

Randomized, double-blind, placebo-controlled and active-controlled study to assess the relative abuse potential of oxycodone HCl-niacin tablets compared with oxycodone alone in nondependent, recreational opioid users

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Background: Abuse-deterrent formulations attempt to address public health and societal concerns regarding opioid abuse. Oxycodone HCl-niacin tablets combine oxycodone HCl with niacin and functional inactive excipients to create potential barriers to oral, intranasal, and intravenous abuse. This study compared the relative abuse potential of oral immediate-release oxycodone HCl-niacin with that of oral immediate-release oxycodone HCl and placebo in nondependent, recreational opioid users.

Methods: Forty-nine participants received oxycodone HCl-niacin 40/240 mg and 80/480 mg, oxycodone 40 mg and 80 mg, and placebo in a randomized, double-blind, placebo-controlled and active-controlled, five-way crossover study. Primary endpoints based on a bipolar 100 mm visual analog scale for drug liking were area under effect curve (AUE_{0-1h} , AUE_{0-2h} , AUE_{0-3h}), peak disliking, and effect at 0.5 hours post-dose ($E_{0.5h}$). Other endpoints included take drug again assessment, overall drug liking, and pupillometry.

Results: There were statistically significant differences between oxycodone HCl-niacin and oxycodone HCl doses for all primary endpoints ($P < 0.0001$, all comparisons), suggesting reduced abuse potential with oxycodone HCl-niacin. Take drug again and overall drug liking showed greater liking of oxycodone alone. Oxycodone HCl-niacin 80/480 mg had consistently lower liking assessments than oxycodone HCl-niacin 40/240 mg, suggesting a dose-response to the aversive effects of niacin. Opioid-related adverse events were similar for equivalent oxycodone doses. The treatment-emergent adverse events most specifically associated with oxycodone HCl-niacin (ie, skin-burning sensation, warmth, and flushing) were consistent with the expected vasocutaneous effects of niacin. No serious adverse events were reported.

Conclusion: Oxycodone HCl-niacin tablets may, in a dose-dependent manner, decrease the potential for oral abuse of oxycodone without unexpected adverse events or clinically significant differences in safety parameters compared with oxycodone alone. Although statistically powered, the small size of the study sample and the characteristics of its participants may not be generalizable to the population that abuses prescription opioid medications.

Keywords: drug abuse, opioid, oxycodone, niacin

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Introduction

Increased medical use of opioids for the management of moderate to severe pain has been paralleled by increased nonmedical use and abuse of these drugs.¹⁻³ In 2009,

approximately 5.3 million people aged ≥ 12 years in the United States reported that they had used prescription pain relievers nonmedically within the past month, and approximately 2.2 million people initiated nonmedical use of prescription pain relievers within the past year.⁴ Pain management must be balanced with the need to minimize the risks of opioid misuse, abuse, and diversion.⁵

Immediate-release opioid products are associated with a higher incidence of abuse than extended-release opioids,⁶ likely owing to the greater volume of immediate-release prescriptions⁷ and that first-time abusers often start by misusing immediate-release opioids orally.⁸ Over time, abusers may advance to intranasal and intravenous use.⁹

A product that provides the analgesia of oxycodone and is designed to impede the most common routes of abuse (oral, intranasal, and intravenous) may help to reduce the abuse potential of this medication. Oxycodone HCl-niacin is a novel oxycodone product composed of two active ingredients (oxycodone HCl, active analgesic; niacin, aversive agent) and functional but inactive excipients. Niacin is an essential B vitamin, with a recommended dietary allowance of 16 mg/day for men and 14 mg/day for women¹⁰ and is administered at doses up to 6000 mg/day (immediate-release) when treating dyslipidemia.¹¹ Following an oral dose, niacin is rapidly absorbed, with peak concentrations occurring within one hour after dosing. The vasocutaneous flushing reaction of niacin occurs quickly and is consistent with its short elimination half-life of 20–45 minutes.¹¹ Niacin is considered an ideal substance to produce aversive effects immediately after ingesting with oxycodone because these effects are transient and occur at the time when abusers seek the “high” from the maximal concentration of oxycodone. A ratio of 30 mg of niacin to 5 mg of oxycodone was the minimal ratio found to reduce drug liking and aversion to taking the drug again across a number of oxycodone doses above the therapeutic amounts for an immediate-release formulation in a previous study.¹² Based on this study, a niacin only arm was not thought to be needed because it had already been studied at a variety of doses without oxycodone and found to produce only aversive effects.¹² The inactive excipients are added to impede extraction for intravenous injection and to cause mucosal irritation to discourage snorting.

A previous study showed that oxycodone HCl-niacin and immediate-release oxycodone were bioequivalent in healthy participants under fasting conditions, indicating that the presence of niacin does not affect oxycodone bioavailability.¹³ Niacin did not compromise the analgesic efficacy of oxycodone HCl-niacin in a clinical efficacy

and safety study in 405 bunionectomy patients; this study confirmed that two dose levels of oxycodone HCl-niacin (10/60 mg and 15/60 mg) provided statistically significant pain relief compared with placebo.¹⁴

The purpose of this study was to assess the oral abuse potential of oxycodone HCl-niacin tablets compared with orally administered immediate-release oxycodone HCl tablets in nondependent, recreational opioid users. Dose response for relative abuse liability of two different doses of orally administered oxycodone HCl-niacin tablets and the safety of high doses of oxycodone HCl-niacin tablets were also assessed. The design and endpoints were consistent with current standards to evaluate the abuse potential of a drug (ClinicalTrials.gov identifier NCT01030406).¹⁵

Materials and methods

Study sample

Men and women aged 18–55 years in generally good health were eligible if they were recreational opioid users (ie, had used opioids on ≥ 10 occasions in the preceding 12 months and at least once within the preceding 12 weeks) but not physically dependent on opioids, according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR).¹⁶ Eligible females were nonlactating and postmenopausal, surgically sterile, or practicing an acceptable method of birth control. Participants who had a positive urine drug screen, excluding tetrahydrocannabinol, at visit 1 were eligible if they tested negative at visit 2. Participants were excluded if they tested positive for alcohol, as assessed by the alcohol breath test, at visit 1 or on admission to the study center at visit 2, and/or were currently physically dependent on alcohol as determined by clinical evaluation and the DSM-IV-TR.

Participants with a history of, diagnosis of, or current treatment for substance dependence (except nicotine and caffeine) and/or alcohol abuse¹⁶ were ineligible. Additional exclusion criteria included a history or current diagnosis of significant disease, any condition for which an opioid was contraindicated, known allergy or history of hypersensitivity to opioids or niacin, or unwillingness to comply with the study protocol.

