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Effects of cold pressor pain on the abuse liability of intranasal oxycodone in male and female prescription opioid abusers

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Abstract

Background—Approximately 1.9 million persons in the U.S. have prescription opioid use disorders often with concomitant bodily pain, but systematic data on the impact of pain on abuse liability of opioids is lacking. The purpose of this study was to determine whether pain alters the intranasal abuse liability of oxycodone, a commonly prescribed and abused analgesic, in males and females.

Methods—Sporadic prescription opioid abusers (10 females, 10 males) participated in this mixed (between and within-subject), randomized inpatient study. Experimental sessions (n=6) tested intranasal placebo, oxycodone 15 or 30 mg/70 kg during cold pressor testing (CPT) and a warm water control. Observer- and subject-rated drug effect measures, analgesia, physiologic and cognitive effects were assessed.

Results—The CPT significantly increased blood pressure, heart rate, pain, stress, and “opiate desire” compared to the no-pain control but did not alter opioid liking, high or street value. Intranasal oxycodone produced effects within 10 minutes, significantly decreasing pain and significantly increasing subjective measures of abuse liability (e.g., high). Females had higher ratings of street value, high, and liking for one or both active doses.

Conclusions—The CPT was a reliably painful and stressful stimulus that did not diminish the abuse liability of intranasal Oxycodone®. Females were more sensitive to oxycodone on several abuse liability measures that warrant further follow-up. Snorting oxycodone rapidly produced psychoactive effects indicative of substantial abuse liability.

Keywords

abuse liability; prescription opioids; pain; gender

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1. Introduction

There are an estimated 1.9 million persons in the United States (U.S.) classified with prescription opioid abuse or dependence according to the 2009 National Household Survey on Drug Abuse (SAMHSA, 2010). Both males and females are affected; 4.3% of females and 5.6% of males age 12 years and older reported past month non-medical prescription opioid use (SAMHSA, 2009). Despite the widespread misuse of these medications, studies have only recently evaluated the abuse liability of the most commonly prescribed opioid analgesics (e.g., oxycodone and hydrocodone products) within opioid abusing populations (Comer et al., 2010; Comer et al., 2008; Jones et al., 2011; Stoops et al., 2010; Walsh et al., 2008). These studies have shown that both oral and intravenous oxycodone, hydrocodone and hydromorphone produce prototypic *mu*-opioid agonist effects (i.e., miosis, high, liking). However, the intranasal (IN) abuse liability of opioid analgesics has not been systematically evaluated, despite common misuse by this route. Specifically, 15% of publically funded substance abuse treatment admissions in the U.S. with prescription opioid abuse report intranasal insufflation or “snorting” of prescription opioids (SAMHSA, 2008).

There is also significant interest in how pain may modulate the abuse liability of prescription opioids as they are routinely prescribed for pain relief. It is clear that opioids function as a negative reinforcer (i.e., decreasing pain) in non-drug abusing populations; both males and females reliably self-administer opioids after painful medical procedures (Berman et al., 1990; Parker et al., 1991). Pain also can alter the pharmacodynamic effects of opioids. For instance, in non-drug abusing primarily male subjects, experimentally-induced tourniquet and cold pressor pain attenuated morphine-induced respiratory depression (Borgbjerg et al., 1996) and feelings of ‘high,’ ‘coasting,’ ‘sleepy,’ and ‘lightheadedness’ (Conley et al., 1997). Other studies have shown gender-specific side effect profiles that varied across opioids. For instance, cold pressor pain modulated the response to butorphanol, but only for women (Zacny and Beckman, 2004). That is, women felt less, ‘tired,’ ‘heavy/sluggish,’ and ‘spaced out’ when in pain compared to when they were not in pain; men reported no differences. Women reported more nausea and vomiting after morphine compared to men (Fillingim et al., 2005; Sinclair et al., 1999; Zacny, 2002) but not after meperidine administration (Zacny, 2002). Thus, the pharmacodynamic effects of opioids can vary in gender-specific ways depending on the opioid administered and how pain is evaluated (for review see Niesters et al., 2010).

An important clinical question with regard to pain, opioids and gender is whether acute pain modulates the abuse liability of opioid analgesics among persons who currently abuse these medications for non-medical reasons. Opioid abusing populations often have a high prevalence of pain conditions, which may indicate a need for opioid analgesics. For instance, studies have reported that 37% of methadone maintenance patients reported chronic severe pain and over 80% of opioid abusers undergoing residential detoxification reported persistent or acute intermittent pain (Larson et al., 2007; Rosenblum et al., 2003). However, there remains controversy and concern about the risk of prescription opioid analgesic misuse and worsening of addiction in dually diagnosed populations (i.e., pain and opioid use disorders). Controlled experimental research could provide a better understanding of how pain impacts the abuse liability of commonly prescribed opioids, such as oxycodone, and contribute to an evidence-base to guide clinical care decisions, particularly for the dually diagnosed.

This study employed a placebo-controlled, randomized, double-blind design examining experimentally-induced pain and a no-pain control with the primary aim of determining whether the abuse liability and physiologic effects of a commonly misused opioid, intranasal crushed oxycodone, is altered by an acute pain state in prescription opioid abusers.

