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The relationship between primary prescription opioid and buprenorphine-naloxone induction outcomes in a prescription opioid dependent sample

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Abstract

Background and objectives—This analysis aims to: (1) compare induction experiences among participants who self-reported using one of the 4 most commonly reported POs, and (2) examine factors associated with difficult bup-nx induction. Our hypothesis, based on previous research and current guidelines, is that those on longer-acting opioids will have experienced more difficult inductions.

Methods—The Prescription Opioid Addiction Treatment Study (POATS) was a multi-site, randomized clinical trial, using a two-phase adaptive treatment research design. This analysis examines bup-nx induction of participants who self-reported primary PO use of methadone, ER-oxycodeone, IR-oxycodeone and hydrocodeone (n = 569). Analyses examined characteristics associated with difficult induction, defined as increased withdrawal symptoms measured by the Clinical Opiate Withdrawal Scale (COWS) after the first bup-nx dose with higher scores denoting greater withdrawal symptoms/severity.

Results—Contrary to our hypothesis, difficult induction experiences did not differ by primary PO type. Those who experienced a post-induction increase in COWS score had lower pre-dose COWS scores compared to those who did not experience a post-induction increase in COWS

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score (10.09 vs. 12.77, $t(624) = -13.56$, $p < .001$). Demographics characteristics, depression, and pain history did not predict a difficult induction.

Conclusions and scientific significance—Difficult bup-nx inductions were not associated with participants' primary PO. Severity of withdrawal, measured with the COWS, was an important variable, reminding clinicians that bup-nx should not be commenced prior to evidence of moderate opioid withdrawal. These findings add to the evidence that with careful procedures, bup-nx can be used with few difficulties in PO-dependent patients.

Keywords

buprenorphine; induction; prescription opioid dependence

1. Introduction

The increase in prescription opioid (PO) dependence and related mortality^[1–3] has made treatment-related research critical. PO dependence has been documented in the US and other countries, including Canada^[4], and prescription drug abuse has been noted by the International Narcotics Control Board to be one of the fastest growing drug problems in several regions around the globe^[5].

The use of buprenorphine-naloxone (bup-nx) to treat PO dependence is increasing^[6, 7]. However, few studies have addressed bup-nx for treatment of PO dependence despite the fact that prevalence of non-medical opioid analgesic use far exceeds prevalence of heroin use^[8]. Furthermore, there has been little research examining differences in treatment experiences by PO type, despite reports suggesting differences in patient characteristics by PO type^[9, 10].

Previous research also indicates that use of certain opioids is associated with difficult buprenorphine induction. One retrospective case review found that those prescribed methadone may have more difficult inductions including greater level of withdrawal symptoms, than those prescribed other opioids^[11]. This is of concern since an association was found between withdrawal symptoms during treatment and the likelihood of dropping out of treatment^[11]. Guidelines advise that different procedures are required for long- and short-acting opioids^[12] but little research informs these guidelines. A recently published study suggests that induction outcomes of PO users are generally comparable to those of heroin users^[13]; however, the relatively small sample of PO users ($n = 61$) precluded examining induction experience by specific PO type.

The multi-site Prescription Opioid Addiction Treatment Study (POATS), conducted by the Clinical Trials Network of the National Institute on Drug Abuse is the largest published study using bup-nx for treatment of PO dependence. Due to the sample size ($n = 653$), POATS provides an opportunity to examine induction experience by PO type. We hypothesized, based on previous research and current guidelines, that those on longer-acting opioids will have experienced more difficult inductions.

2. Methods

2.1 Study design

POATS employed a randomized, two-phase adaptive treatment research design^[14]. In Phase 1, participants were inducted onto bup-nx for a two-week stabilization period, followed by a two-week taper. The outcome of Phase 1 determined whether participants would require extended bup-nx treatment provided in Phase 2. Study methods are described in greater detail elsewhere^[15].

2.2 Study population

Participants age 18 or older who met DSM-IV^[16] criteria for current PO dependence were recruited from 10 U.S. treatment sites. Enrollment began June 12, 2006; the last study visit occurred July 9, 2009. Eligibility criteria included physiological dependence, willingness to be detoxified from opioids, prescribing physician clearance if prescribed opioids for pain, and birth control use for women of childbearing potential.

