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**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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## Introduction

In the United States (US), the problem of non-medical use of prescription opioids (PO) has emerged as a major public health issue [2]. Other countries, such as Australia, New Zealand [12], and Canada [33], also are concerned about the phenomenon of PO abuse. In the US, oxycodone and hydrocodone are among the most commonly prescribed or regularly used opioid, as well as the most commonly diverted PO analgesics [5, 25]. These data have indicated that PO abuse has steadily increased among heroin and recreational polydrug users since 2000 [5]. An additional concern related to the increased use of PO is opioid overdose, which increased in the US from the mid-1990s to the present time [11, 10] and recently became a leading cause of accidental death in the US [1]. Thus, the risks of PO abuse and overdose make physicians reluctant to prescribe POs in general, and access to adequate pain management in drug users in particular is becoming increasingly difficult [39, 20]. In those patients who are prescribed POs 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 pre-existing 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].

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 mu-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 FDA 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 opioid 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 PO abuse. In the current study, patients with chronic, non-malignant pain who were abusing their prescription opioid 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.

## **Methods**

### Participants

All of the participants were currently under the care of a physician for mild to moderate chronic, non-malignant 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 (i.e. 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.

### 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 opioid use was ascertained in multiple ways (self-report, verification with prescribing physician, and/or presentation of prescription opioid 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 (using 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, as described below.

### Study Design

This study was described in detail in a previous paper that presented 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 opioid to buprenorphine/naloxone combination (Bup/Nx). During the first week after admission, participants were withdrawn from their previous opioid analgesic regimen and stabilized on one of three doses of Bup/Nx (2/0.5, 8/2, or 16/4 mg/day). The total daily Bup/Nx dose was administered QID in equal divided doses throughout the day (Figure 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 three Bup/Nx doses in random order under double-blind conditions.

### 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 two 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 given 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 following 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 (Figure 1).

### Subjective Effects

All of the questionnaires used in this study were described in our previous article [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 using 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 MPQ at the first screening visit prior to initiation of Bup/Nx maintenance.

### Statistical analyses

For the present analysis, we used only a subset of the dependent variables collected during the study because of our focused interest in the impact of Bup/Nx maintenance dose, pain level, and withdrawal symptoms on oxycodone self-administration. The time point used in our analyses was 1 hour after the first Bup/Nx dose administration in order to capture peak Bup/Nx effects on pain and opioid withdrawal symptoms in the absence of oxycodone effects.

In addition, as we selected only individuals who completed the 7-week inpatient laboratory period, we compared participants who had complete data for the outcomes of interest to those who did not in order to confirm the absence of a selection bias.

The first analysis consisted of assessing the effectiveness of Bup/Nx on pain perception comparing the MPQ score at baseline before Bup/Nx initiation and at each laboratory session under the different Bup/Nx maintenance doses. We performed a bivariate analysis between MPQ score at baseline and MPQ score under each Bup/Nx maintenance dose using a generalized estimating equations (GEE) model to take into account the intra-individual correlation for pain measurements under Bup/Nx maintenance. In addition, we used a linear regression model based on GEE to assess the association between MPQ pain score and Bup/Nx maintenance doses.

Next, we confirmed the results of our previous paper [17] comparing the reinforcing effect of oxycodone among the different dosing conditions (Bup/Nx and oxycodone) using a repeated-measures ANOVA with a significance level of alpha at 0.05. A Mann-Whitney test was performed to compare the difference between percent drug choice for placebo and each active oxycodone dose condition: placebo versus 10, 20, 40 and 60 mg.

To investigate the risk of oxycodone self-administration, we generated a variable called “oxycodone preference,” defined as self-administration of 60% or more of the dose of oxycodone during the choice sessions. Then we used a logit model based on generalized estimating equations (GEE) [40] to identify variables associated with oxycodone preference. This approach was used in order to study factors associated with oxycodone preference during laboratory sessions, while taking into account the correlation between repeated measures on the same individuals [3]. We used an unstructured covariance matrix to model the correlation between the repeated measures. Variables with  $p$ -values  $<0.20$  in the bivariate analysis were considered eligible for the final model, which was built using a backward procedure based on the log-likelihood ratio-test.

