Characterizing opioid withdrawal during double-blind buprenorphine detoxification

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Abstract

Background—Prescription opioid (PO) abuse has become an urgent public health issue in the United States. Detoxification is one important treatment option, yet relatively little is known about the time course and severity of opioid withdrawal during buprenorphine detoxification.

Methods—This is a secondary analysis of data from a randomized, placebo-controlled, double-blind evaluation of 1, 2, and 4-week outpatient buprenorphine tapers among primary prescription opioid (PO) abusers. The aim is to characterize the time course and severity of buprenorphine withdrawal under rigorous, double-blind conditions, across multiple taper durations, and using multiple withdrawal-related measures (i.e., self-report and observer ratings, pupil diameter, ancillary medication utilization). Participants were PO-dependent adults undergoing buprenorphine detoxification and biochemically-verified to be continuously abstinent from opioids during their taper (*N*=28).

Results—Participants randomly assigned to the 4-week taper regimen experienced a relatively mild and stable course of withdrawal, with few peaks in severity. In contrast, the 1- and 2-week taper groups experienced stark increases in withdrawal severity during the week following the last buprenorphine dose, followed by declines in withdrawal severity thereafter. The 4-week taper group also reported significantly fewer disruptions in sleep compared to the other experimental

groups. When predictors of withdrawal were examined, baseline ratings of "Expected Withdrawal Severity" was the most robust predictor of withdrawal experienced during the taper.

Conclusion—Data from this trial may inform clinicians about the expected time course, magnitude, and pattern of buprenorphine withdrawal and aid efforts to identify patients who may need additional clinical support during outpatient buprenorphine detoxification.

Keywords

buprenorphine; detoxification; taper; withdrawal; prescription opioid

1. INTRODUCTION

In 2013, over 13 million people had abused a prescription opioid (PO) and approximately 2 million people required treatment (Substance Abuse and Mental Health Services Administration (SAMHSA), 2014). POs are now the second most commonly used drug in the United States, and annual treatment admissions for PO abuse have increased 32% in the past 10 years. PO abuse costs society over $56 billion annually in premature death, criminality, and other societal consequences (Centers for Disease Control, 2012; SAMHSA, 2013). Opioid-related overdose, which is largely driven by PO abuse, has increased by 114% between 2002 and 2012 (Warner et al., 2014). Finally, PO abuse has now been independently related to risky drug use behaviors and acquisition of HIV and hepatitis C (Havens et al., 2011; Bruneau et al., 2012; Havens et al., 2013).

While maintenance treatment with opioid agonist medications (i.e., methadone, buprenorphine) is widely-used and effective for many opioid-dependent patients, detoxification remains an important treatment option for several reasons. First, many PO abusers may be unwilling or unable to enter maintenance, perhaps due to stigma associated with methadone or because less severe opioid histories make them ineligible (Zacny et al., 2003; Appel et al., 2004; Kleber, 2007; Pinto et al., 2010). Second, access to maintenance can also be limited, particularly in rural areas where PO abuse is often most prevalent (Rounsaville and Kosten, 2000; Cicero et al., 2007; Rosenblum et al., 2011; Sigmon, 2014). Third, primary PO abusers may respond favorably to a detoxification treatment approach. For example, previously-reported comparisons of primary PO and heroin abusers have noted that PO abusers experienced less severe withdrawal during buprenorphine induction, provided more opioid-negative urine samples during a buprenorphine taper, were more likely to be retained in a buprenorphine taper, and were more likely to be opioid-negative at the end of a buprenorphine taper, compared to primary heroin abusers (Nielsen et al., 2012, 2013, 2014). Finally, the recent increases in adolescent opioid abuse warrant exploring potential alternatives to long-term maintenance (Zacny et al., 2003; McLellan and Turner, 2008; Volkow and McLellan, 2011), particularly given evidence that long-term opioid maintenance may alter cognitive functions (Gruber et al., 2007).

When considering the available pharmacotherapies for use in opioid detoxification, the partial mu-opioid agonist buprenorphine has a pharmacological profile that lends toward its use in taper regimens. Buprenorphine has a long plasma half-life and slow dissociation from the receptor (Hambrook and Rance, 1976; Jasinski et al., 1978; Bullingham et al., 1980;

Bickel et al., 1988a; Fudala et al., 1990), which results in a more limited withdrawal syndrome when compared to other full opioid agonists (e.g., methadone; Jasinski et al., 1978; Bickel et al., 1988b; Fudala et al., 1990) and adrenergic agonists (e.g., clonidine; Janiri et al., 1994; O'Connor et al., 1997; Lintzeris et al., 2002; Ling et al., 2005; Marsch et al., 2005; Oreskovich et al., 2005). However, despite the data suggesting a favorable withdrawal profile for buprenorphine over other medications, few studies have directly evaluated the time course and severity of withdrawal during buprenorphine detoxification, and the existing studies on this topic have generally failed to account for ongoing illicit opioid and ancillary medication use that can confound assessments of opioid withdrawal (Dunn et al., 2011). Considering the association between opioid withdrawal severity and patient outcomes (Best et al., 1999), a thorough understanding of buprenorphine withdrawal across multiple taper durations could enhance efforts to develop more effective detoxification regimens.

We recently conducted a randomized, double-blind, placebo-controlled parametric comparison of three outpatient buprenorphine taper durations (i.e., 1-, 2-, or 4-week) in PO-dependent individuals (Sigmon et al., 2013). In the present analyses, we sought to characterize the time course and severity of withdrawal under rigorous, double-blind conditions, across multiple taper durations, and using multiple withdrawal-related measures (i.e., self-report and observer ratings, pupil diameter, ancillary medication utilization).

