Drug and Alcohol Dependence 101 (2009) 107–114

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Within-subject comparison of the psychopharmacological profiles of oral hydrocodone and oxycodone combination products in non-drug-abusing volunteers

James P. Zacny*, Sandra Gutierrez

Department of Anesthesia and Critical Care, The University of Chicago, Chicago, IL, USA

ARTICLE INFO

Article history:
Received 26 September 2008
Received in revised form
18 November 2008
Accepted 20 November 2008
Available online 31 December 2008

Keywords:
Oxycodone
Hydrocodone
Prescription opioid
Subjective
Potency
Human

ABSTRACT

Background: Non-medical use and abuse of prescription opioids is a significant problem in the United States. Little attention has been paid to assessing the relative psychopharmacological profile (including abuse liability-related effects) of specific prescription opioids. The purpose of this study was to directly compare the psychopharmacological profile of two widely prescribed and abused oral opioid combination products within the same subject.

Methods: Twenty non-drug-abusing volunteers participated in a crossover, randomized, double-blind study in which they received, all p.o.: placebo; 975 mg acetaminophen (ACET); 10 mg oxycodone (OXY)/487 mg ACET; 20 mg OXY/975 mg ACET; 15 mg hydrocodone (HYD)/487 mg ACET; and 30 mg HYD/975 mg ACET. OXY and HYD doses were chosen to equate the drugs on an objective measure of opiate effects: miosis. Dependent measures were subjective, psychomotor/cognitive, reinforcing, and physiological effects, and relative potency estimates.

Results: In general, the two opioid combination products at equi-miotic doses produced similar prototypic opiate-like effects and psychomotor impairment, and of similar magnitude. The higher dose of OXY/ACET produced slightly more abuse liability-related subjective effects than the higher dose of HYD/OXY, but also produced slightly more negative effects. Neither drug at either dose functioned as a reinforcer, as measured by the Multiple Choice Procedure. Relative potency ratios indicated that OXY/ACET was approximately 1.5 times more potent than HYD/ACET.

Conclusions: Consistent with a recent study published in this journal using identical doses of HYD and OXY (without ACET) in prescription opioid abusers (Walsh, S.L., Nuzzo, P.A., Lofwall, M.R., Holtman Jr., J.R., 2008. The relative abuse liability of oral oxycodone, hydrocodone and hydromorphone assessed in prescription drug abusers. Drug Alcohol Depend. 198, 191–202), we found little difference in the pharmacodynamic effects of HYD/ACET and OXY/ACET in non-drug-abusing volunteers.

1. Introduction

Over the last ten years, non-medical use and abuse of prescription opioids has been a serious problem in the United States and has caused a great deal of concern amongst law enforcement officials, and medical, regulatory, pain relief advocacy, and drug abuse organizations. The National Survey on Drug Use and Health reported that in 2007, the percentage of people aged 12 years and old who had used prescription opioids for non-medical purposes in the prior 12 months was 5%. This past-year prevalence rate exceeded that of cocaine, hallucinogens and inhalants and was only exceeded by marijuana (10.1%) [Substance Abuse and Mental Health Services Administration (SAMHSA), 2008a]. Other epidemiological databases that track prevalence of drug use in secondary school students (Monitoring the Future study), emergency room admissions related to drug abuse (Drug Abuse Warning Network), and admission to drug abuse treatment centers (Treatment Episode Data Set) also reflect the magnitude of the problem (Johnston et al., 2008; SAMHSA, 2007, 2008c). One potential cause of the problem is that over the last 15 years or so, availability of prescription opioids for medical purposes has increased markedly (Caudill-Slosberg et al., 2004; Gilson et al., 2004; Zacny et al., 2003), thus increasing amount of drug available for diversion (Dasgupta et al., 2006; Katz et al., 2007). One recent study determined that increasing sales of specific prescription opioids were correlated with increased prescription opioid poisoning deaths, and the authors presented evidence that some of these deaths were most likely due to misuse of opioids, alone or with other drugs (e.g., alcohol) [Paulozzi et al., 2006]. It

* Corresponding author at: Department of Anesthesia and Critical Care, MC4028, The University of Chicago, 5841 S. Maryland Avenue, Chicago, IL 60637, USA. Tel.: +1 773 702 9920; fax: +1 773 834 9714.
E-mail address: jzacny@dacc.uchicago.edu (J.P. Zacny).

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doi:10.1016/j.drugalcdep.2008.11.013

should be pointed out that other countries are starting to report that abuse of prescription opioids is on the rise (Fischer et al., 2008), so the problem is not limited to the United States.

Oxycodone (OXY) and hydrocodone (HYD) are semi-synthetic opioids prescribed in oral form for the treatment of moderately severe to severe pain. In the United States, prevalence of non-medical use of products containing OXY and HYD is relatively high (Cicero et al., 2005; SAMHSA, 2008b; Zacny et al., 2003). Despite the substantial prevalence in non-medical use, when reviewing the literature several years ago, we were surprised to find no studies that had tested the relative abuse liability of the two opioids. In fact, we found few studies that had tested the relative abuse liability of prescription opioids in the formulations by which they are prescribed. Such studies are important given the magnitude of non-medical use of prescription opioids, relative to other psychotherapeutic drugs and illicit drugs in the United States (SAMHSA, 2008a).

