Intravenous Buprenorphine Self-Administration by Detoxified Heroin Abusers

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ABSTRACT

Several sources indicate that intravenously administered buprenorphine may have significant abuse liability in humans. The present study evaluated the reinforcing effects of intravenously administered buprenorphine (0, 2, and 8 mg) in detoxified heroin-dependent participants during a 7.5-week inpatient study. Participants (n = 6) were detoxified from heroin over a 1.5-week period immediately after admission. Testing subsequently occurred in three 2-week blocks. During the first week of each 2-week block, the reinforcing effects of buprenorphine were evaluated. Participants first received a dose of buprenorphine and $20 and then were given either the opportunity to self-administer the dose or $20 during choice sessions. During the second week of each 2-week block, the direct effects of heroin were measured to evaluate potential long-lasting antagonist effects of buprenorphine. Progressive ratio break-point values were significantly higher after 2 and 8 mg of buprenorphine compared with placebo. Correspondingly, several positive subjective ratings increased after administration of active buprenorphine relative to placebo. Although there were few differences in peak effects produced by 2 versus 8 mg of buprenorphine, the higher buprenorphine dose generally produced longer-lasting effects. Heroin also produced dose-related increases in several subjective effects. Peak ratings produced by heroin were generally higher than peak ratings produced by buprenorphine. There was little evidence of residual antagonism produced by buprenorphine. These results demonstrate that buprenorphine served as a reinforcer under these conditions, and that it may have abuse liability in nonopioid-dependent individuals who abuse heroin.

Buprenorphine, a κ-opioid receptor antagonist and partial μ-opioid receptor agonist, is currently approved by the Food and Drug Administration for treating pain. It is also under investigation as a maintenance medication for the treatment of opioid dependence, for which it has demonstrated effectiveness (for review, see Bickel and Amass, 1995). Studies have shown that maintenance on approximately 8 mg of sublingual liquid buprenorphine is as effective as 50 to 60 mg of oral methadone in reducing illicit opioid use (Johnson et al., 1992; Strain et al., 1994; however, see Ling et al., 1996). One purported advantage of buprenorphine compared with methadone is that the abuse liability of buprenorphine is thought to be lower. However, several preclinical studies have demonstrated that buprenorphine is self-administered above placebo levels in both drug-experienced and -naive nonhuman primates (for review, see Negus and Woods, 1995), and some studies demonstrated that the magnitude of buprenorphine self-administration was similar to that of full μ-agonists. For example, the maximal rates of responding maintained by buprenorphine and the full μ-agonists alfentanil and heroin were equivalent in rhesus monkeys self-administering these drugs intravenously (Winger et al., 1992; but see Winger and Woods, 2001). Another study showed that buprenorphine was less reinforcing than heroin, but equivalent to methadone (Mello et al., 1988). Thus, buprenorphine is self-administered by laboratory animals and, under some conditions, is self-administered at rates comparable to full μ-agonists.

In humans, only two studies have examined the reinforcing effects of buprenorphine. In one study, participants maintained on 8 or 16 mg/70 kg of sublingual buprenorphine in an outpatient treatment setting were given the opportunity to choose between sublingual buprenorphine and money (Petry and Bickel, 1999). When the alternative money value was low, buprenorphine was almost exclusively self-administered, but when the alternative money value increased, buprenorphine self-administration decreased. These results demonstrate that buprenorphine self-administration is malleable and that context plays an important role in drug self-administration. In another study, the reinforcing effects of intravenously administered placebo, buprenorphine (4 and

ABBREVIATIONS: SOWS, subjective opioid withdrawal scale; DEQ, drug effects questionnaire; VAS, visual analog scale; HR, heart rate; SP, systolic pressure; DP, diastolic pressure; DSST, digit symbol substitution task; DAT, divided attention task.
the study protocol, one left because he became bored with the study
tolerate the detoxification, two left for personal reasons unrelated to
regarding the time course of buprenorphine
Although it was not possible to make definitive conclusions
fects of opioid agonists. Therefore, in the present study, her-
demonstrated that after its agonist effects dissipate, bu-
sublingual tablets that will be available for clinical use and,
sublingual) in an outpatient treatment setting (Amass et al.,
2000). When given the opportunity to choose between in-
creasing amounts of money and drug, participants almost
exclusively chose money, suggesting a low abuse liability of
buprenorphine in abstinent buprenorphine/naloxone-main-
tained individuals. However, five of the seven individuals
expressed a desire to completely avoid drugs and, in fact,
would have been excluded from the study if they were not abstinent from all illicit drugs. Therefore, the ability to gen-
eralize these results is limited. Another important variable
that almost certainly influenced the reinforcing effects of
buprenorphine in the above studies was the fact that partic-
ipants were maintained on buprenorphine and were, there-
fore, dependent. Winger and Woods (2001) demonstrated
that buprenorphine was self-administered by nondependent
rhesus monkeys, but during morphine maintenance, a wide
range of buprenorphine doses did not maintain response
rates above those maintained by saline. These investigators
suggested that tolerance was probably responsible for the
failure of buprenorphine to maintain response in monkeys
who were given morphine chronically.
The present study was designed to assess the reinforcing
effects of intravenous buprenorphine in detoxified heroin
abusers who were not seeking treatment for their drug use.
Subjective, performance, and physiological effects were also
assessed both before and repeatedly after buprenorphine ad-
ministration. Doses of 2 and 8 mg of buprenorphine were
selected for study because these are the dosage forms of the
sublingual tablets that will be available for clinical use and,
therefore, are the doses likely to be abused. The primary
hypothesis in this study was that progressive ratio break
points would be higher following active buprenorphine, rela-
tive to placebo. Secondary hypotheses were that buprenor-
phine would increase subjective ratings, impair performance,
and decrease pupil diameter. In addition to assessing the
agonist effects of buprenorphine, its potential antagonist ef-
effects also were assessed in the present study. Previous stud-
ies in both nonhuman primates (Walker et al., 1995; Kishi-
oka et al., 2000) and humans (Schuh et al., 1999)
demonstrated that after its agonist effects dissipate, bu-
phrenorphine produces a long-lasting antagonism of the ef-
effects of opioid agonists. Therefore, in the present study, her-
oin dose-response functions were generated 3 and 5 days
after buprenorphine was available for self-administration.
Although it was not possible to make definitive conclusions
regarding the time course of buprenorphine's antagonist ef-
effects because differing amounts of buprenorphine were self-
administered across participants, the data provide approxi-
mate indications of the duration of antagonism produced by
buprenorphine.

