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Unobserved versus observed office buprenorphine/naloxone induction: A pilot randomized clinical trial

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Abstract

Physician adoption of buprenorphine treatment of opioid dependence may be limited in part by concerns regarding the induction process. Although national guidelines recommend observed induction, some physicians utilize unobserved induction outside the office. The aim of this pilot randomized clinical trial was to assess preliminary safety and effectiveness of unobserved versus observed office buprenorphine/naloxone induction among patients entering a 12-week primary care maintenance study. Participants (N=20) with DSM-IV opioid dependence were randomly assigned to unobserved or office induction, stratifying by past buprenorphine use. All patients received verbal and written instructions. A withdrawal scale was used during initiation and to monitor treatment response. Clinic visits occurred weekly for 4 weeks then decreased to monthly. The primary outcome, successful induction one week after the initial clinic visit, was defined as retention in buprenorphine/naloxone treatment and being withdrawal free. Secondary outcomes included prolonged withdrawal beyond 2 days after medication initiation and stabilization at week 4, defined as being in treatment without illicit opioid use for the preceding 2 weeks. Outcome results were similar in the two groups: 6/10 (60%) successfully inducted in each group, 3/10 (30%) experienced prolonged withdrawal, and 4/10 (40%) stabilized by week 4. These pilot study results suggest comparable safety and effectiveness of unobserved and office induction and point toward utilization of non-inferiority design during future definitive protocol development. By addressing an important barrier for physician adoption, further validation of the unobserved buprenorphine induction method will hopefully lead to increased availability of effective opioid dependence treatment.

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Contributors

Authors EWG, DAF, and FRL designed the study and wrote the protocol. Authors XQW and EWG conducted the statistical analysis. Author EWG wrote the first draft of the manuscript and all authors contributed to and have approved the final manuscript.

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Keywords

buprenorphine; buprenorphine-naloxone; induction; opioid dependence treatment

Opioid dependence remains an undertreated public health problem. Approximately 800,000 individuals are heroin dependent in the U.S. (Lloyd, 2003), while 1.7 million reported a prescription opioid use disorder in 2007 (SAMHSA, 2008). Unfortunately, methadone maintenance is only available to approximately 250,000 patients at unevenly geographically dispersed programs (DASIS, 2006). Office-based treatment with buprenorphine (BUP) and buprenorphine-naloxone (BUP/NX) has been available in the U.S. since 2002. Increasing evidence supports buprenorphine treatment as an effective means of expanding access in general office settings (Gunderson, 2008). However, physician adoption has primarily been among addiction specialists who make up the majority of prescribers (Fiellin, 2007), and opioid dependence remains largely untreated.

Strategies to improve dissemination in general practice are urgently needed given the substantial morbidity of untreated opioid dependence (Hser et al., 2001). One important barrier for uptake involves physician concern about buprenorphine induction particularly among novice prescribers (Kissin et al., 2006; Gunderson et al., 2006; Walley et al., 2008; Barry et al., 2009; Netherland et al., 2009). The induction barrier is due in part to potential for precipitated opioid withdrawal if the first buprenorphine doses occur before the patient is in spontaneous opioid withdrawal. In addition, national practice guidelines recommend office initiation with observation and monitoring for up to 2 hours, which could significantly impact physician and ancillary staff workload (CSAT, 2004). Perhaps as a consequence, some prescribers initiate buprenorphine outside the office (Walley et al., 2008). Although descriptive data suggest the feasibility of unobserved “home” induction with clinician phone support in primary care (Alford et al., 2007; Lee et al., 2009; Mintzer et al., 2007; Soeffing et al., 2009; Sohler et al., 2009), comparative effectiveness data are lacking and unobserved induction is not endorsed in standard practice guidelines (CSAT, 2004). The clear potential for adverse events with unobserved initiation, including incorrect sublingual tablet administration, precipitated withdrawal, and over-sedation, raises concern about the safety and advisability of this practice.

The need for controlled trials of buprenorphine induction models is a national opioid research priority (CSAT & NIDA, 2008). Developing the unobserved induction method will hopefully improve physician adoption and provide a potentially preferable option for patients. Hence, we conducted a pilot randomized clinical trial of unobserved versus office BUP/NX induction at a primary care clinic. We sought to develop standardized induction procedures that would enable operational assessment of safety and effectiveness, as well as determine effect size estimates for future protocol development. The study was not powered to detect statistically significant differences between induction models.

