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The prescription opioid, oxycodone, does not alter behavioral measures of impulsivity in healthy volunteers

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ABSTRACT

This study examined the effects of oral oxycodone, a prescription opioid, on several measures of impulsive behavior in healthy volunteers. Volunteers ($n=12$) participated in a four-session, double-blind, randomized design in which they received capsules containing oxycodone (5, 10, and 20 mg) or placebo. From 70 min to approximately 120 min after ingesting the capsules, subjects completed five impulsivity tasks: delay and probability discounting task, balloon analogue risk task (BART), go/no-go task, stop task, and simple reaction time test. Mood questionnaires were also completed at fixed time points in the sessions. Oxycodone produced prototypic changes in mood in a dose-related manner, but did not affect performance on any of the impulsivity tasks. Lack of effect on impulsivity stands in contrast to other studies in which other psychoactive drugs including ethanol, delta-9-tetrahydrocannabinol, and amphetamine altered behavior on one or more behavioral measures of impulsivity.

1. Introduction

Non-medical use of prescription opioids in the United States has increased markedly over the last decade, raising concern amongst law enforcement officials, regulatory, pain relief advocacy, and drug abuse organizations, as well as the general public (Denisco et al., 2008; Zacny et al., 2003). In 2007, the number of first time non-medical users of prescription opioids aged 12 years and older reached the level of first time users of marijuana, i.e., 2.1 million people (SAMHSA, 2008). One of the more widely abused prescription opioids is oxycodone, which is available as a single entity product in either immediate or controlled release (OxyContin®) form, or combined with other analgesics (e.g., Percocet®). Oral oxycodone has abuse liability in opioid abusers (Epstein et al., 2006; Walsh et al., 2008), and even in non-drug-abusing healthy volunteers it increases ratings of drug liking, and wanting to take the drug again (Zacny and Gutierrez, 2003; Zacny and Lichtor, 2008). In those healthy volunteer studies, oxycodone also produced mild cognitive–psychomotor impairment, as evidenced by fewer symbols drawn on the Digit Symbol Substitution Test (Wechsler, 1958) and fewer statements completed on a logical reasoning test (Baddeley, 1968). It is not known, however, if the drug also impairs performance on measures of impulsivity or self-control.

The term "impulsive" is defined as a range of maladaptive behaviors including an inability to inhibit inappropriate behaviors, risk taking, or a relative insensitivity to negative consequences, particularly delayed or uncertain negative consequences or rewards (Ainslie, 1975; Logan and Cowan, 1984; Mischel et al., 1989; Rachlin and Green, 1972). These behaviors have been operationally defined and assessed using standardized quantifiable tasks. Using these tasks (see below) it has been reported that drug users, including smokers, abstinent alcoholics and opiate users, are more impulsive than nonusers (e.g., Kirby et al., 1999; Madden et al., 1997; Mitchell, 1999; Mitchell et al., 2005). Recent evidence suggests that some CNS-active drugs, such as amphetamine, decrease certain indices of impulsive behavior (de Wit et al., 2000, 2002), while other drugs including alcohol, diazepam and delta-9-tetrahydrocannabinol (THC) increase impulsive behaviors (Acheson et al., 2006; de Wit et al., 2000; McDonald et al., 2003).

No studies that we are aware of have examined the effects of opioids on measures of impulsivity in humans. However, preclinical studies suggest that opioids increase impulsive behaviors. Three studies using rats have shown that acute administration of opioids increased impulsive behaviors, as measured by either a reduced choice of a larger delayed reward over a small immediate reward in a delay discounting test (Kieres et al., 2004; Pattij et al., 2009; Pitts and McKinney, 2005) or a decreased ability to withhold inappropriate responses on a choice serial reaction time test (Pattij et al., 2009).

