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Subjective, psychomotor, and physiological effects of pregabalin alone and in combination with oxycodone in healthy volunteers

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ABSTRACT

Pregabalin is an anticonvulsant drug indicated for neuropathic disorders and fibromyalgia. Some chronic pain patients suffering from these disorders take both this drug and an opioid for pain relief. Pregabalin is a scheduled drug under the Controlled Substances Act. The subjective effects of this drug have not been well-characterized, and the extent to which it alters the subjective effects of opioids has not been studied to the best of our knowledge. Using a double-blind, randomized, crossover design, 16 healthy volunteers were administered (in separate sessions) capsules containing placebo, 75 mg pregabalin, 150 mg pregabalin, 10 mg oxycodone, and 75 mg pregabalin combined with 10 mg oxycodone. Subjective, psychomotor, and physiological measures were assessed during each of the five sessions. Pregabalin produced dose-related increases in some subjective effects and decreased respiration rate, but did not impact on psychomotor performance. Abuse liability-related subjective effects such as drug liking and desire to take the drug again were not increased by either pregabalin dose. Oxycodone produced increases in several subjective effects, including ratings of drug liking. When 75 mg pregabalin was combined with oxycodone some subjective effects were altered relative to placebo, in contrast to when each drug was tested alone. Liking of oxycodone was not increased by 75 mg pregabalin. However, recent studies have suggested that this drug is abused, and we would recommend that further psychopharmacological studies with pregabalin are warranted, including a study assessing its abuse liability across a range of doses in sedative abusers.

1. Introduction

Pregabalin (Lyrica) is an anticonvulsant that is approved in the US for treatment of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia, and for fibromyalgia (http://labeling.pfizer.com/ShowLabeling.aspx?id=561, accessed August 5, 2011). The European Commission approved pregabalin in 2006 for the treatment of generalized anxiety disorder (Gajraj, 2007). Its mechanism of action is thought to reduce neuropathic pain via binding to the α(2)δ-1 subunit of voltage-sensitive calcium channels, thus inhibiting the enhanced release of pain neurotransmitters (e.g., substance P) at the synapses (Chiechio et al., 2009; Field et al., 2006; Sills, 2006). The mechanism of action by which it is thought to produce anxiolysis has not been well-elucidated — although it is a GABA analog, it does not bind to the receptor, is not converted into GABA, nor does it alter GABA uptake or degradation (Gajraj, 2007). When approved by the US Food and Drug Administration in 2005, pregabalin was scheduled by the Drug Enforcement Administration under the Controlled Substances Act as a Schedule V drug, indicating that it had abuse potential (albeit less potential than Schedule IV, III, and II drugs). There were at least two reasons for why it was scheduled. In clinical studies (N = 5500 patients), the percentage of individuals who reported experiencing euphoric effects was higher in those patients receiving pregabalin versus placebo (4% versus 1%, respectively (http://labeling.pfizer.com/ShowLabeling.aspx?id=561, accessed August 5, 2011)). Second, in the package insert of pregabalin (same web address as in preceding sentence), the makers of the drug describe a study with 15 recreational users of sedative/hypnotic drugs including alcohol in which pregabalin (450 mg) and diazepam (30 mg) were given on separate sessions (it is possible that there was a placebo session but this is not stated). Subjective ratings of "good drug effect," "high," and "liking" were increased to the same degree by both drugs. In the patient information sheet that is included with the prescription, several possible common side effects are listed, and one of them is "feeling high" (http://www.lyrica.com/main_patient_info.aspx, accessed on August 5, 2011). More recently, a data-mining algorithm was applied to reports of possible drug abuse or addiction in the Swedish national register of adverse drug reactions (SWEDIS), and of 198 reports, 16 concerned pregabalin (Schwan et al., 2010). Thirteen of the 16 patients in the physicians' reports submitted to SWEDIS had a reported history of substance abuse, and several of the reports stated that the patient took the drug

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to "get high." In another recent study, accounts of pregabalin misuse were found among 32 websites in which recreational drug use was discussed (Schifano et al., 2011).