Recently we examined the relative psychopharmacological profiles of oral OXY and morphine (MOR) in non-drug-abusing volunteers (Zacny and Lichtor, 2008). Key dependent measures included abuse liability-related subjective effects (e.g., euphoria, liking) and reinforcing effects, as measured by a modified version of the Multiple Choice Procedure (MCP) (Griffiths et al., 1993). We based the doses that we tested (10 and 20 mg of OXY, 30 and 60 mg of MOR) on miosis, an objective physiological marker of mu opioid agonist effects, and a standard measure used in abuse liability testing (Bigelow, 1991; Jasinski, 1977). Miosis is correlated with plasma opioid concentration, ability to suppress abstinence, incidence of side effects, and intensity of euphoria (e.g., Fraser et al., 1954; Jasinski, 1977; Lalovic et al., 2006). At the two higher doses of OXY and MOR that produced equivalent degrees of miosis, the two drugs produced a number of similar effects. However there were some differences—20 mg of OXY, but not 60 mg of MOR, increased visual analog scale (VAS) ratings of "elated," "drunk," and "stimulated," and ratings on a bipolar VAS of "drug liking." Both drugs produced unpleasant effects (e.g., VAS ratings of nauseated, drug disliking) but the effects were more pronounced in the 60 mg MOR condition. Neither drug functioned as a reinforcer as measured by the MCP. The fact that there were some differences, coupled with the paucity of studies examining relative psychopharmacological profiles of widely prescribed and abused prescription opioids, prompted us to conduct the present study comparing OXY and HYD at equi-miotic doses. Because HYD is not prescribed as a single-entity product in the United States, we chose to compare HYD and OXY in combination with ACET.

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. Upon completion of the study, a debriefing session was held and payment for participation in the study was remitted. To be eligible for the study, subjects had to (1) be between the ages of 21–39, (2) consume at least three alcoholic drinks per month, (3) be verbally fluent in English, and (4) have obtained a high school diploma or equivalent. Subjects were excluded if 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-Text Revision (TR) (DSM-IV-TR) [American Psychiatric Association, 2000].

Three participants did not complete the study for reasons unrelated to the study. A fourth research subject's data were dropped after study completion because, after speaking with the subject during a post-study debriefing session, it was determined that the volunteer did not fully understand how to complete the questionnaires. The four participants' demographic data are not included below. Twenty healthy volunteers, ten men and ten women, with a mean age (+SD) of 24.3 ± 3.0 years and BMI of 23.1 ± 2.6, completed the study. All subjects had some history of recreational drug use, but none had histories indicative of abuse or dependence (American Psychiatric Association, 2000). Self-reported recreational drug use within the 30 days prior to study participation revealed the following: nineteen volunteers consumed alcohol (averaged 4.4 ± 2.1 drinks per week); eight smoked tobacco cigarettes (with the exception of one participant who smoked five, use did not exceed two cigarettes per day); and seven used marijuana (no more than two joints per week). Four subjects reported non-medical opioid use in their lifetimes (reported as Darvocet, opium, Tylenol-3/Codeine, or Vicodin). Two of the subjects reported non-medical use of one opioid (less than ten times lifetime), one subject reported non-medical use of two opioids (each opioid less than 10 times lifetime), and one subject reported non-medical use of the four opioids (two opioids less than 10 times lifetime and two opioids 10–50 times lifetime). Self-reported lifetime medical opioid use revealed that thirteen volunteers used opioids (reported as Demerol or Meperidine, Methadone, Percocet or Percodan, Tylenol-3/Codeine, Vicodin or Lortab, and "opioids not listed above").

2.2. Drugs and doses

In the Zacny and Lichtor (2008) study we compared 10 and 20 mg of OXY to 30 and 60 mg of MOR. In the present study, for the sake of consistency, we chose to test the same doses of OXY. We used miosis data from prior studies conducted in our laboratory to calculate doses of HYD that we estimated would be equi-miotic to OXY (Zacny and Gutierrez, 2003; Zacny et al., 2005), i.e., 12.5 and 25 mg. We have tested 20 mg HYD without any adverse events, but to the best of our knowledge 25 mg had not been tested in healthy volunteers. A group in Canada tested 22.5 mg HYD in recreational drug users, and no adverse events were reported (Kaplan et al., 1997). We conducted a dose run-up pilot study with 0, 20, and 25 mg of HYD ($N = 4$) to ensure 25 mg was well tolerated and to inform us whether miosis was increased with the 25 mg dose, relative to the 20 mg dose. The 25 mg dose was well tolerated but miosis was not appreciably different from the 20 mg dose. We, therefore, initiated another dose run-up pilot study with 0, 25, and 30 mg of HYD ($N = 5$). Thirty mg was well tolerated and produced miotic effects that were clearly different from the 20 mg dose tested in the first pilot study. Therefore, doses of 15 and 30 mg of HYD were tested in the study. After six subjects had completed the study protocol, the miotic effects of the higher dose of HYD/ACET were compared to those of the higher dose of OXY/ACET to determine if both opioids produced similar degrees of miosis, and they did. Had they not, dose adjustments would have been made. Doses of ACET were matched between the two drug combination products as described below.

During separate sessions, participants ingested 150 ml of water with three #00 capsules that contained 15 mg HYD/487 mg ACET; 30 mg HYD/975 mg ACET; 10 mg OXY/487 mg ACET; 20 mg OXY/975 mg ACET; 975 mg ACET; or placebo (lactose). ACET was tested alone to rule out the possibility that it had any psychotropic effects. All drugs were placed into opaque gelatin blinding capsules by an Investigational Drug Service pharmacist at the University of Chicago Hospitals.

2.3. Design and procedures

The study was a randomized, placebo-controlled, double-blind, crossover trial consisting of seven sessions (at least one week apart) that took place in a departmental laboratory from 0845–1430 h. Subjects were instructed to not eat food or drink non-clear liquids for 4 h, drink clear liquids for 2 h, or use any drugs (excluding normal amounts of caffeine and nicotine) 24 h prior to sessions. Breath alcohol, urine toxicology, and pregnancy (for females) tests were given before sessions, and volunteers were in a semi-recumbent position in a hospital bed for all sessions. All breath alcohol, urine toxicology, and pregnancy screens were negative.

For the first six sessions, at baseline, subjects completed several subjective effects forms and psychomotor tests, and their physiological status was assessed. Subjects were then told by the research technician conducting the session that "The capsules you are about to ingest may or may not contain a drug," and the anesthetist administered the capsules. For 300 min after capsule ingestion, mood, psychomotor performance, and physiological measures were assessed at fixed time intervals. After the session ended, participants were instructed not to engage in certain activities for the next 12 h (e.g., cooking, driving, drinking alcohol), given questionnaires to complete at home 24 h after the session, and transported home via a livery service.