In the present study, we examined the direct effects of oral oxycodone on impulsivity in volunteers without a history of opioid abuse. We selected several standardized measures of impulsivity, including delay discounting, which is a measure of the value of immediate versus delayed rewards, probability discounting, which is a measure of the relative value of certain versus uncertain rewards, the Stop Task and a Go/No-go task, which are measures of the ability

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to inhibit prepotent motoric responses and inappropriate responses, respectively, the balloon analogue risk task (BART), which is a measure of risk taking and finally, a measure of lapses of attention based on a simple reaction time task. Based on the preclinical studies described above and the clinical data with opioid abusers (Kirby et al., 1999; Madden et al., 1997), we hypothesized that oral oxycodone would increase impulsivity on each of these measures.

2. Methods

2.1. Subjects

Requirements for participation in this IRB-approved study included age between 21 and 39 years, a high school diploma or the equivalent, verbal fluency in English, and some current level of alcohol use. Exclusion criteria included total abstention from drugs, a history of Substance Abuse or Dependence (American Psychiatric Association, 2000), or any significant medical conditions. Qualifying subjects provided written informed consent. The subject population consisted of six males and six females, with a mean age (±SD) of 25.3 (3.6) years. In the last 30 days all subjects reported drinking alcohol (average of 3.3 ± 1.7 drinks per week); 3 of the 12 smoked tobacco cigarettes, although none of these smoked more than 5 cigarettes a day; and 3 of the 12 used marijuana, although none smoked more than two joints per week. Six subjects reported having been prescribed opioids (reported as Tylenol-3/Codeine [three subjects reported using 1–9 times, two reported using 10–50 times], Darvon/Darvocet [one subject reported using 1–9 times], and Vicodin or Lortab [three subjects reported using 1–9 times]). No subject reported non-medical use of prescription opioids.

2.2. Design, drugs, and procedures

This randomized, placebo-controlled, double-blind, crossover trial consisted of four sessions. On the four sessions subjects ingested capsules containing 0 mg (milk lactose), 5 mg, 10 mg, and 20 mg of immediate-release oxycodone (Mallinckrodt, Inc., St. Louis, MO). Doses of 5 and 10 mg are within the therapeutic dose range, and 20 mg is supratherapeutic, but within the range of doses that might be used by drug abusers. The experiment took place in a laboratory located in a hospital, and an anesthetist was present at all times during the sessions. Experimental sessions were separated by at least seven days, and took place from 0830 to 1430 h. Subjects were instructed not to eat food or drink non-clear liquids for 4 h, not to drink clear liquids for 2 h, and not to use any drugs (including alcohol, marijuana, over-the-counter drugs, and prescription drugs, but excluding normal amounts of caffeine and nicotine) 24 h prior to sessions. In the consent form, subjects were informed that they would be ingesting capsules that might contain "a sedative/tranquilizer (for example, Valium®), stimulant (for example, amphetamine or speed), opiate (for example, morphine), non-prescription pain relievers (for example, Tylenol®, also known as acetaminophen, Motrin®, also known as ibuprofen, and aspirin), or placebo (no active drug at all)."

Upon arrival for each session, participants signed a compliance form stating that they had complied with the eating and drug restrictions, and provided a urine sample for pregnancy (women) and toxicology (QuikScreen, Syntron Bioresearch, Carlsbad, CA). Urines were tested for the presence of amphetamines, barbiturates, benzodiazepines, cocaine metabolites, opiates, and phencyclidine. Breath alcohol was also measured.

After the drug screening, subjects remained in a semi-recumbent position in a hospital bed for the remainder of the session. First, they completed subjective effects questionnaires, and their respiration and heart rate, arterial oxygen hemoglobin saturation rate (measured by a non-invasive pulse oximeter on the non-dominant hand), and blood pressure (measured using the dominant arm) were monitored. After these baseline measures an anesthetist watched the subject swallow the capsules with 150 ml of water. Neither the technician nor the anesthetist monitoring the sessions was aware of which drug or dose was being administered on any particular session. At periodic intervals after ingestion of the capsules, mood and physiological status were assessed. At 70 min post-capsule ingestion, subjects completed the impulsivity tests (see below). The impulsivity tests took approximately 50 min to complete. The period of testing, from 70 to 120 min post-drug ingestion, was based on the estimated t_{max} of the drug; the estimated time at which peak plasma concentrations of oxycodone occur after oral administration is 60–84 min (Lalovic et al., 2006; Mandema et al., 1996; Poyhia et al., 1992). Thus, impulsivity-related measures coincided with peak oxycodone plasma levels.

