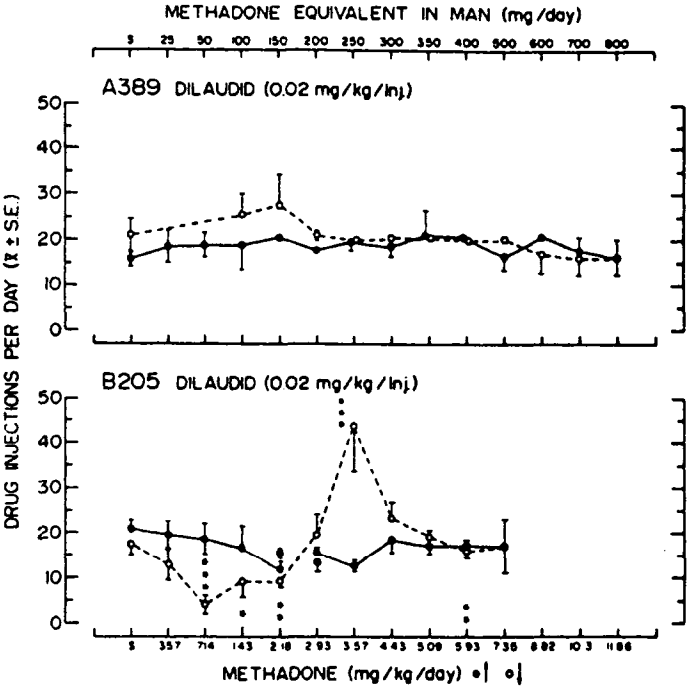


FIGURE 2. *Opiate self-administration during methadone maintenance treatment in monkeys previously studied under buprenorphine maintenance treatment*

*p<.05
**p<.01
***p<.001

NOTE: Saline control treatment (S) was followed by methadone treatment over an ascending (●) and descending (○) dose series. Methadone doses (milligrams per kilogram per day) are shown on the lower abscissa, and the equivalent dose in humans (milligrams per day) is shown on the top abscissa. Total drug injections per day (mean±S.E.) are shown on the left ordinate. Each point reflects 20 sessions over 5 days with the following exceptions: monkey A389—saline (●) was run for 120 sessions over 30 days; monkey B205—saline (●) was run for 60 sessions over 15 days; methadone doses of 2.18 and 2.93 mg/kg/day (●) were run for 40 sessions over 10 days (the most proximal point is joined to the preceding and following values by a solid line); and the

highest methadone dose was run for only eight sessions over 2 days. Statistically significant changes from saline control levels are indicated by open stars for the descending series.

SOURCE: Mello, N.K.; Bree, M.P.; and Mendelson, J.H. Comparison of buprenorphine and methadone effects on opiate self-administration in primates. *J Pharmacol Exp Ther* 225(2):378-386, 1983. Copyright 1983 by American Society for Pharmacology and Experimental Therapeutics.

(1981). For example, they used an FR 1 schedule of reinforcement and 15-minute drug access periods and alternated 3 days of morphine availability with 2 days of methamphetamine and 2 days of saline availability.

Food Self-Administration During Buprenorphine and Methadone Maintenance Treatment

Food self-administration also was affected differently by buprenorphine and methadone. Maintenance on buprenorphine at doses of 0.014 to 0.789 mg/kg/day for more than 6.5 months was not associated with a reduction in food intake, and two monkeys showed significant increases in food intake at higher buprenorphine doses. These data confirm previous observations that food intake increased significantly in monkeys that self-administered up to 3 mg/kg/day of buprenorphine (Mello et al. 1981). Monkeys maintained on buprenorphine remained generally healthy and alert, and these data further testify to the safety of daily buprenorphine treatment at high doses over several months.

Methadone suppressed food intake significantly below baseline in all monkeys at some point during the course of methadone maintenance treatment. An opiate-related decrease in food intake has been reported consistently in the experimental (Cochin et al. 1948; Crowley et al. 1975; Lukas et al. 1988) and clinical (Isbell 1948) literature. Moreover, methadone-maintained monkeys appeared very debilitated by the prolonged course of high-dose opiate exposure. Methadone administration over a dose range of 7.35 to 11.86 mg/kg/day resulted in transient seizures. Profound intoxication and respiratory depression at the highest doses studied required administration of naloxone (0.2 mg/kg/injection). It was necessary to limit methadone doses to the equivalent of 500 to 800 mg/day in humans to prevent methadone-related lethality. Comparable methadone toxicity has been reported by several other laboratories (Crowley et al. 1975; Harrigan and Downs 1981; Snyder et al. 1977).

BUPRENORPHINE'S EFFECTS ON COCAINE AND FOOD SELF-ADMINISTRATION: PRIMATE STUDIES

Cocaine abuse has increased among heroin-dependent persons, including those in methadone maintenance treatment programs (Kosten et al. 1986, 1987a, 1987b; Kaul and Davidow 1981), and has reached epidemic proportions in the general population (Kozel and Adams 1986). At present, there is no uniformly effective pharmacotherapy for cocaine abuse (Kleber and Gawin 1984; Gawin and Ellinwood 1988) and the dual abuse of cocaine plus heroin is a difficult treatment challenge. The opiate agonists methadone and IAAM and the opiate antagonist naltrexone are useful for the treatment of heroin abuse (Dole and Nyswander 1965; Blaine et al. 1978, 1981; Meyer and Mirin 1979; Martin et al. 1973a, 1973b; Mello et al. 1981). But these pharmacotherapies have not proven useful for combined cocaine and heroin abuse (Kosten et al. 1987a). Although desipramine (a tricyclic antidepressant) reduces cocaine abuse in some patients (Gawin and Kleber 1984; Tennant and Rawson 1983; Kosten et al. 1987b; Gawin and Ellinwood 1988), desipramine may stimulate relapse to cocaine abuse in abstinent patients (Weiss 1988). Treatment with methadone and desipramine has yielded inconsistent results on cocaine use by heroin abusers (O'Brien et al. 1988; Kosten et al. 1987b).

The effects of daily buprenorphine treatment on cocaine self-administration by five rhesus monkeys were examined (Mello et al. 1989, 1990a). Two male and three female adult rhesus monkeys with a 262±79-day history of cocaine self-administration were studied. Each monkey was surgically implanted with a double-lumen silicon rubber IV catheter under aseptic conditions to permit administration of buprenorphine or saline during each cocaine self-administration. The IV catheter was protected by a custom-designed tether system that permits monkeys to move freely. Monkeys worked for food (1 g banana pellets) and for IV cocaine (0.05 or 0.10 mg/kg/injection) on an FR 4 (VR 16:S) operant schedule of reinforcement. An average of 64 responses was required for each food pellet or cocaine injection. Food and cocaine were available during four 1-hour sessions each day. Food sessions began at 11 a.m., 3 p.m., 7 p.m., and 7 a.m.; cocaine sessions began at 12 noon, 4 p.m., 8 p.m., and 8 a.m. Each food or drug session lasted for 1 hour or until 20 drug injections or 65 food pellets were delivered. The total number of cocaine injections was limited to 80 per day to minimize the possibility of adverse drug effects (Johanson et al. 1976). The nutritionally fortified banana pellet diet was supplemented with fresh fruit, vegetables, biscuits, and multiple vitamins each day.

Daily buprenorphine treatment (or an equal volume saline control solution) was administered each day beginning at 9:30 a.m. Buprenorphine and saline were

gradually infused at a rate of 1 mL solution every 12 minutes and flushed through the catheter with sterile saline in a volume that exceeded the catheter dead space. Buprenorphine was administered at two doses (0.40 and 0.70 mg/kg/day) that effectively suppressed opiate self-administration in previous studies in the primate model (Mello et al. 1983). Each dose of buprenorphine and saline was studied for 15 consecutive days (60 sessions). After 30 days of treatment, buprenorphine was abruptly discontinued, and daily saline treatment was resumed.

Cocaine Self-Administration During Buprenorphine and Saline Maintenance Treatment

Figure 3 shows cocaine and food self-administration during 15 days of baseline saline treatment and six successive 5-day periods of buprenorphine treatment. Each of the five monkeys self-administered relatively high doses of cocaine during baseline saline treatment (2.1 to 4 mg/kg/day; group average of 3.07±0.17mg/kg/day). This dose of cocaine is comparable to that often reported by cocaine abusers; 1 to 2 gms of cocaine per week is equivalent to 2.04 to 4.08 mg/kg/day in a 70-kg human (Mendelson et al. 1988). All monkeys reduced cocaine self-administration during buprenorphine treatment ($p<.0001$) (figure 3). On the first day of buprenorphine treatment, cocaine self-administration decreased by 50 percent or more in four of the five subjects (range 50 to 67 percent). Average cocaine self-administration decreased by 49 percent to an average dose of 1.60±.25 mg/kg/day during the first 5 days of buprenorphine treatment ($p<.01$). Average cocaine self-administration fell to 77 and 83 percent below baseline during days 6 to 10 and 11 to 15, respectively, of buprenorphine treatment. Cocaine self-administration averaged 0.98±0.11 mg/kg/day during 15 days of buprenorphine treatment at 0.40 mg/kg/day.

During the second 15 days of buprenorphine treatment at 0.70 mg/kg/day, cocaine self-administration decreased to between 91 and 97 percent below baseline levels. Monkeys self-administered an average of 0.19+0.03 mg/kg/day of cocaine. Analysis of data from individual subjects showed that both the time course and the degree of buprenorphine's suppression of cocaine-maintained responding were equivalent in animals that self-administered relatively high (4 mg/kg/day) and low (2.1 mg/kg/day) doses of cocaine during the saline baseline treatment period. After abrupt cessation of 30 days of buprenorphine treatment, cocaine-maintained responding remained suppressed for at least 15 days in all animals. Individual monkeys returned to baseline levels of cocaine self-administration at different rates, ranging from 15 to 58 days (mean 30.5±10 days).

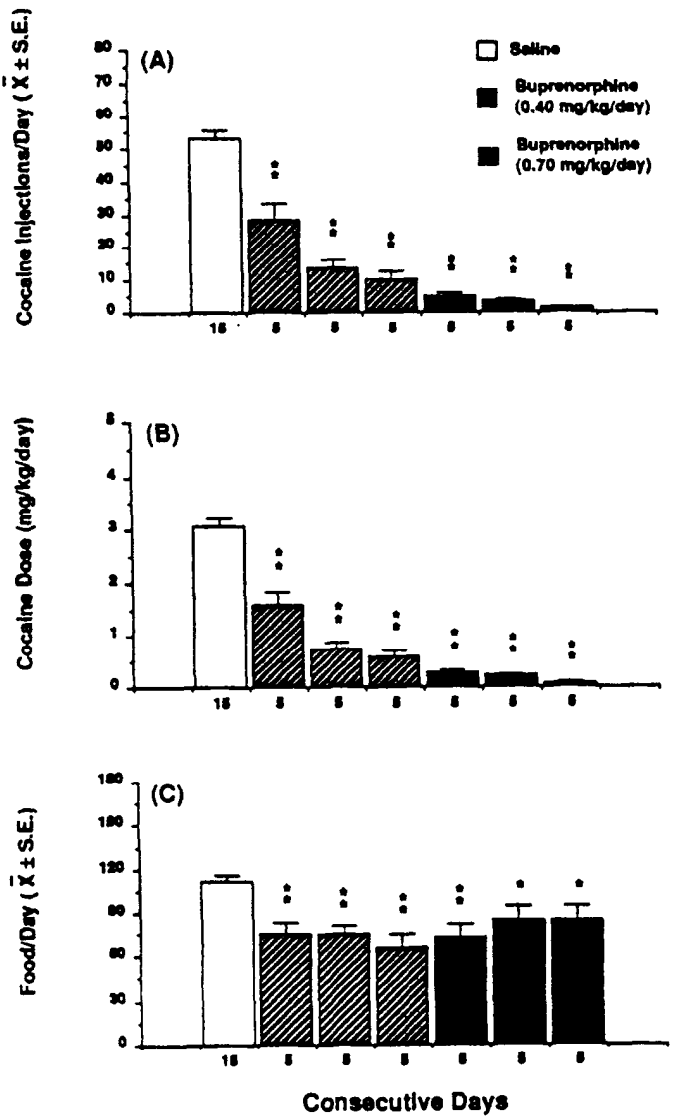


FIGURE 3. *Buprenorphine suppression of cocaine self-administration: The effects of single daily infusions of buprenotphine or a saline control solution on cocaine and food self-administration*

*p<.05
**p<.01

NOTE: Saline treatment is shown as an open bar and buprenorphine treatment as a striped bar (0.40 mg/kg/day) and a solid bar (0.70 mg/kg/day). The number of days that each treatment condition was in effect is shown on the abscissa. Each data point is the mean±SEM of five subjects. (A)=the average number of cocaine injections self-administered; (B)=the average dose of cocaine (mg/kglday) self-administered; (C)=the average number of food pellets self-administered. The statistical significance of each change from the saline treatment baseline as determined by analysis of variance for repeated measures and Dunnett's tests for multiple comparisons is shown by an asterisk.

SOURCE: Mello N.K.; Mendelson, J.H.; Bree, M.P.; and Lukas, S.E. Buprenorphine suppresses cocaine self-administration by rhesus monkeys. *Science* 245:859-862, 1989. Copyright 1989 by American Association for the Advancement of Science.

The prolonged suppression of cocaine self-administration after termination of buprenorphine treatment is comparable to clinical reports of delayed onset of buprenorphine withdrawal signs and symptoms. Peak abstinence signs and symptoms occurred within 15 to 21 days after abrupt cessation of buprenorphine (8 mg/day SC) treatment for 54 days (Jasinski et al. 1978). After 36 days of sublingual buprenorphine treatment (8 mg/day), mild withdrawal symptoms were reported 3 to 5 days after the last dose of buprenorphine (Fudala et al. 1989). This sublingual dose is equivalent to 5.3 mg SC (R.E. Johnson, personal communication, June 1988). Differences in the effective dose of buprenorphine and the duration of treatment as well as the measures of withdrawal may account for the differences between the two studies (Jasinski et al. 1978; Fudala et al. 1989). The delay (days or weeks) in appearance of mild buprenorphine withdrawal signs and symptoms probably reflects the slow dissociation of buprenorphine from the opiate receptor (Lewis et al. 1983). Moreover, studies of buprenorphine kinetics in rhesus monkeys have shown that multiple doses (1.0 mg/kg every 6 hours over 4 weeks) increased the biological half-life of buprenorphine threefold in comparison to a single 1.0 mg/kg SC injection (Numata et al. 1981).

Food Self-Administration During Buprenorphine and Cocaine Self-Administration

Food-maintained responding also was suppressed by 31 percent during the first 15 days of buprenorphine treatment (0.40 mg/kg/day) (figure 3). During the second 15 days of treatment, with a higher dose of buprenorphine (0.70 mg/kg/

day), food self-administration gradually recovered to average 20 percent below baseline. Although these changes in food-maintained responding were statistically significant ($p<.05$-$.01$), it is unlikely that they were biologically significant. There were no correlated changes in body weight, and animals continued to eat daily fruit and vegetable supplements.

Analysis of the pattern of food self-administration by individual monkeys indicated that buprenorphine treatment did not change the overall daily distribution of sessions in comparison to saline treatment. For example, food intake during the first session at 11 a.m. after buprenorphine treatment (9:30 a.m. to 10:30 a.m.) was not suppressed in comparison to saline treatment. Within 3 to 7 days after cessation of buprenorphine treatment (mean=8.5±2.9 days), four of five animals returned to baseline levels of food-maintained operant responding. Animals did not appear sedated during buprenotphine treatment, and activity levels were normal. The authors conclude that buprenorphine treatment suppressed cocaine-maintained responding but did not produce a generalized suppression of behavior.

Implications of Buprenorphine's Suppression of Cocaine Self-Administration for Drug Abuse Treatment

These data suggest that buprenorphine may be an effective pharmacotherapy for treatment of cocaine abuse. The primate model for preclinical evaluation of pharmacotherapies has several advantages, including ensured compliance with the treatment regimen and no confounding by polydrug abuse. Clinical evaluation of buprenorphine treatment of cocaine abuse, however, will require double-blind (buprenorphine vs. placebo) trials with randomized patient assignment and independent indices of compliance with the treatment regimen (buprenorphine blood levels) and objective measures of illicit drug use (frequent drug urine screens). If buprenorphine treatment of cocaine abuse proves to be clinically efficacious, this would not be a "substitute addiction" with a less toxic cocaine-like stimulant drug analogous to methadone treatment of heroin dependence.

These data also suggest that buprenorphine may be potentially valuable for the treatment of dual addiction to cocaine and heroin because it suppresses heroin use by heroin addicts (Mello and Mendelson 1980, 1985; Mello et al. 1982). One open clinical trial of buprenorphine treatment is consistent with the hypothesis that buprenorphine may be efficacious for reduction of cocaine abuse as well as heroin abuse (Kosten et al. 1989). Opioid-dependent patients treated with daily sublingual doses of buprenorphine for 1 month (average 3.2 mg/day; range 2-8 mg) had significantly fewer cocaine-positive urines than did patients treated with methadone (Kosten et al. 1989). If buprenorphine reduces

cocaine abuse as well as dual cocaine and heroin abuse, the potential benefits to society in terms of reduction of drug abuse problems and the associated risks for human immunodeficiency virus infection are incalculable.