For the seventh session ("Lottery Session"), volunteers were presented with a bowl containing 234 slips of paper (representing all of the choices they made on a Multiple Choice Procedure Form [see below] 24 h after each of the first six sessions). Participants randomly selected one slip from among the 234 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 all other experimental sessions.

2.4. Dependent measures

The following tests were completed before capsule ingestion (baseline), as well as at fixed time points thereafter (at 60, 120, 180, 240, and 300 min unless otherwise noted).

2.4.1. 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 VAS, a Drug Effect/Drug Liking/Take Again (DEL/TA) questionnaire, and a locally developed 20-item post-session sequelae questionnaire (PSQ) that assessed residual effects of the drug that subjects were asked to complete 24 h after the session. The VAS and DEL/TA questionnaire were administered at 15, 30, 90, 150, 210, and 270 min after capsule ingestion, in addition to the time points listed above. 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]. Overall drug liking and overall "want to take drug again" were also assessed at the end of each session and 24 h later on a modified version of the DEL/TA.

2.4.2. Multiple Choice Procedure

The reinforcing effects of each drug 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). The participant randomly selected from among his/her 234 choices (39 choices × 6 experimental sessions), with each choice on a slip of paper at the beginning of his/her seventh session to provide intermittent reinforcement of drug vs. money choices made on the previous sessions. Subjects were instructed to complete the MCP 24 h following each of the first six sessions. The choice behavior was reinforced: 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 MCP has been utilized in a number of studies that putatively measure reinforcing effects of drugs (e.g., Alessi et al., 2003; Stoops et al., 2003; Tancer and Johanson, 2003). The MCP 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).

2.4.3. Psychomotor/cognitive performance

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. The DSST was administered at 15, 30, 90, 150, 210, and 270 min after capsule ingestion, in addition to the time points listed above. The memory test was administered 90 min after capsule ingestion and immediate recall was assessed, and then 210 min later subjects were tested for delayed recall.

2.4.4. Physiological measures

Six physiological measures were assessed: heart rate, blood pressure, arterial oxygen saturation, respiration rate, exophoria, and pupil size. Eye pictures were taken at baseline and at 30, 60, 120, 180, and 300 min post-capsule ingestion.

2.5. Statistical analyses

Repeated-measures analysis of variance (ANOVA) was used for statistical treatment of the data (SigmaStat, Point Richmond, CA). The primary analysis compared peak (highest value obtained), trough (lowest value obtained), or mean effects of the six drug conditions. In the peak and trough analyses, only post-capsule administration values were included, and values were determined for each subject independent of time point. Mean effect analyses were done on those measures that were assessed only once either during or after experimental sessions. F values were considered significant for $p < 0.05$. Holm-Sidak post hoc testing was done, comparing each of the five active drug conditions to placebo, and when appropriate, comparing one active drug condition to another. A secondary analysis measured time course of drug effects, but for the sake of brevity only a selected number of measures will be presented in the "Results" section.

We conducted a relative potency analysis of the two opioid combination products using the same procedure and criteria as that used in Zacny and Lichtor (2008). Briefly, peak, trough, and mean effects data from the two OXY/ACET conditions and the two HYD/ACET conditions were analyzed using Finney's (1964) method for parallel line bioassays. The analysis of parallel line bioassays is used to determine the relative potency of two compounds. This analysis was used to determine that the dose-response function did not deviate from parallelism ($p > 0.05$) and showed significant regression (the slopes of the dose-response functions were significantly different from 0, $p < 0.05$) without preparation differences (overall effect magnitude did not differ across drugs, $p > 0.05$) Specifically, data that yielded statistically significant effects (i.e., from those measures on which one or more active drug conditions differed significantly from placebo), and which were collected during the session were used in these analyses.

3. Results

Table 1 summarizes mean peak, trough, or average values (±SEM) of measures significantly affected by one or more of the active drug conditions relative to placebo. ACET data are not shown because in all measures of the study, this drug did not differ from placebo. It is important to emphasize at the outset that the two higher doses of OXY/ACET and HYD/ACET significantly reduced pupil size to the same extent relative to placebo, and this also held true at the lower doses, although the degree of miosis was lesser. The time course of miosis for OXY/ACET was similar to that of HYD/ACET (Fig. 1, top frame).

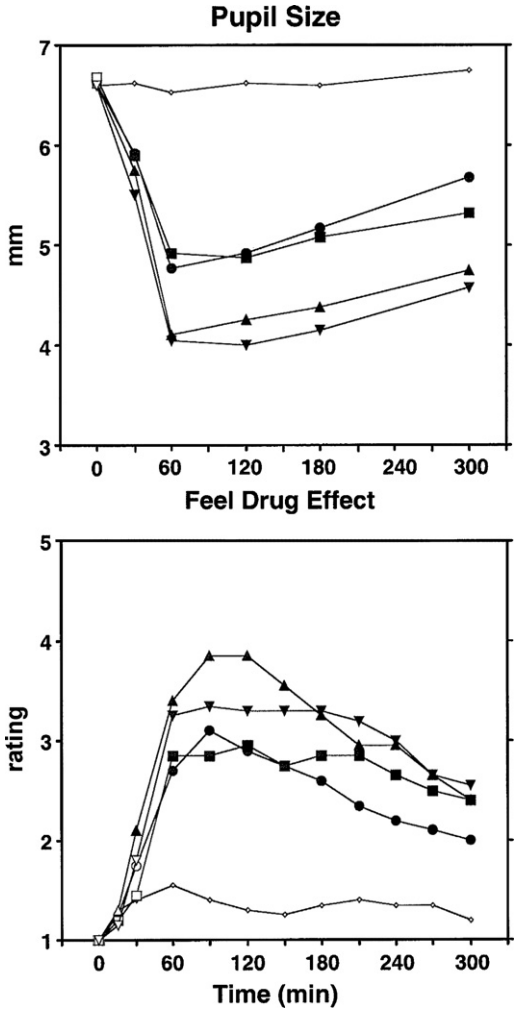

Fig. 1. Time course of the effects of 10 mg OXY/487 mg ACET (circle), 20 mg OXY/975 mg ACET (triangle), 15 mg HYD/487 mg ACET (square), 30 mg HYD/975 mg ACET (inverted triangle), and placebo (diamond) on pupil size (top frame) and "feel drug effect" ratings from the DEL/TA (bottom frame). Data from the 975 mg ACET condition are excluded from the graphs for the sake of clarity. Each point represents the mean across 20 subjects. Solid symbols on the graph indicate that an active dose of the drug is significantly different from placebo at a given time point (Holm-Sidak post hoc test; $p < 0.05$).

