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Comparison of a drug versus money and drug versus drug self-administration choice procedure with oxycodone and morphine in opioid addicts

Sandra D Comer, PhD[1], **Verena E Metz, PhD**[1], **Ziva D Cooper, PhD**[1], **William J Kowalczyk, PhD**[2], **Jermaine D Jones, PhD**[1], **Maria A Sullivan, MD, PhD**[1], **Jeanne M Manubay, MD**[1], **Suzanne K Vosburg, PhD**[1], **Mary E Smith**, **Deena Peyser**, and **Phillip A Saccone**[3]

[1]Division on Substance Abuse, Department of Psychiatry, New York State Psychiatric Institute, College of Physicians and Surgeons of Columbia University, New York, NY

[2]NIH/NIDA/IRP Clinical Pharmacology & Therapeutics Branch, Nicotine Pharmacology Section, Baltimore, MD

[3]Department of Pharmacology, University of Michigan, Ann Arbor

Abstract

This double-blind, placebo-controlled study investigated effects of oral morphine (0, 45, 135 mg/70kg) and oral oxycodone (0, 15, 45 mg/70kg) in buprenorphine-maintained opioid addicts. Since a 3:1 morphine:oxycodone dose ratio had yielded equivalent subjective and physiological effects in non-dependent individuals, this ratio was used in the present study. Two self-administration laboratory procedures, i.e. a drug vs. money and a drug vs. drug procedure, were assessed. Study participants (N=12) lived in the hospital and were maintained on 4 mg/day sublingual buprenorphine. When participants chose between drug and money, money was preferred over all drug doses; only high-dose oxycodone was self-administered more than placebo. When participants chose between drug and drug, both drugs were chosen more than placebo, high doses of each drug were chosen over low doses, and high-dose oxycodone was preferred over high-dose morphine. The subjective, performance-impairing, and miotic effects of high-dose oxycodone were generally greater compared to high-dose morphine. The study demonstrated that a 3:1 dose ratio of morphine:oxycodone was not equipotent in buprenorphine-dependent subjects. Both self-

Correspondence: Sandra D Comer, PhD, College of Physicians and Surgeons of Columbia University and the New York State Psychiatric Institute, 1051 Riverside Drive, Unit 120, New York, NY 10032, Tel: 1-212-543-5981, FAX: 1-212-543-5991, sdc10@columbia.edu.

CONTRIBUTORS

S.D. Comer designed the study, analyzed the data, and worked with V. Metz in writing the paper. P.A. Saccone and W.J. Kowalczyk collected data. P.A. Saccone, W.J. Kowalczyk, and S.K. Vosburg provided preliminary statistical analyses of the results. D. Peyser graphed portions of the data. Z.D. Cooper, J.D. Jones, M.E. Smith wrote early drafts of sections of the paper. M.A. Sullivan and J.M. Manubay provided medical coverage during the study. S.D. Comer, Z.D. Cooper, and S.K. Vosburg interviewed potential participants and supervised data collection. All of the co-authors read drafts of the paper.

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administration procedures were effective for assessing the relative reinforcing effects of drugs; preference for one procedure should be driven by the specific research question of interest.

Keywords

morphine:oxycodone ratio; buprenorphine-maintenance; opioid dependence; abuse liability; self-administration procedure; physiological and subjective effects

1.0 INTRODUCTION

Currently, prescription pain relievers are among the most highly abused substances in the United States. The 2010 National Survey on Drug Use and Health (NSDUH) report revealed that approximately 2.0 million people in the U.S. reported initiating non-medical use of prescription opioids, which was similar to the number of individuals initiating marijuana use (2.4 million). Among prescription opioids, oxycodone is one of the most commonly prescribed and most commonly abused (Cicero et al., 2011; Schneider et al., 2009). It is an opioid analgesic used medically to treat moderate to severe pain, and is marketed alone (Oxycontin®) or in combination with other analgesics such as acetaminophen (Percocet®) and aspirin (Percodan®). Morphine, another commonly used analgesic, is considered by many to be the prototypical mu opioid agonist. It is the principal active ingredient in opium and is one of the oldest medications used to alleviate pain. For this reason, it is the mu agonist against which other drugs in this class often are compared. Morphine is marketed under such brand names as Avinza®, Kadian®, MS Contin®, and Roxanol®.

Oxycodone and morphine are both strong opioids, but their potencies differ considerably depending on the route by which they are administered (Kalso, 2007; Bostroem et al., 2008). For example, they are equipotent when given intravenously for postoperative patient-controlled analgesia (Silvasti et al., 1998) and in studies assessing their abuse liability after intravenous administration (Comer et al., 2008; Stoops et al., 2010). However, for post-operative pain relief, morphine is approximately 10 times more potent than oxycodone when both medications are given epidurally (Backlund et al., 1997). In contrast, for treating cancer pain, morphine is approximately 1.5–2 times less potent than oxycodone when both drugs are given orally (Mercandonte and Caraceni, 2011). Studies comparing the abuse liability of morphine and oxycodone after oral administration are generally lacking, which is surprising given that this is a highly relevant concern from a public health perspective. We found only one publication (Zacny & Lichtor, 2008) that directly compared the abuse liability of oxycodone and morphine after oral drug administration. Zacny and Lichtor (2008) reported a potency ratio of 3:1 for oral morphine and oral oxycodone in producing miosis in non-opioid-dependent research volunteers. Although the overall subjective effect profiles of the two drugs were similar and, as with miosis, had a potency ratio of 3:1, 20 mg oxycodone produced more abuse liability-related effects and fewer aversive effects than 60 mg morphine. However, neither drug functioned as a reinforcer, which was not entirely surprising given that the participants were non-drug-abusing volunteers. Therefore, the authors suggested testing the psychopharmacological profiles of oxycodone and morphine in drug abusers, preferably those with a history of abusing prescription opioids.

The present study was conducted to meet two objectives. The first objective was to examine the effects of immediate-release oral oxycodone and morphine in opioid addicts. Participants were maintained on a fixed dose of sublingual buprenorphine in order to standardize the level of opioid dependence across subjects and avoid the emergence of opioid withdrawal symptoms, which would have confounded our results. From a more clinical perspective, buprenorphine is approved by the U.S. Food and Drug Administration to treat both pain and opioid use disorders, and the sublingual formulation is increasingly being used to treat patients with both problems. Thus, examining the abuse liability of morphine and oxycodone in participants maintained on sublingual buprenorphine increased the external validity of our study. The second objective of the study was to directly compare a drug versus money and a drug versus drug self-administration choice procedure in order to evaluate the advantages and disadvantages of each procedure. Subjective, performance, and physiological effects were examined in order to provide a more comprehensive profile of the relative pharmacodynamic effects of oxycodone and morphine in an opioid-dependent sample.