The mechanisms accounting for suppression of cocaine self-administration by an opioid mixed agonist-antagonist drug are unclear. The relative contribution of buprenorphine's opioid agonist and antagonist components to its effects on cocaine's reinforcing properties are unknown, but there is considerable evidence that opioid *antagonists* such as naloxone and naltrexone do not suppress cocaine self-administration in primates or in rodents (Woods and Schuster 1972; Killian et al. 1978; Goldberg et al. 1971; Ettenberg et al. 1982; Carroll et al. 1986). We infer that either buprenorphine's opioid *agonist* component or its opioid *agonist-antagonist combination* is critical for suppression of cocaine self-administration. Clinical and primate studies of opioid *agonisteffects* on cocaine self-administration are inconsistent. Methadone treatment did not reduce cocaine-positive urines in heroin-dependent patients (Kosten et al. 1987a, 1989) but morphine pretreatment suppressed cocaine self-administration in a dose-dependent manner in squirrel monkeys (Stretch 1977).

Since cocaine's reinforcing properties are critically modulated by dopaminergic neural systems and buprenorphine appears to modify the reinforcing properties of cocaine, these data suggest an interrelationship between opioid and dopamine systems (Fischman 1987; Dackis and Gold 1985; Kuhar et al. 1988; Ritz et al. 1987; Woolverton et al. 1984; Woolverton 1986). This interpretation is consistent with several lines of evidence indicating comodulatory interactions between endogenous opioid and dopaminergic systems in brain. Neuroendocrine (Mendelson et al. 1986; Kuljis and Advis 1989; Mello et al. 1990b), neuropharmacological (Ishizuka et al. 1988; Di Chiara and Imperato 1988) and behavioral (Bozarth and Wise 1981; Blumberg and Ikeda 1978; Shippenberg and Herz 1987) studies suggest comodulatory interrelationships between dopaminergic and endogenous opioid system activity. These data suggest the importance of examining commonalities in the way in which abused drugs maintain behavior leading to their self-administration (Mello 1983; Di Chiara and Imperato 1986).

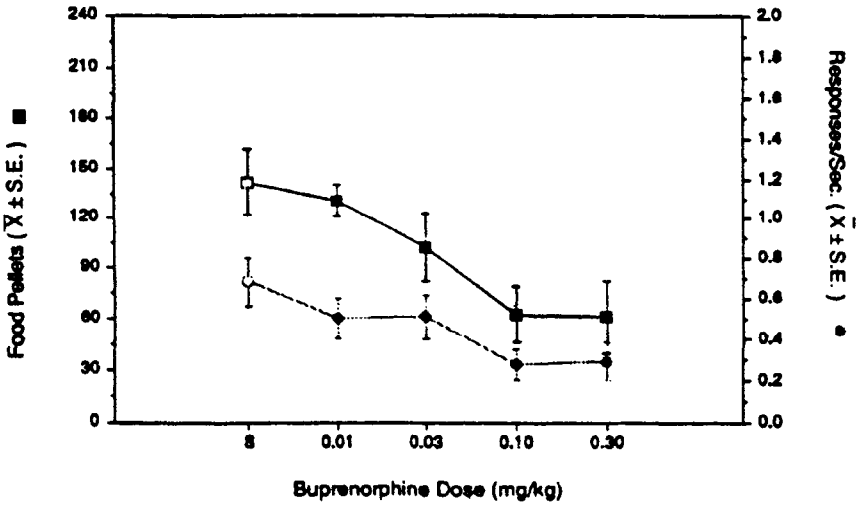
COMPARISON OF BUPRENORPHINE'S ACUTE AND CHRONIC EFFECTS ON FOOD-MAINTAINED RESPONDING

Although *chronic* buprenorphine administration did not suppress food self-administration in rhesus monkeys (Mello et al. 1981, 1982, 1983), the *acute* administration of buprenorphine usually suppresses food-maintained responding in other primates (Dykstra 1983; Lukas et al. 1986) and in pigeons

(Leander 1983). For example, in squirrel monkeys, acute administration of buprenorphine over a dose range of 0.0003 to 1.0 mg/kg suppressed food-maintained responding on a multiple fixed ratio (FR 30) fixed interval (FI 5-minute) schedule of reinforcement (Dykstra 1983). In baboons, acute administration of buprenorphine at a dose of 3.2 mg/kg also significantly suppressed food self-administration maintained on an FR 50 schedule of reinforcement. At lower doses (0.01-1.0 mg/kg), however, buprenorphine did not affect food-maintained responding in baboons (Lukas et al. 1986). in contrast to these findings, fixed-ratio discrimination performance maintained by food was not affected by acute administration of 3.2 mg/kg of buprenorphine in food-deprived rhesus and Patas monkeys (Moerschbaecher et al. 1984). There was no effect of buprenorphine on the rate or the accuracy of responding in this paradigm (Moerschbaecher et al. 1984). Buprenorphine (0.01-3.2 mg/kg) also failed to disrupt performance on a multiple schedule involving complex visual discriminations by food-deprived Patas monkeys (Moerschbaecher et al. 1987). It is possible that relative food deprivation (i.e., maintenance of animals at 85 percent of free-feeding weight) increased the saliency of food reinforcement in these discrimination studies. However, no data on the number of banana pellets earned were presented; accuracy of discrimination performance was the primary dependent variable (Moerschbaecher et al. 1984.1987). The procedural differences among these several studies make it difficult to account for the apparent differences in buprenorphine's acute effects on food-maintained performance.

The discrepancy between acute and chronic drug administration data suggests that although the gradual introduction of buprenorphine does not disrupt food intake in humans or in primates (Jasinski et al. 1978; Mello et al. 1981, 1982, 1983) isolated single doses of buprenorphine may suppress food-maintained behavior for the duration of action of the compound (Dykstra 1983; Lukas et al. 1986). The acute and chronic effects of buprenorphine on food-maintained responding in macaque monkeys were reexamined (Mello et al. 1985). After food self-administration was stable on an FR 4 (VR 16:S) second-order schedule, monkeys were given a single SC injection of either saline or buprenorphine (0.01, 0.03, 0.1, or 0.3 mg/kg) 1 hour before the 11 a.m. food session. Four food sessions were run each day at 4-hour intersession intervals. Buprenorphine doses were given in an ascending order. Saline and each dose of buprenorphine were repeated twice after a 72-hour interval.

Figure 4 shows that pretreatment with low *acute* doses of buprenorphine (0.01 and 0.03 mg/kg) did not change the number of food pellets earned or response rates on an FR 4 (VR 16:S) schedule of reinforcement from saline treatment levels. Acute administration of higher doses of buprenorphine (0.10 and 0.30 mg/kg) significantly suppressed food self-administration ($p<.01$).



FI GURE 4. *The effects of an acute dose of saline or buprenorphine on food-maintained responding by male macaque monkeys*

NOTE: Food self-administration (1 g banana pellet) was maintained on an FR 4 (VR 16:S) schedule of reinforcement that required an average of 64 responses for each food pellet. Saline and buprenorphine doses (0.01-0.30 mg/kg) are shown on the abscissa. Average numbers of food pellets earned in four postdrug food sessions distributed over 20 hours are shown on the left ordinate as black squares. Responses per second are shown on the right ordinate as open squares. Each data point represents an average of 32 food self-administration sessions.

SOURCE: Adapted from Mello, N.K.; Bree, M.P.; Lukas, S.E.; and Mendelson, J.H. Buprenorphine effects on food-maintained responding in macaque monkeys. *Pharmacol Biochem Behav* 23:1037-1044, 1985. Copyright 1985 by Pergamon Press plc.

The rate of food-maintained responding also decreased significantly from saline control levels after acute administration of 0.10 and 0.30 mg/kg of buprenorphine ($p<.01$). Moreover, there was a dose-dependent persistence of buprenorphine's suppressive effects on food self-administration ($p<.02$) and on the rate of food-maintained responding (pc.05). However, after pretreatment with low doses of buprenorphine (0.01 and 0.03 mg/kg), food-maintained responding remained slightly (but not significantly) depressed for 48 hours. Food self-administration was significantly suppressed by an acute dose of

0.10 mg/kg of buprenorphine, but the total number of food pellets earned returned to within 4 percent of the saline control baseline within 48 hours after buprenorphine administration. However, after pretreatment with the highest dose of buprenorphine (0.30 mg/kg), food-maintained responding was suppressed for up to 72 hours (Mello et al. 1985).

The effects of chronic buprenorphine self-administration (0.01-0.10 mg/kg/injection) and heroin self-administration (0.01-0.10 mg/kg/injection) on food-maintained responding also were examined (Mello et at. 1985). Four doses of buprenorphine over a range of 0.01 to 0.10 mg/kg/injection were studied in five monkeys. All monkeys were not studied at every dose of each drug. Three doses of heroin over a range of 0.01 to 0.10 mg/kg/injection were studied in two monkeys. Monkeys were exposed to an ascending series of doses of buprenorphine and heroin.

Drug and food self-administration were maintained on the same second-order schedule of reinforcement FR 4 (VR 16:S) for a minimum of 40 sessions over 10 days or until food and drug self-administration were stable. In the progressive ratio studies, the number of responses required for each drug injection was increased systematically, but food-maintained responding was controlled by the same FR 4 (VR 16:S) schedule of reinforcement. The average response requirement for each drug injection was increased from 64 to 96 to 128 to 160 by increasing the value of the FR component of the second-order schedule from FR 4 to FR 6 to FR 8 to FR 10, etc. Each increase in the FR schedule component was run for eight sessions over 2 days. Progressive increases in the response requirement for drug injections were continued until the monkey stopped responding for drug for 2 consecutive days.

Chronic buprenorphine self-administration (0.01-0.10 mg/kg/injection) did not significantly suppress food intake. When average daily doses of buprenorphine self-administered were three to nine times higher than the highest dose studied in the acute buprenorphine administration paradigm, there was no suppression of food-maintained responding. As progressive ratio-response requirements increased, buprenorphine intake fell to 30 or 40 percent of baseline levels, but food self-administration remained constant. For example, total daily buprenorphine intake was more than 0.90 mg/kg/day during baseline and declined to approximately 0.30 mg/kg/day with no corresponding changes in food intake. Food intake increased significantly in two monkeys when buprenorphine self-administration (mg/kg/day) was equivalent to or double the acute dose that significantly suppressed food intake. At higher doses per injection (0.10 mg/kg/injection), total daily buprenorphine intake decreased from more than 2.5 mg/kg/day to approximately 1.5 mg/kg/day with no corresponding changes in food intake. In one monkey, buprenorphine doses as high as 5 mg/

kg/day did not suppress food intake, and gradual decreases in buprenorphine self-administration were not accompanied by increased food self-administration (Mello et al. 1985). Similarly, chronic heroin self-administration (0.01,0.05, and 0.10 mg/kg/injection) was not associated with significant changes in food self-administration.

The most parsimonious explanation of these differences between *acute* and *chronic* effects of buprenorphine on food-maintained responding appears to be that tolerance develops to buprenorphine's effects. This interpretation is necessarily inferential since this study was not designed to measure tolerance per se. But this hypothesis is consistent with clinical observations that tolerance to the opioid agonist-like side effects of buprenorphine developed within 21 days (Mello et al. 1982). This is also consistent with other evidence of tolerance to the behavioral and physiological effects of buprenorphine (Lewis et al. 1983; Mello et al. 1982). However, a tolerance hypothesis is not consistent with observations in squirrel monkeys, where repeated administration of 0.01 mg/kg/day of buprenorphine for 17 days continued to suppress food-maintained rates of responding (Dykstra 1983). In an effort to assess whether or not tolerance occurs to buprenorphine's acute suppressive effects on food-maintained responding, this issue was reexamined in rhesus monkeys (Lukas et al. 1988).

Analysis of Tolerance to Buprenorphine's Effects on Food-Maintained Responding

The time course of the development of tolerance to buprenorphine's effects on food-maintained responding was examined by exposing rhesus monkeys to 25 consecutive days of single SC injections of buprenorphine (1.0 mg/kg/day) (Lukas et al. 1988). Monkeys worked for food (1 g banana pellets) on a second-order FR 4 (VR 16:S) schedule that required an average of 64 responses for each food pellet. Food was available at 11 a.m., 3 p.m., and 7 a.m., and each session lasted for 1 hour or until 65 food pellets were delivered. Buprenorphine or saline control injections were given 1 hour before the 11 a.m. food session.

Figure 5 shows that the first injection of buprenorphine (1.0 mg/kg) significantly suppressed food-maintained responding and suppression was greatest on the second day of treatment. Food-maintained responding returned to control levels within 4 days of buprenotphine treatment and remained at or slightly above control levels for the next 21 days.

Substitution of saline for buprenorphine was followed by a further increase in food self-administration and then by a gradual decline over 7 to 10 days. This was not accompanied by any discernible signs of buprenorphine withdrawal

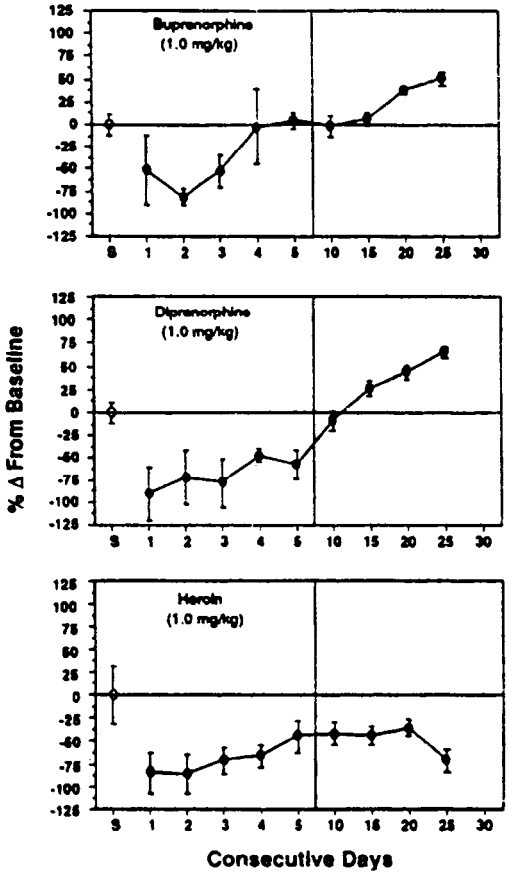


FIGURE 5. *Changes in total daily food pellets (mean±S. E.) earned during 25 wnsewtive days of buprenorphine (1.0 mg/kg), diprenorphine (1.0 mg/kg), or heroin (7.0 mg/kg) administration*

NOTE: Each data point represents the percent change from 10 days of saline control treatment for three monkeys. Monkeys self-administered between 125 and 224 pellets per day during saline treatment. Consecutive days are shown on the abscissa. Daily averages are shown for the first 5 days, and 5-day averages are shown for days 10 through 25.

SOURCE: Adapted from Lukas, S.E.; Mello, N.K.; Bree, M.P.; and Mendelson, J.H. Differential tolerance development to buprenorphine-,

diprenorphine-, and heroin-induced disruption of food-maintained responding in macaque monkeys. *Pharmacol Biochem Behav* 30:977-982, 1988. Copyright 1988 by Pergamon Press plc.

(Lukas et al. 1988). These data confirm the hypothesis that tolerance develops rapidly to buprenorphine's disruptive effects on food-maintained responding (Mello et al. 1983). These data are consistent with the interpretation that tolerance accounts for the reported differences between the acute and chronic effects of buprenorphine on food-maintained responding (Mello et al. 1985). It was found that gradual induction of buprenorphine maintenance treatment and daily buprenorphine administration at doses of 0.014 to 0.789 mg/kg/day over 6 months did not produce suppression of food-maintained responding (Mello et al. 1983). Similarly, chronic buprenorphine self-administration of 0.3 to above 2.8 mg/kg/day did not suppress food-maintained responding (Mello et al. 1981, 1965).

Comparison of the Effects of Buprenorphine, Diprenorphine, and Heroin on Food-Maintained Responding

There is an extensive literature indicating that, in general, opiate agonists increase food intake in several species, whereas opiate antagonists usually suppress feeding behavior (Morley et al. 1983a, 1983b; Yim and Lowy 1984). Since buprenorphine is a congener of diprenorphine, a potent opioid antagonist, and etorphine, an opioid agonist (Lewis et al. 1983) it is a unique compound for studying opiate effects on food intake. However, it is unclear whether buprenorphine's opioid agonist or antagonist effects were primarily responsible for its *acute* suppressive effects on food-maintained responding (Mello et al. 1985; Lukas et al. 1988).

Diprenorphine, the antagonist component of buprenorphine (Lewis et al. 1983) suppresses rates of food-maintained responding (Dykstra 1983; DeRossett and Holtzman 1984) and decreases body weight in squirrel monkeys (Herman and Holtzman 1984) but comparable data were not available for rhesus monkeys. If the acute suppression of food-maintained responding by buprenorphine does reflect predominantly antagonist effects, this might explain the duration of buprenorphine's acute effects. Diprenorphine (1.0 mg/kg) and buprenorphine (0.1 mg/kg) each suppressed food-maintained responding for 24 to 48 hours in squirrel monkeys (DeRossett and Holtzman 1984). A protracted suppression of food-maintained responding would be expected, since the opioid antagonist effects of buprenorphine persist for up to 72 hours, while its opioid agonist effects persist for about 6 hours (Jasinski et al. 1978; Lewis et al. 1983). In an effort to clarify the relative contribution of the agonist and antagonist

components of opioid mixed agonist-antagonist drugs to effects on food-maintained behavior, the acute effects of diprenorphine and heroin were compared to buprenorphine under identical conditions (Lukas et al. 1988).

