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Abuse liability of oxycodone as a function of pain and drug use history

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Abstract

The relationship between pain and prescription opioid abuse is poorly understood. Determining whether a patient is seeking additional opioid medications in order to alleviate pain or to abuse the drugs can be difficult. The present study was designed to evaluate two variables that may influence the abuse liability of opioids: drug use history and the presence or absence of experimentally induced pain. Eighteen healthy participants completed this outpatient study. One group was abusing prescription opioids (N=9) and one group had used prescription opioids medically but did not abuse them (N=9). All participants completed twelve sessions during which the effects of orally delivered oxycodone (0, 15, 30 mg/70 kg, PO) were examined. One dose was tested per day under double-blind conditions and sessions were separated by at least 48 h. During the first “sample” session each week, participants were given $10 and the dose that was available later that week. During the second “choice” session, participants could self-administer either money or the previously sampled dose. Six sessions involved repeated hand immersions in cold water (4°C) and six sessions involved immersions in warm water (37°C). Most of the positive subjective effects of oxycodone were similar between the groups, but oxycodone self-administration significantly differed between groups. Non-abusers self-administered active doses

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CONTRIBUTORS
S.D. Comer designed the study, analyzed the data, and wrote the paper. W.J. Kowalczyk collected data and provided preliminary statistical analyses of the results. J. Houser wrote first drafts of the Introduction and Methods sections of the paper. M.A. Sullivan provided overall medical coverage during the study. S.K. Vosburg interviewed potential participants and supervised data collection. All of the co-authors read drafts of the paper. The authors gratefully acknowledge the nursing care provided by Ms. Janet Murray and Ronnie Shapiro, as well as the technical assistance of Ms. Susanna Stephens.

CONFLICT OF INTEREST
S.D.C. has served as a consultant to Abbott Pharmaceuticals, Alpharma Pharmaceuticals LLC, BioDelivery Sciences Inc., Cephalon Pharmaceuticals, King Pharmaceuticals, Pain Therapeutics, and Purdue Pharmaceuticals, manufacturers of opioid medications. She has also consulted for Analgesic Research and Inflexxion, Inc. In addition, she has received research funding from Endo, Johnson & Johnson, Reckitt-Benckiser, and Schering-Plough Corporation. Dr. Comer also received honoraria from the Rehabilitation Institute of Chicago for presenting her research at a conference entitled “Examining Critical Issues in Opioid Management,” Yale University for presenting her research on a depot formulation of naltrexone, and Wake Forest University and the University of Michigan, Ann Arbor for presenting her research on opioid abuse liability. S.K.V. received partial salary support from and served as a consultant to Grunenthal USA, Inc. S.K.V. also serves as a consultant to Analgesic Research. The other authors have no conflicts to declare.

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of oxycodone only when they were in pain while abusers self-administered oxycodone regardless of the pain condition. These data suggest that an assessment of the reinforcing effects of opioids may be a sensitive method for differentiating opioid abusers from non-abusers.

Key Words/Phrases

prescription opioid abuse; self-administration; oxycodone; drug use history; humans; pain

1.0 INTRODUCTION

The non-medical use and abuse of prescription opioids has increased substantially in the United States since the mid-1990s (SAMHSA, 2007). The latest report from the National Survey on Drug Use and Health revealed that approximately 2.2 million persons in the U.S. aged 12 and older reported initiating non-medical use of prescription opioids in 2008, which was equivalent to the number of individuals initiating marijuana use (SAMHSA, 2009). Among prescription opioids, products containing oxycodone and hydrocodone are the most commonly abused (Mendelson et al., 2008). Despite the scope and seriousness of the problem, relatively few studies have examined the pharmacodynamic effects of these commonly prescribed medications and even fewer studies have examined the ability of pain to modulate their effects.

A number of studies have demonstrated that patients in pain readily self-administer opioids using a patient-controlled analgesia procedure, and some studies suggest that the amount of drug self-administered varies directly with the level of pain being experienced (e.g., Berman et al., 1990; Gil et al., 1990; Graves et al., 1985; Mowbray & Gaukroger, 1990; Parker et al., 1991; Schechter et al., 1988; Sidebotham et al., 1997). Consistent with the clinical data, Zacny and colleagues (1996) reported that when normal, healthy volunteers were given the opportunity to self-administer fentanyl intravenously, drug self-administration was significantly greater in the presence of experimentally induced pain than in the absence of pain (Zacny et al., 1996). Studies conducted in laboratory animals also demonstrated that opioid self-administration varies directly as a function of pain. For example, Colpaert and colleagues (1982, 2001) reported that fentanyl self-administration was significantly greater in "arthritic" rats inoculated with *Myobacterium butyricum*, compared to control rats. The time course of drug self-administration corresponded with the expected time course of pain produced by the inoculation. Taken together, these data demonstrate that drugs that do not function as reinforcers in the absence of pain may become reinforcing in the presence of pain.

In addition to its modulatory effects on self-administration, the presence of pain also may modulate the subjective effects of opioids (Conley et al., 1997; Wolff et al., 1940; Zacny et al., 1996). For example, Conley and colleagues (1997) reported that, relative to saline, morphine-induced ratings of "Coasting," "Lightheaded," and "Sleepy" were significantly elevated in a no-pain condition, but not in an experimentally induced pain condition. Whether and to what degree this outcome extends to commonly prescribed opioids such as oxycodone is unknown.

As described above, pain may modulate the reinforcing and subjective effects of opioids. Another variable that may affect the pharmacodynamic response to opioids is drug use history (Comer and Zacny, 2005). While comparisons of subjective effects can be made across separate studies of drug and non-drug abusers, methodological differences make these comparisons difficult to interpret. For example, routes of administration and drug doses differ in studies conducted in abusers and non-abusers. Only two studies directly

compared, within the same study, the subjective reactions of drug abusers and non-drug abusers to opioids. Lasagna and colleagues (1955) compared the responses of non-drug abusers, chronically ill patients (some of whom experienced chronic pain), and drug abusers. Greater inter-individual variability in ratings of drug pleasantness was found in the non-drug abuser group compared to the abuser group. Most of the chronically ill patients reported “negative euphoria.” That is, they experienced the drug as pleasant only because it reduced pain. A more recent study directly compared the subjective effects of morphine in opioid abusers and non-drug abusers (Azorlosa et al., 1994). Abusers reported more drug “Liking” and “Good drug effects” than non-abusers. The abusers also had lower ratings of “Coasting” and “Tired or sluggish.” Thus, it appears that subjective responses to opioids may vary as a function of drug use history.