Table 1
Mean peak, trough, or average values (± SEM) of measures significantly affected by one or more of the active drug conditions relative to placebo.

Dependent Measures	Overall *p* value	PLACEBO	10 mg OXY/487 mg ACET	15 mg HYD/487 mg ACET	20 mg OXY/975 mg ACET	30 mg HYD/975 mg ACET
Subjective Measures						
Addiction Research Center Inventory						
A[a] (range: 0–11)	0.001	1.8 (0.3)	2.7 (0.3)	2.4 (0.3)	3.0 (0.4)[d]	2.3 (0.2)
BG[b] (range: 0–13)	<0.001	4.1 (0.3)	2.5 (0.4)[d]	3.1 (0.4)	2.3 (0.4)[d]	2.0 (0.4)[d]
LSD[a] (range: 0–14)	<0.001	3.4 (0.2)	4.8 (0.5)	4.2 (0.4)	6.5 (0.5)[d]	5.2 (0.5)[d]
PCAG[a] (range: 0–15)	<0.001	5.8 (0.6)	8.6 (0.7)[d]	8.2 (0.7)[d]	9.2 (0.7)[d]	9.4 (0.6)[d]
Visual Analog Scale (range: 0–100)						
Coasting ('spaced out')[a]	<0.001	6.9 (2.7)	24.0 (5.2)	22.5 (6.5)	37.9 (6.4)[d]	42.5 (6.3)[d]
Difficulty concentrating[a]	<0.001	16.0 (5.7)	37.0 (7.6)[d]	32.3 (7.3)	48.3 (7.1)[d]	49.5 (8.0)[d]
Dizzy[a]	<0.001	2.3 (0.9)	12.7 (4.6)	13.0 (4.4)	29.1 (6.9)[d]	25.0 (6.6)[d]
Dreamy[a]	<0.001	9.1 (4.3)	28.1 (7.3)[d]	19.3 (6.3)	35.2 (6.7)[d]	39.5 (7.2)[d]
Feel bad[a]	<0.001	7.5 (3.0)	14.6 (4.8)	14.5 (4.3)	29.3 (6.9)[d]	25.5 (7.0)[d]
Floating[a]	<0.001	1.6 (0.5)	17.8 (6.4)	16.0 (5.6)	30.9 (6.3)[d]	22.1 (5.2)[d]
Having unpleasant bodily sensations[a]	<0.001	6.0 (2.2)	16.4 (6.0)	12.1 (4.0)	31.1 (6.8)[d]	28.0 (6.6)[d]
Heavy or sluggish feeling[a]	<0.001	18.7 (5.6)	40.8 (7.3)[d]	36.5 (7.5)	53.5 (6.5)[d]	58.9 (7.3)[d]
High ('drug' high)[a]	<0.001	5.3 (3.8)	22.4 (5.5)	16.2 (4.6)	44.9 (7.2)[d]	37.1 (7.6)[d]
In control of body[b]	<0.01	95.9 (1.6)	72.1 (7.6)[d]	83.3 (6.4)	69.8 (6.7)[d]	73.8 (5.6)
Lightheaded[a]	<0.001	3.6 (1.2)	15.2 (5.6)	15.9 (4.9)	35.4 (8.0)[d]	30.8 (7.3)[d]
Nauseated[a]	<0.001	1.1 (0.5)	16.8 (5.4)	16.0 (6.7)	33.9 (8.2)[d]	30.4 (8.0)[d]
Sedated (calm, tranquil)[a]	<0.001	24.1 (6.6)	38.2 (5.9)	34.1 (6.7)	46.1 (7.5)[d]	51.2 (6.0)[d]
Sleepy (drowsy, tired)[a]	<0.001	44.0 (6.6)	55.0 (6.5)	50.5 (6.6)	64.4 (5.9)[d]	70.1 (6.1)[d]
Tingling[a]	0.01	2.6 (1.3)	8.5 (4.2)	5.2 (1.3)	18.0 (5.1)[d]	9.8 (3.7)
Opiate Adjective Rating Scale (range: 0–4)						
Dry mouth[a]	<0.05	0.1 (0.1)	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)	0.9 (0.3)[d]
Flushing[a]	<0.005	0.1 (0.1)	0.3 (0.1)	0.4 (0.2)	0.9 (0.3)[d]	0.5 (0.2)
Nodding[a]	<0.001	0.3 (0.1)	1.2 (0.3)[d]	0.9 (0.3)	1.5 (0.3)[d]	1.2 (0.3)[d]
Numb[a]	<0.01	0.0 (0.0)	0.2 (0.1)	0.4 (0.2)	0.7 (0.3)[d]	0.6 (0.2)
Skin itchy[a]	<0.001	0.1 (0.1)	0.9 (0.3)[d]	1.0 (0.2)[d]	1.8 (0.3)[d]	1.4 (0.3)[d]
Sweating[a]	<0.001	0.0 (0.0)	0.2 (0.1)	0.3 (0.1)	0.9 (0.3)[d]	0.7 (0.3)[d]
Turning of stomach[a]	<0.001	0.0 (0.0)	0.5 (0.2)	0.5 (0.2)	1.1 (0.3)[d]	1.2 (0.3)[d]
Drug Effect/Drug Liking/Take Again (range: 1–5/0–100/0–100)						
Feel drug effect[a]	<0.001	2.0 (0.2)	3.4 (0.2)[d]	3.3 (0.2)[d]	4.2 (0.2)[d]	4.0 (0.2)[d]
Drug liking[a]	<0.001	55.0 (2.3)	65.7 (3.6)[d]	59.1 (3.1)	65.9 (3.0)[d]	63.2 (3.4)
Drug liking[b]	<0.001	46.9 (1.4)	39.6 (3.2)	34.1 (3.5)[d]	26.8 (4.3)[d]	33.2 (3.7)[d]
Drug liking (24 h after session)[c]	<0.005	50.8 (2.2)	51.6 (4.3)	41.7 (4.2)	34.5 (6.0)[d]	37.1 (5.6)
Take again[a]	<0.005	56.3 (2.3)	67.8 (3.6)[d]	59.8 (3.3)	64.8 (3.0)	62.4 (3.4)
Take again[b]	<0.001	47.4 (1.6)	40.6 (3.6)	34.2 (3.8)[d]	29.2 (4.8)[d]	34.1 (4.2)[d]
Take again (24 h after session)[c]	<0.001	50.8 (2.9)	49.5 (5.4)	45.0 (5.0)	29.0 (5.9)[d]	37.3 (5.8)
Post Session Sequelae Questionnaire (range: 0–4)						
Coasting ('spaced out')[c]	<0.001	0.0 (0.0)	0.1 (0.1)	0.2 (0.1)	0.4 (0.1)[d]	0.2 (0.1)
Difficulty concentrating[c]	<0.005	0.1 (0.1)	0.1 (0.1)	0.2 (0.1)	0.3 (0.1)	0.5 (0.2)[d]
Drowsiness[c]	<0.001	0.2 (0.1)	0.6 (0.2)	0.6 (0.2)	0.5 (0.2)	1.2 (0.3)[d]
Feel bad[c]	<0.05	0.1 (0.1)	0.3 (0.1)	0.6 (0.2)	0.8 (0.2)	0.9 (0.3)[d]
Heavy or sluggish feeling[c]	<0.001	0.1 (0.1)	0.5 (0.2)	0.5 (0.2)	0.9 (0.2)[d]	1.0 (0.2)[d]
Nausea[c]	<0.001	0.0 (0.0)	0.4 (0.2)	0.6 (0.3)	1.0 (0.2)[d]	0.9 (0.2)[d]
Skin itchy[c]	<0.05	0.0 (0.0)	0.2 (0.1)	0.1 (0.1)	0.4 (0.1)[d]	0.1 (0.1)
Reinforcing Measures						
Multiple Choice Procedure (range: -$10–$10)						
Crossover point (dollars)[c]	<0.001	−0.6 (0.3)	−0.6 (0.9)	−1.1 (0.6)	−4.5 (1.1)[d]	−2.1 (1.0)
Psychomotor/Cognitive Measures						
DSST						
Number of symbols drawn[b]	<0.001	45.0 (2.3)	39.4 (2.5)[d]	40.9 (2.5)	35.8 (2.0)[d]	38.1 (2.7)[d]
Number of symbols drawn correctly[b]	<0.001	44.4 (2.3)	38.7 (2.5)[d]	40.4 (2.6)	35.2 (2.0)[d]	37.4 (2.6)[d]
Logical Reasoning Test						
Number of statements answered[b]	<0.001	18.4 (1.0)	15.2 (1.1)[d]	15.6 (0.9)[d]	13.8 (0.8)[d]	14.9 (1.0)[d]
Number of statements answered correctly[b]	<0.001	17.7 (1.1)	14.1 (1.1)[d]	14.4 (0.9)[d]	12.6 (0.7)[d]	14.0 (1.0)[d]
Eye-Hand Coordination Test						
Seconds outside of circle[a]	<0.05	9.4 (0.8)	14.2 (2.3)	13.3 (2.0)	14.6 (1.5)	16.1 (2.3)[d]
Auditory Reaction Test						
Mean reaction time (milliseconds)[a]	<0.01	317 (12)	339 (12)	336 (17)	335 (11)	362 (16)[d]
Physiological Measures						
Respiration rate (breaths/min)[b]	<0.005	12.2 (0.6)	10.5 (0.4)[d]	11.6 (0.5)	10.9 (0.4)	10.6 (0.4)[d]
Exophoria (prism diopters)[a]	<0.001	3.5 (0.8)	5.5 (0.8)	5.7 (0.9)[d]	9.1 (1.0)[d]	7.7 (1.2)[d]
Pupil size (mm)[b]	<0.001	6.2 (0.2)	4.5 (0.3)[d]	4.6 (0.3)[d]	3.7 (0.2)[d]	3.8 (0.3)[d]