Materials and Methods

Participants. Fourteen heroin-dependent individuals, who were
not seeking treatment for their drug use, began the 7.5-week proto-
col. Eight participants did not complete the study: two were dis-
charged because of noncompliance with unit policies, two could not
tolerate the detoxification, two left for personal reasons unrelated to
the study protocol, one left because he became bored with the study
procedures, and one was discharged to law enforcement officials for
an outstanding felony warrant. One of the participants who could not
tolerate the detoxification became delirious and agitated after receiv-
ing his first dose of 8 mg of sublingual buprenorphine. He subse-
quently aspirated fluids and developed pneumonia. He was treated
accordingly, and then discharged from the hospital. Six men (five
non-Hispanic Caucasian and one Hispanic) aged 22 to 36 years
(mean: 31.2) completed the study. Volunteers reported using heroin
for an average of 7.8 years (range: 3 to 20 years). All participants
used heroin by the intravenous route, were currently dependent on it
as verified by a naloxone challenge test before admission, and re-
ported spending an average of $69 per day on heroin (range: $20 to
$100). All six participants smoked tobacco cigarettes (20 to 30 ciga-
rettes per day), four participants used cocaine (two times per week or
less), three participants used alcohol (once per week), two partici-
pants used marijuana (three times per week or less), and one partici-
part used sedatives (twice per month).

After an initial telephone interview, eligible participants received
additional screening at the laboratory, which included completing
detailed questionnaires on drug use, general health, and medical
history, and a medical and psychological evaluation. Participants
were told that they would receive opioids during the study and that
different doses would be tested. An electrocardiogram and Mantoux
test or chest X-ray were also performed. Routine laboratory analyses
included a hematology screen, blood chemistry panel, liver function
tests, thyroid function tests, syphilis serology, and urinalysis. Urine
drug toxicologies (opioids, cocaine, benzodiazepines, cannabinoids,
and amphetamines) were also performed using a radiative energy
attenuation and fluorescence polarization immunoassay system
(ADX System, Abbott Laboratories, Abbott Park, IL).

Participants were excluded from the study if they were seeking
drug treatment, were dependent on alcohol or illicit drugs other than
opioids, or had a major Axis I psychiatric diagnosis other than heroin
dependence. Those who had recent histories of violence or who were
on parole/probation were excluded from the study. Although both
men and women were screened for the study, none of the women met
the eligibility requirements. Participants were required to be phy-
siologically healthy, fully able to perform all study procedures, and
dependent on heroin, as verified by a naloxone challenge test.

Before admission, participants completed a training session, dur-
ing which the study procedures were explained to them in detail.
Volunteers were paid $25 per inpatient day and an additional $25
per day bonus if they completed the study. In addition, they could
receive an additional $40 per day during some of the experimental
sessions. Participants signed consent forms describing the aims of
the study and the potential risks and benefits of participation. Par-
ticipants were offered free HIV testing and drug and risk reduction
education and were offered referrals for treatment. This study was
approved by the Institutional Review Board of the New York State
Psychiatric Institute.

Apparatus. During experimental sessions, participants were
seated in a room equipped with Macintosh computers. All computer
activities, vital signs, and behaviors were continuously monitored by
the experimenters in an adjacent control room via a continuous
on-line computer network, one-way mirror, and vital signs monitors.
Cardiovascular function was measured using a Sentry II Vital Signs
Monitor (NBS Medical, Costa Mesa, CA); arterial oxygen saturation
was measured using a model 400 pulse oximeter (Palco Laboratories,
Santa Cruz, CA). Communication between the staff and participants
was kept to a minimum during experimental sessions.

Detoxification Procedures. Participants were admitted into
the hospital and detoxified during approximately the first 9 days of
their admission. Buprenorphine (8-mg sublingual tablet; National
Institute on Drug Abuse, Rockville, MD) was administered during
the first 2 days after admission. Clonidine HCl (0.2 mg p.o., q. 6 h;
Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT), ketoro-
lac tromethamine (190 mg i.m., q. 6 h; Roche Laboratories, Nutley,
NJ), prochlorperazine (10 mg p.o. or i.m., q. 8 h; SmithKline

8 mg), buprenorphine/naloxone combination (4:1 and 8:2 mg),
and hydromorphone (9 and 18 mg) were evaluated in seven
buprenorphine/naloxone-maintained individuals (8:2 mg,
sublingual) in an outpatient treatment setting (Amass et al.,
2000).
Beecham Consumer Healthcare, Pittsburgh, PA), and clonazepam (2 mg p.o., q. 8 h; Roche Laboratories Inc., Nutley, NJ) were available, as needed. All of these medications were discontinued approximately 36 h before the first experimental session. Ketorolac tromethamine was only available for the first 5 days after admission.

**General Procedures.** After detoxification, the reinforcing effects of intravenous buprenorphine (i.v.; 0, 2, and 8 mg) were evaluated during study weeks 1, 3, and 5 (Table 1). Buprenorphine doses were administered in nonsystematic order both within and between participants. On Mondays, a sample dose of buprenorphine and $20 was administered, and the subjective, performance, and physiological effects of buprenorphine were examined both before and repeatedly after buprenorphine administration. On Tuesday (24 h) and Wednesday (48 h), the time course of buprenorphine’s agonist effects was evaluated, but no drug was administered. On Thursday and Friday, participants completed two choice sessions per day, for a total of four choice opportunities. They could work to receive all, or part of the sampled buprenorphine dose or $20. The total amount of buprenorphine and/or money chosen during the self-administration task was given i.v. as a bolus dose at the end of the task. Within each choice day, an interdose interval of 5 h was used for buprenorphine administration. This interdose interval was used because it mimics the typical pattern of heroin use reported by heroin-dependent individuals.