Given the extent of prescription opioid abuse in the U.S., it is surprising that relatively few studies have examined potential variables that may influence the abuse liabilities of commonly prescribed opioid medications. Accordingly, the present study was designed to evaluate both the reinforcing and subjective effects of oxycodone in prescription opioid abusers compared to non-abusers, and to determine whether they are modulated by the presence or absence of experimentally induced pain.

2.0 METHODS

2.1 Screening

Participants were recruited from the New York City metropolitan area using advertisements posted in newspapers, the internet, and on fliers. Volunteers who were found to be eligible during an initial telephone interview were asked to come to the laboratory to complete detailed questionnaires on drug use, general health, and medical history. The State-Trait Anxiety Inventory (Spielberger et al., 1970) and Beck Depression Inventory II (Beck et al., 1996) were completed, and a medical evaluation was performed. In addition, all participants received a semi-structured psychiatric interview by a physician using a locally developed instrument. Laboratory analyses included a hematology screen, blood chemistry panel, liver function tests, urinalysis, and, for women, a serum pregnancy test. Urine drug toxicologies were also performed.

Volunteers were excluded from the study if they were seeking treatment for drug use, physiologically dependent on alcohol or illicit drugs including opioids, had a major Axis I psychiatric diagnosis, or were taking psychotropic medications that were expected to interfere with the study measures. Exclusion criteria also included high blood pressure, abnormal body weight, current or history of chronic pain, and contraindication to opioids. Participants who routinely used over-the-counter analgesics and who were not willing/able to refrain from use during the study were excluded.

Participants were told that they would receive opioids during the study and that either placebo or active doses would be tested. They were paid $35 per study session, and they had the opportunity to earn an additional $10 per session as part of the study procedures. If they completed all 12 sessions, they received an additional $420 bonus ($35 per session). Participants also received $15 per week for completing daily rating forms. Total study earnings amounted to approximately $1,000. Ethics approval was obtained from the Institutional Review Board of the New York State Psychiatric Institute.

2.2 Pain Procedure

Cold Pressor Test (CPT)—The CPT is a well-established model for producing pain in humans (e.g., Chen et al., 1989; Conley et al., 1997; Zacny et al., 1996). The CPT apparatus

consisted of two 1-gallon coolers filled with either warm (37.0 ± 0.2°C) or cold (4.0 ± 0.2°C) water and a cradle upon which the participant could rest his/her hand. An aquarium pump was used to constantly circulate the water in the tanks.

The CPT condition (pain vs. no pain) was varied both within and between participants. For the pain condition, each participant was asked to first immerse the hand in the warm water for 2 min (to equalize baseline skin temperature across participants) and then to immerse the same hand in the cold water for 2 min. The no pain condition was identical to the pain condition except that participants immersed the hand into the warm water twice. The State Anxiety Inventory was measured during the first immersion, and skin temperature between the thumb and forefinger of the immersed hand and blood pressure were measured before and after the second immersion. During the second immersion, pain intensity/bothersome ratings were recorded 10, 30, 90, and 110 sec after immersion. Forty sec after immersion, the Short Form of the McGill Pain Questionnaire was completed.

The CPT was completed before and 30, 60, 120, 180, and 240 min after drug administration. Previous investigators have shown that multiple tests can be carried out within the same day with few between-test differences (e.g., Conley et al., 1997; Zacny et al., 1996). Because the sex of the experimenter may influence responding to painful stimuli (Clark and Mehl, 1971; Clark and Goodman, 1974; Levine and DeSimone, 1991), the sex of the experimenter was always the same as the research participant.

2.3 Subjective Effects

The following computerized questionnaires were completed during sessions:

2.3.1 Short-Form of the McGill Pain Questionnaire (MPQ; Melzack, 1987)—This questionnaire consists of 15 descriptors representing sensory and affective dimensions of pain. Participants described their experience of pain (e.g., throbbing, shooting) by choosing among four possible answers: None, Mild, Moderate, and Severe. They completed the MPQ during the second water immersion of the CPT.

2.3.2 Pain Intensity/Bothersomeness Scales (Zacny et al., 1995)—Participants also described their experience of pain by answering two questions: “How painful is it?” and “How much does it bother you?” Participants rated pain intensity and bothersomeness on a scale of 0 (not painful/bothersome at all) to 10 (the most painful/bothersome feeling imaginable). The Pain Intensity/Bothersomeness Scales were administered four times during the second water immersion of the CPT.

2.3.3 State Anxiety Inventory (Spielberger, et al., 1970)—The State version of the State-Trait Anxiety Inventory consists of 22 items designed to assess state, or transitory, anxiety. Participants completed the State during the first water immersion of each CPT and at the end of the experimental session.

2.3.4 Visual Analog Scales (VAS)—A series of lines, each 100 mm long and labeled “not at all” at one end and “extremely” at the other end were presented one at a time. Eighteen lines were labeled with adjectives describing mood states (e.g., “I feel…” “Stimulated,” “High,” etc.), four lines were labeled with questions about the dose, and four lines were labeled with questions about how much participants wanted heroin, cocaine, alcohol, and tobacco. The VAS was completed after each task battery.

2.3.5 Opioid Symptom Checklist (Fraser et al., 1961; Martin and Fraser, 1961)—A series of 13 true/false questions designed to describe opioid effects (e.g., “I feel like I

am nodding,") were presented in order to demonstrate prototypic opioid effects. This questionnaire was completed after each performance battery.

2.3.6 Drug Effects Questionnaire (DEQ; Evans et al., 1995)—Six questions relating to drug effects, as well as the degree to which they would be willing to take the drug again, were presented. Participants chose among answers ranging from "No effects at all" to "Very strong (good, bad, etc.) effects." Participants also indicated whether they thought the effects were most like a placebo, stimulant, or sedative. The DEQ was completed repeatedly after drug administration.

2.4 Performance Effects

Participants completed computerized task batteries throughout the laboratory sessions. The battery consisted of two tasks: a 3-minute digit-symbol substitution task and a 3-minute repeated acquisition of response sequences task (Comer et al., 1999).

2.5 Physiological Effects

A cuff was attached to the upper arm and blood pressure was recorded every 15 minutes. A soft sensor on a finger was connected to a pulse oximeter, which continuously monitored arterial oxygen saturation. If SpO2 decreased below 93%, breaths were prompted verbally by staff. Due to repeated problems with the printer attached to the pulse oximeter for several of the participants on several of the sessions, arterial oxygen saturation was not recorded consistently and will not be reported here. A Canon Powershot G2 camera with a Canon Zoom Lens 7-21 MM 1:2.0-2.5 was used to take pupil photographs. All photographs were taken under ambient light.