Study design

This was a single-center, randomized, double-blind, active-controlled and placebo-controlled, five-way crossover study consisting of a screening phase, naloxone challenge/drug discrimination phase, treatment phase, and an end-of-study safety evaluation (ClinicalTrials.gov NCT01030406).

The study was conducted at Lifetree Clinical Research (Salt Lake City, UT) from December 2009 to February 2010. Participants for this study were recruited from the clinical site's research database and via advertisements in local newspapers and radio stations that were approved by the institutional review board. The participants were recompensed for taking part in this study. Participants who passed screening (visit 1) returned to the study center as inpatients (visit 2). During the inpatient stay, a naloxone challenge test (visit 2, day 1) was performed to exclude physical dependence on opioids. During the naloxone challenge, all participants received an intravenous bolus dose of 0.2 mg naloxone HCl, followed by an assessment for signs of withdrawal using the Clinical Opiate Withdrawal Scale (COWS). If no evidence of withdrawal (COWS score < 5) occurred within 30 seconds, an additional 0.6 mg naloxone HCl bolus was administered and the participant was observed for 5 minutes for signs and symptoms of withdrawal by an additional assessment of the COWS. Only participants displaying no signs of withdrawal (COWS score < 5) were eligible to continue in this study. The drug discrimination test (visit 2, days 2–3) was performed to ensure that participants could differentiate between placebo and oxycodone HCl immediate-release 40 mg on drug liking. During the drug discrimination test, participants were randomized to receive a single dose of oxycodone HCl (40 mg) on study day 2 followed by placebo on study day 3, or vice versa. After each dose, pharmacodynamic (drug liking, take drug again, and overall drug liking visual analog scores and pupillometry) and safety measures were recorded. Participants were not eligible to continue in the study if they had one or more episodes of vomiting or if they could not adequately discriminate between the two treatments. Adequate discrimination was based on a ≥ 15 -point difference on the bipolar drug liking visual analog scale between placebo and immediate-release oxycodone HCl for at least one time point during the 2 hours following drug administration. Participants who successfully completed the naloxone challenge and the drug discrimination test, and who continued to be compliant with study procedures and requirements, entered the treatment phase.

In the treatment phase (visit 2, days 4–13), participants received each of five treatments, separated by 48 ± 1 hours, in a crossover treatment phase, ie, treatment A (oxycodone HCl 40 mg), treatment B (oxycodone HCl 80 mg), treatment C (oxycodone HCl-niacin 40/240 mg), treatment D (oxycodone HCl-niacin 80/480 mg), and treatment E (placebo). The doses of oxycodone HCl in this study were chosen based on drug-liking information for oxycodone HCl from the

literature, as well as on the street value of a 40 mg dose and 80 mg dose of a popular controlled-release oxycodone product.^{17,18} Participants were randomized to one of ten treatment sequences using a computer-generated randomization schedule in a Williams square design. Each treatment was administered as a single dose with water in the fasted state. Each dose was administered at approximately the same time each day by clinic staff who performed hand and mouth checks to ensure complete ingestion of drugs. All tablets were unmarked, identical in shape and size, and contained the functional excipients. After each treatment, pharmacodynamic measures (visual analog scores and pupillometry) and safety assessments were conducted within 10 minutes for 30-minute post-dose time points, and ± 15 minutes for all remaining time points. Final safety assessments were conducted approximately 24 hours following the final dose of study drug (visit 2, day 14).

The study was conducted in accordance with Good Clinical Practice requirements and all applicable regulations described in the current revision of International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guidelines.¹⁹ Additionally, this study was carried out in accordance with local legal requirements. The protocol and informed consent form were reviewed and approved by the institutional review board (NEIRB, Newton, MA). All participants signed and dated their informed consent form before any study-related procedures.

Pharmacodynamic assessments

Pharmacodynamic assessments were conducted during drug discrimination and treatment phases. The primary pharmacodynamic assessment was the 100 mm bipolar drug liking visual analog scale that assessed response to the question “Do you dislike or like the drug effect you are feeling now?” It was anchored in the center with a neutral response “neither like nor dislike” (score of 50), on the left with a negative “dislike an awful lot” (score of 0), and on the right with a positive “like an awful lot” (score of 100).²⁰ The question was assessed 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 hours post-dose.

Secondary assessments were the take drug again assessment and the global assessment of overall drug liking.²⁰ The take drug again visual analog scale assessed response to the question, “Would you want to take the drug you just received again, if given the opportunity?” The neutral response was “do not care,” negative was “definitely would not,” and positive was “definitely would,” assessed 1, 2, and 8 hours following administration of the study drug. The overall drug liking visual

analog scale assessed response to the question “My overall liking to the drug is ...”. The neutral response was “neither like nor dislike,” negative was “strong disliking,” and positive was “strong liking”. Overall drug liking was assessed 12 hours following administration of the study drug.

Pupillometry following each dose of drug was an objective measure of oxycodone pharmacology. Analyses of pupillometry included measurement at pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, and 12 hours post-dose.

Pharmacodynamic endpoints

The primary study objective was to compare the relative abuse potential of two doses of oxycodone HCl-niacin with that of equivalent doses of oxycodone. Primary pharmacodynamic endpoints were area under the drug effect curve from time 0–1 hour (AUE_{0-1h}), 0–2 hours (AUE_{0-2h}), and 0–3 hours (AUE_{0-3h}); peak disliking effect (E_{min}); and effect at 0.5 hours post-dose ($E_{0.5h}$) for the drug liking visual analog scale. This sampling time was taken to test an early time interval when the effects of niacin were expected to be occurring in view of the short half-life of 20–45 minutes. Supporting endpoints were AUE_{0-12h} , peak liking effect (E_{max}), time to peak liking (T_{Emax}), time to peak disliking (T_{Emin}), and effect at each time point post-dose. Secondary pharmacodynamic endpoints included take drug again responses at 1, 2, and 8 hours post-dose, overall drug liking assessment at 12 hours post-dose, and pupillometric effects.

Safety assessments

Safety assessments included physical examination, vital signs (blood pressure, heart rate, and respiratory rate), oxygen saturation of hemoglobin measured by pulse oximetry, clinical laboratory tests (hematology, serum chemistry, and urinalysis), and 12-lead electrocardiograms. Adverse events were assessed throughout the study.

Statistical analysis

The completer sample (all randomized participants who completed all five dosing periods of the treatment phase and contributed post-dose pharmacodynamic data) was used for the pharmacodynamic analyses. All participants who received at least one dose of study drug in any study phase were used for the safety analyses.

