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Separate and combined psychopharmacological effects of alprazolam and oxycodone in healthy volunteers

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Abstract

Background—There are epidemiological data indicating that medical and/or nonmedical use of prescription opioids oftentimes involves concurrent use of other substances. One of those substances is benzodiazepines. It would be of relevance to characterize the effects of an opioid and a benzodiazepine when taken together to determine if measures related to abuse liability-related effects and psychomotor performance impairment are increased compared to when the drugs are taken alone.

Methods—Twenty volunteers participated in a crossover, randomized, double-blind study in which they received placebo, 0.5 mg alprazolam, 10mg oxycodone, and 0.5 mg alprazolam combined with 10mg oxycodone, all p.o. Subjective, psychomotor, and physiological measures were assessed during each of the four sessions.

Results—Oxycodone by itself increased drug liking and “take again” ratings relative to placebo, but these ratings were not increased when oxycodone was taken with alprazolam, which by itself did not increase either of these ratings. The two drugs in combination produced stronger effects (larger in magnitude or longer lasting) than when either was taken alone on a number of measures, including psychomotor performance impairment.

Conclusions—In healthy volunteers, abuse liability-related subjective effects of oxycodone were not enhanced by alprazolam. There was enhanced behavioral toxicity when the drugs were taken together, and thus, this is of significant concern from a public safety standpoint.

Keywords

Alprazolam; Benzodiazepine; Oxycodone; Prescription opioid; Subjective effects; Abuse liability; Psychomotor performance; Drug interaction; Healthy volunteer

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1. Introduction

Over the past decade, prescription opioid abuse has been a major problem in the medical, public health, and law enforcement communities in the US (Birnbaum et al, 2011; Compton and Volkow, 2006; Hansen et al., 2011; Paulozzi and Xi, 2008). The problem shows no signs of abatement. The latest National Survey on Drug Use and Health (NSDUH) showed that in 2010 two million people reported first-time nonmedical use of these drugs, which was only eclipsed by marijuana (2.4 million recent initiates; Substance Abuse and Mental Health Services Administration, 2011a). As the abuse of prescription opioids has become increasingly prevalent, a growing number of studies characterizing their psychopharmacological effects in non-drug abusing volunteers and in prescription opioid abusers have been conducted (Comer et al, 2010; Stoops et al., 2009; Walsh et al., 2008; Zacny and Gutierrez, 2003, 2009). In both populations, opioids that have strong efficacy at the mu-opioid receptor reliably generate abuse liability-related subjective effects (i.e., positive or pleasant effects including liking the effects and desiring to take the drug again; McColl and Sellers, 2006), although in non-drug-abusing volunteers, negative effects are also in evidence.

Recently, we embarked on a line of research that examined whether other CNS-active drugs increase the abuse liability-related effects of prescription opioids. There were two reasons for doing this. One, some people who are using opioids for relief of pain, including chronic nonmalignant pain (CNMP) patients, are also using other centrally acting drugs for either enhanced relief of pain, or for treatment of other disorders (e.g., Ciccone et al., 2000; Fillingim et al., 2003; Gilron et al., 2005). These drugs included musculoskeletal relaxants, anticonvulsants, antidepressants, and benzodiazepines. The issue of whether abuse liability-related effects of opioids are enhanced by such drugs, termed adjuvants, is relevant given the existing controversy surrounding risk of addiction to prescription opioids in CNMP patients (Ballantyne and LaForge, 2007; Højsted and Sjøgren, 2007). Secondly, there is emerging data showing that nonmedical use of prescription opioids is sometimes accompanied by use of alcohol or drugs with abuse potential. One group of researchers examined prevalence of concurrent use of prescription opioids in combination with alcohol or drugs in two separate studies. In the first study, undergraduates at a large public midwestern university in the US were asked to participate in a Web survey on drug use. Of those who reported nonmedical use of prescription opioids within the previous year, 52% of them reported using alcohol at the same time (McCabe et al, 2006). In the second study, data from the Monitoring the Future survey were examined, to determine prevalence of concurrent nonmedical use of prescription opioids with a number of other drugs in the nation's high school seniors (McCabe et al, submitted for publication). The estimated prevalence of any past-year co-ingestion of prescription opioids and other drugs among nonmedical users of prescription opioids was 70%. The substances most commonly co-ingested with prescription opioids included marijuana (59%), alcohol (52%), cocaine (11%), tranquilizers (i.e., benzodiazepines; 10%), and amphetamines (10%). Thus, these studies further establish the importance of examining the psychopharmacological effects of opioids and these CNS-active substances to determine if there is concordance between the profile of effects when these substances are taken together (e.g., a more positive profile of subjective effects) and the prevalence of the co-ingestion.

Recently, we examined the interaction of the prescription opioid oxycodone with alcohol (Zacny and Gutierrez, 2011) and two adjuvant drugs that are sometimes prescribed to CNMP patients on long-term opioid therapy, carisoprodol (Zacny et al., 2012a), and pregabalin (Zacny et al., 2012b). We will briefly describe the results of one of these studies to highlight the importance and need for such drug interaction studies. Therapeutic doses of carisoprodol, a musculoskeletal relaxant, and oxycodone did not produce abuse liability-

related subjective effects when they were tested alone, but did when tested together (Zacny et al., 2012a). In addition, psychomotor performance followed the same pattern with neither drug impairing performance when tested alone, but impairing performance when tested together.

