PAIN® 154 (2013) 1442–1448

www.elsevier.com/locate/pain

Buprenorphine/naloxone as a promising therapeutic option for opioid abusing patients with chronic pain: Reduction of pain, opioid withdrawal symptoms, and abuse liability of oral oxycodone

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

ARTICLE INFO

Article history:
Received 20 November 2012
Received in revised form 12 April 2013
Accepted 1 May 2013

Keywords:
Buprenorphine
Chronic pain
Opioid dependence
Oxycodone
Reinforcing effect

ABSTRACT

Few studies have examined abuse of prescription opioids among individuals with chronic pain under buprenorphine/naloxone (Bup/Nx) maintenance. The current 7-week inpatient study assessed oral oxycodone self-administration by patients with chronic pain who had a history of opioid abuse. Participants ($n = 25$) were transitioned from their preadmission prescribed opioid to Bup/Nx. All of the participants were tested under each of the sublingual Bup/Nx maintenance doses (2/0.5, 8/2 or 16/4 mg) in random order. During each maintenance period, participants could self-administer oxycodone orally (0, 10, 20, 40 or 60 mg prescription opioids) or receive money during laboratory sessions. Drug choice (percentage) was the primary dependent variable. Subjective ratings of clinical pain and withdrawal symptoms also were measured. Mann-Whitney tests compared percentage of drug choice for each active oxycodone dose to placebo. Logistic regression analyses identified correlates of oxycodone preference, defined as 60% or greater choice of oxycodone compared to money. Pain was significantly reduced while participants were maintained on Bup/Nx compared to preadmission ratings. No differences in percentage drug choice were observed between the active oxycodone doses and placebo under each Bup/Nx maintenance dose. However, factors associated with oxycodone preference were lower Bup/Nx maintenance dose, more withdrawal symptoms and more pain. These data suggest that Bup/Nx was effective in reducing pain and supplemental oxycodone use. Importantly, adequate management of pain and withdrawal symptoms by Bup/Nx may reduce oxycodone preference in this population.

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1. Introduction

In the United States, the problem of nonmedical use of prescription opioids has emerged as a major public health issue [1]. Other countries, such as Australia, New Zealand [12] and Canada [33], also are concerned about the phenomenon of prescription opioids abuse. In the United States, oxycodone and hydrocodone are among the most commonly prescribed or regularly used opioids, as well as the most commonly diverted prescription opioids analgesics [5,25]. These data indicate that prescription opioids abuse has steadily increased among heroin and recreational polydrug users since 2000 [5]. An additional concern related to the increased use of prescription opioids is opioid overdose, which increased in the United States from the mid-1990s to the present time [10,11] and recently became a leading cause of accidental death in the United States [4]. Thus, the risks of prescription opioids abuse and overdose make physicians reluctant to prescribe prescription opioids in general, and access to adequate pain management in drug users in particular is becoming increasingly difficult [20,39]. In those patients who are prescribed prescription opioids for pain relief, misuse may occur in pain patients with no history of opioid abuse who become dependent on the medications for their reinforcing properties, whether good drug effects or relief of anxiety or mood symptoms, or misuse may occur in drug-seeking individuals with preexisting opioid abuse histories. Thus, balancing the need for effective pain relief and reducing the risks of opioid abuse and overdose remains a challenge for public health policy [7].

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0304-3959/$36.00 Published by Elsevier B.V. on behalf of International Association for the Study of Pain.
http://dx.doi.org/10.1016/j.pain.2013.05.004

In this context of easy access to opioid analgesics for the general population, opioid overdoses due to diversion [8] and difficulties in accessing treatment for pain and opioid dependence, expanding access to a less risky treatment for pain and opioid dependence is a logical and plausible public health response.

For decades, buprenorphine, a partial μ-opioid agonist, has been used to treat acute and chronic pain [16]. More recently, a sublingual formulation of buprenorphine has been used to treat opioid dependence [38] in both substance abuse treatment clinics and in primary care settings [18]. Although sublingual buprenorphine is not approved by the U.S. Food and Drug Administration for treating pain, some have suggested its use in the management of concurrent pain and opioid dependence [23]. However, few studies have systematically examined whether buprenorphine maintenance alters prescription opioids abuse in this population. Thus, assessment of the effectiveness of buprenorphine in treating pain and also reducing the abuse liability of oxycodone would be relevant to the public health problem of prescription opioids abuse. In the current study, patients with chronic, nonmalignant pain who were abusing their prescription opioids medications were maintained on different doses of sublingual buprenorphine/naloxone (2/0.5, 8/2 and 16/4 mg per day in divided doses) and given the opportunity to self-administer oxycodone in a laboratory setting.

