A double-blind, within subject comparison of spontaneous opioid withdrawal from buprenorphine versus morphine

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ABSTRACT

Preliminary evidence suggests there is minimal withdrawal following cessation of chronically administered buprenorphine and that opioid withdrawal symptoms are delayed compared to other opioids. The present study compared the time course and magnitude of buprenorphine withdrawal versus a prototypical mu opioid agonist, morphine. Healthy, out-of-treatment opioid dependent residential volunteers (N=7) were stabilized either on intramuscular buprenorphine (32 mg/day) or morphine (120 mg/day) administered in four divided doses for nine days. They then underwent an 18-day period of spontaneous withdrawal during which four double-blind IM 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 was significantly (p<0.05) greater than 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 two of morphine withdrawal and were significantly greater than day two of buprenorphine withdrawal. Subjective reports of morphine withdrawal resolved on average by day seven. There was minimal evidence of buprenorphine withdrawal on any measure. In conclusion, spontaneous withdrawal from high-dose buprenorphine appears subjectively and objectively milder as compared to morphine for at least 18 days after drug cessation.
INTRODUCTION

Buprenorphine is a derivative of the morphine alkaloid thebaaine and is an efficacious treatment for 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 mu 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 persons maintained on another primary MOR agonist (Strain et al., 1995). Buprenorphine’s partial agonist properties can be explained by its greater MOR affinity as compared to other opioids (Dun 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). The majority of its pharmacodynamic effects are related to activity at the MOR, although buprenorphine is a weak kappa-opioid receptor antagonist (Lewis and Husbands, 2004), delta-opioid receptor antagonist (Negus et al., 2002), and nociceptin receptor agonist (Bloms-Funke et al., 2000). Recent evidence shows concomitant activation of nociceptin receptors by buprenorphine inhibits its anti-nociceptive 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 withdrawal). Both of these methods produce signs and symptoms of the classic opioid withdrawal syndrome, e.g. body aches, rhinorrhea, and
pupillary dilatation (Himmelsbach, 1941). There have been conflicting reports from laboratory studies of buprenorphine physical dependence. Early pre-clinical studies showed little evidence of spontaneous or precipitated buprenorphine withdrawal in patas monkeys (Cowan et al., 1977) or rats (Dum et al., 1981), but there were signs of withdrawal in chronic spinal dogs (Martin et al., 1976).

An early human clinical pharmacology study assessed effects that occurred after abrupt cessation of 8 mg daily subcutaneous buprenorphine in three participants, and found a low level of withdrawal symptoms was produced (Jasinski et al., 1978). This withdrawal tended to have a delayed peak, occurring about two weeks after the last dose of buprenorphine. Another study examined withdrawal in 19 heroin dependent participants after cessation of 8 mg daily sublingual (SL) buprenorphine and found no objective withdrawal signs during 15 days of observation; but, mild subjective withdrawal symptoms did occur, peaking on day three to five and lasting up to 10 days (Fudala et al., 1990). A third study examined withdrawal after a five-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 it took approximately ten times higher doses of naloxone or naltrexone to precipitate buprenorphine related withdrawal as compared to 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 (Fudala et al., 1990; Jasinski et al., 1978; Mello and Mendelson, 1980), short periods of follow-up (Correia et
al., 2006), or lack of a control group (Fudala et al., 1990; Jasinski et al., 1978; Mello and Mendelson, 1980). There is also a lack of controlled withdrawal studies from a buprenorphine daily maintenance dose higher than 8 mg. Current treatment guidelines recommend SL maintenance doses between 16-24 mg (Center for Substance Abuse Treatment, 2004). Thus, assessing a controlled withdrawal procedure following 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 intramuscular (IM) dose) compared to morphine (120 mg IM) during a 59-day residential stay in seven non-treatment seeking opioid dependent volunteers. Although not equipotent, these doses and routes 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.

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 21-55 years of age; meet 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 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). Persons 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 for their substance dependence. If persons 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 inclusion and exclusion criteria for this study. Five participants did not complete the protocol. Four men left voluntarily due to opioid withdrawal symptoms (all during morphine withdrawal) and one was withdrawn by study investigators (due to an insufficient supply of study medication). Of the men who left due to 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 non-completers, except in SCL-90 Anxiety subscale T-scores – with completers having higher levels of anxiety during screening compared to non-completers (Table 1).