In addition, we assessed the association between the two variables that have pain dimensions, the pain score and the withdrawal score measured respectively with the MPQ and the SOWS, and also their possible interaction with oxycodone self-administration. Then, we performed two separate multivariate models to identify factors associated with “oxycodone preference” using first MPQ score and then SOWS score as explanatory variables.

All of the analyses were performed using SPSS version 18.0 (SPSS Inc, Chicago, IL, USA) and Stata version 10.1 (Stata Corp, Texas, USA) for Windows software packages.

## **Results**

During the enrollment phase of the study, 191 individuals were assessed for eligibility and 140 were excluded because they did not meet the inclusion criteria (N=78; medical rule out (N=21), psychiatric rule out (N=10), not opioid abusing/dependent (N=29), other



substance dependence (N=13), or other (N=5)) or lost to follow-up (N=62). Of the 51 who were randomized to the trial, 8 discontinued prior to the inpatient phase (medical drop (N=2), not interested in treatment (N=5) and lost to follow-up (N=1)). Among the 43 participants who entered the inpatient study, 12 dropped before the end of the study (2 for medical reasons, 2 for non-compliance, 7 for self-withdrawal and 1 for another reason). Of the 31 participants who completed the 7-week inpatient laboratory period, 6 participants completed a pilot phase during which a different oxycodone dose range was tested, so we only used data from the remaining 25 participants for our analyses. The participants who were selected for the analyses were similar to the others who were excluded regarding all the socio-demographic variables. Data from a total of 25 participants were used in the analyses, accounting for 375 observations. Of the 25 participants selected for the analyses, the median [interquartile range (IQR)] age was 48 (43–54) years and 9 (36%) were women. Nine (36%) of the participants were African American, 8 (32%) were Hispanic and 8 (32%) were Caucasian. Reasons for study discontinuation among the 18 participants who did not complete the 7-week study were: psychiatric issues (2), intolerance to environment (2), intolerance to Bup/Nx (2 for nausea and 1 for heavy sedation), behavioral issues (5), seeking treatment (1) and lost to follow-up (5).

The median [IQR] duration of PO use was 5 [2-8] years. Prescription opioids that were used during screening included mainly oxycodone, hydrocodone, hydromorphone and tramadol. The median [IQR] number of pills used per day was 7 [4-10], corresponding to 60 [38-144] mg of morphine equivalents (Table 1). At the screening visit, 9 (36%) of the participants had urine samples positive for cocaine. Only one participant reported using heroin during the previous month. Among the 21 participants who completed the McGill Pain Questionnaire at baseline, the median [IQR] pain score at the screening visit was

38 [30-50]. The median [IQR] MPQ score under Bup/Nx maintenance for the 25 participants accounting for 375 timepoints was 21 [15-31]. MPQ score significantly decreased between baseline and laboratory sessions (coefficient [95% CI] = -15.88 [-18.67, -13.10],  $p < 0.001$ ), suggesting that Bup/Nx had a positive impact on pain score relative to pre-study pain ratings. Moreover, compared to 2 mg Bup/Nx, 8 mg Bup/Nx significantly decreased MPQ pain score [OR (95%CI) = -1.68 (-3.15 ; -0.21);  $P = 0.03$ ] and even more under the 16 mg Bup/Nx dose condition [OR (95%CI) = -2.74 (-4.21 ; -1.27);  $P < 0.001$ ].

Consistent with our previous paper [17], oxycodone was not self-administered above placebo levels at any dose tested nor did it vary as a function of Bup/Nx maintenance dose condition (Figure 2). Mann-Whitney tests revealed no significant differences ( $p > 0.05$ ) between oxycodone placebo and active oxycodone doses under the 3 Bup/Nx doses (2/0.5, 8/2 and 16/4 mg). Although oxycodone produced minimal reinforcing effects overall, during 41 (11%) of the sessions, participants chose more than 60% of the available dose of oxycodone, accounting for 9 (36%) participants. Withdrawal symptoms were reported in 307 (83%) sessions with a median [IQR] score of 4 [1-9] out of a maximum possible score of 64.