2. Methods

2.1. Participants

All of the participants were under the care of a physician for mild to moderate chronic, nonmalignant pain. They were also required to meet DSM-IV criteria for opioid dependence, but were not seeking treatment for their opioid dependence. Potential participants were excluded from the study if they had a current major axis I psychopathology other than opioid dependence (ie, schizophrenia or bipolar disorder) or met DSM-IV criteria for dependence on drugs other than opioids, nicotine or caffeine, or had a primary diagnosis of neuropathic pain, malignant pain, headache or chronic lower back pain with failed surgeries. Current buprenorphine maintenance and history of failed treatment with buprenorphine maintenance for pain also were exclusionary.

2.2. Data collection

After completing an initial telephone interview, eligible participants came into the laboratory to provide consent to receive additional screening, which included completing detailed medical history and drug use questionnaires, interviews with a psychologist and psychiatrist, and a medical evaluation conducted by a physician. Prescription opioids use was ascertained in multiple ways (self-report, verification with prescribing physician and/or presentation of prescription opioids bottles) and was converted to number of morphine equivalents used per day. We also collected sociodemographic data such as age, gender, ethnicity, education and employment. Urine drug toxicologies (assessed by urine quick tests) also were performed several times during screening to test for opioids, benzoylecgonine (cocaine metabolite), benzodiazepines, cannabinoids and amphetamines. During laboratory sessions, subjective responses were measured and reinforcing effects of oxycodone were assessed.

2.3. Study design

This study was described in detail elsewhere in a report of preliminary results [17]. Individuals who met the eligibility criteria were admitted to an inpatient research unit for 7 weeks and transitioned from their baseline prescription opioids to buprenorphine/naloxone combination (Bup/Nx). During the first week after admission, participants were withdrawn from their previous opioid analgesic regimen and stabilized on 1 of 3 doses of Bup/Nx (2/0.5, 8/2 or 16/4 mg/d). The total daily Bup/Nx dose was administered q.i.d. in equally divided doses throughout the day (Fig. 1). Participants were treated for emergent withdrawal symptoms with various supplemental medications until withdrawal symptoms dissipated based on self-report and observer ratings. Patients were maintained on each Bup/Nx dose for approximately 2 weeks: 1 week of stabilization followed by 1 week of laboratory testing. Each participant received all 3 Bup/Nx doses in random order under double-blind conditions.

2.4. Reinforcing effects

During each maintenance period, participants could self-administer oral oxycodone (0, 10, 20, 40 or 60 mg) during separate laboratory sessions. Each laboratory day consisted of 2 types of sessions, a sample session during which participants were provided with one of the possible doses of drug (oxycodone) and US$20, and a self-administration (choice) session that occurred a few hours later on the same day. During the sample session, the subjective, physiological and analgesic effects of oxycodone were measured. During the choice session, participants could self-administer the dose of oxycodone that was provided during the sample session or receive money. Participants then completed a self-administration task to receive portions of the dose of drug or money they sampled (0–100% in increments of 10%). For each 10% increment of drug or money, participants were required to complete an increasing number of finger presses on a computer mouse (50, 100, 200, 400, 800, 1200, 1600, 2000, 2400, 2800). Immediately after the self-administration task, money and/or the total amount of drug earned during the task was administered. The sample session began at approximately 11 AM, and the choice session began at approximately 3 PM (Fig. 1).

2.5. Subjective effects

All of the questionnaires used in this study have been described previously [17]. For the present analysis, opioid withdrawal symptoms and clinical pain were measured after administration of the first daily Bup/Nx maintenance dose. Subjective symptoms of opioid withdrawal were assessed with the Subjective Opioid Withdrawal Scale (SOWS; range 0–64 [9]). Clinical pain assessment was made with the 15-item Short-Form McGill Pain Questionnaire [26] based on their general pain condition while maintained on Bup/Nx. Clinical pain was also assessed with the McGill Pain Questionnaire (MPQ) at the first screening visit before initiation of Bup/Nx maintenance.

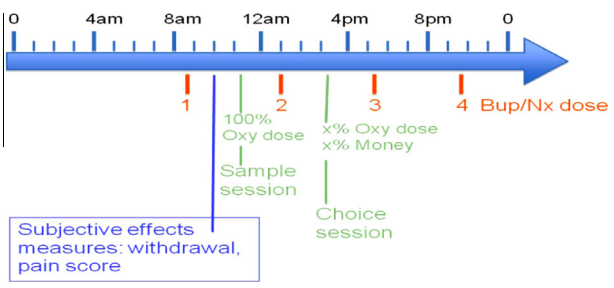

Fig. 1. Time points of a laboratory session day during the second week of maintenance. Oxy, oxycodone; Bup, buprenorphine; Nx, naloxone.