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Human abuse liability assessment of oxycodone combined with ultra-low-dose naltrexone

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Abstract

Rationale—Prescription opioid abuse has risen dramatically in the United States as clinicians have increased opioid prescribing for alleviation of both acute and chronic pain. Opioid analgesics with decreased risk for abuse are needed.

Objective—Preclinical and clinical studies have shown that opioids combined with ultra-low-dose naltrexone (NTX) may have increased analgesic potency and have suggested reduced abuse or dependence liability. This study addressed whether addition of ultra-low-dose naltrexone might decrease the abuse liability of oxycodone (OXY) in humans.

Materials and methods—This double-blind, placebo-controlled study systematically examined the subjective and physiological effects of combining oral OXY and ultra-low NTX doses in 14 experienced opioid abusers. Seven acute drug conditions given at least 5 days apart were compared in a within-subject crossover design: placebo, OXY 20 mg, OXY 40 mg, plus each of the active OXY doses combined with 0.0001 and 0.001 mg NTX.

Results—The methods were sensitive to detecting opioid effects on abuse liability indices, with significant differences between all OXY conditions and placebo as well as between 20 and 40 mg OXY doses on positive subjective ratings (e.g., “I feel a good drug effect” or “I like the drug”), on observer- and participant-rated opioid agonist effects, and on a drug-versus-money value rating.

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There were no significant differences or evident trends associated with the addition of either NTX dose on any abuse liability indices.

Conclusions—The addition of ultra-low-dose NTX to OXY did not decrease abuse liability of acutely administered OXY in experienced opioid abusers.

Keywords

Abuse liability; Ultra-low-dose naltrexone; Oxytrex; OPIOID; PTI-801

Introduction

As clinicians have attended increasingly to the diagnosis and treatment of pain, use of prescription analgesics has grown markedly (Novak et al. 2004). Both patients and physicians worry about the risk of prescription opioid addiction, and often forego clinically indicated analgesics (Flugsrud-Breckenridge et al. 2007; Morley-Forster et al. 2003). Data validate some of these concerns, indicating the rates of illicit prescription opioid abuse and dependence have risen dramatically in the United States. Since the mid-1990s, the Drug Abuse Warning Network reported a greater than 2.5 times increase in the rate of emergency department visits involving prescription opioid analgesics (SAMHSA 2004). As well, between 1997 and 2007 prescription opioids were increasingly identified as the primary drug of abuse at drug treatment entry (SAMHSA 2007).

Given these trends, there is a need for development of analgesics with decreased risk for abuse. One promising approach is the combination of a mu-opioid receptor agonist with an ultra-low-dose opioid receptor antagonist (i.e., pico- or nanomolar additions of naloxone or naltrex-one [NTX]). Although this combination seems paradoxical as a pain treatment, early research has shown promise. Naloxone alone has a bimodal effect on analgesia: low intravenous doses (1–2 mg) produce analgesia and higher doses (3+ mg) produce hyperalgesia in healthy normal volunteers (Buchsbaum et al. 1977) and in postoperative patients (Levine et al. 1979). Clinical trials showed that intravenous and epidural opioids combined with naloxone could produce greater analgesia than opioids alone (Rawal et al. 1986; Gueneron et al. 1988; Gan et al. 1997); these studies revealed the importance of the ratio of opioid agonist to antagonist in enhancing analgesia, showing ultra-low naloxone doses (ng/kg to pg/kg) are needed for optimal effect. Concurrent preclinical work showed that G-protein coupled mu-opioid receptors have dual actions with excitatory effects (leading to anti-analgesia) in addition to the widely known inhibitory effects (analgesia; Crain and Shen 2000). These observations helped elucidate the neurobiological underpinnings of the original clinical observations with naloxone, showing that pM concentrations of naloxone or NTX could block excitatory firing (increase analgesia) and mM concentrations could block inhibitory firing (produce anti-analgesia).