Abbreviations: ACET = acetaminophen; OXY = oxycodone; HYD = hydrocodone; A = Amphetamine Scale (amphetamine-like effects); BG = Benzedrine Group (benzedrine-like effects, intellectual efficiency, and energy); LSD = Lysergic Acid Diethylamide Scale (somatic-dysphoric effects); MBG = Morphine-Benzedrine Group (euphoria and positive mood); PCAG = Pentobarbital-Chlorpromazine-Alcohol Group (sedation).

[a] Peak rating analysis.

[b] Trough rating analysis.

[c] Average rating analysis.

[d] Peak/trough/average analyses: Holm-Sidak post hoc analysis determined significant difference from placebo.

3.1. Subjective effects

3.1.1. Addiction Research Center Inventory. Analyses of peak/trough scores indicated that four scales of the ARCI were altered by one or more of the drug conditions. Apart from the A scale, the two lower doses of OXY/ACET and HYD/ACET produced effects similar in magnitude to each other (although some effects did not achieve statistical significance relative to placebo), and the two higher doses produced greater effects that were also similar in magnitude to each other. Only the higher dose of OXY/ACET significantly increased peak scores on the A scale relative to placebo. Time course analyses revealed that both doses of OXY/ACET increased scores on the A scale at the 60-min post-capsule-ingestion time point. Time course analyses also showed that scores on the MBG scale were significantly increased by the higher dose of OXY/ACET (score of 2.8) at the 60-min time point relative to not only placebo (score of 1.45) but also to the higher dose of HYD/ACET (score of 1.35).

