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Acute effects of intramuscular and sublingual buprenorphine and buprenorphine/naloxone in non-dependent opioid abusers

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Abstract

Rationale—Buprenorphine is a partial mu opioid receptor agonist with clinical efficacy as a pharmacotherapy for opioid dependence. A sublingual combination formulation was developed containing buprenorphine and naloxone with the intent of decreasing abuse liability in opioid dependent individuals. However, the addition of naloxone may not limit abuse potential of this medication when taken by individuals without opioid physical dependence.

Objectives—The present study investigated the effects of buprenorphine alone and in combination with naloxone administered intramuscularly and sublingually to non-dependent opioid abusers.

Methods—In a within-subject crossover design, non-dependent opioid-experienced volunteers (N=8) were administered acute doses of buprenorphine (4, 8, 16 mg) and buprenorphine/naloxone (4/1, 8/2, 16/4 mg) via both intramuscular and sublingual routes, intramuscular hydromorphone (2, 4 mg as an opioid agonist control), and placebo, for a total of 15 drug conditions. Laboratory sessions were conducted twice per week using a double blind, double-dummy design.

Results—Buprenorphine and buprenorphine/naloxone engendered effects similar to hydromorphone. Intramuscular administration produced a greater magnitude of effects compared to the sublingual route at the intermediate dose of buprenorphine and at both the low and high doses of the buprenorphine/naloxone combination. The addition of naloxone did not significantly alter the effects of buprenorphine.

Conclusions—These results suggest that buprenorphine and buprenorphine/naloxone have similar abuse potential in non-dependent opioid abusers, and that the addition of naloxone at these doses and in this dose ratio confers no evident advantage for decreasing the abuse potential of intramuscular or sublingual buprenorphine in this population.

Keywords

buprenorphine; buprenorphine/naloxone; non-dependent; opioid; human

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Disclosure

Drugs used in the study described in this article are manufactured by Reckitt Benckiser Pharmaceuticals Inc. Dr. Strain also is a consultant to and paid member of the Scientific Advisory Board of Reckitt Benckiser Pharmaceuticals. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict of interest policies.

Introduction

Buprenorphine is an efficacious pharmacotherapy for opioid dependence treatment (e.g., Johnson et al. 1992, Strain et al. 1994, Ling et al. 1998, Schottenfeld et al. 1997, Johnson et al. 2000). It is a partial agonist at mu opioid receptors, an antagonist at kappa opioid receptors, and an ORL-1 agonist (e.g., Cowan et al. 1977, Dum et al. 1981, Lutfy et al. 2003). Despite a profile of safety and effectiveness, buprenorphine has abuse liability when administered parenterally and, under certain conditions, sublingually (Lewis 1985, Weinhold et al. 1992, Comer and Collins 2002, Alho et al. 2007).

In an effort to decrease the abuse liability of buprenorphine, naloxone was added to the sublingual formulation and marketed as Suboxone®. Naloxone is an opioid antagonist and can precipitate withdrawal in opioid-dependent individuals when administered parenterally. However, the bioavailability of naloxone when given sublingually is poor (Weinberg et al. 1988, Preston et al. 1990, Harris et al. 2000). When taken sublingually, buprenorphine/naloxone tablets produce an opioid agonist effect with a slow onset of action. However, if the tablets are dissolved and injected, naloxone will precipitate withdrawal in an opioid dependent user. These effects have been demonstrated in laboratory studies using opioid dependent volunteers (Preston et al. 1988, Mendelson et al. 1996, 1997a, 1999, Fudala et al. 1998, Stoller et al. 2001). However, the effects of this combination in non-dependent opioid users are not completely understood. Previously, it has been shown that sublingual buprenorphine and buprenorphine/naloxone produced similar opioid agonist-like effects in opioid users who were not physically dependent (Strain et al. 2000). However, investigation of the effects of buprenorphine and buprenorphine/naloxone administered parenterally in opioid non-dependent volunteers has not been conducted and is warranted.