2.0 METHODS

2.1 Screening

After completing an initial telephone interview, eligible participants who endorsed daily opioid use came into the hospital and signed a screening consent form. They then completed detailed medical history, drug use, and depression questionnaires (Drug History Questionnaire, General Health Questionnaire, Short Michigan Alcohol Screening Test, Medical History Questionnaire, Beck Depression Inventory), clinical interviews (SCID, mental status evaluation, drug history interview) with a psychologist and psychiatrist, and a medical evaluation. Screening procedures also included an electrocardiogram and tuberculosis (Mantoux) test or chest X-ray. Laboratory analyses consisted of a hematology screen, blood chemistry panel, thyroid function tests, liver function tests, syphilis serology, and urinalysis. Urine drug testing was performed to assess use of opioids, cocaine, benzodiazepines, cannabinoids, and amphetamines. A naloxone challenge test or visual inspection of withdrawal symptoms was carried out as part of the screening process on all potential participants to confirm current dependence on opioids. For the naloxone challenge, an initial dose of 0.2 mg of naloxone was injected intramuscularly. If no withdrawal symptoms were observed after 10 minutes, an additional dose of 0.2 mg was given; if no withdrawal signs occurred after an additional 20 minutes, a dose of 0.4 mg naloxone was administered. A cut-off score of at least 10 was used to confirm the presence of physiological dependence on opioids (Wang et al., 1974). Further study inclusion criteria were 21–45 years of age, normal body weight (within 20% of the body weight range specified for a given height according to the 1983 Metropolitan Life Insurance Height/Weight tables), and ability to perform study procedures (verified in a practice session during the screening process). Exclusion criteria were sensitivity, allergy, or contraindication to opioids, current or history of chronic pain, significant suicide risk, active hepatitis with SGOT or SGPT > 3 times the upper limit of normal, and pregnancy, lactation, birth, miscarriage or abortion within the previous 6 months. Moreover, individuals who were diagnosed with a current major Axis I disorder or who met Diagnostic and Statistical

Manual of Mental Disorders 4th Edition Text Revision criteria for dependence on drugs other than opioids, nicotine, or caffeine were excluded from the study. Those on parole or probation, or with histories of significant violent behavior were also excluded. In addition, individuals requesting treatment for their drug use were excluded from the study and offered referrals to treatment.

2.2 Enrollment Procedures

Before admission, all participants signed study consent forms that explained the overall aims of the study and described the risks and benefits of participation. A practice session familiarized participants with study tasks and procedures and ensured that they were capable of performing them during the study. Volunteers were housed on 5-South, a locked inpatient research unit of the New York State Psychiatric Institute (NYSPI). Participants were paid for study participation.

The Institutional Review Board of the NYSPI approved the study. Moreover, a Certificate of Confidentiality (DA-95-28) was issued for this study, which was performed under IND#44,716.

2.3 Experimental Sessions: General Procedures

This within-subject, double-blind, placebo-controlled study consisted of two types of experimental sessions: sample sessions and choice sessions (Table 1). During sample sessions, participants received an experimenter-administered dose of drug that would be available later during the choice session(s). During both sample and choice sessions, the subjective, performance, and physiological effects of the drug were measured. Two different self-administration procedures, during which participants could choose between two reinforcers, were used during the study: A drug versus money procedure (Week 2) and a drug versus drug procedure (Weeks 3–8). Drugs and doses were administered in random order both within and across participants.

Throughout each experimental session, participants were seated in a room equipped with Macintosh computers that were connected to another computer in an adjacent room where experimenters continuously monitored their computer activities and behaviors. Vital signs monitors (Criticare Poet Plus 8100 vital signs monitor, Critical Systems Inc., Waukesha, WI) were used to collect data on respiration (respiratory rate, SpO_2 (an estimate of arterial oxygen saturation), and end tidal CO_2 (expired carbon dioxide levels)) and cardiovascular function (heart rate, systolic pressure, and diastolic pressure).

Participants' physiological responses were monitored continuously throughout the experimental sessions. Baseline physiological measures were taken and sufficient oxygen saturation (>92%) was verified prior to drug administration. Participants wore a blood pressure cuff on the non-dominant arm and were connected to a pulse oximeter. Supplemental oxygen at a constant flow rate of 2 L/min was provided via a nasal cannula for safety, as required by our Institutional Review Board. Pupil photographs were taken at designated time points (Table 2) using a digital pupillometer (Model #59001, Neuroptics, Inc., San Clemente, CA) under ambient lighting conditions.

2.4 Experimental Sessions: Specific Procedures

2.4.1 WEEK 1: STABILIZATION—During Week 1, participants were stabilized on sublingual buprenorphine and no laboratory sessions were completed (Table 1). Throughout their inpatient stay, participants received 4 mg sublingual buprenorphine each evening at 8 p.m. in order to maintain a consistent level of opioid dependence and to avoid long-term withdrawal effects potentially interfering with outcome measures throughout the study, and to standardize the test condition. Ancillary medications, such as clonidine and clonazepam, were available as needed to alleviate mild opioid withdrawal symptoms during Week 1 and on weekends throughout the study; these medications were only available until 6 p.m. each day when a lab session was planned for the following day to ensure an adequate washout period.

2.4.2 WEEK 2: DRUG VS MONEY—During Week 2, drug administration occurred twice daily, once during a morning sample session at 11 am and once during an afternoon choice session at 4 pm (if drug was chosen). One dose was tested each day on Mondays through Fridays (Table 1). During the sample session, participants were simultaneously given drug and $20. During the choice session, they chose between these two options using a drug versus money self-administration task (see below). Throughout both sessions, subjective, performance, and physiological effects were measured before and at predetermined time points after drug administration (Table 2).

The drug versus money self-administration task was completed during the choice session and then drug and/or money were delivered at time 0 (see Table 2). Participants chose between fractions of the money and drug dose they had received during the morning sample session. They were instructed to “work” for all or part of the sampled dose or sampled money amount ($20) by making finger presses on a computer mouse. Ten choice trials were presented, and drug and money were available during each choice trial in 10% increments (i.e., if the dose for that day was 15 mg, during each trial participants could work for either 1.5 mg of drug or $2). Participants had to click the mouse a set number of times (the “ratio requirement”) to achieve either the drug or money increment. The ratio requirement for the drug and money options increased independently each time that option was selected. The initial requirement was 50 clicks on the mouse, and the ratio increased each time that option was selected (50, 100, 200, 400, 800, 1200, 1600, 2000, 2400, and 2800). Thus, to receive all of the drug or all of the money available, the participant had to make 11,550 mouse clicks within 40 minutes. The fraction of drug earned during the choice session was administered at the end of the task; the fraction of money earned was added to total study earnings, and disbursed upon study completion. Regardless of the participants’ choices, the duration of the choice session remained the same during Week 2.

2.4.3 WEEKS 3–8: DRUGS VERSUS DRUG—During Weeks 3–8, drug administration occurred daily on Mondays through Fridays (Table 1). Participants received a sample dose of drug at 11 am on Day 1 and Day 2 of each week (one session per day) and they were given the opportunity to self-administer drug at 11 am and 4 pm (two sessions per day) on Days 3–5 (see below and Table 1). One dose combination was tested each week. Subjective,

performance, and physiological effects were measured before and at predetermined time points after drug administration (see Table 2 for session overview).