2.6 Experimental Sessions

Upon arrival at the laboratory, participants provided a urine sample for pregnancy (women only) and drug testing. A breathalyzer was used to assess recent alcohol use. If the urine sample was positive for any drug or if the breathalyzer was positive, the session was rescheduled. All participants were instructed not to eat solid foods or drink non-clear beverages, other than their normal morning caffeinated beverage, for at least 8 hr prior to arriving at the laboratory in an attempt to minimize potential adverse effects of opioid administration. Participants received a light breakfast consisting of a bagel/toast and juice. The same breakfast was given to each participant during each session to minimize the influence of variable macronutrient content on the bioavailability of oxycodone (Benzigeret al., 1996) and responses to the CPT (Zamarty et al., 1997). To minimize effects of nicotine withdrawal, cigarette smokers were allowed one cigarette after breakfast, 15 min prior to initiation of physiological monitoring. Additional cigarettes were allowed approximately every two hours during the experimental session.

Laboratory sessions alternated between two types: a sample session and a choice session (see below). During sample sessions, participants were given one of three possible doses of drug and $10. Choice (self-administration) sessions were similar to sample sessions except that participants were given the opportunity to work for units of either the dose of drug that was given during the sample session or for units of money. Each choice session took place at least 48 hrs but not more than 1 week after the sample session. The duration of each session was between 5 and 6 hrs.

2.6.1 Sample Sessions—Analgesic effects, pupil diameter, subjective responses, and task performance were measured before and 30, 60, 120, 180, and 240 min after drug/money administration.

2.6.2 Choice Sessions—Choice sessions were similar to sample sessions, except that participants completed a self-administration task after the baseline measurements. Drug/money was delivered at the end of the task, and subjective responses, analgesic effects, task performance, and pupil diameter were measured 30, 60, 120, 180, and 240 min after delivery of the chosen reinforcer (drug, money, or both). Because different amounts of drug were self-administered across participants, these data were not analyzed statistically.

2.6.3 Self-administration Task—During each choice session, participants were given 40 min to work for all or part of the drug and/or money they sampled earlier in the week with the same water conditions (warm or cold). There were 10 opportunities to work for units of drug or money by making finger presses on a computer mouse, and 10% of the total drug or money available that day was obtainable at each opportunity. Thus, if the participant received 30 mg oxycodone and $10 during the sample session, then at each of the 10 choice opportunities, he or she would choose between 3 mg oxycodone (10% of 30 mg) and $1 (10% of $10). Completion of the ratio requirement for each trial was accompanied by a visual stimulus on the computer screen. After a choice was made for one option, responding for the other option was not possible until the ratio was completed and another trial was initiated. The response requirements to choose drug or money increased independently as follows: 50, 100, 200, 400, 800, 1200, 1600, 2000, 2400, and 2800 responses. In order to receive 100% of either reinforcer, a participant was required to emit 11,550 responses within 40 min. Fewer total responses were required if choices were distributed between the two options. The highest ratios completed for money and/or drug were considered to be the progressive ratio breakpoint values. These ratio values were chosen based on previous research conducted in our laboratory (e.g., Comer et al., 1999). Although sustained high rates of responding were required, participants were capable of completing 11,550 responses in 40 min. Participants were not informed about the number of responses needed in order to obtain each choice, but feedback about what choices had already been made in each trial and how much time was remaining was provided to participants on the computer screen. At the end of the task, the participant received whatever s/he had chosen.

2.7 Drugs

Oxycodone HCL (Cardinal Health, immediate-release oral solution 20 mg/ml) was administered orally at doses of 0, 15, and 30 mg/70 kg with one dose tested each week in a sample and a choice session. The recommended dose range of orally administered immediate-release oxycodone for treating pain is 5 mg every 6 hr (Physician’s Desk Reference, 2009). The dose range used here was tested safely in a previous study conducted in normal, healthy volunteers (Zacny and Gutierrez, 2003). Order of dose administration was varied non-systematically within and between participants, with the exception that the first exposure to the highest dose never occurred before the first exposure to the lower dose. Each dose was delivered under double-blind conditions in a solution mixed in 200 ml concentrated orange Gatorade with 1 ml peppermint oil floated on top. Participants were required to consume the entire beverage within 5 min.

At the end of the study, participants who completed the study provided a blood sample for analyses of CPY2D6 genotype (Quest Diagnostics Inc., Teterboro, NJ). In addition, CYP2D6 phenotype was estimated using dextromethorphan. Specifically, a single oral dose of dextromethorphan (30 mg, Robitussin-DM) was administered and two hours later, a blood sample was collected to measure serum concentrations of dextromethorphan (Quest Diagnostics Inc., Teterboro, NJ). We were not able to obtain data from one non-abuser because he was lost to contact after he completed the study.

2.8 Statistical Analyses

A mixed within- and between-subjects design was used. Pain condition (pain, no pain), oxycodone dose (0, 15, 30 mg/70 kg), and time served as within-subject variables and drug use history served as the between-subject variable. The primary dependent measure was progressive ratio breakpoint value for drug. Secondary dependent variables included subjective, performance, and physiologic effects. Repeated measures analyses of variance (ANOVAs) for within-subject variables were performed. Planned comparisons were made between each active dose and placebo. ANOVAs using paired t-tests were used to determine the effects of drug use history. Comparisons with $p<0.05$ were considered significant. Due to the large number of subjective effects that were examined, $p<0.01$ was used to control for Type 1 errors.

3.0 RESULTS

3.1 Participants

3.1.1 Non-drug Abusers—Nine normal, healthy volunteers (5 men, 4 women; 5 White, 1 Black, 1 Hispanic, 1 Asian, 1 Indian) completed the 6-week protocol. Participants in this group were 28 +/− 6 years of age on average (range: 22–42) and reported opioid use for medical purposes at least twice in their lives with no serious side effects (Table 1). None of the volunteers in this group met current or lifetime history of any substance abuse or dependence according to DSM-IV. Two additional participants (1 man, 1 woman) in the non-drug abusers group began the study but did not complete it. One participant discontinued because of excessive nausea and vomiting and the other discontinued for personal reasons unrelated to the study.

3.1.2 Drug Abusers—The ten drug using individuals (8 men, 2 women; 9 White, 1 Black) who completed the 6-week protocol were not seeking treatment for their drug use. Participants were 32 +/− 8 years of age on average (range: 20–44). All participants reported current recreational opioid use varying in frequency from one time per month to 4–5 times per week (Table 1). Four of the participants met DSM-IV criteria for current opioid abuse (400, 419, and 421 and 434), and one met criteria for past opioid dependence (400). One participant met criteria for past alcohol and cocaine dependence (400) and one met criteria for past benzodiazepine abuse and current marijuana abuse (419). None of the participants endorsed use of only one prescription opioid. The most commonly reported opioids used were Vicodin, Percocet, and Tylenol 3’s (Tylenol with codeine). Data from one male participant in this group were not included in the analyses because at the end of the study he reported that he had lied about the extent of his drug use in order to gain entry into the study. Six additional participants (3 men, 3 women) in the abuser group began the study but did not complete it. Three discontinued for personal reasons unrelated to the study, two were discontinued because they were unreliable, and one was discontinued because of failure to comply with drug restrictions during the study.