Secondary aims included evaluating: 1) the abuse liability profile of intranasal oxycodone under normal no-pain conditions, 2) the role of gender on the pharmacodynamic effects in a pain or no-pain state, including those related to abuse liability and analgesia, and 3) the time course of these cold pressor pain-induced changes during and after the removal of the painful stimulus.

2. Methods

2.1 Participants

Healthy adult volunteers ages 18-55 years with current recreational use of prescription opioids (confirmed by self-report and positive opiate or oxycodone urine drug test) and a history of intranasal opioid abuse were recruited to participate in this study. Volunteers were determined to be in good health by history and physical examination, laboratory testing and electrocardiogram. Exclusion criteria included: weight greater than 220 pounds, currently pregnant or breastfeeding, seeking substance abuse treatment, taking daily prescribed medications, inability to tolerate the cold water immersion procedure (all persons screened tolerated this procedure; see below for details about procedure), anatomical nasal abnormality (e.g., deviated nasal septum) or physical dependence on opioids, alcohol, or sedative/hypnotics. Volunteers with current medical illnesses (e.g., diabetes, asthma) or psychiatric problems (e.g., bipolar disorder) also were excluded. Participants gave written informed consent prior to participation. The University of Kentucky (UK) Institutional Review Board approved this study, which was conducted in accordance with the Declaration of Helsinki. A Certificate of Confidentiality was obtained from the National Institute on Drug Abuse. Subjects were paid for participation.

2.2 Study setting

Subjects resided on the UK residential research unit for approximately 2 ½ weeks. Urine samples were tested daily for illicit drugs (cocaine, amphetamine, methamphetamine, THC, methadone, opiates, phencyclidine, barbiturates, benzodiazepines, tricyclic antidepressants, and oxycodone); all results were consistent with no unauthorized drug use. Females had weekly urine pregnancy tests; all results were negative. Subjects received a caffeine-free diet. No smoking was allowed 1 hr prior to and during study sessions. Acetaminophen, alumina/magnesia/simethicone, and ibuprofen were available to subjects as needed but were never given after midnight preceding study session days or during the 24 hr blood-sampling period. Females were not taking oral or depot contraceptives.

2.3 Study design and procedure

The study employed a within-subjects, double-blind, randomized, placebo-controlled design. There were six experimental sessions, separated by at least 48 hours, in which a single drug was giving by the intranasal route [placebo (lactose) and crushed oxycodone (15 mg and 30 mg/70 kg)]. Drug conditions were randomized; however, the 15 mg/70 kg doses always preceded the 30 mg/70 kg doses for safety reasons. Each drug condition was tested twice in separate sessions in order to determine whether pain versus no-pain affects the pharmacodynamic effects of oxycodone; one session with a hand immersed for five 2-min trials in room temperature water (37.0 ± 0.1 °C; no-pain control) and one session with a hand immersed for five 2-min trials in cold water (5.0 ± 0.2 °C; pain condition). The water was circulated in a cooler equipped with an aquarium pump in order to maintain consistent temperature. The cold water immersion or cold pressor test (CPT) is a well-established experimental model used to induce pain in populations with and without substance abuse histories (Comer et al., 2010; Conley et al., 1997; Zacny, 2002; Zacny and Beckman, 2004; Zacny et al., 1996). There was also an IV session without water immersions in which oxycodone 5 mg/70 kg was administered primarily for determining the bioavailability of

intranasal oxycodone (Lofwall et al., 2011). Results from the six IN sessions are presented here.

2.4 Drugs

The IN placebo dose (lactose monohydrate powder; Mallinckrodt Chemical, Paris, KY) was individualized for each subject to match the volume of their active oxycodone doses. IN oxycodone 15 mg/70 kg doses were prepared using 40 mg oxycodone tablets (Cardinal Health, Knoxville, TN), and IN oxycodone 30 mg/70 kg doses were prepared using oxycodone 80 mg tablets (Cardinal Health, Knoxville, TN). These were the original formulation of oxycodone tablets® approved in 1995. The 40 and 80 mg tablets weigh approximately the same (i.e., 133 mg) ensuring the same insufflation volume for both doses. Tablets were wetted with sterile saline to remove the outer coating and then crushed before weighing. All IN doses were packaged in 1-gram glass vials (Health Care Logistics, Circleville, OH). Subjects separated the dose into two identically sized lines on a clean mirror using a clean razor blade and insufflated one line in each nostril through a clear 65 mm straw within 1-min.

2.5 Intranasal Experimental Sessions

Sessions took place on the UK inpatient research unit in a quiet room with a trained research assistant. Sessions lasted from approximately 09:00 to 14:30 hours. Drug administration occurred at 09:30 AM. Non-physiologic outcome measures were presented on a computer screen. Subjects used a keypad to record their answers. Physiologic measures (blood pressure, pulse, oxygen saturation) were recorded directly to the computer. During the water immersions, subjects immersed their non-dominant hand and wrist so that they could use their dominant hand to enter responses.

2.6 Outcome measures

The study timeline and outcome measures are listed in Table 1. Immersions occurred 25 min before and 30, 90, 150 and 210 min after drug administration. Five sec after each hand immersion, the following battery of subject-rated measures were completed in the order listed: Visual analog scale (VAS) of pain/stress items, drug identification, VAS of opioid drug effect items, street value, VAS of pain/stress items (for a second time). Each measure immediately followed the previous measure without time limits given for each measure; however, each immersion battery was completed prior to the end of each 2 min immersion. Subjects were trained and familiarized on the study questionnaires prior to the first session.