This paper will report on our most recent study in which we examined the interaction between oxycodone and the benzodiazepine, alprazolam. The two drugs are sometimes used concurrently for medical purposes in CNMP patients on long-term opioid therapy for treatment related to anxiety or sleep disorders (Dellemijn and Fields, 1994; Fillingim et al, 2003; Hermos et al, 2004). The McCabe et al. (submitted for publication) study cited above demonstrated that nonmedical use of prescription opioids sometimes occurs in the context of simultaneous use of tranquilizers (i.e., benzodiazepines). Other studies provide evidence of polydrug use involving prescription opioids and benzodiazepines. For example, in one study, 54% of treatment-seeking prescription opioid abusing adolescents also met psychiatric criteria for sedative abuse disorder (Subramaniam and Stitzer, 2009). In another study, 52.3% of prescription opioid abusers reported benzodiazepine use in the past 30 days (Fischer et al., 2008). Epidemiological data also indicate that benzodiazepines are widely abused by heroin users and those in methadone maintenance therapy (e.g., Lintzeris et al., 2006; Segura et al., 2001). For example, in one study the prevalence of benzodiazepine abuse was 51% in methadone maintenance patients (Gelkopf et al., 1999). In an interview of 29 methadone maintenance patients who also used benzodiazepines, 72% reported taking benzodiazepines (usually diazepam) to boost the effects obtained from their daily methadone dose (Stitzer et al, 1981).

There are at least two clinical pharmacology studies in methadone maintenance patients to suggest that abuse liability-related effects of opioids are enhanced by benzodiazepines. In one study, the combination of a larger-than-normal methadone maintenance dose with 40 mg diazepam produced greater subjective opioid effects scores than did the methadone or diazepam doses alone (Preston et al, 1984). Similar results were obtained in a later study in which pretreatment with 10 and 20 mg diazepam prior to a methadone self-administration session increased ratings of drug liking, goodness, and strength of drug effect during the methadone self-administration sessions, relative to sessions when subjects received a placebo pretreatment (Spiga et al., 2001).

The primary purpose of the present study was to determine if the combination of a benzodiazepine with an opioid would produce greater abuse liability-related subjective effects than when the two drugs were administered alone. A secondary purpose of the study was to examine the behavioral toxicity (i.e., psychomotor performance impairment) of the two drugs combined compared to either drug alone. The benzodiazepine we chose to study was alprazolam, both because it is both widely prescribed (http://www.deadiversion.usdoj.gov/drugs_concern/benzo1.htm, last accessed 29.10.11) and abused (Substance Abuse and Mental Health Services Administration, 2011b, Tables 1.90A,B). Also, there is evidence that alprazolam is used with oxycodone as a form of polydrug abuse: alprazolam was present in 7% of drug abuse-related emergency department visits involving oxycodone (Substance Abuse and Mental Health Services Administration, 2004).

2. Methods

2.1. Subjects

Requirements for participation in this IRB-approved study included: age between 21 and 39 years, a high school diploma or the equivalent, verbal fluency in English, body mass index between 18 and 27, and some current level of alcohol use. Exclusion criteria included: total

abstention from drugs, a history of psychiatric or substance use disorders as determined from a structured interview using DSM-IV diagnostic criteria (American Psychiatric Association, 2000), or any significant medical conditions. Qualifying subjects provided written informed consent. Twenty-three subjects enrolled in the study; however three subjects did not complete the study. Two subjects withdrew from the study, one because he changed his mind about participating in the study, and the other because she got a job. One subject was withdrawn after one experimental session due to an episode of oxycodone-induced pruritis which was severe enough in nature to necessitate the intramuscular injection of diphenhydramine. During her debriefing, the subject was cautioned that if she needed to take prescription opioids for pain relief in the future that she should inform the medical caregiver of her strong negative reaction to oxycodone.

The subjects who completed the study consisted of 10 males and 10 females, with a mean age ($\pm$ SD) of 25.1 (4.8) years and a mean BMI of 23.3 (1.8). Ten, seven, and two subjects identified themselves as White, Black, and Alaskan Native/American Indian, respectively, and four reported they were of Hispanic ethnicity. (There were missing data on race and ethnicity for one subject.) One, eight, eight, and three subjects reported they had a high school diploma, completed some college courses, had a college degree, and had advanced degrees, respectively. In the last 30 days all subjects reported drinking alcohol (average of 3.8 (3.2) drinks per week); 5 of the 20 smoked tobacco cigarettes, although none of them smoked more than 2 cigarettes per day; and 6 of the 20 used marijuana (average of 1.7 (1.4) joints per week). Regarding lifetime non-medical drug use, eighteen volunteers reported use of cannabinoids (primarily marijuana), and some subjects reported use of stimulants (3), club drugs (e.g., ecstasy) (3), hallucinogens (6), sedatives (2), and/or inhalants (1). No subject reported nonmedical use of prescription opioids. With the exception of cannabinoids and cocaine (one subject reported using 13 times), self-reported lifetime recreational drug use of any drug from the above classes was less than 10 times in any one person. Regarding lifetime medical drug use, 9 subjects reported use of opioids, and 2 reported use of sedatives.