1. Method

1.1 Participants

Twenty patients aged 18–65 were recruited December 2007–June 2008 through referrals from clinical and research programs at Columbia University Medical Center and locally posted flyers. After a structured telephone interview with a research assistant, participants completed in-person screening after obtaining informed consent. Eligible patients were DSM-IV opioid dependent male or non-pregnant/non-lactating females seeking BUP/NX maintenance treatment. Criteria for exclusion were: 1) long-acting opioid use such as methadone due to concern about greater induction difficulty (CSAT, 2004), 2) active DSM-IV alcohol or

benzodiazepine dependence, 3) lacking physical opioid dependence (e.g., post-detoxification), 4) unstable medical or psychiatric condition requiring urgent treatment assessed by psychiatric screening instruments (Hamilton, 1959; Hamilton, 1960; Young et al., 1978; Spitzer et al., 1999), clinical exam, and laboratory tests; 5) lacking insurance or ability to cover clinical costs during the naturalistic study, including visit and medication co-payments.

1.2 Treatment conditions

Patients (N=20) were randomized to observed or unobserved induction stratifying by past BUP use. Patients were instructed to abstain from short-acting opioids for 16 hours before induction. Treatment was provided at an urban, academic-affiliated primary care clinic by an internist with BUP treatment experience (EWG). In the unobserved induction arm, BUP/NX was initiated outside the office after patients received verbal and written instructions and completed a Subjective Opioid Withdrawal Scale (SOWS; Handelsman et al., 1987), a self-administered withdrawal scale. Patients received a prescription for BUP/NX, usually sixteen 2mg/0.5mg tablets filled at a local pharmacy. They were instructed to initiate medication taking 1–2 tablets after abstaining 16 hours or more from opioids and when the SOWS reached ≥17 (Lintzeris et al., 2003). Office induction followed national guidelines (CSAT, 2004), using the SOWS and Clinical Opioid Withdrawal Scale (COWS; Wesson & Ling, 2003), which includes objective and subjective items.

For in-office patients, a prescription for sixteen 2/0.5mg BUP/NX tablets was filled at a pharmacy and picked up by study personnel prior to induction with clinic storage available in a locked medication cabinet. Medication was typically initiated for SOWS ≥ 17 and/or COWS ≥ 8 (Collins et al., 2007) with 1–2 tablets, with additional dosing based on clinical response. The patient left clinic after withdrawal improved. Office inducted patients similarly received verbal and written instructions on use of the SOWS. Medication was titrated over several days based on persistent or recurrent withdrawal, side effects, and cravings.

Both groups were instructed to take no more than 16mg on Day 1 (dosages hereafter refer to BUP content of the BUP/NX preparation). The target daily maintenance dose ranged between 12–16mg for most patients with a maximum 32mg. Daily SOWS were administered by phone for both groups until the participant was on BUP/NX and withdrawal free for two consecutive days, defined as SOWS <10 (Lintzeris et al., 2003). SOWS were performed during physician clinical phone contacts or by a research assistant.

Clinical visits occurred weekly during a 4-week induction and stabilization phase, then decreased to monthly. Brief medical management took place at each visit (Fiellin et al., 2006). Formal ancillary psychosocial treatment and self-help group participation was encouraged but not required. Urine toxicology including a BUP-specific immunoassay was performed at all clinical visits. Research visits occurred every 4 weeks, during which urine toxicology was performed, self-reported substance use was assessed (Sobell & Sobell, 1996) and research scales administered (Hamilton, 1959; Hamilton, 1960; Young et al., 1978; McLellan et al., 1992; Tracy et al., 2000). Participants received a small amount of monetary compensation for their time and travel for research but not clinical visits. The New York State Psychiatric Institute Institutional Review Board approved the protocol.

1.3 Outcome measures

The primary outcome was successful induction one week after the initial clinic visit, defined as in treatment, on BUP/NX, and withdrawal free. Secondary outcomes included: 1) prolonged withdrawal, defined as SOWS ≥10 beyond two days after BUP/NX initiation (Lee et al., 2009), and 2) clinical stabilization at 4 weeks, defined as retained-in-treatment, on BUP/NX, and illicit opioid free by urine toxicology testing and self report during the past 2 weeks.