During study weeks 2, 4, and 6, the subjective, performance, and physiological effects of heroin (i.v., 0, 10, and 20 mg) were evaluated to assess possible antagonist effects of buprenorphine. On Monday (3 days) and Wednesday (5 days) after buprenorphine self-administration, heroin doses were administered in a cumulative fashion (0 mg followed by 10 mg followed by 20 mg), using a 45-min interdose interval. The reinforcing effects of heroin were not assessed during these sessions. Sessions on Monday and Wednesday were identical; no sessions were conducted on Tuesday, Thursday, and Friday during study weeks 2, 4, and 6.

**Experimental Sessions.** During all sessions, participants completed computerized tasks and subjective-effects questionnaires. Heart rate and blood pressure were measured every 5 min, and blood oxygen saturation was monitored continuously with a pulse oximeter and recorded every minute during experimental sessions. Pupil photographs were taken repeatedly during the sessions. Participants were not allowed to smoke tobacco cigarettes during experimental sessions.

**Sample Session.** Physiological, subjective, and performance effects were measured both before and repeatedly after drug administration (see descriptions below). Following baseline measures, buprenorphine and $20 were administered simultaneously at time 0, assuming vital signs were within safe limits (SpO2 > 93%). A photograph was taken of the right pupil before and 4, 10, 40, 60, 90, 120, and 180 min after drug administration. The reinforcing effects of heroin were not assessed during these sessions. Sessions on Monday and Wednesday were identical; no sessions were conducted on Tuesday, Thursday, and Friday during study weeks 2, 4, and 6.

**Choice Sessions.** Choice sessions were similar in design to the sample session, except that participants completed a self-administration task (see below) after the baseline assessments. Participants were instructed to choose between $20 and the dose of buprenorphine that they received during the sample session. A pupil photograph was taken before buprenorphine administration. The subjective-effects battery (see description below) was administered before and 4 and 40 min after drug administration. The performance battery was completed before and 10 min after drug administration. The SOWS was completed before drug administration. The DEQ was completed before and 10 min after drug administration. Choice sessions were otherwise identical to the sample session.

**Heroin Cumulative Dosing Sessions.** Physiological, subjective, and performance effects were measured both before and after each dose of heroin. After baseline assessments, placebo, 10 mg of heroin, and 20 mg of heroin was administered intravenously using a 45-min interdose interval. A pupil photograph was taken before and 10 min after each dose of heroin. The subjective-effects battery was administered at baseline and 4 and 40 min after each dose of heroin. The performance battery was administered at baseline and 10 min after each dose of heroin. The SOWS was administered at baseline, and the DEQ was administered 10 min after each heroin dose.

**Self-Administration Task.** Participants were told that they could work for all or part of the sampled dose of buprenorphine or the sampled money amount ($20) by choosing the drug or money option each time a choice was available. Responses consisted of finger presses on a computer mouse. Standardized instructions were read to each participant explaining the self-administration task. Buprenorphine and money were available under independent progressive ratio schedules, and participants were given 10 opportunities to choose between the two options. Ten percent of that day’s buprenorphine dose or money value was available at each choice opportunity. Thus, if the dose of buprenorphine for that day was 8 mg, at each opportunity participants could respond for 0.8 mg (10% of 8 mg) or $2 (10% of $20). Completion of the ratio requirement for each choice was accompanied by a visual stimulus on the computer screen. The response requirement for each of the two options increased independently such that the initial ratio requirement for each option was 50 responses; the ratio increased progressively each time the option was selected (50, 100, 200, 400, 800, 1200, 1600, 2000, 2400, and 2800). To receive all of the buprenorphine or money available that day, participants were required to emit 11,550 responses within 40 min. Fewer total responses were required if choices were distributed between the two options. These ratio values were chosen based on previous research conducted in our laboratory (Comer et al., 1997, 2017).

### TABLE 1

<table>
<thead>
<tr>
<th>Schedule of events</th>
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<tbody>
<tr>
<td><strong>Monday</strong></td>
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<tr>
<td>Week 1</td>
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<td>Week 2</td>
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<td>Week 3</td>
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<td>Week 4</td>
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<td>Week 5</td>
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<tr>
<td>Week 6</td>
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</table>

*Bup, buprenorphine*.
1998, 1999). Although it required sustained, high rates of responding, participants were capable of completing 11,550 responses in the allotted time. At the start of each self-administration task, two illustrations appeared on the computer screen: an empty balance scale and an empty bank. As each choice was completed, either the scale was implemented with a pile of powder or a dollar sign was added to the bank. Thus, participants could always see how many money and drug choices had been made. At the end of the 40-min self-administration task, the participant received whatever he had chosen: money and/or drug.

**Subjective Measures.** Four questionnaires were used to assess subjective effects (see Comer et al., 1999 for details). The first questionnaire was a 26-item visual analog scale (VAS) designed to assess subjective and physiological effects. The first 18 lines were labeled with adjectives describing mood states (e.g., “I feel . . .“: “high” and four additional lines, labeled with questions about the dose just received (e.g., “I liked the dose” or “For this dose, I would pay”). Participants also indicated, by making a mark along a 100-mm line, how much they “wanted” each of the following drugs: heroin, cocaine, alcohol, and tobacco. Participants rated each item on the VAS from “Not at all” (0 mm) to “Extremely” (100 mm), except for the “For this dose, I would pay” question, which ranged between $0 (0 mm) and $20 (100 mm). The second questionnaire was a 13-item opioid symptom checklist consisting of true/false questions designed to measure opioid effects (e.g., “My skin is itchy”). The VAS and opioid symptom checklist together constituted the subjective-effects battery. The third questionnaire was the 16-item SOWS. Participants rated each item on a scale from 0 to 4, with 0 being “Not at all” and 4 being “Extremely” (e.g., “I have gooseflesh” etc.). The fourth questionnaire was a six-item DEQ. Participants described drug effects by selecting among a series of possible answers ranging from 0 (“No, good, bad, etc., effect at all”) to 4 (“Very strong effects”). Ratings of drug liking ranged between –4 (“Dislike very much”) to 4 (“Like very much”).

