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Buprenorphine Dose Induction in Non-Opioid-Tolerant Pre-release Prisoners

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Abstract

Background—In a previously reported randomized controlled trial, formerly opioid-dependent prisoners were more likely to enter community drug abuse treatment when they were inducted in prison onto buprenorphine/naloxone (hereafter called buprenorphine) than when they received counseling without buprenorphine in prison (47.5% vs. 33.7%, $p = 0.012$) (Gordon et al., 2014). In this communication we report on the results of the induction schedule and the adverse event profile seen in pre-release prisoners inducted onto buprenorphine.

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Contributors

All authors contributed to and approved the final manuscript. This manuscript is the work of the authors alone. Authors Kinlock, Gordon, Schwartz, and O'Grady designed the study and wrote the protocol. Authors Jaffe and Wilson contributed to the first draft of the manuscript. Authors Schwartz and Vocci converted the adverse events into MedDRA coding. Authors Vocci and O'Grady planned and analyzed the data, created the tables and figure, and revised the manuscript.

Conflicts of Interest

Authors Gordon, Kinlock, Jaffe, and Fitzgerald report no conflicts of interest. Drs. Vocci, Schwartz, and O'Grady have, in the past, received reimbursement for their time from Reckitt-Benckiser, one of the manufacturers of buprenorphine. Dr. Vocci has also consulted for generic buprenorphine manufacturers, and been a consultant and investigator for studies funded by Titan Pharmaceuticals and Braeburn Pharmaceuticals. All consulting fees for Drs. Vocci and Schwartz went directly to their employer, Friends Research Institute. Reckitt-Benckiser also supplied buprenorphine/naloxone tablets and film for the study. Reckitt-Benckiser had no role in the design, data collection, and analysis and interpretation of data; in the writing of the manuscript; or in the decision to submit the manuscript for publication. The authors alone are responsible for the content and writing of the manuscript.

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Method—This paper examines the dose induction procedure, a comparison of the proposed versus actual doses given per week, and side effects reported for 104 adult participants who were randomized to buprenorphine treatment in prison. Self-reported side effects were analyzed using generalized estimated equations to determine changes over time in side effects.

Results—Study participants were inducted onto buprenorphine at a rate faster than the induction schedule. Of the 104 (72 males, 32 females) buprenorphine recipients, 64 (37 males, 27 females) remained on medication at release from prison. Nine participants (8.6%) discontinued buprenorphine because of unpleasant opioid side effects. There were no serious adverse events reported during the in-prison phase of the study. Constipation was the most frequent symptom reported (69 percent).

Conclusion—Our findings suggest that buprenorphine administered to non-opioid-tolerant adults should be started at a lower, individualized dose than customarily used for adults actively using opioids, and that non-opioid-tolerant pre-release prisoners can be successfully inducted onto therapeutic doses prior to release.

Keywords

Buprenorphine dose; Buprenorphine induction; Opioid-dependent prisoners

1. INTRODUCTION

Research studies conducted across several continents indicate that newly-released prisoners who were opioid dependent prior to incarceration are at elevated risk of opioid overdose death within the first few weeks of prison release (Binswanger et al., 2007; Bird and Hutchinson, 2003; Merrill et al., 2010; Stewart et al., 2004). Newly released prisoners are also likely to rapidly relapse to opioid dependence (Kinlock et al., 2007). These findings lend support to the concept of providing opioid agonist treatment prior to release to prisoners with a history of opioid use disorder. The purpose of initiating opioid agonist treatment under such circumstances would be to increase the likelihood of continuation in treatment upon release, and to reduce the likelihood that opioid use subsequent to release would lead to fatal opioid overdoses.