Given the early clinical findings and replication in controlled preclinical experiments using morphine (Powell et al. 2002; Crain and Shen 1995) as well as oxycodone (OXY; Largent-Milnes et al. 2008; Webster 2007), development of an oral agonist/antagonist combination product was begun. Oxytrex (PTI-801) is an oral combination of OXY with ultra-low-dose NTX (either 0.0001 or 0.001 mg). Two clinical trials with Oxytrex have shown that it is safe and efficacious in the management of osteoarthritis pain (Chindalore et al. 2005), and it can produce similar reductions in chronic pain as OXY alone with on average a slightly lower total dose of OXY (Webster et al. 2006). This latter study also found a reduction in physical dependence as measured by the degree of opioid withdrawal present 24 h after double-blind medication cessation in participants given OXY 40 mg + NTX 0.001 mg twice daily (BID), as compared to the groups given OXY 20 mg + NTX 0.001 mg four times daily (QID) or OXY 20 mg QID. However, the experiment had a high placebo response, a significant dropout rate

due to adverse events in all opioid groups, and relatively small reductions in opioid withdrawal indices. As well, the enhanced analgesia provided by the OXY 40+NTX 0.001 mg BID group may have resulted from the higher individual OXY doses. Although all groups received OXY 80 mg total per day, the NTX group received two doses of OXY 40 mg while the comparison group received four doses of OXY 20 mg. Despite these limitations, the study provided some evidence that the combination of OXY with an ultra-low-dose of NTX may be a promising analgesic formulation.

The potential for abuse of opioid agonist/antagonist combinations has been examined in animal models. The results from preclinical studies have shown the addition of ultra-low doses of naloxone or NTX may decrease the reinforcing effects of opioids. One of the earliest studies showed an increase in conditioned place preference (CPP) in rats given simultaneous injections of morphine and ultra-low-dose NTX (Powell et al. 2002) while another study showed a small but significant decrease in CPP in rats given injections of ultra-low-dose NTX and OXY in a 1:10⁸ ratio (Olmstead and Burns 2005). The latter study also found that rats given OXY + ultra-low-dose NTX had decreased conditioned place aversion to precipitated opioid withdrawal. A third study showed an increase in self-administration of OXY when ultra-low-dose NTX was added but a lowered response to reinstatement from an OXY priming injection and foot shock stress cue (Leri and Burns 2005). Due to these mixed findings in the preclinical literature, clinical studies of the abuse potential of OXY+ ultra-low-dose NTX are needed. Given concern over widespread prescription opioid abuse and the consequences to individual and public health, it is important to examine abuse liability profiles in humans prior to approval and use of new analgesic formulations (Griffiths et al. 2003).

The brain regions controlling opioid analgesia and reward overlap (Wise 1989; Borsook et al. 2007), and it has generally been believed that opioid analgesia and reward covary—that effective analgesics also have abuse potential. However, the preclinical data with Oxytrex suggest a potential for disaggregating these two features. Therefore, the present study was designed to test the hypothesis that addition of ultra-low-dose NTX would decrease the abuse potential of OXY. The study used well-established clinical pharmacology methods to examine the subjective and objective effects of OXY + ultra-low-dose NTX combinations as compared to OXY alone or placebo in volunteers with a history of opioid abuse.

Materials and methods

Study sample

The protocol and recruitment materials were approved by the Institutional Review Board at Johns Hopkins University, conducted in accordance with the Declaration of Helsinki, and registered at www.clinicaltrials.gov (NCT00734461). Participants were screened on an outpatient basis and then admitted to a residential research unit for the primary study. All participants gave written, informed consent after full explanation of procedures before entering the study.

Inclusion criteria were: English speaker, age 18–65, current opioid abuse, negative urine drug screen and ethanol breath test before beginning the qualifying phase, able to provide written informed consent, use of an acceptable method of birth control if female, and adequate differentiation of the effects of an opioid agonist versus placebo during two qualifying sessions.