For drug liking visual analog score data, a neutral value baseline visual analog score was set at 50 mm for calculation of AUE. The primary endpoints were analyzed using a linear mixed model with fixed effects for sequence, period, and treatment, and a random effect for subject nested in sequence.

Least squares means, least squares mean differences between the treatment groups, and 95% confidence intervals were reported. All pairwise combinations were evaluated and unadjusted P values reported. The primary comparisons had P values adjusted for multiple comparisons using the Benjamini-Hochberg method.^{21–23} Supporting and secondary pharmacodynamic endpoints were analyzed similarly to the primary pharmacodynamic endpoints, without adjustment of P values. Statistical significance was defined as a P value ≤ 0.05 .

Results

Participants

Sixty-four participants entered the naloxone challenge and drug discrimination test. Of these, 49 (77%) entered the treatment phase, and 15 participants discontinued for the following reasons: drug discrimination criteria were not met ($n = 10$), investigator discretion owing to intolerance to treatment ($n = 3$), and noncompliance with study procedures ($n = 2$). Forty-seven participants completed all five dosing periods and two participants discontinued, ie, one withdrew consent and one discontinued for an adverse event (vomiting). The safety sample was predominantly male (78%) and white (94%). The median age was 23 (18–47) years and the mean body mass index was 24.3 kg/m².

Outcomes

Assay sensitivity

The validity of the study was confirmed (assay sensitivity) by statistically significant increases in the relevant primary endpoints (drug liking AUE_{0-1h} , AUE_{0-2h} , AUE_{0-3h} , $E_{0.5h}$) comparing oxycodone 40/0 mg and 80/0 mg with placebo ($P < 0.0001$, all comparisons, Table 1).

Primary endpoints

All comparisons of the primary endpoints (drug liking AUE_{0-1h} , AUE_{0-2h} , AUE_{0-3h} , $E_{0.5h}$, E_{min}) were statistically significant in the direction of reduced abuse potential of oxycodone HCl-niacin tablets (Tables 1 and 2, Figure 1).

Mean drug liking visual analog scores demonstrated significant differences over the initial 1.5 hours post-dose (Figure 2 and Table 3) between both doses of oxycodone HCl-niacin and equivalent oxycodone doses. At 30 minutes post-dose, mean drug liking visual analog scores were 66.0 mm and 74.8 mm for the oxycodone 40/0 mg and 80/0 mg doses, respectively, versus scores below neutral (ie, disliking) of 47.0 mm and 40.1 mm for the oxycodone HCl-niacin 40/240 mg and 80/480 mg doses. By one-hour post-dosing, mean scores remained positive at

Table 1 Primary drug liking parameters (completer sample, n = 47)

Parameter	Oxycodone HCl		Oxycodone HCl-niacin		Placebo	SE for all treatments
	40/0 mg (A)	80/0 mg (B)	40/240 mg (C)	80/480 mg (D)	0/0 mg (E)	
AUE _{0-1h} (h · mm)	63.5	69.1	50.4	46.0	50.4	1.74
AUE _{0-2h} (h · mm)	136.2	142.4	112.4	105.3	101.4	3.64
AUE _{0-3h} (h · mm)	205.8	209.1	176.6	168.5	152.5	5.65
E _{0.5h} (mm)	65.9	75.0	47.2	40.3	50.5	2.56
E _{min} (mm)	49.5	44.1	39.1	30.0	49.3	2.01

Note: Values are least squares means.

Abbreviations: AUE_{0-1h}, area under the drug effect curve from time 0–1 hour; E_{0.5h}, effect at 0.5 hours post-dose; E_{min}, peak disliking effect; SE, standard error.

72.1 mm and 76.0 mm for the oxycodone 40/0 mg and 80/0 mg doses, respectively, while scores were just above the neutral line at 56.6 mm and 53.0 mm for the oxycodone HCl-niacin 40/240 mg and 80/480 mg doses, respectively. Mean drug liking visual analog scores of oxycodone HCl-niacin were comparable with oxycodone alone by 3–5 hours post-dose but were higher than for placebo.

The percentage of participants who disliked (liking scores < 50) oxycodone HCl-niacin (40/240 mg and 80/480 mg) at 30 minutes was 60% and 64%, respectively, compared with 15% and 4% of participants who disliked oxycodone 40/0 mg and 80/0 mg, at 30 minutes. Similarly, 45% and 53% had at least a 10% reduction in

drug liking visual analog score for E_{max} with oxycodone HCl-niacin (40/240 mg and 80/480 mg, respectively) using oxycodone alone as a reference.

Secondary endpoints

Statistically significant decreases in take drug again were observed at all assessments (1, 2, and 8 hours) comparing oxycodone HCl-niacin with the respective oxycodone doses (Figure 3). Global assessment of overall drug liking demonstrated similar statistically significant differences at 12 hours (Figure 4).

Mean pupillometry scores over time are shown in Figure 5. All oxycodone-containing treatments elicited miotic

Table 2 Drug liking comparisons for oxycodone HCl-niacin versus oxycodone (completer sample, n = 47)