**Study Setting**

Participants resided on 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 on the RRU was meant to be the same for participants and research staff. Participants received intramuscular (IM) injections of study medication at 0600, 1000, 1600, and 2200. Thirty minutes before and after each injection, the participant and research staff completed standardized assessments of opioid agonist and withdrawal effects. Once daily (1330), 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 below.

**Measures**

This study involved the collection of five types of opioid withdrawal measures: observer-rated, subject-rated, psychomotor/cognitive performance, physiological, and sleep. Previous studies have demonstrated the sensitivity of these multidimensional outcome measures for detecting the agonist and antagonist effects of opioids (for example, see: Preston and Bigelow, 1993; Stoller et al., 2001; Strain et al., 2000). 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; (Tompkins et al., 2009; Wesson and Ling, 2003)), 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 scales (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?”, and “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/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 ten randomly selected 8-digit
numbers, which were displayed on a computer screen one 8-digit number at a time. The circular
lights task assessed psychomotor functioning using a commercially available device. Previous
research had shown this task was sensitive to the sedating effects of drugs (Griffiths et al., 1983).
A Macintosh-based task analogous to the Trail-Making Test (Mintzer et al., 1997; Reitan, 1958)
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 following an
alternating sequence of numbers and letters (e.g., 1, A, 2, B, 3, C...).

Physiological 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 (thirty
minutes before and after each injection). Respiratory rate (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 two. Oxygen saturation, skin temperature, systolic and diastolic blood pressure and
heart rate were collected by use of an automatic physiologic monitoring device (Noninvasive
Patient Monitor model 506, Criti-care Systems, Waukesha, WI, USA). Pupil diameter was
assessed with a digital pupillometer (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 were 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 of Drug Abuse (NIDA) Addiction Research Center (ARC). 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 ARC (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. While such would be ideal, the relative dose potency of buprenorphine and morphine has been estimated to be between 25-50 (Jasinski et al., 1978), suggesting excessively high morphine doses (e.g., 800 mg) would have been needed for this study. The active buprenorphine condition consisted of a total daily IM dose of 32 mg (i.e., 8 mg four times per day) and was prepared using buprenorphine hydrochloride (Research Triangle Institute, NC) and sterile water. As IM 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 IM represents a total buprenorphine dose that is approximately 33% greater than the highest recommended SL buprenorphine maintenance dose (32 mg). However, the 32 mg IM 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 (College Station, TX: StataCorp, LLP). The pre-specified 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-x-time). Of most interest for this study were day-by-day comparisons of withdrawal during the two 18-day placebo administration phases (Figure 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 as they were told they would be withdrawn off of opioids by the end of the study.

RESULTS

There was a consistent finding on a wide variety of measures that the placebo dosing period following morphine was associated with significantly greater opioid withdrawal compared to the corresponding placebo dosing period following buprenorphine. The mean peak subjective and objective ratings of morphine withdrawal occurred on day 2, with the majority of measures showing resolution of morphine withdrawal by day 7. There was little evidence of withdrawal during the 18 days following cessation of buprenorphine.

Observer-rated measures. On repeated measures 2-factor ANOVA of mean peak daily COWS ratings, there was a significant condition-x-time interaction effect (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 7 participants demonstrated opioid withdrawal following cessation of morphine administration. Comparing morphine to buprenorphine, there were significant differences on Tukey’s HSD analyses 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. There were no days following buprenorphine cessation when mean peak COWS ratings were ≥5 (a score < 5 indicates 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 2-factor ANOVA of mean peak daily SOWS ratings, there was a significant condition-x-time interaction effect (F=5.44, df=17, p<0.0001). Figure 2B shows the time course of the mean peak SOWS ratings. Like the COWS ratings, there were significant differences 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 were not statistically different from morphine. An analysis using change from baseline values showed similar findings (Supplemental Table 1).

