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A Double Blind, within Subject Comparison of Spontaneous Opioid Withdrawal from Buprenorphine versus Morphine[S]

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ABSTRACT

Preliminary evidence suggests that there is minimal withdrawal after the cessation of chronically administered buprenorphine and that opioid withdrawal symptoms are delayed compared with those of other opioids. The present study compared the time course and magnitude of buprenorphine withdrawal with a prototypical μ-opioid agonist, morphine. Healthy, out-of-treatment opioid-dependent residential volunteers ($N = 7$) were stabilized on either buprenorphine (32 mg/day i.m.) or morphine (120 mg/day i.m.) administered in four divided doses for 9 days. They then underwent an 18-day period of spontaneous withdrawal, during which four double-blind i.m. placebo injections were administered daily. Stabilization and spontaneous withdrawal were assessed for the second opioid using the same time course. Opioid withdrawal measures were collected eight times daily. Morphine withdrawal symptoms were significantly ($P < 0.05$) greater than those of buprenorphine withdrawal as measured by mean peak ratings of Clinical Opiate Withdrawal Scale (COWS), Subjective Opiate Withdrawal Scale (SOWS), all subscales of the Profile of Mood States (POMS), sick and pain (0–100) Visual Analog Scales, systolic and diastolic blood pressure, heart rate, respiratory rate, and pupil dilation. Peak ratings on COWS and SOWS occurred on day 2 of morphine withdrawal and were significantly greater than on day 2 of buprenorphine withdrawal. Subjective reports of morphine withdrawal resolved on average by day 7. There was minimal evidence of buprenorphine withdrawal on any measure. In conclusion, spontaneous withdrawal from high-dose buprenorphine appears subjectively and objectively milder compared with that of morphine for at least 18 days after drug cessation.

Introduction

Buprenorphine is a derivative of the morphine alkaloid thebaine and is an efficacious treatment of opioid use disorders (Johnson et al., 2000; Mattick et al., 2008) and moderate to severe pain (Wolff et al., 2012). It is a partial agonist at the μ-opioid receptor (MOR), with lower buprenorphine doses producing prototypical agonist effects (e.g., analgesia and miosis) and higher doses producing antagonist effects when given to individuals maintained on another primary MOR agonist (Strain et al., 1995). Buprenorphine's partial agonist properties can be explained by its greater MOR affinity compared with that of other opioids (Dum and Herz, 1981; Lee et al., 1999), allowing buprenorphine to competitively displace other MOR agonists. In addition, buprenorphine has a long duration of action, which is likely due to its slow dissociation from MOR (Greenwald et al., 2007). Most of its pharmacodynamic effects are related to activity at the MOR, although buprenorphine is a weak κ-opioid receptor antagonist (Lewis and Husbands, 2004), δ-opioid receptor antagonist (Negus et al., 2002), and nociceptin receptor agonist (Bloms-Funke et al., 2000). Recent evidence shows that concomitant activation of nociceptin receptors by buprenorphine inhibits its antinociceptive properties mediated through MOR activation (Lutfy et al., 2003; Yamamoto et al., 2006). Therefore, nociceptin receptor agonist activity may explain buprenorphine's bell-shaped curve of analgesic properties across increasing doses.

One potential clinical advantage of buprenorphine is due in part to its low level of physical dependence. Opioid physical dependence can be demonstrated by abrupt discontinuation of chronically administered drug (spontaneous withdrawal) or the acute administration of an opioid antagonist (precipitated

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ABBREVIATIONS: ANOVA, analysis of variance; CNS, central nervous system; COWS, Clinical Opiate Withdrawal Scale; DBP, diastolic blood pressure; DSM, Diagnostic and Statistical Manual of Mental Disorders; DSST, digit symbol substitution task; HR, heart rate; ISI, Insomnia Severity Index; HSD, honestly significant difference; MOR, μ-opioid receptor; NIDA, National Institute on Drug Abuse; POMS, Profile of Mood States; PSQI, Pittsburgh Sleep Quality Index; RR, respiratory rate; RRU, residential research unit; SBP, systolic blood pressure; SL, sublingual; SOWS, Subjective Opiate Withdrawal Scale.

withdrawal). Both these methods produce signs and symptoms of the classic opioid withdrawal syndrome (e.g., body aches, rhinorrhea, pupillary dilatation) (Himmelsbach, 1941). There have been conflicting reports from laboratory studies of buprenorphine physical dependence. Early preclinical studies showed little evidence of spontaneous or precipitated buprenorphine withdrawal in patas monkeys (Cowan et al., 1977) or in rats (Dum et al., 1981), but chronic spinal dogs showed signs of withdrawal (Martin et al., 1976).

An early human clinical pharmacology study assessed the effects that occurred after abrupt cessation of 8 mg s.c. of daily buprenorphine in three participants and found that a low level of withdrawal symptoms was produced (Jasinski et al., 1978). This withdrawal tended to have a delayed peak, occurring approximately 2 weeks after the last dose of buprenorphine. Another study examined withdrawal in 19 heroin-dependent participants after cessation of 8 mg of daily sublingual (SL) buprenorphine and found no objective withdrawal signs during 15 days of observation; but mild subjective withdrawal symptoms did occur, peaking on days 3 to 5 and lasting up to 10 days (Fudala et al., 1990). A third study examined withdrawal after a 5-day supervised buprenorphine detoxification and demonstrated a lack of withdrawal symptoms in all participants during a 30-day observation period (Mello and Mendelson, 1980). Human laboratory studies using a naloxone challenge were able to precipitate withdrawal in buprenorphine-maintained participants (Kosten, 1990; Nigam et al., 1994), but one controlled study showed that it took approximately 10 times greater doses of naloxone or naltrexone to precipitate buprenorphine-related withdrawal compared with participants maintained on morphine or methadone (Eissenberg et al., 1996).

Each of the existing human laboratory studies has one or more significant limitations: few participants (Jasinski et al., 1978), low buprenorphine maintenance doses (Jasinski et al., 1978; Mello and Mendelson, 1980; Fudala et al., 1990), short periods of follow-up (Correia et al., 2006), or lack of a control group (Jasinski et al., 1978; Mello and Mendelson, 1980; Fudala et al., 1990). There is also a lack of controlled withdrawal studies from a buprenorphine daily maintenance dose greater than 8 mg. Current treatment guidelines recommend SL maintenance doses between 16 and 24 mg (Center for Substance Abuse Treatment, 2004). Thus, assessing a controlled withdrawal procedure using a higher maintenance dose of buprenorphine is needed.

This within-subject study was designed to address prior study limitations and systematically examined spontaneous withdrawal from buprenorphine (32 mg daily i.m. dose) compared with morphine (120 mg i.m.) during a 59-day residential stay in seven nontreatment-seeking opioid-dependent volunteers. Although not equipotent, these doses and routs of administration were chosen to maximize the potential of demonstrating withdrawal after cessation of both opioids and to maintain blinding. It was hypothesized that morphine cessation would produce a typical opioid withdrawal syndrome, predominantly occurring within the first week. In contrast, buprenorphine cessation was expected to produce withdrawal symptoms that had a slower onset and delayed peak relative to morphine's profile.

