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Psychopharmacological Effects of Oxycodone in Healthy Volunteers: Roles of Alcohol-Drinking Status and Sex

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Abstract

Background—Studies have shown that alcohol-drinking status modulates psychopharmacological effects of several drugs. We sought to determine if drinking status modulates the effects of a prescription opioid, oxycodone, in healthy volunteers. We included sex of the volunteer in the statistical analyses since this is a factor that is known to alter several pharmacodynamic effects of opioids in nonhumans and humans.

Methods—Fifteen light drinkers (eight males) and 14 moderate drinkers (eight males) participated in a crossover, randomized, double-blind study in which they received 0, 10, and 20 mg of oxycodone (p.o.). Dependent measures were subjective, psychomotor/cognitive, reinforcing, and physiological effects.

Results—Self-reported alcohol drinking status did not modulate the effects of oxycodone. However, there were a number of Sex × Dose interactions with females reporting more and larger unpleasant effects than males (e.g., visual analog scale ratings of “nauseated” greater in females than in males).

Conclusions—Studies have established that moderate drinkers report a greater degree of abuse liability-related effects than do light drinkers with several different drugs, including diazepam, amphetamine, and nitrous oxide, but we were unable to establish this with the prescription opioid, oxycodone. However, we did observe sex differences in several subjective effects of oxycodone, a finding that is consistent with the extant literature showing sex differences in pharmacodynamic effects of opioids.

Keywords

Oxycodone; Opioid; Prescription; Alcohol; Subjective effects; Psychomotor; Multiple-Choice Procedure; Sex differences; Gender; Human

1. Introduction

Nonmedical use of prescription opioids has been a serious problem in the United States over the last decade and has caused a great deal of concern amongst law enforcement officials, medical, regulatory, pain relief advocacy, and drug abuse organizations, as well as the general

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public (Birnbaum et al., 2006; Compton and Volkow, 2006; Wright et al., 2006; Zacny et al., 2003). The 2008 National Survey on Drug Use and Health (NSDUH) documented that the percentage of people aged 12 years and older who had used prescription opioids for nonmedical purposes in the prior 12 months was 4.8% [Substance Abuse and Mental Health Services Administration (SAMHSA), 2009]. This past-year prevalence rate was greater than that of cocaine, hallucinogens and inhalants and was only exceeded by marijuana (10.3%). There have been a number of studies that have sought to determine what demographic and clinical characteristics are associated with nonmedical use of prescription opioids, and it has been established that heavy alcohol use (including binge drinking) and alcohol use disorders are two such characteristics (Becker et al., 2008; Boyd et al., 2006; Huang et al., 2006; McCabe et al., 2005, 2006, 2007; Novak et al., 2009; Tetrault et al., 2007). The 2007 NSDUH survey reported that heavy drinkers (defined as five or more drinks on the same occasion on each of five days in the last 30 days) are more likely to use prescription opioids for nonmedical purposes than are lighter drinkers or non-drinkers (SAMHSA, 2008a [Table 7.11b]). It is conceivable that abuse liability-related effects (e.g., positive subjective effects, reinforcing effects) of prescription opioids are of greater magnitude in heavier drinkers than in lighter drinkers, but this has not been explored to our knowledge. Other studies have established that abuse liability-related effects of diazepam, *d*-amphetamine, alcohol itself, and two inhaled general anesthetics at subanesthetic concentrations, nitrous oxide and sevoflurane, are greater in moderate drinkers compared to light drinkers (de Wit et al, 1989; de Wit and Doty, 1994; Evans et al., 1996; Evans and Levin, 2004; Stoops et al., 2003; Zacny et al., 2008ab).