Exclusion criteria were: use of prescription opioids for chronic pain, use of illicit drugs in the prior 7 days or over-the-counter medications in the prior 48 h, abuse of opioids more than 20 days in the last month, clinically significant medical or psychiatric illness other than substance abuse, allergy to NTX or opioid agonists, pregnant or breastfeeding, receipt of an investigational drug in the 30 days prior to intake, signs/symptoms of opioid withdrawal during

the observation period, or experience of adverse events requiring opioid antagonist administration within 4 h after administration of OXY.

In order not to bias results, participants were not told the exact composition of the study drugs but were told they could receive drugs from multiple classes or combinations of those classes, including opioids and opioid antagonists, among others. Participants were paid for their participation.

Of the 35 persons consented, two were disqualified at admission/intake for hypertension and five for positive urine drug screen. Twenty-eight entered the qualifying phase, and 14 of these qualified and entered the primary study phase. There were no significant differences between the 14 primary study participants and the 14 disqualified (Table 1). Reasons for disqualification included clinically significant hypertension (1), opioid withdrawal symptoms (1) and failure to differentiate adequately between 30 mg oral OXY and placebo (12), a priori specified as a 20-point higher rating on the “liking” visual analog scale (VAS) during the OXY session versus the placebo session.

Screening phase

Initial prescreening occurred over the telephone and consisted of basic demographic and substance use history questions. Those meeting preset criteria were invited to an in-person screening, at which informed consent was obtained, and a medical and substance use history, physical examination, serum pregnancy test for females, and other basic laboratory assessments were completed.

Qualifying phase

Participants admitted to the residential research unit were observed for signs and symptoms of opioid withdrawal by trained nursing staff for 24 h. The Objective Opioid Withdrawal Scale (Handelsman et al. 1987) was then administered; participants were required to score ≤ 4 in order to remain in the study.

Participants then had a 2-day qualifying dosing period. Participants were blinded to the purpose of these sessions and to the qualification requirements. Two test sessions each of 4-h duration were conducted, with collection of baseline data prior to randomized, double-blind oral drug administration (OXY 30 mg or placebo), and then repeated data collection at 30 min intervals. This dose of OXY was chosen as providing an adequate safety screen before administering OXY 40 mg and as typically producing sufficient opioid agonist subjective effects to serve as a screening tool (Zacny and Gutierrez 2003; Walsh et al. 2008). If the participant met preset qualification criteria, he or she continued into the primary study phase.

Primary study phase

During the primary study phase, participants had seven test sessions at least 5 days apart. Study drugs were administered double-blind in a mixed, balanced, block order, with a different order for each participant; doses within a block were in random order, and blocks were in random order for each subject. The within-subject crossover design exposed each participant once to each of the following: placebo, OXY 20 mg, OXY 40 mg, OXY 20 mg + NTX 0.0001 mg, OXY 40 mg + NTX 0.0001 mg, OXY 20 mg + NTX 0.001 mg, and OXY 40 mg + NTX 0.001 mg. Thus, the study had a placebo control, a dose-effect evaluation of OXY at each level of naltrexone, and a dose-effect evaluation of NTX at each level of active OXY. Each of the study sessions followed the same format as the qualifying phase session.

Investigational drug supply

Drug capsules for the qualifying period and drug tablets for the active study phase were provided by Pain Therapeutics, Inc. (San Mateo, CA, USA). Drugs were stored in a secure pharmacy at room temperature.

Assessment of opioid agonist/antagonist effects

Subjective effects assessments consisted of VAS items, participant- and observer-rated adjective scales, and a pharmacologic class questionnaire (these and physiologic measures have been described in detail in prior studies; Strain et al. 1997, 2000). If appropriate, baseline measurements were obtained for scales (e.g., not for items that explicitly asked subjects to describe the effect of the drug not yet administered); then, measurements were collected at 30, 60, 90, 120, 150, 180, and 210 min after drug administration. In addition, a drug versus money questionnaire and a 24-h drug questionnaire were completed. The drug versus money questionnaire asked the participant to indicate a dollar value above which they would choose money and below which they would choose the study drug, modeled on the Multiple Choice Procedure used to measure drug reinforcement (Griffiths et al. 1993). Twenty-four hours after each session, participants were asked similar abuse liability questions.