Parameter	Pairwise comparisons	LS mean difference (SE)	95% CI difference	Unadjusted P value ^b	Adjusted P value ^c
AUE _{0-1h} (h · mm)	40/240 mg (C) vs 40/0 mg (A) ^a	-13.2 (2.15)	-17.4, -8.9	<0.0001	<0.0001
	80/480 mg (D) vs 80/0 mg (B) ^a	-23.1 (2.15)	-27.3, -18.8	<0.0001	<0.0001
	80/0 mg (B) vs 40/0 mg (A)	5.5 (2.15)	1.3, 9.8	0.0112	
	80/480 mg (D) vs 40/240 mg (C)	-4.4 (2.15)	-8.7, -0.2	0.0418	
AUE _{0-2h} (h · mm)	40/240 mg (C) vs 40/0 mg (A) ^a	-23.8 (4.42)	-32.5, -15.1	<0.0001	<0.0001
	80/480 mg (D) vs 80/0 mg (B) ^a	-37.2 (4.41)	-45.9, -28.5	<0.0001	<0.0001
	80/0 mg (B) vs 40/0 mg (A)	6.2 (4.42)	-2.5, 15.0	0.1595	
	80/480 mg (D) vs 40/240 mg (C)	-7.1 (4.41)	-15.8, 1.6	0.1085	
AUE _{0-3h} (h · mm)	40/240 mg (C) vs 40/0 mg (A) ^a	-29.2 (6.66)	-42.4, -16.1	<0.0001	<0.0001
	80/480 mg (D) vs 80/0 mg (B) ^a	-40.6 (6.66)	-53.8, -27.5	<0.0001	<0.0001
	80/0 mg (B) vs 40/0 mg (A)	3.3 (6.66)	-9.8, 16.5	0.6209	
	80/480 mg (D) vs 40/240 mg (C)	-8.1 (6.65)	-21.3, 5.0	0.2235	
E _{0.5h} (mm)	40/240 mg (C) vs 40/0 mg (A) ^a	-18.7 (3.12)	-24.8, -12.5	<0.0001	<0.0001
	80/480 mg (D) vs 80/0 mg (B) ^a	-34.8 (3.12)	-40.9, -28.6	<0.0001	<0.0001
	80/0 mg (B) vs 40/0 mg (A)	9.1 (3.12)	3.0, 15.3	0.0039	
	80/480 mg (D) vs 40/240 mg (C)	-7.0 (3.12)	-13.1, -0.8	0.0264	
E _{min} (mm)	40/240 mg (C) vs 40/0 mg (A) ^a	-10.4 (2.54)	-15.4, -5.3	<0.0001	<0.0001
	80/480 mg (D) vs 80/0 mg (B) ^a	-14.1 (2.54)	-19.1, -9.1	<0.0001	<0.0001
	80/0 mg (B) vs 40/0 mg (A)	-5.4 (2.54)	-10.4, -0.3	0.0366	
	80/480 mg (D) vs 40/240 mg (C)	-9.1 (2.54)	-14.1, -4.1	0.0004	

Notes: ^aPrimary drug liking comparisons for oxycodone HCl-niacin versus oxycodone; ^bpairwise comparisons unadjusted P values are from a linear mixed model with fixed effects for sequence, period, and treatment, and a random effect for subject nested in sequence; ^cpairwise comparisons adjusted P values are calculated using the Benjamini-Hochberg method. Treatments: A, oxycodone 40/0 mg; B, oxycodone 80/0 mg; C, oxycodone HCl-niacin 40/240 mg; D, oxycodone HCl-niacin 80/480 mg.

Abbreviations: AUE_{0-1h}, area under the drug effect curve from time 0–1 hour; CI, confidence interval; E_{0.5h}, effect at 0.5 hours post-dose; E_{min}, peak disliking effect; LS, least squares; SE, standard error; vs, versus.

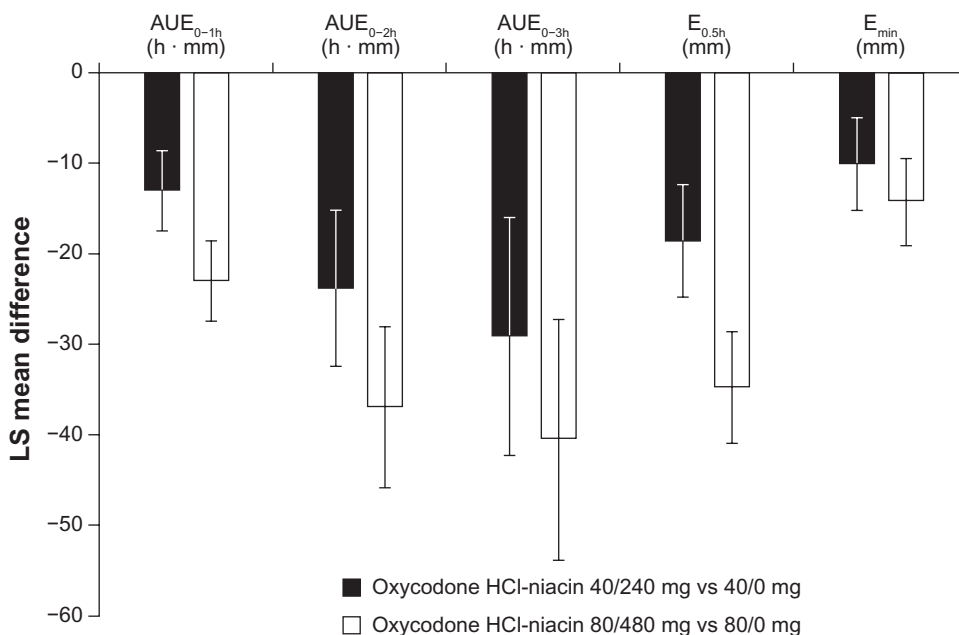


Figure 1 Least squares mean difference (95% confidence interval) in primary drug liking parameters (completer sample, n = 47).

Note: All adjusted *P* values <0.0001.

Abbreviations: AUE_{0-1h}, area under the drug effect curve from time 0–1 hour; E_{0.5h}, effect at 0.5 hours post-dose; E_{min}, peak disliking effect; LS, least squares.

effects typical of opioids. Treatment with oxycodone HCl-niacin resulted in less miosis over the first hour post-dose compared with treatment using an equivalent oxycodone dose. Minimum pupil size post-dose was not significantly different between oxycodone alone and oxycodone with niacin,

but there was a significant delay in the time to minimum pupillary effect. The least squares mean differences for T_{Emin} comparing the 40/0 mg and 40/240 mg doses and the 80/0 mg and 80/480 mg doses were 0.92 hours (*P* = 0.0164) and 0.93 hours (*P* = 0.0153), respectively. AUE analyses were