**Task Battery.** The task battery consisted of four tasks: a 3-min digit-symbol substitution task, a 10-min divided attention task, a 10-min rapid information processing task, and a 3-min repeated acquisition of response sequences task (for details, see Comer et al., 1999).

**Physiological Measures.** A blood pressure cuff was attached to the nondominant arm, and blood pressure was recorded automatically every 5 min. Participants were also connected to a pulse oximeter via a soft sensor on a finger of the nondominant hand, which monitored arterial blood oxygen saturation (%SpO2). For safety, supplemental oxygen (2 L/min) was provided via a nasal cannula during all experimental sessions. If oxygen saturation decreased below 90%, breaths were prompted verbally by staff and the oxygen flow rate was increased. Average arterial oxygen saturation remained above 95% during all sessions. A specially modified Polaroid camera with a close-up lens (2× magnification) was used to take pupil photographs. All photographs were taken under ambient lighting conditions. Horizontal and vertical measurements of pupil diameter were made using a calipers, and then these two measurements were averaged and divided by 2 to correct for the 2× magnification.

**Drugs.** Buprenorphine HCl for injection (4 mg/ml) was provided by the National Institutes on Drug Abuse. Buprenorphine was diluted in 5% dextrose to produce each dose. Placebo (5% dextrose) or buprenorphine was administered intravenously through a catheter over a 30-s period in a total volume of 2 ml. Heroin HCl powder was provided by the National Institutes on Drug Abuse and prepared by the Columbia-Presbyterian Medical Center research pharmacy. A 25 mg/ml heroin concentration was prepared in a 5% dextrose solution to enhance stability. Dose calculations were based on the hydrochloride salt form. Heroin was stored in a freezer and used within 3 months of preparation. The stock solution was diluted in 5% dextrose to produce each dose. Placebo (5% dextrose solution) or heroin (10 and 20 mg) was administered intravenously through a catheter over a 30-s period in a total volume of 2 ml. Physiological saline solution was infused continuously during experimental sessions, except during drug administration. Between 1 and 2 ml of heparinized saline (10 units/ml) was flushed into the catheter four to eight times each day. All venous catheters were maintained as heparlocks and were removed within 60 h of insertion.

Supplemental medications available to all participants for the duration of the study included Mylantra, acetaminophen, ibuprofen, Colace, Milk of Magnesia, and multivitamins with iron. Trazodone (50 mg p.o., at bedtime; Warner Chilcott, Morris Plains, NJ) was available if participants reported having trouble sleeping.

Morning urine samples were collected daily, and one random sample per week was screened for the presence of other illicit substances. No illicit substances other than opioids were found in the participants’ urine.

**Statistical Analyses.** Repeated measures analyses of variance with planned comparisons were performed to answer the following questions: 1) Does buprenorphine function as a reinforcer? 2) Do the reinforcing effects of buprenorphine vary across choice sessions? 3) What is the duration of action of buprenorphine’s subjective, performance, and physiological effects? and 4) Does buprenorphine produce long-lasting antagonist effects? 1) To evaluate the reinforcing effects of buprenorphine, the progressive ratio break-point value for each active buprenorphine dose was compared with placebo. In addition, the break-point value for 2 mg of buprenorphine was compared with 8 mg of buprenorphine to evaluate dose-related effects. 2) To assess changes in the reinforcing effects of buprenorphine within and across days, break-point values during the morning choice session were compared with the afternoon choice session, and break-point values during the first choice day were compared with the second choice day. 3) To measure the time course of effects produced by the sample dose of buprenorphine, the subjective, physiological, and performance effects produced by each active dose were compared with placebo at each time point. In addition, 2 mg of buprenorphine was compared with 8 mg of buprenorphine at each time point to evaluate dose-related effects. 4) To evaluate potential long-lasting antagonist effects of buprenorphine, the dose-response curves for heroin 3 and 5 days after the last dose of buprenorphine were compared. Within each day, heroin dose-response curves after each active buprenorphine dose were compared with the heroin dose-response curve after placebo buprenorphine. In addition, heroin dose-response curves on day 3 were compared with heroin dose-response curves on day 5.

Buprenorphine and money break-point values were analyzed as a function of buprenorphine dose (0, 2, and 8 mg) and choice session (1–4). Pupil diameter, cardiovascular measures, task performance, and subjective ratings during the sample session were analyzed as a function of buprenorphine dose and time. SOWS data during the last 5 days of the detoxification week were also analyzed using repeated measures analyses of variance. To control for type I errors, a modified Bonferroni test was used in that only those comparisons with P values less than 0.01 were considered statistically significant.

**Results**

**Choice.** Figure 1 shows progressive ratio break-point values for buprenorphine (top panel) and money (bottom panel) as a function of buprenorphine dose and choice opportunity. Mean buprenorphine break-point values for both 2 mg (F(1,10) = 21.1, P < 0.001) and 8 mg (F(1,10) = 18.9, P < 0.001) were significantly greater than for placebo. Buprenorphine break-point values at each choice opportunity were also significantly different from the corresponding placebo break-point value, with the exception of the fourth choice opportunity after 2 mg of buprenorphine. Break-point values for 2 and 8 mg of buprenorphine did not significantly differ from each other. Across the four choice opportunities, buprenorphine break-point values did not differ after placebo or
8 mg, but break-point values were lower in the afternoons compared with the mornings after 2 mg of buprenorphine (choice 1 versus 2: \( F(1,30) = 5.3, P < 0.03 \); choice 3 versus 4: \( F(1,30) = 9.8, P < 0.004 \)). Under the 2-mg condition, all participants self-administered some amount of buprenorphine during all choice opportunities; across individual participants, the amount self-administered ranged between 1 and 2 mg. The average amount of buprenorphine self-administered during the four choice opportunities was 1.7 (±0.2), 1.3 (±0.2), 1.7 (±0.1), and 1.2 (±0.1) mg, respectively. Under the 8-mg condition, one participant chose not to self-administer any buprenorphine during the first choice opportunity. Thereafter, all participants self-administered some amount of buprenorphine: across individual participants, the amount self-administered ranged between 4 and 8 mg. The average amount of buprenorphine self-administered during the four choice opportunities was 4.9 (±1.2), 5.6 (±0.6), 6.5 (±0.4), and 5.9 (±0.5) mg, respectively. Mean money break-point values for both 2 mg (\( F(1,10) = 15.4, P < 0.003 \)) and 8 mg (\( F(1,10) = 13.8, P < 0.004 \)) of buprenorphine were significantly lower than for placebo (Fig. 1, bottom panel) and did not differ from each other. There were no statistically significant differences in break-point values for money across the four choice opportunities.