2.3. Dependent measures

2.3.1. Subjective and physiological measures

Subjective and physiological measures were obtained at regular intervals (i.e., at baseline and either every 30 min or on the hour after capsule administration). Subjective effects were measured by five forms: a computerized, short form of the Addiction Research Center Inventory (ARCI) (Haertzen, 1966; Martin et al., 1971), a locally developed 12-item opiate adjective rating scale (OARS) derived from two questionnaires sensitive to the somatic and subjective effects of opioids (Fraser et al., 1961; Preston et al., 1989), a locally developed 28-item visual analog scale (VAS), a Drug Effect/Drug Liking/Take Again (DEL/TA) questionnaire, and a locally developed 20-item post-session sequelae questionnaire that assessed residual effects of the drug that subjects were asked to complete 24 h after the session. The DEL/TA assessed the extent to which subjects currently felt a drug effect on a scale of 1 (I feel no effect from it at all) to 5 (I feel a very strong effect); assessed drug liking and disliking on a 100-mm line (0 mm = dislike a lot; 50 mm = neutral; 100 mm = like a lot); and assessed how much subjects "would want to take the drug you received today again on another session, if given the opportunity" on a 100-mm line [0 mm = definitely would not; 50 mm = neutral (don't care); 100 mm = definitely would]. Physiological effects measured were pupil constriction, exophoria (tendency of visual axes to diverge outwards), arterial oxygen hemoglobin saturation rate, respiration rate, heart rate, and blood pressure.

2.3.2. Impulsivity tasks

Four of the five behavioral measures of impulsivity were administered in random order, both within and between subjects, across the four sessions. The Go/No-Go test was always administered last.

2.3.2.1. Delay and probability discounting task (DPD; Richards et al., 1999). The DPD measures the discounting or de-evaluation of rewards by delay and probability (uncertainty). Participants have the opportunity to choose between different amounts of money available after varying delays or probabilities. The test consists of about 100 questions, such as: (1) Would you rather have $10.00 in 30 days or $2.00 at the end of the session, or (2) Would you rather have $5.00 for sure or $10.00 with a 25% chance? The task uses an adjusting amount procedure (Richards et al., 1999) to derive an indifference point at which the delayed and immediate options (for delay discounting) or probabilistic and certain options (for probability discounting) are judged to be of equivalent subjective value for a respondent. The obtained delay and probability indifference points are then plotted to form two separate discount functions. An area under the curve (AUC; Myerson et al., 2001) was calculated for each discount function for each session for each subject. AUC values could range from 1 (no discounting) to 0 (maximum discounting). At the end of the session, one of the choices subjects made during the session was selected at random, and the subjects received whatever they chose in response to the selected question. If for that question, subjects chose an immediate amount of money, they received

the money in cash at the end of the session. If subjects selected delayed money, the money was placed in an envelope with their name and forwarding address on it (in the event they moved during the interval between the last session and the scheduled time for their monetary reward), and the money was sent to them after that amount of time had elapsed. If subjects selected a probabilistic amount, they drew a token from a bag containing two colors of tokens in the proportion that reflected the probability, and they received the amount of money indicated by the color of the token in cash at the end of the session.

2.3.2.2. Balloon analogue risk task (BART; Lejuez et al., 2002). The BART is a measure of risk taking in which participants could earn or lose points redeemable for money. Participants "pumped up" a balloon presented on a screen by clicking a computerized mouse. For each pump, a counter on the screen increased by a certain amount of money (1, 5, or 25 cents). After an unpredictable number of "pumps," the balloon could "explode," resulting in a loss of the money accumulated on the counter. Participants could stop pumping at any time and bank their accumulated money. Once completed, the test calculated participants' total earnings for all 30 balloons (10 balloons per monetary amount) and displayed the reward amount on the screen. Participants received their earnings from this task at the end of the session. Participants who emit more pumps are considered to be more impulsive.