The drug versus drug self-administration task was completed and then the dose chosen (or nothing) was delivered at time 0 (Table 2). Doses were identified with letters ("A" and "B") and colored cups (red and blue). Participants subsequently were given the opportunity to verbally choose between "Dose A" and "Dose B," or they could choose "Neither" option. Participants then made 200 finger presses on the computer mouse. At the end of this 5-minute task, the individual received whichever drug dose (or no dose) he/she had chosen. The six dose combinations were: placebo versus 45 mg/70 kg oxycodone, 15 versus 45 mg/70 kg oxycodone, placebo versus 135 mg/70 kg morphine, 45 versus 135 mg/70 kg morphine, 15 mg/70 kg oxycodone versus 45 mg/70 kg morphine, and 45 mg/70 kg oxycodone versus 135 mg/70 kg morphine. The total duration of the choice sessions during weeks 3 to 8 was the same regardless of the participants' choices.

2.5 Experimental Measures

2.5.1 SUBJECTIVE EFFECTS—Subjective effects were measured with four questionnaires (for a more detailed description, see Comer et al, 1999):

Participants completed 1) a visual analog scale (VAS), 2) a drug effects questionnaire (DEQ), 3) an opioid symptom checklist, and 4) a subjective opioid withdrawal scale (SOWS). The VAS consisted of questions about the individual's mood state, quality of the dose just received, and drug craving (for heroin, cocaine, alcohol, and tobacco). Participants rated each item by marking along a 100-mm line from "Not at all" (0 mm) to "Extremely" (100 mm). One item on the VAS asked participants to rate the monetary value of the dose, ranging from $0 (0 mm) to $20 (100 mm). The DEQ consisted of 6 questions used to rate drug effects and drug liking. The series of possible answers ranged from 0 ("No good/bad effects at all") to 4 ("Very strong effects"), and from −4 ("Dislike very much") to 4 ("Like very much"). The opioid symptom checklist consisted of a series of 13 true/false questions (e.g., "I feel like I am nodding") presented in order to measure prototypic opioid effects. Sum scores on the opioid symptom checklist could range between 0 and 12 (one point was added to the sum score for each "true" answer, but if participants answered "true" to the item "I feel normal," one point was subtracted from the sum score). The SOWS was a 16-item questionnaire in which participants rated different withdrawal symptoms on a scale from 0 to 4 (0 being "Not at all," 4 being "Extremely"). SOWS sum scores could range between 0 and 64, with higher scores indicating higher levels of opioid withdrawal symptoms.

2.5.2 PERFORMANCE EFFECTS—Participants completed computerized task batteries throughout the laboratory sessions. The battery consisted of four tasks: a 3-minute digit-symbol substitution task used to assess changes in psychomotor skill, a 10-min divided attention task used to assess vigilance, a 10-min rapid information processing task used to assess information processing, and a 3-minute repeated acquisition of response sequences task used to assess learning and memory (Comer et al., 1999).

2.5.3 PHYSIOLOGICAL EFFECTS—Pupil diameter was measured at various times throughout each session. Respiration was recorded every minute and measured by respiratory rate (breaths/min), an indirect measure of arterial oxygen saturation (SpO_2; %), and an indirect measure of expired CO_2 (end tidal CO_2; mm Hg). Heart rate (beats per min), systolic blood pressure (mm Hg), and diastolic blood pressure (mm Hg) were automatically recorded every 5 minutes.

2.6 Drugs and Doses

Test drugs included placebo, oxycodone (15 mg and 45 mg/70 kg), and morphine (45 mg and 135 mg/70 kg), which were administered orally during laboratory sessions. Additionally, participants were maintained on 4 mg sublingual buprenorphine throughout the study.

Oxycodone hydrochloride (20 mg/ml) was purchased from Purdue Pharma L.P. (Ardsley, NY). Morphine sulfate (20 mg/ml) was purchased from Cardinal Distribution Company (Syracuse, NY). Solutions were mixed in an orange-flavored drink with 1 ml of peppermint oil floated on top to mask the taste of the drug; a total volume of 200 ml was administered at each dosing. Buprenorphine tablets were obtained from the National Institute on Drug Abuse via the Research Triangle Institute.

Buprenorphine was chosen over other possible maintenance agents such as methadone because opioid dependent patients medicated with buprenorphine are comparably more reality-oriented and clearheaded (Fischer et al, 1999), which is advantageous for completing neuropsychological tests/lab sessions. The oxycodone doses were chosen based on pilot work conducted in our laboratory showing them to be pharmacologically active and well tolerated. The morphine doses were chosen for comparison, with a previous study demonstrating that a 3:1 potency ratio between oral morphine and oral oxycodone produced equivalent miotic effects in healthy non-opioid-dependent volunteers (Zacny and Lichtor, 2008).

2.7 Statistical Analyses

Repeated measures ANOVAs were used to analyze the data for the Drug versus Money comparisons. Breakpoint values (the highest ratio values completed for drug and for money), percentage of trials chosen for drug and money, and amount of drug and money delivered were analyzed. Paired t-tests were used for the Drug versus Drug comparisons to analyze the average percentage of each option chosen (Dose A, Dose B, Neither) during the six choice sessions for each dose combination. Planned comparisons were made between each active dose and placebo, between the active doses of each drug to assess dose dependency, and between the two low and two high doses of drug to explore differences between morphine and oxycodone. Subjective, performance, and physiological effects were analyzed using repeated measures analyses of variance (ANOVAs). Both peak (or trough) and time course data were examined. For peak/trough data, only data points after drug administration were assessed. Peak effects were analyzed for most of the measures, but trough effects were analyzed for certain measures if they more accurately reflected drug-induced responses (e.g., miosis). For time course data, effects before and after drug

administration were assessed. Comparisons with $P \leq 0.05$ were considered statistically significant.

3.0 RESULTS

3.1 Participants

Twelve participants (11 men, 1 woman; 4 Hispanic, 4 Black, 3 White, 1 Native American) completed the study. On average, participants were 40 ± 3 years of age (range: 34–45) and had used heroin for 18 ± 7 years (range: 7–25). All participants reported current use of heroin and spent an average of $70 per day on it (range: $25–125). Participants also reported current (within the past 30 days, n=8) or previous (n=12) recreational use of prescription opioids. The most commonly used prescription opioid was oxycodone (n=11), although use of codeine (n=6), morphine (n=5), hydrocodone (n=3), meperidine (n=3), hydromorphone (n=2), and fentanyl (n=1) also was reported. Methadone and buprenorphine were used occasionally by all of the participants, but use of these drugs was primarily for alleviation of withdrawal symptoms. Typically, the prescription opioids were ingested orally, although some participants reported intravenous or intranasal use as well. In addition, all participants smoked tobacco cigarettes (1/2 – 2 packs per day), 4 drank alcohol (1 each drank alcohol 2, 4, 8, and 12 times per month), 6 used cocaine (3 used once per month, 2 used twice per month, and 1 used 8 times per month), and 2 used marijuana (1 used once per week and 1 used 3 times per week). Six additional participants dropped out of the study; two discontinued because they did not like being confined on the inpatient unit, 1 was dropped because of an outstanding warrant, and 3 were administratively discharged for noncompliance with unit policies.