2.2. Experimental design and drugs

The study was a double-blind, randomized, placebo-controlled, crossover trial consisting of four experimental conditions. The conditions were: placebo, 0.5 mg alprazolam, 10 mg oxycodone, and the two active drugs combined. The drugs were put in opaque capsules by our pharmaceutical services department. The 0.5 mg dose of alprazolam is a recommended dose when first starting use of this drug for the treatment of anxiety disorders (<http://www.drugs.com/pro/alprazolam.html>, accessed on November 5, 2011); the 10-mg dose of oxycodone is on the higher end of the prescribed range in opioid-naïve adults (i.e., 2.5–10 mg, <http://www.rxlist.com/percocet-drug.htm>, accessed on August 3, 2011). For the condition in which alprazolam and oxycodone were to be studied when given within the same session, they were given at the same time because the time to peak plasma concentration of the two drugs (i.e., $t_{\max}$) is approximately the same, i.e., 60–90 min (Hall et al., 2003; Pöyhkä et al., 1992). Our goal was to study the drugs so that their peak effects would coincide with one another.

2.3. Procedures

During an orientation session, participants signed a written consent form that described the study in detail. In the consent form they were told that the purpose of the study was to “see how different drugs, alone and in combination with each other, affect mood and psychomotor functioning in healthy volunteers.” They were informed that the oral drugs to be used in the study were drugs that had been approved by the Food and Drug Administration, were not experimental, and might come from one or more of the following

drug classes: sedative/tranquilizer, stimulant (for example, amphetamine or speed), opiate (for example, morphine), non-prescription pain relievers (for example, acetaminophen, ibuprofen, and aspirin), or placebo (no active drug at all).

The study consisted of four sessions, spaced at least one week apart, which took place in a departmental laboratory from 08:15 to 14:00 h. Subjects were instructed to not eat food for 4h, and not drink liquids for 2h, prior to experimental session. They were also instructed to not use any drugs (excluding normal amounts of caffeine and nicotine) in the 24 h prior to sessions. Upon arrival, breath alcohol, urine toxicology, and pregnancy (for females) tests were given, and subjects signed a form indicating that they had followed the food and drug restrictions.

Volunteers were in a semi-recumbent position in a hospital bed throughout the session (except for bathroom breaks). At baseline, subjects completed several subjective effects forms and psychomotor tests, and their physiological status was assessed. After baseline measures were collected, subjects ingested one capsule with 150 cm³ of water. Subjects were told at this time that “The capsule you are about to ingest may or may not contain a drug or drugs.” Mood, psychomotor/cognitive performance, and physiological measures were assessed throughout the session at prescribed time points for 300 min after capsule ingestion. After the session ended, provided that they met certain discharge criteria, participants were transported to their home via a livery service.

2.4. Dependent measures

The dependent measures were assessed before the capsule administration period (baseline), as well as at fixed time points thereafter. The measures are briefly described below (please see Zacny et al., 2011, for a more detailed description of the measures).

2.4.1 Subjective effects—Five forms were used: a computerized, short form of the Addiction Research Center Inventory (ARCI, 49 items grouped into five scales; Haertzen, 1966; Martin et al., 1971); a 12-item adjective rating scale (ARS) derived from two questionnaires sensitive to the somatic and mood-altering effects of opioids (Fraser et al., 1961; Preston et al., 1989); a locally developed 28-item visual analog scale (VAS); a locally developed Drug Effect/Drug Liking/Take Again questionnaire (DEL/TA); and a locally developed 20-item Post-Session Sequelae questionnaire. The VAS and DEL/TA were completed every 30 min, and the ARCI and ARS were completed at hourly intervals. A modified version of the DEL/TA was filled out at the end of the session and subjects were asked to fill out another modified version 24 h later to assess overall liking and wanting (to receive the drug(s) again). Subjects were also asked to complete the Post-Session Sequelae questionnaire 24 h after the end of the session. Measures that we considered to be abuse liability-related were: the Morphine Benzadrine Group scale of the ARCI; ARS measures of “carefree” and “good mood”; VAS measures of “elated (very happy),” “feel good,” “having pleasant bodily sensations,” “having pleasant thoughts,” and “sedated (calm, tranquil); and DEL/TA measures of “drug liking” and “take again” (measured during the session, at the end of the session, and 24 h later).

2.4.2 Psychomotor and physiological measures—Psychomotor and cognitive performance were measured with five tests: the Digit Symbol Substitution Test (DSST) (Wechsler, 1958); a logical reasoning test (LRT) (Baddeley, 1968); an auditory reaction time (ART) test (Nuotto and Korttila, 1991); an eye-hand coordination (EHC) test (Nuotto and Korttila, 1991); and a free recall memory test. The DSST was completed every 30 min, the LRT, ART, and EHC tests were completed at hourly intervals, and the memory test was completed two times during each session (90 min and 300 min after capsule administration).

Six physiological measures were assessed at hourly intervals: blood pressure, heart rate, arterial oxygen saturation, respiration rate, exophoria, and pupil size.