2.3.2.3. Go/no-go task (Newman et al., 1985). The go/no-go task is a learning task designed to assess participants' ability to inhibit inappropriate responses. It consisted of repeated presentations of eight two-digit numbers, of which four were designated "correct" and four "incorrect." A different list of numbers was used for each session. Participants were required to respond to correct numbers, and withhold responses to incorrect numbers. They were rewarded for correct responses (+10 cents) and penalized for incorrect responses (−10 cents). Errors of omission (withholding a response when a correct stimulus is presented) and errors of commission/false alarms (responding to an incorrect stimulus) were recorded, and the total amount earned was displayed on the screen at the end of the task. Errors of commission were the primary measure of impulsivity in this task (Hamidovic et al., 2008). Participants received their earnings at the end of the session.

2.3.2.4. Stop task (Logan et al., 1997). The stop task is designed to assess the ability to inhibit a prepotent motoric response. Participants were instructed to respond as quickly as possible when a certain letter (go signal) appeared on a computer screen, and to inhibit their responses when a tone was heard (stop signal). The tone was presented on random trials and at different delays following the letter presentation. The delays to the stop signal were adjusted until the participant inhibited his or her responses on approximately 50% of trials. At this 50% criterion, the stop reaction time was calculated by subtracting the final mean delay at which the tone was presented from the mean go reaction time. Both go and stop reaction times were measured in milliseconds. Stop reaction time was the measure of impulsivity in this task (de Wit, 2008).

2.3.2.5. Simple reaction time test (Bleiberg et al., 2000). This test detects lapses in attention, which is thought to be related to impulsive behavior. A large asterisk-like symbol appeared on the monitor screen at variable time intervals, and subjects were instructed to press a mouse button as quickly as possible when the asterisk appeared. There were 100 trials on this task. Analysis involved determining the mean, estimated mode and deviation from the mode for reaction times of the 100 trials to distinguish drug effects on psychomotor speed from lapses in attention. Trials in which subjects failed to respond to the stimulus were assigned a value of 1500 ms, the maximum duration of the visual stimulus. The estimated mode was determined by grouping the reaction times in 10 ms bins and computing a running frequency for each bin. The midpoint of the 10 ms bin with the highest frequency of response times was considered the mode. The deviation from the mode was determined by subtracting the estimated mode from the mean of the reaction times. Large deviations from the mode are considered to be lapses in attention, indicative of impulsivity (de Wit, 2008).

2.4. Personality questionnaire

Subjects were instructed to complete the Barratt Impulsiveness Scale-11 (BIS-11; Patton et al., 1995) at least 24 h following the final experimental session. The BIS-11 is used to assess impulsivity as a personality trait, and consists of 30 statements (e.g., I plan trips well ahead of time) to which subjects respond by choosing one of the following responses: rarely/never, occasionally, often, and almost always, which correspond to scores of 1, 2, 3, and 4, respectively. Total maximum score is 120, and scores of 52–71 are considered within the range of normal impulsiveness (Stanford et al., 2009).

2.5. Data analysis

Repeated measures analysis of variance (ANOVA) was used for statistical treatment of the data. Sigma Stat (Point Richmond, CA) was used to analyze peak or trough subjective and physiological effects (excluding the baseline time point) of the four drug conditions. SPSS (Version 16.0, Chicago, IL) was used to analyze data from the impulsivity tests.

3. Results

3.1. Subjective and physiological effects

Oxycodone produced subjective and physiological effects typical of this drug in healthy volunteers (Zacny and Gutierrez, 2003; Zacny and Lichtor, 2008). These effects tended to be dose-related and are summarized in Table 1. Although trough drug liking and "take again" ratings were significantly lower in the 20-mg oxycodone condition relative to placebo, there was considerable variability with these measures: five of the subjects had markedly lower ratings in the oxycodone condition (i.e., close to 0 mm on the 100-mm line), and six subjects had ratings similar to that of placebo.