Participant-rated measures included: 1) Visual Analog Scales (VAS) of opioid drug effects (i.e., overall drug effect, high, good effects, liking, bad effects, and desire for opiates) that were scored from 0 (none) to 100 (extremely; Lofwall et al., 2007); 2) the estimated street value of the drug that they received; 3) drug class identifications whereby participants identified the drug class that they believed they had received from a list of ten choices (Lofwall et al., 2007); and 4) the Profile of Mood States (POMS) (McNair and Heuchert, 2005), which contains six empirically derived distinct mood subscales [i.e., Tension-Anxiety (range: 0-36), Depression-Dejection (range: 0-60), Anger-Hostility (0-48), Fatigue-Inertia (range: 0-28), Vigor-Activity (range: 0-32), and Confusion-Bewilderment (range: 0-28)] and Total Mood Disturbance (TMD range: -32 to 200)].

Both participants and a trained research assistant observer completed three VAS pain items scored from 0 (none) to 100 (extremely): 1) How much physical pain do you have right now? (or does your subject have [observer]); 2) How bothersome is your physical pain right now; and 3) How stressed are you right now?. Subjects completed these three items during non-immersion time points and twice during immersions; 5 sec after hand immersion (VAS

1) and after completion (VAS 2) of the other immersion measures prior to hand removal from the water. Participants and observers also completed the opioid agonist adjectives questionnaire (Preston et al., 1987). There were 12 items for observers (nervous, skin itchy, friendly, nodding, relaxed, coasting or spaced out, talkative, heavy or sluggish feeling, sleepy, drunken, good mood, energetic) and 17 items (the 12 items listed above plus carefree, drive, turning of stomach, dry mouth, and pleasant sick) for participants. Each item had five answer options ranging from 0 (not at all) to 4 (extremely). The sum of the scores from the 17 participant and 12 subject-rated items each yielded a total agonist scale score.

The computerized Digit Symbol Substitution Task is a cognitive and psychomotor task (McLeod et al., 1982); the dependent outcome was accuracy (proportion of trials attempted that were correct). Physiologic outcome measures included systolic and diastolic blood pressure and pulse that were collected every minute using a noninvasive Criticare Scholar III Model 507ELC2 Series Vital Signs Monitor (Criticare Systems, Waukesha, Wisconsin). Respiratory rate (breaths/min) was measured by counting breaths for 30 seconds and then multiplying by 2. Pupil diameter was measured using Polaroid camera photographs with a 2× magnification. Salivary cortisol levels were determined using a high sensitivity quantitative competitive immunoassay (Salimetrics LLC, State College, Pennsylvania). Salivary cortisol concentration is independent of saliva flow rate, reflects biologically active unbound serum cortisol levels (Kumar et al., 2005), and increases in response to stressors, including the CPT (al'Absi and Petersen, 2003; al'Absi et al., 2002). Cortisol was evaluated 5 min before and 20 min after each immersion to evaluate the adrenocortical stress response to the CPT. Only 7 of 1200 samples (3 from the 15- and 4 from the 30-mg/70 kg conditions; all females) had inadequate saliva to complete cortisol analyses.

2.7 Data Analysis

Demographics and substance use characteristics were compared between males and females using independent t-tests. The majority of data were analyzed using repeated measures analysis of variance (ANOVA) in SAS PROC MIXED (9.1 for Windows). Analyses evaluated the time course and peak change from baseline effects of CPT on the outcomes measures listed in Table 1. Time course analyses used 4-factor ANOVA (gender, dose, water, time). For outcomes that were collected both during and after immersions, separate analyses were conducted (one for immersion data and one for non-immersion data because there were not an equal number of data points for each). If there were no water effects in both analyses, the immersion and non-immersion data then were combined for analysis. Drug identification data are described descriptively and were analyzed using 3-factor (gender, dose, and water) Generalizing Estimating Equation (GEE) after dichotomizing responses into placebo and non-placebo identifications. Peak effect ANOVA analyses had three factors (gender, dose, and water); however, peak analyses for immersion pain/bother/sore/stress VAS had two factors (gender and dose) because only data from cold water sessions were used (pain/stress/vas ratings had mean values less than 1.00 in warm water sessions). Data are shown averaged across cold and warm water immersions when there were no significant main effects of water or water interactions. Tukey post-hoc tests were done to explore significant main effects or interactions. Statistical significance was set at $p < 0.05$. Data are presented as means (standard error). Data on frequency of vomiting are described descriptively.

3. Results

3.1 Participants

Forty-nine subjects were screened for the study and signed consent. Twenty-nine met study inclusion and exclusion screening criteria. Contact was lost with three of the 29 who were

qualified. Twenty-six subjects were admitted to the inpatient research unit. Six were discharged early for the following reasons: 1 refused to cooperate, 1 did not like waking up early for sessions, 1 gave no reason, 2 missed their family, and 1 was “bored.” Twenty Caucasian healthy adult volunteers (10 male, 10 female) completed the study, and results reported here are from these completers. Their demographic characteristics and recent drug use are shown in Table 2. There were no gender differences except that females weighed significantly less on average than males.

