Published in final edited form as:

Drug Alcohol Depend. 2010 March 1; 107(2-3): 253–256. doi:10.1016/j.drugalcdep.2009.10.014.

Predictors of buprenorphine-naloxone dosing in a 12-week treatment trial for opioid-dependent youth: Secondary analyses from a NIDA Clinical Trials Network study

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Abstract

Introduction—The present investigation examines baseline patient characteristics to predict dosing of buprenorphine-naloxone, a promising treatment for opioid addiction in youths.

Methods—This study of 69 opioid-dependent youths is a secondary analysis of data collected during a National Institute on Drug Abuse (NIDA) Clinical Trials Network study. Outpatients aged 15-21 were randomized to a 12-week buprenorphine-naloxone dosing condition (including 4 weeks of taper). Predictors of dosing included sociodemographic characteristics (gender, race, age, and education), substance use (alcohol, cannabis, cocaine, and nicotine use), and clinical characteristics (pain and withdrawal severity).

Results—Most (75.4%) reported having either “some” (n=40, 58.0 %) or “extreme” (n=12, 17.4%) pain on enrollment. Maximum daily dose of buprenorphine-naloxone (19.7 mg) received by patients reporting “extreme” pain at baseline was significantly higher than the dose received by patients reporting “some” pain (15.0 mg) and those without pain (12.8 mg). In the adjusted analysis, only severity of pain and withdrawal significantly predicted dose. During the dosing period, there were no significant differences in opioid use, as measured by urinalysis, by level of pain.

Conclusion—These data suggest that the presence of pain predicts buprenorphine-naloxone dose levels in opioid-dependent youth, and that patients with pain have comparable opioid use outcomes to those without pain, but require higher buprenorphine-naloxone doses.

Keywords

Buprenorphine; Naloxone; Opioid dependence; Treatment; Dose

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Trial Registration: clinicaltrials.gov Identifier: NCT00078130

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1. Introduction

The use and abuse of opioids, including heroin and prescription pain medication, are major public health concerns in the, for example, a recent survey in the U.S. estimated that 153,000 persons aged 12 and older are current heroin users and 5.2 million are non-medical users of prescription opioids (Substance Abuse and Mental Health Services Administration (SAMHSA), 2008). Currently, methadone (Faggiano et al., 2003; Johansson et al., 2007; Kreek, 2000) and the partial agonist buprenorphine (Boothby and Doering, 2007; Collins et al., 2007; Galanter et al., 2003) are the most widely used FDA-approved pharmacotherapies for opioid dependence. Buprenorphine, combined with naloxone in a 4:1 ratio (Bell et al., 2004; Comer et al., 2005) to lower its abuse potential, has been effective for detoxification and maintenance treatment (Bell et al., 2007; Kosten and Fiellin, 2004; Ling et al., 2005).

Research suggests that dosing levels in opioid dependence treatment are associated with patient-related factors: race (Kosten and Rayford, 1995), psychiatric symptoms (Wedekind et al., 2008), gender (Schottenfeld et al., 1998), and, potentially, chronic pain (Ballantyne and LaForge, 2007; Clark et al., 2008).

The National Institute on Drug Abuse (NIDA) Clinical Trials Network recently completed a buprenorphine-naloxone treatment study in opioid-dependent youth. This 6-site trial randomized 154 opioid-dependent youths, aged 15–21, to an extended (12-week) buprenorphine-naloxone treatment with a dose tapering during the last 4 weeks, or a short-term (2-week) detoxification. Patients randomized to the 12-week condition had significantly better outcomes in a wide range of measures, including opioid use, than did those in the 2-week detoxification condition (see Woody et al., 2008 for further details).

The youth of the sample and the exclusion of psychotropic medications other than selective serotonin reuptake inhibitors provided an opportunity to explore predictors of dosing free from the influence of chronic medical illnesses and medications that could influence dosing in older populations. Therefore, the present investigation explored differences in maximum daily dose of buprenorphine-naloxone as a function of baseline sociodemographic, substance use, and clinical characteristics.

2. Methods

2.1. Overview

The institutional review boards at the coordinating center and at each site approved the study. The trial was open to 14–21 year olds seeking outpatient treatment who met DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 1994) criteria for opioid dependence with physiologic features. This secondary analysis excluded 1) patients who did not name one main problem drug ($n=5$), since primary drug of abuse was one of the variables examined, and 2) those in the 2-week arm ($n=80$) because 2 weeks could not provide much dosing variability. Hence, 69 patients from the original study were included in this analysis.

2.2. Medication and dosing

Patients were instructed to abstain from opioids for 6 hours and be in mild or moderate withdrawal before their first dose, which was 2 mg buprenorphine/0.5 mg naloxone. A second dose of 2–6 mg of buprenorphine was administered if appropriate, based upon withdrawal, signs and symptoms of sedation, or other medication-related adverse events. On day 2, patients received the total dose from day 1 (unless the physician judged that they had been overmedicated), were observed for 1.5–2 hours, and the dose was adjusted by 2–6 mg based on medication response. On day 3, patients were given the day 2 dose, observed for

1.5-2 hours, and given another dose adjustment as appropriate. Subsequent dosing was based on medication response, i.e., substance use (including urine toxicology results), withdrawal, and medication-related adverse events, with a maximum of 24 mg per day. Reports of pain were not used for dose adjustment. Doses were gradually reduced from the first day of week 9, completing the taper by the end of week 12.