2. MATERIALS AND METHODS

2.1 Study Design

As a full description of the study methods has been reported elsewhere (Sigmon et al., 2013), only a brief summary of relevant details is presented here. Participants were 18 years old, met DSM-IV-TR criteria for opioid dependence, provided an opioid-positive urine sample, were seeking or willing to accept opioid detoxification, reported a PO as their primary drug of abuse, and reported using the PO illicitly (e.g., without a valid prescription). Those who required ongoing opioids for pain, were pregnant or nursing, or had a significant and unstable psychiatric or medical illness that could interfere with consent or participation were excluded.

Following a brief period of buprenorphine stabilization, 70 PO-dependent adults were randomized into a 12-week study in which they received either a 1-, 2-, or 4-week buprenorphine taper, followed by oral naltrexone therapy for those who successfully tapered without relapse to opioid use. Participants and research staff remained blind to participants' buprenorphine dose, their assigned taper duration, and the timing of their naltrexone initiation. Participants visited the clinic daily during Phase 1 (Weeks 1–5 after randomization) and three times weekly during Phase 2 (Weeks 6–12). They received behavioral therapy based on the Community Reinforcement Approach (see Sigmon et al., 2013) and thrice-weekly urine toxicology testing throughout the trial. The present analyses focused on Phase 1, the 5-week period during which participants were undergoing their assigned double-blind taper regimen and visiting the clinic daily for assessments of withdrawal and illicit drug use.

2.2 Participants

The primary study enrolled 70 participants. Data from those participants were examined and only those who were biochemically-verified to be continuously abstinent from opioids throughout their assigned taper duration plus one additional week post-taper (*N*=28) were included in these analyses (40% of the original sample). This criterion was chosen to permit a thorough evaluation of withdrawal unconfounded by illicit opioid use. The additional post-taper week was included to permit examination of withdrawal in the days following the final buprenorphine dose, since several previous studies have reported a potential delayed onset of withdrawal following buprenorphine taper (see Dunn et al., 2011).

2.3 Study Medications

Each day throughout the study, participants received 5.5 active and color-matched placebo sublingual buprenorphine tablets, as well as three gelatin capsules that contained either naltrexone or placebo. All study medication was ingested daily onsite under nurse observation. Five ancillary nonopioid medications (i.e., clonidine, hydroxyzine, ibuprofen, loperamide, promethazine) were available but not required and were dispensed according to a protocol based on Clinical Institute Narcotic Assessment (CINA; Peachey and Lei, 1988) scores. Participants ingested ancillary medications in the clinic and also received take-home doses of medications as needed. Take-home ancillary medication packages were returned at the next visit and logged for documentation.

2.4 Measures

At intake, participants completed a questionnaire to assess their history of opioid and other drug use, the Beck Depression Inventory (Beck et al., 1961), and the Brief Pain Inventory (Cleeland and Ryan, 1994). They also completed the following two Visual Analog Scale (VAS) ratings on a scale of 0 (None) -100 (Worst ever): "In general, how severe do you expect withdrawal from opioids to be?" (Expected Withdrawal Severity) and "How would you rate your average craving for opioids during the past month?" (Past 30-Day Cravings). The intake assessment also included other self-report and experimenter-administered measures that are not relevant to withdrawal and described in full elsewhere (Sigmon et al., 2013).

Withdrawal was assessed via self-report ratings, observer ratings, and pupil diameter measurements at each study visit. A research nurse blinded to taper group assignment and buprenorphine dose conducted all withdrawal assessments prior to dosing. The self-report ratings included five VAS items, each rated on a scale of 0 (Not at all) to 100 (Extremely): "Do you feel any withdrawal discomfort right now?" (Withdrawal), "How high are you?" (High), "Do you like the way you feel?" (Like The Way I Feel), "Do you feel sick?" (Sick), and "Do you crave opiates right now?" (Crave). Participants also rated the number of hours they slept the preceding night (Sleep Quantity) and the quality of their sleep (Sleep Quality) on a scale of 0 (Poor) to 10 (High). Observer ratings were conducted using the CINA, a widely-used 12-item clinical instrument that yields a withdrawal severity score from a combination of self-report and observer ratings. Finally, pupil diameter (millimeters (mm)), a physiological measure of withdrawal, was assessed in constant ambient lighting using a

pupillometer (NeurOptics, San Clemente, CA), a handheld device that uses infrared technology to estimate pupil diameter over a 3-second period.

2.5 Data Analyses

Demographic (i.e., age, race), drug use (i.e., route of administration, duration of use), and study characteristics (i.e., number stabilization days, missed visits) that were hypothesized *a priori* to influence withdrawal were compared across the three taper duration groups using chi-square and one-way analysis of variance (ANOVA) tests. No significant differences were found.

Between-group (taper group) comparisons of mean peak ratings over the 5-week evaluation period were conducted, permitting an evaluation of withdrawal time course. Self-report VAS, CINA, and sleep measures were converted into maximum peak values (VAS, CINA) or lowest mean values (sleep measures) for each participant each week, representing the peak level of impairment and discomfort, and were averaged across taper duration for Weeks 1–5. Scores from both the individual items and the total overall CINA score were examined. CINA scores are presented using the severity score (Severity; range 0–31) as well as a symptom incidence score (Incidence; range 0–11), with incidence operationalized as an endorsement of a symptom at any level of severity. Pupil diameter (mm) was analyzed using final stabilization buprenorphine dose as a covariate. Ancillary medication utilization, collapsed across medications, was evaluated as the mean number of different medications taken per day (range 0–5). In order to evaluate between-group effects of taper group, within-subject effects of study week, and taper group x study week interactions, mean peak values were compared across taper durations using SAS Proc Mixed models for continuous measures and SAS Generalized Estimating Equations for dichotomous measures, with follow-up Tukey's posthoc tests to identify specific group differences.