On repeated measures 2-factor ANOVA of mean peak daily POMS ratings, there were significant main effects of condition for each of the 6 subscales and for total mood disturbance (Table 2). There were significantly higher mean peak ratings for total mood disturbance during days 2-3 of morphine withdrawal as compared to buprenorphine withdrawal (Figure 3A). There was some evidence of buprenorphine withdrawal during the 2nd week of the 18-day period, with significantly lower mean ratings compared to morphine on the vigor subscale (Figure 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 similar findings as 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 2-factor ANOVA for the mean peak daily VAS ratings, there were significant main effects for condition on HIGH, SICK and PAIN 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 (Figure 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, while there were PAIN VAS ratings >10 (indicating mild withdrawal-associated hyperalgesia) during the 2nd week of withdrawal for both conditions (Figure 3D). As there were large differences on VASs on the last day of active medication administration between buprenorphine versus morphine, change from baseline ANOVA showed different results then 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). There were no significant effects of time or condition-x-time on change from baseline ANOVA.

**Physiological measures.** For pupil diameter results, there was a significant condition-x-time interaction effect (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 two, whereas dilation occurred more gradually during buprenorphine withdrawal. Morphine and buprenorphine mean maximum pupil diameters were significantly different until day nine of the withdrawal periods.

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

**Psychomotor/cognitive measures.** On repeated measures 2-factor ANOVA, there was no significant main effect of withdrawal condition on percent trials correct for digit recall (Table 2). There were significant main effects of condition on DSST percent trials correct, Trails A and Trails B completion times, and number of responses correct on the circular lights task. There was also a significant main effect of time on the circular lights task. Post-hoc analyses (Tukey’s HSD test) revealed that DSST percent 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 to 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 to 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) as compared to 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 due to the baseline differences on each cognitive measure on the last day of buprenorphine as compared to 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 time (for these measures only, time = week of withdrawal), or condition-x-time. There were no significant findings on 2-factor ANOVA of ISI total scores. Post hoc testing showed there was a significantly higher PSQI total score during the last 2 weeks of morphine withdrawal compared to buprenorphine (week 2 morphine vs. buprenorphine (SEM): 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). There were no significant condition, time, or condition-x-time effects on 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. There was a significant condition-x-time interaction effect (F=2.49, df=17, p=0.0024). The peak in number of medications consumed following morphine cessation corresponded to the peak subjective and objective withdrawal measures (Figure 5). Even though morphine withdrawal signs and symptoms had mostly resolved by day 5, there were still significantly more doses of medications consumed compared to buprenorphine withdrawal until day 11. There was a small increase 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 meds 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 persons, compared to abrupt cessation of buprenorphine, 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 the seventh day of placebo administration.
Unlike the a priori hypothesis, there was no evidence of buprenorphine cessation being
associated with subjective or objective measures of opioid withdrawal over the entire 18 day
placebo administration phase, and very little evidence of withdrawal overall. The few withdrawal
effects that were significantly greater following buprenorphine cessation as compared to 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 on 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 mu opioid receptor (MOR) affinity of buprenorphine. This medication is highly lipophilic,
has a large volume of distribution, and a relatively long half-life compared to other opioids
(Kuhlman Jr. 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 SL buprenorphine for 36 days and the mean
elimination half-life was shown to be 73.3 hours. As elimination half-life is determined both by
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 due to 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 no illicit substances were consumed during the course of trial participation. Buprenorphine metabolites were only tested in the last two study completers. One completer was buprenorphine positive during the last week of placebo administration following buprenorphine maintenance and the other one was negative during that same time period. Even if a small amount of buprenorphine metabolites were present in plasma, the return of maximum pupil diameter to baseline levels by day eight of withdrawal (Figure 4A) and the lack of miosis for the final 10 days argues 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, though subjective effects ratings remained >0 during the majority placebo administration following buprenorphine maintenance (Supplemental Figure 1), these ratings were not statistically different from ratings collected after morphine cessation, which were also elevated.

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 (Greenwald et al., 2003; Zubieta et al., 2000); and, there is a higher correlation with withdrawal suppression for CNS MOR occupancy compared to plasma drug concentration (Greenwald et al., 2003). Given 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 (<8mg). A randomized controlled trial comparing 12 mg IM buprenorphine given over 24 hours to five days of SL buprenorphine tapering demonstrated similar success in controlling withdrawal symptoms and in retention between conditions (Assadi et al., 2004). As suppression of withdrawal symptoms is important for long-term success following detoxification (Ziedonis et al., 2009) and the potential length of medical detoxification that is reimbursable by insurance has been shortened due to fiscal constraints, buprenorphine may be the preferable maintenance strategy in populations that request long-term abstinence as a clinical goal. However, those persons should be maintained on larger buprenorphine doses prior to attempting detoxification. Second, maintenance patients that 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 an every week or perhaps even every other week 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 that cannot or prefer not to take daily medications (e.g., persons with cognitive limitations or severe and persistent mental illness).