Diprenorphine (1.0 mg/kg/day) significantly suppressed food-maintained responding on the first day of treatment (figure 5). Food intake remained suppressed for 5 days but gradually returned to control levels by day 10. Food-maintained responding then increased significantly above control levels between days 15 and 25 of diprenorphine treatment ($p<.05$). Heroin (1.0 mg/kg) also decreased food-maintained responding on the first day of treatment. A slight recovery of food-maintained responding occurred between days 5 and 7 of heroin treatment, but food-maintained responding was significantly below the saline baseline throughout heroin treatment ($p<.01$).

Figure 6 shows the rates of tolerance development to buprenorphine, heroin, and diprenorphine. The linear portion of the time/effect curve was subjected to regression analysis (Tallarida and Jacob 1979). The regression lines for buprenorphine and diprenorphine were significantly different from heroin but were not different from each other. The buprenorphine and diprenorphine regression lines for recovery of food-maintained performance were parallel, but the diprenorphine curve was shifted to the right, indicating that recovery was delayed by 3 days. These data show that the rates of tolerance development to diprenorphine and buprenorphine were the same. The 3-day delay in development of tolerance to diprenorphine may result from the fact that diprenorphine has a shorter duration of antagonist action than does buprenorphine (DeRossett and Holtzman 1984; Dykstra 1983) and it may have taken longer for effective drug levels to accumulate in the blood.

The lack of tolerance to heroin is inconsistent with previous observations that 20 days of heroin self-administration did not significantly suppress food-maintained responding when the total daily intake was 0.18, 1.12, and 1.79 mg/kg (Mello et al. 1985). In that study, however, heroin intake was more evenly distributed throughout the day across four drug sessions between noon and midnight. A single bolus dose of heroin (1.0 mg/kg/day) was more disruptive than a comparable daily dose distributed over 12 hours. The exact mechanisms of the observed differences in the rate of tolerance development between buprenorphine, diprenorphine, and heroin are unknown, but it is likely that one major contributing factor is the difference in pharmacokinetic properties of these drugs (Lukas et al. 1988).

PREDICTION OF BUPRENORPHINE'S ABUSE LIABILITY

Buprenorphine suppresses opiate self-administration in human heroin addicts (Mello and Mendelson 1980; Mello et al. 1982) and in a primate model (Mello

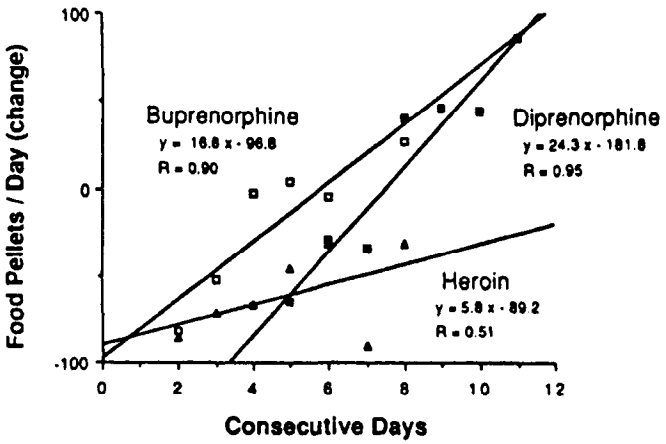


FIGURE 6. *Regression analysis of the rate of recovery from heroin-, buprenorphine-, and diprenorphine-induced suppression of food-maintained behavior*

NOTE: Only the linear portion of the time-effect curve was analyzed; this included days 2 to 8 of the heroin and buprenorphine treatment and days 5 to 11 of diprenorphine treatment.

SOURCE: Adapted from Lukas, S.E.; Mello, N.K.; Bree, M.P.; and Mendelson, J.H. Differential tolerance development to buprenorphine-, diprenorphine-, and heroin-induced disruption of food-maintained responding in macaque monkeys. *Pharmacol Biochem Behav* 30:977-982, 1988. Copyright 1988 by Pergamon Press plc.

et al. 1983). Recent studies suggest that buprenorphine may also suppress cocaine self-administration in primates (Mello et al. 1989, 1990a) and reduce cocaine use by heroin-dependent persons (Kosten et al. 1989). An unresolved issue affecting clinical deployment of buprenorphine, however, is its abuse liability relative to other opiates such as methadone and heroin.

It is well established that buprenorphine produces opiate agonist-like subjective effects comparable to morphine and methadone. A comparison of the subjective effects of single doses of buprenorphine (0.2-2.0 mg), morphine (15-40 mg), and methadone (30 mg) revealed similar euphoria and liking scores on several self-report measures (Jasinski et al. 1978). Moreover, subjects reported similar degrees of "liking" during chronic buprenorphine or morphine maintenance (Jasinski et al. 1978). An 8-mg/day dose of

buprenorphine produced subjective effects and euphoria equivalent to that produced by 120 mg/day of morphine (30 mg q.i.d.) or 40 to 60 mg of methadone (Jasinski et al. 1978). Although SC injection of buprenorphine did not produce a rapid high or "rush" similar to IV heroin injection, buprenorphine-maintained subjects did report a generalized feeling of contentment (Mello and Mendelson 1980; Mello et al. 1982).

Since buprenorphine and other mixed agonist-antagonist drugs have minimal physical dependence producing capacities, this has refocused attention on the adequacy of using physical dependence as a criterion for predicting abuse liability (Woolverton and Schuster 1983). Although it has long been known that the reinforcing properties of psychomotor stimulants and low doses of opiates are independent of physical dependence (Schuster and Johanson 1974), the assumption that opiate abuse is critically modulated by physical dependence and the avoidance of withdrawal has remained a central concept in drug abuse liability evaluation (Thompson and Unna 1977; Martin and Jasinski 1977). The primate drug self-administration model has been shown to be a powerful tool for evaluating reinforcing efficacy and predicting the abuse potential of new compounds (Griffiths et al. 1979, 1980; Schuster and Johanson 1974; Thompson and Unna 1977; Brady and Lukas 1984) and a high concordance between animal drug self-administration data and subjective reports of opiate effects has been reported consistently (Griffiths and Balster 1979). However, there have been relatively few studies of the reinforcing properties of buprenorphine or other opioid mixed agonist-antagonist drugs (Balster and Lukas 1983).

Buprenorphine has consistently been shown to be a positive reinforcer in rhesus monkeys (Woods 1977; Mello et al. 1981; Yanagita et at. 1982; Young et al. 1984). Woods (1977) was the first to report that substitution of buprenorphine (0.003-0.10 mg/kg/injection) for codeine (0.32 mg/kg/injection) maintained responding on an FR 30 schedule of reinforcement. However, response rates for buprenorphine were lower than response rates for codeine, morphine, or heroin (Woods 1977). These original findings were recently confirmed under the same experimental conditions, and buprenorphine maintained the highest rates of responding at a dose of 0.1 mg/kg/injection (Young et al. 1984).

It was reported that buprenorphine maintained operant responding on a second-order FR 3 (VR 16:S) schedule that required an average of 48 responses per injection (Mello et al. 1981). Monkeys self-administered buprenorphine across a dose range of 0.005 to 0.10 mg/kg/injection and took significantly more buprenorphine injections than saline ($p<.01$). Four monkeys took progressively more buprenorphine (mg/kg/day) as the dose per injection

increased from 0.01 to 0.10 mg/kg (Mello et al. 1981). Yanagita and coworkers (1982) also have reported that buprenorphine was clearly reinforcing at unit doses of 0.004 mg/kg/injection and above.

Relative Reinforcing Properties of Buprenorphine and Opioid Agonists

Although buprenorphine consistently maintains behavior leading to its administration, recent studies suggest that it is less reinforcing than other opioid agonist drugs (Mello et al. 1988a). One way to evaluate the relative reinforcing efficacy of two compounds is to use a progressive ratio procedure. The response requirement for each drug injection is progressively increased until the animal stops responding (i.e., reaches a "breakpoint").

Progressive ratio performances for buprenorphine with heroin, methadone, and saline were compared (Mello et al. 1988a). Eight monkeys with a history of opioid agonist and opioid mixed agonist-antagonist self-administration and two initially drug-naive monkeys were subjects. Buprenorphine was studied over a dose range of 0.01 to 0.10 mg/kg/injection and methadone over a dose range of 0.03, 0.10, and 0.25 mg/kg/injection. Each drug dose was available for 40 sessions over 10 days at the lowest response requirement (FR 4 [VR 16:S]) or until baseline drug self-administration was stable. Subsequently, the response requirement for each drug injection was increased by 32 responses every eight sessions (2 days) until drug self-administration ceased for 2 consecutive days. The immediately preceding drug-response requirement defined the breakpoint, or the maximum number of responses that the monkey would emit for a single drug injection. After the breakpoint at one drug dose was reached, the monkey was returned to the baseline schedule (FR 4 (VR 16:S]) at the **same** dose until drug self-administration resumed. Monkeys then were given access to another drug dose and run on the baseline schedule until drug self-administration was stable for 40 consecutive sessions. Response requirements then were increased progressively as before and continued until the monkey reached the breakpoint at that dose.

Figures 7a and 7b show progressive ratio data for buprenorphine (0.01-0.10 mg/kg/injection), heroin (0.01-0.10 mg/kg/injection), and methadone (0.03-0.25 mg/kg/injection). Both heroin (0.01-0.10 mg/kg/injection) and intermediate doses of methadone (0.10 mg/kg/injection) appeared to be significantly more reinforcing than buprenorphine. Monkeys consistently emitted more responses for heroin and for methadone (0.10 mg/kg/injection) than for any dose of buprenorphine. In contrast to buprenorphine, the progressive ratio breakpoint for heroin increased as a function of increased heroin doses per injection (Mello et al. 1988a). These progressive ratio studies suggest that buprenorphine is less reinforcing than two opioid agonists that are known to be abused by humans (Mello et al. 1988a).

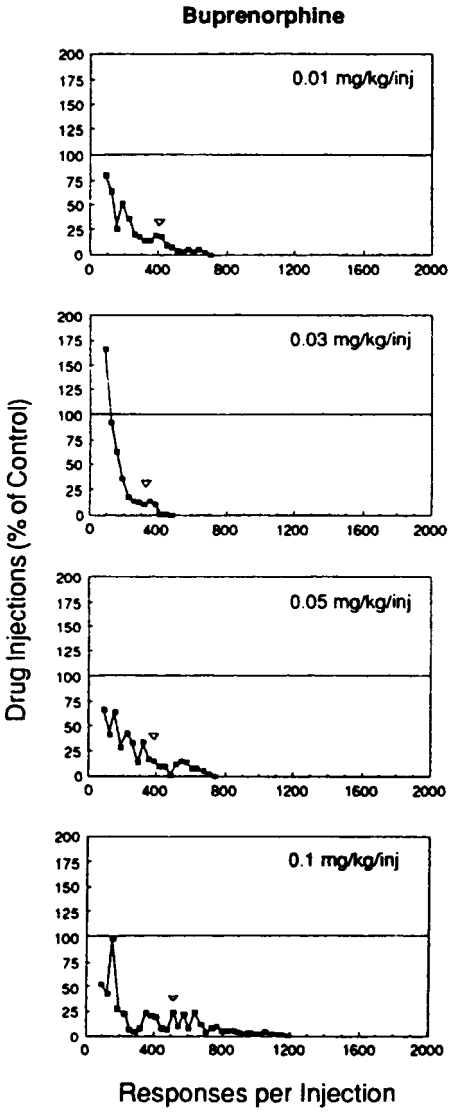


FIGURE 7a. *Percent change in responding for buprenorphine from baseline control levels as a function of progressive increases in the number of responses required for each injection*

NOTE: The percent change from baseline control levels on an FR 4 (VR 16:S) schedule is shown on the left ordinate. The number

of responses required for each drug injection is shown on the abscissa. The group average progressive ratio breakpoint is indicated by ∇ in each panel. The group average for 0.01 mg/kg/injection buprenorphine represents five animals; the group average for 0.03 mg/kg/injection buprenorphine represents six animals; the group averages for 0.05 and 0.10 mg/kg/injection buprenorphine represent three or four animals, respectively.

SOURCE: Mello et al. 1988a. Copyright 1988 by Elsevier Scientific Publishers Ireland Ltd.

Relative Reinforcing Properties of Buprenorphine and Other Opioid Mixed Agonist-Antagonists

The relative reinforcing properties of nalbuphine (Nubain), butorphanol (Stadol), and pentazocine (Talwin) were compared with saline and buprenorphine in male rhesus monkeys (Mello et al. 1988b; Yanagita et al. 1982). Yanagita and coworkers (1982) compared buprenorphine and another opioid mixed agonist-antagonist, pentazocine, on a progressive ratio procedure and found that the breakpoint was lower for buprenorphine (0.015 and 0.06 mg/kg/injection) than for pentazocine (0.06 and 0.25 mg/kg/injection). These data suggest that buprenorphine has lower potential for abuse than pentazocine. Progressive ratio performances for nalbuphine (0.010, 0.032, and 0.100 mg/kg/injection), butorphanol (0.0010, 0.0032, and 0.0100 mg/kg/injection), pentazocine (0.10, 0.32, and 0.56 mg/kg/injection), and saline were compared. After baseline drug self-administration was stable, the second-order schedule response requirement per injection was increased in increments of 64 until the monkey stopped responding for eight consecutive sessions (Mello et al. 1988b).

All three drugs at each dose maintained more responding and higher progressive ratio breakpoints than did saline. Group average progressive ratio breakpoints for butorphanol showed dose-related increases of 576, 1,173, and 1,963 responses per injection. Progressive ratio breakpoints for the highest dose of butorphanol were higher than for any dose of nalbuphine. The low and high doses of nalbuphine maintained higher progressive ratio breakpoints (1,600 and 1,472 responses per injection) than did the intermediate dose of nalbuphine (618 responses per injection). Group average breakpoints for pentazocine also showed dose-related increases (864 and 1,824 responses per injection), and these studies are still in progress. In contrast, group average breakpoints for saline-maintained responding ranged between 64 and 170 responses per injection. These data suggest that the relative reinforcing efficacy of each of these three opioid mixed agonist-antagonist drugs is quite

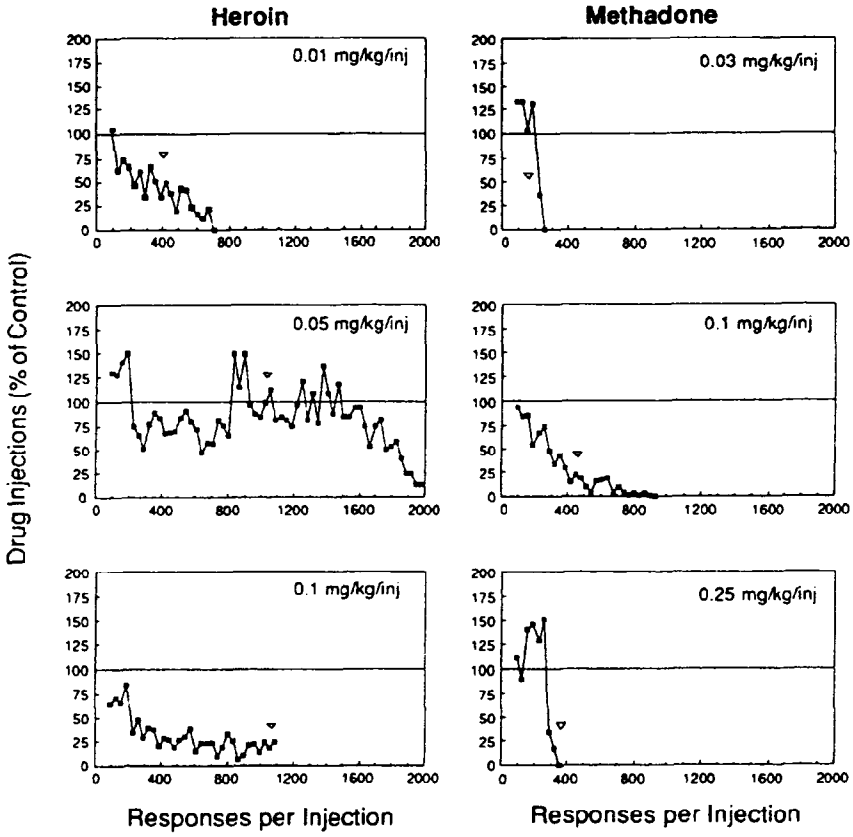


FIGURE 7b. *Percent change in responding for heroin and methadone from baseline control levels as a function of progressive increases in the number of responses required for each injection*

NOTE: The percent change from baseline control levels on an FR 4 (VR 16:S) schedule is shown on the left ordinate. The number of responses required for each drug injection is shown on the abscissa. The group average progressive ratio breakpoint is indicated by ∇ in each panel. Each data point for heroin represents an average of three or four animals. Data points for methadone (0.03 and 0.10 mg/kg/injection) represent three animals; data for methadone (0.25 mg/kg/injection) represent one animal.

SOURCE: Mello et al. 1988a. Copyright 1988 by Elsevier Scientific Publishers Ireland Ltd.

similar to those of the others (Mello et al. 1988b). These data obtained in a primate drug self-administration model are consistent with clinical observations of pentazocine abuse and predictions of abuse liability of butorphanol and nalbuphine (Jaffe 1985). Progressive ratio breakpoints for nalbuphine, butorphanol, and pentazocine were consistently higher than previously reported for buprenorphine (0.10 mg/kg/injection) or heroin (0.10 mgikg/injection) (522 and 1,067 responses per injection) (Mello et al. 1988a). These data suggest that these opioid mixed agonist-antagonists may have a greater potential for abuse than buprenorphine.