2.5. Data analysis

Repeated-measures analyses of variance (ANOVA) were used for statistical treatment of the data. The first set of analyses was a one-way ANOVA with Drug Condition as the factor, and it compared peak (highest value obtained) or trough (lowest value obtained) effects of placebo, 0.5 mg alprazolam, 10 mg oxycodone, and the two active drugs combined. Only post-capsule ingestion values were included in the analyses, and values were determined for each subject independent of time point. Mean effect analyses were done on measures that were assessed only once during or after sessions (e.g., Post-Session Sequelae questionnaire). The second set of analyses involved a two-way ANOVA with Drug Condition and Time as factors, and examined time course of effects, including all measures that involved multiple testing. F values were considered significant for $p \leq 0.05$. When significance was achieved, the Holm-Sidak method for pairwise multiple comparison tests was employed.

We should note that an additional analysis, post hoc in nature, included Sex as a factor on 16 measures encompassing subjective effects (including those that were abuse liability-related) and psychomotor performance. No Sex $\times$ Drug interactions were obtained. Therefore, the decision was made to not include Sex as a factor in the statistical analyses of the data to be presented in this paper.

3. Results

3.1. Subjective effects

3.1.1. Peak/trough/average effect analysis—Table 1 summarizes mean peak, mean trough, or mean values ($\pm$ SEM) of subjective effects (as well as psychomotor and physiological effects; see below) that were sensitive to one or more of the three active drug conditions (relative to placebo). Whether alprazolam in combination with oxycodone produced significantly greater effects than either drug alone is also indicated in the table.

Alprazolam combined with oxycodone did not produce greater abuse liability-related subjective effects than either drug alone. Ratings of two key abuse liability-related measures, liking and “take drug(s) again,” were significantly increased relative to placebo in only the oxycodone-alone condition.

There were five instances in which the combination of alprazolam and oxycodone produced significant effects whereas either drug given alone did not: ARS ratings of “drive” and “dry mouth,” and VAS ratings of “coasting (‘spaced out’),” “dreamy,” and “floating.” The combination of alprazolam and oxycodone also produced significantly larger effects than either drug alone on three measures in which one or both of these conditions by themselves were significantly different from placebo: scores on the BG scale of the ARCI, and VAS ratings of “difficulty concentrating” and “heavy or sluggish feeling.” Interestingly, ARS ratings of “numb,” “skin itchy” and “sweating” were significantly increased by oxycodone relative to placebo but when combined with alprazolam were not. In general although alprazolam by itself produced a number of changes on subjective effects measures, only a few of the changes were significantly different from placebo. Oxycodone produced more subjective effects that were significantly different from placebo than alprazolam. It should be noted that such negative or unpleasant effects as VAS ratings of “anxious,” “feel bad,” “having unpleasant bodily sensations,” “irritated,” and “nauseated,” were not increased by oxycodone or alprazolam, alone or in combination. In addition, trough ratings of drug liking and “take again” ratings were not decreased by the drugs alone or in combination. On the

Post Session Sequelae questionnaire, there were no significant differences in any of the ratings in the three active drug conditions compared to the placebo condition.

3.1.2. Time course analysis—Table 2 presents those measures in which significant Drug $\times$ Time interactions were obtained. The numbers refer to the time point(s) when a given drug condition differed significantly from placebo (e.g., 60 = 60 min time point; 60–210 = time points between and including 60 and 210 min). Of particular interest was whether the length of time in which a drug effect was present (i.e., significantly different from placebo) was longer when alprazolam and oxycodone were given together relative to when given alone. Drug effects occurred earlier in the session and lasted longer when the drugs were given together compared to when given alone with three measures (i.e., scores on the ARCI PCAG scale compared to oxycodone alone; VAS ratings of “difficulty concentrating” (Fig. 1, top left frame) and “dreamy,” compared to both drugs when given alone). With five other measures, time to onset of effect was not shortened, but duration of effect was lengthened when the two drugs were given together (scores on the ARCI BG scale compared to both drugs when given alone; VAS ratings of “dizzy,” “heavy or sluggish feeling, and “high (drug ‘high’)” compared to oxycodone alone; DEL/TA ratings of “feel drug effect” compared to both drugs when given alone (Fig. 1, top right frame)). In the time course analysis, no abuse liability-related measures were increased by either drug alone or when they were given together, including the measure of drug liking (bottom left frame). Consistent with the peak/trough/average effect analysis, oxycodone produced more subjective effects than alprazolam.

3.2. Psychomotor measures

3.2.1. Peak/trough/average effect analysis—Performance on the DSST was impaired to a significantly greater degree when the two drugs were given together compared to either drug alone on the measures of total number of symbols drawn, and drawn correctly (Table 1). Subjects were overall less accurate after having received alprazolam relative to placebo. Eye-hand coordination was not impaired by either drug alone but was when the two were given together. Short-term and long-term memory was impaired by alprazolam, and the impairment was not significantly exacerbated by oxycodone, which had no effects by itself. Neither auditory reaction time nor performance on the LRT was affected by the drugs when given alone or together.