Dose induction of formerly opioid-dependent but currently non-opioid-tolerant individuals (including prisoners) with opioid medications should proceed cautiously to avoid potential harm to patients. Dole et al. (1969), in a random assignment study, compared a no-treatment control group with a small group of inmates started on a low dose (10mg) of methadone with gradual increases in methadone prior to release. These authors found that the group started on methadone was less likely to become “readdicted” (Dole’s term for regular, daily use) to heroin and to be re-arrested after release. More recently, in a randomized trial comparing counseling and pre-release methadone treatment versus counseling without methadone for non-opioid-tolerant male prisoners with histories of opioid dependence prior to incarceration, there were no opioid overdose deaths in the group that started methadone prior to release ($N = 71$), or in the group that started methadone in the community at release ($N = 70$) compared to four in the counseling only condition ($N = 70$) (Kinlock et al., 2009).

Stabilization on methadone prior to release is now an established practice, at least for some prisoners in a number of countries (Kastelic et al., 2008 ; Stallwitz and Stover, 2007).

Buprenorphine, a μ opioid partial agonist, has been approved for sublingual administration in the US for the treatment of opioid dependence since 2002. While buprenorphine is substantially more potent than morphine (Jasinski et al., 1978) it has a plateau effect with respect to respiratory depression and at higher doses affords a superior safety profile to methadone and other full opioid agonists (Walsh et al., 1994). Nearly all of the extant studies of sublingual buprenorphine for drug dependence have been conducted with research participants who had a history of opioid dependence and were either physiologically dependent at the time of the study (Amass et al., 1998; Fudala et al., 2003; Johnson et al., 1989; Ling et al., 1998; Magura et al., 2009) or were actively using (and likely tolerant to some degree) at study enrollment (Strain et al., 2000; Walsh et al., 1994).

There are few reports of administration of buprenorphine to formerly opioid-dependent but currently non-opioid-tolerant individuals. In likely the first study that buprenorphine was administered to individuals with a history of opioid dependence who were believed not to be tolerant at the time of the study, Jasinski and colleagues (1989) found that 2 mg (but not 1 mg) of sublingual buprenorphine solution produced significantly greater amounts of euphoria with little sedation than did placebo. Since that time, there has been some limited experience in inducing non-opioid-tolerant prisoners on buprenorphine prior to release (Garcia et al., 2007; Springer et al., 2010, 2012; Zaller et al., 2013).

In a random assignment study reported elsewhere (Gordon et al., 2014), two hundred eleven (211) adult prisoners with a history of opioid dependence who were presumed not to be tolerant at the time of dose induction were randomly assigned to begin buprenorphine induction prior to or after release from prison (Kinlock et al., 2010). This report describes the buprenorphine dose induction, a comparison of the proposed versus actual doses administered, and the reported side effects in the 104 study participants reported in Gordon et al. (2014) who were assigned to begin buprenorphine prior to release from prison.

2. METHODS

2.1 Participants

There were 104 male and female participants enrolled between September, 2008 to August, 2012, all of whom were inmates in one of two prison facilities in Baltimore, Maryland (Metropolitan Transition Center and the Maryland Correctional Institution for Women). One participant refused buprenorphine. Another inmate was originally assigned to receive counseling only, was released, started on buprenorphine in the community, and then remanded back to prison where he continued on buprenorphine. Thus, the denominator for buprenorphine administration was 104 participants. Inclusion criteria for study participation were: meeting DSM-IV criteria (DSM-IV; American Psychiatric Association, 1994) for heroin dependence and manifesting physical dependence during the year preceding incarceration, willingness to provide informed consent and to take buprenorphine, being 3–6 months prior to release. Exclusion criteria were having evidence of renal or liver failure, a

history of psychosis, having a pending parole hearing, or unadjudicated charges that could result in transfer to another facility and/or additional prison time.

2.2 Procedure

Participants were screened for study participation by a research assistant who obtained informed consent according to procedures approved by the Friends Research Institute's Institutional Review Board (IRB), the Office for Human Research Protection (OHRP), and a Data and Safety Monitoring Board (DSMB). A baseline assessment that included the Addiction Severity Index (McLellan et al., 1985) was then administered to consenting participants. The study physician then obtained a medical history and conducted a physical exam to confirm study eligibility and willingness to participate. Blood was drawn to obtain liver function tests and hepatitis C status.