In addition, between-group comparisons regarding the time to first report of CINA symptoms and first ancillary medication use were evaluated using SAS Proc Mixed analyses, to determine whether the onset of symptoms (independent of symptom severity) or utilization of ancillary medications differed across taper durations. Cohen's D effect sizes for between-group effects were calculated and are provided in Tables 2 and 3.

Finally, multiple linear regressions were conducted to evaluate whether any baseline demographic or drug use characteristics predicted withdrawal outcomes. Independent variables included VAS rating of Expected Withdrawal Severity and Past 30-Day Cravings, as well as sex, age, duration (years) of regular opioid use prior to the study, primary route of opioid administration, presence of pain (assessed via the BPI), cigarette smoker status, and mean BDI score. Missing data was minimal (only 6% of scheduled visits missed), therefore no statistical corrections were made. Statistical significance was defined as $p<.05$, and analyses were conducted on SPSS 21 and SAS 9.3.

3. RESULTS

3.1 Participants

Participant characteristics are presented in Table 1. There were no significant differences between the three taper duration groups on demographic, drug use, or parent study characteristics.

3.2 Primary Withdrawal Outcomes

Withdrawal outcomes (i.e., CINA total score, VAS Withdrawal) are presented in Figure 1 as a function of study day for the 1, 2, and 4-week taper groups, with participants' mean buprenorphine dose (SEM) also shown in order to aid interpretation. Visual inspection of these data suggest that the 4-week taper group experienced a relatively mild and stable course of withdrawal with fewer peaks in severity, compared to the 1- and 2-week taper groups who reported increases in withdrawal severity the week following the last buprenorphine dose that decreased thereafter. This general pattern was seen for almost every individual symptom examined. There were no significant effects of taper group on the CINA Total Severity and individual item scores, though the tremor item approached significance (p=.06; Table 2). Several CINA scores did reveal main effects of study week, including the CINA Total Severity score, as well as individual items of abdominal changes, muscle aches and pains, and tremor (Table 2; Figure 2). There was also a significant taper group x study week interaction for the CINA Total Severity score (p =.04). Finally, the peak number of CINA items endorsed (a measure of symptom incidence) varied significantly as a function of study week (p <.001), and the taper group x study week interaction approached significance (p =.06).

A similar pattern of withdrawal (marked increases and subsequent decreases in severity in the briefer taper durations vs. more steady levels of mild withdrawal in the 4-week group) was seen on the self-report, ancillary medication, and pupil diameter measures. A significant effect of taper group was evident on lowest mean hours of sleep, with the 4-week taper group reporting less loss of sleep compared to the 1- and 2-week groups (p =.04; Table 3; Figure 3). A significant effect of study week (p =.01) and interaction between taper group and study week (p <.001) were also observed for the number of ancillary medications used during the study (Table 3; Figure 3). No additional effects of taper group were found, though VAS ratings of Sick (p =.04), Withdrawal (p =.01), and mean pupil diameter (p =.001) (covaried for final buprenorphine stabilization dose) varied significantly as a function of study week (Table 3; Figure 3).

3.3 Time to Onset of Withdrawal and Ancillary Medication Use

There were no between-group differences in time to onset of CINA symptoms, use of any ancillary medication (collapsed across medications), or use of specific individual ancillary medications (data not shown).

3.4 Predictors of Withdrawal

Participants' baseline ratings of Expected Withdrawal Severity were significantly associated with several subsequent VAS withdrawal ratings, even after controlling for other potential

predictors. More specifically, ratings of Expected Withdrawal Severity significantly predicted mean peak VAS ratings of Withdrawal (R^2=.28; B=.65, t(26)=2.6, p =.02) and Feel Sick (R^2=.39; B=.60, t(26)=2.5, p =.02), as well as CINA Total Severity (R^2=.37; B=. 74, t(26)=3.08, p <.01), with higher baseline ratings predicting greater subsequent withdrawal severity. In contrast, the other intake variables examined (i.e., sex, age, mean duration of regular opioid use, primary route of opioid administration, presence of pain, being a cigarette smoker, mean BDI score) were not significantly predictive of withdrawal. Total number of CINA items endorsed (i.e., CINA Incidence) was positively predicted (R^2=. 47) by Expected Withdrawal Severity (B=.57, t(26)=2.98, p <.01) and being male (B=−.54, t(26)=−2.17), p =.04). Finally, Experiencing Pain was significantly predictive of subsequent mean peak ratings of Like How I Feel (R^2=.31; B=−.56, t(26)−2.26, p =.04).