**Subjective Effects of Buprenorphine.** Both 2 and 8 mg of buprenorphine produced significant increases in ratings of “Good Effect” (Fig. 2, top panel), “Strength of Drug Effect” (Fig. 2, bottom panel), drug “Liking” (Table 2), and “Desire to Take the Drug Again” (Table 2). In general, the drug effects were rated as being “mild” in magnitude. Peak ratings were not different for 2 and 8 mg of buprenorphine and tended to occur within the first hour after administration. The duration of effect, however, was generally longer for 8 mg of buprenorphine, compared with 2 mg. Ratings of drug “Liking” after 8 mg of buprenorphine were still significantly elevated 24 h after buprenorphine administration (\( F(1,60) = 6.9, P < 0.01 \)), and ratings of “Desire to Take the Drug Again” approached statistical significance at 24 h (\( F(1,60) = 6.1, P < 0.016 \)). All of the DEQ ratings returned to placebo levels 48 h after administration of buprenorphine.
The pattern of results obtained from the opioid symptom checklist and visual analog scales was somewhat similar to the DEQ. Sum scores on the opioid symptom checklist and visual analog scales were somewhat similar to the DEQ, the opioid symptom checklist (OSC), and the VAS after buprenorphine administration.

**Table 2**

<table>
<thead>
<tr>
<th>Buprenorphine Dose (mg)</th>
<th>0</th>
<th>4 min</th>
<th>10 min</th>
<th>60 min</th>
<th>120 min</th>
<th>180 min</th>
<th>24 h</th>
<th>48 h</th>
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<td><strong>DEQ</strong></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Liking</td>
<td></td>
<td>-0.7 (0.7)</td>
<td>-0.7 (0.7)</td>
<td>-1.3 (0.8)</td>
<td>-2.0 (0.9)</td>
<td>-1.8 (0.8)</td>
<td>-0.7 (0.7)</td>
<td>-0.7 (0.8)</td>
</tr>
<tr>
<td>Take again</td>
<td></td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0.2 (0.2)</td>
<td>0.2 (0.2)</td>
<td>0.2 (0.2)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td><strong>OSC</strong></td>
<td></td>
<td>2.0 (0.4)</td>
<td>1.2 (0.3)</td>
<td>1.3 (0.4)</td>
<td>1.8 (0.3)</td>
<td>1.5 (0.4)</td>
<td>1.3 (0.3)</td>
<td>1.7 (0.3)</td>
</tr>
<tr>
<td>Good effect</td>
<td></td>
<td>0.2 (0.2)</td>
<td>0.3 (0.3)</td>
<td>3.8 (3.2)</td>
<td>2.8 (2.4)</td>
<td>1.3 (1.1)</td>
<td>0.5 (0.3)</td>
<td>0.2 (0.2)</td>
</tr>
<tr>
<td>High</td>
<td></td>
<td>0.3 (0.2)</td>
<td>0.0 (0.0)</td>
<td>4.5 (4.5)</td>
<td>2.0 (2.0)</td>
<td>3.2 (3.2)</td>
<td>3.5 (3.3)</td>
<td>0.0 (0.0)</td>
</tr>
<tr>
<td>Liking</td>
<td></td>
<td>0.7 (0.4)</td>
<td>0.3 (0.2)</td>
<td>1.0 (0.8)</td>
<td>0.3 (0.3)</td>
<td>0.8 (0.8)</td>
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<td>0.8 (8.5)</td>
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<td>0.3 (4.1)</td>
<td>0.2 (5.4)</td>
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<tr>
<td>Would pay ($)</td>
<td></td>
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<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
<td>0.0 (0.0)</td>
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</tr>
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</table>

BL, baseline.

* Significant difference between placebo and 2 or 8 mg of buprenorphine at that time point.

The pattern of results obtained from the opioid symptom checklist and visual analog scales was somewhat similar to the DEQ. Sum scores on the opioid symptom checklist and ratings of “Good Effect,” “High,” “Liking,” “Potency,” and “Quality” were significantly greater after active buprenorphine relative to placebo (Table 2) and tended to peak within the first hour after administration of buprenorphine. Peak ratings did not differ for 2 and 8 mg of buprenorphine, but in contrast to the DEQ, the time course of ratings after 2 and 8 mg of buprenorphine was similar. All of the ratings returned to placebo levels 48 h after administration of buprenorphine. Participants reported that they would pay a maximum of $4 to $5 for 2 or 8 mg of buprenorphine.

Subjective ratings of opioid withdrawal, as measured by total scores on the SOWS (maximum score = 64), were generally low during the last 5 days of the detoxification (mean range: 3.0–5.0), and throughout the study (mean range: 1.3–6.2).