Buprenorphine also has proved to be less reinforcing than other opioids and some opioid mixed agonist-antagonists in baboons and in rhesus monkeys, as evaluated with a simple drug substitution procedure (Lukas et al. 1983, 1986; Young et al. 1984). Baboons were trained to self-administer cocaine (0.32 mg/kg/injection) on an FR 160 schedule of reinforcement. Baboons could earn a maximum of eight injections per day, and a 3-hour timeout interval was imposed after each drug injection. The self-administration patterns of codeine and morphine were compared to four mixed agonist-antagonist drugs (butorphanol, nalbuphine, pentazocine, and buprenorphine) and one antagonist (naloxone) and SKF-10047, a prototype sigma agonist. Each of the mixed agonist-antagonists-nalbuphine (0.001-1.0 mg/kg/injection), butorphanol (0.0001-0.1 mg/kg/injection), and pentazocine (0.32-10.0 mg.kg/injection)-was self-administered at higher levels than buprenorphine across a dose range of 0.00032 to 0.32 mg/kg/injection (Lukas et al. 1983, 1986). Moreover, each mixed agonist-antagonist drug, except buprenorphine, showed a drug self-administration profile similar to that of codeine (i.e., more injections were self-administered at higher doses per injection than at lower doses per injection). These drug self-administration profiles contrast sharply with the relatively flat dose-response curve observed for buprenorphine in baboons (Lukas et al. 1986).

Similar findings were obtained in rhesus monkeys using drug substitution procedures with response rate as a measure. Monkeys were trained to self-administer codeine (0.32 mg/kg/injection) on an FR 30 to 600 seconds in 2 daily sessions that terminated after 13 infusions or 130 minutes (Young et al. 1984). The opioid mixed agonist-antagonist butorphanol (0.001-0.0032 mg/kg/injection) and propriam (0.03-1.0 mg/kg/injection) maintained response rates between 1.25 and 1.5 per second, whereas buprenorphine maintained response rates that averaged one per second at doses of 0.0032 to 0.01 mg/kg/injection (Young et al. 1984). In contrast to data in baboons, nalbuphine (0.001-0.32 mg/kg/injection) maintained response rates consistently below one per second. However, interpretation of data obtained in a substitution procedure in terms of relative reinforcing efficacy is limited by several problems associated

with using response rate as a measure (Schuster and Johanson 1974; Schuster and Balster 1973).

CONCLUSIONS: THE POTENTIAL USEFULNESS OF BUPRENORPHINE AS A PHARMACOTHERAPY FOR HEROIN AND COCAINE ABUSE

Ultimately, the abuse potential of any pharmacotherapy must be balanced against its safety and efficacy relative to other drugs (Mello and Mendelson 1988). Buprenorphine maintenance treatment effectively reduced heroin self-administration by heroin addicts (Mello and Mendelson 1980; Mello et al. 1982) and offers some advantages as an analgesic (Houde 1979). Buprenorphine appears to be as effective as methadone for detoxification of heroin addicts (Bickel et al. 1988b; Kosten and Kleber 1988). Buprenorphine, however, has two important advantages over the opiate agonist methadone as a pharmacotherapy for opiate addiction: (1) Buprenorphine does not induce significant physical dependence in humans, and consequently, buprenorphine treatment can be discontinued without severe withdrawal signs and symptoms (Jasinski et al. 1978; Fudala et al. 1989; Lukas et al. 1984); and (2) the possibility of lethal overdose is remote due to the opiate antagonist properties of buprenorphine (Lewis et al. 1983; Jasinski et al. 1978; Banks 1979; Mello et al. 1982).

The opiate agonist component of buprenorphine that raises concern about its potential abuse liability is buprenorphine's primary advantage over treatment with the opiate antagonist naltrexone. It is likely that the agonist component of this opioid mixed agonist-antagonist is important for patient acceptance, since naltrexone, an equally potent opioid antagonist, has not been widely effective in the treatment of heroin addiction. It has been very difficult to retain heroin abusers in naltrexone treatment programs (Julius and Renault 1976; Resnick and Washton 1978; Meyer and Mirin 1979; Schecter 1980; Crabtree 1984). We conclude that the safety and potential therapeutic benefits of buprenorphine probably outweigh the possible risks associated with its abuse potential. To date, illicit diversion of buprenorphine has been minimal compared to that of heroin (O'Connor et al. 1988).

However promising buprenorphine appears to be as a pharmacotherapy for heroin addiction (Mello and Mendelson 1980), dual addiction to heroin and cocaine (Kosten et al. 1989) and perhaps cocaine abuse per se (Mello et al. 1989,1990a), it is not a chemical panacea. Even though an effective pharmacotherapy may antagonize drug effects and improve mood, there is always the possibility that drug abusers may engage in other forms of addictive drug use. Drug addiction is a complicated and multiply determined behavior disorder. It is realistic to anticipate that buprenorphine, and its successor

pharmacotherapies, may attenuate drug abuse but probably will not completely eliminate it.

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ACKNOWLEDGMENT

Preparation of this chapter was supported in part by National Institute on Drug Abuse grants DA-02519, DA-04059, DA-00101, and DA-00064.

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Phase II Clinical Trials of Buprenorphine: Detoxification and Induction Onto Naltrexone

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INTRODUCTION

Pharmacologic treatment strategies for heroin addiction currently employ two general approaches: detoxification followed by drug-free abstinence and maintenance treatment with either opioid agonists or antagonists (Cushman and Dole 1973; Gold et al. 1978; Kleber et al. 1985; Kosten and Kleber 1984; Resnick et al. 1977). Since the goal of agonist maintenance with methadone is usually the eventual detoxification to a drug-free state, detoxification from methadone or heroin to either drug-free or antagonist treatment is a clinically important treatment strategy. Detoxification techniques have ranged from methadone-dosage tapering to clonidine substitution and the combination of clonidine substitution with naloxone (Cushman and Dole 1973; Gold et al. 1978; Kleber et al. 1985; Resnick et al. 1977). Transition to antagonists, such as naltrexone, has been clinically difficult, however, because naltrexone introduction must be delayed to allow for an adequate opioid-free interval during which physical dependence will be lost to avoid precipitating withdrawal (Kosten and Kleber 1984). Previous work has shown that naltrexone, even at very low doses (1 mg), will precipitate substantial withdrawal symptoms in patients discontinued from methadone 18 hours earlier (Charney et al. 1984). Typically, 10 to 14 days must intervene between the last methadone dose and the first naltrexone dose to avoid precipitating withdrawal (Kosten and Kleber 1984).

As an alternative to this long opioid-free period, during which relapse to drug abuse is likely, the authors have explored the early introduction of the antagonist naltrexone (Charney et al. 1981, 1982; Kleber et al. 1987; Vining et al. 1988). In the initial studies, an attempt was made to introduce very small doses of antagonist directly after stopping the agonist (Charney et al. 1982; Kleber et al. 1987). Conceptually, this was an attempt to introduce opioid antagonism gradually to avoid precipitating withdrawal. Because even low naltrexone doses precipitated withdrawal, it was necessary to administer

clonidine to suppress these symptoms. Opioid-dependent patients detoxified with clonidine and naltrexone exhibited approximately a 50-percent reduction in the duration of their acute withdrawal symptoms (Charney et al. 1982; Kleber et al. 1987; Vining et al. 1988). These studies suggested that recovery from opioid physical dependency might be accelerated by the introduction of an opioid antagonist.

Another strategy to accelerate reduction in opioid dependency would be to introduce a partial opioid agonist that could precipitate mild withdrawal and at the same time minimize these symptoms by its agonist activity. This strategy has not been feasible with previously available partial agonists such as pentazocine, cyclazocine, butorphanol, or nalorphine, since they precipitate significant withdrawal in morphine-dependent patients and may cause psychosis in some patients (Jacob et al. 1977; Martin 1967; Martin et al. 1966; Pircio et al. 1976; Woods and Gmerek 1983). A new partial agonist, buprenorphine, however, showed therapeutic promise because of early work indicating that it did not precipitate significant withdrawal in methadone- or morphine-dependent patients (Jasinski et al. 1978, 1984; Mello and Mendelson 1980; Mello et al. 1982).

Buprenorphine is a partial opioid agonist or mixed agonist antagonist that addicts report does not produce a heroin-like rush (Jasinski et al. 1984). Buprenorphine doses of 2 to 4 mg have been substituted for 20 to 30 mg of methadone without precipitating substantial withdrawal symptoms, although buprenorphine may act as an opioid antagonist at doses as low as 8 mg (Jasinski et al. 1978; Mello and Mendelson 1980; Mello et al. 1982). After chronic administration, buprenorphine does not produce significant physical dependence, as suggested by the minimal withdrawal symptoms that occur when it is stopped (Dum et al. 1981; Jasinski et al. 1984; Lewis 1986). Because of these properties, buprenorphine was examined to determine whether it might facilitate the transition from opioid agonists to antagonists in a three-step process: (1) buprenorphine substitution for agonists such as methadone, (2) buprenorphine-induced reduction in physical dependency, and (3) discontinuation of buprenorphine with rapid introduction of naltrexone.

The design for this study with opioid-dependent patients involved an initial outpatient protocol followed by an inpatient protocol for patients in the last two-thirds of this study. The outpatient protocol included discontinuation of either heroin or methadone followed by a 30-day trial on a range of buprenorphine dosages (protocol A). Induction onto naltrexone was attempted in all those patients who completed 30 days on buprenorphine. For the first one-third of the subjects, there was an attempt to complete their induction as outpatients, but because this was generally unsuccessful, a second inpatient protocol was

developed. The inpatient protocol (protocol B) began after the 30-day outpatient buprenorphine maintenance and included blinded discontinuation of the buprenorphine followed by double-blind placebo-controlled challenges with either low-dose naltrexone or high-dose naloxone. These two inpatient challenges carefully compared the capacities of low-dose naltrexone and high-dose naloxone to precipitate withdrawal in buprenorphine-maintained patients.

Although the initial challenge studies were done with low-dose naltrexone (1 mg oral P.O.) to parallel earlier work with naltrexone in methadone-maintained patients (Charney et al. 1984), the subsequent studies were high-dose naloxone rather than naltrexone for three reasons. First, previous work with partial agonists such as butorphanol, nalbuphine, and pentazocine had used high doses of naloxone to precipitate a withdrawal syndrome after chronic treatment with these agents, thereby providing some guidelines for its use with buprenorphine. In these studies with nalbuphine and butorphanol, a withdrawal syndrome could be precipitated by 4 mg naloxone (Jacob et al. 1977; Jasinski et al. 1968; Pircio et al. 1976; Woods and Gmerek 1985). With pentazocine, 10 to 15 mg of naloxone was necessary to reverse its agonist as well as dysphoric effects, whereas up to 16 mg of naloxone did not reverse respiratory depression associated with buprenorphine (Dum et al. 1981; Jasinski et al. 1978; Kallos and Smith 1968; Quigley et al. 1984; Kosten et al. 1988, Lewis 1985). Thus, high doses of naloxone had been given previously to patients treated with these partial agonists, and it appeared that over 16 mg of naloxone might be needed with buprenorphine to precipitate any withdrawal.

Second, translating this naloxone dose into an equivalent dose of naltrexone is not straightforward because the half-life is markedly longer for naltrexone than for naloxone and because two indicators of antagonist potency—recipitating withdrawal or blocking exogenous opioids-suggest different relative potencies of these two medications (Kosten and Kleber 1984; Martin 1967). Precipitation of withdrawal in opioid-dependent patients can be induced by as little as 0.1 mg of naloxone or 1 mg of naltrexone, while blocking a 25-mg injection of heroin after antagonist administration requires 1 mg of intravenous (IV) naloxone or 50 mg of oral naltrexone (Charney et al. 1982, 1984; Kleber et al. 1987; Vining et al. 1988). These two assessments indicate a tenfold to fiftyfold relative potency of naloxone over naltrexone, suggesting that unacceptably large naltrexone doses, theoretically more than 800 mg (50 times 16 mg naloxone), would be required to precipitate significant withdrawal in buprenorphine-maintained patients. This high-dose naltrexone (above 200 mg daily) has been associated with liver toxicity.

Third, any substantial withdrawal syndrome precipitated by the high-dose antagonist would last substantially longer with naltrexone than with naloxone

(Charney et al. 1982; Kleber et al. 1987; Kosten and Kleber 1984; Resnick et al. 1977). In addition to behavioral ratings of withdrawal symptoms, physiological (blood pressure) and biochemical (3-methoxy-hydroxyphenethylamine glycol [MHPG]) responses to antagonist challenge were monitored. Previous work had demonstrated increases in both blood pressure and plasma-free MHPG, an index of norepinephrine turnover, during low-dose naltrexone-precipitated withdrawal in methadone-maintained patients (Charney et al. 1984). Thus, these two other measurements could be used to provide important objective correlates of any opioid withdrawal precipitated by naltrexone in buprenorphine-maintained patients.

METHODS

Subjects

Forty-one opioid-dependent patients were entered into the month-long outpatient protocol A. The patients included 31 males and 10 females with a mean age of 31 (±SEM 1) years. Of these, 14 patients came from methadone maintenance at a dose of 25 mg/day, and the other 27 patients were using street heroin. For those using heroin, opioid addiction was confirmed using urine toxicology and challenge with naloxone at 0.8 mg intramuscularly (Wang et al. 1974; Kleber et al. 1985). To qualify for inclusion, these heroin abusers had to attain a withdrawal score above 35 on the laboratory's clinician-rated scale within 15 minutes of naloxone injection. The outpatient withdrawal-rating scale includes 24 items with 0- to 3-point severity ratings and has a score range of 0 to 72 (Kosten et al. 1985). An item score of 3 indicates "severe" withdrawal, and a total score of less than 20 indicates minimal withdrawal. For the inpatient challenges, a 15-item subscale ranging from 0 to 45 was used. This shorter subscale allowed more rapid administration and used items considered more responsive to acute change over the course of the antagonist challenges.

Of the 41 patients, 18 entered the inpatient protocol B after completion of the 30-day outpatient protocol A. The inpatient protocol included double-blind challenges with either lowdose naltrexone in 13 patients or high-dose naloxone in 5 patients. The other 23 patients either dropped out of the outpatient protocol A before 30 days (n=13) or completed the open outpatient protocol A and attempted outpatient induction onto naltrexone from buprenorphine (n=10). The 18 patients entering the inpatient protocol and the 23 other patients were not significantly different in demographics or percentage from the methadone maintenance group (26 percent inpatient vs. 39 percent outpatient).

The findings from the inpatient protocol were compared with those of a previously published study in which 15 methadone-maintained patients (mean dose 35 mg daily; range 20 to 65 mg) were given low-dose (1 mg) oral naltrexone challenges (Charney et al. 1984). These patients included 10 males and 5 females and had a mean age of 31±1 years. The mean duration of methadone treatment was 3±1 years. Eight other methadone-maintained patients were given a blinded challenge with placebo, but data were incomplete on one of them. The seven placebo patients included five males and two females and had a mean age of 3±1 years.

Study Design

Protocol A: Outpatient. Patients starting buprenorphine treatment were discontinued from either methadone maintenance or street heroin and within 24 hours of their last dose were started on sublingual buprenorphine at 2 mg, except for four patients. Two of the four started at 4 mg, and the other two started at 8 mg in a dosage-induction experiment that examined whether opioid withdrawal would be precipitated by the higher buprenorphine dosages. Among the 37 patients starting at 2 mg, a wider range of maintenance dosages was examined, and after the first 5 days, the maintenance dosages were 2 mg (n=16), 3 mg (n=14), 4 mg (n=4), and 6 mg (n=3). This was an open trial with single daily dosing 7 days a week. After the first 5 days, patients remained on fixed dosages of buprenorphine for days 6 to 30 as outpatients and then either stopped the buprenorphine as outpatients or entered protocol B. During this 30-day outpatient trial, withdrawal symptoms were rated daily by a clinician, and urine toxicologies were obtained twice weekly on a randomized schedule. For the 12 patients who had been transferred from methadone maintenance to buprenorphine, urine toxicologies for the 2 months before starting buprenorphine also were obtained. Two months of urines were used, because only random weekly urines, rather than twice weekly urines, were obtained in the methadone program. The rates of cocaine- and opioid-positive urines were compared for methadone and buprenorphine treatments.

Buprenorphine was discontinued abruptly in an open trial with 10 outpatients who took buprenorphine for 30 days. Maintenance dosages for these patients were 2 mg (n=3), 3 mg (n=2), 4 mg (n=3), 6 mg (n=1), and 8 mg (n=1). They reported few withdrawal symptoms during the 3 to 5 days that the authors were able to follow them after discontinuation of buprenorphine, but only two (at 2 mg and 4 mg) took any naltrexone, and they all returned to methadone maintenance or illicit opioid use.

Protocol B: Inpatient. Following the 30 days on buprenorphine, 18 patients were hospitalized at the Connecticut Mental Health Center Clinical

Neuroscience Research Unit for 4 to 7 days. Upon admission to the hospital, each patient received a maintenance dose of buprenorphine once daily at 5 p.m. for 3 days. The maintenance doses were 2 mg (n=7), 3 mg (n=8), 4 mg (n=2), and 6 mg (n=1). The buprenorphine then was discontinued abruptly by blinded substitution of placebo on day 3 after each patient had completed a placebo antagonist challenge. In the naltrexone challenge, an oral placebo was given at 9 a.m. on that day. In the naloxone challenge, an IV placebo was given instead. The day after buprenorphine placebo substitution, patients were given a challenge of either active naltrexone (1 mg P.O.) or active naloxone (0.5 mg/kg IV) at 9 a.m. The IV naloxone infusion was given over a 20-minute period using a 10-mg/mL naloxone solution. Throughout the hospitalization, all patients received a vanillylmandelic acid exclusion diet (Chamey et al. 1964).