Materials and Methods

Participants. The study was approved by the Johns Hopkins Institutional Review Board, and each participant provided written informed consent prior to participation. To be eligible for the study, participants had to be between 21 and 55 years of age; meet *Diagnostic and Statistical Manual of Mental Disorders IV* (DSM-IV; American Psychiatric Association, 2000) criteria for current opioid dependence and show evidence of active opioid use; be willing to undergo opioid detoxification; be in good health without evidence of chronic pain; and be fluent in English. Eligibility was assessed via medical history and physical examination, electrocardiogram, blood chemistry, hematology, urinalysis, breathalyzer, and structured psychiatric examination (First et al., 2002). Individuals were excluded if they had a documented allergy to buprenorphine or morphine, met DSM-IV criteria for dependence on other drugs of abuse except for tobacco, had current significant use of alcohol or sedative/hypnotics, were pregnant, showed evidence of QTc prolongation on electrocardiogram, or were seeking treatment of their substance dependence. If individuals did express interest in treatment, they were referred to local addiction treatment providers.

Twelve male participants met entry criteria and began the 59-day residential protocol; there were seven completers. Although women were recruited, no women met the inclusion and exclusion criteria for this study. Five participants did not complete the protocol. Four men left voluntarily because of opioid withdrawal symptoms (all during morphine withdrawal), and one was withdrawn by study investigators because of an insufficient supply of study medication). Of the men who left because of opioid withdrawal symptoms, three received morphine first and left during the first cycle of withdrawal, and one received morphine second and left during the second cycle of withdrawal. There were no significant demographic differences between completers and noncompleters, except in the Symptoms Checklist-90 Anxiety subscale T-scores, with completers having higher levels of anxiety during screening compared with noncompleters (Table 1).

Study Setting. Participants resided in a 14-bed residential research unit (RRU), which was staffed 24 hours a day by licensed nursing personnel. Recreational activities, exercise equipment, arts and crafts projects, television, video games, and Internet access were available on the unit. Abstinence from drugs other than those administered experimentally was achieved by the security of the closed unit and was confirmed by weekly random urine toxicology testing. Participants were maintained on a caffeine-free diet and allowed to smoke freely except during testing sessions.

General Methods. Participants were admitted to the RRU and instructed that they would undergo periods of opioid withdrawal but were not told the number, length, or duration of withdrawal periods. They were also instructed that they could receive drugs from a number of classes besides opioids, including stimulants, sedatives, and opioid blockers throughout the trial; this instruction regarding the variety of drugs was done to reduce expectancy bias. When participants were first admitted to the residential unit, they were escorted to the laboratory session room by the research data assistant and familiarized with the experimental equipment and procedures. Each day in the RRU was meant to be the same for participants and research staff. Participants received intramuscular injections of study medication at 6:00 AM, 10:00 AM, 4:00 PM, and 10:00 PM. Thirty minutes before and after each injection, the participant and research staff completed standardized assessments of opioid agonist and withdrawal effects. Once daily (1:30 PM), participants also completed a set of cognitive tasks. Although not reported here, there were 10 days spread throughout the study during which participants underwent quantitative sensory testing to assess withdrawal-associated hyperalgesia and more comprehensive cognitive testing to assess differences between withdrawal conditions. During the course of the study, participants could request concomitant medications for the treatment of withdrawal that were similar to those used in clinical practice. However, no opioid agonist medications were available to the participants. Further details of assessments and study medications are provided in the following sections.

TABLE 1
Participant demographics

	Completer (n = 7)	Noncompleter (n = 5)	Total (N = 12)	P Value
African-American (%)	86	80	83	0.79
Age, yr (S.D.)	48.6 (3.4)	44.6 (3.3)	46.9 (3.8)	0.07
Education ≥12 yr (%)	57	100	75	0.09
Heroin use metrics				
Length of use, yr (S.D.)	9.6 (5.9)	9 (7.28)	9.4 (6.2)	0.87
No. of days used in past month (S.D.)	26.7 (5.8)	30 (0)	28.1 (4.6)	0.24
Amount per using day ($)	38.6 (9.4)	126 (127)	75 (90)	0.20
Route (% i.v.)	43	20	33	0.57
Percent (%) reporting other drug use at admission				
Alcohol	71	80	75	1.00
Cocaine	43	40	42	1.00
Cannabis	43	20	33	0.57
Benzodiazepine	0	0	0	–
No. of prior opioid detoxifications (S.D.)	1.3 (1.2)	2 (1.2)	1.6 (1.2)	0.35
Symptoms Checklist-90 T-scores (S.D.)				
Global Severity Index	63.4 (14.9)	53 (11.7)	59.1 (14.1)	0.22
Depression	66.9 (11.3)	59.6 (9.3)	63.8 (10.7)	0.27
Anxiety*	61 (13.4)	46.4 (6.7)	54.9 (13)	0.03
Body mass index (S.D.)	28.3 (6)	26.5 (8.3)	27.6 (6.8)	0.66
Percent (%) randomized to morphine first	43	60	50	0.56

*$P < 0.05$. Amount per using day ($) = amount of money spent on opioids per day of opioid use. Symptoms Checklist-90 obtained at screening. T-scores normalized for a nonpatient population.

Measures. This study involved the collection of five types of opioid withdrawal measures: observer-rated, subject-rated, psychomotor and cognitive performance, physiologic, and sleep. Previous studies have demonstrated the sensitivity of these multidimensional outcome measures for detecting the agonist and antagonist effects of opioids (e.g., see Preston and Bigelow, 1993; Strain et al., 2000; Stoller et al., 2001). Participants and staff were asked to rate the level of withdrawal or agonist effects at the moment of scale completion.

The Clinical Opiate Withdrawal Scale (COWS) (Wesson and Ling, 2003; Tompkins et al., 2009), an observer-rated tool for quantifying opioid withdrawal, was the a priori primary outcome measure. Subject-reported measures included the Subjective Opioid Withdrawal Scale (SOWS) (Handelsman et al., 1987), Visual Analog Scale (VAS), and the Profile of Mood States (POMS) (McNair et al., 1971). The VAS consisted of seven questions:

Do you feel any *drug effect*?
Does the drug have any *good effects*?
Does the drug have any *bad effects*?
How *high* are you?
Does this drug make you feel *sick*?
Do you *like* the drug?
How much *pain* are you experiencing?

Using a computer mouse, participants responded by positioning an arrow along a 100-mm line labeled at either end with "None" and "Extremely" to yield a score between 0 and 100.

Psychomotor and cognitive tasks were done once daily and included the digit symbol substitution task (DSST), digit recall, circular lights, and trail-making task. The DSST is a component of the Wechsler Adult Intelligence Scale and is frequently used to assess psychomotor performance changes associated with drug effects. A computerized version of the DSST has been developed and shown to be sensitive to the effects of sedating drugs (McLeod et al., 1982). Digit recall is a task that assesses working memory (Kirk et al., 1990; Mintzer and Griffiths, 2003). Participants used a numeric keypad to reproduce 10 randomly selected eight-digit numbers, which were displayed on a computer screen one eight-digit number at a time. The circular lights task assessed psychomotor functioning using a commercially available device. Previous research had shown this task to be sensitive to the sedating effects of drugs (Griffiths et al., 1983). A Macintosh-based task analogous to the Trail-Making Test (Reitan, 1958; Mintzer et al., 1997) was used. In Trail-Making A, which measures psychomotor speed, the computer screen presented a distribution of squares that contained numbers, and the subject was instructed to use a mouse to connect the squares in numerical sequence. In Trail-Making B, which measures set shifting and conceptual flexibility (executive function), the squares contained letters and numbers, and the subject was instructed to use a mouse to connect the squares after an alternating sequence of numbers and letters (e.g., 1, A, 2, B, 3, C).

