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Original Research Article

Abuse Potential with Oral Route of Administration of a Hydrocodone Extended-Release Tablet Formulated with Abuse-Deterrence Technology in Nondependent, Recreational Opioid Users

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Abstract

Objective. To compare the oral abuse potential of hydrocodone extended-release (ER) tablet developed with CIMA® Abuse-Deterrence Technology with that of hydrocodone immediate release (IR).

Design. Randomized, double-blind, placebo-controlled, crossover study.

Setting and Patients. One study site in the United States; adult nondependent, recreational opioid users.

Methods. After confirming their ability to tolerate and discriminate hydrocodone IR 45 mg from placebo, eligible participants were randomized to receive each of the following oral treatments once: finely crushed placebo, hydrocodone IR 45-mg powder, intact hydrocodone ER 45-mg tablet, and finely crushed hydrocodone ER 45-mg tablet. Primary pharmacodynamic measure was "at the moment" drug liking. Secondary measures included overall drug liking, drug effects (e.g., balance, positive, negative, sedative), pupillometry, pharmacokinetics, and safety.

Results. Mean maximum effect (E_{max}) for "at the moment" drug liking was significantly lower for intact

(53.9) and finely crushed hydrocodone ER (66.9) vs. hydrocodone IR (85.2; $P < 0.001$). Drug liking for intact hydrocodone ER was comparable to placebo (E_{max}: 53.9 vs. 53.2). Secondary measures were consistent with these results, indicating that positive, negative, and sedative drug effects were diminished with intact and crushed hydrocodone ER tablet vs. hydrocodone IR. The 72-hour plasma concentration-time profile for each treatment mimicked its respective "at the moment" drug-liking-over-time profile. Incidence of adverse events was lower with intact hydrocodone ER (53%) vs. hydrocodone IR (79%) and finely crushed hydrocodone ER (73%).

Conclusions. The oral abuse potential of hydrocodone ER (intact and finely crushed) was significantly lower than hydrocodone IR in healthy, nondependent, recreational opioid users. Hydrocodone ER was generally well tolerated.

Key Words. Extended Release; Hydrocodone; Opioid Analgesics; Substance Abuse; Abuse Potential; Drug Liking

Introduction

Recreational use of prescription pain relievers has become more prevalent in the United States than use of cocaine, heroin, and methamphetamine combined [1]. The number of emergency department visits and deaths related to nonmedical use of opioids also has increased substantially over the past decade, prompting serious public health concern over recreational use of prescription opioids [2,3]. As a result, the US Food and Drug Administration (FDA) considers development of opioids formulated to deter abuse to be a high public priority [4]. Recent data suggest that the introduction of abuse-deterrent opioids has been associated with less overdose and abuse [5,6].

Hydrocodone immediate release (IR) reaches peak plasma concentrations within 1 to 2 hours and has a half-life of 4.0 to 4.5 hours, requiring repeated dosing every 4 to 6 hours for adequate management of pain [7–9]. These pharmacokinetic properties may contribute to the likelihood of abuse; the quick onset of action may lead to a faster onset of pleasurable effects, and the short half-life necessitating repeated administration may promote continued use and increase positive reinforcement [10]. Several studies evaluating the abuse potential of hydrocodone IR, alone or in combination with another product, have suggested an increased drug liking and other positive effects with hydrocodone compared with placebo [11–13].

A single-agent (i.e., acetaminophen- and ibuprofen-free) extended-release (ER) formulation of hydrocodone bitartrate (Teva Pharmaceuticals, Frazer, PA, USA) has been developed to provide sustained pain relief with twice-daily dosing [14]. This formulation employs CIMA® Abuse-Deterrence Technology (ADT), a novel platform that allows for controlled release of hydrocodone over an extended period and provides resistance against rapid release of hydrocodone when tablets are comminuted (i.e., broken into small pieces by crushing, milling, grating, or grinding) and resistance against dose dumping when tablets are taken with alcohol [15].

Epidemiologic studies have found that the two most common routes of administration in the abuse of IR hydrocodone products are the oral and the intranasal routes (i.e., snorting) [16,17]. One way individuals may abuse ER products via the oral route is by altering the formulation (i.e., cutting, chewing, or crushing) to change the rate of drug release (dose dumping) [4]. To obtain a better understanding of the impact of a technology on a product's abuse potential, the properties of hydrocodone ER have been thoroughly characterized as recommended by the US FDA in in vitro (data on file, Teva Pharmaceuticals) and pharmacokinetic studies [14,18–21]. The primary objective of the current study was to assess the abuse potential of hydrocodone ER (finely crushed and intact) administered via the oral route compared with hydrocodone IR in healthy, nondependent, recreational opioid users.