Prior to the naltrexone or naloxone challenge procedure, each patient fasted overnight for 10 hours and remained in the fasting state during the procedure until approximately 3 p.m. An IV catheter was placed in the patients arm to obtain two blood samples during the hour before receipt of naltrexone or naloxone (baseline) and then every 30 minutes for the next 3.5 hours after naltrexone or naloxone administration. A separate IV injection site was used for the IV naloxone infusions. Blood pressure measurements and opioid withdrawal ratings were obtained at the same time points. Withdrawal during the inpatient protocol was rated using the 15-item subscale of the 24-item scale, with items scored from 0 to 3, giving a score range from 0 to 45 (Charney et al. 1961, 1964). This shorter subscale had been developed in the authors' earlier methadone-naltrexone challenge study and was adopted to facilitate comparison between the current study and previous work (Chamey et al. 1964). The comparison methadone-maintenance patients had *been* continued on a stable dose of methadone before admission to the Research Unit and then had participated in a procedure identical to the 1-mg oral-naltrexone challenges following abrupt discontinuation of their methadone dose (Charney et at. 1994). Raters and patients were blind as to whether placebo *or* naltrexone was administered.

Biochemical Methods: Protocol B

Two 1-mL aliquots of plasma were taken from iced blood samples that were centrifuged within 2 hours. Assays for MHPG then were conducted on these duplicate samples using selected ion monitoring with a gas chromatograph/ mass spectrometer (Finnegan Model 3300 series) (Elsworth et al. 1962). Because of difficulties in finding adequate veins for blood sampling, MHPG determinations could be made at antagonist challenges for only eight of the naltrexonechallenged and four of the naloxone-challenged buprenorphine patients.

Data Analysis

For protocols A and B, data analysis induded simple descriptive measures of treatment retention, withdrawal symptoms, and illicit drug use. Comparisons were made across buprenorphine dosages as well as between dropouts and the remaining sample using contingency tables or repeated measures analysts of variance (ANOVA), as appropriate. To facilitate data analyses, ANOVA-R of withdrawal ratings in the outpatient trial (protocol A) use ratings from days 2, 5, 8, 11, 14, 17, 20, 23, 26, and 29. For protocol B, withdrawal ratings over a 3-hour period were compared for the naltrexone- and naloxone-challenged buprenorphine patients and the naltrexone-challenged methadone patients (TREATMENT type) as well as for the placebo and naltrexone challenges (CHALLENGE type) using a three-way analysis of covariance (ANCOVA) (e.g., treatment type by challenge type by time point-repeated measure). The naltrexone-challenged methadone patients were used as a further historical comparison group. Mean blood pressures were calculated as 2 (systolic-diastolic)/3+diastolic pressure. Blood pressures and plasma levels of MHPG were analyzed by determining the peak change in blood pressure or MHPG for each patient because of considerable variability in the time course of withdrawal symptoms induced by naloxone in the buprenorphine patients and by naltrexone in the methadone-maintained patients. The peak changes in blood pressure and in MHPG were compared for the various groups using covariance adjustment for baseline differences (ANCOVA).

RESULTS

Outpatient Buprenorphine and Overall Outcome: Protocol A

The 41 opioiddependent patients generally had minimal withdrawal symptoms while maintained on buprenorphine. Patients had mild withdrawal symptoms when started on buprenorphine, but this declined over the first 2 weeks on buprenorphine. The mean score (on the 24-item, 72-point scale) was 18±15 (SD) at day 2 and had declined to 11±9 by day 14 and to 9±8 by day 21. Maintenance doses of buprenorphine during the course of the trial were examined using only those patients started at 2 mg (four were started at higher doses) and categorizing the patients into three groups: 2 mg (n=16), 3 mg (n=14), and 4 or 6 mg (n=7). Because all three groups were on 2 mg during the first 5 days, analyses were run using only days 8 through 29. Withdrawal symptoms for the three DOSE groups were similar for weeks 2 to 4 of the trial, and no significant DOSE effect was seen. Withdrawal symptoms at day 2 were more intense among patients getting the 2-mg standard induction dose (18.6±15) than among the four patients started at either 4 mg or 8 mg of buprenorphine (8±8) ($t=2.3$; $p<.05$; one tail), suggesting that higher

buprenorphine doses did not precipitate withdrawal. Instead, the starting dose of 2 mg may have been somewhat low for the patients coming from methadone maintenance (all at 25 mg) because the 10 methadone patients who started at 2 mg had fairly sustained mild withdrawal symptoms over the first 2 weeks, while the 27 street heroin addicts showed a decline in symptom levels (repeated measures ANCOVA, TIME: $F=2.9$; $df=4,35$; $p<.03$) (TREATMENT: $F=2.1$; $df=1,35$; $p<.1$). At day 2 the methadone and street groups were equivalent (18 vs. 19), but by day 8 the methadone group remained at 18±15, whereas the street group dropped to 11±8 ($t=2.1$; $df=25$; $p<.05$). The methadone group remained above the street group at days 11 (18 vs. 11) ($t=2.2$; $p<.03$) and 14 (16 vs. 9) ($t=2.3$; $p<.03$). Interestingly, the four patients starting above 2 mg, who had lower levels of withdrawal than the 2-mg patients (see above), had all come from methadone maintenance, and they had somewhat lower withdrawal levels throughout the first (mean=13) and second (mean=8) weeks of buprenorphine treatment. Thus, although these levels of withdrawal symptoms were mild and generally not related to maintenance doses of buprenorphine, the patients coming from methadone maintenance appeared to have a more sustained period of withdrawal adjustment and may have benefited from a starting dose higher than 2 mg.

During the 30-day outpatient protocol, patients showed good retention and reduced illicit opioid use. Of the 41 entrants, 29 patients (71 percent) came in daily and completed this protocol. The mean stay was 25±8 days, and several of the 12 dropouts left due to circumstances unrelated to the medication (e.g., unexpected job transfer) or to illicit drug abuse. Illicit opioid use for the patients completing treatment declined from 33 percent of urines in week 1 to 19 percent in week 4 and was not related to dosage of buprenorphine. For the dropouts, illicit opioid use remained at 50 percent of urines through week 3, and both dropouts in week 4 were using illicit opioids. For the whole trial, the percentage of illicit opioid urines was greater among dropouts (51 percent) than among those remaining in treatment (27 percent) ($t=2.3$; $p<.03$) and there was an inverse correlation between days in treatment and number of illicit urines ($r=.34$; $p<.03$) (more illicit urines with fewer days in treatment).

Demographic comparisons and overall outcome for the various maintenance dosages of buprenorphine are shown in table 1. None of the outcomes, including retention for 30 days, percentage of urines positive for illicit opioid use, taking at least one dose of naltrexone, and being maintained on naltrexone for at least 2 weeks, were significantly different among the dosage groups. Although the rate of successful naltrexone maintenance appears to be best with a 3-mg dose of buprenorphine (22 percent vs. 7 percent and 0 percent), this is an artifact of the allocation of patients to naloxone challenges compared with naltrexone challenges. All naloxone-challenge patients had been maintained at

TABLE 1. *Sample characteristics and global outcome by maintenance dose of buprenorphine (n=41)*

Characteristic	Buprenorphine Dose			
	2 mg	3 mg	4,6,8 mg	All
Sample size	16	14	11 (6,3,2)	41
Males (%)	69	79	91	77
Age (years±SD)	31±7	29±6	33±7	31±7
From "street" (%)	69	70	55	68
Outcomes				
Stay 30 days (%)	63	70	82	71
Opiate use (%)	37	27	37	33
Take naltrexone (%)	50	50	46	49
Naltrexone>2 weeks (%)	6	22	0	10

NOTE: No differences were statistically significant.

3 mg of buprenorphine, and this naloxone procedure, rather than dose of buprenorphine, seemed generally more effective at eventual naltrexone induction. The patients who received a high-dose naloxone challenge were successful at being maintained on naltrexone. This success appeared to result from the tolerance of these patients to a rapid increase in naltrexone dosage from 6 mg to full 50 mg over the 24 to 36 hours after the withdrawal from high-dose naloxone had resolved (within 4 to 5 hours). During this rapid induction onto naltrexone, patients had trouble sleeping and one had vague muscle aches, but none showed severe signs of withdrawal. Thus, the high-dose naloxone enabled a very rapid detoxification from buprenorphine. These challenges are addressed in more detail below.

Another interesting finding among these patients was a remarkably low level of cocaine abuse. Overall, these patients on buprenorphine had a 3-percent rate of cocaine urine toxicologies (SD=2 percent), which is substantially less than the 30- to 40-percent rates that are found in the authors' methadone-maintenance program.

When the 12 patients who had been on this methadone maintenance program were examined before starting buprenorphine, the six patients who had been abusing cocaine demonstrated a dramatic reduction in cocaine use on buprenorphine, as shown in figure 1.

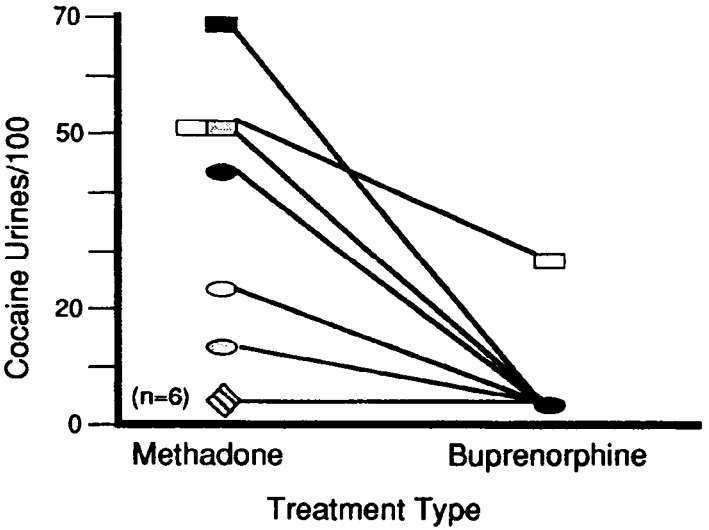

FIGURE 1. *Plot of rates of cocaine-positive urine toxicologies (cocaine urines per 100) in 12 patients switched from methadone maintenance to buprenorphine protocol for 1 month*

NOTE: Each symbol represents one patient, except for the large diamond representing the six cocaine nonabusers.

Only one patient did not stop completely, and this patient showed a 50-percent reduction in use. When asked why they had stopped abusing cocaine, the patients reported less pleasure from cocaine and, specifically, dysphoric "crash" symptoms after its use. These crash symptoms had been ameliorated in the past by “speedball” use of opioids such as heroin or methadone along with the cocaine. Apparently, this speedball effect was blunted by the use of buprenorphine.

inpatient Antagonist Challenges: Protocol B

Of the 18 inpatients given antagonist challenges, 13 received naltrexone and 5 received naloxone. None of the 13 patients on buprenorphine had marked differences in their responses to 1 mg of oral naltrexone as compared to their responses to placebo. In contrast, naltrexone (1 mg) induced substantial withdrawal symptoms in 13 of 15 methadone-maintained patients in an earlier study (Charney et al. 1984). Significant increases in withdrawal symptoms were

induced in five buprenorphine patients by high-dose naloxone infusions (0.5 mg/kg IV) (mean weight=746 kg). This naloxone dose (mean=35 mg) is about 100 times the dose usually needed to precipitate withdrawal in methadone- or heroin-dependent subjects and is about 50 times greater than the 0.8-mg dose that precipitated withdrawal in the heroin-dependent patients before they started on buprenorphine 30 days earlier.

The withdrawal symptoms (and standard errors) for the two buprenorphine groups are shown in figure 2 along with the methadone group response to 1 mg naltrexone for comparison. The placebo responses for the three different conditions were indistinguishable from the 1-mg naltrexone response in the buprenorphine group (n=13) and were omitted for clarity. .

The withdrawal symptoms among the buprenorphine patients were significantly greater for the naloxone-challenged (0.5 mg/kg) than for the naltrexone-challenged (1 mg) patients (TREATMENT type), as shown by

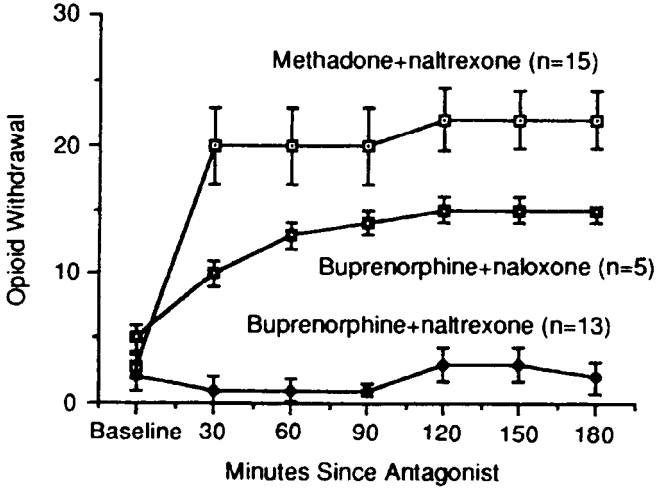

FIGURE 2. *Plot of opioid-withdrawal symptoms for patients maintained on buprenorphine and given either naltrexone 1 mg P.O. or naloxone 0.5 mg/kg (mean=35 mg) IV and for methadone-maintained patients given naltrexone 1 mg P.O.*

NOTE: Because placebo challenges for all three groups did not differ from buprenorpine with naltrexone, they are not shown for clarity. The mean scores standard errors are plotted.

main effects (TREATMENT: F=10.5; df=1,32; p<.003) (CHALLENGE: F=2.7; df=1,32; p<.05, one tail) and interaction with TIME or the repeated measure (TREATMENT X CHALLENGE X TIME: F=7.0; df=5,160; p<.0001). The comparison of withdrawal seventy scores among the methadone and two buprenorphine groups (TREATMENT type) also was highly significant for main effects (TREATMENT: F=18.7; df=2,52; p<.0001) (CHALLENGE: F=20.5; df=1,52; p<.001) and for TIME interaction (TREATMENT X CHALLENGE X TIME: F=5.8; df=10,260; p<.0001). As figure 2 shows, the withdrawal response for the naloxone-challenged buprenorphine patients was substantially less than that for the naltrexone-challenged methadone patients. The placebo challenge responses in the methadone and both buprenorphine groups were not significantly different from each other or from the naltrexone challenge in the buprenorphine patients. The withdrawal symptom severity was not related to either dose of buprenorphine or methadone vs. ‘street” induction onto buprenorphine.

Before giving the active naltrexone challenge, the baseline plasma-free MHPG levels were not significantly different among the two buprenorphine (3.3±0.6 ng/mL and 3.6±0.7 ng/mL) and methadone groups (3.1±0.9 ng/mL), as shown in table 2.

TABLE 2. *The* effect of *naltrexone- or naloxone-precipitated opiate withdrawal on plasma-free MHPG levels in buprenorphine- and methadone-maintained patients*

		MHPG (ng/mL±SD)	
Treatment Group	Number	Baseline	Peak
Buprenorphine			
Naltrexone	8	3.3±0.6	3.5±O.7
Placebo	8	3.2±0.9	3.6±0.8
Naloxone	4	3.6±0.7	3.7±0.7
Placebo	4	3.5±0.8	3.9±1.0
Methadone			
Naltrexone	15	3.1±0.9	4.0±1.2
Placebo	7	3.9±0.6	4.4±0.7

NOTE: Significant differences are indicated in text.

The peak increase in plasma MHPG, however, was significantly greater for the methadone (0.9 ng/mL) than for either the naltrexone-challenged (0.2 ng/mL) or the naloxone-challenged (0.1 ng/mL) buprenorphine groups. Using ANCOVA (covariance) to adjust for baseline levels, the overall F ratio was 54 (df=6,45; p<.0001), with significant CHALLENGE (F=4.6; df=1,45; p<.04), TREATMENT type (methadone and two buprenorphine groups) (F=8.6; df=2,45; p<.001), and interaction effects (F=5.0; df=2,45; p<.01). The major source of this MHPG interaction was that the buprenorphine patients showed lesser MHPG responses to active challenge than to placebo, while the methadone patients showed greater responses to active challenge than to placebo.

Among the buprenorphine-maintained patients, a significant change in blood pressure was induced by the naloxone but not by the naltrexone challenge compared to placebo challenge. Because the baseline mean blood pressures ranged from 93 to 104 mm Hg, as shown in table 3, covariance adjustments were used for comparisons. Using ANCOVA to compare the two CHALLENGES for the three TREATMENTS gave an overall F ratio of 12.4 (df=6,57; p<.0001), with significant TREATMENT (F=11.4; df=2,57) and CHALLENGE (F=11.5; df=1,57) effects but no significant interaction.

TABLE 3. *The effects of naltrexone- and naloxone-precipitated opiate withdrawal on mean standing blood pressure in buprenorphine- and methadone-maintained patients*

		Mean Blood Pressure ±SD)		
Treatment Group	Number	Baseline	Peak	Differ
Buprenorphine				
Naltrexone	13	96.7±10.5	106.6±10.5	9.9
Placebo	13	93.3 ± 8.9	102.0±10.3	8.7
Naloxone	5	94.8 ± 4.8	105.3 ± 7.0	10.5
Placebo	5	104.7±14.0	102.3 ± 8.7	-2.4
Methadone				
Naltrexone	15	103.5±11.7	117.1±8.6	13.6
Placebo	7	101.3 ± 9.1	105.9 ± 9.2	4.6

NOTE: Significant differences are indicated in text.

The difference between the placebo and naloxone challenges for the buprenorphine patients (2.4-mm drop for placebo and 10.5-mm rise for naloxone) was substantially greater than the difference for the naltrexone-challenged buprenorphine patients (8.7-mm rise for placebo and 9.9-mm rise for naltrexone) and equivalent to the difference for the methadone patients (4.6-mm rise for placebo and 13.6-mm rise for naltrexone). Thus, the blood pressure changes were consistent with the differences in withdrawal symptoms among the three TREATMENT groups.