3.1.2. Visual analog scale. Analyses of peak ratings indicated that there were a number of VAS ratings that were significantly increased by both the higher doses of OXY/ACET and HYD/ACET, and the magnitude of effects were similar. In general, these ratings were not significantly increased by the two lower doses of OXY/ACET and HYD/ACET, although oftentimes there was a trend for values to be higher than in the placebo condition. Time course analyses showed that in most cases onset of effects occurred 60–90 min after ingestion of OXY/ACET and HYD/ACET. Two subjective effects, "in control of body" and "in control of thoughts," were significantly decreased by both doses of OXY/ACET, relative to placebo. The latter effect was only detected in the time course analysis.

3.1.3. Opiate adjective rating scale. Analyses of peak ratings indicated that there were a number of ratings that were significantly increased by both the higher doses of OXY/ACET and HYD/ACET, and the magnitude of effects were similar. Ratings of "skin itchy" were increased by both the lower and higher doses of OXY/ACET and HYD/ACET. Ratings of "dry mouth" were significantly increased only by the higher dose of HYD/ACET, relative to placebo. Although there was no significant effect on the peak rating of "vomiting," time course analyses revealed that at the 180-min post-capsule administration time point, ratings in the higher dose OXY/ACET condition (0.3) were significantly higher than ratings in the placebo condition (0.0).

3.1.4. Drug effect/drug liking/take again. Both doses of OXY/ACET and HYD/ACET increased peak "feel drug effect" ratings relative to placebo. Time course analyses revealed that the ratings were significantly increased 60 min after ingestion of both doses of OXY/ACET and HYD/ACET and remained elevated for the remainder of the sessions (Fig. 1, bottom frame). While the higher dose of OXY/ACET increased ratings of "feel drug effect" approximately 0.5 units higher than that of the higher dose of HYD/ACET at the 90- and 120-min post-capsule ingestion time points, the differences were not statistically significant. Peak ratings of drug liking were significantly increased by both doses of OXY/ACET but not by HYD/ACET. It should be noted, though, that peak liking ratings in the higher dose HYD/ACET condition were elevated relative to the placebo condition, and were similar to ratings in the higher dose OXY/ACET condition. Peak ratings of "take again" were significantly increased by only the lower OXY/ACET dose. Trough ratings of both drug liking and "take again" were significantly lowered relative to placebo by both doses of HYD/ACET and the higher OXY/ACET dose. Twenty-four hour ratings of drug liking and "take again" were significantly lowered relative to placebo by the higher OXY/ACET dose.

3.1.5. Post-session sequelae questionnaire. Table 1 shows that subjects reported several residual subjective effects occurring in the 24 h following the higher dose OXY/ACET and/or HYD/ACET sessions. Both OXY/ACET and HYD/ACET increased ratings of "nausea" and "heavy or sluggish feeling" relative to placebo. Based on ratings or comments on the PSQ, one and two subjects vomited in the lower dose OXY/ACET and HYD/ACET conditions, respectively, and five and five subjects vomited in the higher dose OXY/ACET and HYD/ACET conditions, respectively. It should be noted that based on comments made during the debriefing session, only one subject reported vomiting and feeling sick on the day following a session, and that was a session in which the higher dose of OXY/ACET was administered.

3.2. Multiple Choice Procedure

No dose of any active drug had crossover values that were significantly higher than placebo, which according to the MCP would have been indicative of reinforcing effects. Crossover values in the higher dose OXY/ACET condition were significantly lower than that of placebo; on average, subjects were willing to give up as much as $4.53 from their earnings to not receive the drug during the Lottery Session.

3.3. Psychomotor/cognitive performance

Performance on the DSST (number of symbols drawn, and drawn correctly) was significantly impaired relative to placebo, by both doses of OXY/ACET and the higher dose of HYD/ACET, as determined by analysis of trough values. Time course analyses revealed that both doses of OXY/ACET and HYD/ACET impaired DSST performance (number of symbols drawn, and drawn correctly). Impairment was detected as early as 30 min after capsule ingestion in the higher dose OXY/ACET condition and persisted to the end of the session. Performance on the logical reasoning test (number of completed and correct statements) was impaired by both doses of OXY/ACET and HYD/ACET, as determined by both analyses of trough and time course values. As with the DSST, impairment was evident up to or close to the end of the session. Eye-hand coordination was impaired by the higher dose of HYD/ACET in the trough analysis, but the time course analysis detected impairment by both doses of HYD/ACET and OXY/ACET. Auditory reaction time was longer in the higher dose HYD/ACET condition, relative to placebo, as determined by both peak and time course analyses. Immediate and delayed recall of a 15-word list did not differ significantly between conditions.

3.4. Physiological measures

Exophoria was induced by both doses of HYD/ACET and the higher dose of OXY/ACET, as determined by analysis of peak values. The time course analysis detected exophoria with both doses of OXY/ACET and HYD/ACET. Exophoria at the two higher doses of OXY/ACET and HYD/ACET was detected 60 min after capsule ingestion and persisted to the end of the session. Respiration rate was significantly decreased by both doses of OXY/ACET relative to placebo, as determined by analysis of trough values. Time course analyses revealed a significant decrease in rate by the higher doses of OXY/ACET and HYD/ACET at the 180-min post-capsule-ingestion time point.

3.5. Relative potency analysis

Table 2 lists relative potency estimates and 95% confidence intervals for those variables listed in Table 1 that met criteria for a valid bioassay. Out of the 41 variables listed in Table 1 that were assessed within the session, 20 met criteria. Relative potency estimates for

Table 2
Relative potency expressed as milligrams of hydrocodone necessary to produce the same effect as 1 mg oxycodone of all measures satisfying criteria for valid bioassay.