2.3 Dose Induction

Dose induction was initiated by cutting a 2mg/0.5 mg buprenorphine/naloxone tablet in half by the study nursing staff using a tablet cutter. Medication was administered sublingually under direct observation by the nurse. Each participant waited in front of the nurse for at least 5 minutes until the medication was dissolved. Participants were instructed to keep their hands to their sides and not to attempt to divert the medication. Nonetheless, there were 15 attempted diversions among the first 81 enrollees randomized to buprenorphine in prison. The sublingual medication was switched, after consultation and discussion with the IRB and the DSMB, to the more rapidly dissolving film strips for the last 23 study participants in the hopes of preventing continued attempted diversion. A 1 mg dose was achieved by cutting the film strip in half for the first week's dosing.

Dose induction followed a general protocol as follows: after 7 days of 1 mg, the dose was increased by 1 mg per week to 4 mg and thereupon increased in 2 mg weekly intervals to 6 and then 8 mg. After two weeks at 8 mg, the dose was doubled to 16 mg and administered every other day. Finally, if this schedule was tolerated for 2 weeks, the dosing was changed to a thrice weekly, Monday – Wednesday – Friday schedule, with the Friday dose increased as needed to cover the 72 hours until the Monday dose. All doses and reports of side effects were recorded daily on a log by the nurse administering the medication.

2.4 Side effect Monitoring

Nursing staff asked the participants on a daily basis whether they experienced any side effects and these reports were recorded on the daily medication log. Nursing staff also inquired on a weekly basis (generally on Mondays) about side effects using a structured form which asks regarding: constipation, sweating, drowsiness and "other" symptoms which the participant could volunteer and the nurse would record verbatim on the form. The study physician adjusted participants' dosing based on clinical response and participant request. The symptom complaints or lack thereof were discussed with the physician who then decided to reexamine the participant or to hold the dose, reduce it in the case of complaints of drowsiness, increase the dose in the absence of complaints per the protocol proposed increase, or an increase above the proposed protocol increase in the case of complaints of inter-dosing withdrawal.

2.5 Statistical analysis

Average weekly dose of buprenorphine for each participant for the first 10 weeks of treatment was analyzed with a generalized linear mixed model with the repeated effect of week having a compound symmetric heterogeneous structure, and assuming a Poisson distribution of weekly dose to examine change over time in dosing. A generalized estimating equations (GEE) approach was used in separate analyses of weekly symptoms of constipation, sedation, and sweating for the first 10 weeks of treatment in order to determine change over time in each of the three symptoms. The statistical model included a repeated effect for week having an exchangeable structure, and assuming the outcome followed a binomial distribution. Due to the sparseness of the data beyond 10 weeks, only the first 10 weeks of symptom data could be analyzed. Moreover, it was necessary to omit week 5 from the analysis of drowsiness due to lack of variance for that week.

3. RESULTS

3.1 Participants

The demographic characteristics and drug and criminal history at baseline of the 104 participants who started on buprenorphine are shown in Table 1. The mean (*SD*) length of the participants' index incarceration was 16.5 (26.3) months with a range from 2.9 to 184 months.

3.2 Treatment

Of the 104 participants randomized to buprenorphine in prison, 1 refused to participate after consent, 19 (18%) were discontinued with a dose taper by staff because the study nursing staff believed they were attempting to divert buprenorphine, 9 (8%) were discontinued through a dose taper at the request of the participant because of symptoms attributed to buprenorphine by the participant, 12 (11%) were transferred to another facility, and 63 participants (62%) remained on buprenorphine at release from prison. Of the 104 participants who received at least one dose of buprenorphine, the mean (*SD*) number of weeks of dosing was 11.8 (8.9) (range 1 to 49 weeks). Their mean (*SD*) weekly buprenorphine dose in mgs was 72.2 (58.9) (range 1 to 252).