The groups did not significantly differ on the basis of age, sex, or race.

3.2 CYP2D6 Genotype and Phenotype

Eight of the 9 participants in the prescription opioid abuser group (89% of the sample) possessed a genotype consistent with either a poor or intermediate metabolizer of CYP 2D6 substrates, while only 3 of the 8 non-drug abusers (38%) for whom data were available showed this pattern (data from one participant could not be obtained because he was lost to follow up). The groups did not differ significantly based on phenotype as defined by the results of the dextromethorphan test ($p=0.33$ based on the Fisher exact test and $p=0.15$ based on the more conservative chi-square test).

Post-hoc comparisons of the reinforcing and subjective effects for the poor (N=5) and extensive (N=4) metabolizers within the abuser group based on the dextromethorphan levels revealed no significant effects for any of the measures.

3.3 Reinforcing Effects

Figure 1 shows mean progressive ratio break point values for drug (left panel) and money (middle panel), as well as amount of drug self-administered (right panel) for non-drug abusers (top panels) and prescription opioid abusers (bottom panels) as a function of oxycodone dose and pain condition. For non-drug abusers, oxycodone significantly increased breakpoint values for drug, but only in the cold water condition. Correspondingly, breakpoint values for money significantly decreased in non-abusers when active doses of oxycodone were available, but only in the cold water condition. The amount of drug self-administered by non-abusers increased as a function of dose and was lower in the warm water condition.

In drug abusers, breakpoint values for drug also significantly increased in the cold water condition, but the effect of pain condition was not statistically significant after administration of the active doses of oxycodone. That is, drug abusers self-administered active oxycodone to a similar extent regardless of pain condition. Interestingly, drug abusers self-administered significantly more placebo in the warm water condition than in the cold water condition. Breakpoint values did not significantly differ when active oxycodone doses were available compared to placebo under the warm water condition. Therefore, by definition, oxycodone did not serve as a reinforcer in abusers under the warm water condition. This outcome was due to two participants who chose the drug option on all 10 trials after receiving placebo in the warm water condition. One participant experienced this condition first and the other experienced it last. Furthermore, three additional drug abusers responded for placebo about as much as they did for the two active doses of oxycodone under the warm water condition. Breakpoint values for money in abusers mirrored the breakpoint values for drug. That is, breakpoints for money significantly decreased as a function of dose in the cold water condition and abusers chose significantly less money when placebo was available during the warm water condition. The amount of drug self-administered was higher when active doses were available, but it did not vary as a function of pain condition.

Between-groups analyses showed a significant difference in drug breakpoint values in the warm but not the cold water condition for the active doses of oxycodone. Money break point values also significantly differed between groups in the warm but not the cold water condition for the active doses of oxycodone. The differences in drug and money break point values between groups after placebo administration in the warm and cold water conditions did not reach statistical significance. The amount of active drug that was self-administered also significantly differed between groups in the warm but not the cold water condition. When 30 mg/70 kg oxycodone was available during the cold water condition, the non-abusers and abusers self-administered comparable amounts of oxycodone (11.6 ± 3.9 mg and 12.4 ± 4.1 mg, respectively).

3.4 Subjective Effects

In contrast to the self-administration data, the subjective effects of oxycodone were remarkably similar between the two groups and did not systematically vary as a function of pain condition. Therefore, the data were collapsed across pain conditions. Figure 2 shows mean ratings on the visual analog scale for good effects (left panels), bad effects (middle panels), and liking (right panels) in non-drug abusers (top panels) and drug abusers (bottom panels) as a function of oxycodone dose and time. Relative to placebo, oxycodone produced

significant increases in ratings of good effects (non-abusers: $F(2,16)=6.8$, $p<0.01$; abusers: $F(2,16)=14.5$, $p<0.001$). Ratings of bad effects significantly varied as a function of dose in non-abusers ($F(2,16)=16.4$, $p<0.0001$) and it approached statistical significance in abusers ($F(2,16)=5.3$, $p=0.017$). For several other subjective measures, such as ratings of high, sleepy, quality, potency, and strength of drug effect, the results were also similar between groups (Table 2).

For other measures, some differences did appear to emerge between groups, although the between groups analyses were not statistically significant. For example, in the non-abuser group, ratings of drug liking on the visual analog scale were lower when 30 mg/70 kg oxycodone was administered relative to 15 mg/70 kg, whereas drug abusers liked both active doses equally well (Figure 2, right panels; Table 2). When the data were averaged across the session or when mean peak ratings were examined (Table 2), this difference between active doses in the non-abuser group did not reach statistical significance. However, post-hoc comparisons of the dose by time interaction revealed that non-abusers liked the high dose of oxycodone less than the low dose ($p<0.01$ 60 and 120 min post-drug). Interestingly, both active doses of oxycodone significantly increased ratings of feeling nauseated in the abusers, but only the high dose did so in the non-abusers (Table 2). In fact, a higher percentage of abusers vomited during and after the session than non-abusers (62.5% compared to 37.5%). A few other measures appeared to be different between abusers and non-abusers. Abusers reported feeling significantly more social, stimulated, and talkative after the active doses of oxycodone, but non-abusers did not (Table 2). The abusers reported that they would pay significantly more money for active oxycodone than placebo (Table 2), but the increases in amount that non-abusers were willing to pay for the drug after active oxycodone doses compared to placebo did not reach statistical significance ($p=0.02$ for 15 mg/70 kg and $p=0.04$ for 30 mg/70 kg compared to placebo). Not surprisingly, the amount of money participants were willing to pay for active oxycodone was higher in the abuser group than the non-abuser group, particularly under the cold water condition ($p<0.01$). Peak amounts that abusers would pay for oxycodone were approximately $7, compared to approximately $2 in the non-abusers.