The primary purpose of the present study was to characterize the subjective effects of pregabalin alone and in combination with oral oxycodone. We did the study for two reasons. First, the subjective effects of the drug have not been well characterized, and there continues to be some concern that it has abuse liability (Schifano et al., 2011; Schwan et al., 2010). Yet to the best of our knowledge there is no study in the peer-reviewed literature that has assessed pregabalin for abuse liability or abuse liability-related effects. Second, this drug is used in combination with an opioid in some chronic pain patients suffering from neuropathic pain (Dworkin et al., 2010; Gatti et al., 2011). We wanted to elucidate the profile of effects of the two drugs when combined. Given its scheduled status we hypothesized that the abuse liability-related effects of oxycodone that we have detected in other studies (Zacny and Drum, 2010; Zacny and Gutierrez, 2003) would be potentiated by pregabalin. In this paper, we report on the subjective effects of two doses of pregabalin, 75 and 150 mg, 10 mg of oxycodone, and 75 mg of pregabalin and oxycodone administered within the same session. Secondary measures included psychomotor and physiological responses. In this study some subjects were exposed to other drug conditions — these conditions will be enumerated in Section 2.2, including the reasons why they were eliminated from the study.

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, 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. The subject population consisted of 8 males and 8 females, with a mean age (±SEM) of 26.9 (5.0) years. In the last 30 days all subjects reported drinking alcohol (average of 3.3 (2.7) drinks per week); 3 of the 16 smoked tobacco cigarettes, although none of these smoked more than 1 cigarette a day; and 5 of the 16 used marijuana (average of 0.8 (0.7) joints per week). Regarding lifetime non-medical drug use, fifteen volunteers reported use of cannabinoids (primarily marijuana), and some subjects reported use of stimulants, club drugs (e.g., ecstasy), hallucinogens, and/or opioids. With the exception of cannabinoids, self-reported lifetime recreational drug use of any drug from the above classes was less than 50 times in any one person, and in most cases was less than 10 times. Regarding opioids, three volunteers reported smoking opium (<10 times lifetime), one reported nonmedical use of prescription opioids, and 15 reported medical use.

2.2. Experimental design and drugs

The study was a double-blind, randomized, placebo-controlled, double-dummy, crossover trial consisting of 5–8 experimental conditions. All 16 subjects were exposed to the following five conditions that form the basis of this report: placebo, 75 and 150 mg of pregabalin, 10 mg oxycodone, and 75 mg of pregabalin followed 1 h later by 10 mg oxycodone. The 75 mg dose of pregabalin is a recommended dose when first starting use with this drug for the treatment of postherpetic neuralgia and fibromyalgia — the dose is taken twice a day and then titrated upwards as needed (Lyrica package insert). The 150 mg dose is a supratherapeutic dose (i.e., this is an acute dose not typically prescribed when the drug is initially used), but it has been safely tested in healthy volunteers in a previous study (Hindmarch et al., 2005). The dose of oxycodone is on the higher end of the prescribed range in opioid-naive adults (i.e., 2.5–10 mg, http://www.rxlist.com/percocet-drug.htm, accessed August 3, 2011). There were two different time points in the session when capsules were given because in the session when we tested the effects of 75 mg pregabalin in combination with 10 mg oxycodone, we wanted to measure their effects when the drugs were both close to, or at, their peak effects. In a preliminary pilot study we noted that the psychoactive effects of pregabalin tended to peak 2 h after its administration, and prior studies with 10 mg oxycodone conducted in our laboratory indicated peak effects 1 h after its administration (Zacny and Gutierrez, 2011; Zacny and Lichtor, 2008).