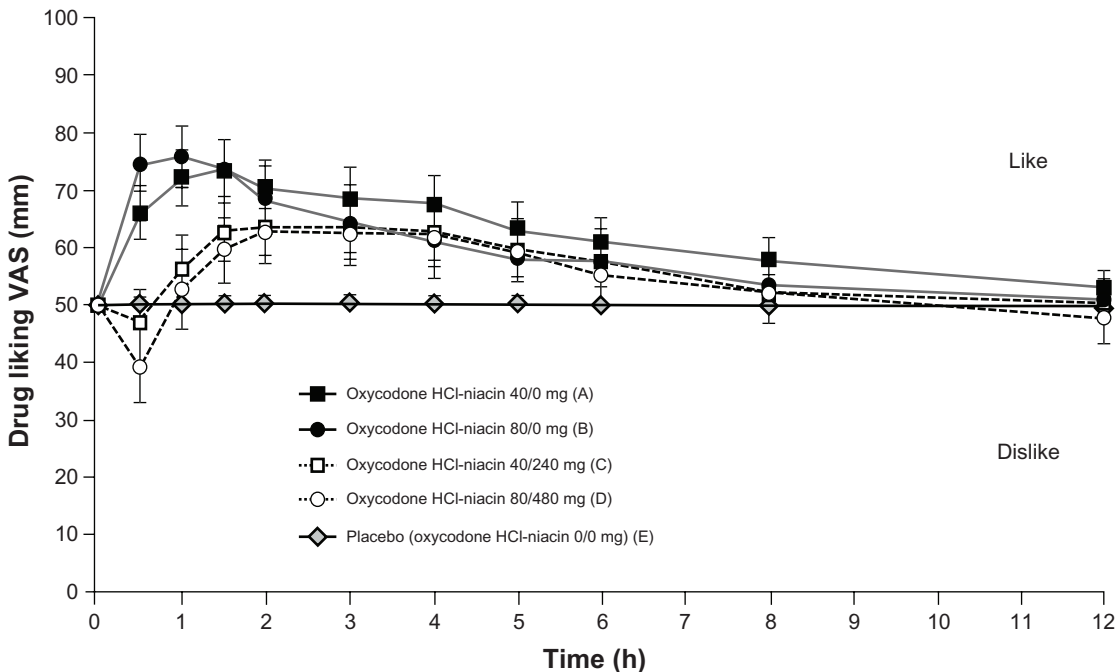


Figure 2 Mean (95% confidence interval) drug liking over time during treatment period (completer sample, n = 47).

Abbreviation: VAS, visual analog scale.

Table 3 Supporting primary drug parameters (completer sample, n = 47)

Parameter	Oxycodone HCl-niacin pairwise comparisons	LS mean difference (SE)	95% CI difference	Unadjusted P value ^a
AUE _{0-12h} (h · mm)	40/240 mg vs 40/0 mg	-68.3 (24.12)	-115.9, -20.7	0.0052
	80/480 mg vs 80/0 mg	-53.3 (24.11)	-100.9, -5.8	0.0282
E _{max} (mm)	40/240 mg vs 40/0 mg	-6.3 (2.16)	-10.6, -2.0	0.0040
	80/480 mg vs 80/0 mg	-9.3 (2.16)	-13.6, -5.0	<0.0001
T _{E_{max}} (h)	40/240 mg vs 40/0 mg	0.45 (0.51)	-0.55, 1.45	0.3787
	80/480 mg vs 80/0 mg	1.51 (0.51)	0.51, 2.51	0.0032
T _{E_{min}} (h)	40/240 mg vs 40/0 mg	-2.80 (0.82)	-4.42, -1.18	0.0008
	80/480 mg vs 80/0 mg	-3.46 (0.82)	-5.08, -1.85	<0.0001
E _{1h} (mm)	40/240 mg vs 40/0 mg	-15.3 (3.19)	-21.6, -9.0	<0.0001
	80/480 mg vs 80/0 mg	-22.9 (3.19)	-29.2, -16.6	<0.0001
E _{1.5h} (mm)	40/240 mg vs 40/0 mg	-10.1 (2.79)	-15.6, -4.6	0.0004
	80/480 mg vs 80/0 mg	-14.2 (2.79)	-19.7, -8.7	<0.0001
E _{2h} (mm)	40/240 mg vs 40/0 mg	-6.3 (2.93)	-12.1, -0.5	0.0329
	80/480 mg vs 80/0 mg	-5.0 (2.93)	-10.8, 0.8	0.0899
E _{3h} (mm)	40/240 mg vs 40/0 mg	-4.9 (2.91)	-10.7, 0.8	0.0923
	80/480 mg vs 80/0 mg	-1.9 (2.91)	-7.6, 3.9	0.5187

Note: ^aPairwise comparisons unadjusted P values are from a linear mixed model with fixed effects for sequence, period, and treatment, and a random effect for subject nested in sequence.

Abbreviations: AUE_{0-12h}, area under the drug effect curve from time 0 to 12 hours; CI, confidence interval; E_{1h}, effect at one hour post-dose; E_{max}, peak liking effect; LS, least squares; SE, standard error; T_{E_{max}}, time to peak liking; T_{E_{min}}, time to peak disliking; vs, versus; h, hours.

statistically significant out to 2 hours for both oxycodone HCl-niacin doses and to 12 hours for the 40/240 mg versus 40/0 mg comparison.

Dose-response comparisons for the primary drug liking endpoints are summarized in Table 2. The oxycodone HCl-niacin 80/480 mg dose had lower AUEs than the oxycodone HCl-niacin 40/240 mg dose. The oxycodone

80/0 mg dose had higher AUEs than the oxycodone 40/0 mg dose. Similarly, the oxycodone HCl-niacin 80/480 mg dose had lower liking based on both E_{min} and E_{0.5h} than the oxycodone HCl-niacin 40/240 mg dose. For oxycodone, the 80/0 mg dose was liked more at 30 minutes than oxycodone 40/0 mg (E_{0.5h}); however, the 80/0 mg dose was disliked more than the 40/0 mg dose based on E_{min}. Similarly, as

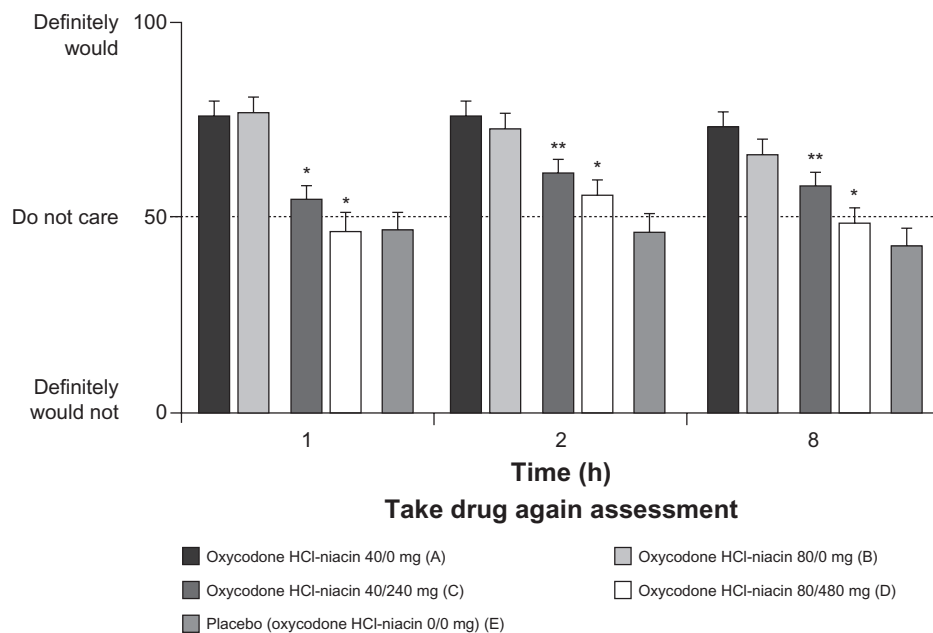


Figure 3 Least squares mean (standard error) take drug again assessment.