Adverse events (AEs) were collected through participant spontaneous report and by observer assessments. Each event was categorized using the Medical Dictionary for Regulatory Activities. AEs were categorized as mild, moderate, or severe based upon preset criterion, and as to whether or not they were likely related to the study drug.

Statistical analysis

The prespecified primary outcome variable was the subjective “liking” VAS. Peak effects on this VAS were examined with repeated measures 1-factor (drug condition) analysis of variance (ANOVA). Tukey’s honestly significant difference tests were used to perform pairwise comparisons among all test conditions. Other analyses of opioid agonist effects, both peak and change from baseline, were performed using similar ANOVA techniques. In order to utilize all available data, uncollected baseline data on 7% of the opioid adjectives questionnaires were replaced with interpolated values using mean ratings of the other participants for that drug condition. (Of note, the ANOVA results did not significantly change when these observations were dropped from analysis). Two-factor ANOVA (drug condition, time, and a condition $\times$ time interaction term) was performed to examine time course differences. *P* values below 0.05 were considered statistically significant.

Results

Subjective effects

Visual analog scales—Table 2 and Fig. 1 show that all OXY conditions significantly differed from placebo for peak VAS ratings of “liking,” “drug effect,” “good effects,” and “high.” There were also significant differences for VAS ratings of “drug effect,” “good effects,” and “high” between the OXY 20 and 40 mg conditions. There were no significant differences for the same OXY dose with and without ultra-low-dose NTX on ratings of “liking” (Table 1).

Figure 2 illustrates the time course of “liking” and “good effects” VAS ratings. Each of the OXY drug conditions showed acute opioid effects that were evident by 30 min and peaked between 60 and 120 min, whereas placebo showed no appreciable effects throughout the study session. Similar time course differences for “drug effect” and “high” ratings were seen.

In general, the higher dose of OXY (40 mg) produced greater effects than the lower dose (20 mg), with some evidence of more sustained effects with the 40 mg condition (e.g., “liking”

ratings, Fig. 2). The combination of NTX with the OXY 40 mg condition produced no clear change in the time course VAS ratings (Fig. 2a and b). However, the combination of NTX with OXY 20 mg appeared to produce some small increase in VAS ratings of “good effects” and perhaps “liking,” and these effects generally appeared to peak within 3 h of drug administration. “Sick” and “bad effects” VAS ratings showed no significant differences between any of the drug conditions. Mean values on the VASs asked 24 h after each session were consistent with the mean peak values obtained within session (Table 2).

Adjectives questionnaire—Using peak change from baseline, adjective agonist subscale scores showed a main effect for drug condition (Table 2). Pairwise comparisons revealed significant differences between placebo and all other drug conditions. Observer-rated “magnitude of drug effect” also showed significant differences between the OXY drug conditions and placebo as well as between the higher and lower OXY drug conditions. Time course analysis revealed significant main effects for drug condition ($F=7.75$; $df=6, 78$; $p<0.0001$), time ($F=39.3$; $df=7, 91$; $p<0.0001$), and condition $\times$ time ($F=1.43$, $df=42, 545$; $p=0.042$) for the overall agonist subscale. There was no significant difference between drug conditions on subjective antagonist adjective subscale scores (Table 2).

Drug versus money questionnaire—The mean amount of money participants would hypothetically pay for a specific drug was highest for OXY 40 mg + NTX 0.001 mg and lowest for placebo at the end of the session. When asked the same question the next day, the pattern of these results remained the same (Table 2). There were significant pairwise differences for both the end of session and next day ratings for this measure, generally showing differences by OXY dose, e.g., values for the OXY 40 mg conditions were generally higher than OXY 20 mg conditions and OXY 20 mg conditions were higher than placebo. However, the pattern of these differences did not show significant orderly effects as a function of NTX dose.