3.2 Self-Administration

3.2.1 Drug versus Money (Week 2)—During all choice sessions, breakpoint values for money (range: 1417–2333) were higher than for drug (range: 133–942; Figure 1, top panels). The high dose of oxycodone was the only active drug dose to differ significantly from placebo in both drug and money progressive ratio breakpoint values ($P \leq 0.05$). Additionally, breakpoint values for the low and high doses of oxycodone were significantly different from one another (for money and drug: $P \leq 0.01$). However, breakpoints did not significantly differ when oxycodone was compared to morphine.

During all choice sessions, the percentage of choices for money (range: 58%–88%) was higher than for drug (range: 8%–40%; Figure 1, middle panels). The high dose of oxycodone also was the only active drug dose to differ significantly from placebo in percentage of choices for both drug and money ($P \leq 0.05$). The percentage of choices for the low and high doses of oxycodone also significantly differed from one another ($P \leq 0.01$). However, the percentages of drug and money that were self-administered did not differ considerably between oxycodone and morphine.

When 135 mg/70 kg morphine was available, participants self-administered 41 mg drug (Figure 1, bottom panels; 30% of the available dose) and when 45 mg/70 kg oxycodone was available, participants self-administered 21 mg drug (47% of the available dose). The amounts of morphine and oxycodone that were self-administered did not significantly differ

from each other, although the amount of high dose morphine that was self-administered differed significantly from placebo ($P \leq 0.001$) and from the low dose of morphine ($P \leq 0.01$). In contrast, the amount of high dose oxycodone that was self-administered did not significantly differ from placebo ($P = 0.053$) or the low dose of oxycodone ($P = 0.068$), although the difference approached statistical significance. The amount of money self-administered when high dose oxycodone was available ($11.50) was considerably lower than when placebo was available ($16.67; $P \leq 0.05$) and when low dose oxycodone was available ($17.50; $P \leq 0.01$). However, the amount of money that was self-administered when high dose oxycodone was available did not significantly differ from the amount of money self-administered when high dose morphine was available.

3.2.2 Drug versus Drug (Weeks 3–8)—The high doses of both oxycodone and morphine were chosen significantly more than placebo (Figure 2, top panels) and the respective low doses (Figure 2, middle panels). No significant preference emerged between the low morphine and oxycodone doses (Figure 2, bottom panels). However, the high dose of oxycodone was chosen more frequently than the high dose of morphine (79% versus 15%, respectively; Figure 2, bottom panels).

3.3 Subjective Effects

3.3.1 Visual Analog Scale

Peak: The high doses of oxycodone and morphine (OXY-45 and MOR-135) produced significantly greater effects than placebo in several mean peak VAS ratings (Table 3; Figure 3, top panels). OXY-45 frequently produced a significantly larger effect than the low dose (OXY-15), with the only exceptions being “Bad” and “Sedated.” In contrast, morphine produced smaller dose-related changes in VAS ratings. Although the absolute mean peak values were consistently higher for the high dose of morphine compared to the low dose, none of the differences were statistically significant. The high doses of each drug differed significantly from each other in mean peak VAS ratings of “High,” “High quality,” “I would pay,” “Like,” and “Potent” (all P’s ≤ 0.05). In all cases, the high dose of oxycodone produced greater effects than the high dose of morphine.

Time Course: The dose x time interaction was significant for ratings of “Good,” “High,” “High quality,” “I would pay,” “Like,” and “Potent” (all P’s ≤ 0.01) (data not shown). Relative to placebo, OXY-45 produced a significant increase in several VAS ratings, such as “Good,” “Like,” and “Potent” (all P’s ≤ 0.0001) that peaked at different time points after dosing. For example, maximum ratings of “Good” and “Like” occurred 60 minutes after the dose was administered, while the maximum rating for “Potent” occurred 120 minutes after dosing. Ratings after administration of the high dose of morphine fell consistently below those of the high dose of oxycodone, but no clear time point at which maximum ratings occurred during the session could be identified.

3.3.2 Drug Effects Questionnaire

Peak: The high doses of oxycodone and morphine differed significantly from placebo in mean peak ratings of “Good,” “Like,” and “Take again” (Table 3; Figure 3, bottom panels). The high dose of oxycodone produced significantly greater mean peak DEQ ratings than the

low dose for “Good,” “Like,” “Strong,” and “Take again” (Table 3; Figure 3, bottom panels). Peak ratings after administration of the high dose of morphine only differed from the low dose for ratings of desire to “Take again.” Interestingly, none of the comparisons of OXY-45 and MOR-135 on the DEQ were significantly different. As with the VAS, placebo produced the greatest “Bad” effects peak ratings, and it did not differ significantly from MOR-135, although it approached significance ($P = 0.07$). MOR-45, OXY-15, and OXY-45 all produced significantly lower scores than placebo for ratings of “Bad” effects (all P’s ≤ 0.05).

Time Course: The dose x time interaction was significant for DEQ ratings of “Good,” “Like,” “Strong,” and “Take again” (all P’s ≤ 0.0001; data not shown). Relative to placebo, the high dose of oxycodone produced a significant increase in DEQ ratings of “Good,” “Like,” “Strong,” and “Take again” (all P’s ≤ 0.001). Similar results were obtained for the high dose of morphine compared to placebo (“Good” and “Like”: $P \leq 0.01$; “Strong” and “Take Again”: $P \leq 0.05$). Only ratings of “Take again” were significantly lower for high dose morphine compared to high dose oxycodone ($P \leq 0.05$). The time course data for selected DEQ ratings were similar to those for the corresponding VAS ratings, with the high dose of oxycodone having the highest ratings 1–2 hours after dosing (at 90 minutes for “Good,” “Like,” “Strong,” and “Take again”; data not shown). The high dose of morphine did not appear to produce a distinct peak rating for “Good,” “Like,” “Strong,” or “Take again.”

3.3.3 Opioid Symptom Checklist

Peak: The mean peak sum scores on the opioid symptom checklist were similar to the pattern of responses on the drug effects questionnaire. Namely, ratings after administration of O-45 and M-135 were significantly greater than placebo ($P \leq 0.01$) and O-45 produced effects that were significantly greater than O-15 ($P \leq 0.05$), but the effects of the high doses of oxycodone and morphine were not significantly different from each other.

Time Course: In contrast to the VAS and DEQ, the time to peak effects on the OSC occurred 15 min after administration of high dose oxycodone (score = 3.0; data not shown). Ratings were similar 15 min (score = 2.3) and 60 min (score = 2.5) after administration of high dose morphine. Thus, the high doses of both morphine and oxycodone produced maximal or near-maximal effects within 15 min, indicating that participants were able to detect opioid effects soon after dose administration.

3.3.4 Subjective Opioid Withdrawal Scale—The sum SOWS score after placebo administration was significantly greater than the SOWS scores of all four active doses of drug (MOR 45, MOR 135, and OXY 15 versus placebo: $P \leq 0.05$; OXY 45 versus placebo: $P \leq 0.01$; Table 3). There were no significant differences between the low and high doses of each drug, or between the high dose of morphine and the high dose of oxycodone.