The present study examined psychopharmacological effects of a prescription opioid, oxycodone, in light and moderate drinkers. Measures that were studied included subjective, psychomotor/cognitive, reinforcing (as measured by the Multiple-Choice Procedure [Griffiths et al., 1993]), and physiological effects. Oxycodone is available in prescription form as a single entity product in either immediate or controlled release form, or combined with other analgesics (e.g., acetaminophen). Oxycodone is one of the more widely abused prescription opioids (Cicero et al, 2005; Gilson et al., 2004: SAMHSA 2008b [Table 1.89B]). 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). Oral oxycodone has abuse liability in opioid abusers (Epstein et al., 2006; Walsh et al., 2008). Given the fact that people who are moderate drinkers react more positively to a number of different abused drugs, and given the epidemiological data cited above linking alcohol use to nonmedical use of prescription opioids, we hypothesized that moderate drinkers would show greater abuse liability-related effects of oxycodone than would light drinkers. Because we had approximately the same number of males and females in each group, we also included sex into the statistical analyses. There are numerous studies demonstrating sex differences in several pharmacodynamic effects of opioids in both nonhumans and humans, including analgesia, respiratory depression, and self-administration (Craft, 2003, 2008; Dahan et al., 2008; Fillingim and Gear, 2004; Kest et al., 2000; Lynch et al., 2002).

2. Methods

2.1. Participants

The local Institutional Review Board approved the study. Prior to study participation, volunteers provided informed written consent and underwent a semi-structured psychiatric interview and medical examination. To be eligible for the study, subjects had to 1) be between the ages of 21-39, 2) have a body mass index between 18 and 27, 3) be verbally fluent in English, 4) have obtained a high school diploma or equivalent, and 5) have some level of current recreational drug use. Light drinkers (LDs) had to meet the following two criteria: 1) consume at least one but no more than four drinks/month and 2) drink two or fewer drinks/occasion.

Moderate drinkers (MDs) had to meet two or more of the following criteria (Evans et al., 1996; Stoops et al., 2003): 1) ingest at least seven drinks/week, 2) drink at least three drinks/occasion at least once/week, and/or 3) consume alcohol at least four days/week. Subjects were excluded if 1) they had any medical problems or a history of Axis-I psychiatric disorders, including drug- or alcohol-related disorders, as defined by the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) (American Psychiatric Association, 2000), 2) reported smoking more than 5 cigarettes a day, or 3) reported consuming more than 20 alcoholic drinks a week. As part of the screening process, prospective subjects completed the Michigan Alcoholism Screening Test (MAST) (Selzer 1971).

2.2. Design, drugs and procedures

This randomized, placebo-controlled, double-blind, crossover trial consisted of four sessions. On the first three sessions subjects ingested capsules containing 0 mg (milk lactose), 10 mg, and 20 mg of immediate-release oxycodone, in randomized order (Mallinckrodt, Inc., St. Louis, MO). The 10 mg dose is at the higher range for therapeutic use, and 20 mg is supratherapeutic.

The procedures of this study, as well as the dependent measures and the time points at which the measures were assessed, are similar to those of a study previously published (Zacny and Gutierrez, 2009). Briefly, 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 0845-1430 h. Upon arrival for each session, participants blew into a breathylyzer, and delivered a urine sample for pregnancy (women) and toxicology (QuikScreen, Syntron Bioresearch, Carlsbad, CA) screening; tests had to be negative for the session to proceed. After the screening, subjects remained in a semi-recumbent position in a hospital bed for the remainder of the session. In the first three sessions, they completed subjective effects questionnaires, and their respiration and heart rate, arterial oxygen hemoglobin saturation rate, and blood pressure were monitored. After these baseline measures, subjects were told “the capsules you are about to ingest may or may not contain a drug,” and 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, cognitive/psychomotor performance, and physiological status were assessed.

For the fourth session (“Lottery Session”), volunteers were presented with a bowl containing 117 slips of paper (representing all of the choices they made on a Multiple-Choice Procedure form [see below] 24 hours after each of the first three sessions). Participants randomly selected one slip from among the 117 slips of paper at the beginning of the lottery session. If they selected a drug, baseline measurements of their vital signs were taken, capsules containing that drug were then administered, and their vital signs were monitored throughout the remainder of the session. No other testing occurred. If they selected a monetary amount, vital signs were not monitored and no testing occurred. Otherwise, the “Lottery Session” ran exactly as the first three sessions.

2.3. Dependent measures

2.3.1. Subjective effects—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 questionnaire 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]. Overall drug liking and overall "want to take drug again" were assessed at the end of each session on a modified version of the DEL/TA questionnaire (i.e., end-of-session DEL/TA). In addition, subjects were instructed to again rate their overall drug liking and overall "want to take drug again" 24 hours after completion of the session on another modified version of the DEL/TA questionnaire (i.e., post-session DEL/TA).