3.2. Impulsivity tests

Data from some subjects are not included on three of the five impulsivity tasks. On the Go/No-Go task, data were lost from four subjects due to experimenter error (one subject) or equipment malfunctions (three subjects) on one or more sessions. On the Stop task, data from two subjects were not included in the go and stop reaction time analysis because they discriminated the two go signals less than 75% of the time on one or more sessions (i.e., they failed to meet accuracy criteria). Data from another three subjects were not included in the stop reaction time analysis because their delay times (used to calculate stop reaction times) were considered aberrant on one or more sessions. On the simple reaction time test, five subjects' data were not usable on one or more sessions.

Of those subjects that did have evaluable data, oxycodone did not significantly alter performance on any of the impulsivity measures. Mean data from the five impulsivity tests are shown in Table 2. There were no discernible trends of an effect of oxycodone on the DPD, BART, or simple reaction time tasks. On the Go/No-Go task, there was a trend for the drug (20 mg) to increase errors of omission and commission relative to placebo, although there was wide variability among subjects (e.g., errors of commission increased in four subjects and were unaffected in four). There was also a trend for oxycodone

Table 1
Mean peak or trough (±SEM) values of representative measures significantly affected by one or more of the oxycodone conditions relative to placebo.[a]

	Placebo	5 mg OXY	10 mg OXY	20 mg OXY
ARCI				
BG[b]	4.3 (0.5)	3.3 (0.4)	2.3 (0.6)[c]	1.6 (0.5)[c]
Visual analog scale[d]				
Difficulty concentrating	14.3 (7.7)	23.0 (9.0)	26.8 (7.4)	56.8 (12.1)[c]
Dizzy	1.8 (1.1)	11.6 (8.4)	24.4 (10.1)	35.6 (12.7)[c]
Dreamy	13.8 (6.2)	15.0 (3.6)	28.9 (9.8)	42.7 (8.3)[c]
Having unpleasant bodily sensations	2.7 (1.3)	14.8 (7.8)	30.8 (10.5)[c]	35.1 (11.1)[c]
Heavy or sluggish feeling	20.1 (6.4)	33.7 (9.7)	51.5 (11.2)[c]	70.4 (8.8)[c]
High (drug 'high')	3.8 (2.5)	9.7 (4.4)	24.9 (9.4)	34.7 (9.7)[c]
Nauseated	0.8 (0.3)	12.2 (8.6)	26.6 (10.7)	31.9 (11.8)[c]
Sleepy (drowsy, tired)	48.2 (11.1)	52.0 (10.7)	66.7 (9.0)[c]	76.5 (6.8)[c]
Opiate adjective rating scale[e]				
Dry mouth	0.3 (0.2)	0.3 (0.3)	1.1 (0.3)	1.2 (0.4)[c]
Nodding	0.3 (0.2)	1.2 (0.4)	0.8 (0.3)	1.8 (0.5)[c]
Skin itchy	0.3 (0.2)	0.4 (0.1)	0.9 (0.4)	1.4 (0.3)[c]
DEL/TA				
Feel drug[f]	1.8 (0.3)	2.8 (0.3)[c]	3.1 (0.3)[c]	3.8 (0.3)[c]
Like drug[b,g]	47.3 (0.8)	39.3 (5.0)	36.4 (5.6)	29.0 (6.4)[c]
Take again[b,h]	50.2 (0.5)	39.5 (5.4)	37.3 (6.2)	29.8 (6.5)[c]
Pupil size (mm)[b]	5.7 (0.4)	4.9 (0.3)[c]	4.3 (0.3)[c]	3.6 (0.3)[c]
Exophoria (prism diopters)	4.8 (1.0)	5.3 (1.3)	5.3 (1.5)	7.6 (1.4)[c]

OXY = oxycodone; ARCI = Addiction Research Center Inventory; BG = Benzedrine Group scale (Benzedrine-like effects, intellectual efficiency, and energy); DEL/TA = Drug effect/Drug liking/Take again scale.

[a] Except where otherwise noted, all measures are peak measures.

[b] trough measure.

[c] Peak/trough analyses: Holm-Sidek post hoc analysis determined significant difference from placebo.