There were some important limitations to the study. First, 18 days may not have been enough time to demonstrate significant buprenorphine withdrawal after high maintenance doses. The 32 mg IM buprenorphine dose represents a 33% increase in bioavailable buprenorphine as compared to the largest clinically used SL buprenorphine dose (32 mg). As buprenorphine has a relatively long elimination half-life (Walker et al., 1995; Schuh et al., 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 females and only one Caucasian participant. However, there are only a few studies showing 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 amongst different races and sexes. Third, these results were based upon seven persons who completed both cycles of maintenance and withdrawal. There were four persons who were unable to complete the study due to opioid withdrawal – all who left after morphine cessation. Two of these were able to complete buprenorphine withdrawal without sequelae prior to 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 to after buprenorphine cessation; therefore the lack of opioid withdrawal seen following buprenorphine cessation is not likely due to excessive use of concomitant medications. Fifth, the IM buprenorphine route is not used in clinical practice for the maintenance or withdrawal treatment of opioid use disorders. Therefore, this may limit the generalizability of these results to the withdrawal from SL buprenorphine.

In conclusion, this study demonstrated that there was minimal withdrawal after cessation of 32 mg IM buprenorphine, in comparison to marked withdrawal in the same individuals after cessation of morphine 120 mg IM. This study comprehensively examined withdrawal, using standard subjective and objective withdrawal rating scales, physiological 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 persons 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 to full mu opioid agonists.

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AUTHORSHIP CONTRIBUTIONS
Participated in research design: Strain, Tompkins, Mintzer, Campbell, Smith.

Performed data analysis: Tompkins

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


Tompkins DA, Bigelow GE, Harrison JA, Johnson RE, Fudala PJ, Strain EC. (2009) Concurrent validation of the clinical opiate withdrawal scale (COWS) and single-item indices


availability in male heroin-dependent volunteers: A preliminary study.

*Neuropsychopharmacology* 23:326-334.
FOOTNOTES

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Limited data from this manuscript were previously presented at the 2013 annual meetings of the American Pain Society and College on Problems of Drug Dependence.

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LEGENDS

Figure 1. Experimental Design.

Figure 2. Mean Peak Daily Clinical Opiate Withdrawal Scale (COWS) and Subjective Opiate Withdrawal Scale (SOWS) Ratings (+/- SEM) during and after Active Drug Cessation.

Figure 3. Mean Peak Daily Profile of Mood States (POMS) and Visual Analog Scale (VAS) Ratings (+/- SEM) during and after Active Drug Cessation.

Figure 4. Mean Peak Daily Physiological Measurements (+/- SEM) during and after Active Drug Cessation.

Figure 5. Mean Peak Number of Concomitant Medications (Con Meds; +/- SEM) for the Treatment of Withdrawal Symptoms during and after Active Drug Cessation.
Table 1. Participant Demographics.