The current study investigated the subjective and physiological effects of buprenorphine and buprenorphine/naloxone when administered intramuscularly versus sublingually in opioid users who were not physically dependent. The aims of this experiment were two-fold. First, the study compared the acute effects of buprenorphine and buprenorphine/naloxone when administered intramuscularly versus sublingually. Second, the effects of administering buprenorphine in combination with naloxone by both routes of administration were also investigated. It was hypothesized that 1) greater magnitude effects would occur when buprenorphine was given intramuscularly versus sublingually, and 2) naloxone would reduce the effects of buprenorphine when administered intramuscularly but not sublingually.

Materials and Methods

Subjects

Participants were volunteers with current sporadic opioid use but not physically dependent on opioids. Six males and two females with an average age of 37 (range 22–51) years participated. Volunteers weighed on average 158 pounds (range 123–215). Their average duration of illicit opioid use was approximately 15 (range 2–33) years. Volunteers used heroin an average of approximately 8 out of the 30 days preceding participation in this study (range: 4–11 days). Participants also used cocaine (N=8), alcohol (N=5), cannabis (N=2), and sedative/hypnotics (e.g., benzodiazepines; N=2) during the 30 days preceding admission to the study. Participants underwent routine medical screening that included a medical history, physical examination, EKG, chemistry, hematology, urine drug testing, and routine medical urinalysis testing (e.g., specific gravity, pH, etc.). Medical staff not involved in the study as investigators reviewed all results and all subjects were found to be without significant medical problems. The Structured Clinical Interview for the DSM-IV (SCID) was completed to ensure volunteers were not physically dependent on substances (except caffeine and nicotine). In addition, participants

were monitored drug-free for 48 hours following admission to ensure there was no evidence of physical dependence on opioids or other drugs (except caffeine and nicotine).

Pregnancy and significant medical or psychiatric illness (e.g., insulin-dependent diabetes, schizophrenia) were exclusionary. Individuals seeking treatment were not enrolled in the study and were assisted in referral to community-based treatment programs. The Institutional Review Board approved the study, and all volunteers gave written informed consent and were paid for their participation.

Study Setting

Participants lived on a closed, 14-bed residential unit for the duration of the study. Breathalyzer testing for alcohol was completed on the day of admission and randomly at least twice weekly. In addition, urine samples were collected at admission and daily throughout the study, and tested intermittently for the presence of illicit drugs using an EMIT system (Syva Co.). No evidence of unauthorized alcohol or drug abuse was detected during the study. Participants did not have access to caffeinated beverages and were allowed to smoke cigarettes ad libitum, except during experimental sessions.

Study Procedure

Participants were screened on an outpatient basis to determine eligibility. Those who met inclusion and exclusion criteria completed informed consent, were admitted and oriented to the residential unit. Each volunteer participated in a minimum of 15 experimental sessions and typically resided on the unit for 9 weeks. After completion of the residential portion of the study, volunteers were discharged to an outpatient treatment/research clinic and encouraged to participate in drug-free counseling services offered without charge.

There were a total of 17 sessions possible. The first session was always a double blind placebo training session, and results from this session were not included in analyses. The seventeenth session was scheduled, but not always run, in the event that a test condition needed to be repeated due to an unexpected occurrence (e.g., a computer malfunction during a session). The order of drug conditions was derived from a Latin-square for fifteen conditions and 30 subjects. Volunteers were assigned one of the schedules using a random number table.

Laboratory Sessions

Double blind experimental sessions were conducted by a trained research technician and followed procedures described in Strain et al. (2000). Participants were informed they could receive placebo, opioid agonists, opioid antagonists, or combinations of these drugs during experimental sessions. Sessions began at 8:30 AM and lasted approximately 4 hours, and occurred twice weekly, with at least 72 hours between sessions. Baseline physiological data, pupil photos, and subject and observer questionnaires were completed during the first 30 min of each session. At 9:15 AM volunteers received an intramuscular (IM) injection followed by sublingual (SL) tablets. Following drug administration, these measures were repeated at 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, and 180 min following drug administration.

