Published in final edited form as:

J Subst Abuse Treat. 2012 October ; 43(3): 285–290. doi:10.1016/j.jsat.2011.12.009.

Comparing buprenorphine induction experience with heroin and prescription opioid users

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Abstract

Prescription opioid (PO) dependent treatment presentations are becoming increasingly common, however, most research on the treatment of opioid dependent populations has been conducted in heroin users. The aim of this secondary data analysis was to compare the buprenorphine induction experience of 167 heroin and 61 PO users. Results demonstrate that although the groups differed on some baseline characteristics, many of the key induction experience variables were comparable between the groups. Heroin users were found to have significantly higher pre-induction Clinical Opiate Withdrawal Scale (COWS) scores ($p = .014$) and post-induction COWS score ($p = .008$) compared to the PO users. No differences between groups were found for self-reported craving and withdrawal scores, mean buprenorphine dose on day 1, or retention at the end of the first week. The findings of this study suggest existing buprenorphine induction practices developed for heroin users appear to be equally effective with PO users.

Keywords

Buprenorphine induction; prescription opioid; treatment

Introduction

Over the past decade there has been a proliferation of prescription opioid (PO) use and dependence in the United States .Buprenorphine has become a widely used medication, with research demonstrating that buprenorphine is an effective treatment for opioid dependence, and an effective alternative to methadone. In a meta-analysis, Mattick et al (2004) found that higher doses of buprenorphine may suppress heroin use better than higher doses of methadone, although treatment retention may be poorer. The authors noted that slow buprenorphine induction in some studies may be associated with poorer retention. An earlier meta-analysis found that buprenorphine may have lower retention compared to methadone. It is important to note that the doses of buprenorphine used in some of these clinical trials are also lower than doses of buprenorphine currently recommended.

Treatment of PO dependence is increasingly provided, yet almost all research on treatment of opioid dependence was conducted in heroin dependent patient populations. Research on treatment interventions such as buprenorphine for PO dependent patients is required.

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Induction is one important phase of buprenorphine treatment. The risk of causing a precipitated withdrawal means that treatment initiation needs to be planned for when the patient is showing some signs of opioid withdrawal, which may vary depending on the half life of the opioid used. Current recommendations for uncomplicated induction from short acting opioids suggest an initial dose of 4mg, with a second dose of 4mg two hours later, and subsequent days' dosing adjusted following monitoring for withdrawal and/or craving. These guidelines recommend longer periods of abstinence before induction and smaller doses for longer acting opioids. Difficult inductions with PO dependent patients, notably methadone patients, has been documented. Furthermore, an association was established between withdrawal symptoms and patients dropping out of treatment. This makes it important to understand how the type of opioid used (heroin or POs) affects the induction experience. This is particularly important where a difficult induction has been shown to be associated with poorer treatment retention and outcomes.

Previous research has identified some differences between heroin and PO users in methadone treatment. In one study of patients in a treatment program in Vermont, PO users were observed to use smaller amounts of opioids and to display lower severity of opioid dependence than heroin users. A separate study of methadone maintenance patients in Ontario, Canada, reported that PO users were generally older, more likely to report oral rather than injection use, and more likely to have histories of pain and mental health problems, despite no differences in social stability. When prescription opioid dependent patients and heroin dependent patients in buprenorphine treatment were compared, prescription opioid users had better outcomes including opioid use and treatment retention.

Given the potential differences in patient characteristics and co-morbidities, it is important to compare experiences of PO users and heroin users in treatment to ensure that treatment practices established for heroin users are appropriate for prescription opioid users. This study examined variations in induction experience according to opioid type (PO or heroin).

Methods

Design

This is a secondary analysis of induction data from a NIDA-funded study “Optimizing Outcomes Using Suboxone for Opiate Dependence” (Op-Bup), designed to evaluate the added therapeutic effects of three behavioral strategies delivered with a platform of buprenorphine pharmacotherapy. All patients received buprenorphine in conjunction with basic medication management, consisting of a standardized 10–15 minute visit with the buprenorphine prescriber in which medication compliance, recent drug use, and other measures of treatment progress were assessed. Participants in the study were maintained on buprenorphine for approximately 40 weeks. This analysis reports on the induction phase of the study, which occurred prior to randomization to behavioral condition. This analysis compares baseline characteristics and induction experiences for participants who reported heroin use and those who reported only PO use.