DISCUSSION

This study showed that heroin addicts or methadone-maintained patients can be transferred onto the partial opioid agonist buprenorphine for a 1 -month outpatient program with good retention, minimal withdrawal symptoms, and a reduction in illicit opioid and cocaine use. The reduction in cocaine abuse was particularly striking and may offer a potential new treatment for this serious addiction. The optimal dose of buprenorphine for outpatient treatment or for the transition to naltrexone appears to be quite flexible within the sublingual range of 2 to 8 mg, and dosing may be quite similar to that with methadone maintenance in which wide individual variations are common. Based on the good retention and limited illicit drug use, buprenorphine clearly holds promise as a treatment agent for opioid addicts.

Following a month on buprenorphine, patients can be given low doses of the opioid antagonist naltrexone (1 mg) without precipitating withdrawal symptoms or increases in blood pressure and norepinephrine turnover, as reflected by plasma MHPG levels. When given to patients maintained on the pure agonist methadone, the same dose of naltrexone precipitated substantial withdrawal symptoms and increases in blood pressure and MHPG levels. Withdrawal can be precipitated in buprenorphine patients using high-dose IV naloxone (0.5 mg/kg), but this withdrawal syndrome is less intense than that produced by even low-dose naltrexone in methadone-maintained patients. More importantly, naltrexone maintenance can be rapidly initiated after the naloxone-precipitated withdrawal without precipitating further withdrawal symptoms. These findings suggest an attenuation of opioid physical dependence by the limited antagonist activity of buprenorphine, since these buprenorphine patients had been dependent on the opioid agonists methadone or heroin before starting buprenorphine. In several previous reports, this group and others have shown that opioiddependent patients can be switched from the pure agonists to buprenorphine with minimal withdrawal symptoms (Kosten and Kleber 1988; Jasinski et al. 1978, 1984) but systematic examination of the transition from buprenorphine to a pure antagonist has not been previously reported.

Two concepts seem important in explaining the authors' findings concerning antagonist challenge in the buprenorphine patients—the higher opioid receptor affinity of buprenorphine compared with commonly prescribed antagonists and antagonist resetting of receptor mechanisms from an opioid-dependent to an opioid-naive state.

Whereas naltrexone has a greater affinity for the p-receptor than does methadone or heroin, buprenorphine is an unusual partial agonist in apparently binding more tightly than naltrexone to these receptors (Neil 1984; Lewis 1985). This difference in affinity has been offered as an explanation for naloxone's inability to precipitate withdrawal in buprenorphine-maintained animals (Kosten et al. 1988; Lewis 1985). Thus, one reason low-dose naltrexone probably produced minimal withdrawal was the inability of this pure antagonist to displace buprenorphine, while the highdose naloxone worked by the law of mass action to occupy enough of the receptors long enough to precipitate withdrawal.

The capacity of opioid antagonists to actively reset receptor mechanisms, thereby decreasing physical dependence, also may contribute to the minimal withdrawal response exhibited by the naloxone-challenged patients when they were rapidly inducted onto naltrexone over a 36-hour period. Previous studies have shown that coadministration of opioid agonists with antagonists inhibited the development of physical dependency or accelerated recovery (Cochin and Mushlin 1976). Also, clinical studies with rapid donidine naltrexone detoxification found that giving the antagonist naltrexone to opioid-dependent patients can compress the abstinence syndrome into a relatively brief period (Chamey et al. 1982; Kleber et al. 1987; Vining et al. 1988). Antagonist exposure appears to actively reset relevant receptor mechanisms, not only attenuating the development of physical dependence, but also reversing receptor changes and receptor coupling to second messengers induced during physical dependence on opioids (Aceto et al. 1977; Bardo et al. 1983; Cochin and Mushlin 1976; Collier et al. 1983; Krystal et al. 1989; Rothman et al. 1986; Zukin and Tempel 1986). Buprenorphine may have induced some receptor resetting during the month of treatment. Clearly, some mild withdrawal was produced by buprenorphine over the first 1 or 2 weeks after the transition from the pure agonists, and less severe withdrawal, minimal MHPG elevation, and a relatively small blood pressure increase compared with that found in the methadone patients were precipitated by the high-dose naloxone.

Buprenorphine in this dosage range, however, has predominantly agonist activity, as suggested by neuroendocrine assessments (Rolande et al. 1983; Mendelson et al. 1982). Using cortisol, growth hormone, prolactin, and luteinizing hormone as markers, it has been concluded that the pattern

of hormonal response to acute and repeated dosing of buprenorphine is consistent with an agonist rather than antagonist profile (Rolande et al. 1983; Mendelson et al. 1982; Brown et al. 1978). This agonist profile is consistent with the easy transition from methadone to buprenorphine. Further work may explore the neuroendocrine profile of buprenorphine after a month of treatment, since previous studies have involved only several days of treatment. Perhaps with longer treatment, buprenorphine accumulates, resulting in more antagonist activity, as has been shown acutely in animals given much higher dosages of buprenorphine (Cowan et al. 1977; Lewis 1985). A definitive test of the antagonist hypothesis could best be obtained using an antagonist with a higher receptor affinity than buprenorphine, but such a drug is not available.

Clinically, previous studies have shown that buprenorphine withdrawal may be substantially less severe than withdrawal from pure agonists, such as methadone (Jasinski et al. 1984). Since a major problem with methadone maintenance treatment for opioid abuse has been the continuation of substantial withdrawal symptoms following attainment of a drug-free state, buprenorphine may offer a method for minimizing the withdrawal symptoms that follow detoxification from maintenance treatment (Cushman and Dole 1973; Kosten and Kleber 1988). Furthermore, patients may start naltrexone more readily after buprenorphine and thereby have a greater chance of remaining drug free (Kosten and Kleber 1984). The endogenous opioid system may indeed be set closer to normal baseline functioning when chronically exposed to the partial antagonist buprenorphine rather than to the pure agonist methadone. The rapid detoxification from buprenorphine with high-dose naloxone seems to offer an exciting possibility of stabilizing buprenorphine-treated patients on naltrexone within a day, and the low abuse of cocaine while they are on buprenorphine suggests that patients with combined addiction may have an ideal treatment available. Both treatment issues deserve more careful evaluation in future studies.

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ACKNOWLEDGMENT

Support was provided by National Institute on Drug Abuse grants DA-00112 (TRK) and DA-04060.

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Development of Buprenorphine for the Treatment of Opioid Dependence

Rolley E. Johnson and Paul J. Fudala

INTRODUCTION

The only available morphine-like agent currently approved by the Food and Drug Administration for the treatment of opioid dependence is methadone. Methadone is given orally to substitute for illicit opioids, thereby preventing symptoms of withdrawal and helping individuals to maintain abstinence from illicit drugs (Greenstein et al. 1984; Higgins et al. 1986; U.S. Department of Health and Human Services 1988). Other drugs that have been extensively studied for the maintenance, detoxification, or abstinence treatment of opioid addicts include *l*-alpha-acetylmethadol (LAAM), clonidine, propoxyphene, and naltrexone.

The Addiction Research Center (ARC) has had an active research program for nearly 50 years studying these and other pharmacotherapies (U.S. Department of Health, Education, and Welfare 1978) some of which have demonstrated potential utility as treatment agents for opioid dependence. This research has included studies of agonists such as methadone (Isbell et al. 1948; Martin et al. 1973a; Nutt and Jasinski 1974; Wikler 1977a, 1977b), LAAM (Fraser and Isbell 1952) and propoxyphene (Jasinski et al. 1977); antagonists like nalorphine (Wikler et al. 1953; Fraser 1957; Martin and Gorodetzky 1965), naloxone (Jasinski et al. 1967) naltrexone (Martin et al. 1973b), and cyclazocine (Martin et al. 1965, 1966); and mixed agonists/antagonists, including propiram (Jasinski et al. 1971) butorphanol (Jasinski et al. 1975) pentazocine (Jasinski et al. 1970), nalbuphine (Jasinski and Mansky 1972), and buprenorphine (Jasinski et al. 1978). Since the original study of buprenorphine by Jasinski and colleagues (1978) additional studies have been conducted by investigators at ARC to characterize further the pharmacologic, pharmacodynamic, and pharmacokinetic properties of buprenorphine and to assess its utility in the treatment of opioid dependence. Phase I inpatient studies were conducted to evaluate different doses and routes of administration and the agonist and antagonist properties of buprenorphine; phase II studies were conducted to assess the utility of

buprenorphine in outpatient populations. Results from these earlier phase I and II studies are summarized in this chapter to provide a chronology of the development of buprenorphine and to provide the information that formed the basis for a dose-scheduling investigation-the major focus of this report.

EARLY PHASE I AND II STUDIES

Determination of Route of Administration

Jasinski and colleagues (1982) reported the results of single-dose studies comparing the oral (P.O.) and sublingual (SL) routes of administration to the subcutaneous (SC) route. They found the onset, time to peak, and duration of effect to be similar among the three routes of administration. For sublingually and subcutaneously administered buprenorphine, onset of action for physiologic and behavioral effects was evident within 0.5 to 1 hour, with peak effects for these measures occurring between 1 and 4 hours (figure 1).

Duration of these effects was similar for both SL and SC routes and may persist for 24 hours (Jasinski et al. 1978, 1989). Orally administered buprenorphine had one-fifth the potency (figure 2) and sublingually administered buprenorphine had two-thirds the potency of buprenorphine given subcutaneously. Given the low relative potency of oral buprenorphine and the desire not to use a parenteral dosage form in treatment, the SL route was determined to be the most appropriate for chronic administration.

Determination of the Antagonist Properties of Buprenorphine

Buprenorphine has been shown to precipitate an opioid-withdrawal syndrome in nonhuman primates (Aceto 1984). The use of buprenorphine as a detoxification or maintenance agent requires the substitution of buprenorphine for heroin, methadone, or other opioids. To determine the potential for buprenorphine to precipitate a withdrawal syndrome in opioid-dependent humans, the intensity of opioid-withdrawal signs and symptoms was measured following the administration of SL buprenorphine (0, 2, and 4 mg) and intramuscular (IM) naloxone (0.5 mg) under double-blind, double-dummy procedures to six subjects maintained on a mean methadone dose of 38 mg (Jasinski et al. 1983). The possibility of precipitating an opioid-withdrawal syndrome was increased by administering buprenorphine or naloxone 3 hours following the last methadone dose. Although only naloxone precipitated a significant withdrawal syndrome, there was a trend (which followed the onset and time course of buprenorphine effects) toward increased physiologic withdrawal signs as the dose of buprenorphine was increased (figure 3). These data suggested that initial doses of 2 mg, and probably

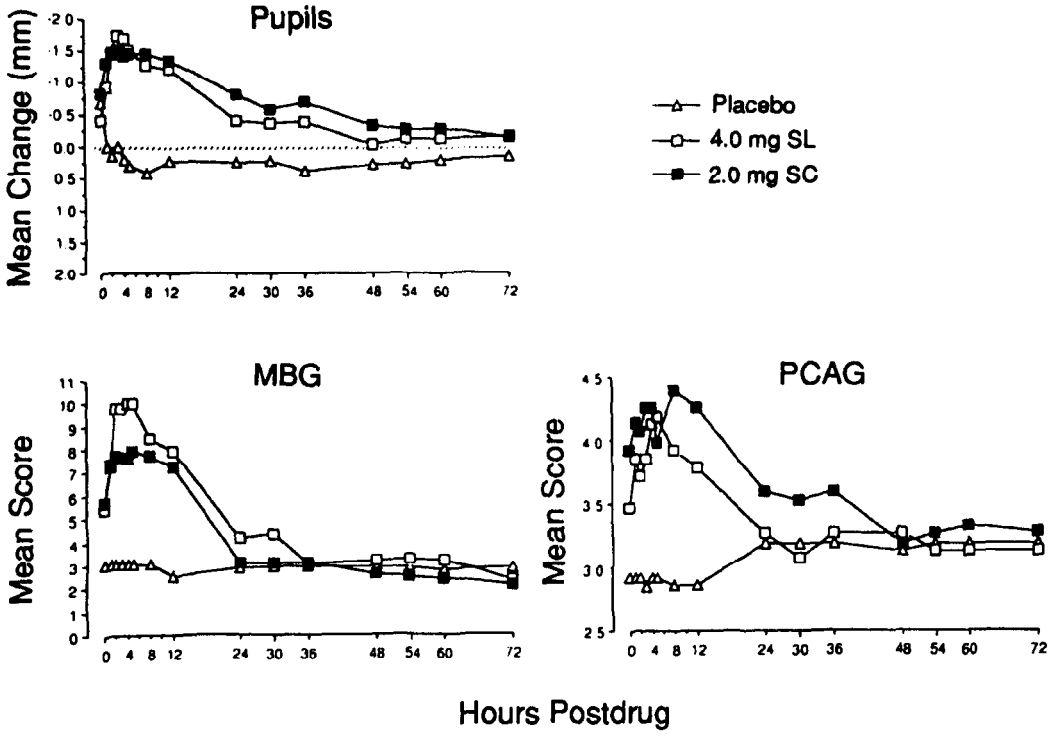

FIGURE 1. *Mean change from baseline (pupil diameter) and mean scores on the MBG and PCAG subscales of the ARC Inventory*

NOTE: Responses were measured over 72 hours following the administration of buprenorphine or placebo. Each point represents the mean value of 10 subjects.

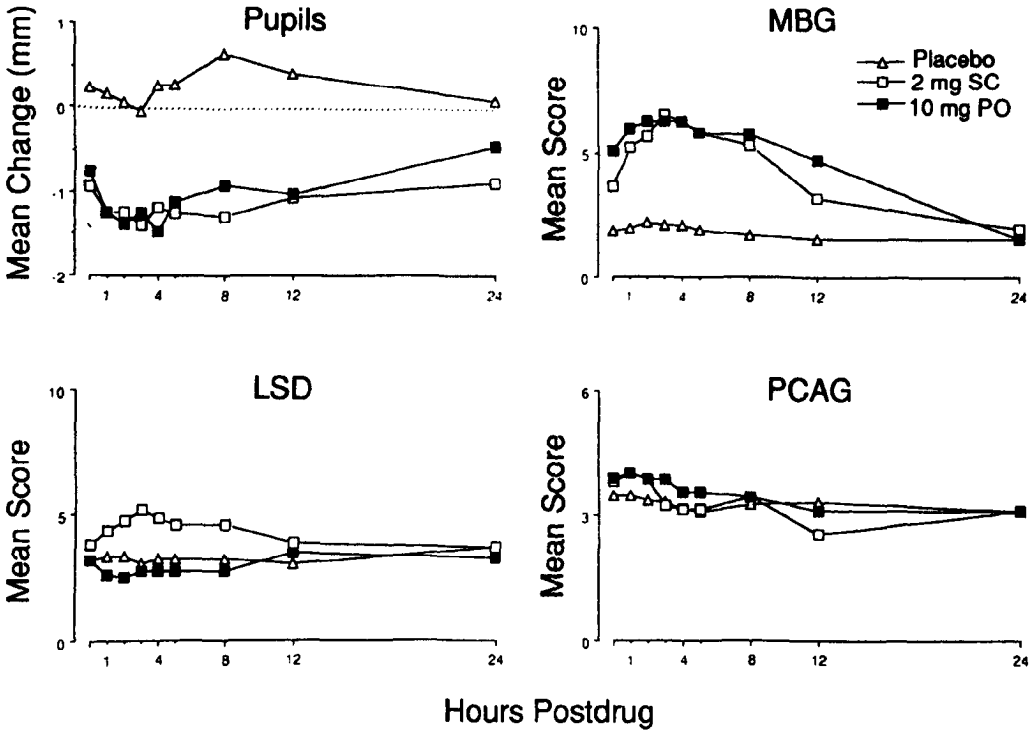

FIGURE 2. *Mean change from baseline (pupil diameter) and mean scores on the MBG, LSD, and PCAG subscales of the ARC Inventoty*

NOTE: Responses were measured over 24 hours following the administration of buprenorphine or placebo. Each point represents the mean value of 10 subjects.

SOURCE: D.R. Jasinski and R.E. Johnson, unpublished data

4 mg, of buprenorphine could be used without precipitating a withdrawal syndrome.

Determination of the Ability of Buprenorphine to Substitute for Heroin and Methadone

Following the study of buprenorphine-precipitated withdrawal, studies were initiated to substitute buprenorphine in morphine- and methadone-dependent individuals. Results of these studies indicated that 2 mg of subcutaneously administered buprenorphine produced no change in self-reported sickness during the transition from morphine (15 mg, 4 times daily), while the transition from methadone (54 mg daily) to buprenorphine was associated with a mild to moderate withdrawal syndrome of shorter duration than that seen following untreated withdrawal from methadone (Jasinski and Johnson, unpublished observations).