Subjective and Observer Measures

Volunteers completed visual analog scales (VASs) and an adjective rating questionnaire following procedures similar to those in previous studies (e.g., Strain et al. 2000), and were instructed to respond by describing how they felt at the time each question was being answered. There were six VASs: Drug Effect, Liking, High, Good Effects, Bad Effects and Sick. The adjective rating questionnaire consisted of 37 items that the participant rated on a five-point scale from 0 (not at all) to 4 (extremely); items constituted an Agonist scale (adjectives

associated with morphine-like effects) and a Withdrawal scale (adjectives associated with opioid withdrawal-like effects; Fraser et al. 1961, Jasinski 1977, Strain et al. 1993). Observer ratings included the same adjectives presented to the volunteer as described above and entered at the time of subject ratings. Items were summed to produce total scores for the Agonist scale and Withdrawal scale.

Physiological Measures

Heart rate, blood pressure, skin temperature, respiratory rate, and oxygen saturation were monitored throughout the session following procedures used in similar studies (Strain et al. 2000, Rosado et al. 2007). With the exception of respiratory rate, these measures were recorded once per minute using a Criticare Non-Invasive Patient Monitor (model 507S, Criticare Systems, Inc., Waukesha, MI) and averaged across 15 min time intervals. Respiration rate was recorded manually once every fifteen minutes. Pupil diameter was determined from photographs taken in standardized ambient room lighting using a Polaroid camera with a 2x magnification.

Drugs and Doses

All medications were administered using double blind, double-dummy procedures. Fifteen drug conditions were tested: placebo, two doses of hydromorphone (2, 4 mg) administered intramuscularly, 3 doses of buprenorphine administered intramuscularly and sublingually (4, 8, 16 mg), and buprenorphine/naloxone combinations, prepared as a 4:1 ratio, administered intramuscularly and sublingually (4/1, 8/2, 16/4 mg). Each volunteer was exposed to all drug conditions. A commercial preparation of hydromorphone hydrochloride (10 mg/ml; Knoll Pharmaceuticals, Whippany, NJ) was diluted to the appropriate volume with bacteriostatic saline. Buprenorphine doses given intramuscularly were prepared using buprenorphine hydrochloride (Research Triangle Institute, NC) and sterile water. Naloxone injections were prepared using naloxone hydrochloride (Mallinckrodt Chemical Inc., St. Louis, MO) and sterile water.

Buprenorphine and buprenorphine/naloxone tablets were supplied by the National Institute on Drug Abuse, Research Technology Branch (Rockville, MD, USA) from a supply provided by Reckitt Benckiser Pharmaceuticals (Hull, UK). Each tablet had a total weight (active plus inactive ingredients) of 100 mg. Volunteers were administered a total of 16 tablets during each session: 8 tablets containing either placebo or 2 mg buprenorphine, and 8 tablets containing either placebo or 2 mg of buprenorphine combined with 0.5 mg of naloxone. Combinations of active and placebo tablets were used to achieve the target dose for a given challenge session.

Data Analysis

Peak effects for each session were determined for each measure. For most measures, the reported value was a peak increase (e.g., subjective and observer ratings); however, for some measures the value was a peak decrease (e.g., pupil diameter).

A repeated measures analysis of variance was used to examine significant differences in peak effects; the main effect was drug condition. Pairwise comparisons were examined using a conservative one-step procedure, Tukey's honestly significant difference (HSD). Peak placebo effects and peak effects for hydromorphone (2 mg and 4 mg) were compared to the peak effect of each active drug condition. In addition, route of administration was compared within a given dose (e.g., 4 mg IM buprenorphine vs. 4 mg SL buprenorphine), and the addition of naloxone was compared within a given route of administration and dose (e.g., 4 mg IM buprenorphine vs. 4/1 mg IM buprenorphine/naloxone). Differences between means that were greater than the Tukey HSD are reported as significant ($p \leq 0.05$).

The time course for each VAS was separately examined using a repeated measures regression analysis with effects of drug condition, time and their interaction. Planned comparisons were performed for specific time points (15, 30, 45 min) within drug conditions to capture differences in the onset of effects. Active drug conditions were compared to placebo and hydromorphone (2 and 4 mg). Route of administration within a given dose of buprenorphine, and buprenorphine alone and in combination with naloxone within a route of administration were also examined. Significant differences ($p \leq 0.05$) are reported.