3.2.2. Time course analysis—Performance decrements on the DSST occurred earlier and lasted for a longer duration when the two drugs were given together relative to when they were given alone (Table 2; Fig. 1, bottom right frame). Alprazolam impaired eye-hand coordination, and the duration of the impairment was lengthened by the addition of oxycodone. Alprazolam had a more marked effect on psychomotor performance than oxycodone, both in number of tests impacted and in duration of impairment. Fewer words were recalled on the memory test at the 300-min time point than at the 90-min time point (significant Time effect), and the drug effect was confined to when alprazolam was given alone or with oxycodone.

3.3. Physiological measures

Both drugs alone induced exophoria to approximately the same degree, and when given together the impairment was significantly greater compared to either drug alone. Only oxycodone induced miosis, and the time course analysis indicated it occurred for most (when combined with alprazolam) or all (when given alone) of the post-capsule administration period. While neither drug alone decreased oxygen saturation rates, the two drugs combined did. Alprazolam reduced systolic and diastolic blood pressure in the trough analysis, but the time course analysis did not reveal such an effect.

4. Discussion

Alprazolam did not intensify abuse liability-related subjective effects of oxycodone. Subjects did report liking oxycodone and that they were willing to take it again on another session, but alprazolam did not increase the magnitude of these effects. In fact, ratings of drug liking and “take again” were no different when the two drugs were taken together compared to placebo. The drug combination did produce several subjective effects that were not present when the drugs were tested alone. In some other cases in which one or both the drugs tested alone produced significant increases in subjective effects or psychomotor impairment, testing the drugs in combination produced significantly stronger effects, as manifested in both the peak/trough and the time course analyses.

One might argue that the results demonstrating that alprazolam did not increase abuse liability-related effects of oxycodone are not surprising in light of the fact that a number of studies have failed to find such effects (including the ability for the drugs to function as reinforcers) with benzodiazepines in healthy volunteers (e.g., de Wit et al., 1986; Evans et al., 1995; Johanson and Uhlenhuth, 1980). However, there are some studies which show that non-drug-abusing volunteers do report positive subjective effects (Babalonis et al., 2008, 2011; Lile et al., 2010), so at present we would say that there are some inconsistencies in the literature on the abuse liability-related effects of benzodiazepines in this population. In addition, carisoprodol which is similar to benzodiazepines in terms of having sedative properties and acting at the same receptor (GABA_A receptor; Gonzalez et al, 2009), increased drug liking at a supratherapeutic dose (Zacny et al., 2011), and at a therapeutic dose when combined with oxycodone increased ratings of drug liking and “take again” (Zacny et al., 2012a). Thus we had reason to believe that there was a possibility for the drug combination to produce abuse liability-related effects. Finally, it should be noted that there appears to be a subpopulation of healthy volunteers in which abuse liability-related effects of benzodiazepines are more reliably observed, i.e., moderate drinkers (as opposed to light drinkers; de Wit et al, 1989; de Wit and Doty, 1994; Evans et al., 1996). It would therefore be of interest to systematically replicate the present study using that subpopulation of healthy volunteers.

Several points can be made regarding the effects of the two drugs when given alone versus when given together. First, in those cases in which both drugs were given alone and had peak or trough effects that differed significantly from placebo (ARCIBG scores, VAS ratings of “difficulty concentrating,” DEL/TA ratings of “feel drug effect,” number of symbols completed and correct in the DSST, degree of euphoria on the Maddox Wing test), when given together not only were the effects significantly greater in absolute magnitude relative to placebo but also to either drug alone. The one exception was with the rating of “feel drug effect,” and it can be seen from Fig. 1 that in this case, the greater drug effect was manifested as an extended duration of effect. An extended duration of effect when oxycodone and alprazolam were administered together compared to when administered separately (in which one or both drugs differed from placebo) was observed with ARCI BG and PCAG measures, VAS measures of “difficulty concentrating” “dizzy,” “dreamy,” “heavy or sluggish feeling,” and “high (drug ‘high’),” and the EHC test and DSST (Table 2). Some subjective effects of oxycodone appeared to be attenuated by alprazolam, including self-reports of itchy skin, a proxy for pruritis and a prototypic opioid side effect. Inspection of individual subject data revealed that this reduction was present in seven of the 11 subjects who reported itching in the oxycodone-alone condition. It is not clear why oxycodone-induced itching would be reduced by alprazolam, but it could be the case that the increase in drowsiness made subjects less aware of this side effect. In any event, the reduction in ratings of “skin itchy,” “sweating,” and “numb” did not translate into increased liking of the drug combination. By the same token the longer duration of the subjective effect of “high” (see

Table 2) when alprazolam was combined with oxycodone, compared to oxycodone alone, was not associated with concomitant increases in ratings of two key abuse liability measures: drug liking and “take again” (McColl and Sellers, 2006).