Subjective ratings of pain were also similar in the two groups. Figure 3 shows mean sum scores on the McGill Pain Questionnaire (left panels), as well as responses to the questions “How painful is it?” (middle panels), and “How much does it bother you?” (right panels) in non-drug abusers (top panels) and drug abusers (bottom panels) as a function of oxycodone dose and time. For all three measures in both groups, the temperature by oxycodone dose by time interaction was significant ($p < 0.01$). For the abusers, both the pain intensity and bothersomeness ratings were lower under each active dose condition compared to placebo, and the two active doses were significantly different from each other (all $p<0.01$). While the MPQ ratings in the abusers were also lower under each active dose compared to placebo ($p<0.001$), the difference between the two active doses only approached statistical significance ($p<0.07$). For the non-abusers, the pain intensity and bothersomeness ratings were lower under the 30 mg oxycodone condition compared to placebo ($p<0.01$), but there was no significant difference between the active doses, although ratings of pain bothersomeness in the non-abusers approached statistical significance ($p<0.03$). The MPQ ratings were not significantly different among non-abusers (placebo versus 15 mg/70 kg oxycodone: $p=0.04$; placebo versus 30 mg/70 kg oxycodone: $p=0.016$). There were no statistically significant between-group differences in any of the subjective ratings of pain. Similarly, no between-group differences in skin temperature were observed after hand immersion in the cold or warm water. Average skin temperatures across both groups after the warm and cold water immersions were 34.7±0.03°C and 10.6±0.08°C, respectively.

Sum scores on the State Anxiety Inventory remained stable throughout the study in both groups, with average scores of approximately 30. In the non-abusers, oxycodone appeared to be anxiolytic. Post-hoc analyses revealed that scores were elevated during the cold water condition when placebo was given ($p<0.01$ at virtually all of the time points post-drug administration and $p<0.05$ at all of the other time points including baseline). This effect disappeared when active oxycodone was administered. No changes in anxiety as a function of oxycodone dose were found in the abusers.

3.5 Performance Effects

The total number of correct responses on the digit-symbol substitution task declined from 81.3 to 73.7 in the non-abusers ($F(1,16)=5.0$, $p<0.05$) and from 75.5 to 69.8 in the abusers ($F(1,16)=5.2$, $p<0.05$) after administration of placebo and 30 mg/70 kg oxycodone, respectively.

3.6 Physiological Effects

In both groups of participants, oxycodone produced dose-related reductions in pupil diameter ($p<0.0001$). No between-group differences in pupil diameter were found.

During sessions involving cold-water immersions, participants first placed their hand in warm water for 2 min and then immediately afterward, they placed that hand in cold water for 2 min. Both systolic and diastolic pressure significantly increased in both groups of participants when the hand was immersed in cold water compared to when it was immersed in warm water ($p<0.01$). Heart rate decreased in abusers ($F(1,8)=6.0$, $p<0.05$) during cold water immersions compared to warm water immersions, but it did not change in non-abusers as a function of water temperature. Please note that these changes in heart rate and blood pressure were statistically, but not clinically, significant.

4.0 DISCUSSION

The present results demonstrate that oxycodone served as a reinforcer in both prescription opioid abusers and non-drug abusers in the presence of experimentally induced pain. Although the prescription opioid abusers self-administered similar amounts of oxycodone in both the presence and absence of pain, by definition oxycodone did not serve as a reinforcer in the abusers under the no-pain condition because of the high placebo response rate (i.e., breakpoint values did not significantly differ after administration of placebo compared to active oxycodone under the no-pain condition). This may have been a spurious finding in the present study because numerous other studies across a number of drug classes have shown that abusers can reliably differentiate placebo from active drug in self-administration paradigms, and indeed the abusers in the present study did clearly differentiate placebo from active drug when they experienced pain. Why they self-administered placebo at such high levels in the warm water condition is not clear, although one possibility is that the dose order contributed to this finding. As noted above in the Results section, one participant experienced the placebo-warm water condition first and the other experienced it last. We have observed in previous studies that some drug abusers choose the drug option, even if the dose is placebo, when it is the first condition that they experience because they expect (hope) to receive active doses. Similarly, some participants choose the drug option regardless of dose on the last session because they hope to experience a “last hurrah” before ending study participation. In general, however, these data are consistent with the limited pre-clinical and clinical laboratory observations that under some conditions, opioids are reinforcing only in the presence of pain (e.g., Colpaert et al., 1982, 2001; Zacny et al., 1996). The data also support the observation that many patients with clinical pain only self-administer opioids for pain relief and when the clinical pain dissipates, opioid use declines.

Not surprisingly, in prescription opioid abusers, a substantial amount of oxycodone was self-administered regardless of the presence or absence of pain.

Another important contribution of the present study is that it was possible to demonstrate within the same study that the subjective effects of oxycodone are remarkably similar in prescription opioid abusers compared to non-drug abusers. It has long been thought that non-drug abusers may experience the effects of opioids differently than abusers, who have used the drugs repeatedly (e.g., Azorlosa et al., 1994; Lasagne et al., 1955). In the present study, several positive subjective ratings that are typically indicative of abuse liability, such as ratings of good drug effects, high, and liking were quite similar between the two groups. Two recent publications, one conducted in non-drug-abusing volunteers (Zacny and Lichtor, 2008) and one conducted in prescription opioid abusers (Walsh et al., 2008), also showed similar results with oral oxycodone. Aversive effects, captured by ratings of bad drug effects and nausea, were also quite similar between the groups in the present study, and reports of vomiting were actually higher in the abusers compared to the non-abusers. While this result initially may seem surprising, it could be due to the fact that only a subset of abusers ever used opioids to the point of becoming physically dependent on them, so they may not ever have become tolerant to this effect. Other effects that may be viewed as positive in nature, such as feeling social and talkative, did appear to be differentially affected by oxycodone in the two groups. Specifically, abusers reported feeling more social and talkative after oxycodone administration, but non-abusers did not. Another difference that emerged was that the non-abusers reported feeling less alert and less anxious after administration of oxycodone compared to placebo, while abusers did not. Whether these relatively subtle differences are predictive of who will or will not ultimately abuse prescription opioids is not known.

In addition to the subjective and reinforcing effects of oral oxycodone, physiological and performance effects were also measured in the present study and were similar to those reported in previous studies (Walsh et al., 2008; Zacny and Lichtor, 2008). Most of these effects were not different in drug abusers and non-drug abusers. The analgesic effects of oxycodone, which were dose-related, also were similar in the two groups. As expected, both systolic and diastolic pressure increased in abusers and non-abusers during immersion of the hand in cold water.