Results

There are two comparisons of interest in these analyses: 1) for a given formulation, how effects differed by route of administration (IM vs. SL), and 2) for a given route of administration, how presence versus absence of naloxone affected the abuse liability profile of buprenorphine. Results are presented to illustrate the IM and SL comparisons (Tables 1, 2), and the presence versus absence of naloxone comparisons (Figure 1). Comparisons are addressed in more detail below.

Route of Administration Comparisons

A significant main effect was shown for VAS ratings of Drug Effect, Liking, High, and Good Effects ($p < 0.05$; Table 1). There were no significant differences between placebo and the two doses of hydromorphone for these four VAS measures. Pairwise comparisons did not reveal statistically significant differences between routes of administration for any dose of buprenorphine and buprenorphine/naloxone. No overall significant effects were found for VAS ratings of Bad Effects or Sick (data not shown).

There were four adjective scale scores: Agonist scores and Withdrawal scores, from subject ratings and from observer ratings (Table 1, Withdrawal scores not shown). There was a significant main effect for observer adjective Agonist scale scores, but there were no other significant main effects for the other adjective scale scores (subject or observer; Table 1). Pairwise comparisons failed to reveal statistical significance between placebo and either dose of hydromorphone for any of the four scales (Table 1). Subject rated and observer rated Agonist and Withdrawal scores were generally of low magnitude and did not significantly differ between routes of administration (Table 1).

Outcomes on physiological measures are shown in Table 1. For pupil diameter, both hydromorphone doses decreased pupil diameter (by about 1 mm), although these decreases were not significantly different from placebo. In contrast, the 8 mg SL dose of buprenorphine administered alone, the 8/2 mg and 16/4 mg SL doses of buprenorphine/naloxone, and the 16/4 mg IM buprenorphine/naloxone dose significantly decreased pupil diameter compared to placebo ($p < 0.05$). There were no significant differences in pupil diameter by route of administration for a given dose of buprenorphine or buprenorphine/naloxone (Figure 1). No significant differences were found between drug conditions for all other physiological measures.

Presence versus Absence of Naloxone Comparisons

Pairwise comparisons within a given route of administration, and within a given dose of buprenorphine found no statistically significant differences as a function of the presence versus absence of naloxone. Figure 1 provides an illustrative example of a subject-rated VAS item (Drug Effect), an observer rated adjective scale (Agonist), and a physiological measure (pupil diameter). For the IM route of administration (squares), there was no evidence that the inclusion of naloxone (filled squares) significantly affected these measures compared to buprenorphine alone (open squares).

Time Course Analysis

In addition to peak change from baseline analyses, the time dependent changes for each VAS measure were examined in order to determine onset differences by route of administration (IM vs. SL) or differences resulting from the addition of naloxone (i.e., buprenorphine alone vs. buprenorphine in combination with naloxone). Statistical differences were found for both main effects (Condition and Time) for Drug Effect [$F(14,98)=2.16$, $p<0.05$; $F(12,84)=18.05$, $p<0.0001$], Liking [$F(14,98)=1.84$, $p<0.05$; $F(12,84)=16.94$, $p<0.0001$], High [$F(14,98)=2.1$, $p<0.05$; $F(12,84)=19.24$, $p<0.0001$], and Good Effects [$F(14,98)=1.91$, $p<0.05$; $F(12,84)=18.01$, $p<0.0001$]. No differences were found for Bad Effects or Sick (data not shown). Figure 2 provides an illustrative example of these time course results for VAS ratings of Liking, highlighting differences as a function of route of administration. Overall, there was a pattern of generally higher ratings of Liking associated with IM compared to SL administration for a given dose of buprenorphine and buprenorphine/naloxone, with the magnitude of this difference greatest for the 4/1 and 16/4 mg buprenorphine/naloxone conditions (Figure 2).