Sample

Two hundred and forty-one participants were inducted onto buprenorphine at the Integrated Substance Abuse Programs Outpatient Clinical Research Center, in Los Angeles. Eligible participants were males and non-pregnant, non-lactating females of all racial/ethnic groups who were at least 15 years of age. Participants met DSM-IV-TR criteria for opioid dependence and were in good general health with no medical or psychological conditions that might have made participation difficult or unsafe. Female participants were required to agree to use an acceptable form of birth control. Individuals were not eligible if they were

dependent on any non-opioid drug that required immediate medical attention, or had a pattern of benzodiazepine use that would have made their participation unsafe. Participants were excluded from this analysis if they were receiving a prescription for buprenorphine-naloxone prior to being recruited into the study, as participants who were maintained on buprenorphine-naloxone did not undergo an induction procedure. Following exclusion of these participants, 228 participants were included in this analysis.

Assessments

The secondary data analysis examined the following variables: Basic demographics data: gender, age, ethnicity/race, education, employment pattern, and marital status.

The Addiction Severity Index-Lite (ASI-Lite), an abbreviated version of the ASI, a standardized clinical interview that collects problem severity profiles in seven domains commonly affected in substance abuse, including alcohol and drug use, medical, psychiatric, legal, family/social and employment/support. Items from the substance abuse and employment domains were included in this analysis.

Visual Analog Craving Scales (VAS) were used to assess self-reported craving for opioids and ratings of opioid withdrawal. The scale is a 100mm line that ranges from 0 (no craving or withdrawal) to 100 (most intense craving/withdrawal).

The Clinical Opiate Withdrawal Scale (COWS) was used to provide a description of signs and symptoms of opioid withdrawal.

An Opioid Use Questionnaire collected information on types of opioids used.

The Beck Depression Inventory (BDI) assessed symptoms of depression.

The Short Form-36 Health Survey (SF-36) examined self-reported general health, vitality, social functioning, role-emotional and mental health.

A Dose Log (DL) collected information about the amount of study medication dispensed and amount of study medication the participant reported as taken each day since the last clinic visit.

Procedures

Interested participants who contacted study personnel were scheduled for an initial interview to complete the consent process and screening/baseline assessments. All procedures took approximately 4 to 8 hours, excluding review of returned lab results. Eligible participants were described the study procedures including a two-week induction and stabilization phase, 16-week combination medication and randomly assigned psychosocial treatment phase (through week 18), 16-week medication only phase (through week 34), taper phase (variable length, but up to week 40), and follow-up assessments at 40 and 52 weeks. Those wishing to participate were scheduled for a clinic visit to begin the medication induction/stabilization phase.

Medication

To facilitate a comfortable transition onto buprenorphine, participants were instructed not to use heroin or other opioids for at least 10 hours prior to the time scheduled to receive their first dose of medication. Participants were advised to wait longer than 10 hours where, based on the history of when they usually felt withdrawal symptoms emerge, they would not be experiencing withdrawal symptoms after only 10 hours. Participants on methadone were instructed to wait at least 72 hours after their last methadone dose. The 4:1 combination

tablet of sublingual buprenorphine: naloxone (as Suboxone®) was used, which is available in two formulas to provide a range of doses to allow individualized medication plans, and contains either 2mg/0.5mg of buprenorphine/naloxone, or 8mg/2mg buprenorphine/naloxone. Tablets were manufactured by Reckitt-Benckiser Pharmaceuticals, Inc. (Hull, UK) and were supplied to participants at no cost.

Prior to taking the first buprenorphine dose, a urine drug screen was obtained to determine recent benzodiazepine use and pregnancy status in females. Withdrawal signs and symptoms, vital signs, adverse events, concomitant medications, VAS and BDI were assessed prior to induction. Vital signs and COWS were again assessed one hour after first dose administration to assess the need for additional buprenorphine dosage and determine stability before leaving the clinic.