There were three experimental conditions that during the course of the study were eliminated from the study protocol, and data from those conditions were not included in the final analysis: 150 mg pregabalin combined with 10 mg oxycodone, 200 mg zonisamide (Zonegran), and 200 mg zonisamide combined with 10 mg oxycodone. The higher dose of pregabalin combined with oxycodone was eliminated approximately halfway through the study for safety reasons: two subjects were extremely sedated during the session (slept most of the time in between testing) and reported excessive drowsiness for some period of time after the session in which 75 mg of pregabalin was given with 10 mg oxycodone, and we did not wish to expose them to the higher pregabalin dose with oxycodone (they had not been exposed to that condition but were scheduled to receive it in a later session). After the second subject had this reaction, we decided to eliminate the 150 mg pregabalin/10 mg oxycodone condition from the study. It should be noted that prior to eliminating that condition, five subjects were able to tolerate 75 mg of pregabalin combined with oxycodone, and 6 subjects were able to tolerate 150 mg of pregabalin combined with oxycodone, but the intersubject variability that we observed with the 75 mg dose combined with oxycodone informed our decision to terminate the higher dose drug combination condition.

Zonisamide was included in the original study design as a negative control anticonvulsant — in preclinical studies using self-administration studies and drug discrimination studies it did not show any evidence of abuse liability (http://www.changingfacesofepilepsy.com/docs/ZonegranPI.pdf, accessed August 2, 2011). Thus we hypothesized that unlike pregabalin it would not increase the abuse liability-related effects of oxycodone. If this were the case, we reasoned that zonisamide might be an alternative treatment for patients at risk for prescription drug abuse who were in need of both an opioid and an anticonvulsant for treatment of neuropathic pain. However, we dropped zonisamide (alone and combined with oxycodone) from the study because in 2010 it became apparent to us that the drug was not being used as a treatment for neuropathic pain. When the study was designed in 2008 there was some suggestion in the literature that zonisamide might be used in the treatment of neuropathic pain (Hasegawa, 2004; Krusz, 2003), but more recent literature searches (Goodyear-Smith and Halliwell, 2009) and discussions with physicians who specialized in treatment of chronic pain indicated that this was not the case. Thus there was no reason to test this drug anymore from a clinical standpoint. Six of the 16 subjects had been exposed to the two zonisamide conditions.

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 (for example, Valium®), stimulant (for example, amphetamine or speed), opiate (for example, morphine), non-prescription pain relievers (for example, Tylenol®, also known as acetaminophen, Motrin®, also known as ibuprofen, and aspirin), anticonvulsant (for example, Zonegran®), or placebo (no active drug at all).

The study was a double-blind, randomized, placebo-controlled, double-dummy, crossover trial consisting of 5–8 sessions (at least 1 week apart) that took place in a departmental laboratory from 0815–1500 h. Subjects were instructed to not eat food the morning of sessions or 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 effect forms and psychomotor tests, and their physiological status was assessed. After baseline measures were collected, subjects ingested two capsules containing pregabalin or placebo with 150 cm^3 of water. Sixty minutes later, subjects ingested another two capsules containing oxycodone or placebo. At each ingestion time, subjects were told by the research technologist conducting the session that "The capsules 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 360 min after the first capsule ingestion period. After the session ended, provided 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 first capsule administration period (baseline), as well as at fixed time points thereafter. Data used in the analysis included only those measures that were collected starting 30 min after the second capsule ingestion period (after oxycodone or placebo was consumed). All measures were collected at hourly intervals, and some measures were collected every 30 min (those will be noted below).

2.4.1. Subjective effects

Five forms were used: a computerized, short form of the Addiction Research Center Inventory (ARCI) (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 (see Zacny et al., 2011 for a description of these forms). The VAS and DEL/TA were filled out at baseline and every 30 min thereafter up to the end of the session. 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.