Pairwise comparisons were performed for early time points (15, 30, 45 min) to capture differences in the onset of effects and are summarized in Table 2. Overall, the SL route of administration for both buprenorphine alone and in combination with naloxone did not significantly increase subjective ratings on VAS items when compared to placebo or hydromorphone during the first 45 minutes after administration. Generally, IM buprenorphine alone did not significantly alter subjective ratings compared to placebo or hydromorphone (4 mg). The combination of buprenorphine/naloxone (4/1 and 16/4 mg) administered intramuscularly significantly increased ratings on some VAS items (Table 2, Figure 2). These increases occurred earlier for the 16/4 versus 4/1 mg dose of buprenorphine/naloxone, suggesting the higher dose combination (16/4 mg) produced a quicker onset of action for these subjective measures.

The SL and IM routes of administration for buprenorphine and buprenorphine/naloxone also were compared within each dose. Generally, IM administration was associated with increased positive subject ratings (e.g., Drug Effect, Liking, High, Good Effects) compared to SL dosing (Table 2) with a statistically significant difference found for the intermediate dose of buprenorphine alone (8 mg).

In contrast to these buprenorphine alone findings, buprenorphine/naloxone (4/1 and 16/4 mg) administered intramuscularly increased ratings of Drug Effect, Liking, High, and Good Effects compared to the SL preparation ($p<0.05$). The addition of naloxone to buprenorphine (4/1 and 16/4) increased positive ratings following IM administration compared to placebo and hydromorphone (4 mg); however, there were no statistically significant differences between buprenorphine and buprenorphine/naloxone within a given dose or route of administration.

Discussion

In a previous study it was shown that SL administration of buprenorphine and buprenorphine/naloxone exhibited abuse liability and effects similar to a full mu opioid receptor agonist in non-dependent opioid users (Strain et al. 2000). However, that study did not address if the addition of naloxone alters the effects when given parenterally in non-dependent humans. The current study addressed this question by examining the relative abuse liability of buprenorphine and buprenorphine/naloxone administered both sublingually and intramuscularly in opioid users who were not physically dependent on opioids. Generally, buprenorphine and buprenorphine/naloxone engendered greater effects when a given dose was administered intramuscularly compared to sublingually. Both preparations produced mild to moderate increases in positive subject ratings, indicating some abuse potential. However, the finding in this study of a relatively flat dose-response function and a slow time to peak effect in response

to SL administration are features consistent with findings in other studies, and suggests a lower abuse potential of both buprenorphine and buprenorphine/naloxone when given sublingually compared to parenteral administration (Jasinski et al. 1978, Lewis 1985, Weinhold et al. 1992, Comer and Collins 2002).

The magnitude of effects produced in the present study by SL and IM buprenorphine and buprenorphine/naloxone was similar to that seen in previous studies (Jasinski et al. 1989, Jones et al. 1999, Preston and Bigelow 2000, Strain et al. 2000, Comer and Collins 2002). The peak effects analysis did not reveal statistically significant differences between doses within a given route of administration or between buprenorphine alone and in combination with naloxone within a given dose (Table 1). However, time course effects for each condition revealed a mild to moderate opioid agonist effect in response to buprenorphine and buprenorphine/naloxone. VAS ratings of Drug Effect, Liking, High, and Good Effects increased as SL and IM buprenorphine or buprenorphine/naloxone dose increased (Table 2, Figure 2). As expected, the addition of naloxone did not clearly or consistently attenuate the effects of SL buprenorphine (Strain et al. 2000). IM administration of buprenorphine/naloxone was associated with a non-orderly and non-statistically significant pattern of dose effects for subject ratings, suggesting variable modulation of buprenorphine by naloxone (Table 2, Figure 2). While these effects did not reach statistical significance, the use of higher doses or higher ratios of naloxone might have attenuated the effects of IM buprenorphine alone. The effects on subject ratings of the highest dose of IM buprenorphine/naloxone were significantly different from placebo and hydromorphone; however, comparisons of route of administration and the presence versus absence of naloxone within a dose were not significant (Figure 2).