[d] range: 0 = not at all, 100 = extremely.

[e] range: 0–4, 0 = not at all, 4 = extremely.

[f] Feel drug effect range: 1–5, 1 = I feel no effect from it at all, 5 = I feel a very strong effect.

[g] Drug liking range: 0 = dislike a lot, 50 = neutral, 100 = like a lot.

[h] Take again range: 0 = definitely would not, 50 = don't care, 100 = definitely would.

Table 2
Mean (±SEM) scores on the impulsivity tasks as a function of oxycodone dose.

	Placebo	5 mg OXY	10 mg OXY	20 mg OXY
Delay discounting ($n=12$)				
AUC	0.34 (0.08)	0.32 (0.08)	0.34 (0.08)	0.34 (0.08)
Probability discounting ($n=12$)				
AUC	0.47 (0.06)	0.50 (0.05)	0.46 (0.05)	0.49 (0.06)
BART ($n=12$)				
Mean adjusted average number of pumps[a]	38.4 (4.6)	40.7 (3.8)	36.0 (3.6)	38.4 (4.0)
Go/No-Go ($n=8$)[b]				
Errors of omission	0.9 (1.7)	1.1 (0.6)	0.8 (0.3)	3.1 (1.5)
Errors of commission	4.1 (1.9)	6.5 (3.6)	5.6 (2.2)	7.5 (2.0)
Stop task				
Go reaction time (ms) ($n=10$)[c]	700.2 (40.6)	710.3 (45.2)	672.5 (46.1)	728.7 (26.7)
Stop reaction time (ms) ($n=7$)[d]	184.9 (18.4)	184.6 (18.9)	185.5 (20.0)	224.5 (23.7)
Simple reaction time ($n=7$)[e]				
Mean reaction time (ms)	398.3 (16.8)	373.3 (26.1)	386.1 (34.6)	407.7 (34.8)
Log estimated mode reaction time (ms)	312.0 (11.7)	316.3 (18.4)	311.0 (16.7)	325.9 (15.8)
Deviation from estimated mode reaction time (ms)	86.3 (15.8)	57.1 (15.0)	75.1 (21.1)	81.9 (26.5)

The drug did not significantly change performance on any of these measures.

[a] Adjusted average number of pumps on the BART are averaged across all three monetary conditions (1, 5, and 25 cents).

[b] On the Go/No-Go task, four subjects' data were lost on one or more sessions due primarily to equipment malfunctioning.

[c] On the Go reaction time component of the Stop task, two subjects' data were excluded because they did not meet accuracy criteria.

[d] On the Stop reaction time component of the Stop task, five subjects' data were excluded because three had delay times (that are used to calculate Stop reaction time) that were considered aberrant, and two did not meet accuracy criteria.

[e] On the simple reaction time measures, five subjects' data were not usable on one or more sessions.

(20 mg) to increase go- and stop reaction times on the Stop task, relative to placebo, but again there was wide variability between subjects.

3.3. Personality data

One subject did not complete the questionnaire. The mean (±SD) score on the BIS-11 for the other 11 subjects was 62.5±14.7. This value is similar to the mean value reported by Stanford et al., 2009, using a comparable population, 62.3+10.3. Seven subjects scored within the "normal impulsiveness" range, and four subjects scored outside of the range (two above and two below). Visual inspection of data on the BART (a measure in which we had data from all subjects) comparing the outlier subjects to the other subjects did not reveal any noticeable differences in number of pumps (e.g., the high-impulsive outliers did not pump more than the other subjects).

4. Discussion

Oxycodone at doses at and beyond the therapeutic range for treatment of acute pain did not increase impulsive behavior on any of the standardized tasks. The subjective and physiological effects were dose-dependent, and typical of responses among healthy volunteers in previous studies (Zacny and Gutierrez, 2003, 2009; Zacny and Lichtor, 2008). Also, as noted in other opioid studies in which non-drug-abusing volunteers were subjects, there was considerable intersubject variability in ratings of liking and "take again" (e.g., Zacny et al., 1992; Zacny et al., 1994; Zacny and Gutierrez, 2003).