3.2 Effects of CPT on subject and observer pain/bothersome/stress ratings

All participants completed all CPT immersions for the full 2 min. Time course analysis showed that the CPT produced significantly higher subject- and observer-rated pain/bothersome/stress ratings than the warm water control ($p < 0.0001$). Mean values were zero during warm immersion time points for all measures except subject-rated stress VAS 1 and 2 scores, which had scores of 5 (of 100). There also was no evidence of participant sensitization or tolerance to the CPT procedure; pain ratings were stable over time within the placebo condition (see Figure 1 placebo condition).

Active opioid doses significantly decreased observed and subject-rated pain, bothersome and stress ratings during the CPT more than placebo in both time course and peak decrease from baseline analyses (except for pain VAS 1 and stress VAS 2 time course analyses). Subject ratings over time for “How much pain” are shown in Figure 1 and peak decrease results are shown in Table 3. Interestingly, there was no significant difference in the amount of maximal decrease from baseline subject-rated pain (i.e., analgesia) between 15 and 30 mg/70 kg doses, but the observers' ratings did show a significant dose response, whereby there was a greater decrease in pain/stress/bothersome ratings in the 30 mg/70 kg condition compared to the 15 mg/70 kg condition. There were no significant gender differences during the CPT on these outcomes.

3.3 Effects of CPT on subject- and observer-rated non-analgesic measures

3.3.1 Opioid drug effect VAS and street value—Immersion and non-immersion data for these outcomes were analyzed in a single time course analysis because there were no significant main or interaction effects of water (i.e., no effects of the painful CPT). There were significant dose and time effects for these six outcomes. Figure 2 illustrates the results for high, liking, and street value, which also are indicative of the results for good effects and overall drug effects. High, liking, good effects, and street value also showed significant gender, gender $\times$ time, and/or gender $\times$ dose $\times$ time interactions whereby females appeared to have: 1) higher mean “high” and “like the drug” ratings than males in the 15 mg/70 kg condition at several time points, 2) a more prolonged duration of “like the drug” in the 30 mg/70 kg condition than males, and 3) greater estimated street values for active doses compared to males. However, individual post hoc comparisons were not significant. Bad effects were rated low overall with highest mean scores by dose and time of 5.7 in the 30 mg/70kg condition, 4.6 in the 15 mg/70 kg condition, and 1.5 in the placebo condition. There were no significant main effects of gender or gender interactions on bad effect ratings.

Maximum peak increase analyses (from baseline) for these measures all showed significant dose effects (see Table 4). Only street value showed a significant main effect of gender whereby compared to males, females valued placebo \$1.48 more, 15 mg/70 kg \$7.35 more, and 30 mg/70 kg \$7.70 more. However, post-hoc tests were not statistically significant.

Ratings of “opiate desire” were significantly higher during the painful CPT [53.5 (2.4)] compared to during the warm water no-pain control [33.9 (2.2)]; main effect of water $p < 0.0001$ (Figure 3 upper left panel). Active opioid doses partially but significantly

reversed the pain-induced increased ratings of “opiate desire” (Figure 3 upper right panel). When the painful stimulus was *not* present (i.e., during non-immersion time points), “opiate desire” ratings decreased after active doses (Figure 3 lower left panel). Similarly, peak decreases in desire during non-immersion time points showed significant dose effects (Figure 3 lower right panel).

3.3.2 Opioid agonist adjectives and episodes of vomiting—Total scores for subject- and observer-rated opioid agonist scales showed a similar pattern of results as the opioid VAS drug effects whereby active doses produced higher scores than placebo for both males and females in CPT and warm water sessions (significant main effects of dose and dose $\times$ time interaction). Additionally, for the observer-rated adjectives, females were rated as displaying significantly more opiate effects after the 30 mg/70kg dose than males regardless of water condition (post hoc: $p=0.007$). Table 4 shows the results from the peak analyses, which mirrored the time course results.

One male vomited twice; one time after receiving the 15 mg/70 kg dose during a cold session and one time after receiving the 30 mg/70 kg dose during a warm session. In comparison, three women had a total of 17 episodes of vomiting. Two women vomited after receiving the 15 mg/70 kg dose during a cold session (one vomited three times and one vomited six times) and the 30 mg/70 kg dose during a warm session (both vomited twice). One of these two women also vomited three times after receiving the 30 mg/70 kg dose during a cold session. The third woman vomited once after the 30 mg/70 kg dose in a cold session.

3.3.3 Drug identification—There were significant dose dependent effects for the drug identification questionnaire, whereby more opiate agonist identifications were made after active drug administration (54.2% after 15 mg/70 kg dose and 74.1% after 30 mg/70 kg dose) compared to placebo (8.4%).

3.3.4 POMS—There were no significant results for the Anger-Hostility scale. Despite several statistically significant results for the remainder of the POMS scales, the mean scores and variability were low, suggesting results have limited clinical significance. For instance, there were significant gender effects for Depression-Dejection, but mean scores were never higher than 1.3 at any time point for either gender in any dose condition in warm or cold sessions. The range of mean scores by time, gender, dose and water for the remaining scales were: 2.1 to 4.0 for Tension-Anxiety, 2.4 to 6.2 for Vigor, 0.0 to 2.8 for Fatigue-Inertia, and 2.6 to 5.1 for Confused-Bewildered, -2.6 to 9.6 for TMD.