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. 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 analysis of variance was used for statistical treatment of the data. The analysis compared peak (highest value obtained) or trough (lowest value obtained) effects of placebo, 75 mg pregabalin, 150 mg pregabalin, 10 mg oxycodone, and 75 mg pregabalin and 10 mg oxycodone given in the same session. Whether peak or trough values were used for a particular variable was determined by the expected direction of the drug effect trend (e.g., peak values used for variables that should increase as a result of the drug(s) and trough values used for variables that should decrease as a result of the drug(s)). In the analyses, only values collected between 30 min after the second capsule administration period (i.e., earliest time point that drug interaction effects could be tested) and through to the end of the session were included (300 min after the second capsule administration period), 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). F values were considered significant for $p \leq 0.05$. When significance was achieved, the Holm–Sidak method for pairwise multiple comparison tests was done.

3. Results

3.1. Subjective effects

Table 1 summarizes mean peak, mean trough, or mean values ($\pm$SEM) of subjective effects that were sensitive to one or more of the four active drug conditions (relative to placebo). The lower dose of pregabalin increased ratings of "feel drug effect," but this was the only subjective effect measure altered by that dose. The higher dose of 150 mg decreased scores on the BG scale of the ARCI and decreased VAS ratings of "in control of body." This dose also increased ratings of "difficulty concentrating," "heavy or sluggish feeling," and "feel drug effect." On the post-session questionnaire, ratings of "dreaminess" were also increased. There were no increased ratings of abuse liability-related effects with either dose of pregabalin (e.g., "elated," "having pleasant bodily sensations," "like drug," "take again"). Oxycodone by itself increased scores on the LSD scale of the ARCI, increased ratings of "skin itchy" on the adjective rating scale, and increased ratings of "feel drug effect" and "like drug" on the DEL/TA questionnaire. There were ten instances in which 75 mg of pregabalin alone and 10 mg of oxycodone alone did not alter subjective effects, but when combined did: decreased scores on the BG scale of the ARCI, increased ratings of "flushing" on the adjective rating scale, increased VAS ratings of "difficulty concentrating," "feel bad," "having pleasant bodily sensations," "having unpleasant bodily sensations," and "lightheaded," increased ratings of "take again" on the DEL/TA, and increased ratings of "coasting (spaced out)" and "headache" on the Post-Session Sequelae questionnaire.

3.2. Psychomotor and physiological effects

Neither pregabalin nor oxycodone had any effects on the psychomotor tests used in the study. Pregabalin at the higher dose as well as oxycodone increased exophoria on the Maddox Wing Test. Oxycodone alone and in combination with 75 mg pregabalin decreased pupil size and respiration rate. Respiration rate was also decreased by 75 and 150 mg of pregabalin. Although the Holm–Sidak method for pairwise multiple comparison tests did not reveal differences between the active drug conditions, the decrease in respiration rate

Table 1
Mean peak or trough or average scores/ratings (±SEM) of subjective and physiological effects measures significantly affected by one or more of the active drug conditions relative to placebo.