Drug identification—At the end of each session, participants indicated from which drug class they thought that session’s study drug came. For the 84 sessions in which an opioid was administered, participants chose opioid correctly 90% of the time; incorrect responses included placebo (6%), benzodiazepine (2%), and cocaine/stimulants (2%). When asked this question again 24 h after drug administration, participants chose opioid (86%), placebo (5%), benzodiazepine (1%), and cocaine (1%); 7% of answers were not collected. During placebo sessions, placebo was correctly chosen 85% of the time. OXY dose was associated with correct identification as an opioid: seven of the OXY 20 mg sessions were not identified as opioid as compared to only one of the OXY 40 mg sessions. NTX dose did not affect these results.

Physiologic effects

Heart rate, oxygen saturation, and respiratory rate were decreased by one or more OXY drug conditions, but these decreases were not clinically significant (changes were within 20% of placebo values). Figure 1c shows the mean oxygen saturation at the peak drug effect for each drug condition while Fig. 2c shows mean values of oxygen saturation over time. Both of these figures illustrate the small differences between active and placebo conditions. There was no incidence of respiratory depression requiring clinical intervention. Blood pressure did not show any significant main effects in the time course analysis, and there were no significant pairwise differences in mean peak change from baseline values.

Figure 2d shows the mean pupil diameter over time for each of the seven drug conditions. As expected, increasing doses of OXY led to smaller pupil diameters in a dose-dependent manner. These miotic changes remained throughout the session. Time course analysis revealed a significant difference by drug condition ($F=36.84$; $df=6, 78$; $p<0.0001$), time ($F=179.94$; $df=7, 91$; $p<0.0001$), and condition $\times$ time ($F=4.19$; $df=42, 541$; $p<0.0001$). In pairwise analyses of

peak change from baseline, there were significant differences between all active drugs versus placebo as well as between OXY 20 mg versus OXY 40 mg conditions (Fig. 1d). There was no significant difference in peak change from baseline values for pupil diameter caused by the addition of ultra-low-dose NTX. Finally, there were no clinically significant ECG or serum blood work changes from pre- to posttesting.

Adverse events

There were a total of 86 AEs, with the highest number in the placebo condition. For OXY 20 mg, conditions with low-dose NTX had a greater number of AEs (16 and 12) versus OXY alone (5). For OXY 40 mg, the naltrexone-containing conditions had lower numbers of AEs (10 and 6) versus OXY alone (17) and even less than the 20 mg OXY dose containing the same amount of NTX. There were no serious AEs, and no AEs resulted in study discontinuation after the qualifying phase.

Discussion

This study used state-of-the-art abuse liability assessment procedures, including internal controls (placebo, multiple dose levels) that document the sensitivity of the measures for detecting effects when present, and found no significant effects of concomitant ultra-low-dose NTX on the abuse liability of OXY. At the outset of the study there was a reasonable basis to expect that combining the two medications might decrease abuse liability. Preclinical work with OXY and ultra-low-dose NTX had suggested that analgesia might be increased and abuse liability decreased by their combination (Olmstead and Burns 2005; Leri and Burns 2005). The present results in humans failed to confirm that abuse liability is decreased with this combination, as measured by self-reported and observer-rated acute drug effects. The combination of OXY + NTX had similar positive subjective effects as OXY alone.

Since the analgesic and abuse liability effects of mu-opioid agonists have generally appeared to be linked, one might have expected the combination to enhance abuse liability, irrespective of the preclinical results. However, the recognition of a new binding site for naloxone and NTX may offer an explanation for possible dissociation of opioid analgesia and reward. Naloxone and NTX bind with picomolar affinity to filamin A, a scaffolding protein that appears to regulate mu-opioid receptor signaling via G-proteins (Wang et al. 2008). This high-affinity interaction prevents the switch from Gi/o to Gs coupling by the mu-opioid receptor that is associated with chronic opioid administration and the development of analgesic tolerance (Wang et al. 2005; Chakrabarti et al. 2005) as well as addiction (Nestler 2004). The acute administration of morphine is associated with Gs coupling and the release of second messengers associated with addiction. Blockade of this coupling with picomolar doses of NTX or naloxone could explain enhancement of analgesia in the absence of an effect on abuse liability (Wang and Burns 2009).