Methods

This randomized, double-blind, triple-dummy, placebo-controlled, crossover study was conducted at one study site in the United States between January 2012 and May 2012 in accordance with the Good Clinical Practice: Consolidated Guideline approved by the International Conference on Harmonisation and applicable national and local laws and regulations [22]. All study materials were reviewed and approved by the institutional review board before study initiation, and all subjects provided written informed consent before any study-related procedures were performed. The study protocol was registered at clinicaltrials.gov (NCT01596673).

Subjects

The study enrolled men and women age 18 to 50 years who were not physically dependent on opioids as shown by successful completion of a naloxone challenge (i.e., no signs or symptoms of opioid withdrawal as assessed by a Clinical Opiate Withdrawal Scale score of <5 after administration of 0.8 mg intravenous naloxone). Subjects were required to have a history of recreational opioid use aimed at achieving a "high" at least 10 times in the last year and on at least one occasion within 12 weeks before screening. Those who abused multiple drugs must have expressed a preference for opioids.

Inclusion criteria at screening and baseline also required subjects to have a minimum body weight of 50 kg and a body mass index of 18.0 to 32.0 kg/m^2; to be in good health, as determined by a medical and psychiatric history, physical examination, electrocardiogram (ECG),

serum chemistry, hematology, urinalysis, and serology; and to have a negative urine drug screening (except for tetrahydrocannabinol) and a negative alcohol breath test at screening. Drug, alcohol, and pregnancy tests were also conducted before study drug administration on the first day of the qualification and treatment phases of the study, at which point participants with positive test results (other than for tetrahydrocannabinol) were excluded from the study.

Additional exclusion criteria included any clinically significant uncontrolled medical conditions; abnormal laboratory, ECG, or physical examination findings; oxygen saturation <95% after resting 5 minutes; disorders that would interfere with drug absorption, distribution, metabolism, or excretion; or a history of drug or alcohol abuse. Subjects also were excluded if they were poor metabolizers of cytochrome P450 2D6 substrates; were pregnant or lactating; had donated blood (>450 mL) within 56 days of the first dose of study drug; had abnormal heart rate or blood pressure; were heavy smokers (>20 cigarettes per day), chewed tobacco, or were unable to abstain from smoking for at least 6 hours a day; or had a history of hypersensitivity or idiosyncratic reaction to study drugs.

Study Design

After completing screening procedures, eligible subjects participated in a qualification phase to ensure they could tolerate a 45-mg dose of hydrocodone IR and could discriminate between the effects of hydrocodone and placebo. The qualification phase was conducted in a randomized, double-blind, placebo-controlled, crossover manner. Eligible subjects were randomly assigned in a 1:1 ratio to receive each of the following once via the oral route: 60 mL of a noncarbonated flavored beverage (placebo) and 45 mg of hydrocodone bitartrate powder (representative of hydrocodone IR) reconstituted in 60 mL of a noncarbonated flavored beverage. Each treatment in the qualification phase was separated by at least 48 hours.

To be eligible to continue into the treatment phase, subjects had to have tolerated the oral 45-mg dose of hydrocodone IR, had a response to hydrocodone IR greater than their response to placebo (≥15-point difference in peak score) for "at the moment" drug liking and Overall Drug Liking (both 100-point bipolar drug-liking visual analog scales [VAS; 0 = strong disliking, 50 = neutral, 100 = strong liking]), and shown behaviors consistent with an ability to complete the study.

After a minimum 7-day washout, qualified subjects entered the treatment phase, the randomized, double-blind, triple-dummy, placebo-controlled, 4-period crossover portion of the study. Eligible subjects were randomly assigned to receive each of the following via the oral route of administration once: one finely crushed 45-mg hydrocodone ER tablet; 45 mg of hydrocodone bitartrate powder (representative of hydrocodone IR); 1 intact 45-mg hydrocodone ER tablet; and placebo. Each treatment was separated by a minimum 14-day washout period.