2.3. Measures

Buprenorphine-naloxone levels were obtained from study dosing logs, based on medication administration and observation 5-7 days per week. Baseline measures examined to predict dosing included 1) gender; 2) race; 3) age; 4) years of education; 5) type of opioid identified as the main problem (heroin vs. prescription opioids; Substance Dependence Severity Scale-Lite; Miele et al., 2000); 6) number of days of alcohol, cannabis, cocaine, and cigarette use in the 30 days prior to baseline (Baseline Demographics Form); and 7) degree of pain one week before induction (EuroQol; Rabin and de Charro, 2001), measured as pain or discomfort experienced “today” and coded as 0=no pain, 1=some pain, or 2=extreme pain. Finally, withdrawal severity at the end of the first dosing week was assessed (Short Opiate Withdrawal Scale; Gossup, 1990). These variables have been shown to be related to treatment outcome, or to clinical effects of opioids (Clark et al., 2008; Hermann et al., 2005; Kosten and Rayford, 1995; Schottenfeld et al., 1998; Stein and Anderson, 2003)

2.4. Data analysis

The relation between patient characteristics and maximum dose during treatment was investigated using Pearson's correlation coefficient for continuous variables, independent t-tests for dichotomous variables, and one-way analysis of variance for ordinal variables. Linear regression models assessed which variables predicted maximum dose. All predictor analyses were adjusted for duration of treatment and site, since treatment outcome can vary across sites (Gossop et al., 2003). With a sample size of 69, this study has power 80% to detect bivariate correlations between the predictors and the maximum daily dose of 0.33; thus the study has adequate power to detect “medium” effect sizes. Data were analyzed with SPSS 15.0.

3. Results

3.1. Sample

Most subjects completed the full 12-week treatment (n=50); 19 dropped out (median=week 5, range=2-12). Patients were 15–21 years old; 36 (52.1%) were high school graduates. The majority were white (n=51, 73.9%), and 39 (56.5%) were male. Most (n=42, 60.9%) reported heroin as their main problem; the remainder reported prescription opioids.

Most heroin users (28/42, 66.6%) reported daily use compared to approximately one-third of prescription opioid users (10/27, 37.0%). Injection was the preferred route for about half of the heroin users (23/42, 54.8%), and was less common among prescription opioid users (2/27, 7.4%). Alcohol (n=33, 47.8%), cannabis (n=43, 62.3%) and cocaine (n=27, 39.1%) were the most common other substances used in the 30 days preceding enrollment; most patients were daily cigarette smokers (n=59, 85.5%). Alcohol and cocaine use levels were moderate, with most patients reporting alcohol (26/33, 78.8%) or cocaine use (24/27, 88.9%) on <10 of the 30 days prior to enrollment; cannabis users typically reported more days using that drug, with 55.8% (24/43) using for 10 of the past 30 days. Assessment of pain was available for 68/69 patients; 40 (58.8 %) reported some pain, 12 (17.6%) reported extreme pain, and 16 (23.5%) reported no pain at baseline. Reports of pain were similar for heroin (n=35, 83.3%) and prescription opioid (n=17, 65.4%) users.

3.2. Relation of patient characteristics to maximum dose

Maximum daily dose was examined across 3 sets of patient variables: sociodemographic (gender, race, age, and years of education), substance use (type of opioid used and number of days of alcohol, cannabis, cocaine, and nicotine use), and clinical (baseline pain severity and withdrawal score at induction). Initial analyses showed that only one of the sociodemographic or substance use variables was associated with dose: more days of cannabis use was correlated with higher maximum daily dose ($r=0.34$, $p=0.01$). Both clinical variables were associated with dose. Patients with “extreme” pain had higher doses (mean=19.7, $sd=5.9$) than patients with no pain (mean=12.8, $sd=4.5$) and patients with “some” pain (mean=15.0, $sd=4.1$) ($F_{(2,65)}=8.10$, $p=0.001$). Bivariate analyses showed a trend toward higher withdrawal scores at the end of the first post-baseline week related to higher maximum daily dose ($r=0.25$, $p=0.06$).

3.2.1. Relation of adjusted patient characteristics to maximum dose—First, demographic variables were entered in the model to predict dose: gender, race, age, and years of education; none were related to maximum dose (see Table 1). Second, substance use variables were entered in the model: type of opioid used and number of days using alcohol, cannabis, cocaine, and nicotine in the 30 days prior to baseline; again, none were related to maximum dose (see Table 1). Finally, clinical variables were entered in the model. Both were significant: higher maximum doses were prescribed to patients with greater baseline pain and more severe withdrawal at the end of the first post-baseline week. When baseline pain was assessed, patients were not in withdrawal; further, baseline pain was not correlated with severity of withdrawal one week post-baseline. Pain at baseline was thus unlikely to be a function of withdrawal.

