Drug and Alcohol Dependence 107 (2010) 253–256

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Short communication

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

Amit Chakrabarti[a,b], George E. Woody[c], Margaret L. Griffin[a,b], Geetha Subramaniam[d], Roger D. Weiss[a,b,*]

[a] Division of Alcohol & Drug Abuse, McLean Hospital, Belmont, MA 02478, USA
[b] Department of Psychiatry, Harvard Medical School, Boston, MA 02115, USA
[c] Department of Psychiatry, University of Pennsylvania and Treatment Research Institute, Philadelphia, PA 19106, USA
[d] Department of Psychiatry, Johns Hopkins University, Baltimore, MD 21229, USA

ARTICLE INFO

Article history:
Received 31 August 2009
Received in revised form 20 October 2009
Accepted 23 October 2009
Available online 30 November 2009

Keywords:
Buprenorphine
Naloxone
Opioid dependence
Treatment
Dose

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.

1. Introduction

The use and abuse of opioids, including heroin and prescription pain medication, are major public health concerns in the U.S. A recent survey estimated that 153,000 persons aged 12 and older are current heroin users and 5.2 million are non-medical users of prescription opioids (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).

☆ Trial Registration: clinicaltrials.gov. Identifier: NCT00078130.

* Corresponding author at: Division of Alcohol and Drug Abuse, Harvard Medical School & McLean Hospital, 115 Mill Street, Belmont, MA 02478, USA.
Tel.: +1 617 855 2242; fax: +1 617 855 2699.
E-mail address: rweiss@mclean.harvard.edu (R.D. Weiss).

0376-8716/$ – see front matter © 2009 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.drugalcdep.2009.10.014

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 (DSMMD, 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 h 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 h, 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 h, 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 1 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; Gossop, 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 three 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

Table 1
Prediction model for maximum daily dose of buprenorphine–naloxone in a 12-week treatment condition[a].

Baseline predictors		Maximum daily dose	
		Standardized beta	*R*
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
	Nicotine (days)	−0.07	0.62
Clinical symptoms	Pain (degree)	0.33	0.01
	Withdrawal (severity)	0.32	0.01

[a] All analyses were adjusted for treatment site and duration of treatment.