3.3 Dose induction and maintenance in participants who completed 10 weeks

The mean daily dose of buprenorphine administered to the 60 participants who completed 10 weeks of therapy is represented by the orange line in Figure 1 with its standard error bars. In general, doses exceeded those recommended in the dosing protocol (see above). The mean daily dose exceeded 8 mg per day by week 5 when the recommended dose was 6 mg and then reached an asymptote of 12.5 mg at week 8. Slight variations occurred thereafter. One plausible explanation for the more-rapid-than-expected dose run-up would be that some participants had access to opioids in prison and had some residual tolerance as a consequence of this use.

Of the 68 participants who could have been transitioned to every other day dosing at week 8, only 6 actually received this regimen before being converted to three times per week dosing. An additional 21 participants transitioned from daily dosing to three times per week dosing.

Eight of the 27 participants who received either every other day dosing (2 participants) or three times per week dosing (6 participants) went back to daily dosing. Five of these participants were put back on daily dosing because of complaints consistent with interdosing withdrawal symptoms, two received a daily dosing taper due to diversion, and the last participants received a daily dosing taper due to a rules infraction causing administrative termination from the study. Thus, only 19 of the 68 eligible participants (28 %) were maintained on three times per week dosing.

Nineteen participants were withdrawn from the study due to attempted diversion. There was no difference in the rate of attempted diversion with the tablet (15/81; 19 %) or the film (4/23, 17%).

3.4 Adverse Events

There were no serious adverse events reported during the “in-prison” phase of the study. Most of the medication-related discontinuations occurred within the first two weeks of dosing. Three participants discontinued medication during the first week prior to responding to the weekly side effect summary questionnaire while taking 1 mg buprenorphine. One participant reported feeling “sluggish” after the first dose and quit after 3 days, a second participant quit after three days reporting nausea, vomiting, itching and feeling high, and the third participant quit after 5 doses reporting nausea, vomiting and itching. Two other participants who discontinued buprenorphine reported feeling ill, another described headaches as the reason for discontinuation, two others reported constipation, another reported erectile dysfunction and a rash, and one discontinued after other inmates told him he looked “high”. There were also two reports of drowsiness among the group that discontinued. All side effects are known to occur with buprenorphine with the exception of the one case of erectile dysfunction. Side effects were not attributed to concomitant medications as only two were on any other concomitant medications (one taking lisinopril for hypertension and one using beclomethasone and albuterol inhalers for asthma).

For the 60 participants who completed 10 weeks of dosing, Figure 1 shows the weekly plot of the mean estimated probabilities of reports of constipation, drowsiness, and sweating, respectively, plotted against the average weekly dose of buprenorphine. Constipation, which was dose-related ($p = 0.01$), was the most frequently reported symptom (28% to 55% of participants endorsing it each week). As shown in the Figure, reports of constipation decreased over time as the medical staff treated constipation with advice about diet, fluid intake, exercise, administration of colace, and, if needed, lactulose. All but one of the participants who reported constipation were treated with colace, lactulose, or both medications. There were fewer reports of drowsiness and sweating than of constipation; sweating was also-dose related ($p = 0.03$).

A total of 1,777 adverse events were reported by 95 of the buprenorphine study participants. Of these, 1,775 were recoded into Medical Dictionary for Regulatory Activities (MedDRA) terms with 2 events unclassifiable. The percentage of study participants reporting adverse events and the incidence of adverse events at the 1% level or greater is presented in Table 2. The adverse events reported are a mixture of medication-related, withdrawal-related, and possibly “other” related signs and symptoms. For example, constipation is likely attributable

solely to a medication-related cause whereas nausea may be related to withdrawal, medication, or some current illness. Interestingly, withdrawal symptoms at the end of the dosing interval were reported by several participants (38/104) throughout the study, necessitating dose adjustments to higher doses or a return to daily dosing (see above).