4. DISCUSSION

In this study, we sought to characterize opioid withdrawal among opioid-dependent patients who successfully completed double-blind, outpatient buprenorphine detoxification. Participants randomly assigned to the 1- and 2-week taper regimens experienced increases in withdrawal in the week following their final buprenorphine dose, followed by a decline in symptom severity thereafter. In contrast, those randomized to the 4-week taper group generally experienced a steady but relatively mild level of withdrawal across all study weeks with no delayed emergence of withdrawal in the week following buprenorphine discontinuation. Only two other published reports have examined withdrawal during multiple buprenorphine taper durations (Amass et al., 1994; Ling et al., 2009), and only one of those evaluated how withdrawal changed over time (Amass et al., 1994). In that study, and similar to our results, a 36-day gradual taper was associated with a more continuous withdrawal syndrome without extreme peaks in severity over time, whereas the briefer 12-day taper produced a marked increase in self-reported withdrawal severity following discontinuation of buprenorphine. Our results build upon that prior finding by parametrically comparing three buprenorphine taper durations on multiple, frequent withdrawal measures and in participants biochemically-verified to be abstinent from additional opioid use. These data may inform both providers and patients about the time course, magnitude, and pattern of buprenorphine withdrawal that patients might experience during and in the weeks following different taper durations.

The only item to show a significant effect of taper duration was sleep quantity, with the 4-week taper group reporting greater sleep quantity (indicating less sleep impairment) compared to the 1- and 2-week groups. Although the role of sleep and sleep impairment in opioid detoxification has not been well characterized, at least one study has reported that self-reported sleeping problems was predictive of attrition from opioid detoxification (Dijkstra et al., 2008). A more recent study also reported that provision of sleep medication during the first two weeks of opioid detoxification was predictive of better treatment outcomes (Warden et al., 2012). These data suggest that that clinical support and perhaps medications aimed at managing sleep problems during opioid detoxification might be warranted.

Several measures revealed significant effects of study week, including changes in CINA Total Severity Scores, individual CINA items (i.e., abdominal changes, muscle aches and pain, tremor), the peak number of CINA items endorsed, and VAS ratings of Sick and Withdrawal. In all cases, participants assigned to the 1- and 2-week taper groups experienced a peak in withdrawal severity the week following buprenorphine termination and then a subsequent decline in withdrawal severity, compared to the 4-week taper group who reported a more steady and mild withdrawal time course with fewer peaks in severity. The general decline in severity ratings over time that was observed in the 1 and 2 week groups is an expected result following discontinuation of buprenorphine, and it is interesting that the 4-week taper duration did not show this same profile. Analysis of CINA symptoms and ancillary medication utilization showed that the onset of withdrawal symptoms did not vary as a function of taper duration.

Interestingly, participants' baseline expectations of withdrawal severity were strong predictors of subsequent withdrawal experienced during and following the buprenorphine taper, independent of a variety of other covariates that were hypothesized *a priori* to be associated with withdrawal magnitude and/or self-report. This is consistent with a previous study that reported self-report of withdrawal is a robust predictor of opioid treatment outcome (Kosten et al., 1985), and with prior studies suggesting that fear of withdrawal is associated with poor detoxification outcomes (Hollonds et al., 1980; Phillips et al., 1986; Milby et al., 1987; Gentile and Milby, 1992). There may be value in evaluating whether a single-item question that asks patients to rate their expected withdrawal severity during the taper might aid clinician efforts to identify those at higher risk for experiencing withdrawal and thus failing treatment.

Strengths of this study include the randomization of participants to double-blind buprenorphine taper duration conditions, the frequent (i.e., daily) assessments of withdrawal, and the comprehensive set of withdrawal measures. An additional strength was the effort taken to minimize confounding of withdrawal data by any ongoing illicit opioid use. Several potential limitations should also be noted. First, as this was a secondary analysis of a previously-completed randomized trial, there was a limited sample size in which to investigate withdrawal. Several outcomes that approached but did not achieve statistical significance may have been underpowered to detect an effect. Future efforts to evaluate withdrawal outcomes in larger samples are important. Second, participants were primary PO (vs. heroin) abusers, which may limit generality to the larger opioid-dependent population. That said, 46% of these participants had a history of heroin use, and 85% of those participants reported having used heroin more than 5 times in their life. Third, withdrawal ratings may have been influenced by concurrent ancillary medication use during taper or naltrexone initiation following the taper. However, inspection of our data produced no evidence that naltrexone initiation in the days after the taper influenced withdrawal, and ancillary medications were protocolized and administered to participants in a uniform way across all taper groups. While our data do not permit us to isolate the effect of buprenorphine vs. ancillary medications on withdrawal outcomes, they do provide the most complete picture to date of the time course and severity of withdrawal that a patient might expect during outpatient buprenorphine detoxification. Fourth, although we controlled for

several variables likely to contribute to withdrawal outcomes, other characteristics remain which may predict individual differences in withdrawal (e.g., prior experience with withdrawal, primary opioid of abuse, route of administration). We did not collect detailed information on participants' prior withdrawal experiences, but doing so in future studies could aid interpretation of withdrawal data. Finally, we excluded participants who relapsed to illicit opioid use during the trial, and it is possible that those participants experienced a unique profile of withdrawal that is not captured here. Future studies should examine whether withdrawal severity and time course, particularly in the days before relapse, may be useful in identifying patients who need more intensive support to prevent resumption of illicit opioid use.

In summary, this study provides new information regarding the time course and severity of withdrawal during outpatient buprenorphine taper. These data may inform clinicians and patients alike about what to expect during detoxification, as prior data suggest that patients' knowledge of the opioid withdrawal syndrome is associated with lower peak withdrawal score and symptomatology (Green and Gossop, 1988). They may also assist clinicians in identifying critical time points (e.g., in the week following the last buprenorphine dose rather than earlier in the taper) and areas (e.g., assistance with managing sleep-related problems) with which patients may need additional support for favorable outcomes. Taken together, an improved understanding of withdrawal during buprenorphine taper will aid efforts to develop more effective detoxification strategies as one possible treatment for opioid-dependent patients.