3.4 Effects of CPT on DSST performance and physiologic outcomes

Analysis of DSST accuracy showed significant gender, time, and dose $\times$ time effects without water effects. Females had significantly lower accuracy [89.6 (0.6) %] overall compared to males [94.8 (0.2) %], and active doses reduced accuracy over time compared to placebo. Peak decreases from baseline performance showed no significant differences although they decreased most in the high dose condition (see Table 4).

Heart rate and pupil diameter time course analyses included both immersion and non-immersion time points because there were no significant water effects in separate immersion and non-immersion analyses. Figure 4 shows the results for these measures, which showed that active drug decreased pupil diameter and heart rate significantly in both genders. Also, women had significantly larger pupil diameters and higher heart rates than men across nearly all time points, including baseline. Analyses of maximum decrease from baseline in pupil diameter and heart rate showed significant effects of dose only (see Table 4).

Time course analysis of respiratory rate (collected only after immersions) showed that it declined in a dose-related manner after drug administration (significant dose and time effects). Mean values over time by dose condition were never below 13 breaths per minute. Peak decrease from baseline analysis showed that the CPT attenuated declines in respirations after placebo administration [i.e., respirations declined 5.2 (0.5) in warm sessions versus 3.2 (0.5)] in CPT sessions], but not after active opioid doses (significant dose $\times$ water interaction).

SBP, DBP, and oxygen saturation were significantly higher during the CPT compared to the no-pain warm immersions for all doses (significant water effect), but this difference was not present once the hand was removed from water (during non-immersion time points). Blood pressure and oxygen saturation generally decreased more after active doses both when the hand was in and out of water (significant dose $\times$ time effects). Additionally, females had significantly higher DBP [64.6 (0.4)] than males [60.9 (0.4)] averaged across all doses during non-immersion time points (significant gender effect). Peak decrease from baseline analyses for SBP, DBP, and oxygen saturation showed one significant result. Compared to placebo [-0.9 (0.1)], oxygen saturation was reduced significantly more after the 30 mg/70 kg dose [-1.6 (0.2)] and after the 15 mg/70 kg dose [-1.5 (0.2)] during non-immersion time points. Analysis of peak decrease from baseline oxygen saturation values during immersions showed no significant results [placebo warm: -1.04 (0.2); placebo cold: -1.07 (0.4); 15 mg/70 kg warm: -1.6 (0.4); 15 mg/70 kg cold: -1.3 (0.3); 30 mg/70 kg warm: -1.3 (0.3); 30 mg/70 kg cold: -1.6 (0.5)].

The cortisol response to the first water immersion before drug administration showed that cortisol decreased significantly more after the no-pain warm immersion [-0.14 (0.02)] compared to after the painful CPT [-0.02 (0.03)]. There were no gender differences. Time course analysis of the raw data (Figure 5) showed a main effect of water and a water $\times$ time interaction only. Visual inspection of the data showed increased variability in cortisol at 85+ min among females in CPT sessions after receiving active opioid doses; this was due to a subset of females (1 to 4 at any given 85+ min time point) with outlying high values. Due to this variability, the data were evaluated subsequently by determining the number (range: 0-4) of times that cortisol increased in value from 5 min before to 20 min after each cold and warm immersion occurring after drug administration. Results from this 3-factor (gender, dose, water) ANOVA analysis showed a significant dose effect only. Specifically, there were significantly fewer increases in cortisol after the 15 mg/70 kg [0.9 (0.2)] and 30 mg/70 kg [1.1 (0.1)] compared to placebo [2.0 (0.1)].

4. Discussion

This study evaluated the abuse liability of crushed intranasal oxycodone tablets in non-physically dependent male and female prescription opioid abusers under the conditions of cold pressor-induced pain and a no-pain warm water control. The CPT produced pain and stress. It increased blood pressure, pulse, and ratings of "opiate desire" compared to the warm water no-pain control. Despite these differences, the painful CPT did not modulate (neither by increasing nor decreasing) the liking, high, or street value of intranasal oxycodone. Oxycodone produced a prototypic profile of *mu*-opioid agonist effects (e.g., miosis, good effects) that was dose-dependent, rapidly detected (within 10 min of drug administration), and present in both males and females while in a state of pain and no-pain. Females also appeared to be more sensitive to the positive subjective effects of this opioid than males (despite weight-corrected dosing), rating one or more doses with higher street value estimates, liking and high.