Study participants were followed for one year in the post-release period. One participant was admitted to hospital for an apparent opioid overdose 53 days post-release. This individual did not continue on buprenorphine in the post-release period prior to or after the hospitalization for the overdose.

4. DISCUSSION

This is one of the first reports of detailed dose induction results of non-opioid-tolerant adults with a history of opioid use disorder in a prison setting with a current preparation of buprenorphine/naloxone combination sublingual tablet and, later, the film strip. In prisoners who may have not used opioids for substantial periods of time, it seemed prudent to begin a low dose to avoid symptoms of euphoria, sedation, and respiratory depression rather than having to escalate the dose rapidly to modulate withdrawal as is usually done in community settings. The initial low dose of 1 mg of buprenorphine sublingual with very gradual weekly increases was generally well tolerated with 64 (62%) of participants continuing on buprenorphine at the time of their release from prison. Evidence of acceptability of the side effect profile can be shown with a few examples. Seventy-two participants reported constipation; only three of the medication-associated dropouts reported constipation as the reason for dropout. Although 30 participants reported 47 incidences of sedation/drowsiness/somnolence (a symptom of possible overmedication), only 2 reported these adverse events as a cause of their study discontinuation.

Buprenorphine's long duration of action and ceiling effects at high doses make it a candidate for providing it on a less than daily basis (Fudala et al., 1990; Walsh et al., 1994). There are several potential advantages in providing opioid agonist treatment on a less than daily dosing schedule. In a prison setting, it obviates the need to bring the prisoners on a daily basis to the medication window (Kinlock et al., 2005).

Nineteen participants (18%) attempted to divert the medication. This is somewhat higher than the rate of attempted buprenorphine diversion (10%) reported in a study comparing buprenorphine to methadone treatment at the Rikers Island jail in New York City (Magura et al., 2009). We found no reduction in the rate of attempted diversion when we switched to the sublingual film at the end of the study. With the new formulation of buprenorphine sublingual film, it is conceivable that the rate of diversion could be reduced although a larger sample size than that enrolled in this study would be needed to test this hypothesis.

Study participants were queried about adverse events on a daily basis. Constipation was the most frequently reported side effect. The symptoms were reportedly more frequently during the first month and may have abated in conjunction with symptomatic treatment provided by the medical staff. Constipation is a well-known side effect of opioids, including buprenorphine.

Drowsiness was reported less frequently than constipation. Several participants discontinued medication early in the induction period because of symptoms of opioid agonist effects including drowsiness, nausea and vomiting, itching and euphoria. Participants experiencing drowsiness and or euphoria reported not feeling safe in the prison environment because of reduced alertness on medication. These symptoms were experienced as unwanted by the participants. Alteration in consciousness and affect are not considered desirable in the prison setting and may lead inmates to being more vulnerable to manipulation or violent victimization (Inciardi, 2008). In a study in a Rhode Island prison, Rich and colleagues (2011) reported on a case of non-lethal overdose presenting with marked sedation during buprenorphine induction of an obese, non-opioid-tolerant prisoner who was also being treated with benzodiazepines and anti-psychotic medications for psychiatric illness. The individual began buprenorphine at 4 mg and had a dose increase to 8 mg on the second and third day dosing, which, combined with other medications, led to the adverse event. This case illustrates that caution is advised in dose induction of non-opioid-tolerant patients, particularly those on other CNS depressants.