Physiologic measures collected were respiratory rate (RR), arterial oxygen saturation, skin temperature, systolic and diastolic blood pressure (SBP and DBP), heart rate (HR) and pupil diameter. These were measured by nursing staff at the same time as other measures (30 minutes before and after each injection). RR (breaths per minute) was recorded by an observer who counted the number of breaths taken by the subject for a 30-second period and multiplied by 2. Oxygen saturation, skin temperature, SBP and DBP and HR were collected by use of an automatic physiologic monitoring device (Noninvasive Patient Monitor model 506; Criti-care Systems, Waukesha, WI). Pupil diameter was assessed with a digital pupilometer (Neuroptics, Inc., Irvine, CA) in constant room lighting.

Assessments of sleep included the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) and the Insomnia Severity Index (ISI; Bastien et al., 2001). The PSQI and ISI were modified to be collected once a week.

Medications. Morphine, buprenorphine, and placebo intramuscular injections were prepared by pharmacy staff and administered by trained nursing staff using double blind procedures. All injections were of the same volume (1.0 ml) and administered in the deltoid muscles, alternating sides between successive administrations. Dosing occurred at the same times as used in prior studies conducted by the National Institute on Drug Abuse (NIDA) Addiction Research Center. The placebo injection was prepared from bacteriostatic saline (0.9% NaCl). The active morphine condition consisted of a total daily dose of 120 mg (i.e., 30 mg four times per day) and was prepared using a commercially available supply (Hospira, Inc., Lake Forest, IL). This dose was selected to represent the middle of the range of morphine maintenance doses used in studies conducted at NIDA's Addiction Research Center (Jasinski, 1977) that reliably produced demonstrable opioid withdrawal when placebo doses were substituted. The goal was to show that participants in the study were sensitive to detecting opioid withdrawal, and the dose was not selected to be equipotent to the dose of buprenorphine. Although such would be ideal, the relative

dose potency of buprenorphine has been estimated to be 25 to 50 times that of morphine (Jasinski et al., 1978), suggesting that excessively high morphine doses (e.g., 800 mg) would have been needed for this study. The active buprenorphine condition consisted of a total daily dose of 32 mg i.m. (i.e., 8 mg four times per day) and was prepared using buprenorphine hydrochloride (Research Triangle Institute, NC) and sterile water. As intramuscular buprenorphine has a 90%–100% relative bioavailability (Bullingham et al., 1980) and SL buprenorphine has a 60%–70% bioavailability during maintenance dosing (Strain et al., 2004; Compton et al., 2006), 32 mg i.m. represents a total buprenorphine dose that is approximately 33% greater than the highest recommended SL buprenorphine maintenance dose (32 mg). However, the 32-mg i.m. buprenorphine dose used in this study was selected to maximize the opportunity to detect buprenorphine-related withdrawal.

Commercially available medications that participants could request to help treat opioid withdrawal symptoms included clonidine, zolpidem, acetaminophen, ibuprofen, dicyclomine, diphenhydramine, loperamide, magnesium hydroxide, simethicone, and an antacid. These were dispensed using clinical judgment by nursing staff typical of an inpatient detoxification ward.

Data Analysis. All analyses were performed using Stata version 11 (StataCorp, LLP, College Station, TX). The prespecified primary outcome variable was the COWS. Peak scores on each measure were determined for each day of withdrawal, and data were analyzed using repeated-measures one-factor (withdrawal condition, morphine vs. buprenorphine) analysis of variance (ANOVA). Pairwise comparisons for significant main effects were examined using a conservative one-step procedure, Tukey's honestly significant difference (HSD). Statistical significance was indicated when $P < 0.05$. Time-course differences were examined using two-factor repeated measures ANOVA (withdrawal condition, time, and condition-×-time). Of most interest for this study were day-by-day comparisons of withdrawal during the two 18-day placebo administration phases (Fig. 1). Similar ANOVA procedures were also done for change from baseline (last day of active medication administration) values for each measure. The last 4 days of data during the final placebo administration phase were not used. The additional days in the fourth phase were designed to control for possible expectancy effects by participants as they neared the end of their study time because they were told they would be withdrawn from opioids by the end of the study.

Results

Findings were consistent for a wide variety of measures that the placebo dosing period after morphine was associated with significantly greater opioid withdrawal compared with the corresponding placebo dosing period after buprenorphine. The mean peak subjective and objective ratings of morphine withdrawal occurred on day 2, with most measures showing resolution of morphine withdrawal by day 7. Little evidence of withdrawal was seen during the 18 days after cessation of buprenorphine.

Observer-Rated Measures. On repeated-measures two-factor ANOVA of mean peak daily COWS ratings, a significant condition-×-time interaction effect was observed ($F = 7.07$, df = 17, $P < 0.0001$). Figure 2A illustrates the time course of mean peak COWS ratings during 18-day withdrawal period, with day 0 indicating ratings on the last day of active drug maintenance. All seven participants demonstrated opioid withdrawal after the cessation of morphine administration. Comparing morphine with buprenorphine, significant differences on Tukey's HSD analyses were found between mean daily peak COWS ratings on days 1–4 of the withdrawal period, with day 2 of morphine withdrawal showing the largest mean peak COWS ratings. Morphine withdrawal largely resolved by day 5. After buprenorphine cessation, there were no days when mean peak COWS ratings were ≥5 (a score <5 indicates an absence of withdrawal) (Wesson and Ling, 2003). An analysis using change from baseline values showed similar findings (Supplemental Table 1).

Subject-Rated Measures. On repeated-measures two-factor ANOVA of mean peak daily SOWS ratings, a significant condition-×-time interaction effect was noted ($F = 5.44$, df = 17, $P < 0.0001$). Figure 2B shows the time course of the mean peak SOWS ratings. Like the COWS ratings, significant differences were seen on Tukey's HSD analyses between SOWS ratings on days 1–4 for morphine versus buprenorphine withdrawal, with day 2 of morphine withdrawal showing the largest mean peak SOWS ratings. On days 9, 10, and 15 of buprenorphine withdrawal, mean daily peak SOWS scores were >5, but these scores were not statistically different from those with morphine. An analysis using change from baseline values showed similar findings (Supplemental Table 1).

On repeated-measures two-factor ANOVA of mean peak daily POMS ratings, significant main effects of condition were observed for each of the six subscales and for total mood disturbance (Table 2). Significantly higher mean peak ratings were noted for total mood disturbance during days 2 and 3 of morphine withdrawal compared with buprenorphine withdrawal (Fig. 3A). Some evidence of buprenorphine withdrawal was seen during the 2nd week of the 18-day period, with significantly lower mean ratings compared with morphine on the vigor subscale (Fig. 3B). In addition, the mean total mood disturbance rating for buprenorphine was 20.9 versus 6.9 for morphine on day 17, but this difference was not statistically significant. An analysis using change from baseline values showed findings similar to those seen with these analyses (Supplemental Table 1), except that the confusion-bewilderment subscale no longer had a significant main effect of withdrawal condition (Table 2).