3.3. Baseline pain and drug use outcome

Since patients with greater pain received higher doses of buprenorphine-naloxone, we examined the relation between degree of pain and drug use outcome. Overall, illicit drug use was confirmed by urinalysis at weeks 4, 8, and 12, for 26.8% (15/56), 22.4% (11/49), and 44.7% (21/47) of the sample, respectively, with no significant differences by level of baseline pain (see Table 2). On the contrary, frequencies of opioid-positive urine samples were remarkably similar for all levels of pain.

4. Discussion

The present investigation explored predictors of buprenorphine-naloxone dosing in a multi-site trial of opioid-dependent youth with a flexible dosing schedule. Patients were young and not taking medications that could interact with buprenorphine-naloxone and influence dosing decisions. Pain was quite prevalent in this sample; the fact that pain assessment occurred one week before induction, when patients were not in withdrawal, suggests that the pain was not related to withdrawal. Lack of a significant relationship between pain and withdrawal is further strengthened by the nonsignificant correlation between baseline pain and withdrawal at treatment induction. Reports of pain from patients could have been related to several factors. One possibility is that these patients may have chronic physical pain, despite their relative youth. This is consistent with evidence that some opioid-dependent individuals initially use opioids to relieve pain (Brands et al., 2004). Alternatively, hyperalgesia may have resulted from chronic exposure to opioids (Hay et al., 2009). Perhaps patients experienced pain from hepatitis C, which was surprisingly prevalent in this sample (15%), although pain was not more common among those with hepatitis C. In any case, the high prevalence of reported pain in this young population suggests that pain may have contributed to the initiation or maintenance of addiction in some patients.

Dose did not vary by gender, race, age, or type of opioid; we found no evidence from other studies suggestive of such dose differences. Cannabis use prior to baseline significantly correlated with maximum daily dose, consistent with evidence that cannabis may worsen opioid withdrawal (Hermann et al., 2005) and thus contribute to the need for higher doses. However, cocaine use had no effect on maximum buprenorphine-naloxone dose, even though it has been found to worsen opioid withdrawal more than cannabis (Hermann et al., 2005).

The presence of pain was the most consistent predictor of higher doses. Interestingly, patients reporting “extreme” pain primarily accounted for this effect; patients with “some” pain did not require significantly higher doses than those reporting no pain. The correlation between maximum dose and withdrawal symptoms was not surprising, since withdrawal symptomatology was used to titrate dose.

Interestingly, patients with “extreme” pain, who might be expected to have worse outcomes (Clark et al., 2008), did as well as the other patients, suggesting that patients with opioid dependence and pain, given appropriate buprenorphine-naloxone doses, can have outcomes similar to patients without pain. This is consistent with previous observations that outcomes for drug-dependent patients with co-occurring disorders or other poor prognostic factors can be improved by modifying or intensifying treatment to address the co-morbidity (Trafton et al., 2006; Weiss et al., 1996).

It is important to emphasize that this is an exploratory analysis, limited by sample size, unbalanced subgroups, no measure of the nature and treatment history of pain or prescription opioid use, and a single measure of withdrawal.

This study provides initial evidence regarding factors that may influence dosing of buprenorphine-naloxone dosing in youths. The findings suggest that pain may be quite prevalent in this population. Further research is needed to assess the clinical importance of pain preceding vs. following opioid use. This study further suggests that patients with pain respond to higher buprenorphine doses; hence buprenorphine may have a role in managing pain in opioid-dependent youth.

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Table 1Prediction model for maximum daily dose of buprenorphine-naloxone in a 12-week treatment condition^a

		Maximum Daily Dose	
Baseline predictors		Standardized beta	<i>p</i>
Sociodemographic	Gender	0.05	0.66
	Race	-0.18	0.40
	Age	0.18	0.22
	Education (years)	-0.17	0.25
Substance use	Opioid type	0.11	0.45
	Alcohol (days)	0.14	0.29
	Cannabis (days)	0.11	0.41
	Cocaine (days)	0.01	0.89
Clinical symptoms	Nicotine (days)	-0.07	0.62
	Pain (degree)	0.33	0.01
	Withdrawal (severity)	0.32	0.01

^a All analyses were adjusted for treatment site & duration of treatment.

Table 2Degree of pain at baseline by opioid-positive urines at weeks 4, 8, and 12^a

Degree of pain	Opioid-positive urine (%)		
	Week 4	Week 8	Week 12
Extreme	22.2% (2/9)	12.5% (1/8)	37.5% (3/8)
Some	31.3% (10/32)	26.7% (8/30)	37.9% (11/29)
None	21.4% (3/14)	20% (2/10)	66.7% (6/9)
$\chi^2(2)=0.61, p=0.74$ $\chi^2(2)=0.78, p=0.68$ $\chi^2(2)=2.45, p=0.30$			

^aPercentages are followed by number of patients with opioid-positive urines/total number of patients at each assessment point.