Our data on the CYP2D6 genotype and phenotype profiles of individual participants were quite interesting. Cytochrome P450 2D6 is involved in the metabolism of many non-opioid and opioid medications, including oxycodone. Polymorphisms of the CYP2D6 gene induce phenotypes that are relatively well defined with respect to enzymatic activity of cytochrome P450 2D6. Four primary subgroups have been identified based on CYP2D6 genotype: poor, intermediate, extensive (normal), and ultrarapid metabolizers (Ingelman-Sundberg, et al., 2007). In the present study 89% of the prescription opioid abusers had a genotype consistent with either a poor or intermediate metabolizer phenotype, compared to 38% of the non-drug abusers. Furthermore, 56% of the abusers had a phenotype consistent with a poor or intermediate metabolizer compared to 25% of the non-drug abusers. This finding in abusers is striking because the incidence of CYP2D6 poor metabolizers has been reported to be up to only about 20% in the general population (Sistonen, et al., 2009), which is consistent with our results in the non-drug abuser group. These data must be viewed with caution, however, because of the small sample sizes in each group. We currently are combining data across a number of different studies to further examine this effect.

In sum, the present results demonstrate that in non-drug abusers, oxycodone self administration occurred in a pattern similar to that seen in many clinical pain patients who use patient-controlled analgesia devices post-operatively. Namely, they ingested the

medication only when they were in pain. In contrast, drug abusers ingested the medication regardless of the presence or absence of pain. Somewhat surprisingly, the pattern of subjective responses was quite similar in non-drug abusers and in experienced opioid abusers for several measures typically used to assess abuse liability such as “I feel a good drug effect” and “I feel high.” Future studies conducted in patients with clinical pain should further clarify the relationship between pain and the abuse liability of prescription opioids.

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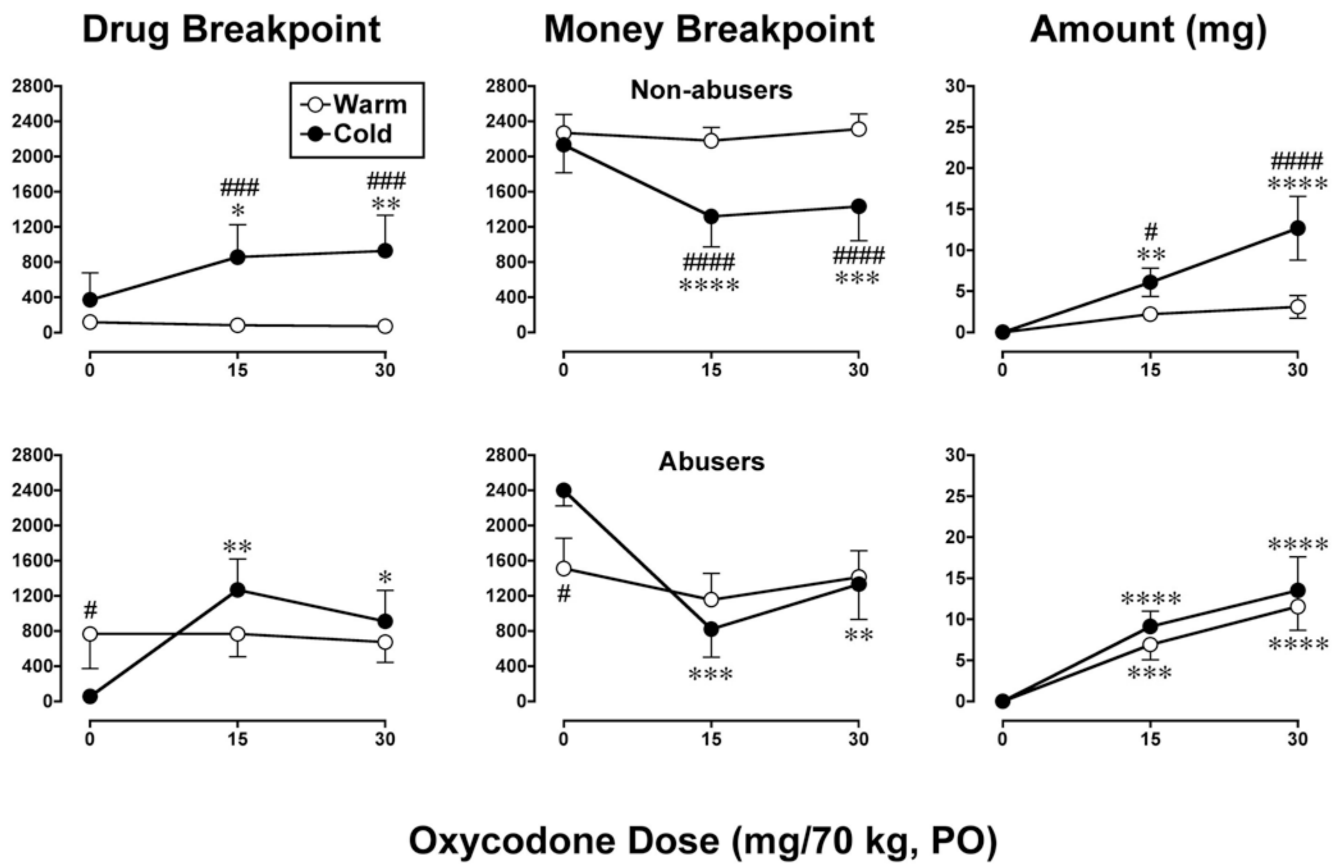

Figure 1.

Average (± 1 standard error of the mean, SEM) progressive ratio breakpoint values for drug (left panels) and money (middle panels), and amount of drug self-administered (right panels) as a function of available dose and water temperature (4°C, 37°C) in non-drug abusers (top panels) and drug abusers (bottom panels). * represents a significant difference from placebo, # represents a significant difference between the cold and warm water conditions. One symbol represents $p<0.05$, two symbols represent $p<0.01$, three symbols represent $p<0.001$, and four symbols represent $p<0.0001$.