3.4 Physiological Effects

3.4.1 Pupil Diameter

Trough: All four active doses of drug produced significant decreases in mean trough pupil diameter compared to placebo (Figure 4, top panel). The high dose of oxycodone produced the lowest mean trough value, which was significantly different from placebo ($P \leq 0.0001$), the low dose of oxycodone ($P \leq 0.0001$), and the high dose of morphine ($P \leq 0.01$). Trough pupil diameter did not significantly differ for the two active doses of morphine.

Time Course: Examination of the time course of changes in pupil diameter revealed that the dose x time interaction was significant ($P \leq 0.0001$; Figure 4, bottom panel). Both doses of morphine and the high dose of oxycodone decreased pupil diameter significantly more than placebo ($P \leq 0.01$). Pupil diameters after administration of the two active doses of morphine did not differ from each other. However, the high dose of oxycodone produced a smaller pupil diameter than the low dose of oxycodone and the high dose of morphine ($P \leq 0.01$). Minimal values for pupil diameter occurred 60 min after administration of the high dose of oxycodone and 90 min after administration of the high dose of morphine, demonstrating that morphine's maximal miotic effects occurred later than oxycodone.

3.4.2 Respiration

Respiratory Rate: Trough respiratory rate (data not shown) was significantly lower for the high dose of oxycodone (O-45 = 10.47 breaths/min) compared to placebo (11.21 breaths/min; $P \leq 0.05$) and the low dose of oxycodone (O-15 = 11.36 breaths/min; $P \leq 0.05$). However, trough respiratory rates did not differ between placebo and the low dose of oxycodone or either dose of morphine (M-45 = 11.27 breaths/min; M-135 = 10.98 breaths/min). Furthermore, trough respiratory rates after administration of the high dose of oxycodone did not significantly differ from the high dose of morphine. Examination of the time course of changes in respiratory rate (Figure 5, top panel) revealed that the maximal decreases in respiratory rates for the two high doses of drug were similar and occurred approximately 120 min after dose administration. Respiratory rate for the two lower doses of drug likewise were similar.

End Tidal CO_2: Peak end tidal CO_2 (data not shown) was significantly higher after administration of both high doses of drug (M-135 = 42.06 mm Hg, O-45 = 41.90 mm Hg) relative to placebo (40.18 mm Hg; $P < 0.001$). A dose-response relationship was observed for both morphine ($P \leq 0.05$) and oxycodone ($P \leq 0.01$), with the higher doses increasing end tidal CO_2 more than lower doses. However, the high doses of morphine and oxycodone did not differ significantly from each other, and the low doses of morphine and oxycodone also were similar to each other. Examination of the time course of changes in end tidal CO_2 (Figure 5, middle panel) revealed that the maximal increases occurred approximately 120 min after administration of O-45 and M-135.

Arterial Oxygen Saturation: No significant effects were obtained for trough arterial oxygen saturation when active doses of drug (M-45 = 97.66%, M-135 = 97.48%, O-15 = 97.80%, O-45 = 97.37%) were compared to placebo (97.60%). Similarly, none of the active doses of drug were significantly different from each other. Examination of the time course

of changes in arterial oxygen saturation (Figure 5, bottom panel), however, revealed that the maximal decreases occurred approximately 60–120 min after administration of O-45 and M-135.

3.4.3 Blood Pressure and Heart Rate

Systolic and Diastolic Pressure: No statistically significant changes were observed in trough systolic or diastolic blood pressure as a function of drug dose. When examined as a function of time, both systolic and diastolic pressure significantly decreased over the course of the laboratory session ($P \leq 0.0001$ and $P \leq 0.05$, respectively; from approximately 122/70 to 115/67 mm Hg), but neither systolic nor diastolic pressure changed as a function of dose.

Heart Rate: Similar to blood pressure, few changes were observed in trough heart rate, with the exception that a small but statistically significant increase occurred after administration of the high dose of morphine (65.5 beats per minute) relative to placebo (62.8 beats per minute; $P \leq 0.05$). Similar to blood pressure, heart rate significantly decreased throughout the session ($P \leq 0.0001$; from approximately 81 to 67 beats/min), but it did not change as a function of dose (data not shown).

3.5 Performance Effects

Rapid Information Task: The mean peak number of correct identifications of three consecutive odd or even numbers was significantly lower after administration of the high dose of oxycodone (213) compared to placebo (226; $P \leq 0.05$) and the low dose of oxycodone (227; $P \leq 0.05$). In addition, the number of correct identifications after administration of the high dose of oxycodone was significantly lower than the high dose of morphine (229; $P \leq 0.05$). On the other hand, the number of false alarms was significantly lower after administration of the high dose of oxycodone (92) compared to the low dose of oxycodone (125; $P \leq 0.05$). The number of correct identifications did not significantly vary across time, but the number of false alarms significantly increased ($P \leq 0.001$; data not shown).

Divided Attention Task: Performance on the divided attention task also was impaired by the high dose of oxycodone. Since the speed of the tasks is adapted to the subject's accurate reaction, it directly reflects participants' performance. The maximum speed in the task was significantly lower after the high dose of oxycodone (5.4) compared to the low dose of oxycodone (5.9 ticks; $P \leq 0.05$) and placebo (6.1 ticks; $P \leq 0.01$). The maximum speed after the high dose of oxycodone also was significantly lower than after the high dose of morphine (6.0 ticks; $P \leq 0.05$). Additionally, the maximum speed significantly decreased across time ($P \leq 0.002$).

Repeated Acquisition of Response Sequences Task: Similar to results on the other tasks, the high dose of oxycodone produced impairments on the repeated acquisition of response sequences task, which requires participants to learn a 10-sequence pattern of responding on four individual computer keys. The number of patterns attempted was significantly lower after the high dose of oxycodone (14.6) compared to the low dose of oxycodone (18.4; $P \leq$

0.05) and placebo (17.8; $P \leq 0.05$). The number of patterns attempted also was lower after the high dose of oxycodone compared to the high dose of morphine (18.1; $P \leq 0.05$).

4.0 DISCUSSION

Overall, these data suggest that a 3:1 morphine to oxycodone potency ratio cannot be assumed for pharmacodynamic effects in buprenorphine-dependent individuals. Moreover, while subjective, performance, and reinforcing effects were generally consistent with miosis, they did not necessarily reflect other physiological effects, such as respiration. With regard to drug preference, when high-dose morphine and high-dose oxycodone were compared directly, participants exhibited a clear preference for oxycodone. However, because the high dose of oxycodone also produced greater miotic effects than the high dose of morphine, it is not possible to conclude that oxycodone has greater reinforcing effects than morphine. In fact, drug preference did not differ for the low doses of each drug, which did produce similar subjective, performance, and miotic effects.

