



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, 10 mg oxycodone, and 0.5 mg alprazolam combined with 10 mg 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.

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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

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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 adjuvants 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/benzo.1.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 abstinence 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

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