Acknowledgments

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Highlights

1. Evaluation of withdrawal following 1, 2, or 4-week outpatient buprenorphine taper.

2. Withdrawal assessed daily using self-reports, observer-ratings, and pupillometer measurements

3. 4-week group showed a mild and stable course of withdrawal; 1- and 2-week groups showed marked increases in withdrawal severity that decreased thereafter

4. Single item Visual Analog Scale (VAS) for Expected Withdrawal Severity robustly predicted peak withdrawal ratings

5. Results can help inform providers and patients about the time course, magnitude, and pattern of withdrawal following different outpatient buprenorphine taper durations
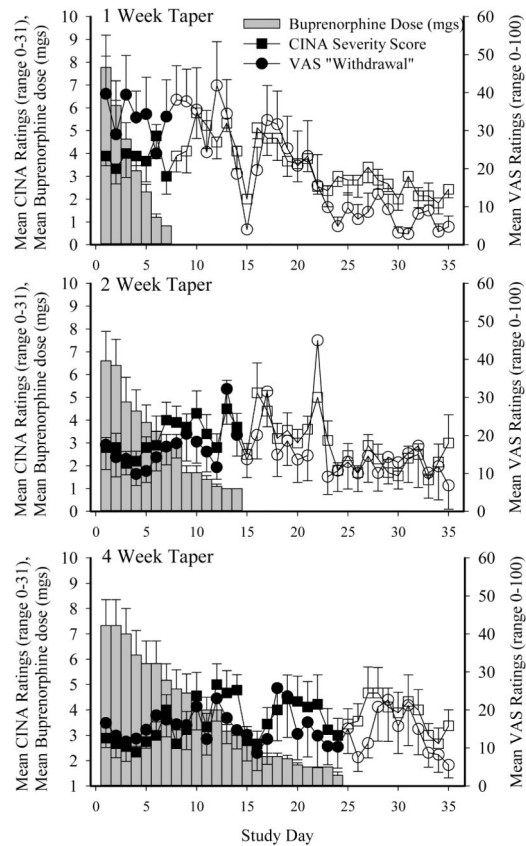
Figure 1. Mean Withdrawal Scores During Buprenorphine Taper

Withdrawal outcomes presented as a function of study day for the 1, 2, and 4-week taper groups, with participants' mean buprenorphine dose (mg; grey bars) also shown to aid interpretation. Mean CINA Total Severity score (square symbols) and mean VAS ratings of Withdrawal (circle symbols) are shown for the 1-week (top panel), 2-week (middle panel), and 4-week (bottom panel) taper groups. Filled symbols represent the days on which participants received an active buprenorphine dose; open symbols represent days on which they received color-matched placebo. Error bars represent SEM.
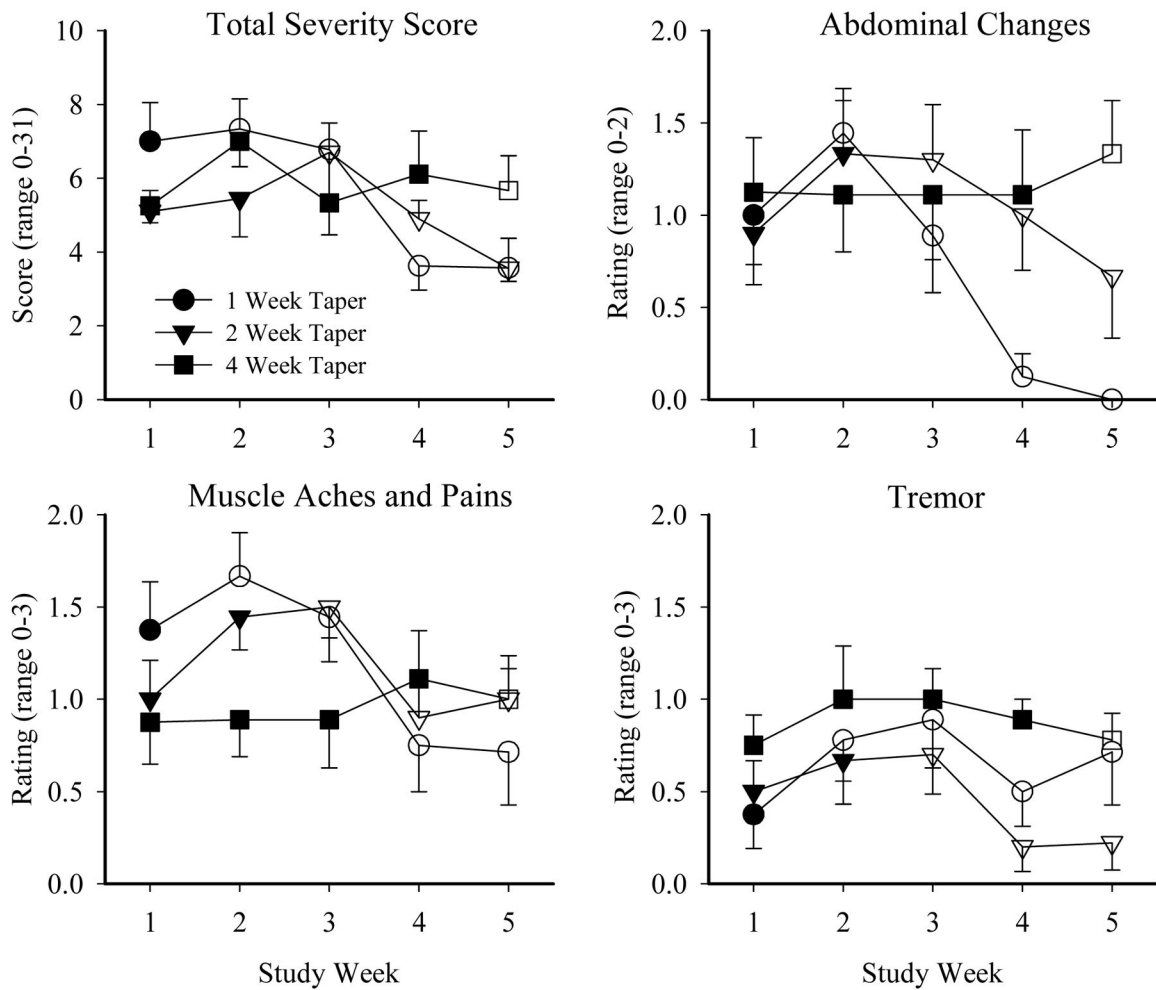
Figure 2. Mean Peak CINA Scores