For induction, the first dose of 4mg (doses expressed as amount of buprenorphine) was taken sublingually and supervised in the clinic. Study personnel monitored dissolution of tablets as clinically warranted, and participants remained in the clinic for a minimum of one hour to monitor adverse events. Participants could receive an additional dose in the clinic or for take home. The Day 1 dose may have been up to 16mg based on the severity of the withdrawal symptoms. Day 2 induction doses ranged between 8 and 16mg, and Day 3 induction doses ranged between 12 and 24 mg. Participants were asked to make contact with study staff on Day 2 and attend the clinic to be seen by study medical staff, at a minimum, one additional day during the first week. At this next scheduled visit (between Days 3 and 7), participants were evaluated for drug use (urine screen), vital signs, any adverse events (AE), or concomitant medication use. All participants were stabilized on buprenorphine doses typically between 8 and 24mg.

Analysis

Participants were identified as either PO(only)users or heroin users by self-report at screening. Those who reported any heroin use in the 30 days prior to screening were classified in the heroin group. Participants who reported only PO use with no heroin use in the last 30 days were defined as the PO group. This categorization was chosen to examine whether induction experience differs for participants based on the specific opioid to which they were currently physically dependent (PO or Heroin) rather than on more distant opioid use history. Baseline analysis compared demographic and screening data between the two groups. Induction variables were then compared between the two groups. Measures of induction experience were withdrawal symptoms, buprenorphine dose, and retention during the induction period. For these analyses, the induction period was defined as the first 7 days of buprenorphine treatment, as this is the period when most induction-related problems are reported to occur and is consistent with the induction period defined in previous studies.

All statistical tests were performed at 95% significance level. Statistical analysis was performed using PASW Version 18. To test for possible effects of non-normal distribution both parametric (Independent Samples t-tests) and non-parametric tests (Independent Samples Mann-Whitney U Tests) were run for all continuous variables with significant results being very similar for parametric and non-parametric tests. Levine's test for equality of variance was used to determine if the assumption of equal variance was violated. Where Levine's test was significant, appropriately adjusted t-scores and levels of significance are reported.

All subjects provided informed consent and all study procedures were approved by UCLA Office of the Human Research Protection Program.

Results

Baseline characteristics

Sixty-one participants met criteria for the prescription opioid (PO) group (reporting PO only use in the 30 days prior to screening). The remaining 167 participants who reported heroin use were classified in the heroin group for these analyses. PO users reported a mean of 29 out of the last 30 days of PO use prior to screening. Heroin users reported a mean of 24 days out of the last 30 days heroin use prior to screening. While the heroin group may have used a combination of opioids, most (80%) used heroin at least every second day and more than 70% used heroin an average of 3 out of every 4 days in the 30 days prior to screening. The main prescription opioids reported as used by the PO group in the 30 days prior to screening were hydrocodone (used by 61% of the sample, and used daily by 38%), oxycodone (used by 44% of the sample, and used daily by 15%), illicit buprenorphine (used by 34% of the sample, and used daily by 15% of the sample), and methadone (used by 18% of the sample, and used daily by 8% of the sample). The PO users differed from heroin users on characteristics of marital status and lifetime years of cannabis use (Table 1).

On a number of variables including age, gender, years of education and mental and physical health (SF-36 and BDI), no significant differences were detected between the two groups. A significant difference was found when collapsing employment categories ($\chi^2 = 3.927$, $p = .048$) into regularly employed (full or part-time) or student and irregularly employed/unemployed/ other. Findings show greater regular employment amongst the PO group (see Table 1)

Induction

PO users did not differ from heroin users in total dose taken on the first day of induction, or the dose participants were on at the end of the first week. Pre-induction Visual Analog Scores (VAS) of craving or withdrawal also did not differ between the two groups. Other withdrawal assessments using the COWS prior to and one hour following initial buprenorphine dose were significantly higher in the heroin group, indicating the heroin group experienced greater opioid withdrawal symptoms at both time points as observed by experienced clinical staff (Table 2).