Oxygen saturation was reduced when the two drugs were administered together which is consistent with the literature showing an additive if not greater-than-additive effect on respiratory depression when opioids and benzodiazepines are administered together (Murray et al, 1995; White and Irvine, 1999). This finding is of concern in that the doses were in the prescribed dosing ranges for people who are not tolerant to these drugs (i.e., patients taking these drugs for the first time). If people take prescription opioids and benzodiazepines concurrently at supratherapeutic doses in recreational settings, or are prescribed these drugs for medical purposes and take the drugs in a manner not prescribed by the physician (i.e., larger doses or more frequent dosing), the degree of respiratory depression that could ensue could result in serious medical consequences to the user. The prevalence of opioid-related unintentional poisonings has substantially increased over the last decade and in a significant proportion of the poisonings, sometimes leading to death, CNS depressants including benzodiazepines were also ingested (Cone et al., 2003; Toblin et al., 2010; Wunsch et al., 2009).

We found that some measures of psychomotor performance were sensitive to the effects of one or both drugs. In particular, performance on the DSST was impaired with both drugs when administered alone, and when administered together the impairment was greater, both in absolute magnitude and in duration of effect. Again it should be pointed out that the doses of the drugs were within the therapeutic range for acute initial dosing. The fact that we found greater impairment with alprazolam and oxycodone taken at the same time is of concern because if individuals who are relatively naive to these drugs take these drugs together for whatever reason (medical or nonmedical), even at doses within the therapeutic range, they may put themselves and/or others at risk for injury (e.g., automobile accident). This concern might also apply to those people who are tolerant to the impairing effects of one of these drugs, such as a CNMP patient on long-term opioid therapy who is initiated on benzodiazepine treatment for an anxiety or sleep anxiety disorder.

In the present study, approximately the same number of subjects reported lifetime medical use of opioids (nine subjects: 5 females, 4 males) as those who reported no such use (11 subjects: 5 females, 6 males). Given the similar proportions, we conducted a post hoc analysis to determine whether prior exposure to opioids for medical use modulated responses to alprazolam, oxycodone, and/or the two drugs given in combination. All dependent measures in the study were included in a mixed model repeated measures ANOVA, using Opioid History (present vs. absent) as the grouping factor and Drug Condition as the repeated measures factor, and examining peak, trough, or mean values of the measures. There were significant Opioid History (i.e., group) effects and Opioid History $\times$ Drug interactions on some measures, including those that were abuse liability-related. For example, there were significant Opioid History main effects on 24-h liking ($p = 0.04$) and “take again” ($p = 0.03$) ratings, and significant Opioid History $\times$ Drug interactions on End-of-Session liking and “take again” ratings (p values of 0.01 and 0.02, respectively). These are measures that putatively measure subjects' overall hedonic reactions to a drug or drugs (Griffiths et al, 2003). Subjects with an opioid history reported liking oxycodone and the combination of oxycodone and alprazolam (with little difference between conditions), and also reported higher “take again” ratings in these conditions when compared to placebo. In contrast, subjects without an opioid history reported lower ratings in these conditions than in the placebo condition, indicative of some disliking and not wanting to take again oxycodone or oxycodone when combined with alprazolam. However we should also note that five of the nine subjects in the group with a history of medical use of opioids were current light

smokers and no subjects in the group without a history of medical use of opioids were smokers. Smoking is a risk factor for prescription opioid misuse and abuse (e.g., Becker et al., 2008, 2009; Meltzer et al, 2011; Michna et al., 2004; Schepis and Krishnan-Sarin, 2008). Indeed, when assessing End-of-Session liking ratings in the oxycodone and placebo conditions in the group with a history of medical use of opioids, mean change scores (oxycodone minus placebo) were 17.0 and -4.5 in the smokers and nonsmokers, respectively. End-of-Session “take again” ratings followed the same pattern, 13.6 and -0.3. Thus, conclusions regarding whether history of medical use of opioids altered abuse liability-related effects of oxycodone (alone or with alprazolam) cannot be drawn from our post hoc analysis. Rather, the analysis points to the need for separate prospective studies to examine the potential modulatory effects of smoking status (matching subjects on history of medical use of opioids) and history of medical use of opioids (matching subjects on smoking status) on psychopharmacological effects of prescription opioids.

There were several limitations to this study. We tested only one dose of each drug. Ideally in a drug interaction study more than one dose of each drug is tested to more fully characterize the nature of the interactions. However, increasing number of doses of both drugs to be tested, using a crossover design, would have created problems of subject recruitment and retention, because of the necessary additional sessions. Higher doses would have also led to safety concerns in naive volunteers (i.e., we were already detecting decreases in oxygen saturation rate at the selected doses). Secondly, the findings from this study may not generalize to other populations. As stated in the Introduction, benzodiazepine abuse is prevalent in methadone maintenance patients. Whether these results have applicability to CNMP patients on both opioids and benzodiazepines is also open to question, because they differ from healthy volunteers in a number of ways. Our subjects were given drugs on an acute basis, in contrast to chronic pain patients on opioid and adjuvant therapy who are typically given these drugs on a chronic basis, several times a day (for immediate release formulations), in which habituation or tolerance to some drug effects can occur. Chronic pain patients could be on higher doses of opioids and benzodiazepines than our healthy volunteers were given. We were testing drugs in individuals who were not in pain and did not have comorbidities for which benzodiazepines might be prescribed for some CNMP patients on opioid therapy (i.e., emotional or sleep disorders; Haller and Acosta, 2010; Gerhardt et al., 2011; Jordan and Okifuji, 2011). We acknowledge that there are fundamental differences between our subject population and chronic pain patients, as well as other populations. We believe, however, that this study and the other opioid-adjuvant studies we have completed (Zacny et al, 2012a,b) are important “first steps” in characterizing psychopharmacological interactions between drugs with possible abuse potential and prescription opioids. Specifically with regards to the classes of drugs examined in this study, further studies testing other populations as well as other benzodiazepines and opioids with different pharmacokinetic profiles would yield valuable information at a time when these prescription drugs are posing significant public health problems related to their substantial prevalence of misuse and abuse (Hernandez and Nelson, 2010).