There have been several other reports of buprenorphine induction in non-opioid-tolerant prisoners with a history of opioid dependence. Zaller and colleagues (2013) reported initiating 12 adult prisoners on buprenorphine at 2 – 4 mg per day and increasing to 8 mg in the first week. The participants remained on buprenorphine 6.3 days (range 2 – 14 days) prior to release. In a report on the use of anti-retroviral medications among 23 non-opioid-tolerant adult prisoners with histories of opioid dependence, Springer and coworkers (2010) offered buprenorphine treatment to non-opioid-tolerant HIV positive prisoners in the immediate post-release period. Buprenorphine was started at 2 mg po daily and increased by 2 mg per day until a craving score of 1 or less was achieved. Buprenorphine reached an average daily dose of 9.5 mg (range of 2 – 16 mg) over an average of 8.5 days (range 0 to 30 days) in the post-release period. Adverse events related to opioid agonist effects were reported to be infrequent (17%) and included drowsiness, nausea, headache, and constipation.

The effects of buprenorphine, like other opioids, vary with the patients' level of recent opioid use, tolerance, and concomitant medications (Walsh and Eissenberg, 2003). Our results suggest buprenorphine, when administered to individuals who are not tolerant to the sedative and respiratory depressant effects of opioids, should be started at a lower dose than is customarily provided for individuals actively using opioids. The precise speed of dose induction should be individualized. Non-opioid tolerant inmates can be successfully inducted onto therapeutic doses of buprenorphine prior to release. Future research could examine more rapid dose escalation and more effective ways to convert participants to three times per week dosing in non-opioid-tolerant populations in correctional settings.

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Highlights

1. Buprenorphine induction in non-opioid tolerant prisoners with a dependence history.
2. Adverse events were recorded daily.
3. There were no deaths or serious adverse events.
4. Most common adverse events: constipation, pain, sweating, rhinorrhea, withdrawal.

Figure 1.

Constipation, Drowsiness, Sweating, and Mean Daily Dose of Buprenorphine During the First 10 Weeks Of Pharmacotherapy, Complete Cases ($N=60$). The estimated mean and standard errors for weekly percentages of constipation, drowsiness, sweating, and daily dose for the 60 participants who completed 10 weeks of dosing are displayed. The gray line represents the proposed dose induction scheme in the protocol. From week 7 to 10 the line is dotted as the participants were then switched to every other day dosing, when possible.

Table 1Participant demographics, criminal and drug use histories ($N=104$)

Variable	n (%)	Age (SD)	days/month
Age		39.1 (8.1)	
Gender			
Female	32 (31)		
Male	72 (69)		
Race			
African American	71 (68)		
Caucasian	29 (28)		
Other	4 (3.8)		
Education		11.1 (1.7) ^a	
Age first marijuana use		14.6 (2.8)	
Age first cocaine use		20.9 (7.5)	
Age first heroin use		18.1 (6.0)	
Prior drug treatment	84 (81)		
Prior methadone treatment	38 (37)		
Prior buprenorphine treatment	14 (13)		
Age first crime		14.2 (7.5)	
Age first arrested		19.11 (9.7)	
Age first incarcerated		20.4 (6.9)	
Number of Prior incarcerations		8.5 (9.3)	
Heroin use days ^b			24.2 (10.1)
Cocaine use days ^b			11.2 (12.9)
Crime use days ^b			19.1 (12.95)

^a. Years of education (SD)^b. Within the 30 days prior to incarceration

Table 2MedDRA Classification of Adverse Events (AEs) above the 1 % Level (*N*=104)

MedDRA classification	Number of participants reporting AE	Percentage reporting AE out of 104 participants	Number of AE reports	Percentage of total AE reports
Constipation	72	69	555	31.3
Pain	28	27	157	8.9
Sweating	44	42	140	7.9
Rhinorrhea	41	40	99	5.6
Withdrawal symptoms	38	37	88	5
Insomnia	38	37	88	5
Arthralgia	22	21	88	5
Nausea	34	33	72	4.1
Back pain	24	23	61	3.4
Somnolence	30	29	47	2.7
Lacrimation increased	19	18	34	1.9
Restlessness	15	14	28	1.6
Feeling abnormal	16	15	27	1.5
Abdominal pain	18	17	26	1.5
Diarrhea	10	10	23	1.3
Irritability	13	13	22	1.2
Anxiety	12	12	20	1.1