<table>
<thead>
<tr>
<th></th>
<th>Completer (N=7)</th>
<th>Non-completer (N=5)</th>
<th>Total (N=12)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>African-American (%)</strong></td>
<td>86</td>
<td>80</td>
<td>83</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>Age – yrs. (SD)</strong></td>
<td>48.6 (3.4)</td>
<td>44.6 (3.3)</td>
<td>46.9 (3.8)</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>Education – ≥12 yrs. (%)</strong></td>
<td>57</td>
<td>100</td>
<td>75</td>
<td>0.09</td>
</tr>
<tr>
<td><strong>Heroin Use Metrics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length of use – yrs. (SD)</td>
<td>9.6 (5.9)</td>
<td>9 (7.28)</td>
<td>9.4 (6.2)</td>
<td>0.87</td>
</tr>
<tr>
<td>Number days used in past month (SD)</td>
<td>26.7 (5.8)</td>
<td>30 (0)</td>
<td>28.1 (4.6)</td>
<td>0.24</td>
</tr>
<tr>
<td>Amount per using day ($)</td>
<td>38.6 (9.4)</td>
<td>126 (127)</td>
<td>75 (90)</td>
<td>0.20</td>
</tr>
<tr>
<td>Route (% IV)</td>
<td>43</td>
<td>20</td>
<td>33</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>Percent (%) Reporting Other Drug Use at Admission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>71</td>
<td>80</td>
<td>75</td>
<td>1.00</td>
</tr>
<tr>
<td>Cocaine</td>
<td>43</td>
<td>40</td>
<td>42</td>
<td>1.00</td>
</tr>
<tr>
<td>Cannabis</td>
<td>43</td>
<td>20</td>
<td>33</td>
<td>0.57</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>--</td>
</tr>
<tr>
<td><strong>Number prior opioid detoxifications (SD)</strong></td>
<td>1.3 (1.2)</td>
<td>2 (1.2)</td>
<td>1.6 (1.2)</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>SCL-90 T-scores (SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global Severity Index</td>
<td>63.4 (14.9)</td>
<td>53 (11.7)</td>
<td>59.1 (14.1)</td>
<td>0.22</td>
</tr>
<tr>
<td>Depression</td>
<td>66.9 (11.3)</td>
<td>59.6 (9.3)</td>
<td>63.8 (10.7)</td>
<td>0.27</td>
</tr>
<tr>
<td>Anxiety *</td>
<td>61 (13.4)</td>
<td>46.4 (6.7)</td>
<td>54.9 (13)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>BMI (SD)</strong></td>
<td>28.3 (6)</td>
<td>26.5 (8.3)</td>
<td>27.6 (6.8)</td>
<td>0.66</td>
</tr>
<tr>
<td><strong>Percent (%) Randomized to morphine 1st</strong></td>
<td>43</td>
<td>60</td>
<td>50</td>
<td>0.56</td>
</tr>
</tbody>
</table>

* p<0.05. SD = standard deviation. Yrs. = years. IV = intravenous. Amount per using day ($) = amount of money spent on opioids per day of opioid use. SCL-90 obtained at screening. T-scores normalized for a non-patient population.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Time</th>
<th>Day of Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POMS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tension-Anxiety</td>
<td>11.76** 1 1.1 17</td>
<td>5.9 9.7 14.4 10.9 10.0 10.3 6.9 7.1 6.4 7.1 4.9 7.7 7.7 6.9 4.1 3.6 4.3 5.1 3.9 6.7</td>
</tr>
<tr>
<td>Depression-Dejection</td>
<td>15.53** 1 1.2 17</td>
<td>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</td>
</tr>
<tr>
<td>Anger-Hostility</td>
<td>12.19** 1 0.6 17</td>
<td>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</td>
</tr>
<tr>
<td>Vigor</td>
<td>7.95** 1 0.09 17</td>
<td>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</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8.67** 1 0.7 17</td>
<td>4.7 7.6 12.6 7.6 7.9 3.9 4.1 3.9 3.0 4.1 3.6 4.1 3.6 4.1 3.6 3.5 4.1 3.6 4.1</td>
</tr>
<tr>
<td>Confusion-Bewilderment</td>
<td>6.04** 1 0.92 17</td>
<td>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 3.7 4.3</td>
</tr>
<tr>
<td>Total Mood Disturbance</td>
<td>7.54** 1 0.84 17</td>
<td>6.4 2.4 46.4 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</td>
</tr>
<tr>
<td><strong>VAS</strong></td>
<td></td>
<td></td>
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<tr>
<td>High</td>
<td>6.07* 1 1.06 17</td>
<td>16.6 5.9 11.9 4.6 15.4 16.5 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</td>
</tr>
<tr>
<td>Liking</td>
<td>0.03 1 1.57 17</td>
<td>57.7 50.4 54.4 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</td>
</tr>
<tr>
<td>Drug Effects</td>
<td>1.29 1 1.59 17</td>
<td>15.3 33.3 32.9 29.6 19.4 24.1 17.1 18.9 19.7 18.7 4.9 17.6 16 10.4 3.9 0.6 12.6 9.6 0.9</td>
</tr>
<tr>
<td>Good Effects</td>
<td>3.25 1 1.75* 17</td>
<td>14.7 19.6 26.6 20 31 19 19 20.7 18.7 14 21 5 14.9 3.1 1.1 12</td>
</tr>
<tr>
<td>Bad Effects</td>
<td>3.22 1 2.34** 17</td>
<td>19.3 43.7 30.4 20.1 20.1 16.4 15.3 14.6 20.0 14.6 2.0 26.6 0.3 1.4 0.0 1.3 1.7 1.3</td>
</tr>
<tr>
<td>Total Mood Disturbance</td>
<td>7.53 1 0.84 17</td>
<td>6.4 2.4 46.4 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</td>
</tr>
<tr>
<td><strong>Vital Signs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP</td>
<td>3.93* 1 0.55 17</td>
<td>138 142 148 146 139 139 139 139 139 139 139 134 134 133 132 131 131 130 131 132</td>
</tr>
<tr>
<td>DBP</td>
<td>16.18** 1 0.4 17</td>
<td>135 135 135 135 135 135 135 137 132 133 133 133 133 133 132 131 131 130 131 133</td>
</tr>
<tr>
<td>HR</td>
<td>36.41** 1 0.5 17</td>
<td>84 91 95 95 94 102 96 98 96 98 94 99 99 99 99 101 96 98 99 97 93</td>
</tr>
<tr>
<td>RR</td>
<td>23.68** 1 2.74** 17</td>
<td>18 17 17 17 17 17 17 17 17 17 18 17 17 19 18 19 18 19 19 20 20</td>
</tr>
<tr>
<td>Psychomotor/Cognitive</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digit Recall</td>
<td>0.84 1 0.19 17</td>
<td>41.4 31.4 31.4 21.4 34.3 48.3 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</td>
</tr>
<tr>
<td>DSST</td>
<td>16.99** 1 0.24 17</td>
<td>94 89 88 92 91 90 90 91 96 98 91 97 95 92 93 93 96 90 94</td>
</tr>
<tr>
<td>Trails A</td>
<td>10.73** 1 0.55 17</td>
<td>51.2 51 50.3 56.6 44.2 49.7 39.3 42.1 46.2 41.8 43.4 39.2 41.1 37.2 37.2 39.9 42.2 37.1 41.8</td>
</tr>
<tr>
<td>Trails B</td>
<td>5.06* 1 0.94 17</td>
<td>74.2 89.2 63.4 88.6 53.6 66.4 54.9 75 67.9 58.5 55.7 49 52.7 53.1 49.2 50.2 49.8 52 57.1</td>
</tr>
<tr>
<td>Circular Lights</td>
<td>12.26** 1 2.30** 17</td>
<td>66 65.7 68.7 64.7 67 70 70 72 76.1 73 77.6 78.4 76 73.7 74.3 78 78.3 78.9 75.6 79</td>
</tr>
</tbody>
</table>