On repeated-measures two-factor ANOVA for the mean peak daily VAS ratings, significant main effects for condition on *high*, *sick*, and *pain* were noted during the 18-day withdrawal period (Table 2), as well as significant effects for time on *good effects*, *bad effects*, and *sick*. Mean peak *sick* rating occurred on day 1 of morphine withdrawal, which was the only day with significant differences between conditions (Fig. 3C). During buprenorphine withdrawal, the largest mean peak daily VAS ratings of *sick* occurred during the first 2 days, but then ratings dropped to <10. Mean peak *pain* VAS ratings were highest on day 2 for morphine withdrawal, whereas there were *pain* VAS ratings >10 (indicating mild withdrawal-associated hyperalgesia) during the 2nd week of withdrawal for both conditions (Fig. 3D). Because there were large differences between buprenorphine and morphine on their VASs on the last day of active medication administration, change from baseline ANOVA showed different results, then

Fig. 1. Experimental design.

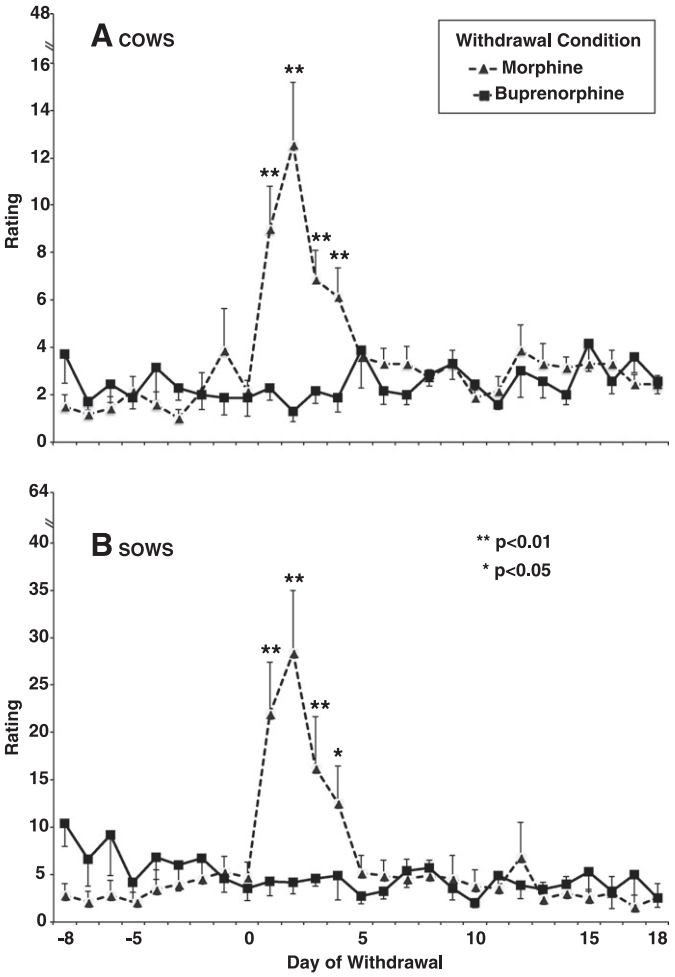

Fig. 2. Mean Peak Daily Clinical Opiate Withdrawal Scale (COWS) and Subjective Opiate Withdrawal Scale (SOWS) ratings (± S.E.M.) during and after active drug cessation.

daily peak rating ANOVA, for these measures. All VASs on change from baseline ANOVA showed a significant main effect for withdrawal condition (Supplemental Table 1). No significant effects of time or condition-×-time of change were observed from baseline ANOVA.

Physiologic Measures. For pupil diameter results, a significant condition-×-time interaction effect was seen ($F = 8.8$; df = 17; $P < 0.0001$). Figure 4A shows mean maximum daily pupil diameter during the two 18-day withdrawal periods. Pupil dilation occurred rapidly during morphine withdrawal and stabilized by day 2, whereas dilation occurred more gradually during buprenorphine withdrawal. Mean maximum pupil diameters were significantly different for morphine and buprenorphine until day 9 of the withdrawal periods.

On repeated-measures two-factor ANOVA for mean peak daily vital signs, significant main effects for condition on SBP, DBP, HR, and RR, as well as significant effects for time on RR (Table 2), were observed. Significant differences were seen between conditions during the first week for SBP, DBP, and HR (Fig. 4, B and C). Mean peak SBP and DBP occurred on day 2 of morphine withdrawal, whereas mean peak HR occurred on day 5. Change from baseline ANOVA showed similar findings on all physiologic measures, except SBP did not show a main effect of withdrawal condition (Supplemental Table 1).

Psychomotor and Cognitive Measures. On repeated-measures two-factor ANOVA, no significant main effect of withdrawal condition was seen on percent trials correct for digit recall (Table 2). Significant main effects were noted of the condition on DSST percent trials correct, Trails A and Trails B completion times, and number of responses correct on the circular lights task, as well as a significant main effect of time on the circular lights task. Post hoc analyses (Tukey's HSD test) revealed that DSST percent of trials correct was significantly higher on day 14 of morphine withdrawal (mean = 92.5%) versus day 14 of buprenorphine withdrawal (mean = 70.2%). In addition, participants completed the Trails A task significantly more quickly on day 12 of morphine withdrawal (mean = 41.1 seconds) compared with day 12 of buprenorphine withdrawal (mean = 65.6 seconds), indicating quicker psychomotor speed. Participants completed Trails B significantly more quickly on day 6 of morphine withdrawal (mean = 54.9 seconds) compared with day 6 of buprenorphine withdrawal (mean = 123.7 seconds), indicating more effective executive function. Finally, significantly more correct responses were seen on day 10 of morphine withdrawal (mean = 78.4) compared with day 10 of buprenorphine withdrawal (mean = 71.4) on the circular lights task. Change from baseline ANOVA showed a significant main effect of withdrawal condition for digit recall and circular lights, but not for DSST, Trails A, or Trails B, perhaps as a result of the baseline differences on each cognitive measure on the last day of buprenorphine compared with morphine maintenance (Supplemental Table 1).

Sleep Measures. For PSQI total scores, there was a significant main effect for withdrawal condition ($F = 7.36$, df = 1, $P = 0.015$), but not for time (for these measures only, time = week of withdrawal) or condition-×-time. No significant findings were seen on two-factor ANOVA of ISI total scores. Post hoc testing showed a significantly higher PSQI total score during the last 2 weeks of morphine withdrawal compared with buprenorphine [week 2 morphine vs. buprenorphine, (S.E.M.): 10.3 (1.7) vs. 5.5 (2); week 3: 11.3 (2.3) vs. 6.9 (1.5). Higher scores on the PSQI indicate worse sleep quality (Buysse et al., 1989). No significant effects on condition, time, or condition-×-time occurred as change from baseline ANOVA (Supplemental Table 1).

Concomitant Medications for Opioid Withdrawal. The number of doses of opioid withdrawal treatment medications per day was averaged for each placebo dosing period and compared. A significant condition-×-time interaction effect ($F = 2.49$, df = 17, $P = 0.0024$) was noted. The peak in the number of medications consumed after morphine cessation corresponded to the peak subjective and objective withdrawal measures (Fig. 5). Even though morphine withdrawal signs and symptoms had mostly resolved by day 5, significantly more doses of medications were still consumed compared with buprenorphine withdrawal until day 11. A small increase occurred in the mean number of medications consumed at the end of buprenorphine withdrawal (days 16–18). An analysis of change from baseline in the number of concomitant medications used showed a similar pattern of findings (Supplemental Table 1).