Dependent Measures	Relative potency	Confidence Interval
Subjective Measures		
Addiction Research Center Inventory		
BG[b]	1.74	0.73–10.53
PCAG[a]	1.62	0.62–6.40
Visual Analog Scale		
Coasting ('spaced out')[a]	1.41	0.72–2.50
Difficulty concentrating[a]	1.63	0.76–4.64
Dizzy[a]	1.64	0.96–3.23
Dreamy[a]	1.69	0.76–6.01
Feel bad[a]	1.67	0.79–5.11
Having unpleasant bodily sensations[a]	1.77	1.03–4.07
Heavy or sluggish feeling[a]	1.47	0.86–2.46
High ('drug' high)[a]	1.88	1.39–2.81
Lightheaded[a]	1.62	1.05–2.67
Nauseated[a]	1.65	0.64–7.39
Sedated[a]	1.46	0.76–2.67
Sleepy (drowsy, tired)[a]	1.46	0.74–2.74
Opiate Adjective Rating Scale		
Skin itchy[a]	1.80	1.13–3.57
Sweating[a]	1.70	0.88–4.60
Turning of stomach[a]	1.38	0.61–2.61
Drug Effect/Drug Liking/Take Again		
Feel drug effect[a]	1.72	1.29–2.44
Physiological Measures		
Exophoria (prism diopters)[a]	1.73	1.25–2.58
Pupil size (mm)[b]	1.61	1.31–2.00
Mean relative potency	1.63	

[a] Peak rating analysis.
[b] Trough rating analysis.

these variables ranged from 1.38 (OARS rating of "turning of stomach") to 1.88 (VAS rating of "high"). The relative potency estimate for pupil size was extremely close to the projected estimate of 1.5; it was 1.61. The overall geometric mean of the 20 variables was 1.63.

4. Discussion

At doses that produced equivalent degrees of miosis, OXY/ACET and HYD/ACET in general produced a similar profile of psychopharmacological effects. At the time we designed and conducted this study, there were no studies that we were aware of in the extant literature that examined the relative psychopharmacological profile of HYD and OXY, two widely prescribed opioids that also have substantial prevalence rates of non-medical use (Cicero et al., 2005; SAMHSA, 2008b; Zacny et al., 2003). A study has recently come out in this journal that conducted such an analysis in prescription opioid abusers (Walsh et al., 2008). Doses of OXY and HYD that were examined in the present study were also examined in the Walsh et al. (2008) study (as well as a higher dose of each). Similar pharmacodynamic assessments were made. The chief differences between the studies was the subject population, that an additional opioid, hydromorphone, was tested by Walsh et al. (2008), and OXY and HYD in the Walsh et al. (2008) study were assessed as single entities and not in combination with ACET. Walsh et al. (2008) concluded that there were no differences of note in the subjective effects profile of the three opioids. As stated above we came to an almost identical conclusion. The two chief differences in the results of the two studies were in the degree of pleasant and unpleasant subjective effects produced by OXY and HYD. In the Walsh et al. (2008) study, more pleasant subjective effects were reported than in our study, and in our study, more unpleasant subjective effects were reported (e.g., increased ratings of "nauseated"). These are not surprising findings in that there are a number of studies demonstrating that volunteers with a history of opioid abuse more reliably report pleasant subjective effects from mu opioid agonists than do non-drug-abusing volunteers (e.g., Azorlosa et al., 1994; Comer et al., 2007; Eissenberg et al., 2000; Lasagna et al., 1955; Petry et al., 1998; Preston et al., 1989). Abuse liability-related subjective effects of opioids have been detected in non-drug-abusing populations, but not to the extent and not as reliably as in opioid abusing populations. The reasons for this are not clear, but as pointed out by Walsh et al. (2008) and others (Azorlosa et al., 1994; Petry et al., 1998), differential degrees of tolerance to unpleasant subjective effects may be involved.

There were some differences in effects between OXY/ACET and HYD/ACET in the present study. We will focus on abuse liability-related effects and one prototypic side effect of mu agonist opioids. Time course analyses revealed that at the 60-min post-capsule-ingestion time point, there were significantly higher scores on the MBG scale in the higher dose OXY/ACET condition, relative to placebo. At that same time point, MBG scores in the higher dose HYD/ACET condition were no different from that of placebo. Increases in MBG scores after administration of 20 mg oxycodone has been observed in one other study conducted in our laboratory (Zacny and Gutierrez, 2003), although in a more recent study while MBG scores were increased by this dose, the increase was not statistically significant (Zacny and Lichtor, 2008). In the present study while peak liking ratings were significantly greater in both the lower and higher dose OXY/ACET conditions relative to placebo, these ratings in both the lower and higher dose HYD/ACET conditions did not differ significantly relative to placebo. These two differences in two hallmark measures of abuse liability would suggest that OXY has greater abuse liability-related effects than HYD in non-drug-abusing volunteers. We do not draw that conclusion for two reasons. For one thing, it should be noted that in a prior study conducted in our laboratory, 20 mg HYD/1000 mg ACET did significantly increase peak liking ratings relative to placebo (Zacny et al., 2005), and in the present study the difference between peak liking ratings in the higher dose OXY/ACET condition and the higher dose HYD/ACET condition were minimal (i.e., 2.7 mm). Peak "take again" ratings were also significantly increased relative to placebo in the 20 mg HYD/1000 mg ACET condition in the Zacny et al. (2005) study. It should also be noted that in the present study, 24-h ratings of liking and "take again," and the crossover value of the MCP, were significantly lower in the higher dose OXY/ACET condition relative to placebo, unlike that of HYD/ACET.

A second difference between the two opioid combinations is that HYD/ACET increased ratings of a common side effect of mu opioids, "dry mouth." OXY/ACET did not. This is the third study we have conducted in which OXY has not increased ratings of "dry mouth" (Zacny and Gutierrez, 2003; Zacny and Lichtor, 2008), and it is interesting to note that in the Walsh et al. (2008) study, ratings of dry mouth were increased by HYD and hydromorphone but not by OXY (dose range of OXY: 10–40 mg). In a meta-analysis, when clinical trials with morphine were compared to trials with oxycodone, pooled odds ratios (OR) established that "dry mouth" was less prevalent with oxycodone relative to morphine (OR: 0.56) (Reid et al., 2006). We have tested many other mu and mixed-action opioid agonists and detected this effect. Why OXY appears to be different from other mu opioid agonists with this particular side effect is unknown.