Mean peak CINA total and individual item scores are presented across study week for the 1-week (circle), 2-week (triangle), and 4-week (square) taper groups. Filled symbols represent weeks in which participants received buprenorphine; open symbols represent weeks in which they received placebo. Error bars represent SEM. Only items with significant effects are presented. No taper group x study week posthoc test results reached significance.
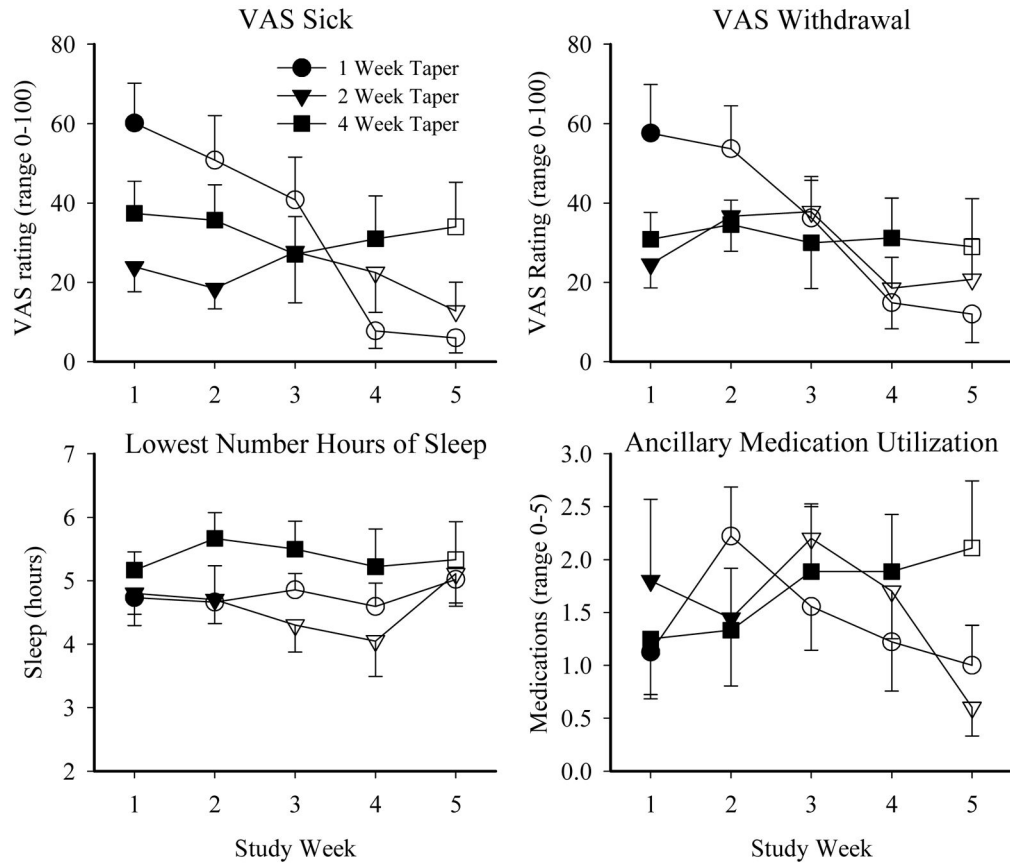
Figure 3. Mean Peak Self-Report Ratings and Ancillary Medication Utilization
Mean peak self-report ratings of VAS items, Sleep Quantity, and ancillary medication utilization are presented across study week for the 1-week (circle), 2-week (triangle), and 4-week (square) taper groups. Filled symbols represent weeks in which participants received buprenorphine; open symbols represent weeks in which they received placebo. Error bars represent SEM. Only items with significant effects are presented. No taper group x study week posthoc test results reached significance.