The two self-administration procedures produced generally similar patterns of effects, but each procedure had certain strengths and weaknesses. In the drug versus drug choice sessions, participants consistently preferred the high dose over the low dose of each drug and the high doses of each drug to placebo. When the high doses of morphine and oxycodone were compared directly, participants strongly preferred oxycodone. When using the drug versus money choice procedure, participants self-administered money more than either drug. When active drug was compared to placebo, only the high dose of oxycodone produced a breakpoint value that was significantly greater than placebo, but breakpoint values for the high doses of each drug did not significantly differ from each other. These findings suggest that both procedures were useful in providing evidence that high-dose oxycodone was preferred over high-dose morphine. The advantage of the drug versus drug procedure was that it was more sensitive to dose effects. However, this procedure is time consuming in that several weeks of testing were required in order to obtain this finding. The drug versus money procedure was less sensitive to dose than the drug versus drug procedure, but it had the advantage of providing evidence that an alternative non-drug reinforcer (money) was preferred over both drugs and that participants were not willing to expend much effort to obtain the drugs. One potential problem with both procedures is that carryover effects from a previous dose could have altered subsequent decisions to self-administer drug. We previously investigated potential carry-over effects from sample to choice sessions (e.g. Comer et al., 1999, 2001) and found that there were generally no changes in drug self-administration unless very high drug doses were administered (Comer et al., 2002). In the present study, the doses of oxycodone and morphine that were tested could be considered low to moderate based on the physiological responses that we observed, so carryover effects were not likely a major factor in the self-administration outcomes. Another potential problem with comparing the two self-administration procedures in the present study is that the order of testing the procedures was not randomized (i.e., the drug versus money procedure was always tested first). In our experience, however, earlier dose exposures generally result in greater self-administration and more robust subjective responses, especially with placebo administration. The outcome in the present study was that participants self administered far less drug with the drug versus money procedure than with

the drug versus drug procedure, so order effects may not have been prominent in the present study. Nevertheless, a stronger experimental design would have employed random order of testing of the self-administration procedures. In sum, both procedures were useful in examining the reinforcing effects of different drugs and doses, and the decision to use one procedure over another should be driven by the specific research question of interest. The data presented also highlight the importance of assessing physiological endpoints, such as miosis and respiration, which are critical for interpreting the measures of abuse liability (namely, subjective and reinforcing effects).

One factor to be taken into consideration when interpreting the present results is that the peak subjective ratings were fairly low overall compared to previous studies conducted in our laboratory in which intranasal or intravenous opioids were administered to opioid abusers (e.g., Comer et al., 2008). Furthermore, the morphine doses used in the present study were low compared to what opioid-dependent individuals take on average when they are in the field; thus, the study participants could have been less motivated to work (hard) for a dose that only represents a small proportion of what they are accustomed to using. Another factor that may have contributed to the low subjective ratings was that all of the participants were accustomed to using heroin daily via the intranasal and/or intravenous routes, so even though they reported abusing prescription opioids orally, they apparently did not find the effects produced by oral morphine and oxycodone in our study to be particularly robust. This finding partly may be due to interaction effects of oxycodone and morphine with buprenorphine. For these reasons, it is important to note that the present results may not be fully generalizable or applicable to other populations of opioid users (e.g., non-dependent recreational prescription opioid abusers). However, we opted to maintain participants in our study on buprenorphine in order to minimize withdrawal symptoms (e.g. runny nose, vomiting, fatigue, insomnia, irritability, anxiety; Collins & Kleber, 2004) and to increase the external validity of our study. That is, from a public health perspective, an increasing number of patients with chronic pain are abusing prescription opioids and clinicians are opting to use sublingual buprenorphine to treat both disorders (Weiss et al. 2011, Manubay et al. 2011, Barry et al. 2012, Heit & Gourlay 2008).

Because oxycodone and morphine did not produce similar miotic effects, it was not possible to determine whether the differences in subjective and reinforcing effects obtained with the high doses of each drug reflected differences between oxycodone and morphine or simply non-equivalence in doses used. Ideally, we would have tested equi-miotic effects of both drugs to examine differences in abuse liability between oxycodone and morphine. Future studies should be conducted in larger samples with differing doses of morphine and oxycodone to more conclusively determine equivalent dose ratios for different effects in populations with substance use disorders. Studies claiming high external validity for their results should also take the average doses used in “the real world” into account when testing and comparing different doses of opioids. Nevertheless, results of the present study were informative in demonstrating the myriad methodological issues that should be considered when examining the abuse liability of opioid medications.

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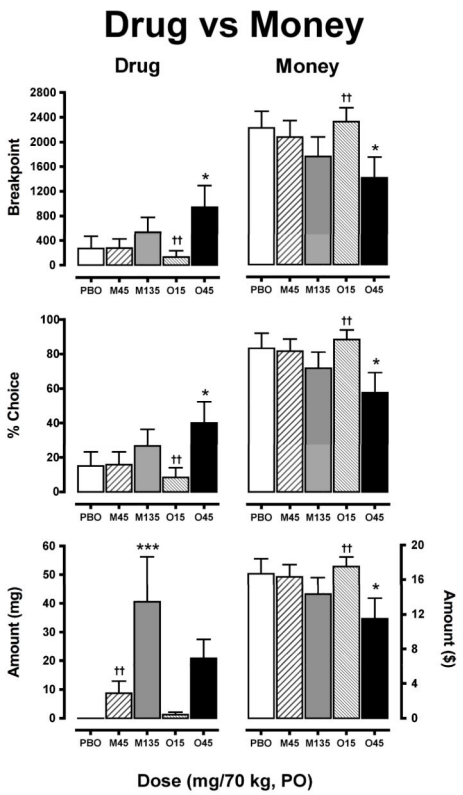

Figure 1.

Mean breakpoint values (top panels), percentage of choices (middle panels), and amount of drug ingested/$ received (bottom panels) for drug (left) and money (right) during the drug vs. money choice sessions of week 2. PBO = placebo, M45 = 45 mg/70 kg morphine, M135 = 135 mg/70 kg morphine, O15 = 15 mg/70 kg oxycodone, and O45 = 45 mg/70 kg oxycodone. * represents a significant difference from placebo; and † represents a significant difference between the low and high doses. One symbol represents $P \leq 0.05$, two symbols represent $P \leq 0.01$, and three symbols represent $P \leq 0.001$.

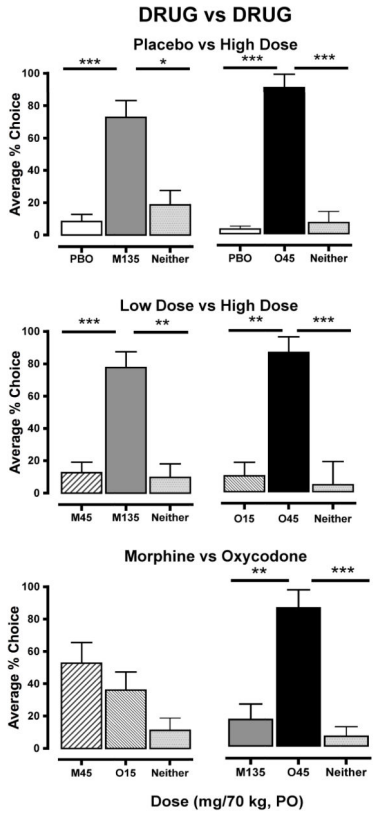

Figure 2.