	P value	PLC	PRG 75	PRG 150	OXY 10	OXY 10/PRG 75
Subjective effects measures						
ARCI						
BG[a]	0.004	4.5 (0.5)	4.0 (0.6)	2.6 (0.6)*	3.8 (0.6)	3.0 (0.8)*
LSD[b]	0.009	3.2 (0.3)	3.5 (0.5)	4.1 (0.4)	4.6 (0.5)*	4.6 (0.6)*
Adjective rating scale						
Flushing[b]	<0.001	0.2 (0.1)	0.1 (0.1)	0.1 (0.1)	0.6 (0.2)	0.8 (0.3)*
Skin itchy[b]	0.001	0.1 (0.1)	0.2 (0.1)	0.1 (0.1)	0.6 (0.2)*	0.4 (0.2)
VAS						
Difficulty concentrating[b]	0.001	15.7 (5.7)	23.1 (6.3)	44.5 (8.9)*	19.3 (6.0)	38.6 (8.6)*
Feel bad[b]	0.012	4.4 (2.4)	11.9 (5.7)	5.9 (2.4)	5.1 (1.7)	20.4 (6.3)*
Having pleasant bodily sensations[b]	0.010	22.0 (8.3)	25.5 (8.6)	24.9 (8.2)	31.6 (8.7)	39.9 (7.5)*
Having unpleasant bodily sensations[b]	0.013	6.1 (2.6)	14.1 (6.3)	8.4 (3.6)	19.9 (7.8)	27.4 (8.4)*
Heavy or sluggish feeling[b]	0.017	22.3 (5.4)	33.4 (9.3)	52.5 (8.0)*	33.1 (8.5)	46.4 (8.3)
In control of body[a]	0.015	93.3 (4.5)	87.4 (5.0)	79.6 (7.1)*	81.9 (8.1)	81.1 (7.2)
Lightheaded[b]	0.011	2.6 (1.8)	5.2 (1.8)	16.4 (7.0)	15.9 (6.1)	23.9 (8.0)*
Drug Effect/Drug Liking/Take Again						
Feel drug effects[b]	<0.001	2.2 (0.3)	2.9 (0.2)*	3.4 (0.3)*	3.5 (0.3)*	3.9 (0.2)*
Like drug(s)[b]	<0.001	56.5 (3.2)	59.3 (3.8)	55.7 (2.2)	68.5 (4.4)*	67.1 (3.3)*
Take drug(s) again[b]	<0.001	59.0 (3.3)	63.9 (3.3)	55.4 (2.4)	69.6 (4.6)	73.3 (4.4)*
Post-Session Sequelae questionnaire						
Coasting ('spaced out')[c]	0.039	0.1 (0.1)	0.1 (0.1)	0.3 (0.2)	0.3 (0.1)	0.6 (0.2)*
Dreaminess[c]	0.031	0.0 (0.0)	0.1 (0.1)	0.3 (0.1)*	0.1 (0.1)	0.1 (0.1)
Headache[c]	0.006	0.2 (0.2)	0.4 (0.2)	0.3 (0.1)	0.6 (0.3)	1.1 (0.3)*
Physiological measures						
Exophoria (prism diopters)[b]	<0.001	4.2 (0.9)	5.3 (1.1)	8.2 (1.2)*	6.5 (1.3)	9.1 (1.0)*
Pupil size (mm)[a]	<0.001	6.4 (0.2)	6.3 (0.2)	6.3 (0.2)	5.3 (0.3)*	5.1 (0.3)*
Respiration rate (breaths/min)[a]	<0.001	12.9 (0.6)	10.3 (0.7)*	10.6 (0.8)*	10.5 (0.7)*	9.6 (0.5)*

Abbreviations: PLC, placebo; PRG 75, 75 mg pregabalin; PRG 150, 150 mg pregabalin; OXY 10, 10 mg oxycodone; OXY 10/PRG 75, 75 mg pregabalin followed 60 min later by 10 mg oxycodone; ARCI, Addiction Research Center Inventory; BG, Benzedrine Group scale; LSD, Lysergic Acid Diethylamide scale.
[a] Trough rating.
* $p<0.05$ compared with placebo.
[b] Peak rating.
[c] Average rating.

in the 75 mg pregabalin conditions (alone and in combination with oxycodone) was clinically significant (i.e., >20% of placebo values).