The CPT reliably produced pain without evidence of tolerance or sensitization. It served as a potent physiological stressor, producing subjective and observer ratings of pain and stress in all subjects, as well as hemodynamic and adrenocortical activation (i.e., increased blood pressure and cortisol). The CPT also produced effects that lasted beyond its 2-min duration. Specifically, the blunting of the normal decrease in morning cortisol levels *after* the CPT is notable; this has been reported previously in healthy non-drug using volunteers (al'Absi and Petersen, 2003; al'Absi et al., 2002) but not in prescription opioid abusers. The CPT also was sensitive to detecting opioid analgesic effects; however, subjects did not report greater analgesia with the higher dose compared to the lower dose of oxycodone. The reason for the lack of dose-related subject rated analgesia is unclear as the blinded observers did report dose-dependent decreases in subjects' pain. However, this finding suggests that the dose-related effects on drug liking were not secondary to pain relief, but rather due to other psychoactive positive effects of oxycodone such as feeling high. Moreover, other subject-rated measures (e.g., liking) and physiological (e.g., pupils) measures were dose dependent. There is a rich literature showing that analgesic response varies depending on multiple factors [e.g., the type of opioid administered, specific clinical pain syndrome, experimental pain modality, analgesic outcome measure and many other individual factors including age, sex, and psychological characteristics (Kindler et al.; Niesters et al., 2010)]. This study did not have the power, nor was it intended, to evaluate the potential influences of these other factors on analgesic response. However, the results here highlight that increasing opioid doses may differentially affect analgesic and drug reinforcement brain pathways and associated neural substrates. That is, higher oxycodone doses increased abuse liability-related measures but did not increase analgesia.

Interestingly, ratings of "opiate desire" were increased when subjects were in pain during the CPT (see left top panel of Figure 3). The reason for this cannot be due to decreased positive opioid effects because ratings of high, liking, and street value, all subjective effects indicative of abuse liability, were not affected by the CPT. Rather, the increased ratings of "opiate desire" appear to be due to desire for pain and/or stress relief, which occurred to a greater extent after administration of active drug than placebo. However, it is not clear whether these increased "opiate desire" ratings would result, for example, in more opioid self-administration in prescription opioid abusers compared to non-substance abusers when in pain. Comer and colleagues (2010) evaluated self-administration of oral oxycodone under the same conditions of experimental pain as this study between individuals with and without light prescription opioid abuse histories (i.e., mean days of use 4.4 of last 30). Both groups self-administered oxycodone, but the amount of drug taken did not significantly differ between groups (Comer et al., 2010). It remains unclear if persons with greater abuse of prescription opioids, or those in recovery with years of drug abstinence would self-administer more opioid while in pain compared to those without such histories. Likewise, it is unclear how repeated opioid dosing, which is typical in clinical practice, may affect opioid abuse liability. These are questions worthy of further research.

There were several interesting gender results. Females, compared to males, vomited more often and reported higher estimates of street value and ratings of drug liking and good effects for oxycodone and observers rated females as displaying more opioid agonist effects. It seems unlikely that these results are due to gender-related pharmacokinetic differences as dosing was weight-based and pharmacokinetic results for a subset of each group (4 males and 4 females) revealed no statistically significant group differences on key pharmacokinetic outcomes. For instance, mean bioavailability for the 15 mg/70 kg dose was 79.5% for females and was 76.5% for males (Lofwall et al., 2011). Several studies have reported that women have more nausea and episodes of vomiting than males after opioid administration, in particular with morphine (Fillingim et al., 2005; Sinclair et al., 1999; Zacny, 2002), but this gender difference is less consistent after oxycodone administration (Zacny and Drum,

2010; Zacny and Gutierrez, 2003, 2009) among non-drug abusing volunteers. Notably, in the current study, despite more vomiting among females, there were no gender differences in ratings of bad effects. This may reflect that vomiting among opioid drug abusers often is a pleasant sickness, indicating that the opioid is of good quality. This too would help explain why women had higher ratings of liking and street value. Also, women in this study reported more use of non-opioid drugs in the last 30 days than men (e.g., marijuana, nicotine, alcohol; see Table 1). These are not statistically significant differences and there are no clinical data that suggest that recent non-opioid drug use affects the abuse liability of opioids; however, we cannot rule out the possibility that females' non-opioid drug use contributed to these gender differences. Surprisingly few human behavioral pharmacology studies have evaluated gender differences in opioid abuse liability; however, several preclinical studies have reported that female rodents acquire and maintain opioid self-administration at a faster rate with equal or higher doses of opioids than male rodents (Cicero et al., 2003; Lynch et al., 2002; Roth et al., 2004). Given these results and the fact both genders are prescribed and exposed to opioid analgesics, it is critical that females be represented in human behavioral pharmacology studies evaluating pain and abuse liability.

A study strength is that it evaluated an opioid agonist when given by the intranasal route, which is not often studied despite this being a common route of abuse (SAMHSA, 2008). Oxycodone, when crushed and "snorted," functioned much like an immediate-release opioid. It produced a rapid onset of subjective effects (i.e., detected within 10 min; see Figure 2), was detected in the blood within 5 min, and had a short half-life (i.e., 3.5 hours), which is more similar to immediate- than extended-release oxycodone (Lofwall et al., 2011). Notably, the oxycodone formulation recently has been modified in order to make it more difficult to crush, helping to keep the extended-release mechanism intact in the presence of tampering attempts. Thus, the results here are not generalizable to the new abuse-deterrent formulation. However, there remain many other prescription opioid analgesics, both immediate and extended-release, that are easily crushed for snorting (e.g., generic oxycodone preparations) such that one would expect to see a similar profile of *mu* opioid agonist effects by this route. As more emphasis is placed on development of abuse-deterrent opioid analgesic formulations, it will be important to evaluate systematically the efficacy of the deterrent strategy by assessing a range of factors that may influence the relative abuse potential, including, for example, the route of misuse and presence/absence of opioid physical dependence.