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Fig. 1.

Time course of the effects of placebo (diamond), 0.5 mg alprazolam (triangle), 10 mg oxycodone (circle), and 0.5 mg alprazolam/10 mg oxycodone (square) on “Difficulty Concentrating” ratings from the VAS (top left frame), “Feel Drug Effect” ratings from the Drug Effect/Drug Liking/Take Again (DEL/TA) questionnaire (top right frame), Drug Liking ratings from the DEL/TA (bottom left frame), and number of symbols drawn correctly on the Digit Symbol Substitution Test (bottom right frame). Each point is the mean across 20 subjects. Solid symbols indicate a significant difference as determined by the Holm–Sidak method compared to the placebo condition for a given time point. Asterisks and pound signs indicate that the 0.5 mg alprazolam/10 mg oxycodone condition differed significantly from the 10 mg oxycodone condition and 0.5 mg alprazolam conditions, respectively. The VAS was a 100-mm line with endpoints labeled as “not at all” and “extremely.” For the Feel Drug Effect question, ratings ranged from 1 to 5 where 1 = I feel no effect from the drug(s) at all, 2 = I think I feel a mild effect, but I’m not sure, 3 = I definitely feel an effect, but it is not really strong, 4 = I feel a strong effect, and 5 = I feel a very strong effect. The Drug Liking rating was a bipolar VAS and assessed drug liking and disliking: subjects were asked to place a mark on a 100-mm line indicating how much they

liked the drug effects as they were currently feeling them, ranging from 0 mm (dislike a lot) through 50 mm (neutral) to 100 mm (like a lot). The Digit Symbol Substitution Test was a 1-min paper-and-pencil test that required the subject to replace digits with corresponding symbols according to a digit-symbol code listed on the top of the paper.

Table 1

Mean peak, trough, or average scores/ratings ($\pm$ SEM) of subjective, psychomotor, and physiological effects significantly affected by one or more of the active drug conditions.

	<i>p</i> Value	Placebo	ALPRAZ 0.5	OXY 10	ALPRAZ 0.5/OXY 10
Subjective effects measures					
ARCI					
BG ^b (range: 0–13)	<0.001	4.8 (0.5)	3.3 (0.5) *	3.1 (0.4) *	1.9 (0.3) *,†, #
LSD ^a (range: 0–14)	0.002	3.6 (0.3)	3.6 (0.2)	5.0 (0.4) *	4.9 (0.5) *, #
PCAG ^a (range: 0–15)	<0.001	5.2 (0.6)	6.5 (0.5)	8.1 (0.7) *	9.4 (0.5) *, #
ARS (range: 0–4)					
Drive ^b	0.03	1.15 (0.32)	0.75 (0.25)	0.50 (0.19)	0.45 (0.14) *
Dry mouth ^a	0.002	0.20 (0.12)	0.30 (0.13)	0.65 (0.20)	0.95 (0.20) *, #
Nodding ^a	<0.001	0.35 (0.17)	1.15 (0.31)	1.65 (0.34) *	2.35 (0.36) *, #
Numb ^a	0.008	0 (0)	0 (0)	0.30 (0.11) *	0.10 (0.10)
Skin itchy ^a	<0.001	0.05 (0.05)	0.05 (0.05)	0.85 (0.22) *	0.45 (0.14)
Sweating ^a	0.002	0 (0)	0 (0)	0.50 (0.20) *	0.05 (0.05)
VAS (range: 0–100)					
Coasting ('spaced out') ^a	<0.001	9.0 (3.0)	21.0 (5.2)	21.1 (5.3)	37.7 (7.0) *
Difficulty concentrating ^a	<0.001	15.1 (5.0)	34.4 (7.5) *	35.0 (7.2) *	58.3 (6.4) *,†, #
Dreamy ^a	<0.001	9.1 (2.3)	23.8 (5.7)	18.0 (3.6)	36.1 (6.0) *,†
Floating ^a	0.04	3.7 (2.0)	7.9 (3.1)	12.0 (3.9)	14.8 (4.3) *
Heavy or sluggish feeling ^a	<0.001	7.6 (2.7)	23.9 (6.0)	30.4 (7.1) *	53.6 (7.1) *,†, #
High (drug 'high') ^a	<0.001	1.8 (0.8)	5.4 (1.9)	20.7 (6.2) *	27.7 (7.8) *, #
Sleepy (drowsy, tired) ^a	<0.001	42.7 (5.7)	60.7 (6.2)	63.9 (7.1) *	80.3 (4.5) *, #
Tingling ^a	0.04	1.8 (0.8)	5.7 (3.4)	17.5 (5.8) *	8.8 (5.2)
DEL/TA					
Feel drug effect ^a	<0.001	1.7 (0.1)	2.6 (0.2) *	3.2 (0.2) *	3.4 (0.2) *, #
Like drug(s) ^a	<0.001	54.0 (1.5)	55.2 (1.5)	65.7 (3.5) *	59.9 (2.2)