**Performance Effects of Buprenorphine.** There were few effects of buprenorphine on performance, with the exception of impairments in performance of the divided attention task. The latency to respond to a brief target randomly appearing on the computer screen was greater after both 2 and 8 mg of buprenorphine, relative to placebo (Fig. 3). At the 10-min assessment point, the latency was significantly greater for 8 mg compared with 2 mg of buprenorphine (F(1,60) = 11.5, P < 0.001). The number of missed targets significantly increased (10 min: F(1,60) = 6.5, P < 0.01; 60 min: F(1,60) = 6.5, P < 0.01; 120 min: F(1,60) = 19.9, P < 0.0001) and the number of correctly identified targets significantly decreased (120 min: F(1,60) = 17.3, P < 0.0001) after 8 but not 2 mg of buprenorphine.

**Physiological Effects of Buprenorphine.** Both 2 and 8 mg of buprenorphine produced significant decreases in pupil diameter (Fig. 4). At the 10-min assessment point, miosis was significantly greater after 2 mg, compared with 8 mg of buprenorphine (F(1,90) = 14.3, P < 0.0003). After both doses of buprenorphine, miosis reached a trough at approximately 60 min and had still not returned to placebo levels 48 h after administration of drug. Although heart rate (HR) significantly decreased from 82 beats per minute at baseline to 63 beats per minute at the end of the session (F(18,90) = 14.1, P < 0.0001), there were no significant effects on HR as a function of buprenorphine dose. Systolic pressure (SP) also significantly decreased during the session: 122 mm Hg at baseline to 115 mm Hg at the end of the session (F(1,90) = 2.3, P < 0.005). SP increased by approximately 5 mm Hg 20 min after 2 mg of buprenorphine. In contrast, SP decreased by approximately 8 mm Hg 20 min after placebo administration. Diastolic pressure (DP) did not significantly change across the session, but DP increased slightly after administration of 2 mg of buprenorphine and decreased after placebo administration.

**Subjective Effects of Heroin after Buprenorphine Administration.** Heroin produced dose-related increases in subjective ratings of “Good Effect” (Fig. 5, top panel; F(2,10) = 77.0, P < 0.0001), “Strength of Drug Effect” (Fig. 5, bottom panel; F(2,10) = 51.3, P < 0.0001), drug “Liking” (F(2,10) = 22.1, P < 0.002), and “Desire to Take the Drug Again” (F(2,10) = 117.7, P < 0.0001). In general, the heroin-induced drug effects were “moderate to strong” in magnitude, and were consistently higher than peak drug effects after buprenorphine administration (compare Figs. 2 and 5). The dose-effect curves for heroin after 0, 2, and 8 mg of buprenorphine were not different from each other, with the exception of the following: for ratings of “Good Effect,” the heroin dose-effect curve 5 days after 8 mg of buprenorphine was significantly lower than the heroin dose-effect curve after 2 mg of buprenorphine (F(1,10) = 9.9, P < 0.01); for ratings of drug “Liking,” the heroin dose-effect curves 3 and 5 days after 8 mg of buprenorphine were significantly lower than the heroin dose-effect curves after placebo buprenorphine (3 days: F(1,10) = 13.6, P < 0.004; 5 days: F(1,10) = 19.6, P < 0.001). The pattern of results obtained from the opioid symptom checklist and visual analog scales was similar to the DEQ, with the exception that peak heroin-induced subjective ratings 3 days after placebo buprenorphine were generally higher than those after 2 or 8 mg of buprenorphine (Table 3). In addition, peak heroin-induced ratings of “Good Effect,” “High,” and “Liking” 3 days after placebo buprenorphine were significantly higher than heroin-induced ratings 5 days after placebo buprenorphine. These results indicate that heroin produced its most robust subjective effects during the first exposure after placebo buprenorphine administration, after 9 opioid-free days. Heroin-induced subjective ratings after administration of 2 and 8 mg of buprenorphine were not different from each other, nor did they differ after 3 versus 5 days.
Performance Effects of Heroin after Buprenorphine Administration. Heroin produced dose-related impairments in performance of the digit symbol substitution task (DSST) and the divided attention task (DAT). The total number of correct responses ($F(2,10) = 17.9, P < 0.0005$) and the total number of patterns attempted ($F(2,10) = 13.2, P < 0.002$) on the DSST significantly decreased with increasing heroin doses. The distance between the cursor and a moving stimulus ($F(1,10) = 77.0, P < 0.0001$), the latency to identify a target ($F(2,10) = 27.5, P < 0.0001$), and the number of missed targets ($F(2,10) = 14.1, P < 0.001$) on the DAT significantly increased across increasing heroin doses. Correspondingly, the maximum speed of the target ($F(2,10) = 14.4, P < 0.001$) and the number of correctly identified targets ($F(2,10) = 14.2, P < 0.001$) on the DAT significantly decreased across heroin doses. In general, there were few heroin-induced impairments in performance as a function of the dose of buprenorphine administered the previous week, with the exception that the total number of correct responses on the DSST was significantly lower 3 days after placebo buprenorphine ($P < 0.004$). In addition, the latency to identify a target was significantly longer 3 versus 5 days after placebo buprenorphine administration ($F(1,10) = 9.5, P < 0.01$).

Physiological Effects of Heroin after Buprenorphine Administration. Heroin produced a dose-related miotic effect ($F(3,15) = 75.1, P < 0.0001$). Pupil diameter, which was approximately 4 mm under baseline conditions (3.9 ± 0.1 mm) and after placebo administration (3.8 ± 0.1 mm) decreased to 2.5 ± 0.1 mm after 20 mg of heroin. There were no significant differences in pupil diameter as a function of the dose of buprenorphine self-administered the previous week, nor did pupil diameter vary 3 versus 5 days after buprenorphine administration. Similarly, there were no significant differences in SP or DP as a function of the dose of buprenorphine self-administered the previous week. However, HR was significantly greater 3 days after placebo buprenorphine administration, relative to 3 days after 2 mg of buprenorphine ($F(1,10) = 10.0, P < 0.01$).