Four subjects in this study reported non-medical use of either prescription opioids and/or opium in the past. We could not do a formal statistical analysis to determine if these four subjects had a different profile of subjective effects (e.g., more positive) than the 16 subjects who did not report a history of non-medical use of opioids. However, we did examine individual subject data of the four subjects and compared their responses when receiving OXY/ACET and HYD/ACET (relative to placebo) to the mean of the 16 subjects on a number of subjective effects that could be considered positive (increased peak MBG scores of the ARCI, increased peak liking and "take again" ratings from the DEL/TA and 24 h ratings of overall liking and "take again") or that could be considered negative

(lower trough liking and "take again" ratings from the DEL/TA and 24 h ratings of overall liking and "take again", increased VAS ratings of "feel bad" and "nauseated"). We also examined MCP crossover values. Those with a history of non-medical use of opioids did not differ appreciably on any of the above effects relative to those without such a history. However, because the behavioral pharmacology literature is replete with studies demonstrating that drug use history is an important modulator of drug effects, it would be of value to conduct a study with sufficient sample sizes to determine in a more rigorous fashion if a history of non-medical use (as well as medical use) of opioids modulates abuse liability-related effects of prescription opioids in a laboratory setting.

The overall geometric mean of relative potency of HYD to OXY was 1.63. This was remarkably close to our estimate that OXY would be 1.5 times more potent than HYD in inducing miosis. The relative potency estimate of miosis, 1.61, was highly predictive of all of the other 19 variables that met criteria for a valid bioassay, 18 subjective effects measures and exophoria. The high degree of concordance of relative potency estimates of miosis and the subjective effects of the two opioid combination products is consistent with the literature that has documented a strong correlation between miosis and prototypic opioid subjective effects (Jasinski, 1977). There are two clinical studies that have compared the analgesic effects of HYD/ACET and OXY/ACET, albeit at lower doses than what were tested in the present study. In one study with emergency department patients suffering from fractures (Marco et al., 2005), pain ratings 30 and 60 min after administration of 5 mg HYD/325 mg ACET and 5 mg OXY/325 mg ACET did not differ. However, baseline pain ratings were higher in the patients who received 5 mg OXY/325 mg ACET than in the patients who received 5 mg HYD/325 mg ACET, suggesting that had an analysis been done incorporating the difference in baseline pain ratings (a change score analysis), the OXY combination product might have been more potent than the HYD combination product. In a placebo-controlled, double-blind, parallel group study, 5 mg OXY/325 mg ACET produced similar degrees of pain relief as did 7.5 mg HYD/500 mg ACET in patients who had two or more ipsilateral, partial or totally impacted wisdom teeth removed (Litkowski et al., 2005). Although ACET doses differed between the two conditions, it would appear that OXY was approximately 1.5 times more potent than HYD using analgesia as an endpoint. This potency difference is similar to what we found in the present study assessing other pharmacodynamic measures.

In 2003, there was a call in a position paper commissioned by the College on Problems of Drug Dependence to conduct relative abuse liability studies with strong opioids to determine if ". . .a de facto or implicit assumption that all the strong opioids are largely interchangeable with respect to abuse liability" is correct (Zacny et al., 2003, p. 225). Walsh et al. (2008) has conducted such a relative abuse liability study with HYD, OXY, and hydromorphone and their data are compelling in indicating that those three opioids, when delivered via the oral route, are interchangeable in terms of abuse liability. The opioids produced other pharmacodynamic effects that indicated the three opioids in general produced similar subjective, psychomotor-impairing, and physiological effects. The present study comparing OXY/ACET to HYD/ACET at equi-miotic doses and finding similar subjective, psychomotor-impairing, and physiological effects provides more evidence, in a different subject population, that OXY and HYD are similar in their pharmacodynamic effects. In a previous study we compared OXY to MOR and found that while the psychopharmacological profile of the two oral drugs at equi-miotic doses had many similarities, there were some differences in subjective effects (Zacny and Lichtor, 2008). Whether there would be differences in the psychopharmacological profile of the two drugs in an opioid abusing population is open to question. When the two drugs were administered via the intravenous route in this population, the subjective and reinforcing effects profile of both drugs was similar (Comer et al., 2007).

Finally, do the present results inform on the abuse liability of OXY and HYD combination products in a non-drug-abusing population? We have used the term "non-drug-abusing volunteers" to mean physically healthy volunteers who have a history of recreational drug use without a history of substance use-related disorders, or other psychiatric disorders, as defined by DSM-IV diagnostic criteria (American Psychiatric Association, 2000). There is little doubt that non-medical use of OXY and HYD products is occurring in this population, but the extent of such use is not well-elucidated. What we do know from a number of studies conducted in our laboratory is that there are individual differences in the degree to which non-drug-abusing volunteers report liking and/or disliking opioid effects, with some subjects reporting liking and positive subjective effects and no disliking, others reporting disliking and negative subjective effects and no liking, and still others reporting both liking and disliking (e.g., Walker et al., 2001; Zacny and Gutierrez, 2003; Zacny et al., 1992, 1994). Therefore it would be difficult if not impossible to make a blanket statement about the abuse liability of OXY/ACET and HYD/ACET in our subject population. A worthwhile research endeavor would be to identify variables, either organismic or environmental, that modulate the abuse liability-related effects of prescription opioids in this population, as these may be risk factors for non-medical use. Such variables could include personality variables such as sensation seeking (Kelly et al., 2006) and a person's history of using particular substances (e.g., alcohol) (de Wit et al., 1989).

Role of funding source

Funding for this study was provided by National Institute on Drug Abuse Grant DA08573. The National Institute on Drug Abuse had no further role in study design; in the collection, analysis and interpretation of the data; in the writing of the report; or in the decision to submit the paper for publication.

Contributors

James Zacny designed the study, wrote the protocol, and had primary responsibility for preparation of the manuscript. Sandra Gutierrez conducted the experimental sessions and assisted in the statistical analyses of the data and preparation of the manuscript. All authors have approved the final version of the manuscript.

Conflict of interest

James Zacny and Sandra Gutierrez have no conflicts of interest to the report.

Acknowledgements

We thank the many anesthesiology residents and nurse anesthetists for administering the drugs and monitoring the physiological status of the volunteers and Karin Kirulis for screening potential volunteers and conducting the structured interviews.

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