Notes: Treatment C versus treatment A; treatment D versus treatment B. *P ≤ 0.0001; **P ≤ 0.001.

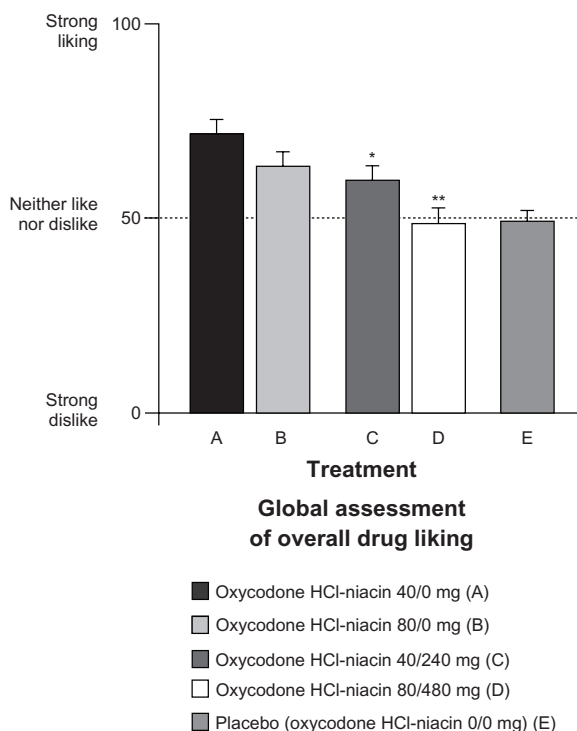


Figure 4 Least squares mean (standard error) global assessment of overall drug liking at 12 hours. **Notes:** Treatment C versus treatment A; treatment D versus treatment B. * $P \leq 0.01$; ** $P \leq 0.001$.

noted in Figure 3 (take drug again) and Figure 4 (overall drug liking), a dose response was apparent between the two doses of oxycodone HCl-niacin tablets. For the take drug again, least squares mean (standard error [SE]) differences between the 80/480 mg and 40/240 mg doses

were -8.2 mm (4.05), -5.4 mm (4.15), and -9.8 mm (4.46) at 1, 2, and 8 hours, respectively. For overall drug liking at 12 hours, the difference was -10.9 mm (4.00).

Supporting pharmacodynamic analyses

The primary pharmacodynamic analysis was corroborated by the supporting analyses for E_{max} , T_{Emax} , T_{Emin} , and AUE_{0-12h} (Table 3). There were significant differences between oxycodone HCl-niacin tablets and equivalent oxycodone doses when comparing peak liking (E_{max}). The magnitude of least squares mean (SE) differences for the 40/240 mg and 80/480 mg doses and their respective immediate-release equivalent doses were -6.3 (2.16) mm ($P = 0.0040$) and -9.3 (2.16) mm ($P < 0.0001$), respectively. The time to reach maximal liking effect for the 80/480 mg dose in comparison with the equivalent oxycodone dose was significant. T_{Emax} for the 80/480 mg dose was 1.51 hours later than for the 80/0 mg dose ($P = 0.0032$). The T_{Emax} for the oxycodone HCl-niacin 40/240 mg dose was 0.45 hours later, but was not significantly different from the equivalent oxycodone dose. Median T_{Emax} occurred later for oxycodone HCl/niacin 80/480 mg (3.0 hours) and 40/240 mg (2.0 hours) than for oxycodone 80/0 mg (1.0 hours) and 40/0 mg (1.5 hours).

Table 4 presents an exploratory analysis of two important measures of abuse liability, ie, E_{max} and T_{Emax} . Niacin is associated with a potentially less desirable combination of E_{max} and T_{Emax} as seen in the shaded area to the upper left, representing a diminished or delayed effect, or both. At the lower dose, 55% (26/47) of participants found the oxycodone

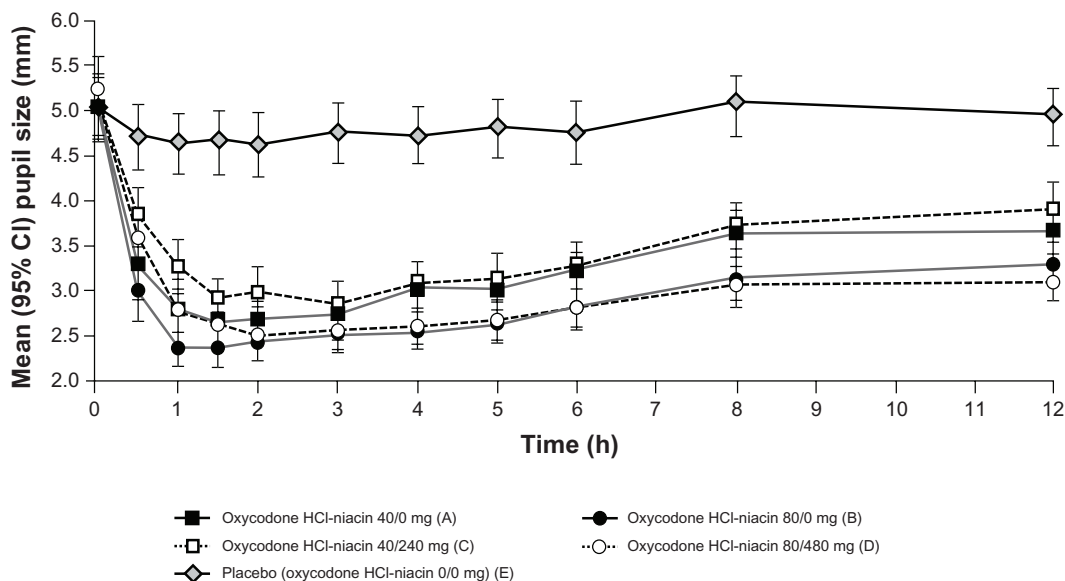


Figure 5 Mean (95% CI) pupil size over time (completer sample, n = 47). **Abbreviation:** CI, confidence interval.