In addition to health and safety exclusions, participants were excluded for: heroin use >4 days in the past month; lifetime opioid dependence diagnosis due to heroin alone; ever having injected heroin; needing PO for ongoing pain management; experience of a major pain event within 6 months; being prescribed methadone >40 mg a day for pain; or psychiatric instability. The parent study screened 870 participants, with 653 participants enrolled. Participants who reported use of one of four PO types: Longer acting opioid formulations – extended- release (ER) oxycodone (n = 219) and methadone (n = 41); and shorter acting opioid formulations – immediate- release (IR) oxycodone (n = 107), or hydrocodone (n = 202), as the opioid they used most in the 30 days before study entry were included in this analysis. An insufficient number of participants reported using opioids other than these 4 types to merit inclusion in this analysis. Only participants who had both pre- and post-dosing withdrawal scores were included (n = 569), since the primary outcome measure was the difference between withdrawal symptoms scores from pre-dose to post-first induction dose.

2.3 Study Measures

Opiate Withdrawal—The Clinical Opiate Withdrawal Scale (COWS)^[17, 18] is an 11-item questionnaire assessing signs and symptoms of opioid withdrawal that can be clinically observed or measured (e.g., sweating, runny nose, etc). Higher scores indicate greater withdrawal symptoms. “Difficult induction” was defined as an increase in withdrawal symptoms, as measured by the COWS, following the first dose of bup-nx.

Variables in the current analyses include demographic characteristics (sex, birth date, ethnicity/race, education, employment, and marital status) and smoking status at baseline. The Pain and Opiate Analgesic Use History Form, developed for the main study, recorded the main type of opioid used by the participant in the 30 days prior to study entry, heroin use history, frequency of PO and heroin use in the past 30 days, routes of administration, and pain history^[19]. The Beck Depression Inventory (BDI)^[20] was used to assess self-reported symptoms of depression. The Brief Pain Inventory:^[21] assessed pain intensity and

interference of pain in life. The SF-36 was used to assess health-related quality of life [22]. Current chronic pain was defined as self report of pain “other than everyday kinds of pain,” excluding withdrawal-related pain, for at least 3 months^[19].

2.4 Buprenorphine-Naloxone Induction Procedure

Participants on short acting opioids were advised to be abstinent from opioids for 12 hours before commencing bup-nx, and those on longer acting opioids (including methadone) were advised to be abstinent for 36 hours. A first dose of 4mg bup-nx was provided to participants with a minimum COWS score of 8, to ensure that participants were in withdrawal prior to the first dose of bup-nx. COWS scores were repeated one hour following the first bup-nx dose. The participant was discharged from the clinic if withdrawal symptoms decreased after the first dose (a COWS score reduction of at least 2 points). At discharge, two 4 mg doses were dispensed to take if needed for withdrawal symptoms. If withdrawal symptoms did not improve, or worsened, an additional 4 mg bup-nx dose was administered in clinic. The participant was observed for another hour, then sent home with the remaining 4 mg dose. At each subsequent clinic visit, the study physician could adjust the daily bup-nx dose by up to 8 mg per week, for a maximum 32mg daily dose. Participants were dispensed take-home study drug for once-daily dosing at weekly clinic visits.

2.5 Statistical analysis

Chi-square tests and one-way ANOVA were used to compare characteristics across the four PO type groups. When significant differences were detected with one-way ANOVA, a post-hoc Bonferroni test was used to detect specific differences among the four groups, with $\alpha = 0.0167$ used to correct for multiple comparisons. Analyses comparing difficult induction by PO type used a two-sided significance level, $\alpha = 0.05$.

Further analyses were conducted to examine possible associations between participant characteristics and the experience of a difficult induction. Initial univariate analyses included factors considered clinically significant, and those at $p < 0.25$ were included in a regression analysis.

3. Results

3.1 Sample Characteristics by Primary Prescription Opioid Type

3.1.1 Demographic characteristics—PO groups did not differ on gender, age, years of education, marital status and employment (Table 1).

3.1.2 Substance use and clinical characteristics—Significant differences were found across PO groups for heroin use history ($p = 0.002$) and prior opioid dependence treatment history ($p = 0.04$). Table 1 shows that the highest levels of heroin use history and previous opioid dependence treatment were reported by the ER oxycodone group, with the lowest levels of heroin use history and prior opioid treatment reported by the hydrocodone group. No significant differences were found for smoking history, chronic pain, or depression by PO group (Table 1).

3.2 Induction Outcomes

No differences were found across PO groups in mean pre- or post-dose COWS scores, or in likelihood of a difficult induction (Table 1). There were a total of 32 difficult inductions out of 569 inductions, representing less than 6% of all inductions.

3.3 Predicting Difficult Inductions

Analyses were conducted to determine whether other characteristics would predict difficult inductions. Few of the characteristics examined were associated with difficult induction, with the exception of a lower pre-dose COWS score, found to be associated with a difficult induction ($p < 0.001$) (Table 2).