Discussion

Across a broad range of measures, this study found that abrupt cessation of daily morphine in opioid-dependent individuals, compared with abrupt cessation of buprenorphine,

TABLE 2
Analysis of variance results and mean daily peak values of Profile of Mood States (POMS), Visual Analog Scale (VAS), vital signs, and psychomotor/cognitive tasks during withdrawal

	Condition		Time		Drug	Day of Withdrawal																	
	F	df	F	df		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
POMS																							
Tension-anxiety	11.76**	1	1.1	17	M	5.9	9.7	**14.4**	**10.9**	10.0	**10.3**	6.9	7.1	6.4	7.1	4.9	7.7	6.9	4.1	3.6	4.3	5.1	3.9	6.7
				17	B	5.3	7.4	**6.0**	**3.9**	9.0	**3.6**	4.3	4.0	5.6	4.3	3.3	5.1	5.1	5.1	5.4	5.0	4.6	7.6	3.9
Depression-dejection	15.53**	1	1.2	17	M	3	6.7	**15.0**	**11.7**	9.6	4.7	6.1	4.9	6.9	4.7	5.1	5.7	4.9	3.3	3.0	2.4	4.4	4.0	4.6
				17	B	4.3	5.3	**3.4**	**2.4**	5.0	3.7	3.6	2.4	3.3	1.6	1.9	2.4	2.7	3.4	2.4	2.6	3.1	5.4	2.0
Anger-hostility	12.19**	1	0.6	17	M	1.9	3.1	**13.7**	**10.1**	**9.9**	7.6	4.6	**10.1**	6.7	6.9	4.9	6.0	4.7	3.7	3.9	2.3	5.9	5.4	3.3
				17	B	2.9	5.1	**1.9**	**1.6**	**2.4**	4.0	4.3	**1.0**	3.1	2.0	1.9	1.7	1.7	2.7	2.0	2.6	3.9	8.4	2.0
Vigor	7.95**	1	0.09	17	M	14.9	14.4	13.1	13.9	17.4	16.7	16.6	17.9	15.9	16.9	17.0	18.1	18.3	18.4	**19.1**	**19.0**	18.1	17.7	17.4
				17	B	14.1	16.0	16.1	16.1	16.3	15.7	14.6	15.7	13.3	16.0	16.3	14.3	13.4	15.9	**14.1**	**12.9**	13.7	16.3	15.7
Fatigue	8.67**	1	0.7	17	M	4	7.6	**12.3**	**7.6**	7.9	3.9	4.1	3.9	3.1	4.0	3.1	4.6	2.6	3.0	4.1	3.3	3.9	2.7	4.1
				17	B	5.4	4.9	**4.1**	**2.9**	4.1	2.3	2.1	1.7	3.9	3.6	2.4	2.7	3.9	3.1	2.4	3.4	3.9	4.3	2.9
Confusion-bewilderment	6.04**	1	0.92	17	M	5.4	6.4	**9.6**	**8.1**	8.3	4.9	4.4	5.0	5.1	4.9	4.0	4.7	4.1	3.6	3.9	3.7	4.4	4.3	4.0
				17	B	4.7	5.4	**4.6**	**3.6**	5.7	3.9	3.3	3.0	4.0	3.9	3.9	3.4	4.1	3.7	3.7	4.0	4.9	6.6	3.1
Total mood disturbance	7.54**	1	0.84	17	M	6.4	24.6	**54.6**	**36.9**	33.9	16.9	12.6	15.9	14.4	12.3	7.4	13.1	7.4	3.4	2.3	4.1	9.9	6.9	7.0
				17	B	11.6	16.3	**8.6**	**0.9**	15.3	5.9	6.3	0.7	8.1	3.7	0.4	5.1	6.0	6.6	5.1	7.0	8.9	20.9	3.6
VAS																							
High	6.07*	1	1.06	17	M	16.6	**5.9**	**11.9**	**4.6**	14.6	15	22	15	11.3	16.9	4.6	7.4	15.4	11.7	3.3	0.6	11.9	9.9	1.1
					B	57.7	**50.4**	**42.4**	**34.7**	23.1	12.9	11.4	11	11.4	11.6	20.6	12.1	11.4	12	11.4	8.6	10.1	2	2.6
Liking	0.03	1	1.57	17	M	16.9	37.6	24.3	19.6	34.7	21.7	20.9	22	17	26.4	10.3	7.9	7.1	0.9	7.4	0.6	4.1	5.4	2.6
					B	33.7	29	31	23.9	16.4	15.3	13.3	12	16.3	16.3	19.3	11.6	11.1	9.6	9	7.1	12.4	1.9	6.6
Drug effects	1.29	1	1.59	17	M	15.3	33.3	32.9	19.6	29.4	14.1	17.1	18.9	14.7	18.7	4.9	17.6	16	10.4	3.9	0.6	12.6	9.6	0.9
					B	57.9	50.6	35	35.3	22.9	14.6	13.3	11.6	14.6	13.4	20.9	15.7	17.3	24.6	16.7	7.6	10.7	9.9	2.7
Good effects	3.25	1	1.75*	17	M	14.7	**19.6**	26.6	20	31	19	20.7	18.7	14.3	21.1	5	14.9	2.4	1.1	2.1	0.7	1.1	9.1	2
					B	47.4	**47.9**	44.2	34	24.7	13.3	10.9	11.7	13.4	14.7	22	12.9	15.9	18	9.7	7.3	11.4	1.6	4
Bad effects	3.22	1	2.34**	17	M	19.3	**46.7**	30.4	20.1	20.1	16.4	15.3	14.6	2.0	27.6	0.6	2.6	15.0	4.1	1.9	0.4	1.0	3.1	0.6
				17	B	27.4	**19.7**	29.4	15.9	14.6	3.3	1.3	2.4	1.0	3.7	0.6	7.0	9.4	3.7	10.1	1.3	1.6	3.9	0.4
Sick	8.69**	1	2.49**	17	M	14.7	**56.9**	34.4	15.4	18.9	14.9	14.9	0.3	13.7	6.3	0.4	0.6	0.9	2.7	4.7	0.9	1.4	1.6	1.1
				17	B	14.9	**14.0**	18.0	1.7	3.6	2.9	0.3	1.6	0.6	3.6	0.7	4.0	7.3	5.1	1.7	0.3	1.9	2.1	0.3
Pain	8.25**	1	0.96	17	M	6.1	**29.3**	**51.6**	**33.1**	**29.9**	20.1	20.3	11.9	6.7	17.0	13.4	4.1	11.7	7.4	6.9	15.6	3.1	7.7	5.9
				17	B	2	**6.3**	**13.3**	**9.4**	**8.6**	11.4	8.6	8.6	13.6	8.6	6.3	8.3	9.1	12.7	7.9	12.9	11.6	6.7	9.4
Vital signs																							
SBP	3.93*	1	0.55	17	M	138	142	**148**	**146**	139	139	135	139	139	136	135	134	133	132	131	133	130	131	132
				17	B	135	135	**135**	**135**	135	137	132	133	133	128	133	133	131	136	135	129	134	137	139
DBP	16.18**	1	0.4	17	M	80	85	**91**	**89**	86	86	**86**	83	87	83	83	84	83	84	85	83	83	83	83
				17	B	83	83	**85**	**81**	81	82	**78**	79	83	80	80	82	81	81	82	82	83	85	84
HR	36.41**	1	0.5	17	M	84	91	95	**95**	**94**	**102**	96	**96**	**98**	96	94	99	99	96	101	96	99	97	93
				17	B	84	85	87	**86**	**83**	**86**	89	**87**	**87**	91	90	92	92	93	94	91	93	94	96
RR	23.68**	1	2.74**	17	M	18	18	19	19	19	17	18	17	**21**	**22**	20	18	**19**	18	19	20	20	20	**20**
				17	B	18	17	17	17	17	18	17	18	**17**	**18**	19	18	**17**	16	18	20	19	19	**17**
Psychomotor/cognitive																							
Digit recall	0.84	1	0.19	17	M	41.4	31.4	31.4	21.4	34.3	48.3	32.9	34.3	44.3	44.3	37.1	42.9	34.3	**48.6**	34.3	42.9	52.9	38.3	35
				17	B	33.3	28.6	31.4	34.3	32.9	32.9	30	28.6	42.9	35.7	38.6	32.9	38.6	**30**	40	38.6	40	47.1	42.9
DSST	16.99**	1	0.24	17	M	94	89	88	92	91	90	90	91	96	98	91	97	95	92	**93**	93	96	90	94
				17	B	79	77	79	82	79	79	80	74	82	80	80	79	78	86	**70**	95	78	92	77
Trails A	10.73**	1	0.55	17	M	51.2	51	50.3	56.8	44.2	49.7	39.3	42.1	46.2	41.8	43.4	39.2	**41.1**	37.2	37.2	39.9	42.4	37.1	41.8
				17	B	59.5	52.3	53.5	46.7	44.5	55.9	52.8	57.6	48.5	45.7	47.4	53.7	**65.6**	48.1	42	45.5	47.6	45.7	48
Trails B	5.06*	1	0.94	17	M	74.2	89.2	63.4	88.6	53.6	66.4	**54.9**	57	65.9	58.5	55.7	49	52.7	53.1	49.2	50.2	49.8	52	57.1
				17	B	89.7	99.2	73.2	65.9	72.1	63.8	**123.7**	69.2	68.5	71.2	58.2	67.6	71.7	56.6	50.9	75	58.7	64.2	65.2
Circular lights	12.26**	1	2.30**	17	M	66.3	68.7	64.4	67	71	70	72	76.1	73.9	77.6	**78.4**	76	75.7	74.3	78	78.3	78.9	75.6	79
					B	66	65.7	68.3	66.9	67.4	66	69.5	70.6	71.3	76.3	**71.4**	71.1	72.1	73.7	78	75.4	73.1	76.4	76