Table 4 Comparison of oxycodone HCl-niacin and oxycodone effects on E_{max} and T_{Emax}

T_{Emax}	E_{max}			Total
	Lower	Same	Higher	
40/240 mg versus 40/0 mg				
Longer	21	0	5	26
Same	5	1	1	7
Shorter	6	1	7	14
Total	32	2	13	47
80/480 mg versus 80/0 mg				
Longer	26	3	7	36
Same	5	1	2	8
Shorter	1	0	2	3
Total	32	4	11	47

Notes: Light shading, potentially less desirable combinations of E_{max} and T_{Emax} for oxycodone HCl-niacin compared with immediate-release oxycodone. Darker shading, potentially less desirable combinations for immediate-release oxycodone compared with oxycodone HCl-niacin.

Abbreviations: E_{max} , peak liking effect; T_{Emax} , time to peak liking.

HCl-niacin dose potentially less desirable than oxycodone alone, which rose to 72% (34/47) at the higher dose.

Safety

The most common (>5%) treatment-emergent adverse events (TEAEs) during the treatment phase are listed in Table 5. The majority of TEAEs were mild to moderate

in intensity. Severe TEAEs in those receiving 40/240 mg were pruritus in two (4%) participants, skin warmth in one (2%) participant, and flushing in one (2%) participant. Severe TEAEs in those receiving 80/480 mg were skin warmth in two (4%) participants, skin burning in one (2%) participant, and flushing in one (2%) participant. Skin burning, skin warmth, and flushing were more common in participants receiving oxycodone HCl-niacin tablets than those receiving oxycodone alone. Opioid-related adverse events (nausea, vomiting, and oxygen saturation of hemoglobin decrease) were similar between equivalent doses and increased at higher doses of oxycodone HCl-niacin and oxycodone. Decreased oxygen saturation of hemoglobin occurred in 10 (21%) participants receiving 80/0 mg, four (8%) participants receiving 80/480 mg, one (2%) participant receiving 40/0 mg, and none for 40/240 mg or placebo. One participant (80/480 mg) discontinued from the study because of an adverse event of vomiting. No other clinically significant abnormal findings were reported. There were no deaths or serious TEAEs reported during the study.

Discussion

This study compared the relative abuse potential of orally administered oxycodone HCl-niacin tablets with orally

Table 5 Most common (>5% in any treatment group) TEAEs during the treatment phase (safety sample)

System organ class	Oxycodone HCl 40/0 mg (n = 48)	Oxycodone HCl 80/0 mg (n = 47)	Oxycodone HCl-niacin 40/240 mg (n = 48)	Oxycodone HCl-niacin 80/480 mg (n = 49)	Placebo (n = 48)
Participants with any TEAE	37 (77)	46 (98)	47 (98)	49 (100)	6 (13)
Skin and subcutaneous tissue disorders	29 (60)	35 (74)	43 (90)	48 (98)	3 (6)
Pruritus	29 (60)	34 (72)	36 (75)	39 (80)	2 (4)
Skin burning sensation	0	1 (2)	24 (50)	40 (82)	1 (2)
Skin warm	1 (2)	3 (6)	15 (31)	9 (18)	0
Nervous system disorders	24 (50)	30 (64)	18 (38)	29 (59)	1 (2)
Dizziness	6 (13)	9 (19)	4 (8)	8 (16)	0
Headache	2 (4)	7 (15)	3 (6)	6 (12)	0
Somnolence	17 (35)	18 (38)	13 (27)	22 (45)	1 (2)
Vascular disorders	0	3 (6)	43 (90)	46 (94)	0
Flushing	0	3 (6)	43 (90)	46 (94)	0
Gastrointestinal disorders	8 (17)	24 (51)	12 (25)	22 (45)	1 (2)
Constipation	2 (4)	6 (13)	5 (10)	3 (6)	0
Nausea	4 (8)	18 (38)	5 (10)	17 (35)	0
Vomiting	1 (2)	11 (23)	4 (8)	8 (16)	0
General disorders and administration site conditions	3 (6)	7 (15)	4 (8)	3 (6)	0
Chills	0	0	1 (2)	3 (6)	0
Feeling hot	1 (2)	3 (6)	1 (2)	0	0
Irritability	2 (4)	4 (9)	1 (2)	0	0
Investigations	1 (2)	10 (21)	0	4 (8)	0
Oxygen saturation decreased	1 (2)	10 (21)	0	4 (8)	0
Renal and urinary disorders	2 (4)	4 (9)	1 (2)	0	0
Dysuria	2 (4)	4 (9)	1 (2)	0	0

Abbreviation: TEAE, treatment-emergent adverse event.

administered oxycodone HCl tablets in nondependent, recreational opioid users. The study design was consistent with published draft guidelines for assessing abuse liability in humans.^{8,15,20,24} The measures used in this study assessed the overall balance of effects, as well as “at this moment” subjective drug effects associated with the abuse potential of a drug.^{15,20,24,25} When determining the abuse potential of a drug, drug liking measured on a visual analog scale is a primary measure of interest. However, for drugs with the potential to deter opioid abuse by causing an aversive effect through the use of another agent, it is also important to evaluate drug disliking using a visual analog score. The measures are sensitive and reliable, and have content and construct validity. The study was well powered, with a sample size of 47 completed participants. The validity of the study was established during the randomized treatment phase by comparing the oxycodone 40/0 mg and oxycodone 80/0 mg doses with placebo. Participants randomized into the treatment phase were able to distinguish between oxycodone and placebo treatments.

Oxycodone results in the current study are consistent with those of six reported studies that examined the abuse liability of oxycodone. These studies confirmed that oxycodone doses ranging from 10 mg to 80 mg were safely administered and produced increased effects on subjective ratings of drug liking and other measures associated with abuse liability and opiate effects.^{17,26–30} The statistically significant lower liking scores observed for oxycodone HCl-niacin tablets compared with equivalent oxycodone doses for all a priori specified primary measures/parameters (drug liking AUE_{0–1h}, AUE_{0–2h}, AUE_{0–3h}, E_{0.5h}, and E_{min}) suggest that oxycodone HCl-niacin tablets may have lower potential for abuse than oxycodone alone in fasted, nondependent, recreational opioid users.