2.3.2. Multiple-Choice Procedure—The reinforcing effects of oxycodone were assessed using a modified version of the Multiple-Choice Procedure (Griffiths et al., 1993). The paper-and-pencil questionnaire consisted of 39 choices to receive the drug received in a session (e.g., "Receive Drug from Session 1") versus giving up or receiving a certain amount of money (ranging from "Give up $10" to "Receive $10"). Participants were required to circle either drug or money for each independent choice. The reinforcing value of the drug was defined as the monetary amount (negative or positive) when the subject switched from choosing drug to choosing to receive or give up a certain amount of money (i.e., crossover point). Subjects were instructed to complete the Multiple-Choice Procedure form 24 h following each of the first three sessions. At the beginning of the fourth ("lottery") session, to provide intermittent reinforcement of drug vs. money choices made on the previous sessions, the participant randomly selected from among his/her 117 choices (39 choices × 3 experimental sessions), with each choice on a slip of paper. Subjects selecting a drug during the lottery session received that drug, and subjects selecting a monetary amount had that amount added to or subtracted from their participation payment and did not receive any drug during the lottery session. The Multiple-Choice Procedure is a novel way of assessing the reinforcing effects of drugs, and its advantages (e.g., limiting drug exposure to volunteers) as well as disadvantages (e.g., substantial delay between when a choice is made and when the consequences of that choice are delivered) have been discussed in a recent review article on human self-administration procedures (Comer et al., 2008).

2.3.3. Psychomotor/cognitive performance and physiological measures—Performance was measured with five tests: an eye-hand coordination test (Nuotto and Korttila, 1991), the Digit Symbol Substitution Test (DSST) (Wechsler, 1958), an auditory reaction test (Nuotto and Korttila, 1991), a logical reasoning test (Baddeley, 1968), and a locally developed recall memory test. Six physiological measures were assessed: heart rate, blood pressure, arterial oxygen saturation, respiration rate, exophoria, and pupil size. Pupil size was measured with a commercial pupillometer (Neuroptics, San Clemente, CA).

2.4. Statistical analyses

Descriptive summaries of demographic characteristics, weight, BMI, and alcohol and drug use are reported as a function of alcohol-drinking status. Differences between light and moderate drinkers were tested using Student's two-sample t-test for continuous variables and Fisher's exact test for categorical variables. Although the difference in mean drinks per week was tested, this measure of current alcohol use differed between groups by definition.

Effects of drinking status (i.e., Group), Sex, and oxycodone dose on subjective, psychomotor/cognitive, reinforcing and physiological measures were tested using repeated measures analysis of covariance (ANCOVA), adjusting for subjects' body weight. Analyses were done on peak (highest value obtained), trough (lowest value obtained), or mean effects. In the peak and trough analyses, only post-capsule administration values were included, and values were

determined for each subject independent of time point. Weight was included as a covariate due to a significant weight difference between light and moderate drinkers. This adjustment allows for interpretation of drinking group effects holding body weight constant, conditional on substantial overlap in the body weight distributions for the two groups, which did occur. Post-hoc testing of specific contrasts and estimation of adjusted means was conducted using repeated measures linear regression models with subject entered as a random effect. These models are equivalent to the ANCOVA models except that interaction terms identified as non-significant in the ANCOVA were omitted. Adjusted means, with 95% confidence intervals, were calculated for each Sex × Dose category as linear combinations of regression parameters at the mean body weights for males and for females.

Due to the low occurrence of vomiting as reported on the OARS, which had positive ratings in 16 of 87 sessions, this variable was dichotomized as "any" versus "none". Effects of drinking group, sex and body weight on vomiting were evaluated using logistic regression, with one observation per subject. Additional comparisons between each pair of drug levels were made using the McNemar exact test. Repeated measures logistic regression was used to assess the effect of drinking status, sex, and oxycodone dose on post-session ratings of subjective effects, which were dichotomized as "any" versus "none," due to marked skewness of their distributions.

Analyses were conducted in Stata/SE 10.1 (Stata Corporation, College Station, TX: StataCorp LP; 2007).

3.0. Results

Table 1 presents demographics of the subjects as a function of self-reported drinking status. There were a number of differences between the two groups, including weight, race, scores on the MAST, and self-reported drug use. MDs on average weighed more than LDs, were all Caucasian, reported higher scores on the MAST (although below the MAST criteria indicative of alcoholism, i.e., a score of five or more), and reported heavier current use of caffeinated beverages, and by definition, alcohol. MDs also reported heavier lifetime use of marijuana, and more MDs reported lifetime use of stimulants and hallucinogens than did LDs.