The proportion of each group who reported an increase in COWS scores one hour after initial buprenorphine dosing (indicative of precipitated withdrawal) did not differ significantly between the two groups, with 8% of the PO group and 15% of the heroin group reporting an increase in COWS scores an hour after their first buprenorphine dose (Table 2). There was a trend towards greater retention in the PO group (89%) at one week after induction compared to the heroin group (78%) that did not reach significance (Table 2).

Discussion

This study is the first to compare the buprenorphine induction experiences of heroin and PO users. Few differences were detected in the induction variables examined, with the findings indicating that PO users had generally comparable induction experiences.

This is an important finding to inform clinical practice as primary PO presentations become increasingly common at treatment services. Much of the research originally informing clinical practices with buprenorphine was conducted in heroin-dependent populations. We found similar induction experiences can be expected with PO-dependent populations. Participants in both groups reported similar withdrawal and craving scores, and also ended up on comparable doses of buprenorphine.

For clinicians seeing increasing numbers of prescription opioid dependent patients, the finding that comparable buprenorphine induction experiences can be expected for PO users should be reassuring. Results from this study suggest that PO users should not be expected to require different induction doses, to report greater withdrawal symptoms, or to have poorer retention at one week post induction. Examining these patients over a longer period of time will provide important information to ascertain whether the PO users' more favorable results at induction translate into good long-term treatment outcomes.

Most participants in both groups were retained in treatment one week after induction, further indicating successful induction onto buprenorphine. Induction doses used in this study are consistent with doses suggested in clinical guidelines, although rate of induction and maximum doses allowable per the study protocol were higher. Evidence suggests that increasing induction doses more quickly is associated with better treatment outcomes, which is consistent with the finding here that most participants were successfully induced and retained on buprenorphine at the end of the induction week using this induction schedule. A feature of the induction procedures was individual tailoring of induction instructions based on half-lives of specific prescription opioids. This is an important caveat in interpreting these findings; this study was conducted in a clinical research setting with significant experience with buprenorphine induction procedures. Standard practices were used for inducing participants on long-acting opioids such as methadone, and staff have been trained to question participants about issues such as usual dose frequency and time to emergence of withdrawal symptoms so that participants could be advised about ideal time to commence buprenorphine. Furthermore, participants were routinely and systematically assessed for the presence of withdrawal symptoms prior to buprenorphine administration. While previous research suggested that using methadone was one factor associated with a more complicated induction, this study found that generally PO users in this study appeared to complete induction with minimal difficulties. In their study, Whitley et al (2010) reviewed charts of patients in an urban community health centre. This present study was conducted in a research centre with specific procedures for methadone, possibly explaining why this group did not appear to have more difficult inductions in this study. Whitley et al (2010) found that with experience, complications from buprenorphine inductions decreased, also consistent with the finding here that with experience, and tailored procedures, difficult inductions are not common amongst PO users.

Limitations of the study include the smaller sample size in the PO group. A larger sample size may have resulted in a difference being detected in retention at 7 days post induction, with a trend towards greater retention in the PO group consistent with findings of better retention with PO users compared with heroin users. Differences may not have been detected for dose or self ratings of withdrawal and craving with a larger sample size due to the similarity in results between the two groups on these measures. The other limitation is that this study only examined a one week induction period, with further analyses required to look at longer term outcomes for this participant population.

Despite some measures suggesting more favorable induction outcomes for PO users compared with heroin users, it is important to note that similar doses of buprenorphine were required for stabilization in both groups. This should inform clinicians that PO users generally do not appear to present with lower buprenorphine dosing requirements, despite presenting with lower COWS scores. As such, while treatment providers may be optimistic about treatment outcomes for PO users, they should not be complacent about buprenorphine dosing requirements.

Although this study informs the field about buprenorphine induction experiences, future studies will be important to better understand the longer term buprenorphine treatment

outcomes for prescription opioid users. Additionally, larger studies in primary care settings are required to see if induction experiences for PO users observed in this clinical research setting are replicated in everyday practice. This study does provide a useful addition to the limited knowledge base on buprenorphine pharmacotherapy treatment for prescription opioid dependence.