Table 1

Demographic, Drug Use, and Parent Study Characteristics

|	1 Week Taper (n=9)	2 Week Taper (n=10)	4 Week Taper (n=9)	p-value[a]
Demographic Characteristics				
Caucasian (%)	88.9	88.9	100	0.58
Male (%)	44.4	70.0	77.8	0.30
Age (yrs)	26.8 ± 7.6	28.2 ± 8.1	24.9 ± 2.5	0.59
Opioid Use Characteristics				
Primary oxycodone abuse (%)	77.8	60.0	66.7	0.71
Mean number other PO abused	2.4 ± 1.7	2.4 ± 1.6	2.3 ± 1.5	0.99
Primary intranasal abuse (%)	100.0	80.0	77.8	0.33
Ever used opioids IV (%)	33.3	50.0	33.3	0.69
Ever used heroin (%)	44.4	50.0	44.4	0.96
Ever overdose on opioids (%)	33.3	10.0	0.0	0.12
Mean days used per week (days)	6.7 ± 0.4	6.0 ± 1.3	6.0 ± 1.3	0.28
Mean opioid craving past month (VAS[b])	72.4 ± 15.2	68.1 ± 11.8	70.8 ± 19.2	0.84
Mean expected withdrawal severity (VAS[b])	75.6 ± 20.9	66.9 ± 24.0	71.8 ± 12.2	0.65
Mean age began regular opioid abuse (yrs)	20.8 ± 6.3	21.9 ± 7.2	20.0 ± 2.6	0.77
Mean length of regular use (yrs)	3.7 ± 2.2	5.5 ± 4.3	3.9 ± 1.9	0.37
Pain or medical issues (%)	33.3	40.0	22.2	0.71
Smoke cigarettes (%)	88.9	70.0	88.9	0.46
Study Characteristics				
Number stabilization days (days)	15 ± 2.5	13 ± 3.6	12.3 ± 3.6	0.78
Final stabilization dose (mgs)	11.3 ± 5.1	7.6 ± 5.0	9.8 ± 5.0	0.28
Missed visits (%)	11.1	5.7	2.2	0.25

Values represent Mean ± SD unless otherwise indicated

[a] Values based on One-way Analysis of Variance comparisons across groups for continuous variables and chi-square analyses for dichotomous variables

[b] VAS scales range 0–100

Table 2

Mean Peak CINA Total and Individual Symptom Ratings

CINA[a]	Week 1	Week 2	Week 3	Week 4	Week 5	Within Subject				Between Subject		Effect Sizes[b]		
						Week (df 4,96)		Week × Taper (df 8,96)		Taper Group (df 2,25)				
		Mean Peak Rating Per Study Week				F	p-value	F	p-value	F	p-value	1 vs. 2	2 vs. 4	1 vs. 4
Total Severity Score (0–31)						4.79	**<.01**	2.19	**0.04**	0.32	0.73	0.18	0.03	0.21
1 week taper	6.8	7.3	6.8	3.6	3.6									
2 week taper	5.1	6.0	6.7	4.9	3.6									
4 week taper	5.1	7.0	5.3	6.1	5.7									
Abdominal Changes (0–2)						2.76	**0.03**	1.39	0.21	1.42	0.26	0.36	0.44	0.08
1 week taper	1.0	1.4	0.9	0.1	0.0									
2 week taper	0.9	1.4	1.3	1.0	0.7									
4 week taper	1.0	1.1	1.1	1.1	1.3									
Body Temperature (0–2)						1.43	0.23	1.58	0.14	1.73	0.20	0.46	0.13	0.34
1 week taper	0.3	0.7	0.6	0.1	0.3									
2 week taper	0.7	0.6	0.7	0.6	0.6									
4 week taper	0.7	0.6	0.4	0.6	0.1									
Nausea/Vomiting (0–6)						1.20	0.32	1.44	0.19	0.41	0.67	0.12	0.13	0.25
1 week taper	2.4	1.3	1.1	0.8	0.0									
2 week taper	1.0	1.6	1.8	1.6	0.9									
4 week taper	0.7	1.6	0.7	1.1	0.9									
Muscle Aches/Pains (0–2)						2.66	**0.04**	1.67	0.17	0.94	0.41	0.08	0.41	0.33
1 week taper	1.4	1.7	1.4	0.8	0.7									
2 week taper	1.0	1.5	1.5	0.9	1.0									
4 week taper	0.9	0.9	0.9	1.1	1.0									
Gooseflesh (0–3)						1.72	0.15	1.41	0.20	2.49	0.10	0.51	0.78	0.28
1 week taper	1.1	1.4	0.7	1.0	0.9									
2 week taper	0.8	0.6	0.7	0.4	0.4									
4 week taper	0.1	0.7	0.2	0.3	0.4									
Nasal Congestion (0–2)						2.32	*0.06*	1.37	0.22	1.50	0.24	0.55	0.25	0.3

						Within Subject				Between Subject		Effect Sizes[b]		
	Week 1	Week 2	Week 3	Week 4	Week 5	Week (df 4,96)		Week × Taper (df 8,96)		Taper Group (df 2,25)				
Restlessness (0–3)						0.98	0.42	1.05	0.41	0.03	0.97	0.04	0.08	0.04
1 week taper	1.0	1.1	1.2	0.8	1.0									
2 week taper	0.8	0.9	1.0	0.6	0.6									
4 week taper	1.0	1.0	0.8	0.9	0.9									
Tremor (0–3)						3.10	**0.02**	0.56	0.81	3.22	$0.06^{2,4}$	0.29	0.42	0.71
1 week taper	0.7	0.8	0.9	0.5	0.7									
2 week taper	0.5	0.7	0.7	0.2	0.2									
4 week taper	0.8	1.0	1.0	0.9	0.8									
Lacrimation (0–2)						1.22	0.31	0.23	0.94	0.02	0.99	0.02	0.02	0.00
1 week taper	0.3	0.3	0.2	0.1	0.1									
2 week taper	0.3	0.4	0.3	0.2	0.0									
4 week taper	0.3	0.3	0.2	0.1	0.2									
Sweating (0–3)						0.39	0.82	0.86	0.55	1.79	0.19	0.09	0.34	0.49
1 week taper	0.7	0.9	0.8	0.6	0.6									
2 week taper	0.7	0.7	0.6	0.8	0.6									
4 week taper	0.9	0.8	1.0	0.9	0.9									
Yawning (0–2)						0.29	0.89	1.29	0.26	1.51	0.24	0.42	0.02	0.39
1 week taper	0.7	0.4	0.6	0.4	0.6									
2 week taper	0.4	0.3	0.2	0.3	0.3									
4 week taper	0.3	0.4	0.6	0.9	0.3									
Total Incidence (1–11)						6.76	**<.001**	*1.97*	*0.06*	1.20	0.32	0.29	0.17	0.47
1 week taper	4.4	5.6	4.9	3.3	3.3									
2 week taper	4.1	4.3	4.6	3.6	2.9									
4 week taper	4.3	5.3	4.4	4.6	4.4									