	<i>p</i> Value	Placebo	ALPRAZ 0.5	OXY 10	ALPRAZ 0.5/OXY 10
Take drug(s) again ^a	0.008	55.8 (0.9)	59.4 (2.6)	66.3 (3.5) *	60.5 (2.2)
Psychomotor measures					
DSST (# of symbols completed) ^b	0.001	44.1 (1.7)	39.2 (2.0) *	40.6 (1.8) *	34.2 (1.7) *,†, #
DSST (# of symbols correct) ^b	<0.001	43.3 (1.7)	37.7 (2.2) *	39.6 (1.7) *	32.7 (1.8) *,†, #
DSST (accuracy, % correct) ^b	0.005	96.1 (0.7)	92.0 (1.6) *	95.2 (0.5)	93.4 (1.0)
EHC (seconds outside circle) ^a	<0.001	10.0 (1.1)	12.5 (1.5)	10.9 (1.1)	15.9 (1.7) *,†
Short-term memory (# items recalled) ^c	<0.001	8.4 (0.5)	6.6 (0.5) *	7.8 (0.4)	6.2 (0.5) *,†
Long term memory (# items recalled) ^c	<0.001	5.6 (0.6)	3.5 (0.5) *	5.8 (0.5)	2.8 (0.5) *,†
Physiological measures					
Maddox Wing (diopters) ^a	<0.001	3.6 (1.1)	7.7 (1.4) *	6.9 (1.3) *	10.3 (1.5) *,†, #
Miosis (mm) ^b	<0.001	6.7 (0.2)	6.6 (0.2)	5.5 (0.3) *	5.1 (0.3) *, #
SaO ₂ (%) ^b	0.002	97.9 (0.3)	97.6 (0.2)	97.7 (0.2)	96.9 (0.3) *,†
SBP(mmHg) ^b	<0.001	112.0 (2.3)	107.2 (2.0) *	108.6 (2.7)	105.1 (2.1) *
DBP (mmHg) ^b	0.02	63.1 (2.2)	59.8 (2.2) *	60.5 (2.3)	59.8 (2.1) *

Abbreviations: ALPRAZ 0.5; 0.5 mg alprazolam; OXY 10; 10 mg oxydodone; ALPRAZ 0.5/OXY 10; 0.5 mg alprazolam combined with 10mg oxydodone; ARCI; Addiction Research Center Inventory; BG; Benzedrine Group scale; LSD; Lysergic Acid Diethylamide scale; PCAG; Pentobarbital-Chlorpromazine-Alcohol Group scale; ARS; adjective rating scale; VAS; visual analog scale; DEL/TA; Drug Effect/Drug Liking/Take Again; DSST; Digit Symbol Substitution Test; EHC; eye-hand coordination test; SaO₂; arterial oxygen saturation; SBP; systolic blood pressure; DBP; diastolic blood pressure.

* $p < 0.05$ compared with placebo.

† $p < 0.05$ compared with OXY 10.

$p < 0.05$ compared with ALPRAZ 0.5.

^a Peak rating.

^b Trough rating.

^c Average rating.

Table 2Time points (min) at which the active drugs differed from placebo.^a

	ALPRAZ 0.5	OXY 10	ALPRAZ 0.5/OXY 10
Subjective effects measures			
ARCI			
BG	60	120,180	60–240 ^b
LSD	–	–	60
PCAG	–	120–240	60–300
ARS			
Drive	–	120	–
Dry mouth	–	–	120–300
Flushing	–	60	–
Nodding	120	60–240	60–240
Skin itchy	–	60–240	180
Sweating	–	60,120	–
VAS			
Coasting ('spaced out')	–	–	60–210
Difficulty concentrating	90,120	90,120	60–210
Dizzy	–	60, 90	60–120
Dreamy	90,120	120	60–180, 240
Drunk	–	60	120,150
Floating	120	90	90
Heavy or sluggish	–	60–120	60–240
High	–	60	60–150
Hungry	–	60,120	–
In control of body	–	–	90
Lightheaded	–	60, 90	–
Sleepy	–	60,120–210	90–210
Stimulated	–	120,150	150
Tingling	–	60	–
Unpleasant bodily sensations	–	60	–
DEL/TA			
Feel drug effect	60–180	60–210	60–240
Psychomotor measures			
Auditory reaction time	60	–	60
EHC	60	–	60–180
DSST (# completed)	60–150	90,120	30–210
DSST (# correct)	60–150	120	30–210
Physiological measures			
Maddox Wing	60–240	120,180	60–240
Miosis	–	60–300	60–240
SaO ₂	–	–	60,120

^aAbbreviations are listed in text and in Table 1.

^bTwo time points separated by a hyphen indicate that the drug effect's duration included those time points and the time points in between them.