Mean percentage drug choices for drug versus drug self-administration sessions during weeks 3–8. The top panels display percentage of choices when participants received placebo versus high doses of morphine (left panel) or oxycodone (right panel). The middle panels display percentage of choices when participants received low versus high doses of morphine (left panel) or oxycodone (right panel). The bottom panels display percentage of choices when participants received oxycodone versus morphine at low doses (left panel) and high doses (right panel). Six separate choice trials occurred after sample sessions of each drug pair, and percent choice (± 1 SEM) represents the average percentage of total times each dose (or neither dose) was chosen. PBO = placebo, M45 = 45 mg/70 kg morphine, M135 = 135 mg/70 kg morphine, O15 = 15 mg/70 kg oxycodone, and O45 = 45 mg/70 kg oxycodone. One asterisk represents $P \leq 0.05$, two asterisks represent $P \leq 0.01$, and three asterisks represent $P \leq 0.001$ for the comparison indicated by the line beneath the asterisk(s).

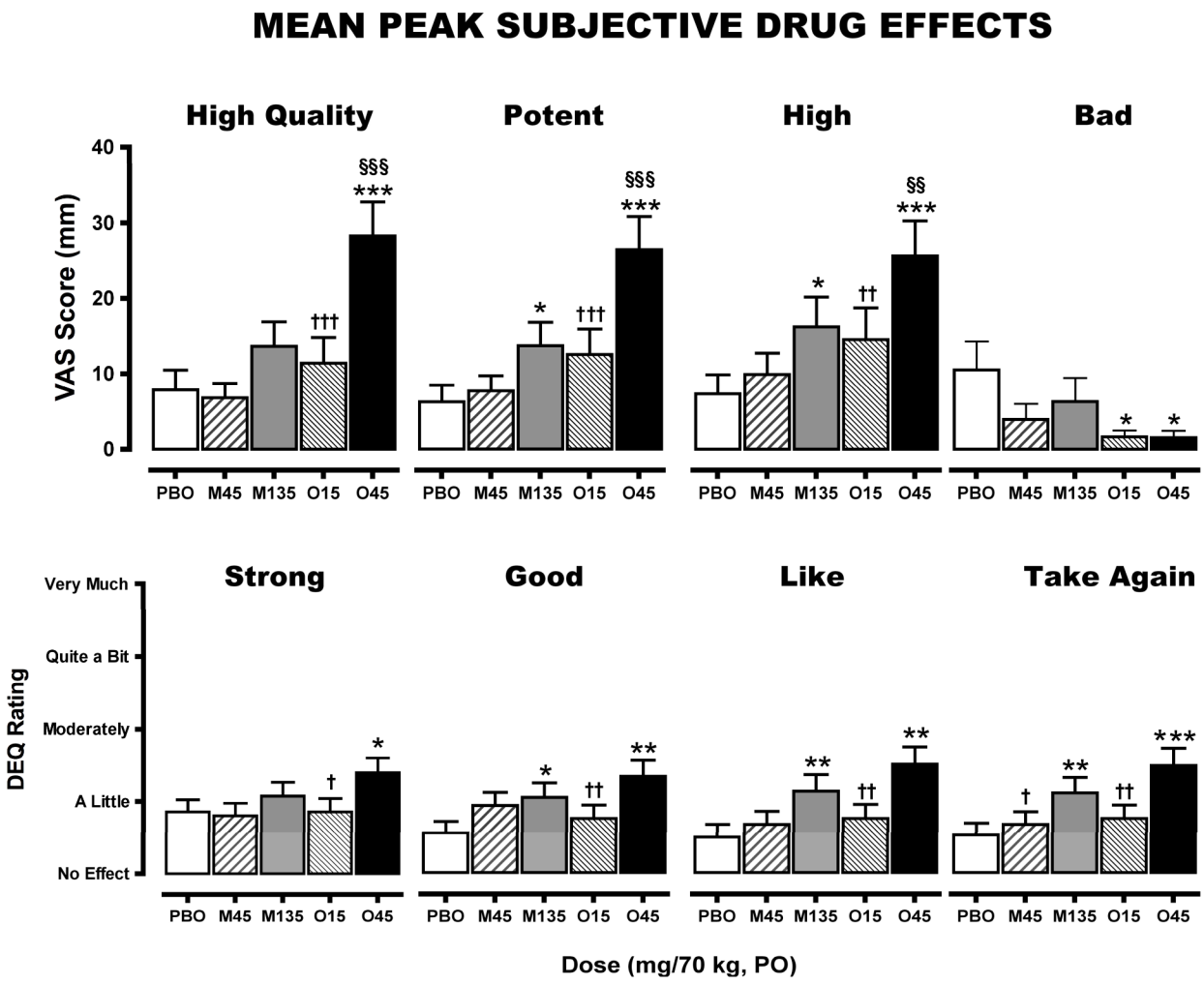

Figure 3.

Select mean peak subjective ratings completed during sample sessions. The top panels display mean peak ratings (± 1 SEM) on the Visual Analog Scale as a function of drug and dose. The bottom panels display mean peak ratings (± 1 SEM) on the Drug Effects Questionnaire as a function of drug and dose. PBO = placebo, M45 = 45 mg/70 kg morphine, M135 = 135 mg/70 kg morphine, O15 = 15 mg/70 kg oxycodone, and O45 = 45 mg/70 kg oxycodone. * represents a significant difference from placebo; † represents a significant difference between the low and high doses, and § represents a significant difference between high dose morphine and high dose oxycodone. One symbol represents $P \leq 0.05$, two symbols represent $P \leq 0.01$, and three symbols represent $P \leq 0.001$.

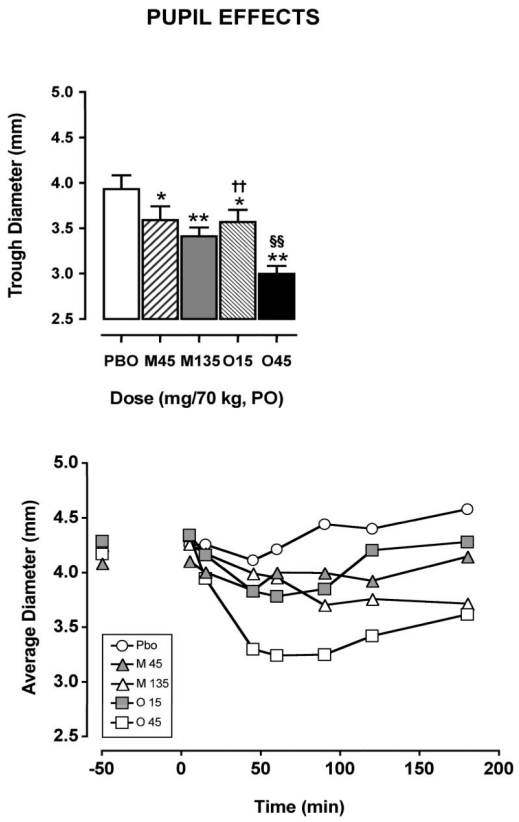

Figure 4.