An abuser expects the maximum drug effect soon after intake of the abused substance.³¹ This experience relates to both the amount of abused substance achieved in the blood (C_{max}) and the time needed to attain the peak effect (T_{max}).¹⁷ The increasing abuse of immediate-release opioids,⁶ the rampant physical manipulation of extended-release opioids,^{9,32,33} and the widespread chemical manipulation of opioids to remove nonopioid drugs and ingredients³⁴ support this concept. The early negative effects of a drug may be an important component in later behavioral effects. In animal models, early aversive effects have been shown to condition behavioral effects of later avoidance.³⁵ The relationship between the pharmacokinetics of oxycodone and its abuse potential is poorly documented in the literature. However, delaying or blunting the pharmacodynamic effects may

produce a less than optimal drug experience for the abuser.³¹ In this study, there was a distinct difference in the mean drug liking time course for both doses of oxycodone HCl-niacin tablets compared with equivalent doses of oxycodone. Unlike the oxycodone doses, which had a rapid increase in participant liking over the first hour, mean oxycodone HCl-niacin scores were initially below the neutral line (in a dose-dependent manner) and remained below the liking curves for oxycodone for the initial 3 hours. This time course is consistent with the pharmacokinetic profile³⁶ and vasocutaneous effects of niacin.¹¹ At the expected time of greatest liking following administration of oxycodone, the greatest disliking occurred with oxycodone HCl-niacin tablets. In addition to its early aversive effect, oxycodone HCl-niacin caused both a reduction in E_{max} and prolongation in T_{E_{max}} compared with an equivalent dose of oxycodone alone.

The results of the primary liking and disliking analyses were supported by secondary analyses. In a dose-dependent manner, 51% and 60% of participants had at least a 10% reduction of drug liking visual analog E_{min} scores with oxycodone HCl-niacin compared with oxycodone alone, and 45% and 53% had at least a 10% reduction in drug liking visual analog score E_{max}. Although some participants experienced smaller or no reductions in E_{max} and E_{min}, the study results suggest that more than half of the participants were affected by the niacin in oxycodone HCl-niacin. There may be concern that the oxycodone HCl-niacin groups had comparable drug liking to the oxycodone only groups at 2–5 hours. This period did not seem to affect the overall assessments of the participants regarding their experiences as noted in the global measures of take drug again and overall drug liking reported below.

The secondary parameters of overall drug liking and take drug again are considered to reflect subsequent behavioral outcomes in the community.^{15,20,24,25} In addition, and as noted previously, animal models indicate that early aversive effects have been shown to condition behavioral effects of later avoidance.³⁵ A key objective of medicines designed to deter abuse is to change the behavior of abuse by introduction of impediments that produce a decrease in drug liking.^{27,37,38} In this study, the early liking and disliking data were strongly supported by the assessment of overall drug liking and take drug again. The magnitude of the differences between oxycodone HCl-niacin tablets and the equivalent doses of oxycodone alone were large, and showed that the relative aversive effects of niacin on the overall drug experience persisted at 8 and 12 hours. These results may be highly relevant to predicting the relative likelihood of abuse of oxycodone

HCl-niacin tablets compared with oxycodone without niacin in the community.

The dose response for oxycodone HCl-niacin tablets is shown on the AUE, E_{\min} , and $E_{0.5h}$ analyses. The 80/480 mg dose had consistently lower AUEs than the 40/240 mg dose. Similarly, the 80/480 mg dose had lower liking based on both E_{\min} and $E_{0.5h}$ than the 40/240 mg dose. This finding may be important clinically in that abusers may be deterred from using higher and potentially lethal doses of oxycodone.

The adverse events experienced by study participants taking oxycodone were typical of opioid use. Nausea, vomiting, pruritus, somnolence, and decreased oxygen saturation of hemoglobin generally showed a dose-related increase with the 80 mg dose compared with the 40 mg dose for both oxycodone HCl-niacin and oxycodone. With the possible exception of pruritus, niacin had no effect on the frequency of these adverse events. The TEAEs most specifically associated with oxycodone HCl-niacin tablets (skin-burning sensation, skin heat, and flushing) were consistent with the expected effects of niacin. Skin-burning sensation and flushing also showed a dose response related to the presence of niacin and likely contributed to the greater disliking of the higher dose of oxycodone HCl-niacin tablets. Nearly all participants (90% with 40/240 mg and 94% with 80/480 mg) reported flushing with oxycodone HCl-niacin tablets, which suggested this event is likely to occur in the majority of abusers taking oxycodone HCl-niacin tablets at these doses. These events, the majority of which were mild to moderate in intensity, did not otherwise affect the safety of participants.

There were several limitations to this study. The outcome measures (liking scores, take drug again, and overall drug liking) are surrogate measures intended to predict behaviors of abusers in the community. It is not definitively established that reductions in these measures will translate into a decrease in the rate of abuse and misuse in the community.³⁹ However, these measures are specified in the US Food and Drug Administration's draft guidance for abuse liability studies^{15,20,24,25} and have been used for decades in the scheduling of drugs. Epidemiologic and surveillance studies following introduction of products intended to impede or limit abuse are required to confirm results of clinical trials. Another limitation is that this study was conducted under fasting conditions. A previous study showed that niacin-induced disliking of oxycodone was attenuated by a high-fat meal in most participants.¹² However, a high-fat meal also delayed by approximately 2 hours the time to maximum oxycodone liking effects and was associated with a numerically lower mean drug liking score;¹² therefore, it is not clear whether a study with fed participants would

show a clear separation between oxycodone HCl with niacin and oxycodone alone. Another limitation to the study is the lack of pharmacokinetic measures to define the dose and effect relationship fully. This was partially addressed by the pupillometry measures, which are a reflection of the physiologic effects of opioids. Although statistically powered, the small size of the study sample and the characteristics of its participants may not be generalizable to the population that abuses prescription opioid medications.

A significant need exists for opioid products that deter oral overconsumption, which is the most common route of abuse.^{7,8} Data from this trial support the abuse-deterrent potential of niacin in oxycodone HCl-niacin tablets among fasted, nondependent, recreational opioid users. A previous study showed that the amount of niacin associated with two doses of oxycodone HCl-niacin tablets ($2 \times 5/30$ mg and $2 \times 7.5/30$ mg) that provided statistically significant pain relief compared with placebo was generally well tolerated in patients with moderate to severe pain.¹⁴ This suggests that, when taken as directed, patients should not be adversely affected by the niacin in oxycodone HCl-niacin tablets. However, if abuse occurs by consuming an excess number of oxycodone HCl-niacin tablets, the niacin in these tablets provides an initial negative experience and delays the time to an expected high. This action may represent an incremental benefit in terms of oral abuse potential over existing immediate-release oxycodone products.

Prior publication of results

Some of these data were presented at the 2011 meetings of the American Academy of Neurology (Presentation 004), April 14, 2011, in Honolulu, HI, and the American Pain Society (Poster 371), May 18–19, 2011, in Austin, TX.

Disclosure

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