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*p<0.05; **p<0.01. **Bold**=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-x-time interaction, except High VAS. M=morphine. B=buprenorphine. POMS=Profile of Mood States. VAS=Visual Analog Scale, range 0-100. SBP=systolic blood pressure (mmHg) DBP=diastolic blood pressure (mmHg). HR=heart rate (beats per minute). RR=respiratory rate (breaths per minute). Digit recall=percent trials correct. DSST= digit symbol substitution task (percent trials correct). Trails A/ B= time in seconds to complete task (shorter is better). Circular Lights=number responses correct during circular lights task.
Figure 1.

Opioid #1  Withdrawal #1  Opioid #2  Withdrawal #2

Nine Days  Eighteen Days  Nine Days  Twenty-two Days
Figure 2.

A) COWS

B) SOWS

Withdrawal Condition

- ▲ - Morphine
- ■ - Buprenorphine

** p<0.01
* p<0.05
Figure 4.

A) Maximum Pupil Diameter

With a noticeable trend, the maximum pupil diameter shows significant differences between the withdrawal conditions. The data points indicate that Buprenorphine treatment resulted in a lower maximum pupil diameter compared to Morphine, with statistical significance indicated by * p<0.05 and ** p<0.01.

B) Blood Pressure

The systolic blood pressure readings show a gradual increase over time, with a significant difference noted between the two withdrawal conditions. The diastolic blood pressure remains relatively stable, with no significant differences observed.

C) Heart Rate

The heart rate data displays a slight increase over the days of withdrawal, with a more pronounced effect seen in the Morphine group. The Buprenorphine group shows a more stable trend. Significant differences are marked by * p<0.05 and ** p<0.01.
Figure 5.

Withdrawal Condition
- ▲ Morphine
- ■ Buprenorphine

** p<0.01
* p<0.05

Number of Con Meds

Day of Withdrawal

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