4. Discussion

We hypothesized that pregabalin would potentiate abuse liability-related effects of oxycodone. The results overall did not support the hypothesis. First, oxycodone did increase drug liking ratings but the addition of 75 mg pregabalin did not increase the ratings any further. Second, although the drug combination increased abuse liability-related effects that neither drug alone did ("having pleasant bodily sensations," "take again"), the drug combination also produced negative effects ("having unpleasant bodily sensations," post-session headache). Notably, end-of-session and 24-h liking and take again ratings that reflect the overall perception of the drug (i.e., positive versus negative evaluation of the drug effects) in the drug combination condition (i.e., pregabalin with oxycodone) did not differ significantly from placebo. As stated in the Introduction another purpose of the study was to characterize the subjective effects of pregabalin by itself. We tested two doses, a dose that would be prescribed when initiating therapy with the drug, 75 mg, and double that dose. Although subjects reported feeling a drug effect from the 75 mg dose, no other subjective effect measure from three other mood assessment batteries administered within sessions was altered. Acute administration of the 150 mg dose increased several subjective effects relative to placebo, but none of them could be characterized as positive or abuse liability-related. A commonly-reported side effect of pregabalin from clinical studies is drowsiness. At the 150 mg pregabalin dose, BG scores were significantly lower relative to placebo. The BG scale is sensitive to amphetamine-like drugs, and other studies have shown decreases on this scale by drugs that are considered to be sedative in nature, including benzodiazepines and barbiturates (Griffiths et al., 1983, 1984; Johnson et al., 2006; Mumford et al., 1995). Also, although not shown in Table 1, there was an overall significant effect on the PCAG, or Sedation, scale of the ARCI, with peak scores in the 150 mg condition being significantly higher than in the 75 mg condition, i.e., 9.9 versus 7.3 respectively (peak score in the placebo condition was 7.4). Although such changes in PCAG and BG scales are not traditionally interpreted as indicators of abuse liability, it is possible that in a sedative-abusing population, such sedating effects could be desirable.

There are at least two studies in the literature that have examined the subjective as well as cognitive and psychomotor effects of pregabalin, albeit with different designs and measures. Hindmarch et al. (2005) examined in 22 healthy volunteers effects of 150 mg pregabalin given thrice daily over the course of 3 days. Using this subchronic dosing regimen, there was negligible cognitive or psychomotor impairment relative to either placebo or to a positive control drug, 1 mg alprazolam, administered thrice daily. On a subjective measure of impairment (derived from VAS measures of tired, drowsy, not energetic, not alert, clumsy, and dizzy), subjects reported increases for the first 2 days under pregabalin treatment versus when they were given placebo. The authors concluded that pregabalin had a "relatively benign side-effect profile" (p. 133). Our results are concordant with that conclusion, in particular with the lack of psychomotor effects of pregabalin detected in the present study. However, another study did detect cognitive and psychomotor decrements, as well as subjective neurotoxicity, in a group of 16 healthy volunteers, after 12 weeks of exposure to pregabalin (Salinsky et al., 2010). In that chronic dosing study, the dose of pregabalin was steadily escalated over the first 8 weeks in the same manner that a patient initiated to treatment with pregabalin would have their dose escalated, and then subjects were maintained on 300 mg of pregabalin twice daily for 4 weeks. Compared to a group administered placebo during this time

frame, performance on several tests that are used to assess neurocognitive performance was impaired, and scores on a scale that measures neurotoxicity symptoms were increased. The design of this study better matches the manner in which pregabalin is administered in patients in need of anticonvulsants than does our acute dosing study. However, the dose chosen in Salinsky et al. (2010) was a dose double that was recommended in the package insert for treatment of neuropathic pain associated with diabetic peripheral neuropathy, and postherpetic neuralgia, and the authors acknowledged that lower doses may have had lesser effects.

Brief mention should be made of the decreased respiration rate that occurred in both the 75- and 150-mg pregabalin dosing conditions in our study. This was an unexpected finding, especially the fact that the decrease in the 75-mg dosing condition was greater than a 20% drop compared to placebo and could be considered as a clinically relevant event. In doing a PubMed search using the terms "pregabalin" and "respiratory depression," no articles were found. The package insert does not mention respiratory depression as a risk associated with the drug. We have no ready explanation for our finding of pregabalin decreasing respiration rate.