When previous opioid treatment, alcohol dependence in the past year, employment, chronic pain at baseline, primary opioid type, and pre-induction COWS score were included in a regression model, the only significant variables in the final model was pre-induction COWS score. The model only explained 7% of the variance, and was not able to correctly predict difficult inductions, only correctly predicting two cases in which difficult induction occurred.

4. Discussion

This study aimed to examine whether induction experience differed by PO type, with a hypothesis that long-acting POs would be associated with more difficult inductions. Contrary to our hypothesis, a significant association was not found between PO type and difficult inductions. This may be because previous research identifying difficulties inducing patients on longer-acting opioids was conducted before the importance the half-life of the opioid on the timing of first dose was widely known^[11]. This is supported by the finding that difficult inductions decreased over time^[11], attributed to increased experience in buprenorphine inductions.

The low rate of difficult inductions observed among PO users (6%) is an important finding, and is comparable with low rates of difficult inductions (8%) seen in a previous study of PO users^[13]. This low rate is also comparable to rates observed by Whitley et al (2010) by the fourth year of observation (6%). Results from these current analyses are consistent with evidence from other published studies suggesting similar or favorable treatment outcomes in PO users given bup-nx compared to heroin users^[6, 13].

Few demographic differences were observed across PO type groups in this sample, although there were some differences in substance use history characteristics. The highest levels of heroin use history were seen in the oxycodone ER group, with lowest levels in the hydrocodone group. Whether differences in substance use history affect longer-term treatment outcomes is an important issue to explore, particularly as any heroin use history has been associated with poorer treatment outcomes in bup-nx treatment^[19]. However, neither differences in baseline characteristics nor primary PO type appeared to predict difficult inductions.

The one variable that appeared important in predicting difficult inductions was a lower pre-dose COWS score. This is a reminder that caution should be used when patients are in minimal withdrawal prior to first dose, to ensure that bup-nx is not given before the patient is in sufficient withdrawal. Delaying induction until withdrawal symptoms are evident is consistent with current guidelines^[12]. While COWS scores of 8 have been accepted in other studies as a cut-off for commencing bup-nx^[13], a pre-dose COWS score of 8 may be insufficient to avoid precipitated withdrawal.

There are some limitations in interpreting these findings. Primary opioid was defined by self-report; while the categories of main opioid used were mutually exclusive, participants may have been using other opioids in lesser amounts. Detailed information about other opioids used in addition to the primary opioid is not available to further explore this. Dose of opioid used and frequency of use was also not available. Dose in particular may be an important predictor of difficult inductions^[23]. Finally, for those using ER Oxycodone, we do not have detailed information on whether the tablets were crushed or injected. For future studies, detailed information on dose of opioid and route of administration would be important variables to collect and examine.

Defining difficult inductions was limited in this study to an increase in COWS scores, reflecting an increase in severity of opioid withdrawal symptoms from pre- to post-dose. Although using the COWS is considered a reliable and valid way to measure opioid withdrawal symptoms^[17], there may other clinically relevant measures of a difficult induction. There were, however, no other objective measures of difficult induction that were available to confirm these findings. A further limitation of the findings is the small size of the methadone group, which may have limited the power to detect differences between the opioid types. A larger sample size may have revealed differences that were not detected in this study due to a lack of power to detect smaller effects. Importantly, it should be noted that people prescribed methadone in doses of greater than 40mg were excluded from the study. Higher doses of methadone may have resulted in more frequent precipitated withdrawal^[24]. Patients on higher doses of methadone should be carefully managed, and method of optimal transfer from high-dose methadone to buprenorphine remains an area for further research.

Important areas of future research include examining longer-term treatment outcomes by primary PO type, to examine if the differences in patient characteristics by PO type identified in this and other studies lead to poorer treatment outcomes.