Twelve-week retention and illicit opioid use were examined for comparison with other BUP/NX maintenance studies.

1.4 Statistical analyses

As a pilot study, our objectives were to assess safety and obtain estimates of variability and effect size for future large-scale clinical trial design. Summary statistical analysis was performed: Chi-square or Fisher's exact tests were used for comparisons of categorical variables. Data on interval level scales were analyzed using t-tests for independent variables. Analyses were performed with SPSS 16.0 (SPSS, Inc., Chicago, IL).

2. Results

2.1 Participant Characteristics

Of 21 patients screened, one was excluded for active alcohol and benzodiazepine dependence. Induction group characteristics were similar and collapsed data are presented (Table 1). The sample was predominantly male, ethnically diverse, and unemployed. Most had a substantial legal history and received prior opioid treatment. Although psychiatric disorder prevalence did not differ between groups (65% overall), the unobserved induction group was more likely to screen positive for depression (70% vs. 10%, $p=0.02$). Most were using heroin, the unobserved induction group was more likely to inject (80% vs. 20%, $p<.05$), and 45% previously used buprenorphine via prescription or purchased illicitly.

2.2 Induction outcome

Outcomes were similar for each group: 6/10 (60%) successfully inducted at Week 1 in each group, 3/10 (30%) experienced prolonged withdrawal, and 4/10 (40%) were stabilized at Week 4. One unobserved induction patient experienced precipitated withdrawal but stabilized by Week 1. The time interval from last opioid use and SOWS score were below recommended levels prior to initiation.

2.3 Treatment provision and maintenance outcome

Medication dosing and phone contacts did not differ between groups (Table 2), although there was a trend toward higher Day 1 mean BUP dose in the unobserved group (14mg ± 5 vs. 10mg ± 5, $p=.08$). There was no difference in number of physician phone contacts or call length during Week 1, with an overall mean (SD) of 5 (4) calls lasting 4 (1) minutes. Overall, 10/20 (50%) were retained at 4 weeks and entered maintenance. Of these 10, only 4 participated in weekly ancillary psychosocial treatment, 3 used illicit opioids during maintenance based on self-report or urine toxicology, and 7 completed the trial.

3. Discussion

To our knowledge, this is the first randomized study examining unobserved versus office BUP/NX induction using standardized induction procedures that enable operational assessment of effectiveness. The findings indicate comparable safety and effectiveness measured by induction success, stabilization, and complication rates. In both groups, 60% successfully inducted by Week 1. The ability of patients to initiate BUP/NX outside the office builds upon retrospective data in general medical settings (Alford et al., 2007; Mintzer et al., 2007; Soeffing et al., 2009; Sohler et al., 2009), including an unobserved induction protocol that found 70% success at Week 1 (Lee et al., 2009). Many published office-based buprenorphine maintenance studies utilizing observed induction do not report confirmation of buprenorphine usage and withdrawal assessment during induction. However, a large primary care BUP/NX maintenance

study with observed dosing during thrice weekly visits found 83% completion of a 2-week induction phase (Fiellin et al., 2006), further suggesting similar effectiveness.

The unobserved induction protocol was well tolerated and mirrors procedures used in other outpatient practices providing verbal and written instructions with relatively limited telephone support (Alford et al., 2007; Lee et al., 2009; Mintzer et al., 2007; Soeffing et al., 2009; Sohler et al., 2009). We utilized prospective serial withdrawal scales to monitor adverse events, building upon retrospective unobserved and observed induction data (Collins et al., 2007; Lee et al., 2009; Sohler et al., 2009). Precipitated withdrawal, a likely concern of many physicians and patients, appears relatively uncommon. However, milder prolonged withdrawal beyond the first two days of treatment occurred in 30% of patients in both groups of our study and is likely more prevalent. Overall retention was lower than many urban primary studies (Stein et al., 2005; Alford et al., 2007; Lee et al., 2009 ; Soeffing et al., 2009; Sohler et al., 2009). However among the 9 (45%) patients retained into the maintenance phase, eight (89%) were stable off illicit opioids by week 4, which did not differ between induction methods.