In general, alcohol-drinking status (i.e., Group) did not modulate the effects of oxycodone, although dose effects did vary with drinking group and sex for a few isolated outcomes. Significant Group × Sex × Dose interactions occurred with VAS ratings of "drunk," post-session DEL/TA ratings of overall "take again," and the post-session monetary crossover point in the Multiple-Choice Procedure. Female MDs reported higher ratings of feeling drunk at the higher oxycodone dose compared to the lower dose or placebo; a similar association was observed in male LDs but did not reach statistical significance ($p=0.06$). On the post-session DEL/TA questionnaire, male LDs had lower overall "take again" ratings at the higher compared to lower oxycodone dose ($p=0.02$) and marginally lower compared to placebo ($p=0.06$); a similar, nonsignificant association was observed in female MDs ($p=0.11$). Among female LDs, the monetary crossover point was lower at either oxycodone dose compared to placebo – they were willing to give up (negative mean crossover point) more money in the 10- and 20-mg oxycodone conditions not to receive drug than in the placebo condition. Female MDs and male LDs showed similar, but non-significant, effects ($p=0.09$); no association of crossover point with oxycodone dose was apparent among male MDs. None of the two-way interactions between dose, sex, and group were statistically significant for these outcomes.

In contrast to the few and disparate effects of drinking status on oxycodone effects within sex, there were a number of significant Sex × Dose interactions, and these are shown in Table 2. All were subjective effects and in general the effects could be considered dysphoric in nature.

Several of these dysphoric effects (dizzy, feel bad, nauseated, turning of stomach, unpleasant bodily sensations) were reported only by females. Effects that were reported by both sexes were considerably greater in magnitude among females. During the sessions, oxycodone was associated with dislike of the drug and desire not to take it again for both males and females, but at the end of sessions, only females continued to make this distinction. The Sex × Dose interaction of end-of-session ratings of "take again" approached significance ($p=0.10$) with a similar pattern of response. Additionally, ratings of drug dislike on the post-session DEL/TA questionnaire were significantly greater among females and at the higher drug dose (not shown). For almost all of these effects, the gender difference was statistically significant at the 20 mg oxycodone dose; the difference was also significant at 10 mg for scores on the LSD scale of the ARCI, and within-session and end-of-session DEL/TA ratings of drug liking, and desire to take drug again.

Any instance of vomiting, as reported on the OARS was infrequent, occurring six times at 10 mg and ten times at 20 mg oxycodone; the difference between the 10 and 20 mg doses was not statistically significant by the exact McNemar test, but the frequency at both active doses differed significantly from no occurrences during placebo sessions. More females than males reported vomiting, as measured by the OARS (62% versus 19%, $p=0.03$ unadjusted for weight).

Oxycodone produced a number of subjective effects that varied significantly with dose, but did not differ by sex or drinking status. Notably, both doses of oxycodone relative to placebo increased the following abuse liability-related (positive) subjective effects - peak VAS ratings of "elated (very happy)" and "pleasant bodily sensations" and DEL/TA ratings of peak liking and "take again." Examples of other subjective effects increased by one or both doses of oxycodone included ARCI peak scores on the A and PCAG scales, VAS peak ratings of "coasting (spaced out)," "high," "sedated (calm, tranquil)," "and sleepy (drowsy, tired)," and OARS peak ratings of "dry mouth," "flushing," "nodding," and "skin itchy." On the post-session sequelae questionnaire, subjects reported a higher incidence of headache with either dose of oxycodone compared to placebo, and a higher incidence of drowsiness and lower incidence of feeling good at the 20 mg dose.

Three psychomotor/cognitive tests and four physiological measures were affected by oxycodone. Performance on the DSST was reduced by both doses of oxycodone in a dose-related manner; only the higher dose of oxycodone impaired eye-hand coordination and short-term and long-term memory recall. Pupil size and heart rate were decreased, and exophoria was increased by both doses of oxycodone; arterial oxygen saturation was decreased by the 20 mg dose.