In summary, the current study demonstrated that snorting crushed oxycodone produced dose-related subjective effects indicative of abuse liability among male and female prescription opioid abusers. Cold pressor pain increased ratings of "opiate desire" more than the no-pain warm water control, but the ratings for street value, high and liking remained unchanged. Thus, pain did not decrease the abuse liability of oxycodone. Notably, females showed signals of increased sensitivity to the abuse liability characteristics of this opioid, which warrant further study. The next step now requires clinical validation of these results utilizing patient populations that are dually diagnosed with prescription opioid abuse and pain syndromes in order to ensure that their care is evidence-based. This will be challenging work; but worthwhile given the growing number of prescribed opioid analgesics, concerns about misuse and diversion, and increased unintentional overdoses involving these medications (Bohnert et al., 2011; Hall et al., 2008; Paulozzi et al., 2006).

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Figure 1.

Time course of subject and observer ratings of pain during cold water immersions before (i.e., baseline [BL]) and after drug administration. Subject ratings occurred after completion of the immersion measure battery prior to hand removal from the water. Data shown are means with unidirectional standard error bars. Three-factor (Gender, Dose, Time) ANOVA showed a significant main effect of Time (subject: $F [4,72] = 5.000$; $p = .001$; observer: $F = 3.000$; $p = .024$) and a Dose $\times$ Time interaction (subject: $F [8,144] = 2.260$; $p = .027$; observer: $F = 3.250$; $p = .002$) for both outcomes. There was a significant Dose effect for observer-rated pain ($F [2,36] = 4.820$; $p = .014$). There were no significant Gender results.

Figure 2.

Time course of street value and visual analog ratings of high and like averaged across warm and cold water sessions. Data shown are means with unidirectional standard error bars. Four-factor ANOVA (Gender, Dose, Time, Water) showed no significant Water results. All outcomes had significant main effects of Dose (high: $F[2,36]=46.880$; $p<.0001$; like: $F=54.680$; $p<.0001$; street value: $F=32.440$; $p<.0001$) and Time (high: $F[20,360]=57.540$; $p<.0001$; like: $F=52.130$; $p<.0001$; street value: $F=52.260$; $p<.0001$). High and street value showed a significant Gender $\times$ Dose $\times$ Time interaction (high: $F[40,720]=1.770$; $p=.003$; street value: $F=2.050$; $p<.0001$). Street value had a significant main effect of Gender ($F[1,18]=6.560$; $p=.020$).

“How much do you DESIRE OPIATES right now?”

Figure 3.

Time course and peak decreases in ratings of “opiate desire” by dose and water (i.e., painful cold water and no-pain warm water control). Data are means with standard error bars averaged across males and females because there were no significant gender results. Four-factor ANOVA (Gender, Dose, Time, Water) showed significant main effects of Water ($F[1,18]=26.450$; $p<.0001$) during immersion time points (upper left panel). During non-immersion time points (lower left panel), there was a significant main effect of Time ($F[16,288]=3.140$, $p<.0001$) and a Dose $\times$ Time interaction ($F[32,576]=2.140$; $p<.001$). Three-factor ANOVA (Gender, Dose, Water) evaluating peak decreases from baseline “opiate desire” showed significant main effects of Dose during immersion (upper right panel; $F[2,36]=6.650$; $p<.004$) and non-immersion time points (lower left panel; $F[2,36]=10.940$; $p<.0001$). * indicates significant ($p<0.05$) Tukey post-hoc difference compared to placebo within the same water condition.

Figure 4.

Heart rate and pupil diameter over time by gender and dose. Data shown are means with unidirectional standard error bars averaged across warm and cold water sessions (no significant Water results). Four-factor ANOVA (Time, Gender, Dose, and Water) showed significant main effects of Time (heart rate: $F[21,378]=33.910$; $p<.0001$ and pupil diameter: $F[20,360]=25.710$; $p<.0001$), Dose (heart rate: $F[2,36]=4.560$; $p=.017$ and pupil diameter: $F=109.600$; $p<.0001$) and Gender (heart rate: $F[1,18]=37.740$; $p<.0001$; pupil diameter: $F=5.38$, $p=.032$) with a dose $\times$ time interaction (heart rate: $F[42,756]=2.230$; $p<.0001$ and pupil diameter: $F[40,719]=7.960$; $p<.0001$).

Figure 5.

Salivary cortisol concentrations over time by gender, dose, and water condition. Vertical bars on x-axes indicate time of water immersions. Data shown are means and unidirectional standard error bars. Four-factor ANOVA (Time, Gender, Dose, and Water) showed significant effects of Water ($F[1,18]=6.200$; $p=0.023$), Time ($F[9,162]=13.090$; $p<.0001$) and a Water $\times$ Time interaction ($F[9,162]=2.040$; $p=0.038$).

Table 1

Session timeline and outcomes measures

	Time in minutes (relative to intranasal drug administration)																							
	-30	-25*	-15	10	20	30*	40	60	80	90*	100	120	140	150*	160	180	200	210*	220	240	260	280	300	
•Heart Rate, Blood Pressure, Oxygen Saturation	Recorded every minute throughout session																							
•Subject-Rated Pain/Stress Visual Analog Scale (VAS)**	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
•Drug Identification	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
•Opiate VAS	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
•Street Value	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
•Pupil Diameter	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
•Observer-Rated Pain/Stress VAS	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
•Salivary Cortisol ***	■					■				■				■					■					
•Subject & Observer Rated Opiate Adjectives			■	■	■		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
•Profile of Mood States			■		■			■				■								■				
•Digit Symbol Substitution Test			■	■	■		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	
•Respiratory Rate	■		■	■	■		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	

* Indicates an immersion timepoint whereby outcomes completed during each immersion are listed in the order that they were completed.