Determination of an Appropriate Dosage for Treatment

Bickel and colleagues (1988a) compared the effectiveness of buprenorphine (2 mg SL) to that of methadone (30 mg P.O.) in a 90-day outpatient detoxification study. In this study, IM hydromorphone injections (0 and 6 mg) were administered while subjects were maintained on the above doses of buprenorphine or methadone to assess each drug's blockade of hydromorphone-induced physiologic and subjective effects. Hydromorphone produced greater pupillary constriction and subject-reported "drug liking" (figure 4) in the buprenorphine group compared with the methadone group. Although previous reports had indicated that subcutaneously administered buprenorphine produced maximal agonist effects at a dose of 2 mg (Jasinski et al. 1982) data from this study indicated that a higher buprenorphine dose (providing more opioid blockade) would be required if buprenorphine were to be an effective treatment agent. These results led to another study to assess further the opioid-blocking properties of buprenorphine. This study was conducted with five subjects who were maintained on ascending doses of 2, 4, 8, and 16 mg of sublingually administered buprenorphine for 2 weeks (Bickel et al. 1988b). Hydromorphone doses of 0, 6, and 12 mg (6 and 18 mg cumulatively) were administered intramuscularly within 24 hours of the last dose of buprenorphine. Results from this study indicated that an SL buprenorphine dose of 8 mg was required to provide sufficient blockade of subject-reported "high" (figure 5), "drug effect," and responses on an opioid-agonist adjective-rating scale following hydromorphone administration.

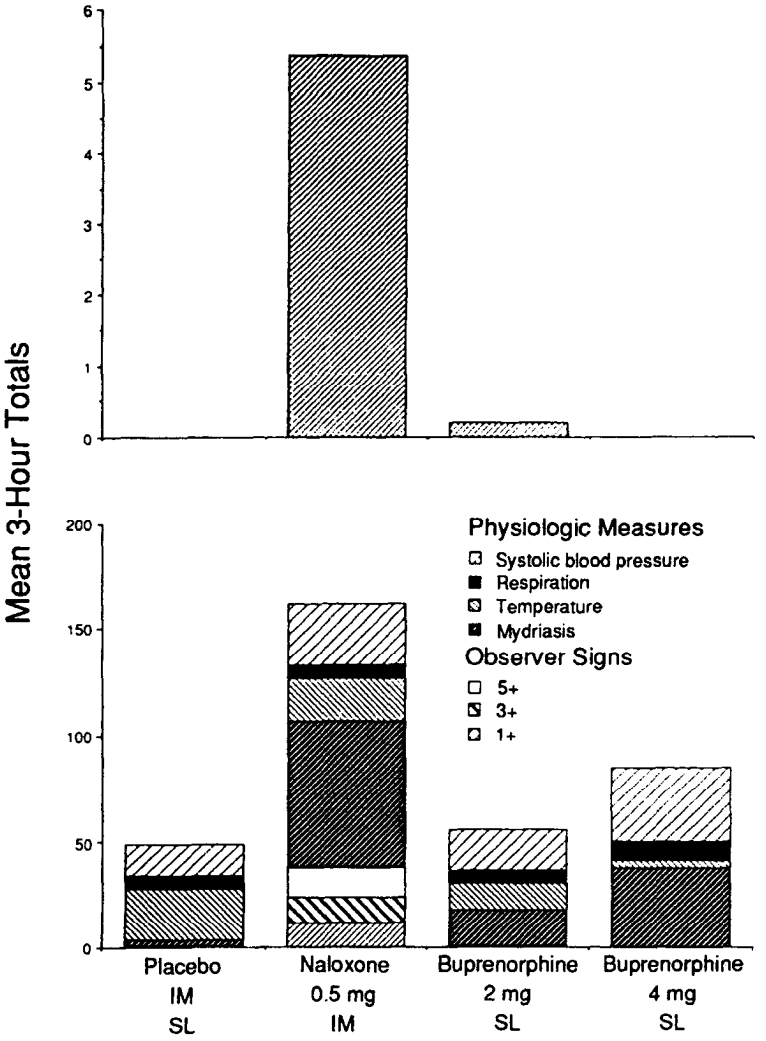

FIGURE 3. *Buprenorphine vs. naloxone-mean 3-hour totals (from six subjects) for Himmelsbach scores (bottom) and subject-reported sickness (top)*

NOTE: For Himmelsbach scores, the histograms show the relative contribution of each component to the total score.

SOURCE: R.E. Johnson and D.R. Jasinski, unpublished data

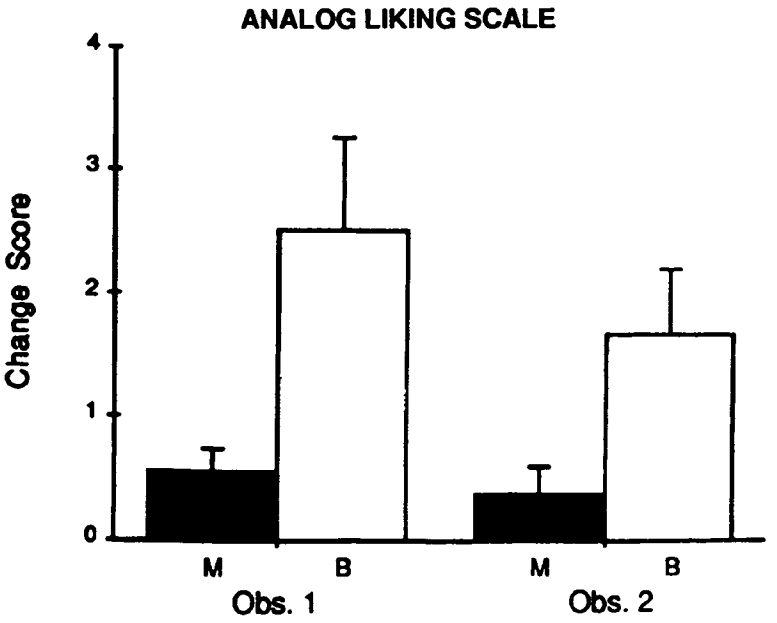

FIGURE 4. *Effects of a 6-mg hydromorphone challenge on subject-rated drug liking shown for subjects* treated *with 2 mg buprenorphine administered sublingually (n=15; unfilled bars) and 30 mg methadone administered orally (n=16; filled bars)*

NOTE: Data are from two observations made after hydromorphone administration and show change from predrug baseline values. Brackets indicate SE.

SOURCE: Bickel, W.K.; Stitzer, M.L.; Bigelow, G.E.; Liebson, I.A.; Jasinski, D.R.; and Johnson, R.E. A clinical trial with buprenorphine: Comparison with methadone in the detoxification of heroin addicts. *Clin Pharmacol Ther* 43:72-78, 1988a. Copyright 1988 by C.V. Mosby Company (St. Louis).

Determination of an Appropriate Dose Schedule for Treatment

Introduction. With the knowledge that buprenorphine was effective sublingually and could substitute for heroin in heroin-dependent individuals and that an 8-mg dose was necessary to achieve adequate blockade of effects from other opioids, a multicomponent, interlaboratory inpatient study

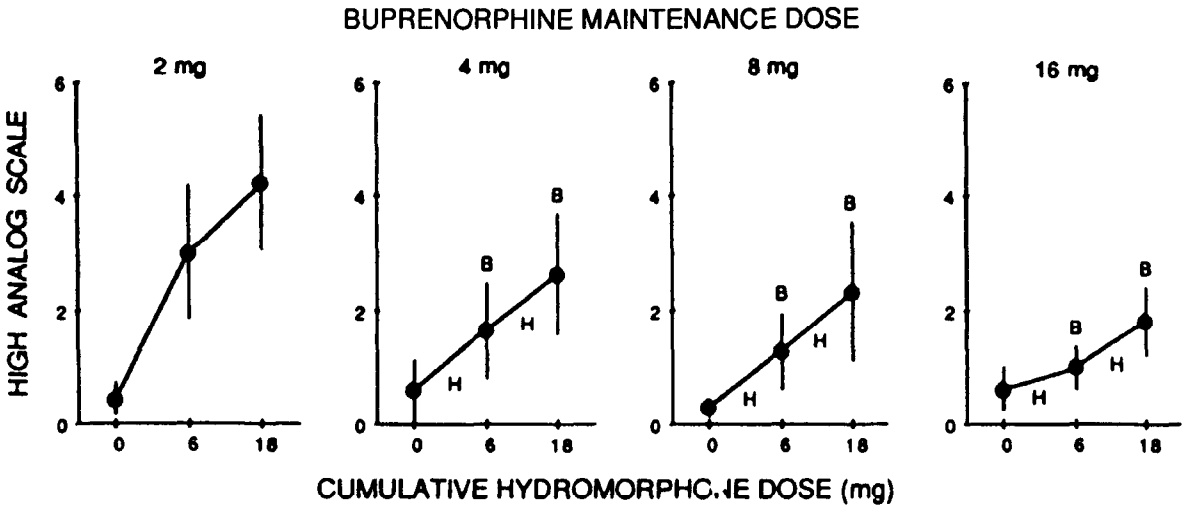

FIGURE 5. *Effects of cumulative hydromotphone doses on subject-rated high measured on an analog scale, with subjects chronically maintained on ascending doses of buprenorphine*

NOTE: The variability bars represent ± 1 SEM. B indicates challenge effects of a dose of hydromorphone that did differ significantly (planned comparisons) from effects of that dose at the 2-mg buprenorphine maintenance dose. H between two dose points indicates challenge doses not significantly different (planned comparisons) from each other.

SOURCE: Bickel, W.K.; Stitzer, M.L.; Bigelow, G.E.; Liebson, I.A.; Jasinski, D.R.; and Johnson, R.E. Buprenorphine: Dose-related blockade of opioid challenge effects in opioid dependent humans. *J Pharmacol Exp Ther* 247:47-53, 1999b. Copyright 1998 by American Society for Pharmacology and Experimental Therapeutics (Davis).

was undertaken to (1) assess a rapid dose-induction procedure for the use of buprenorphine in heroin-dependent individuals; (2) compare the efficacy of once-daily to every-other-day dosing of buprenorphine; (3) characterize the withdrawal syndrome associated with the abrupt termination of buprenorphine; (4) evaluate the ability of buprenorphine to block the subjective and physiologic effects of hydromorphone; and (5) evaluate the rate of relapse to illicit opioid use following the termination of buprenorphine. Dependent variables included physiologic and subject- and observer-reported behavioral measures, as well as pharmacokinetic, neuroendocrine, electroencephalographic, and medical safety parameters.

Methods. The study was conducted in male heroin addicts, ages 26 to 45 years, using a randomized, double-blind, parallel-group design. Inclusion criteria included (1) three consecutively collected urine samples positive for opioids, (2) a current self-reported period of heroin addiction of at least 4 months, (3) self-reported heroin use of $50 to $200 per day, (4) self-reported number of intravenous (IV) heroin injections of at least two per day, and (5) physical examination and self-reported history consistent with heroin addiction. Subjects with active cardiovascular or hepatic disease, those who tested positive for the human immunodeficiency virus antibody, or those presenting more than one urine sample positive for methadone were excluded.

Buprenorphine, in a 30-percent (v/v) aqueous ethanol solution, was administered sublingually in a 1-mL volume; buprenorphine placebo consisted of the vehicle solution only. Hydromorphone HCI and naloxone HCI doses were prepared in sterile saline for injection at concentrations of 0, 2, and 4 mg and 0, 3, 6, and 12 mg, respectively. Initially, doses were prepared in a volume of 2 mL. When it became evident that all doses could not be administered by the IV route, the injection volume was decreased to 1 mL to facilitate IM administration.

The study was conducted in three phases (figure 6). In phase 1 (days 1 through 18), all subjects received ascending buprenorphine doses of 2 ,4, and 8 mg over the first 3 days and were maintained on 8 mg daily for the next 15 days. In phase 2 (days 19 through 36), subjects in group 1 continued to receive buprenorphine daily, while subjects in group 2 received buprenorphine on even-numbered study days and placebo on odd-numbered study days. In phase 3 (days 37 through 56) all subjects received only buprenorphine placebo and were discharged from the research ward on day 57. Hydromorphone challenges were conducted on days 16 through 18 and 31 through 36. For challenges given in phase 2, hydromorphone doses were randomly administered to subjects in group 1 over the 6-day challenge period; however, for subjects in group 2, active hydromorphone doses were randomized

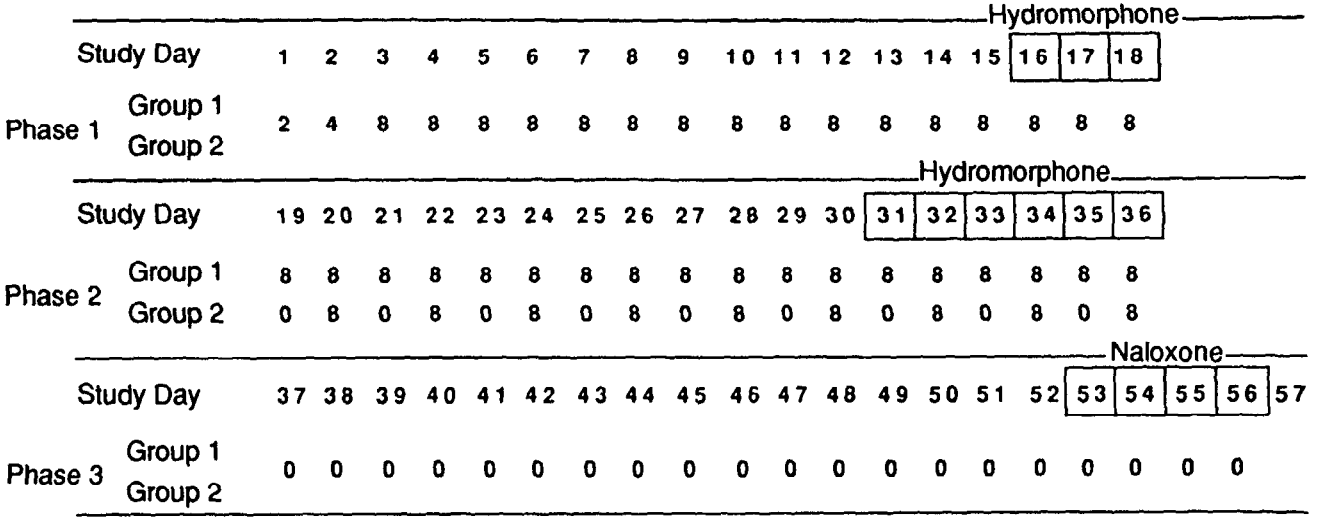

FIGURE 6. *Timeline for the study*

NOTE: The numbers below each study day indicate the dose of buprenorphine HCl (0, 2, 4, or 8 mg) that subjects in each group received on a particular day. Days on which subjects received hydromorphone or naloxone challenges are also indicated.

SOURCE: P.J. Fudala and R.E. Johnson, unpublished data

to days when subjects received buprenorphine placebo. All naloxone challenges were randomly administered on days 53 through 56.

Subscales of the ARC Inventory, observer- and subject-reported drug-effect questionnaires, and a withdrawal-symptom questionnaire were used to rate signs and symptoms of acute and opioid withdrawal effects. Whereas physiologic and behavioral measures were assessed multiple times daily throughout the study, other parameters (e.g., neuroendocrine or electroencephalographic assessments) were assessed at appropriate times that would not violate the blind of the study.

Results.

Dose Induction. Subject-reported "overall sickness" and “level of withdrawal” were significantly greater on day 1 than on any other day (Fudala et al. 1988) (figure 7). No differences were observed among the other 3 days, and no differences between days were noted for observer-reported "subject withdrawing."

Subject-reported “drug liking,” “drug effects,” and “overall well-being" and MBG (euphoria) scale scores increased following buprenorphine administration, whereas "overall sickness" and LSD (dysphoria) and PCAG (apathetic sedation) scats scores decreased. Observer-reported "subject’s liking for drug," "signs of drug effect," and “how subject feels" also increased after buprenorphine administration and followed the same time course as those of comparable subject-reported measures. The peak increase or decrease for each measure occurred between 2 and 4 hours following buprenorphine administration. The responses for each measure at 23 hours after buprenorphine administration were approximately equal to those observed one-half hour following drug administration. Eleven of sixteen behavioral measures normally sensitive to opioid withdrawal effects decreased following buprenorphine administration, but none was significantly different with respect to changes between days.

Increased supine pulse rate, which could be an opioid-withdrawal effect, was greatest on day 4. Pupillary constriction was greatest on days 3 and 4, when the highest doses of buprenorphine were given, which is consistent with a morphinelike effect. Urinary excretion data indicated that all subjects were below the 300-ng/mL positive cutoff level for opioid equivalents by day 4. Results from this phase of the study indicated that heroin-dependent individuals coult be rapidly inducted onto buprenorphine without precipitating an opioid-withdrawal syndrome.