The present findings are not consistent with findings from studies with rats showing that morphine increased impulsive behavior in a delayed discounting test (Kieres et al., 2004; Pattij et al., 2009; Pitts and McKinney, 2005). In the present study, oxycodone did not increase either delay or probability discounting. However, it is important to note that there are fundamental differences in delay discounting tasks used in humans and nonhumans, raising the possibilities that the tasks measure different underlying behaviors in clinical and preclinical models (Tesch and Sanfey, 2008). For example, in the procedures used in animals, the decisions about rewards and the consequences of the decisions (immediate or delayed delivery of the reward) occur while the animal is in the drugged state whereas in the human version of the task, subjects are required to make decisions about rewards that will be obtained after the drug's effects have dissipated. Moreover, although the delay discounting tasks in humans are sensitive as measures of individual differences, they may not be sensitive to state changes in impulsivity, such as the state changes expected with acute drug effects (de Wit and Mitchell, in press). For example, acute administration of alcohol, stimulants, THC, and benzodiazepines failed to alter delay discounting in healthy volunteers (Acheson et al., 2006; Acheson and de Wit, 2008; de Wit et al., 2000; McDonald et al., 2003; Reynolds et al., 2004). The same problem of possible insensitivity to the effects of acute drug administration may exist with the BART (Acheson et al., 2006; Hamidovic et al., 2008; Reynolds et al., 2004; Reynolds et al., 2006).

It is also possible that the differences between the rat studies and the present studies are due to the drug tested (i.e., oxycodone versus morphine). Although there are several preclinical studies in rats that suggest oxycodone has agonist activity at the kappa opioid receptor (Nielsen et al., 2007; Ross and Smith, 1997; Ross et al., 2000), the preponderance of both animal and human data indicate that

oxycodone and morphine produce similar pharmacological, psychopharmacological, and analgesic effects, mediated by the mu receptor (Beardsley et al., 2004; Comer et al., 2008; Deneau and Seevers, 1957; Grach et al., 2004; Heiskanen and Kalso, 1997; Kalso, 2007; Ladd et al., 2005; Zacny and Lichtor, 2008).

In the present study, oxycodone also did not affect performance on the Stop Task. Unlike the delay discounting task, the Stop Task does appear to be sensitive to acute drug effects in humans. Ethanol and THC increased, whereas *d*-amphetamine decreased, Stop reaction time (de Wit et al., 2000, 2002; McDonald et al., 2003; Reynolds et al., 2006). Notably, however, a preclinical study reported that morphine did not affect reaction time in a stop signal task that is analogous to the Stop reaction task (Pattij et al., 2009). Thus, the failure to detect impairment in behavioral inhibition on the Stop Task in the present study is consistent with the single animal study addressing this issue, and thus may truly reflect a lack of effect of opioid drugs on this behavior.

The present study had both strengths and limitations. Strengths included testing multiple doses of oxycodone, including doses that are typically prescribed for acute pain, and a dose that was supratherapeutic. Rather than relying on one test, five tests were used that putatively tap into separate underlying processes that mediate the multidimensional construct of impulsivity (de Wit, 2008). Although 12 subjects were enrolled in the study, some of the impulsivity data were lost or not usable, limiting the sample size. Moreover, there was substantial intersubject variability on both the behavioral and subjective measures. Nevertheless, the partial data that were available did not strongly support the idea that the drug would increase impulsive behaviors in a larger sample. A possible future direction might be to examine the relationships between the mood-altering effects of the drug and its effects on impulsive behaviors, in a larger sample of volunteers. For example, it may be the case that subjects who report primarily positive effects from oxycodone may behave differently on the impulsivity tasks than those who report primarily negative effects from the drug. Another future direction might be to assess the effects of oxycodone or other opioids in people who are using opioids on a chronic basis, either for medical or non-medical purposes. The results of this study suggest, however, that opioids, in the doses prescribed for acute pain, are unlikely to increase impulsive or risky behaviors in most patients, adding to the existing literature that they are generally safe as well as effective.

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