The primary pilot study limitations are sample size and single treatment setting, which restricts statistical comparison of outcomes and generalizability. However, outcomes were surprisingly similar for both groups and, coupled with existing descriptive data, indicate comparable safety and effectiveness. These collective findings support non-inferiority design in more definitive protocol development.

Conducting the pilot study led to several practical methodological considerations regarding implementation and future study design. While utilization of the SOWS and written instructions to guide induction appears feasible and well received, the variable initial dose (2–4mg) and weeklong dosing instructions were confusing to some patients and may not be necessary. Future procedures should consider simplified instructions with a standard single first dose and written instructions for 2–3 days. Use of blinded SOWS assessment during the early phase of induction would minimize bias by separating clinical care provided by the physician from data collection.

In conclusion, buprenorphine induction is an important barrier limiting opioid dependence treatment diffusion nationally. The current pilot data add to accruing evidence for unobserved induction effectiveness. However, before unobserved induction can be actively promulgated in practice guidelines and physician training, clinical trial data are needed to ensure that the approach is no worse than standard-of-care office induction. Hopefully, further validation and development of a standardized unobserved induction methodology will increase implementation in clinical practice and ensure availability and utilization of effective drug treatment nationally.

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Table 1

Demographic and Clinical Characteristics (N=20)

Characteristic	
Age, mean years (range)	45 (23–65)
Sex, male, n (%)	18 (90)
Race/Ethnicity, n (%)	
White	9 (45)
Hispanic	7 (35)
Black	4 (20)
Education, mean years (SD)	13 (2)
Married, non-separated, n (%)	4 (20)
Employed, at least part-time, n (%)	5 (25)
Legal History	
Prior arrest, n (%)	15 (75)
Number of arrests, mean (SD)	7 (6)
Convictions, mean number (SD)	3 (4)
Prior incarceration, n (%)	11 (55)
Number of years incarcerated, mean years (SD)	5 (4)
Comorbidities, n (%)	
Psychiatric disorder (non-substance use)[a]	13 (65)
HIV[b]	3 (15)
Hepatitis C[b]	11 (55)
Substance Use History, n (%)	
Primary Opioid	
Heroin	15 (75)
Prescription opioid only	3 (15)
Heroin/Prescription Opioid	2 (10)
Frequency of use in past 30 days, mean days (SD)	29 (2)
Injection drug use, any time in the past month	10 (50)
Past buprenorphine use (during treatment or illicit)	9 (45)
Cocaine dependence, lifetime	8 (40)
Cocaine use, past month	8 (40)
Benzodiazepine use, past month	6 (30)
Tobacco dependence, current	18 (90)
Substance Treatment History, n (%)	
Any prior opioid dependence treatment	18 (90)
Prior opioid detoxification	16 (80)
Mean number of prior opioid detoxifications (SD)	2 (1)
Methadone maintenance treatment, ever	12 (60)
Buprenorphine maintenance treatment, ever	3 (15)
Outpatient addiction treatment or 12 Step, active	6 (30)

[a] Includes patients currently receiving psychiatric treatment or those screening positive with active symptoms on the Patient Health Questionnaire (Spitzer et al., 1999). Nine (45%) screened positive with active symptoms.

[b] HCV and HIV status by self-report or laboratory testing.

Table 2

Buprenorphine dosing and phone contacts

	Office	Unobserved	P value
Buprenorphine dose, mg[a]			
Induction Day 1	10 (5)	14 (5)	p = .08
Week 2	13 (5)	14 (6)	NS
Week 3	9 (10)	16 (5)	NS
Week 4	11 (6)	14 (5)	NS
Week 8	10 (7)	13 (7)	NS
Week 12	10 (6)	7 (1)	NS
Phone Call Number[a]			
Week 1	4.1 (1.9)	6.4 (5.6)	NS
Week 2	0.7 (1.3)	0.8 (1.0)	NS
Week 3	0.2 (0.4)	0.1 (0.3)	NS
Week 4	0.1 (0.3)	0.0 (0.0)	NS
Phone Call Minutes[a]			
Week 1	3.4 (0.9)	4.3 (1.6)	NS
Week 2	2.5 (1.5)	2.5 (1.3)	NS
Week 3	2.5 (0.7)	3.0 (NA)	NS
Week 4	1.0		

[a]Data presented are means ± standard deviation; NS = non-significant.