4.0. Discussion

There were two major findings in this study. Alcohol-drinking status did not modulate the subjective, reinforcing (as measured by the Multiple-Choice Procedure), psychomotor/cognitive, or physiological effects of the prescription opioid, oxycodone. In particular, abuse liability-related effects were not affected. In contrast, sex of the subject did have an effect on the subjective effects of oxycodone. Although both males and females reported dysphoric effects from oxycodone, females reported larger effects (i.e., greater magnitude) and more effects.

The finding that alcohol-drinking status did not modulate the abuse liability-related effects of oxycodone is discordant with epidemiological studies establishing a link between nonmedical use and abuse of prescription opioids and heavy alcohol use (including binge drinking) and alcohol use disorders (Becker et al., 2008; Boyd et al., 2006; Huang et al., 2006; McCabe et al., 2005, 2006, 2007; Novak et al., 2009; Tetrault et al., 2007). However, the present study

did not examine responses from drinkers who had alcohol abuse disorders or who might be considered as heavy or problematic drinkers, so perhaps this might have accounted for the discordance. But the findings also stand in contrast to those studies that examined the effects of alcohol drinking status on amphetamine, diazepam, alcohol itself, sevoflurane and nitrous oxide, and found that MDs had greater abuse liability-related effects from these drugs than did LDs (de Wit et al, 1989; de Wit and Doty, 1994; Evans et al., 1996; Evans and Levin, 2004; Stoops et al., 2003; Zacny et al., 2008ab). In those studies similar criteria were used in defining moderate and light drinkers as that used in the present study. While MDs in the aforementioned studies either chose the drug more and/or were more likely to report abuse liability-related subjective effects than LDs, the LDs and MDs in the present study had peak liking ratings in the oxycodone conditions that were significantly elevated over those of placebo and that were similar in magnitude. Other subjective effects increased by oxycodone that might be considered positive in nature (pleasant bodily sensations, elated [very happy]) also did not differentiate the two groups.

There were a number of Sex × Dose interactions that showed a consistent pattern with females reporting larger dysphoric effects from oxycodone than males. One explanation could be that because males weighed more than did females in this study (M±SD: 72.9 (13.0) vs. 57.1 (8.5) kg, $p<0.001$), and oxycodone dose was not adjusted for body weight, females were getting a higher dose than males, which was aversive. However this explanation was ruled out because we included body weight into our statistical analyses, and with body weight factored in, sex still modulated the dysphoric effects of oxycodone.

We have conducted three prior studies in our laboratory with 10 and 20 mg of oxycodone (in one study acetaminophen was also co-administered), using an identical methodology to that used in the present study (Zacny and Gutierrez, 2003, 2009; Zacny and Lichtor, 2008). In each study we used an equal number of males (n=9-10) and females (n=9-10). We went back to those data and examined responses to oxycodone as a function of dose and sex, specifically looking at the peak rating of “nauseated” and the trough rating of “drug liking.” In those three studies, there were no significant or discernible differences between males and females at the 10 mg dose, or at the 20 mg dose in the Zacny and Gutierrez (2003) study. In the Zacny and Gutierrez (2009) study, nauseated ratings in the 20 mg oxycodone/975 mg acetaminophen condition were nearly twice as large in the females (44.1 mm) as in males (23.7 mm), but the difference was not statistically significant. However in the Zacny and Lichtor (2008) study, peak nauseated ratings were significantly higher and trough liking ratings were significantly lower in females versus males in the 20 mg oxycodone condition, findings identical to that obtained in this study. As well, some but not all of the other dysphoric effects noted in this study at the 20 mg dose between females and males also occurred in the Zacny and Lichtor (2008) study (feel bad, turning of stomach, trough take again). Thus, a pattern emerging from these studies is that females tend to report higher ratings of nauseated from a supratherapeutic dose of oxycodone as well as, perhaps not surprisingly, higher disliking ratings. In the present study, such dysphoria was also detected at a therapeutic dose, 10 mg.