The study results confirm recent data showing that increased OXY doses (without NTX) have increased drug abuse liability (Walsh et al. 2008; Comer et al. 2008). The present mean VAS ratings and opioid adjective scores for OXY 20 mg and OXY 40 mg, irrespective of ultra-low-dose NTX, are comparable to both Comer and Walsh's findings in similar populations of opioid abusers. This increased risk for OXY abuse has already been demonstrated on a population level in North America by the increased numbers of persons seeking treatment for OXY use disorders as larger-dosage formulations have become available (Sproule et al. 2009; Spiller et al. 2009; SAMHSA 2007). This study did not compare abuse liability across various opioid agonists or with the addition of NTX to other opioid medications. However, recent research suggests there is little difference in abuse liability between different full mu-opioid agonists (Walsh et al. 2008), although there appears to be a difference in full versus partial mu agonists

(Comer et al. 2008). Further research is needed in this area to examine the effects of ultra-low-dose NTX on the abuse liability of other opioid agonists.

Although the NTX dose did not produce any significant effects on the present measures of abuse liability, there was an interesting finding among the two OXY doses. For the lower OXY dose, combinations with NTX usually had higher (but not statistically significant) mean abuse liability ratings. This difference widened somewhat when the participant was asked to remember experiences 24 h after drug administration. The opposite trend was seen for the higher OXY dose; NTX was associated with a decrease in many mean ratings related to abuse liability. This trend is not explained by differences in AEs or negative subjective effects of the drug, as the OXY 20 mg + NTX doses had more AEs and higher relative ratings on “bad effects” VAS compared to OXY 20 mg. These negative effects are usually associated with a decreased abuse liability, as has been shown with the injectable buprenorphine + naloxone combination (Stoller et al. 2001; Alho et al. 2007). Just as the ratio of opioid agonist to antagonist is important in analgesic effects, there might be a similar relationship for abuse liability. Further research is needed in this area and also to replicate these present trends of abuse liability in different OXY + NTX ratios.

There are several limitations to the study. First, there was no measurement of analgesic response. In order to definitively conclude a medication has increased analgesic effect and similar or less abuse potential, a study design needs to measure both outcomes in the same study population. It is difficult to combine the results of prior studies of the analgesic response to Oxytrex and this current study, as there are significant differences in populations tested and dosing patterns. Second, the present study examined only single-dose acute administrations; it is possible that the OXY plus NTX combination has different effects with chronic administration. Third, the study was performed with persons who had a history of opioid abuse. Different results might have occurred if nonsubstance abusing patients taking prescription opioids for the treatment of pain had been sampled. The magnitude of euphoric effects and liking observed in a nonsubstance-abusing population may be fundamentally different than the magnitude of those effects observed in participants with a history of opioid abuse. The greatest risk of substance misuse, however, is in persons with current and former substance use disorders (Cicero et al. 1999; Griffiths et al. 2003). The current work demonstrates that in persons likely to abuse opioids, the abuse potential of OXY + ultra-low-dose NTX is the same as OXY alone. Finally, there was only one female recruited for this study and no persons of Hispanic ethnicity. Consequently, this study’s results may not generalize to the entire population, especially as demographics can be risk factors for abuse of prescription opioids (Tetrault et al. 2008; Cicero et al. 2005; McCabe et al. 2007a; McCabe et al. 2007b).