Mean trough and time course of pupil diameter changes (± 1 SEM) during sample sessions. The top panel displays trough diameters as a function of drug and dose. * represents a significant difference from placebo; † represents a significant difference between the low and high doses, and § represents a significant difference between high dose morphine and high dose oxycodone. One symbol represents $P \leq 0.05$, two symbols represent $P \leq 0.01$, and three symbols represent $P \leq 0.001$. The bottom panel displays mean values as a function of drug and dose across time. Circles represent placebo, grey triangles represent 45 mg/70 kg morphine, open triangles represent 135 mg/70 kg morphine, grey squares represent 15 mg/70 kg oxycodone, and open squares represent 45 mg/70 kg oxycodone. Error bars were omitted for clarity.

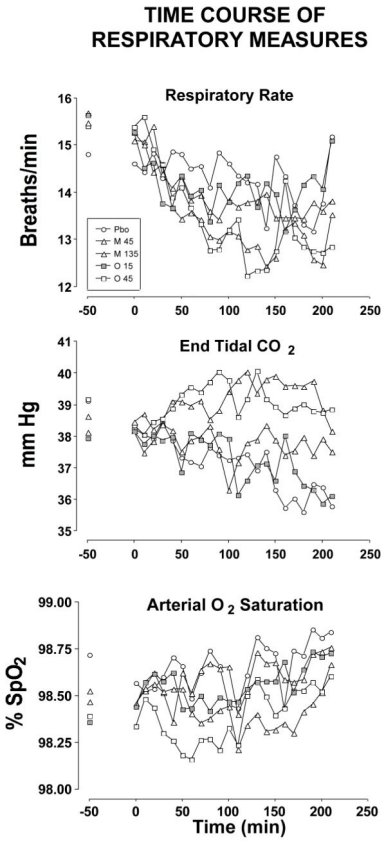

Figure 5.

Time course of respiratory measures collected during sample sessions. The panels display mean values for respiratory rate (top panel), end tidal CO_2 (middle panel), and arterial O_2 saturation (bottom panel) as a function of drug and dose across time. Circles represent placebo, grey triangles represent 45 mg/70 kg morphine, open triangles represent 135 mg/70 kg morphine, grey squares represent 15 mg/70 kg oxycodone, and open squares represent 45 mg/70 kg oxycodone. Error bars were omitted for clarity.

Table 1

Study design.

Study Week	Mon	Tue	Wed	Thu	Fri
Week 1	Stabilization on 4 mg sublingual buprenorphine				
Week 2					
Drug vs Money					
AM	Sample (Dose 1, $)	Sample (Dose 2, $)	Sample (Dose 3, $)	Sample (Dose 4, $)	Sample (Dose 5, $)
PM	Choice (Dose 1 or $)	Choice (Dose 2 or $)	Choice (Dose 3 or $)	Choice (Dose 4 or $)	Choice (Dose 5 or $)
Weeks 3–8					
Drug vs Drug					
AM	Sample (Dose A)	Sample (Dose B)	Choice (A, B, N)*	Choice (A, B, N)	Choice (A, B, N)
PM			Choice (A, B, N)	Choice (A, B, N)	Choice (A, B, N)

*A = Dose A

B = Dose B

N = Neither

Table 2

Sample session events.

Time (min)	Events
Baseline (−40)	Physiological monitoring initiated, Pupil, SOWS, VAS, OSC, performance*
0	**Drug and/or money administration**
5	Pupil, DEQ, VAS, OSC
15	Pupil, DEQ, VAS, OSC, performance
45	Pupil, DEQ
60	Pupil, DEQ, VAS, OSC, performance
90	Pupil, DEQ
120	Pupil, DEQ, VAS, OSC, performance
180**	Pupil, DEQ, VAS, OSC, performance, SOWS

* Session events:

- Physiological monitoring = Respiratory and cardiovascular monitoring initiated
- Pupil = Pupil photograph taken
- SOWS = Subjective Opioid Withdrawal Scale
- VAS = Visual Analog Scale
- OSC = Opioid Symptom Checklist
- DEQ = Drug Effects Questionnaire
- Performance = Digit Symbol Substitution Task, Divided Attention Task, Rapid Information Processing Task, Repeated Acquisition of Response Sequences Task

** During week 2, sample sessions ended after the events were completed at 120 min. During weeks 3–8, the sample sessions were extended to 180 min in order to obtain a more complete assessment of the time course of drug effects. Choice sessions were similar to sample sessions except that the self-administration task was completed prior to drug administration.

Table 3

Mean peak subjective ratings ± 1 standard error of the mean (SEM) for the Visual Analog Scale (VAS), Drug Effects Questionnaire (DEQ), Opioid Symptom Checklist (OSC), and Subjective Opioid Withdrawal Scale (SOWS) after administration of placebo, morphine (45 and 135 mg/70 kg) and oxycodone (15 and 45 mg/70 kg).

	PLACEBO		MOR 45		MOR 135		OXY 15		OXY 45	
	Mean	***SEM***	***Mean***	***SEM***	***Mean***	***SEM***	***Mean***	***SEM***	***Mean***	***SEM***
VAS										
Good	*7.9*	*2.4*	*10.0*	*2.5*	*19.0*[a]	*4.6*	*12.3*	*3.8*	*27.4*[a,b,d]	*4.6*
I Would Pay	*1.0*	*0.4*	*2.0*	*0.6*	*3.7*[a]	*1.0*	*2.3*	*0.7*	*5.8*[a,b,c,d]	*1.0*
Like	*8.1*	*2.5*	*8.4*	*2.3*	*15.5*	*3.9*	*12.7*	*3.7*	*24.7*[a,b,c,d]	*3.9*
Mellow	*13.1*	*3.1*	*19.1*	*3.9*	*22.4*[a]	*4.2*	*16.1*	*3.5*	*26.0*[a,d]	*4.3*
Sedated	*9.4*	*2.9*	*8.5*	*2.6*	*12.5*	*2.7*	*13.5*	*3.2*	*17.9*[a,b]	*4.2*
DEQ										
Bad	*0.4*	*0.1*	*0.1*[a]	*0.1*	*0.2*	*0.1*	*0.03*[a]	*0.03*	*0.2*[a]	*0.1*
OSC										
Sum	*1.9*	*0.3*	*2.6*	*0.4*	*3.2*[a]	*0.4*	*2.7*	*0.4*	*3.8*[a,b,c,d]	*0.5*
SOWS										
Sum	*9.0*	*1.5*	*6.6*[a]	*0.8*	*7.2*[a]	*1.0*	*6.9*[a]	*1.0*	*5.9*[a]	*0.7*

Significant differences are indicated by the superscripts: *a* represents a significant difference from placebo, *b* represents a significant difference from MOR 45, *c* represents a significant difference from MOR 135, and *d* represents a significant difference from OXY 15 ($P \leq 0.05$). For additional VAS and DEQ ratings see figure 3.