The results of the bivariate analysis are presented in Table 1. We excluded from the analyses the variables found in fewer than 10% of the 'participants' such as self-reported heroin use (1 participant), self-reported cannabis use (1 participant), positive cannabis toxicology (2 participants), and positive methadone toxicology (2 participants). The variables eligible for the final model are indicated in bold type in Table 1. Some baseline variables were found to be associated with oxycodone 'preference' such as being Caucasian, reporting use of a higher number of PO pills per day, using more morphine equivalents per day, and having a urine sample positive for benzodiazepines at the

baseline interview. Focusing on the laboratory session dependent variables, the results showed that the highest Bup/Nx maintenance dose (16/4 mg) was associated with less oxycodone preference. Furthermore, higher pain scores using the MPQ were associated with greater oxycodone preference. In addition, higher total SOWS scores were associated with oxycodone preference.

The results presented in Table 2 show two different models after multiple adjustments, one including a withdrawal symptoms variable and the other a pain variable. Both tables, Table 2a and Table 2b, show that two variables remained associated with oxycodone preference, Bup/Nx dose and withdrawal/pain variable. When participants were maintained on the highest dose of Bup/Nx (16/4 mg), they had a two-fold lower risk of preferring oxycodone. Furthermore, those who reported more withdrawal symptoms [OR (95%CI) = 1.96 [1.29-3.00]; P=0.002] and those who had higher pain scores [OR (95%CI)=1.59 [1.15-2.20]; P=0.005] were more likely to self-administer oxycodone. Interestingly, the number of morphine equivalents used per day at baseline did not remain significantly associated with the outcome. No significant interaction was found between MPQ pain score and SOWS score regarding oxycodone preference (P=0.44). However, we found a significant association between MPQ pain score and SOWS score [OR (95%CI)=0.85 (0.63-1.07); P<0.001].

## **Discussion**

Overall, the data indicate that Bup/Nx-maintained opioid-dependent patients with pain do not robustly self-administer oxycodone, as described in our previous article [17]. This result is consistent with the conclusions drawn in a major article on buprenorphine pharmacology showing that the effects of morphine, a full mu-receptor selective opioid

agonist similar to oxycodone [30], were significantly attenuated when given to participants during the time of chronic buprenorphine administration [14].

In addition, Bup/Nx maintenance showed a positive impact on pain in our participants, with greater analgesic effects under maintenance on higher doses of Bup/Nx, especially with 16/4 mg. These findings are of great interest because they demonstrate the potential utility of Bup/Nx for treating pain in populations who also abuse prescription opioids. Indeed, buprenorphine is known as an effective opioid maintenance treatment for opioid dependence and studies have previously shown that buprenorphine is effective in relieving pain in non-dependent and opioid-dependent individuals under certain conditions. For example, a recent randomized study in adults with acute pain showed that sublingual buprenorphine is as effective at reducing pain as intravenous morphine [13]. In a sample of opioid-naive patients with chronic back pain, another randomized trial demonstrated the efficacy of transdermal buprenorphine in reducing pain [34]. Another article reviewed the treatment options for opioid dependence and pain and mentioned the possibility of using the partial mu-agonist buprenorphine in the management of concurrent pain and opioid addiction [23]. In addition, a recent randomized study showed that in patients with chronic pain, there is a similar analgesic and tolerability profile when patients are converted from hydrocodone/acetaminophen (Vicodin<sup>®</sup>) to transdermal buprenorphine [31]. Finally, a retrospective study reported positive results in pain reduction with Bup/Nx to treat co-occurring chronic non-cancer pain and opioid dependence in a primary care setting [28]. Data from our study suggest that among patients with co-occurring pain and opioid abuse, higher doses of buprenorphine are more effective than lower doses for simultaneously controlling both pain and opioid abuse.