Superscript numbers next to p-values convey taper groups who were significantly different (Tukey's posthoc). Only significant differences are reported.

[a] Score ranges presented in parentheses

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[b]Effects sizes reported as Cohen's D

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Table 3

Mean Peak Self-Report Ratings, Pupil Diameter, and Ancillary Medication Utilization

| | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Within Subject | | | | Between Subject | | Effect Sizes[d] | | |
| | | | | | | Week | | Week × Taper | | Taper Group | | Taper Groups | | |
			Mean Peak Rating[a]			F (df)	p-value	F (df)	p-value	F (df)	p-value	1 vs. 2	1 vs. 4	2 vs. 4
Visual Analog Scale (0–100)														
High						1.62 (4,96)	0.18	1.13 (8,96)	0.35	0.91 (2,25)	0.42	0.45	0.09	0.54
1 week taper	1.2	1.6	4.3	2.6	11.6									
2 week taper	8.1	11.6	10.2	7.4	10.7									
4 week taper	5.9	3.2	2.4	1.2	1.2									
Sick						2.70 (4,96)	**0.04**	1.98 (8,96)	0.06	1.36 (2,25)	0.28	0.45	0.10	0.34
1 week taper	61.4	50.8	40.8	7.8	6.0									
2 week taper	23.3	23.7	27.7	22.5	12.8									
4 week taper	33.3	35.7	27.1	31.0	34.0									
Withdrawal						3.38 (4,96)	**0.01**	1.37 (8,96)	0.22	0.28 (2,25)	0.75	0.25	0.19	0.05
1 week taper	57.9	53.7	36.2	14.9	12.0									
2 week taper	29.6	39.5	37.8	18.5	20.8									
4 week taper	30.0	34.6	30.0	31.2	29.0									
Crave						1.20 (4,96)	0.32	0.38 (8,96)	0.93	0.29 (2,25)	0.75	0.18	0.35	0.16
1 week taper	38.4	31.0	25.1	16.9	24.6									
2 week taper	37.2	34.8	36.7	34.4	24.6									
4 week taper	52.4	45.6	35.7	33.7	28.6									
Like the Way I Feel						1.98 (4,96)	0.10	0.92 (8,96)	0.50	0.98 (2,25)	0.39	0.35	0.21	0.56
1 week taper	56.6	64.8	63.8	69.3	75.1									
2 week taper	52.9	47.9	58.8	61.9	64.0									
4 week taper	69.7	64.9	69.9	72.1	75.3									
Pupil Diameter (mm)[b]						5.57 (4,86)	**<0.01**	1.64 (8,86)	0.13	0.10 (2,22)	0.91	0.26	0.26	0.00
1 week taper	6.1	6.5	6.3	6.0	5.9									
2 week taper	6.3	6.4	6.5	6.4	6.2									
4 week taper	6.0	6.5	6.4	6.5	6.4									
Sleep			Lowest Mean Rating[c]											

| | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Within Subject | | Between Subject | Effect Sizes[d] | | |
						Week	Week × Taper	Taper Group	Taper Groups		
Quantity (min hrs)						0.30 (4,96) 0.88	0.64 (8,96) 0.74	3.90 (2,25) **0.04**[1,4]	0.15	0.65	0.50
1 week taper	4.2	3.6	4.8	4.6	4.5						
2 week taper	4.8	4.7	4.3	4.1	5.1						
4 week taper	5.2	5.7	5.5	5.2	5.3						
Quality (min quality, 0–10)						0.28 (4,96) 0.89	1.13 (9,96) 0.25	0.44 (2,25) 0.65	0.13	0.23	0.15
1 week taper	4.2	2.9	4.2	5.4	4.4						
2 week taper	4.8	4.8	3.5	4.6	4.8						
4 week taper	5.2	5.6	5.0	4.0	4.3						
Medication Utilization		Mean Peak Utilization									
Medications Used (1–5)						3.53 (4,100) **0.01**	2.87 (8,100) **<0.001**	0.16 (2,25) 0.86	0.03	0.19	0.16
1 week taper	1.2	2.2	1.6	1.2	0.9						
2 week taper	1.2	1.6	2.2	1.7	0.6						
4 week taper	1.2	1.3	1.9	1.9	2.1						

Superscript numbers next to p-values convey taper groups who were significantly different (Tukey's posthoc). Only significant differences are reported.

[a] Mean peak increase (representing greater levels of withdrawal severity) is used to evaluate VAS outcome severity

[b] Derived from pupillometer assessment; covaried for buprenorphine stabilization dose

[c] Lowest mean rating (representing less sleep and lower sleep quality) is used to evaluate sleep-related outcome severity

[d] Effects sizes reported as Cohen's D