** Subject-rated VAS pain/stress done twice during immersion timepoints; 5 seconds into each immersion and after completion of all subject-rated measures.

*** Salivary cortisol was evaluated 5 minutes before and 20 minutes after each immersion.

Table 2
Participant demographics and substance use characteristics by gender

Characteristic, mean (S.E.)	Females (n=10)	Males (n=10)
Age (years)	28.8 (2.6)	27.4 (1.9)
Education (years)	12.2 (0.6)	11.8 (0.3)
Weight (kg)	68.6 (2.3)	77.8 (3.0) *
** Number of days in the last 30 days use of:		
Prescription opioids (excluding methadone)	10.9 (0.8)	9.6 (0.3)
Methadone (n=1 F, 4 M)	1.0 (0.0)	1.0 (0.0)
Heroin (n=1 F, 1 M)	16.0 (0.0)	1.0 (0.0)
Cocaine (n=4 F, 6 M)	7.5 (2.4)	6.7 (3.8)
Benzodiazepines (n=8 F, 6 M)	5.8 (1.8)	3.0 (1.5)
Alcohol (n=9 F, 8 M)	11.1 (3.0)	7.3 (3.1)
Marijuana (n=7 F, 8 M)	20.1 (4.4)	8.8 (3.5)
** Number of cigarettes smoked/day (n=8 F, 9 M)	16.3 (1.8)	9.7 (1.4)

* indicates significant difference between females and males ($p < 0.05$).

** Means calculated based on number of subjects who reported >0 days use in the last 30 days. N=10 for males and 10 females unless otherwise indicated. F=Females, M=Males.

Table 3
Peak decrease from baseline visual analog scale (VAS) ratings of “pain,” “stress,” and
“bothersome” during cold water immersions

	Intranasal OxyContin®		
	0 mg/70kg (n=20)	15 mg/70kg (n=20)	30 mg/70kg (n=20)
<u>Subject-rated:</u>			
Pain VAS 1	-6.6 (3.9)	-24.5 (5.9)	-20.4 (7.1)
Pain VAS 2	-2.0 (2.8)	-23.4 (5.6)	-18.9 (4.4)
Bothersome VAS 1	-6.5 (3.9)	-33.0 (6.3)	-23.9 (7.6)
Bothersome VAS 2	-1.8 (2.2)	-22.8 (5.9)	-24.0 (5.1)
Stress VAS 1	-6.4 (5.2)	-24.6 (6.5)	-23.2 (7.0)
Stress VAS 2	-8.7 (5.1)	-25.1 (7.6)	-24.6 (5.3)
<u>Observer-rated:</u>			
Pain	-3.8 (3.8)	-13.45 (4.4)	-31.75 (4.7) *
Bothersome	-6.4 (4.8)	-17.4 (5.0)	-39.2 (5.7) *
Stress	-8.3 (5.1)	-17.9 (5.0)	-37.0 (5.5) *

Data presented are means (standard errors). All outcomes had significant main effects of dose ($p < 0.05$). Bolded values indicate significant post-hoc difference compared to placebo.

* indicates significant post-hoc difference compared to 15 mg/70 kg. VAS 1 occurred 5 seconds after the start of the water immersion. VAS 2 occurred after completion of the immersion measure battery prior to hand removal from the cold water.

Table 4
Maximum peak change (increase or decrease) from baseline for non-analgesic measures of opioid effects

		Intranasal OxyContin®		
		0 mg/70kg (n=20)	15 mg/70kg (n=20)	30 mg/70kg (n=20)
<u>Peak increase:</u>				
Drug Effect		8.4 (2.7)	45.3 (3.1)	57.5 (3.4) *
High		6.2 (1.9)	42.0 (3.4)	57.4 (3.4) *
Liking		7.5 (2.7)	53.6 (3.8)	61.3 (3.5)
Good		7.8 (2.9)	47.5 (3.3)	58.9 (3.4) *
Bad		1.5 (1.3)	9.7 (3.3)	11.6 (3.4)
Subjective Opioid Adjectives Agonist		2.5 (0.9)	7.9 (1.1)	11.3 (0.9) *
Observer Opioid Adjectives Agonist		1.7 (0.3)	5.0 (0.6)	7.8 (0.7) *
<u>Peak decrease:</u>				
Pupil Diameter (mm)		-0.7 (0.1)	-2.2 (0.1)	-2.9 (0.1) *
DSST (% Correct)		-11.6 (1.7)	-10.7 (1.4)	-14.8 (2.0)
Heart Rate (beats per minute)		-12.7 (0.9)	-17.3 (0.9)	-14.2 (1.2) *

Data presented are means (standard errors) averaged across cold and warm water sessions. All outcomes had a significant ($p < 0.05$) main effect of dose (except DSST) without significant gender or water main effects or interactions. Bolded values indicate a significant post-hoc compared to placebo.

* indicates a significant post-hoc compared to 15 mg/70 kg.