The lack of a significant effect from the addition of ultra-low-dose NTX to OXY as was seen in previous human analgesia trials may be due to differences in study design. The clinical trials with Oxytrex were used twice and four times daily dosing for 12 weeks in a population with chronic back pain and no substance abuse diagnosis in the previous 5 years (Webster et al. 2006). Perhaps the increased analgesic efficacy reported in that paper requires physiologic changes in brain opioid receptor density that only come with chronic NTX dosing. Additionally, the difference in mean subjective opioid withdrawal scale (SOWS) scores between dose conditions (an indication of abuse liability) seen at 24 h in the Webster study was 1.5 points. The overall SOWS score means for all conditions in that study were less than 5 (out of possible score of 64), indicating minimal opioid withdrawal. Although those results were statistically different, the 1.5-point difference may have little clinical significance in terms of abuse liability.

In conclusion, this study demonstrated that ultra-low-dose NTX does not decrease abuse liability as was predicted by some preclinical models. Although prior clinical trials suggest

that Oxytrex may provide greater analgesia than OXY alone, further work is needed to confirm this and to confirm whether this occurs without an increase in abuse liability. This study also highlights the value and feasibility of abuse liability studies during the drug development process. Candidate medications that may enhance analgesia without enhancing abuse liability certainly warrant further investigation.

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Fig. 1.

Peak naltrexone dose-effect functions under different oxycodone doses. *OXY* oxycodone, *NTX* naltrexone, *PL* placebo, *VAS* visual analog scale. There were no significant effects on mean peak abuse liability measurements (“liking” and “good effects” VASs), mean peak oxygen saturation, or mean peak pupil diameter decreases when ultra-low-dose NTX was added to OXY. There were nonsignificant trends for NTX dose to increase “liking” and “good effects” VASs in OXY 20 mg dose conditions but decrease the VAS ratings in OXY 40 mg conditions. *Single asterisk* indicates significant ($p < 0.05$) difference from placebo

Fig. 2.

Oxycodeone time-effect functions in combination with different naltrexone doses. *OXY* oxycodeone, *NTX* naltrexone, *VAS* visual analog scale, *BL* baseline. The participants were able to differentiate the effects of OXY from placebo as seen in the time course graphs of “liking” and “good effects” VASs. The OXY conditions also produced dose-dependent decreases in pupil diameter but no significant changes in oxygen saturation. Ultra-low NTX doses did not significantly effect any of these measurements

Table 1

Demographics

	Primary study participants <i>N</i> (%)	Disqualified <i>N</i> (%)
Gender		
Male	13 (93)	13 (93)
Female	1 (7)	1 (7)
Race		
Caucasian	8 (57)	4 (29)
African American	6 (43)	10 (71)
Age (years, $\pm$ SD)	43.2 (5.5)	43.3 (8.7)
Weight (kg, $\pm$ SD)	80.8 (11.8)	77 (12)
Opioid abused		
Heroin	6 (43)	7 (50)
Rx opioids	4 (28.5)	4 (29)
Combination	4 (28.5)	3 (21)
Duration of use for preferred opioid abused (years, $\pm$ SD)	7.5 (7.5)	3.9 (6.5)

No differences were significant at the $p < 0.05$ level. There was a trend for those persons who did not qualify to have fewer years of opiate abuse but this was not significant ($p = 0.19$)