Although the effects of the lower dose of IM hydromorphone (2 mg) were similar to those reported in previous studies (Strain et al. 2000, Walsh et al. 2001), the present effects were not dose-dependent. The 4 mg dose of hydromorphone failed to show robustly greater mu opioid agonist effects compared to the 2 mg dose. Previous studies that administered doses of hydromorphone to non-dependent opioid users reported dose-dependent increases in subject ratings on a variety of mu opioid agonist measures (Jones et al. 1999, Strain et al. 2000, Preston and Bigelow 2000, Walsh et al. 2001). The lack of dose-dependent effects for hydromorphone and the low magnitude of subject ratings for the 4 mg dose of hydromorphone is a limitation to the present study, and may reflect a lack of power to detect differences that might otherwise be revealed if higher doses or more subjects were studied. Given the extensive history of opioid use by the subjects studied (an average of 15 years of use), it seems unlikely this was a population that lacked familiarity with opioid effects. It is possible that the 72-hour time period between test sessions was not sufficiently long enough to allow adequate clearance of buprenorphine, which may contribute to these hydromorphone results.

The effects of buprenorphine and buprenorphine/naloxone combinations have been previously investigated in non-dependent volunteers with opioid experience (Weinhold et al. 1992, Strain et al. 2000, Comer and Collins 2002). Similar to the present findings, those studies concluded that buprenorphine/naloxone retained abuse potential in opioid users who are not physically dependent on opioids. Higher doses of naloxone relative to buprenorphine might attenuate the effects of IM buprenorphine if tested in the present study's procedures.

The present study did not collect blood samples, which would have been useful for analyzing pharmacokinetic profiles. There is variability in absorption and plasma levels of SL buprenorphine and buprenorphine/naloxone (Mendelson et al. 1997b, Chiang and Hawks 2003, Strain et al. 2004). While doses used were not weight-based, the doses and buprenorphine/naloxone ratios were clinically relevant (e.g., Mendelson and Jones 2003, Johnson et al. 2003). In an attempt to balance validity (i.e., IM versus intravenous route) and feasibility (e.g., often limited venous access in this population), the present study used the IM

route of administration. Intramuscularly and intravenously administered buprenorphine results in a similar plasma uptake and time course (Bullingham et al. 1981).

The present data suggest that the addition of naloxone at the doses and ratios tested may not confer any benefit in a non-dependent opioid abusing population, even by the IM route of administration. However, it is important to note that a lower dose ratio of buprenorphine to naloxone could be more effective in attenuating the abuse liability of parenteral buprenorphine in non-dependent opioid abusers (Weinhold et al. 1992). Such a higher relative dose of naloxone might, however, produce excessive opioid withdrawal in opioid dependent persons who inject buprenorphine/naloxone. The present findings suggest that at the doses tested, both buprenorphine and buprenorphine/naloxone have some abuse potential when administered either parenterally or sublingually by opioid users who are not physically dependent on opioids, that parenteral administration may have greater abuse potential than SL administration, and that the addition of naloxone has little impact for attenuating abuse of buprenorphine in the non-physically dependent population.

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Figure 1.

Peak change from baseline means ($\pm$ SEM) for visual analog item Drug Effect, observer rated Agonist, and pupil diameter for doses of hydromorphone (2, 4 mg), buprenorphine (4, 8, and 16 mg), and buprenorphine/naloxone (4/2, 8/4, and 16/8 mg). * $p \leq 0.05$ versus placebo.

Figure 2.

Visual Analog Scale for Liking following administration of each dose condition. Filled symbols indicate significant difference between routes of administration within dose condition.

* $p \leq 0.05$ versus placebo, ** $p \leq 0.05$ versus 4 mg hydromorphone.