Acknowledgments

This study was sponsored by The National Institute on Drug Abuse (R01 DA 020210). The first author was the recipient of a NIDA/CTN INVEST fellowship.

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Table 1**Baseline Demographic and Drug Use Characteristics by Opioid Type**

	Heroin User (n = 167)	PO only (n = 61)		p
Gender (% male)	70	59	$\chi^2 (1) = 2.469$	.116
Mean age, yrs (SD)	35.9 (12.6)	37.4 (12.3)	$t(226) = .731$	.466
Age (range in years)	19–69	19–63		
Years of education, mean (SD)	13.1 (1.9)	13.4 (2.1)	$t(226) = 1.034$	.302
Employment (past 30 days, (%))			$\chi^2 (1) = 3.927$	.048
Regular (Full or part time) or student)	57	71		
Irregular/Unemployed/Other	43	29		
Race (%)			$\chi^2 (3) = 4.941$	p = .176
White	65	70		
Black or African-American	18	4		
Hispanic	16	22		
Other	9	2		
Marital status (%)			$\chi^2 (5) = 23.098$	p < .001
Married	7	22		
Widowed	1	3		
Defacto	12	12		
Separated	4	2		
Divorced	25	11		
Never Married	66	38		
SF36 Physical Health Component Score	47.4 (9.2)	45.6 (9.6)	$t(193) = -1.132$	p = .259
SF36 Mental Health Component Score	37.6 (12.3)	39.5 (11.8)	$t(193) = .963$	p = .337
Beck Depression Inventory Score	15.3 (8.9)	13.4 (7.8)	$t(224) = -1.467$	p = .144
Past 30 day opioid use (days)				
Heroin	23.6 (9.8)	0.0 (0.0)	$t(196) = -13.389$	p < .001
Prescription opioids	7.7 (10.4)	28.7 (4.5)	$t(219) = 14.962$	p < .001
Years (SD) of lifetime use (ASI)				
Heroin	9.6 (10.0)	3.2 (7.5)	$t(141.482) = -5.169$	p < .001
Other Opioid	2.1 (4.9)	6.3 (6.0)	$t(91.084) = 4.766$	p < .001
Alcohol	5.6 (8.3)	5.3 (7.1)	$t(226) = -.303$	p = .762
Alcohol to intoxication	4.7 (7.8)	4.2 (6.4)	$t(226) = -.421$	p = .674
Cocaine	2.9 (5.7)	2.1 (3.6)	$t(226) = -.982$	p = .327
Amphetamines/methamphetamines	1.4 (4.4)	1.3 (3.1)	$t(226) = -.135$	p = .893
Sedatives/Hypnotics	1.6 (4.9)	0.8 (2.0)	$t(223.6) = -1.794$	p = .074
Cannabis	6.6 (8.3)	4.5 (6.2)	$t(142.0) = -1.973$	p = .050

Table 2

Induction outcomes by opioid type

	Heroin User (n = 167)	PO only last 30 days (n = 61)		p
Total buprenorphine dose Day 1 (mg)	14.2 (4.3)	14.8 (3.9)	t(212) = 1.116	.265
Total buprenorphine dose Day 7 (mg)	14.3 (6.2)	14.9 (6.2)	t(201) = -.666	.506
Mean pre-induction scores (SD)				
VAS Craving	76.8 (23.6)	75.5 (28.8)	t(226) = -.332	.740
VAS Craving (Range)	1–100	0–100		
VAS Withdrawal	68.3 (20.6)	70.2 (24.3)	t(226) = .599	.550
VAS Craving (Range)	0–99	0–100		
Mean pre-induction COWS (SD)	11.0 (3.7)	9.7 (3.9)	t(226) = -2.471	.014
Mean 1 hr post first dose COWS (SD)	6.9 (4.5)	5.1 (3.6)	t(226) = -2.673	.008
Increase in COWS score (%)	15	8	$\chi^2(1) = 1.794$	.180
Retained at 7 days (%)	78	89	$\chi^2(1) = 2.967$	.085