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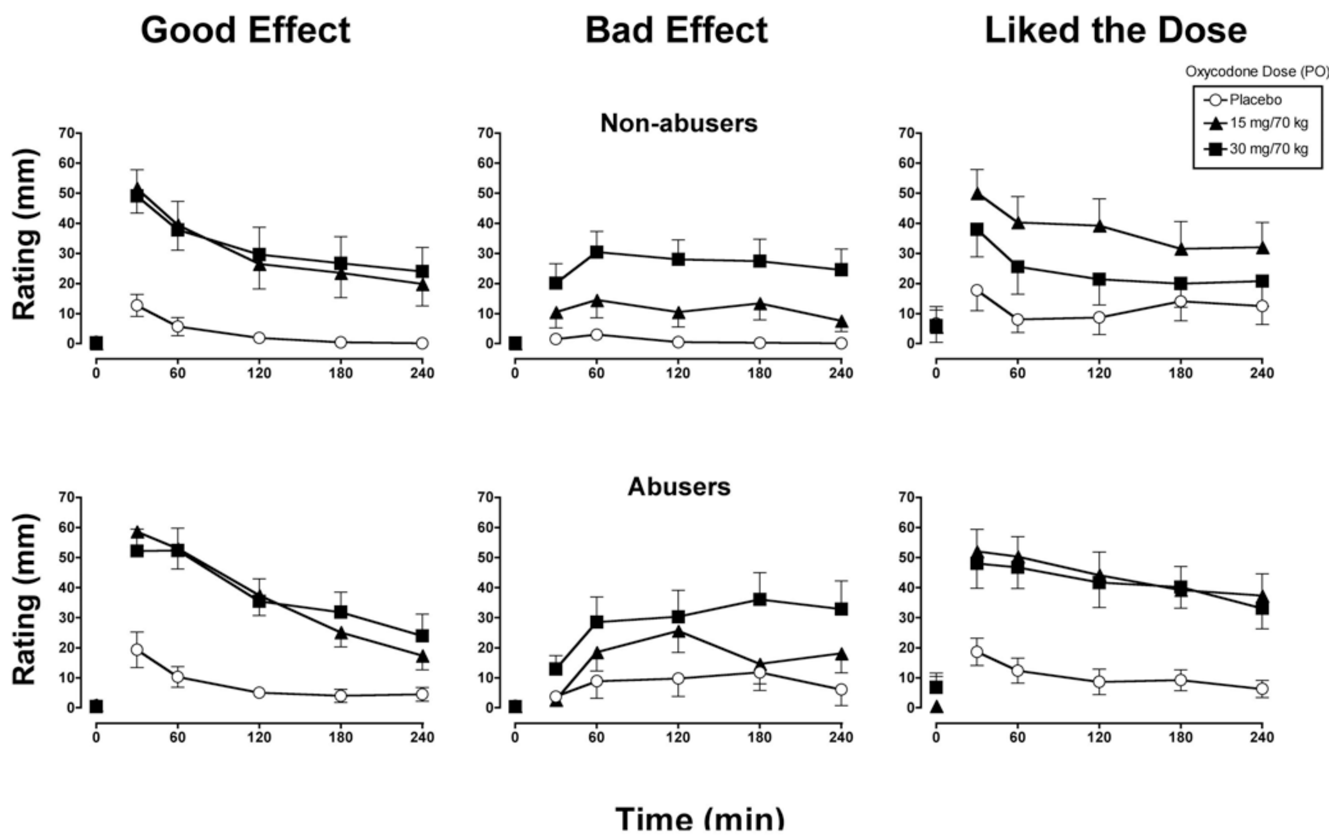

Figure 2.
Average (± 1 SEM) ratings for selected items on the visual analog scale as a function of dose and time in non-drug abusers (top panels) and drug abusers (bottom panels). For clarity, significance symbols are not shown.

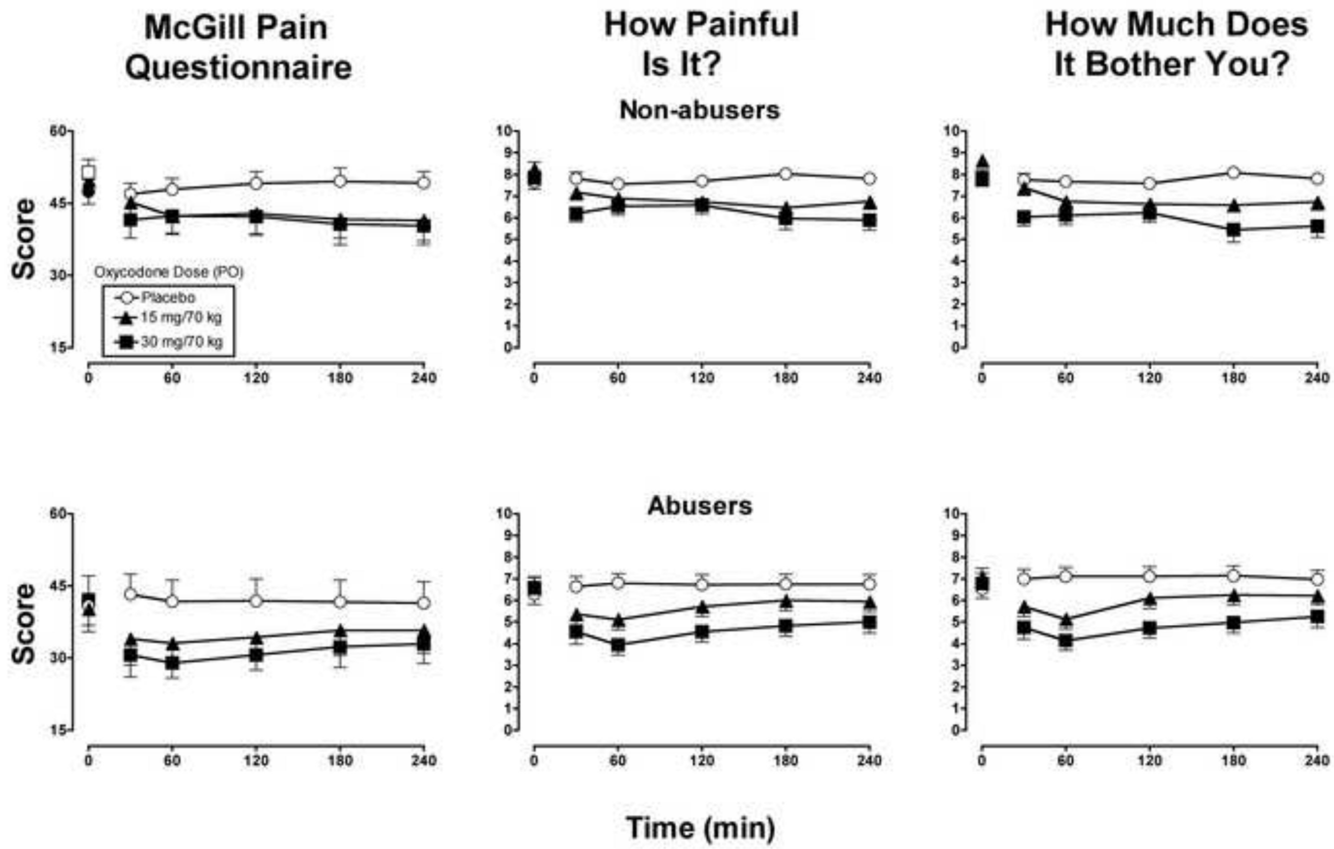

Figure 3.
Average (± 1 SEM) sum scores on the short form of the McGill Pain Questionnaire (range: 15–60; left panels), and responses to the questions “How painful is it?” (middle panels), and “How much does it bother you?” (right panels) after the cold water immersion as a function of dose and time in non-drug abusers (top panels) and drug abusers (bottom panels). For clarity, significance symbols are not shown.