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Table 1

Participant characteristics and induction outcomes by Primary PO Used

Participant characteristics	ER Oxycodone n = 219	IR Oxycodone n = 107	Methadone n = 41	Hydrocodone n = 202	χ^2/F	p-value
<i>Sociodemographics</i>						
Female, (%)	42.9	36.4	48.8	42.3	2.321	.508
Age, mean yrs	34.1 (SD 11.2)	32.7 (SD 9.6)	32.8 (SD 10.0)	33.1 (SD 9.7)	0.430	.731
White race, (%)	89.5	81.3	80.5	87.1	5.458	.141
Education, mean yrs	13.2 (SD 2.2)	13.0 (SD 2.1)	12.8 (SD 2.3)	13.1 (SD 2.4)	0.231	.875
Never married, (%)	47.9	51.1	43.8	50.6	0.769	.857
Employed full-time, (%)	50.7	60.7	46.3	57.9	5.004	.171
Smoker at baseline (%) [†] N = 497	140 (73.7)	71 (76.3)	23(67.6)	127(70.6)	1.566	.667
Ever used heroin, (%)	32.9	26.2	26.8	16.3	15.330	.002
Length of opioid use, n(%)					14.172	0.116
< 1yr	24(11)	8(8)	2(5)	17(8)		
1yr – < 2yrs	44(20)	14(13)	7(17)	27(13)		
2yrs – <4 yrs	65(30)	33(31)	6(15)	59(30)		
4 years or longer	86(39)	51(48)	26(63)	99(49)		
Past year substance dependence, ^{‡‡}						
Alcohol	15 (7.1%)	1 (1%)	3 (8.1%)	5(2.6%)		
Marijuana	9 (4.2%)	4 (4%)	3 (8.1%)	8 (4.1%)		
Stimulant	5(2.4%)	1(1.0%)	0(0.0%)	2 (1.0%)		
Sedatives	16(7.5%)	7(7.0%)	4(10.8%)	8(4.1%)		
Cocaine	9(4.2%)	3(3.0%)	0(0.0%)	7(3.6%)		
Prior opioid dependence treatment, %	35.6	31.8	46.3	26.2	8.201	.042
Rated Health as good to excellent ^{††}	142 (75.1%)	69 (75%)	28(82.4%)	141(78.3%)	1.287	.732
Chronic pain at screening [‡] n	98 (47.1%)	40(41.2%)	19(55.9%)	80(42.1%)	3.195	0.362
Mean BPI Severity (sd) [*]	3.2 (SD2.5)	2.8 (SD2.8)	2.9 (SD2.7)	3.0 (SD2.5)	0.603	0.613
Mean BPI Interference with general activities (sd) [*]	3.3 (SD2.9)	2.9 (SD3.0)	2.6 (SD2.9)	2.8 (SD2.8)	0.964	0.409
Mean Depression (BDI) (sd)	23.5 (SD12.5)	20.1 (SD11.4)	22.9 (SD11.1)	22.4 (SD12.0)	1.687	0.169
Induction Outcomes						

Participant characteristics	ER Oxycodone n = 219	IR Oxycodone n = 107	Methadone n = 41	Hydrocodone n = 202	χ^2/F	p-value
Mean pre-dose COWS Score	12.7 (SD3.5)	12.4 (SD3.5)	13.0 (SD3.6)	12.7 (SD3.5)	0.301	.825
Mean post-dose COWS Score	5.3 (SD3.9)	5.8 (SD3.9)	5.6 (SD4.8)	5.9 (SD4.1)	0.833	.476
Mean reduction in COWS post dose	7.37 (SD4.7)	6.6 (SD5.4)	7.4 (SD5.7)	6.8 (SD5.1)	0.845	.470
Increase COWS post dose	8 (3.7%)	11 (10.3%)	3 (7.3%)	10 (5%)	6.368	.095

* Only completed for participants who reported pain at screening

[†] n = 497

^{††} n = 495

[‡] n = 529

^{‡‡} n = 543, χ^2 not reported as >25% of cells had <5 or one cell had value of 0

Table 2

Characteristics examined for predicting difficult induction onto buprenorphine

Characteristics	Difficult induction (n = 32)	Regular induction (n = 537)	χ^2/t	p
Female, (%)	50.0	41.8	0.834	.361
Age, mean yrs	33.3 (SD11.6)	33.4 (SD10.2)	-0.052	.959
White race, (%)	87.5	86.4	0.032	.857
Education, mean yrs	13.3 (SD2.5)	13.1 (SD2.3)	0.422	.673
Never married, (%)	56.0	48.8	0.489	.485
Employed full-time, (%)	43.8	55.5	1.682	.195
Smoker (baseline) (%)	78.6	72.3	0.526	.468
Chronic pain at baseline (%)	56.2	40.8	2.973	.085
Ever used heroin (%)	30.4	20	1.308	.253
Previous treatment for opioid dependence (%)	21.9	33.0	1.696	.193
Past year substance dependence (%)				
Alcohol	9.7	4.1	2.151	.142
Marijuana	6.5	4.3	0.321	.571
Stimulants	0.0	1.6	0.492	.483
Sedative	3.2	6.6	0.565	.452
Cocaine	6.5	3.3	0.849	.357
BPI Severity Score, mean (Baseline)	2.7 (SD2.6)	3.0 (SD2.6)	0.560	.576
BPI Interference Score, Mean	2.7 (SD2.8)	3.0 (SD2.9)	0.499	.618
Pre-induction COWS score, Mean	10.09 (SD2.30)	12.77 (SD3.52)	-4.388	<.001
Post-induction COWS score, Mean	13.64 (SD2.87)	5.17 (SD3.52)	13.330	<.001