Discussion

The present results demonstrate that intravenously administered buprenorphine served as a reinforcer, as indicated by the fact that progressive ratio break-point values were significantly higher after active buprenorphine, compared with placebo. The maximum break-point values for 2 and 8 mg of buprenorphine (2267 ± 246 and 2067 ± 217, respectively) in the present study were similar to the maximum break-point values for intranasal and intravenous heroin (1900 ± 280 and 2050 ± 256, respectively) in morphine-maintained individuals (Comer et al., 1999), suggesting that buprenorphine may have significant abuse liability in non-dependent, non-treatment-seeking opioid abusers. Break-point values for buprenorphine were not significantly different when 2 versus 8 mg was available for self-administration, which is not entirely surprising, given the partial agonist profile of buprenorphine. Previous studies have demonstrated a "plateau" in buprenorphine’s subjective, physiological, and respiratory effects (Pickworth et al., 1993; Walsh et al., 1994, 1995b). In the present study, it is likely that a more graded dose-effect curve would have been obtained if lower doses of buprenorphine had been tested. Across the four choice opportunities, progressive ratio break-point values after placebo and 8 mg of buprenorphine were not significantly different. In a previous study evaluating the reinforcing effects of i.v. heroin under buprenorphine maintenance conditions (Comer et al., 2001), heroin break-point values also did not vary as a function of choice opportunity. However, break-point values for 2 mg of buprenorphine were higher during the morning sessions, compared with the afternoon sessions. It is unclear why 2 mg of buprenorphine was self-administered more in the morning than the afternoon. As expected, break-point values for money were generally inversely related to break-point values for buprenorphine.

In sum, these results are consistent with numerous studies conducted in nonhuman primates, demonstrating that buprenorphine serves as a reinforcer (e.g., Mello et al., 1988; Winger et al., 1992; Young et al., 1984; Winger and Woods, 2001). The data are also consistent with a number of epidemiological and case report studies worldwide demonstrating buprenorphine abuse (O’Connor et al., 1988; Sakol et al., 1989; Singh et al., 1992; Baumeville et al., 1997). It is important to note, however, that the present study was conducted in nondependent individuals. As demonstrated by Winger and Woods (2001), buprenorphine did not have reinforcing effects in morphine-dependent rhesus monkeys. Similarly, Amass and colleagues (2000) reported that intrave-
nously administered buprenorphine (4 and 8 mg), buprenorphine/naloxone combination (4:1 and 8:2 mg), and hydromorphone (9 and 18 mg) were not self-administered above placebo levels in buprenorphine/naloxone-maintained individuals (8:2 mg, sublingual) in an outpatient treatment setting. Mendelson et al. (1997) further showed that intravenously administered buprenorphine (0.2 mg) did not produce significant physiologic or subjective effects in individuals maintained on 40 to 60 mg of methadone/day. However, a study by Strain et al. (1997) demonstrated that when higher doses of intramuscular buprenorphine (4, 8, and 16 mg) were administered to individuals maintained on 8 mg of sublingual buprenorphine, opioid-like effects were produced. More recently, Stoller et al. (2001) showed that 8 mg of intramuscular buprenorphine administered to hydromorphone-maintained individuals produced opioid agonist effects that were similar in magnitude to 10 mg of intramuscular hydromorphone. These studies support the need for further evaluations of the reinforcing effects of buprenorphine in opioid-dependent individuals.

Although the subjective effects of sublingual, intramuscular, and subcutaneous buprenorphine have been evaluated in numerous studies (Blom et al., 1987; Jasinski et al., 1989; Foltin and Fischman, 1994, 1995; Walsh et al., 1994, 1995a, 1995b), relatively few studies have systematically evaluated the subjective effects of buprenorphine in nondependent individuals after intravenous administration, which is the route by which buprenorphine is most likely to be abused. Saarialho-Kere et al. (1987) and Zacny et al. (1997) evaluated the effects of i.v. buprenorphine in volunteers with no history of drug abuse. In this population, buprenorphine did not appear to have significant abuse liability, predominantly because of aversive side effects such as sedation, dizziness, nausea, and vomiting. In fact, Zacny et al. (1997) showed that participants reported a significant dislike of drug effects after buprenorphine administration. In contrast, Pickworth et al. (1993) evaluated a range of doses of i.v. buprenorphine in nondependent individuals with histories of opioid abuse. Doses of 0.6 and 1.2 mg of buprenorphine increased ratings of “Good Effects” and increased scores on the Morphine-Benzene-

![Fig. 3.](image3.png)  
**Fig. 3.** Latency to respond to a target on the divided attention task during the sample and no drug sessions as a function of buprenorphine dose and time. All else as in Fig. 2.

![Fig. 4.](image4.png)  
**Fig. 4.** Pupil diameter during the sample and no drug sessions as a function of buprenorphine dose and time. All else as in Fig. 2.

### TABLE 2 (Continued)

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<th>Time</th>
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<th>OSC</th>
<th>VAS</th>
</tr>
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</tr>
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</tr>
<tr>
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<td>23.8* (15.8)</td>
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<td>29.0* (11.3)</td>
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</tr>
<tr>
<td>24 h</td>
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<td>3.7* (1.0)</td>
<td>23.7* (14.9)</td>
</tr>
<tr>
<td>48 h</td>
<td>0.0 (0.0)</td>
<td>1.8 (0.4)</td>
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<table>
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<tr>
<th>Time</th>
<th>DEQ</th>
<th>OSC</th>
<th>VAS</th>
</tr>
</thead>
<tbody>
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<td>33.3* (10.9)</td>
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<td>10 min</td>
<td>4.7* (0.8)</td>
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<tr>
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<td>4.0* (0.9)</td>
<td>4.0* (0.9)</td>
<td>24.7* (11.0)</td>
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<td>120 min</td>
<td>3.7* (0.8)</td>
<td>3.7* (1.0)</td>
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<td>1.8 (0.4)</td>
<td>1.8 (0.4)</td>
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<td>48 h</td>
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<td>13.3 (9.1)</td>
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* Significant difference between placebo and 2 or 8 mg of buprenorphine at that time point.
drine group subscale of the Addiction Research Center Inventory, which has been used as a measure of drug-induced euphoria. In the present study, doses of up to 8 mg of buprenorphine were administered intravenously to nondependent opioid abusers. In general, the peak subjective effects of buprenorphine were rated as ‘mild to moderate’ in magnitude, whereas peak ratings after i.v. heroin administration were rated as ‘moderate to strong’ in magnitude. Again, these results are consistent with buprenorphine’s partial agonist profile, and to the extent that subjective effects predict drug self-administration, they suggest that differences may also exist in the reinforcing effects of heroin and buprenorphine. Future studies in our laboratory will directly compare the reinforcing effects of buprenorphine and a full μ-opioid agonist.