Although this is the first study we are aware of that has documented sex differences in nausea and other dysphoric effects of a prescription opioid, such differences have been noted in other laboratory (Comer et al., in press; Fillingim et al., 2005) and clinical settings (Cepeda et al., 2003; Zun et al., 2002) with opioids administered parenterally. For example, in a laboratory study examining effects of intravenous morphine (0 and 0.08 mg/kg) on three different models of pain, degree of analgesia did not differ between males and females but 35% of the females reported nausea as opposed to only 3% of males ($p<0.05$) (Fillingim et al., 2005). In a secondary analysis of a retrospective cohort study involving 8855 hospitalized patients and postoperative parenteral opioid analgesic administration, women had a 60% higher risk of nausea and vomiting than men (Cepeda et al., 2003). Such findings are in agreement with higher rates of

nausea and/or vomiting in females than in males after surgery (Dahan et al., 2008; Myles et al., 2001; Stadler et al., 2003), although this phenomenon cannot be ascribed solely to opioids since other drugs are given during surgery (e.g., general anesthetics).

In conclusion, alcohol-drinking status did not modulate the abuse liability-related effects of oxycodone. Sex of the subject also did not modulate abuse liability-related effects; there was an overall significant Dose effect on ratings of peak liking and take again. However, females reported more dysphoric effects, one of them being nausea. They also reported vomiting more. The sex differences in nausea and emesis are concordant with the literature demonstrating a greater prevalence of nausea and emesis in females than males after receiving opioids, and after surgery (in which opioids are sometimes but not always given).

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Table 1

Participant demographics

	LD	MD
Age (years) M±SD	24.3 (3.5)	25.9 (4.2)
Weight (kg; M±SD)	60.7 (9.0)	71.3 (15.8)[a]
BMI (M±SD)	21.1 (2.1)	22.9 (2.5)[a]
Sex (n; male/female)	8/7	8/6
Race		
Caucasian	8 (53%)	14 (100%)[b]
African American	5 (33%)	0 (0%)[b]
American Indian/Alaskan Native	2 (13%)	0 (0%)
MAST (M±SD)	0.1 (0.25)	1.9 (1.1)[a]
Current drug use (last 30 days)		
Alcohol (M±SD; drinks/week)	0.6 (0.3)	11.3 (3.4)[a]
Caffeine (M±SD; drinks/week)	4.1 (4.1)	8.9 (6.8)[a]
Smokers (n; all <5 cigarettes/day)	2 (13%)	4 (29%)
Marijuana (n)	2 (13%)	4 (29%)
Lifetime recreational drug use		
Marijuana		
Never used (n)	8 (53%)	0 (0%)[b]
Used <10 times (n)	3 (20%)	2 (14%)
Used 10-50 times (n)	3 (20%)	5 (36%)
Used >50 times (n)	1 (7%)	7 (50%)[b]
Stimulants (n; ever used)	1 (7%)	6 (43%)[b]
Sedatives/tranquilizers (n; ever used)	1 (7%)	1 (7%)
Hallucinogens (n; ever used)	0 (0%)	5 (36%)[b]
Ecstasy (n; ever used)	0 (0%)	3 (21%)
Opioids (n; ever used)	1 (7%)	3 (21%)
Lifetime medical opioid use (n; ever used)	9 (60%)	11 (79%)

Abbreviations: LD=light drinker; MD=moderate drinker; BMI= body mass index; MAST=Michigan Alcoholism Screening Test

[a] $p<0.05$ using Student's t test

[b] $p<0.05$ using Fisher's exact test

Table 2

Mean peak, trough, or single values (95% CI) of measures in which there was a significant Sex × Dose interaction. Estimates are adjusted for drinking group and weight.