* $P < 0.05$; ** $P < 0.01$. Values in boldface represent $P < 0.05$ when comparing M vs. B on a given day of withdrawal. Two-factor ANOVA was performed for withdrawal condition and for time (day of withdrawal). Day 0 of withdrawal was the last day of active drug administration. None of the outcomes in this table reached statistical significance ($P < 0.05$) on tests of condition-×-time interaction, with the exception of high VAS. VAS range 0–100; Digit recall = percent trials correct; Trails A/B = time in seconds to complete task (shorter is better); Circular lights = number responses correct during circular lights task. B, buprenorphine; DBP, diastolic blood pressure (mm Hg); DSST, digit symbol substitution task (percent trials correct); HR, heart rate (beats per minute); M, morphine; RR, respiratory rate (breaths per minute); SBP, systolic blood pressure (mm Hg).

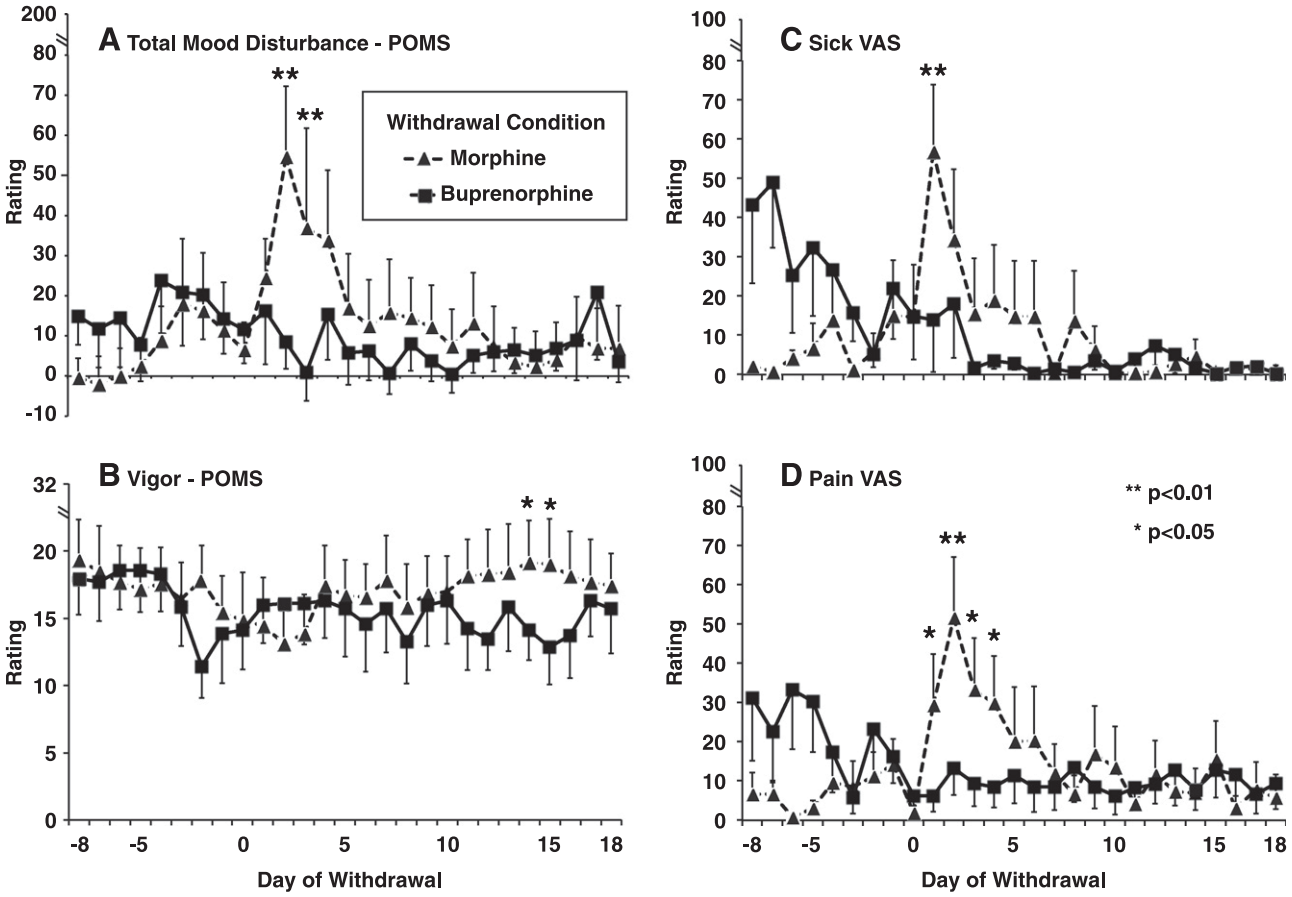

Fig. 3. Mean Peak Daily Profile of Mood States (POMS) and Visual Analog Scale (VAS) ratings (± S.E.M.) during and after active drug cessation.

was associated with evidence of more severe opioid withdrawal; that this occurred more quickly after the last active dose; and this had largely resolved by day 7 of placebo administration. Unlike the a priori hypothesis, we found no evidence of buprenorphine cessation being associated with subjective or objective measures of opioid withdrawal over the entire 18-day placebo administration phase and little evidence of withdrawal overall. The few withdrawal effects that were significantly greater after buprenorphine cessation compared with after morphine cessation were in the second week of placebo administration and were on lower ratings of vigor on POMS subscales, as well as lower measures of psychomotor speed (Trails A), executive functioning (Trails B), and accuracy (DSST). However, the differences in cognitive measures may have been due to differences on these measures during the active medication phase that carried over during placebo administration (withdrawal).