Table 1

Peak Change from Baseline Analysis

	F	Placebo	HM (mg)			Buprenorphine (mg)						Buprenorphine/Naloxone (mg)					
			0	2	4	4		8		16		4/1		8/2		16/4	
						IM	SL	IM	SL	IM	SL	IM	SL	IM	SL	IM	SL
VAS																	
Drug Effect	<u>2.8</u>	7.3 (6.4)	12.4 (6.9)	10.0 (5.2)	19.5 (7.3)	5.0 (2.5)	21.1 (11.0)	13.1 (7.2)	26.3 (10.0)	20.0 (7.8)	27.8 (10.0)	5.1 (2.5)	11.1 (6.2)	8.3 (3.4)	29.5 (12.0)	8.9 (3.5)	
Liking	<u>2.5</u>	5.9 (5.5)	12.3 (7.0)	9.3 (5.1)	19.1 (7.2)	4.5 (2.4)	18.5 (10.0)	13.3 (7.4)	20.8 (8.3)	22.8 (7.2)	27.1 (10.0)	5.3 (2.1)	11.4 (6.0)	9.5 (3.9)	29.5 (13.0)	9.4 (3.4)	
High	<u>2.7</u>	7.3 (6.4)	12.4 (6.9)	10.3 (5.1)	19.0 (7.0)	4.5 (2.3)	20.4 (11.0)	13.0 (7.2)	26.1 (10.0)	19.5 (7.6)	26.8 (10.0)	5.4 (2.6)	11.5 (6.4)	8.4 (3.3)	24.3 (10.0)	8.8 (3.4)	
Good Effects	<u>2.6</u>	6.3 (5.8)	12.3 (7.0)	9.3 (5.0)	19.6 (7.3)	4.5 (2.3)	18.4 (10.0)	13.0 (7.1)	22.0 (8.6)	20.1 (6.5)	27.8 (10.0)	5.5 (2.5)	12.1 (6.4)	8.0 (3.1)	27.6 (11.0)	9.4 (3.6)	
Subject Adj																	
Agonist	1.6	2.0 (0.5)	1.3 (0.6)	3.0 (1.1)	2.6 (1.3)	1.8 (0.8)	4.9 (2.6)	2.6 (1.6)	4.0 (1.6)	2.3 (0.7)	3.3 (1.4)	1.5 (0.7)	1.5 (1.2)	4.4 (2.4)	3.4 (1.2)	4.1 (2.3)	
Observer Adj																	
Agonist	<u>2.8</u>	1.2 (0.4)	2.4 (0.6)	2.6 (0.4)	5.9 (1.4)	1.4 (0.4)	4.9 (1.1)	3.4 (1.0)	6.3 (1.7)	3.9 (0.7)	5.2 (1.5)	2.0 (1.2)	3.8 (1.0)	3.0 (1.1)	5.9 (1.2)	3.3 (0.8)	
Physiological Measures																	
Pupil Diameter (min)	<u>3.2</u>	-0.5 (0.2)	-1.7 (0.2)	-1.4 (0.2)	-1.7 (0.3)	-0.9 (0.1)	-1.5 (0.3)	-2.2* (0.3)	-1.9* (0.3)	-1.9* (0.2)	-1.7 (0.3)	-1.2 (0.4)	-1.4 (0.2)	-2.2* (0.3)	-2.2* (0.3)	-2.1* (0.4)	
O2 Sat (min)	<u>2.8</u>	-0.7 (0.3)	-1.3 (0.2)	-1.5 (0.2)	-1.2 (0.3)	-0.9 (0.2)	-1.8 (0.3)	-1.6 (0.3)	-1.9 (0.5)	-1.7 (0.2)	-1.9 (0.3)	-0.7 (0.3)	-1.7 (0.4)	-1.3 (0.2)	-2.0 (0.3)	-1.9 (0.3)	
Temp (max)	1.8	2.8 (1.2)	9.7 (2.4)	8.6 (2.4)	8.8 (2.3)	5.8 (2.0)	8.2 (1.8)	7.9 (1.8)	10.5 (1.8)	10.7 (2.7)	9.4 (2.5)	5.8 (1.9)	10.9 (2.6)	9.6 (2.2)	12.6 (2.0)	8.9 (2.4)	
Pulse (max)	<u>2.4</u>	-0.2 (1.6)	4.4 (1.9)	3.3 (1.6)	2.6 (2.0)	-0.5 (1.1)	3.2 (2.0)	0.3 (1.7)	4.5 (1.4)	4.2 (2.3)	2.4 (1.0)	1.8 (1.5)	2.4 (1.7)	0.4 (1.3)	3.2 (1.6)	0.5 (1.7)	
Diastolic BP (min)	0.8	-5.5 (3.2)	-3.8 (2.3)	-1.3 (2.2)	-6.3 (3.1)	-4.6 (2.1)	-4.9 (2.2)	-2.3 (1.7)	-5.9 (2.1)	-3.3 (2.3)	-5.3 (1.2)	-3.2 (1.7)	-5.6 (3.8)	-5.6 (2.3)	-8.0 (3.4)	-9.5 (2.9)	
Systolic BP (min)	0.7	-6.4 (3.2)	-6.2 (2.4)	-3.5 (2.3)	-9.7 (4.6)	-7.1 (3.2)	-4.9 (3.4)	-5.7 (2.3)	-5.9 (1.5)	-2.8 (2.1)	-6.5 (3.1)	-6.3 (1.7)	-5.5 (4.3)	-6.2 (2.2)	-6.5 (4.6)	4.3-(3.1)	