		Oxycodone Dose			
Response Variable[a]	**Subgroup**	**placebo**	**10 mg**	**20 mg**	**p-value for Dose effect**
ARCI					
LSD (range: 0-14)	males:	3.81 (2.88, 4.75)	4.81 (3.88, 5.75) *	5.25 (4.32, 6.18) **, §	0.05
	females:	3.60 (2.56, 4.64)	6.37 (5.33, 7.41) ‡	7.60 (6.56, 8.64) ‡	<0.0001
VAS (range: 0-100)					
Dizzy	males:	1.38 (-11.13, 13.88)	12.44 (-0.07, 24.94)	15.94 (3.43, 28.44) **	0.11
	females:	10.58 (-3.30, 24.47)	37.74 (23.85, 51.63) ‡	55.05 (41.16, 68.93) ‡	<0.0001
Feel bad	males:	7.56 (-3.53, 18.65)	11.31 (0.22, 22.40)	17.56 (6.47, 28.65) ***	0.43
	females:	9.52 (-2.79, 21.84)	33.06 (20.75, 45.37) †	63.14 (50.82, 75.45) ‡	<0.0001
Heavy, sluggish feeling	males:	13.94 (-1.11, 28.98)	24.38 (9.33, 39.42)	38.63 (23.58, 53.67) * †	0.01
	females:	20.50 (3.80, 37.21)	44.66 (27.95, 61.37) †	77.04 (60.33, 93.75) ‡	<0.0001
In control of body[b]	males:	80.63 (67.12, 94.13)	75.13 (61.62, 88.63)	60.44 (46.93, 73.95) †	0.03
	females:	94.62 (79.62, 109.6)	62.70 (47.70, 77.70) ‡	43.70 (28.70, 58.70) ‡	<0.0001
Nauseated	males:	2.19 (-9.90, 14.27)	9.88 (-2.21, 21.96)	17.88 (5.79, 29.96) ***	0.11
	females:	1.47 (-11.94, 14.89)	28.40 (14.98, 41.82) ‡	60.17 (46.75, 73.59) ‡	<0.0001
Unpleasant bodily sensations	males:	6.50 (-4.70, 17.70)	12.88 (1.68, 24.07)	17.25 (6.05, 28.45) ***	0.32
	females:	9.77 (-2.66, 22.21)	30.24 (17.80, 42.67) †	59.16 (46.73, 71.59) ‡	<0.0001
OARS (range: 0-4)					
Turning of stomach	males:	0.38 (-0.08, 0.83)	0.63 (0.17, 1.08)	0.56 (0.11, 1.02) ***	0.67
	females:	0.53 (0.02, 1.03)	1.07 (0.56, 1.57)	2.68 (2.18, 3.18) ‡	<0.0001
DEL/TA					
Like drug[b,c]	males:	47.44 (40.61, 54.26)	43.00 (36.18, 49.82) ***	34.00 (27.18, 40.82) ***, †	0.02
	females:	43.34 (35.76, 50.91)	20.49 (12.92, 28.07) ‡	13.18 (5.61, 20.76) ‡	<0.0001

Response Variable[a]	Subgroup	Oxycodone Dose: placebo	10 mg	20 mg	p-value for Dose effect
Take drug again[b,d]	males:	49.56 (42.01, 57.11)	48.56 (41.01, 56.11)***	34.13 (26.57, 41.68)*, †	0.005
	females:	45.94 (37.56, 54.32)	22.33 (13.94, 30.71) ‡	18.48 (10.10, 26.86) ‡	<0.0001
End-of-session DEL/TA[e]					
Like drug[f]	males:	51.94 (42.69, 61.19)	56.38 (47.13, 65.62)**	50.31 (41.06, 59.56) **	0.59
	females:	48.53 (38.26, 58.80)	31.53 (21.26, 41.80) §	26.69 (16.42, 36.95) ‡	0.004
Take drug again[d,g]	males:	53.31 (41.48, 65.14)	59.88 (48.04, 71.71)*	46.56 (34.73, 58.39)	0.26
	females:	53.05 (39.92, 66.19)	33.98 (20.84, 47.11) §	28.59 (15.46, 41.73) †	0.02

Abbreviations:ARCI = Addiction Research Center Inventory; LSD = Lysergic Acid Diethylamide scale; VAS = Visual Analog Scale; OARS = Opiate Adjective Rating Scale; DEL/TA = Drug Effect/Drug Liking/Take Again questionnaire

[a] All measures are peak measures unless noted otherwise

[b] Trough measure

[c] Range:0-100, 0=dislike a lot; 50=neutral; 100=like a lot

[d] Range: 0-100, 0=definitely would not; 50=neutral (don't care); 100=definitely would

[e] Mean measures

[f] Range: 0-100, 0=disliked a lot; 50=neutral; 100=liked a lot

[g] Sex × Dose interaction non-significant (p=0.10); shown for comparison to in-session DEL/TA measures and end-of-session drug liking. In main effects model for this outcome: Sex p=0.06, Dose p=0.055

Active dose comparison vs. 0 mg dose:

‡ p≤0.001,

† p≤0.01,

§ p≤0.05

Sex comparison:

*** p≤0.001,

** p≤0.01,

* p≤0.05