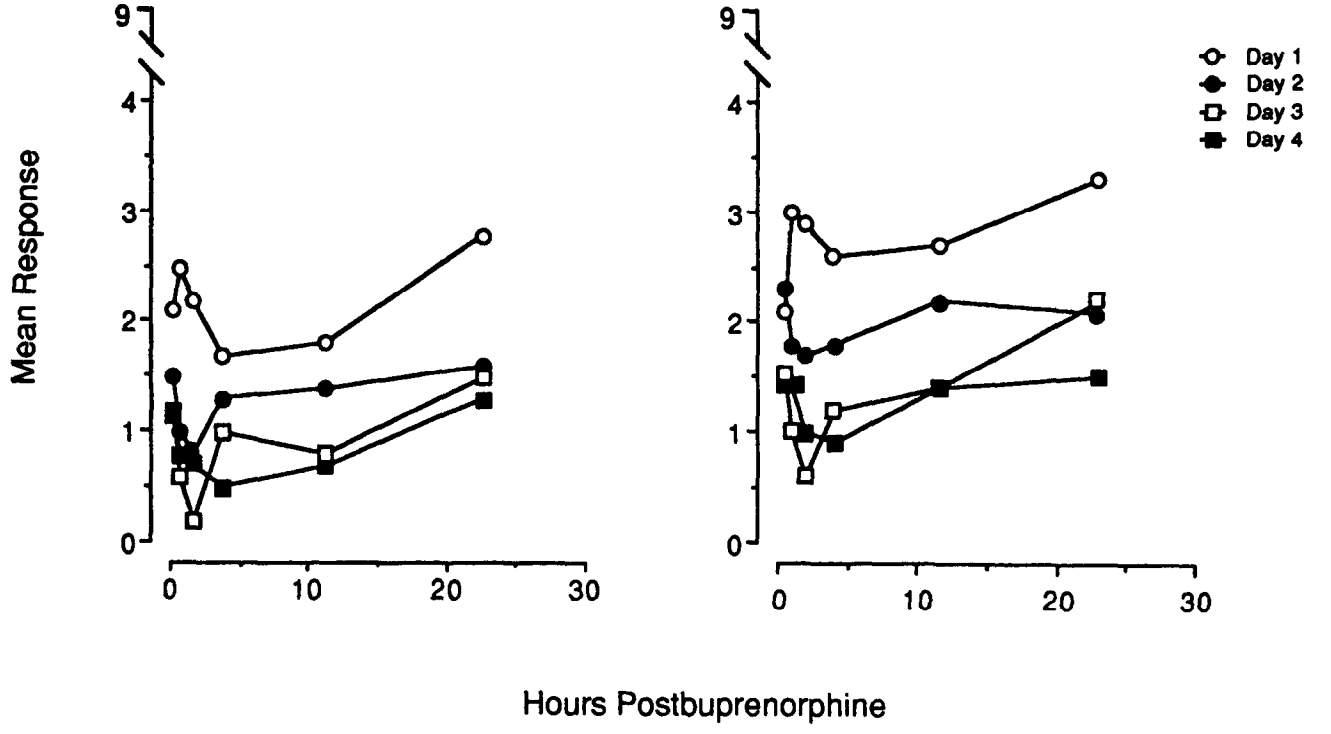

FIGURE 7. *Mean responses for subject-reported "overall sickness" (left.) and "level of withdrawal" (right)*

NOTE: Responses were measured *over 23* hours following buprenorphine administration on each of the first 4 study days. Each point represents the mean value of 11 to 19 subjects.

Everyday vs. Every-Other-Day Dosing. The same subscales and questionnaires from the dose-induction phase were used to measure signs and symptoms of acute drug and opioid withdrawal effects. On the days that subjects in group 2 received no drug, LSD scale scores and reports of symptoms, including muscle cramps and backaches, painful joints and weak knees, and runny noses, all increased. On the days that both groups received buprenorphine, subjects in group 2 reported greater "drug liking," "drug effect," and "good effect" compared with group 1 (table 1).

TABLE 1. *Multiple contrasts performed on measures that showed a significant group by day interaction during the everyday- vs. every-other-day-dosing comparison phase of the study*

	Group 1 Even Days vs. Odd Days		Odd Days Group 1 vs. Group 2	
Pupils	NS		F=50	(2>1)
Self-Reports				
LSD	NS		F=39.2	(2>1)
Liking	NS		F=38	(2>1)
Drug effect	NS		F=19.3	(2>1)
Good effect	NS		F=22.4	(1>2)
Urge for opiate	NS		NS	
Overall discomfort	NS		F=43.6	(2>1)

	Group 2 Even Days vs. Odd Days		Even Days Group 1 vs. Group 2	
Pupils	F=66.4	(O>E)	NS	
Self-Reports				
LSD	F=21.6	(O>E)	NS	
Liking	F=95.9	(E>O)	F=13.6	(2>1)
Drug effect	F=62.7	(E>O)	F=12	(2>1)
Good effect	F=82.1	(E>O)	F=13.8	(2>1)
Urge for opiate	F=27	(O>E)	F=15.9	(1>2)
Overall discomfort	F=38.3	(O>E)	NS	

NOTE: All significant $F(1,187)>3.84$

SOURCE: P.J. Fudala and R.E. Johnson, unpublished data

Subject-reported responses on the withdrawal symptom questionnaire remained constant between days 19 and 30 and baseline (days 14 and 15) for group 2 and decreased from baseline for group 1. Observer-reported withdrawal was generally higher for group 2 and lower for group 1 during this period. There were no differences between groups across days for any physiologic measure except pupil diameter. Pupillary constriction followed buprenorphine administration; however, on nondrug days, the pupils of subjects in group 2 dilated.

Data from several behavioral and physiologic measures normally sensitive to opioid withdrawal symptomatology revealed differences between the two groups. The changes observed were not clinically significant, as evidenced by small changes reported by both subjects and observers and by the fact that no subject discontinued his participation during this phase of the study. Results of this phase of the study indicated that buprenorphine dosed on an every-other-day schedule was associated with reports of mild opioid withdrawal symptoms.

Abrupt Withdrawal of Buprenorphine. Data from seven subjects who did not receive therapeutic intervention for withdrawal signs and symptoms indicated that peak withdrawal effects occurred between 3 and 5 days following the last buprenorphine dose, with group 1 reporting greater effects than group 2. Peak responses of subjects in group 2 occurred earlier than in group 1 for subject-reported “level of withdrawal” and “overall discomfort” and for observer-rated “subject withdrawing” (figure 8). The withdrawal-symptom questionnaire did not indicate significant differences between the two groups, and peak scores occurred 5 days following the last buprenorphine dose. Changes in responses generally returned to baseline within 10 days; however, subjects in group 1 experienced greater decreases in self-reported sleep than did those in group 2, and sleep did not return to baseline within 13 days. Thus, chronically administered buprenorphine, when abruptly terminated, produced mild-to-moderate opioid-withdrawal symptoms that required little or no therapeutic intervention.

Hydromorphone and Naloxone Challenges. Subjects completed self-report questionnaires at 0.5, 1, 2, and 4 hours after hydromorphone and naloxone administration. Observer-reported questionnaires were completed at these same times and at 1.5 hours post-challenge drug. Physiologic measures were assessed at 0.5 hours predrug and at 0.5, 1, 1.5, 2, and 4 hours postdrug.

In the first hydromorphone challenge, there were no significant treatment effects for any subject-reported or physiologic measure. There were significant effects for observer-reported “drug effect,” “high,” and “drug liking.” In the second hydromorphone challenge, there were significant treatment effects for

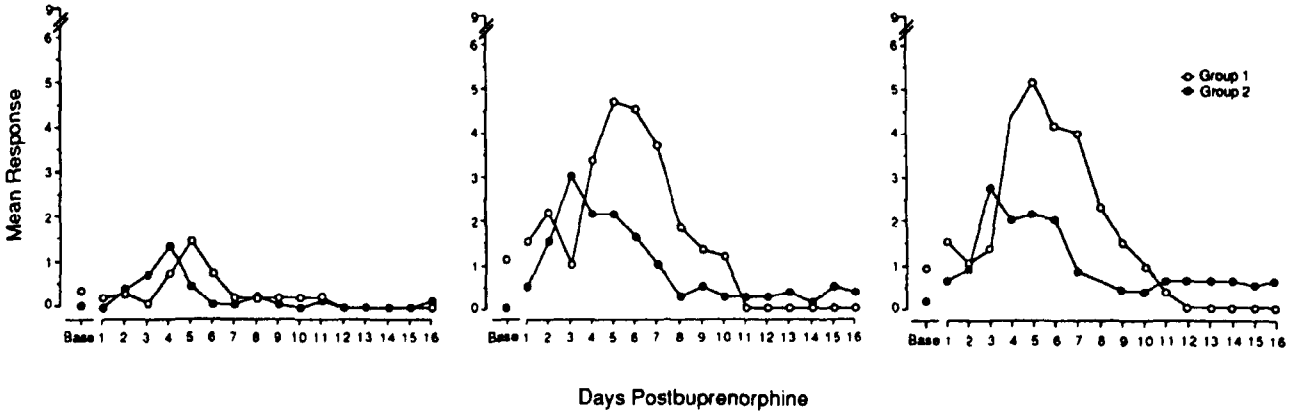

FIGURE 8. *Mean responses for observer-reported "subject withdrawing" (left) and subject-reported "level of withdrawal" (middle) and "overall discomfort" (right)*

NOTE: Responses were measured for 16 days following the last dose of buprenorphine (given on study day 36). Only data from subjects who received no therapeutic intervention for withdrawal signs and symptoms are included.

SOURCE: R.E. Johnson and P.J. Fudala, unpublished data

subject-reported "overall well-being," for observer-reported "how subject feels," and for subject- and observer-reported measures of "drug effect," "high," and "drug liking." Scores on the LSD scale were lower following hydromorphone than after placebo administration. In this challenge, hydromorphone produced greater pupillary constriction in group 2 than in group 1; no change in any other physiologic parameter was noted. In the naloxone challenge, no significant effects were observed for any of the measures assessed.

The challenge doses of hydromorphone and naloxone were originally planned to be administered through an IV catheter that was also used for metabolic and neuroendocrine portions of this study. Due to the subject population's abuse of their veins, however, the veins of only six subjects were suitable for catheter insertion. Two of these subjects completed all three challenges by the IV route. Four and three subjects completed the first and second hydromorphone challenges, respectively, by the IV route. Statistical analyses were not performed on their data. For subjects in group 2 who were administered hydromotphone intravenously in the second challenge, however, clinically significant effects were observed on measures of subject-reported "drug liking," MBG scale scores, and pupillary constriction. This trend was not observed in similarly treated subjects in group 1 or in subjects in either group who were given hydromorphone intramuscularly in either challenge.

Results from the second hydromorphone (IM) challenge could be interpreted to mean that there were no differences between everyday and every-other-day dosing of buprenorphine or that even once-daily dosing of buprenorphine did not provide sufficient blockade of the effects of hydromorphone at the doses tested. The magnitude of these effects was small, however, suggesting limited clinical significance.

Since IV administration is the preferred route of illicit opioid abusers, increases in subjective measures of "liking" and MBG scale scores in subjects who received IV hydromorphone along with the withdrawal symptomatology observed in group 2 during every-other-day dosing suggest that buprenorphine at the dosage tested should be administered no less often than once daily. Results of the naloxone challenge tests indicated that no physical dependence was evident 17 days after cessation of chronic buprenorphine administration.

Postdischarge Followup. Subjects were followed for 4 weeks after discharge from the research ward. They returned twice weekly, with a minimal interval of 1 day between visits, to provide urine samples and receive aftercare (e.g., referrals for abstinence counseling and vocational training). The urine samples of only 2 of 15 subjects were negative for opioids or other drugs of abuse. One of these subjects, however, was incarcerated after the second visit.

Pharmacokinetic, Neuroendocrine, Electroencephalographic, and Medical Safety Parameters. Preliminary data from the pharmacokinetic portion of the study indicated that during the dose-induction phase, buprenorphine equivalents in the urine increased, whereas opioid equivalents decreased. Data from two subjects (figure 9) showed plasma levels ranging from approximately 6 to 7 ng/mL when buprenorphine was dosed once daily. Plasma buprenorphine levels from the subjects given the drug every other day appeared to be about half of those observed during daily dosing. Following abrupt termination of buprenorphine, plasma levels decreased below the 1-ng/mL sensitivity level of the assay within 3 days.

Data from four subjects indicated that plasma testosterone levels increased compared with controls following the withdrawal of buprenorphine (figure 10). No changes were observed in levels of cortisol, prolactin, luteinizing hormone, thyroid-stimulating hormone, or growth hormone for these subjects.

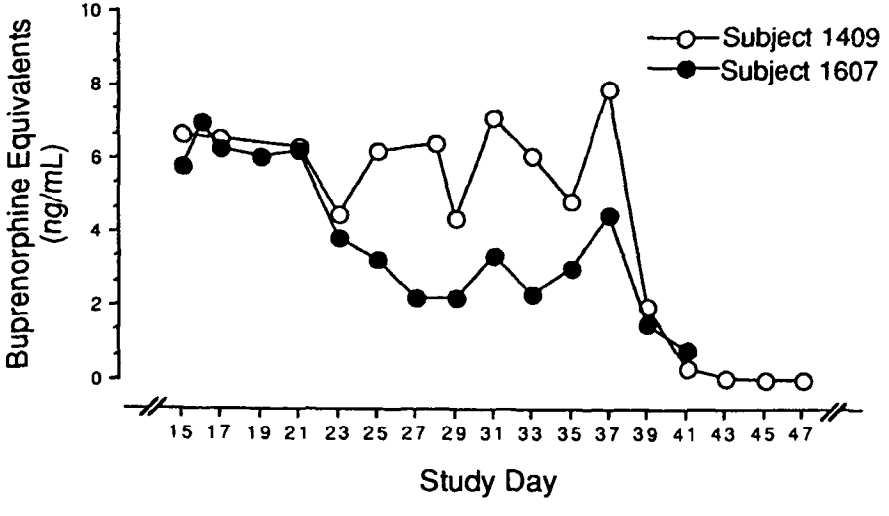

FIGURE 9. *Plasma levels of buprenorphine equivalents from two subjects who received buprenorphine every day (○) or every other day (●) between study days 19 and 36*

NOTE: Both subjects received buprenorphine daily prior to study day 19 and placebo after study day 36.

SOURCE: E.J. Cone, P.J. Fudala, and R.E. Johnson, unpublished data

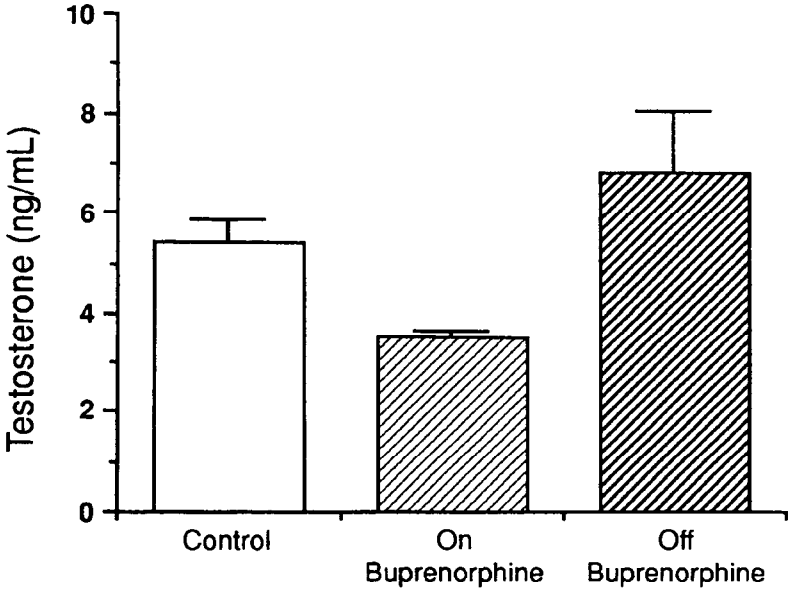

FIGURE 10. *Mean plasma testosterone levels from four subjects while they were receiving buprenorphine (study days 18 and 19) or after drug administration was discontinued (study day 50)*

NOTE: Controls (n=25) were nontreated individuals with no history of opiate abuse. Testosterone levels were measured from 50 mL of unextracted plasma by radioimmunoassay (ICN Biomedical Inc., Carson, CA).

SOURCE: E.M. Dax, P.J. Fudala, J.H. Jaffee, and R.E. Johnson, unpublished data

Spontaneous electroencephalogram (EEG) recordings at four electrode sites were obtained from 16 subjects on days 15, 17, 20, 30, 34,37, 39, 44, 47, and 56. During the placebo-substitution phase of the experiment, an immediate decrease in alpha power and a delayed gradual increase in alpha frequency occurred at the posterior electrode. Changes in characteristics of EEG alpha rhythm are characteristic of opioid withdrawal and have been reported after the discontinuation of buprenorphine (Lukas et al. 1984). There were no significant EEG differences between the experimental groups in any phase of the study.

There were no differences between groups with respect to subject-reported side effects that could be considered “probable” or “possible.”[1] Probable side effects

included constipation and sedation; possible side effects induded headache, nausea and other gastrointestinal distress, and dizziness.

SUMMARY

Data from these studies indicate that buprenorphine is efficacious in treating opioid dependence. It was possible to induct heroin addicts rapidly onto buprenotphine without precipitating an opioid withdrawal syndrome.

A daily 8-mg SL dosage was sufficient to maintain individuals without producing reports of withdrawal symptoms. When buprenorphine was administered at the above dose every other day, however, mild withdrawal symptoms were reported, and responses to challenges with intravenously given hydromorphone appeared greater than when the challenges were given intramuscularly. From these results, the authors conclude that buprenorphine at this dose should be administered on a daily basis. These results are now being applied to a phase II outpatient clinical trial comparing buprenorphine with methadone.

NOTE

1. To classify a side effect as either probable *or* possible, it was necessary that the effect meet all of the criteria for a specific categorization as follows: Probable-(I) reasonable temporal sequence; (2) well-known response pattern; (3) confirmed by dechallenge; and (4) could not be explained by known characteristics of the subject's clinical state or other therapy administered to the subject. Possible-(I) reasonable temporal sequence; (2) known or suspected response pattern; and (3) could not be reasonably explained by known characteristics of the subject's clinical state or other therapy administered to the subject (Karch and Lasagna 1975).

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ACKNOWLEDGEMENTS

Drs. Edward Cone, Elizabeth Dax, Jack Henningfield, Ronald Herning, Jerome Jaffe, W. Robert Lange, and Wallace Pickworth and Mr. Frederick Snyder contributed to the design and analysis of the various component portions of the study assessing the determination of an appropriate dose schedule for the use of buprenorphine in the treatment of heroin-dependent individuals.

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ISBN 0-12-345678-9
50995>
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DHHS Publication No. (ADM) 92-1912
Alcohol, Drug Abuse, and Mental Health Administration
Printed 1992