These findings are likely explained by a combination of the pharmacokinetic properties and MOR affinity of buprenorphine. This medication is highly lipophilic, has a large volume of distribution, and has a relatively long half-life compared with other opioids (Kuhlman et al., 1996). When given in the parenteral form, there is much less first-pass metabolism and greater amounts of the drug reach the central nervous system (CNS). Once in the CNS, buprenorphine has a high affinity for the MOR and disassociates slowly (Dum and Herz, 1981; Lee et al., 1999). Buprenorphine's ability to suppress withdrawal symptoms has been shown to be dose dependent (Kuhlman et al., 1998). In a study of abrupt buprenorphine withdrawal, five participants were given 8 mg of SL buprenorphine for 36 days, and the mean elimination half-life was shown to be 73.3 hours. As elimination half-life is determined by both the volume of distribution and drug clearance, and there is a large individual variation in the elimination half-life of buprenorphine (Elkader and Sproule, 2005), there is a possibility that our participant population had an overall longer suppression of withdrawal as a result of a longer elimination half-life. However, no plasma samples were drawn in this study to examine that hypothesis. We did collect weekly urine samples to ensure that no illicit substances were consumed during the course of trial participation. Buprenorphine metabolites were tested in only the last two study completers. One completer was buprenorphine positive during the last week of placebo administration after buprenorphine maintenance, and the other was negative during that same period. Even if a small amount of buprenorphine metabolites was present in plasma, the return of maximum pupil diameter to baseline levels by day 8 of withdrawal (Fig. 4A) and the lack of miosis for the final 10 days argue against significant buprenorphine being present in the CNS, especially as pupil diameter is a sensitive measure of buprenorphine MOR agonist effects (Pickworth, et al., 1990; Kuhlman et al., 1998). Furthermore, although subjective effects ratings remained >0 during most of the placebo administration after buprenorphine maintenance (Supplemental Fig. 1), these ratings were not statistically different from ratings collected after morphine cessation, which were also elevated.

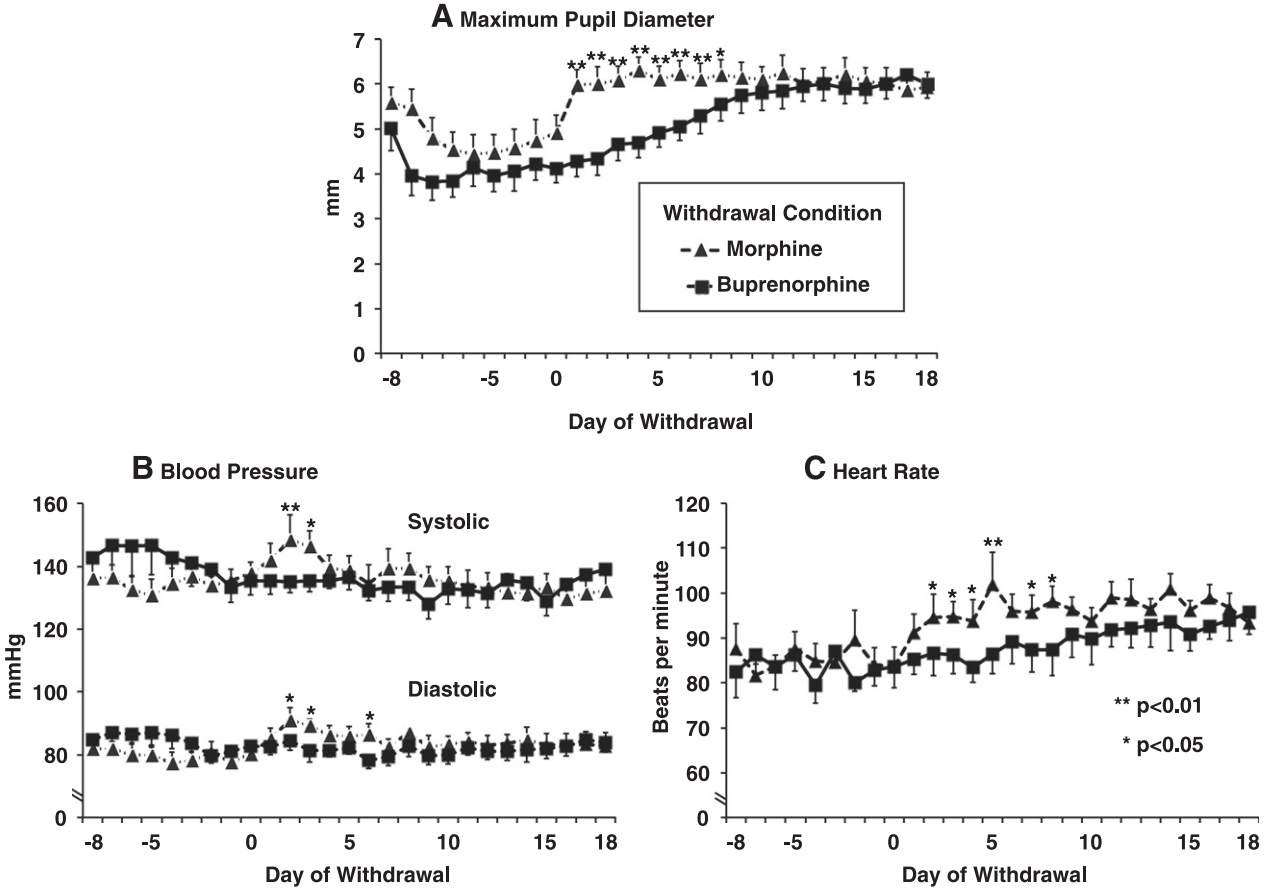

Fig. 4. Mean peak daily physiologic measurements (± S.E.M.) during and after active drug cessation. (A) Pupil diameter. (B) Blood pressure. (C) Heart rate.

A study by Greenwald et al. showed that 50%–60% receptor MOR occupancy is needed to suppress withdrawal symptoms (Greenwald et al., 2007). Two other studies from this same research group have shown that higher buprenorphine doses resulted in greater MOR occupancy, with a 32-mg SL maintenance dose resulting in almost 100% MOR occupancy (Zubieta et al., 2000; Greenwald et al., 2003), and there is a higher correlation with withdrawal suppression for CNS MOR occupancy compared with plasma drug concentration (Greenwald et al., 2003). Given that there was little evidence of opioid withdrawal up to 18 days after buprenorphine cessation in the present study, perhaps the slow rate of buprenorphine disassociation from MOR allowed for a return of cellular homeostasis in the parts of the CNS thought to be responsible for opioid withdrawal (e.g., locus coeruleus, nucleus accumbens, nucleus raphe magnus, and rostral ventromedial medulla) (Christie, 2008) before unopposed neuronal excitation could occur.