Buprenorphine produced mild but statistically significant impairments in performance, which is consistent with other studies showing either mild (Pickworth et al., 1993) or no performance impairing effects of buprenorphine (Walsh et al., 1994). In the present study, heroin also impaired task performance, which was consistent with previous studies in our laboratory (Comer et al., 1997, 1998, 1999). And similar to the subjective effects data described above, heroin produced greater disruptions in performance than buprenorphine. In addition to its effects on performance, buprenorphine also decreased pupil diameter, an effect consistent with other μ-opioid agonists. Heroin also decreased pupil diameter in the present study, but in contrast to the subjective and performance effects, pupil diameter decreased to a comparable degree after buprenorphine and heroin administration. Neither buprenorphine nor heroin produced robust effects on cardiovascular measures.

In addition to evaluating the agonist effects of buprenorphine, the present study sought to examine the duration of buprenorphine’s antagonist effects. Schuh and colleagues (1999) reported that 5 days after discontinuation of 8 mg of sublingual buprenorphine, antagonism of the effects of hydromorphone had not fully dissipated for all measures. Kishiioka et al. (2000) showed that 7 days after acute i.m. administration of 1 mg/kg buprenorphine, antagonism of the respiratory depressant effects of heroin in rhesus monkeys had nearly, but not completely, dissipated. Walker et al. (1995) reported that 10 days after acute administration of 3.2 mg/kg buprenorphine, antagonism of the analgesic effects of alfentanil in rhesus monkeys had fully dissipated. Because of these data demonstrating long-lasting antagonist effects of buprenorphine, the present study examined the effects of heroin 3 and 5 days after the last dose of self-administered buprenorphine. Evidence for residual antagonism after self-administration of buprenorphine was weak. Subjective rat-

### Table 3

Mean (±S.E.M.) peak ratings on the VAS and mean sum scores on the opioid symptom checklist (OSC). Cumulative heroin dose-response determinations were made 3 and 5 days after 0, 2, or 8 mg of buprenorphine was available for self-administration.

<table>
<thead>
<tr>
<th>Buprenorphine Dose (mg)</th>
<th>Heroin Dose (mg)</th>
<th>OSC</th>
<th>VAS</th>
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<td>17.3 (5.7)</td>
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<tr>
<td></td>
<td>8</td>
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<td>24.3 (6.5)</td>
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<td>10.8 (4.4)</td>
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<td></td>
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<td>1.4 (0.3)</td>
<td>50.9 (9.4)</td>
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<tr>
<td></td>
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<td>46.8 (6.4)</td>
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<tr>
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<td>45.2 (8.2)</td>
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<tr>
<td></td>
<td>20</td>
<td>44.2 (10.3)</td>
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<td></td>
<td>10</td>
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<td>46.8 (6.4)</td>
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<tr>
<td></td>
<td>20</td>
<td>44.2 (10.3)</td>
<td>50.9 (9.4)</td>
</tr>
</tbody>
</table>

* Significant difference between the heroin dose-response determination following placebo versus 2 or 8 mg of buprenorphine at that time point (day 3 or 5).

§ Significant difference between the heroin dose-response determination made on day 3 versus day 5.

![Fig. 5](image-url) Selected drug effects questionnaire ratings after cumulative doses of heroin as a function of buprenorphine dose self-administered the previous week, and time since the last self-administered buprenorphine dose. Data points represent mean ratings for the six participants. Error bars represent ±1 S.E.M.
ings on the drug effects questionnaire after heroin administration generally did not differ as a function of the dose of buprenorphine self-administered the previous week. In contrast to ratings on the drug effects questionnaire, ratings on the visual analog scales were generally greater when placebo was self-administered the previous week, relative to when 2 or 8 mg of buprenorphine was self-administered. However, the pattern of changes in the heroin dose-effect function at 3 versus 5 days was not consistent with antagonism because the effects of heroin were reduced on day 5, compared with day 3. If buprenorphine was acting as an antagonist, one would expect that heroin would produce greater effects on day 5, because buprenorphine’s antagonist effects would have dissipated. Instead, heroin’s subjective effects were greatest on day 3, particularly after 10 mg of heroin, which was the first dose of agonist that the participants had received in more than 1 week. Objective measures of heroin’s effects, such as pupil diameter, systolic pressure, and diastolic pressure, did not differ as a function of the dose of buprenorphine self-administered the previous week. Heart rate, however, did increase more following placebo self-administration, relative to 2 and 8 mg of buprenorphine. Taken together, these results suggest that participants were perhaps experiencing an “anticipatory” reaction to heroin after being deprived of opiates for more than 1 week.

In conclusion, the present results confirmed our hypothesis that buprenorphine would serve as a reinforcer under these laboratory conditions. The maximum progressive ratio break point for buprenorphine was somewhat surprising, however, based on the majority of studies in laboratory animals showing that the reinforcing effects of buprenorphine were generally less robust than full μ-opioid agonists (Negus and Woods, 1995; Winger and Woods, 2001). It is possible that the experimental conditions under which buprenorphine was self-administered in the present study contributed to the relatively high break-point values for buprenorphine. One possible explanation for this finding is that relative to our previous studies, participants in the current study were only given the opportunity to self-administer drug every other week. Perhaps the relatively limited opportunities to self-administer drug, as well as the long opioid-free intervals, contributed to the high levels of responding for buprenorphine in the current study. Nevertheless, these results show that buprenorphine has abuse liability in nondependent opioid abusers, and underscores the need for strategies to reduce illicit diversion of buprenorphine, such as the use of a combination of naloxone and buprenorphine.

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