Table 1

Current recreational drug use for non-abusers (top half) and abusers (bottom half). Days used per month (for cigarettes, # smoked/day or month, as indicated).

Subj ID	Opioids	Alcohol	Cigarettes	MJ	Heroin	Cocaine	Sedatives	Comments
406	--	16	--	--	--	--	--	*a*
408	--	2	--	--	--	--	--	*b*
411	--	4	--	--	--	--	--	
412	--	4	--	--	--	--	--	
416	--	8	2/month	--	--	--	--	*c*
417	--	12	4/month	--	--	--	--	*d*
420	--	--	--	--	--	--	--	
422	--	--	--	--	--	--	--	*e*
432	--	8	--	--	--	--	--	*f*
400	18	8	15	--	--	--	--	*g*
404	1–2	30	--	1	--	4	4	*h*
405	1	8	--	--	--	--	--	*i*
419	1	8	10	30	--	--	--	*j*
421	8	8	2	--	--	--	--	
423	1–2	12	--	2	--	--	--	
430	1	8	20	16	--	--	--	*k*
434	4	8	10	1	4	1	4	*l*
436	3–4	8	10	--	--	--	--	*m*

[a] Drank wine with dinner 4 days per week.

[b] Used marijuana in high school.

[c] Tried marijuana and hashish.

[d] Used marijuana infrequently (once per month) during senior year in college. Currently used twice per year.

[e] Tried marijuana.

[f] Smoked marijuana 20 years previously.

[g]Currently used prescription opioids 4–5 times per week, but stopped recently because friend's prescription ran out; had mild withdrawal symptoms during the week prior to screening. Prior physical dependence on heroin and cocaine.

[h]Two weeks previously, used prescription opioids twice weekly. Reported one alcohol drink per day.

[i]One year previously, was using prescription opioids once weekly.

[j]Recreational use of 5 mg OxyContin daily for two months, which occurred two months prior to study participation. Currently smoked 2 hits/day of marijuana.

[k]Used prescription opioids for several days in a row previously (not clear how long ago), but never physically dependent.

[l]One month previously, used prescription opioids 3 times/week.

[m]Reported prior physical dependence on heroin for which he received treatment.

Table 2

Mean peak subjective effects ± one standard error of the mean for non-drug abusers and drug abusers as a function of oxycodone dose (VAS range: 0–100 mm; DEQ range: 0–4, except for drug liking, which ranged from −4 to 4; OSC range: 0–13) Items shown are those for which statistically significant changes were found.

	Non-drug Abusers			Drug Abusers		
	0 mg/70 kg	15 mg/70 kg	30 mg/70 kg	0 mg/70 kg	15 mg/70 kg	30 mg/70 kg
Visual Analog Scales						
Bad Effect	4.2 (1.6)	26.8 (7.8) [a]	46.8 (7.6) [a, b]	14.7 (6.3)	29.8 (7.1)	43.1 (8.1) [a]
Good Effect	13.8 (3.9)	55.7 (7.9) [a]	51.2 (9.2) [a]	21.7 (5.8)	66.3 (6.5) [a]	64.0 (6.6) [a]
High	8.4 (3.6)	61.9 (8.5) [a]	65.2 (7.9) [a]	24.1 (6.8)	68.7 (5.2) [a]	76.4 (6.3) [a]
Liked the Choice	21.4 (6.9)	53.6 (8.1) [a]	40.6 (9.1)	23.0 (5.2)	59.6 (6.8) [a]	58.8 (7.8) [a]
Nauseated	9.7 (4.1)	25.9 (7.4)	41.6 (9.2) [a]	10.6 (6.4)	38.1 (9.4) [a]	44.4 (9.9) [a]
Potent	9.3 (5.8)	63.3 (8.2) [a]	61.4 (9.9) [a]	22.3 (6.6)	64.6 (6.8) [a]	82.3 (6.3) [a]
Quality	13.0 (6.2)	55.2 (9.4) [a]	45.0 (9.9)	18 (4.8)	61.9 (6.6) [a]	62.8 (7.6) [a]
Sleepy	44.3 (8.7)	72.2 (7.0) [a]	68.8 (8.2) [a]	52.1 (8.5)	68.1 (8.5)	71.5 (7.6)
Social	24.9 (5.7)	27.7 (4.6)	28.9 (6.3)	22.4 (5.7)	45.4 (6.5) [a]	41.9 (7.1) [a]
Stimulated	44.6 (5.3)	54.0 (7.3)	51.4 (7.3)	23.6 (5.2)	54.8 (7.8) [a]	52.9 (8.6) [a]
Talkative	18.4 (6.0)	29.5 (5.8)	26.1 (6.3)	21.3 (5.0)	48.9 (6.3) [a]	42.4 (6.3) [a]
Would Pay ($)	0.28 (0.28)	2.28 (0.73)	2.11 (0.68)	1.50 (0.65)	6.89 (1.02) [a]	7.39 (1.40) [a]
Drug Effects Questionnaire						
Bad Effect	0.2 (0.1)	1.6 (0.3) [a]	2.1 (0.3) [a]	0.3 (0.1)	1.1 (0.3)	1.7 (0.3) [a]
Good Effect	0.8 (0.2)	2.6 (0.3) [a]	2.8 (0.3) [a]	1.2 (0.2)	3.0 (0.2) [a]	2.8 (0.3) [a]
Like	0.8 (0.3)	2.3 (0.3) [a]	2.2 (0.3) [a]	1.1 (0.3)	2.8 (0.2) [a]	2.6 (0.3) [a]
Strong	1.4 (0.3)	3.2 (0.2) [a]	3.5 (0.2) [a]	1.7 (0.3)	3.4 (0.1) [a]	3.7 (0.2) [a]
Take Again	2.6 (0.4)	3.3 (0.2)	3.2 (0.2)	1.7 (0.3)	3.1 (0.3) [a]	3.0 (0.3) [a]

	Non-drug Abusers			Drug Abusers		
	0 mg/70 kg	**15 mg/70 kg**	**30 mg/70 kg**	**0 mg/70 kg**	**15 mg/70 kg**	**30 mg/70 kg**
Opiate Symptom Checklist						
Sum	3.2 (0.4)	5.8 (0.4) [a]	6.8 (0.4) [a]	2.9 (0.4)	6.6 (0.5) [a]	7.2 (0.5) [a]

[a] indicates a significant difference from placebo and

[b] indicates a significant difference between 15 and 30 mg/70 kg oxycodone.