To present our findings in a more “public health” approach, we performed further analyses regarding oxycodone preference. Although our findings suggest that buprenorphine may be effective in reducing the reinforcing effects of oxycodone among patients with chronic pain who abuse their prescription opioids, an in-depth analysis of the correlates of preference for oxycodone under buprenorphine/naloxone maintenance seemed to be important to identify some potential factors associated with the abuse liability of oxycodone in this population. After adjusting the model aimed at identifying factors associated with oxycodone preference, no variable related to participant baseline characteristics remained associated with oxycodone preference. It is interesting to note that participants who reported using a higher number of morphine equivalents before entering the study were not more likely to self-administer oxycodone. This result suggests that Bup/Nx is effective in reducing the abuse liability of oxycodone regardless of level of PO use. However, caution is required because our participants were selected according to specific inclusion criteria that could have selected less heavy PO users.

It is known that specific sub-populations might be at risk of abusing prescription opioids such as oxycodone [29]. Our bivariate analysis showed that benzodiazepine users, cannabis users, and those who endorsed using heroin at baseline were more likely to self-administer oxycodone. These findings highlight the importance of identifying patients at higher risk of opioid misuse or addiction as recommended by the Canadian guideline for safe and effective use of opioids for chronic pain [19], as well as circumstances under which opioid misuse is more likely. Interestingly, the variables that remained associated with the oxycodone self-administration were pain score, withdrawal symptoms, and Bup/Nx dose. The results suggested that pain assessment remains a key component to adapt the pharmacological treatment. In this study, higher pain scores and higher withdrawal symptoms scores were associated with more oxycodone self-administration.

It has been shown previously that non-medical use of PO was associated with bodily pain in a population of injecting drug users [21]. Moreover, withdrawal symptoms have been found to be a predictor of non-medical use of opioids during opioid maintenance treatment [32]. Our results highlight the difficulty in differentiating pain from withdrawal and from a chronic pain condition. For this reason, several studies have noted the importance of including opioid withdrawal assessments in the management of pain, especially in an opioid-dependent population [35, 37].

In addition, our findings showed that buprenorphine maintenance dose could play a role in oxycodone preference. It is known that suboptimal doses of buprenorphine may have negative consequences on treatment efficacy [24]. Because dose adjustment depends on multiple pharmacokinetic and pharmacodynamic parameters, characterized by inter-individual differences, it is crucial to measure patient perceptions regarding the effectiveness of buprenorphine in alleviating withdrawal symptoms and pain. One strategy for treating chronic pain is to administer opioid doses in an escalating manner. Naliboff and colleagues used this method and showed some improvements in self-reported acute relief from pain without an increase in supplemental opioid use compared to a stable dose strategy [27]. Previous studies have shown that the analgesic effects of buprenorphine could be improved by increasing the dose or by prescribing daily divided doses [22] and that doses of 32 mg or higher could be safe and effective [15]. Indeed, the therapeutic choice of using a partial mu-agonist medication is known to reduce the risk of overdoses compared to other full agonist analgesics [4]. A previous study showed that buprenorphine causes limited respiratory depression with a ceiling effect at higher dose [6].

Although use of a within-subjects, repeated-measures design in participants housed on an inpatient research unit is strong experimentally, some limitations also must be acknowledged. First, the participants we enrolled had to fulfill several inclusion and exclusion criteria, which may have reduced the external validity of the results. Indeed, our sample excluded the most severely opioid dependent individuals and those with certain types of pain (e.g., those with neuropathic pain, multiple failed back surgeries, as well as those with a previous lack of analgesic response to buprenorphine). Thus, further studies are needed in opioid dependent individuals with other types of pain and a more complex addictive profile. Moreover, the highest dose we tested (16 mg) may be considered as inadequate for some patients and may need to be increased to manage both pain and opioid dependence. Also, because oxycodone is commonly abused by the intranasal or intravenous routes, future studies should test higher doses of Bup/Nx in combination with opioid agonists administered by non-oral routes. Finally, the context of laboratory sessions is different from the ecological context of the participants' lives. Therefore, a clinical trial conducted on an outpatient basis and/or an epidemiological study would be appropriate to confirm the present results [36].

Nevertheless, our data suggest that buprenorphine could be an effective medication for those patients who need to be treated for chronic pain and opioid abuse/dependence. Further studies should be implemented to determine the profile of pain patients most likely to abuse prescription opioids.

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