These results have important clinical implications. First, they support the feasibility of short medically supervised detoxification strategies after a period of stabilization. A larger daily buprenorphine maintenance dose (e.g., 32 mg) before detoxification may provide for a smooth and relatively symptom-free period of withdrawal, unlike what has been seen with smaller doses ($\leq$8 mg). A randomized controlled trial comparing 12 mg i.m. of buprenorphine given over 24 hours, with 5 days of SL buprenorphine tapering, demonstrated similar success in controlling withdrawal symptoms and in retention between conditions (Assadi et al., 2004). Because suppression of withdrawal symptoms is important for long-term success after detoxification (Ziedonis et al., 2009) and the potential length of medical detoxification that is reimbursable by insurance has been shortened by fiscal constraints, buprenorphine may be the preferable maintenance strategy in populations that request long-term abstinence as a clinical goal. However, those individuals should be maintained on larger buprenorphine doses before attempting detoxification. Second, maintenance patients who are incarcerated or otherwise undergo a forced cessation of treatment can be reassured beforehand that the withdrawal symptoms during such periods would most likely be relatively mild, as a recent case series has shown (Westermeyer and McCance-Katz, 2012). Third, these results add to the literature supporting less than daily dosing strategies for buprenorphine (Amass et al., 2001). A prior study showed minimal withdrawal from 98 hours of buprenorphine omission (Correia et al., 2006). The current results show that a large maintenance dose of buprenorphine (32 mg) may be able to suppress withdrawal symptoms even longer, with a weekly or perhaps even biweekly dosing schedule being possible. Although clinical trials will be necessary to establish clinical efficacy, weekly dosing strategies could limit the amount of buprenorphine diversion and be preferable in patients who cannot or do not wish to take daily medications (e.g., individuals with cognitive limitations or severe and persistent mental illness).

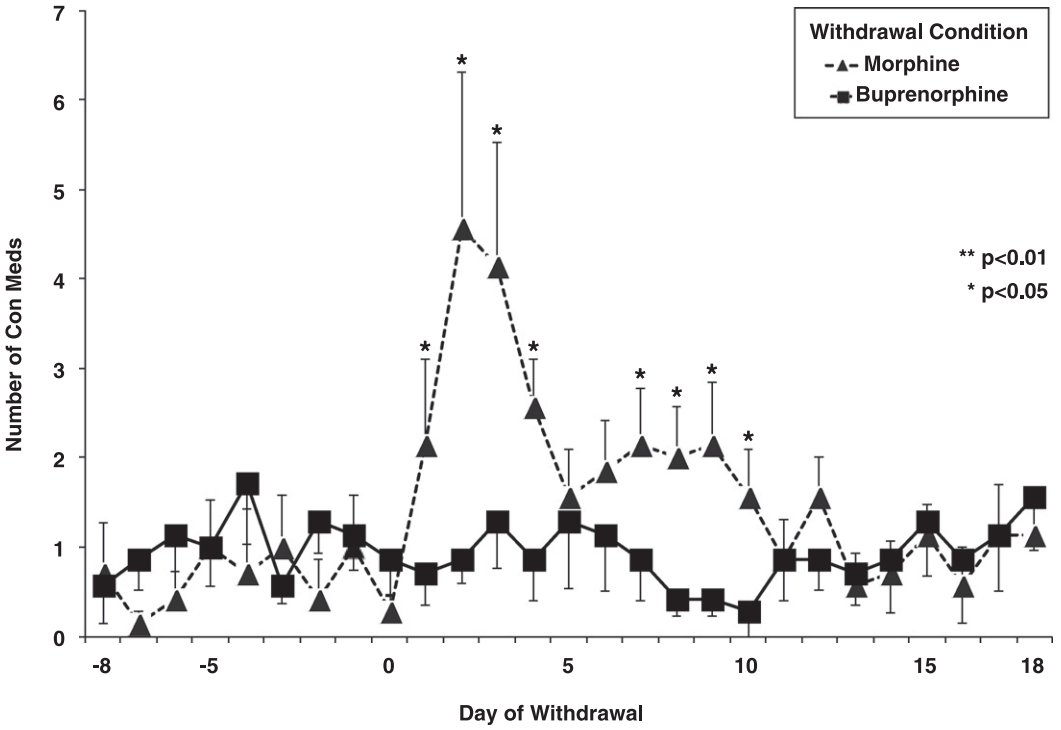

Fig. 5. Mean peak number of concomitant medications (con meds; ±S.E.M.) for the treatment of withdrawal symptoms during and after active drug cessation.

This study has some important limitations. First, 18 days might not have been enough time to demonstrate significant buprenorphine withdrawal after high maintenance doses. The 32-mg i.m. buprenorphine dose represents a 33% increase in bioavailable buprenorphine compared with the largest clinically used SL buprenorphine dose (32 mg). As buprenorphine has a relatively long elimination half-life (Walker et al., 1995; Schuh and Johanson, 1999), there may have been enough CNS buprenorphine still present to suppress withdrawal on day 18. If the observation period would have been longer, withdrawal signs and symptoms may have developed. As stated previously, this is unlikely given the lack of demonstrable MOR agonist effects. In addition, the 59-day study period was already long, and increasing it further may have made recruitment even more challenging for this study. Second, there were no women and only one white participant. However, only a few studies have shown any sex differences in clinical trials of buprenorphine maintenance (Johnson et al., 1995; Moody et al., 2011) and none demonstrating sex or racial differences in detoxification or withdrawal. In addition, there are no known buprenorphine pharmacodynamic or pharmacokinetic differences among different races and sexes. Third, these results were based on seven individuals who completed both cycles of maintenance and withdrawal. Four individuals were unable to complete the study because of opioid withdrawal, all of whom left after morphine cessation. Two of these were able to complete buprenorphine withdrawal without sequelae before leaving, suggesting that the results would not have changed if their data had been included. Fourth, this study did allow the use of concomitant medications that limited the severity of withdrawal. However, clonidine (the only opioid withdrawal medication available in this protocol) was rarely given: twice during buprenorphine withdrawal and 17 times during morphine withdrawal. The use of concomitant medications was greater after morphine cessation compared with after buprenorphine cessation; therefore, the lack of opioid withdrawal seen after buprenorphine cessation is not likely due to excessive use of concomitant medications. Fifth, the intramuscular buprenorphine route is not used in clinical practice for the maintenance or withdrawal treatment of opioid-use disorders, which may limit the generalizability of these results to withdrawal from SL buprenorphine.

In conclusion, this study demonstrated that there was minimal withdrawal after cessation of 32 mg i.m. of buprenorphine compared with marked withdrawal in the same individuals after cessation of morphine 120 mg i.m. This study comprehensively examined withdrawal, using standard subjective and objective withdrawal rating scales, physiologic measures, psychomotor tasks, and validated sleep measures. These results extend the knowledge of buprenorphine's duration of action, indicating that a higher maintenance dose is associated with a longer duration of action for the suppression of withdrawal. In individuals who have a high risk for abrupt cessation of maintenance therapy or are sensitive to opioid withdrawal, buprenorphine maintenance at higher doses may be an optimal clinical choice in comparison with full μ-opioid agonists.

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Authorship Contributions

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Performed data analysis: Tompkins.

Wrote or contributed to the writing of the manuscript: Tompkins, Strain, Mintzer, Campbell, Smith.

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