There were limitations to the study. One purpose of the study was to test abuse liability-related effects of pregabalin by itself, and it could be questioned whether we went up to a high enough dose to determine if the drug indeed had such effects. In the package insert of the drug, a study is briefly described in which the drug at a dose of 450 mg did generate abuse liability-related effects in volunteers who had a history of recreational use of sedative/hypnotic drugs. That dose was three times the highest dose that was included in the present study, but it is quite possible that volunteers in the study that received the 450 mg dose had a more substantial history of sedative/hypnotic use than our subjects did. In regard to the drug interaction aspect of the study, ideally more than one dose of the study drug of interest, pregabalin, should have been tested in combination with oxycodone. We did originally test two doses of pregabalin with oxycodone but safety concerns prompted us to eliminate one of the dose combination conditions (150 mg pregabalin with oxycodone) from the study. Also, pregabalin in combination with an opioid is prescribed for conditions that necessitate taking the drug on an extended (i.e., chronic) basis. We acknowledge that the generality of our findings is limited to the acute doses we chose and the subject population that was tested (non-drug-abusing volunteers). Although it would be desirable to conduct a study of this type in chronic pain patients who would be prescribed these drugs, interpreting some of the outcomes, particularly as they relate to abuse liability, would be difficult. This is because such measures as drug liking and desire to take the drugs again could increase, not necessarily due to positive subjective effects such as euphoria, but due to the pain-relieving properties of the drugs. Such increases then could not be considered as signals of potential abuse.

Although safety concerns prompted us to eliminate from the study the condition in which 150 mg pregabalin and oxycodone were administered in the same session, there were six subjects who did receive this condition prior to our decision. We re-analyzed the data from the six subjects including the 150 mg pregabalin/10 mg oxycodone condition to determine how these subjects reacted to that condition relative to the other five conditions (that all 16 subjects received). We were particularly interested in abuse liability-related subjective effects and whether psychomotor performance was impaired in this condition. There were no trends of greater abuse liability-related effects or impairment in this condition relative to the 10 mg oxycodone or 75 mg pregabalin/10 mg oxycodone conditions. For example, peak "take drug(s) again" ratings were 62.5, 77.2, 85.3, and 78.7 in the placebo, 10 mg oxycodone, 75 mg pregabalin/10 mg oxycodone, and 150 mg pregabalin/10 mg oxycodone conditions, respectively (values in the pregabalin-alone conditions not shown for clarity sake). Some subjective effects were increased by 150 mg pregabalin/10 mg oxycodone compared to 75 mg pregabalin/10 mg oxycodone: LSD scores of the ARCI, and VAS ratings of "heavy or sluggish feeling," "high," and "nauseated," but the differences between the two conditions were not statistically significant, most likely due to variability and the small sample size. The number of symbols drawn correctly on the DSST (trough values) was 41.3, 38.8, 37.3, and 36.5 in the placebo, 10 mg oxycodone, 75 mg pregabalin/10 mg oxycodone, and 150 mg pregabalin/10 mg oxycodone conditions, respectively. This measure was used as an example because it at least indicated a trend toward decreased performance in some of the drug conditions (as it did in the analysis with all 16 subjects minus the 150 mg oxycodone/10 mg oxycodone condition) — the other psychomotor measures showed no discernible differences comparing placebo to any of the active drug conditions. Respiration rate in the placebo, 75 mg pregabalin/10 mg oxycodone, and 150 mg pregabalin/10 mg oxycodone conditions was 12, 9.3, and 10 breaths/min, respectively.

In closing, the results of our study indicate that pregabalin does not have abuse liability-related subjective effects, at least at the acute doses we tested, in non-drug-abusing volunteers, and that it does not potentiate self-reported liking of oxycodone effects, again at the doses we tested. In terms of actual abuse of the drug, there is evidence that it exists, but the extent or prevalence of the abuse is unclear at this point (Filipetto et al., 2010; Schifano et al., 2011; Schwan et al., 2010). We feel that further psychopharmacological studies with pregabalin are warranted, including a study assessing its abuse liability across a range of doses in sedative abusers, as well as testing within the same subject population the drug in combination with other CNS-active drugs such as benzodiazepines and alcohol.

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