Rx prescription

Table 2

Mean peak values of abuse liability measurements by drug condition

	F value	df	PL	OXY 20	OXY 20 +NTX 0.0001	OXY 20 +NTX 0.001	OXY 40	OXY 40 +NTX 0.0001	OXY 40 +NTX 0.001
VAS peak ratings (0– 100)									
Liking	17.4*	6, 78	0.43 ^a	43.07 ^b	51.64 ^b	42.14 ^b	61.93 ^b	58.43 ^b	57.71 ^b
Drug effect	14.8*	6, 78	3.64 ^a	28.43 ^b	37.64 ^{bc}	34.79 ^{bc}	51.21 ^c	48.36 ^c	47.29 ^c
High	17.0*	6, 78	1.07 ^a	29.50 ^b	38.93 ^{bc}	33.86 ^{bc}	52.14 ^c	49.50 ^c	50.14 ^c
Good effects	18.3*	6, 78	1.14 ^a	36.29 ^b	48.86 ^{bc}	42.64 ^b	63.79 ^c	56.43 ^{bc}	54.43 ^{bc}
Bad effects	1.8	6, 78	2.07 ^a	6.36 ^a	8.93 ^a	2.57 ^a	13.29 ^a	2.86 ^a	4.43 ^a
Sick	2.1**	6, 78	0.21 ^a	12.57 ^a	11.14 ^a	3.00 ^a	10.07 ^a	3.71 ^a	14.93 ^a
Adjectives peak change from baseline									
Agonist subscale (Subject)	12.1*	6, 78	0.93 ^a	7.07 ^b	7.14 ^b	8.00 ^b	10.64 ^b	8.93 ^b	8.21 ^b
Antagonist subscale (Subject)	1.1	6, 78	0.86 ^a	1.71 ^a	1.07 ^a	0.86 ^a	1.93 ^a	1.79 ^a	1.79 ^a
Magnitude of drug effect (Observer)	17.8*	6, 78	0.14 ^a	1.07 ^b	1.36 ^{bc}	1.43 ^{bd}	2.07 ^{de}	1.92 ^{cd}	1.71 ^{bef}
Drug vs. money (\$)									
End of session	16.0*	6, 78	0.29 ^a	3.79 ^{ab}	6.00 ^{bde}	6.29 ^{bde}	9.86 ^{cd}	9.71 ^{ce}	11.43 ^c
Next day	6.8*	6, 71	3.31 ^a	5.46 ^{ab}	6.31 ^{ab}	6.46 ^{ab}	10.25 ^{bc}	9.62 ^{bc}	11.29 ^c
Next day questionnaire									
Liking	17.1*	6, 78	0.36 ^a	25.57 ^b	41.36 ^{bc}	35.86 ^{bc}	52.14 ^c	48.86 ^c	54.57 ^c
Drug effect	24.2*	6, 78	1.07 ^a	20.86 ^b	33.86 ^{bd}	29.57 ^{bc}	47.86 ^{cd}	41.29 ^{cde}	50.14 ^c
Good effects	19.9*	6, 78	0.29 ^a	23.21 ^b	42.43 ^{bde}	37.29 ^{bd}	59.50 ^{ce}	49.86 ^{cd}	52.43 ^{cd}
Bad effects	2.1**	6, 78	1.86 ^a	7.29 ^a	9.21 ^a	2.93 ^a	12.00 ^a	2.79 ^a	9.57 ^a
Take again? (0– 4)	17.4*	6, 78	0.07 ^a	1.57 ^b	2.00 ^{bc}	1.93 ^{bc}	2.43 ^c	2.36 ^{bc}	2.36 ^{bc}
Money value on street (\$)	11.0*	6, 78	0.29 ^a	5.07 ^{ab}	6.93 ^{bcd}	6.57 ^{bcd}	11.29 ^{bde}	13.14 ^{de}	14.36 ^e
Money value to subject (\$)	9.9*	6, 78	0.29 ^a	4.29 ^{ab}	6.57 ^{ac}	6.00 ^{ac}	10.36 ^{bcd}	12.29 ^{cd}	13.86 ^d

Dose conditions are in milligrams. For a given abuse liability assessment, alphabetic superscripts are used to showcase significant differences between dose conditions. If the assessment's values were labeled "X^a, Y^{ac}, Z^{bc}," X and Z differ significantly from one another, but neither differs from Y. Proceeding from left to right on "Good Effects" VAS, dose conditions with the letter "a" are not significantly different from placebo, dose conditions with the letter "b" are not significantly different from OXY 20 mg (or other conditions with the letter "b"), and dose conditions with the letter "c" are not significantly different from OXY 40 mg (or the other conditions with the letter "c").

PL placebo, *OXY* oxycodone, *NTX* naltrexone, *df* degrees of freedom

* $p<0.0001$;
** $p=0.06$