HM hydromorphone, IM intramuscular, SL sublingual, VLS visual analog scale, Adj adjectives, O2 oxygen saturation, Temp temperature, BP blood pressure, min minimum, max maximum

Underlined F ratio indicates a significant overall ANOVA (p < 0.05; df = 14,98); numbers are mean peak change from baseline (SEM)

* p ≤ 0.05 vs. placebo, Tukey's HSD; Trail-Making Line Length reported in cm

Table 2
Visual Analog Scale Items at Three Different Time Points for Each Drug Condition

VAS Item	Timepoint	F Cond (14,98)	F Time (12,84)	Placebo	HM (mg)				Buprenorphine (mg)				Buprenorphine/Naloxone (mg)			
					2		4		8		16		4/1		8/2	
					IM	SL	IM	SL	IM	SL	IM	SL	IM	SL	IM	SL
Drug Effect		<u>2.2</u>	<u>18.1</u>													
	15			2.5	10.6	5.1	6.9	1.5	14.0	1.6	8.1	3.5	9.1	1.9	6.4	1.5
	30			6.4	10.9	5.4	9.0	3.3	17.1 ^c	1.4	13.5	6.6	14.0	2.4	7.6	2.4
Liking	45			6.0	9.6	6.0	13.4	3.6	11.5	9.8	13.5	10.9	18.9 ^c	2.8	8.4	3.5
		<u>1.8</u>	<u>16.9</u>													
	15			2.9	10.6	4.3	5.8	1.4	14.1	1.6	8.5	3.6	9.6	2.1	6.0	1.4
High	30			5.4	10.9	5.9	8.5	3.5	16.9 ^c	1.6	14.8	7.1	14.6	2.4	7.3	1.8
	45			4.9	9.9	6.4	12.1	3.6	12.3	9.9	13.6	14.9	19.0 ^{ac}	2.9	9.0	3.3
		<u>2.1</u>	<u>19.2</u>													
Good Effects	15			2.5	10.5	5.3	6.0	1.4	13.9	1.6	8.3	3.5	8.6	2.0	6.5	1.8
	30			6.4	11.3	5.3	8.3	3.6	17.9 ^c	1.6	13.4	6.6	13.5	2.3	8.1	2.0
	45			5.9	9.9	6.4	12.8	3.8	12.5	9.6	13.0	11.0	18.1 ^c	2.9	9.0	3.0
Good Effects		<u>1.9</u>	<u>18.0</u>													
	15			2.6	10.6	4.9	7.0	1.6	13.8	1.8	8.8	4.0	9.4	2.0	7.3	1.5
	30			5.8	10.6	5.8	9.6	3.3	17.3 ^c	1.5	13.9	6.8	14.3	2.3	7.5	2.5
Good Effects	45			4.4	9.9	5.9	13.6	3.6	11.5	10.0	13.8	11.0	19.3 ^{abc}	2.8	8.1	3.5

Underlined *F* ratio indicates a significant difference ($p \leq 0.05$); numbers are means, *HM* hydromorphone, *IM* intramuscular, *SL* sublingual.

^a $p \leq 0.05$ vs. placebo at the same time point

^b $p \leq 0.05$ vs. HM (4mg) at the same time point

^c $p \leq 0.05$ vs. route of administration (IM vs. SL at each dose at the same timepoint)