Extensive in vitro Category 1 testing was performed on the drug product. In vitro dissolution testing and particle size measurements were conducted on tablets manipulated with a wide variety of instruments and mechanisms. Based on the results of these Category 1 tests, a method of manipulation was chosen that represented the worst case that could be reasonably performed in a clinical setting. In each period, subjects consumed:

- an intact tablet (hydrocodone ER or matching placebo)
- a finely crushed tablet (hydrocodone ER or matching placebo): the tablet was crushed in a plastic sleeve using a device provided by the sponsor; the patient dumped the crushed tablet directly onto his or her tongue, ensuring transfer of as much powder as possible
- 60 mL of a noncarbonated strongly flavored beverage (alone or containing 45 mg of hydrocodone bitartrate powder)

Subjects consumed both tablets (intact and finely crushed) together with the flavored beverage; the juice and tablets were to be consumed within 2 minutes. The empty drinking cup was refilled with at least 60 mL of rinse water and then consumed by the subject. Subjects fasted from approximately 10 PM the evening before through 4 hours after each administration of study drug. All subjects were asked to return for a follow-up visit approximately 48 to 72 hours after discharge from the study center after their final dose of study drug.

Pharmacodynamic Assessments

The questionnaires and pharmacodynamic measures used to evaluate subjective abuse potential are summarized in Table 1. Subjects were trained on the completion of pharmacodynamic assessments before the qualification phase and the treatment phase.

Primary Measure

The primary pharmacodynamic measure of abuse potential in the treatment phase of the study was the "at the moment" drug liking question on the Drug Liking and Effects Questionnaire (DLEQ), using the parameter of peak score (maximum effect [E_{max}]). Subjects responded by using a bipolar VAS scored as "strong disliking" (score of 0), "neither like nor dislike" (score of 50), or "strong liking" (score of 100).

Secondary Measures

Subjective secondary pharmacodynamic measures of abuse potential in the treatment phase included the Overall Drug Liking VAS score, measures of balance of

Table 1 Questionnaires used to assess subjective drug effects

Questionnaire	Description	Time point administered	Pharmacodynamic parameters
Drug liking and effects questionnaire	• 6 questions relating to drug liking, drowsiness, good drug effects, bad drug effects, nausea, and any drug effects using a bipolar and unipolar VAS • Bipolar VAS scored as 0 ("strong disliking"), 50 ("neither like nor dislike"), or 100 ("strong liking"). Unipolar VAS ranges from a response of "none" (score of 0) to "extremely" (score of 100)	0.25, 0.75, 1.25, 2.5, 4, 6, 7, 8, 9, 10, 12, 24, 36, 48, 60, and 72 hours after each administration of study medication	E_{max} AUEC E_{min} (drug liking and drowsiness only)
Overall drug liking visual analog scale	100-mm VAS for "My overall liking to the drug is. . ." Scored as 0 ("strongly dislike"), 50 ("neither like nor dislike"), or 100 ("strongly like")	24 hours after each administration of study medication	E_{max} E_{min}
Take drug again assessment	100-mm VAS for "Would you want to take the drug you just received again, if given the opportunity?" Scored as 0 ("definitely would not"), 50 ("do not care"), or 100 ("definitely would")	24 hours after each administration of study medication	Score
Price value assessment questionnaire	"What is the most that you would be willing to pay for the same dose of the drug that you have just taken, if it was offered to you on the street?" Options range in $5 increments from $0–$100	24 hours after each administration of study medication	Score
Addiction research center inventory	Assesses (via true/false questions) euphoria (MBG subscale), dysphoria (LSD drug correction subscale), and sedation (PCAG subscale)	0.25, 0.75, 1.25, 1.75, 2.5, 4, 6, 8,12, 24, 36, 48, 60, and 72 hours after each study drug administration	E_{max} AUEC

AUEC = area under the effect curve; E_{max} = maximum effect; E_{min} = minimum effect; LSD = lysergic acid diethylamide; MBG = morphine-benzedrine group; PCAG = pentobarbital, chlorpromazine, alcohol group; VAS = visual analog scale.

drug effects, positive drug effects, negative drug effects, sedative effects, and other drug effects based on the DLEQ, and subscales of the Addiction Research Center Inventory (ARCI) using the parameters E_{max}, area under the effect curve (AUEC), and minimum effect (E_{min}). Take Drug Again Assessment (TDAA) score and Price Value Assessment Questionnaire (PVAQ) score were also assessed [Table 1]. Pupillometry was assessed as an objective secondary measure of other drug effects using the parameter E_{min}. The same eye for each subject was used for all measurements during the study.

Pharmacokinetic Measures

During the treatment phase, blood samples were collected within 30 minutes before study drug administration and at 0.25, 0.75, 1.25, 1.75, 2.5, 4, 6, 7, 8, 9, 10, 12, 24, 36, 48, 60, and 72 hours after study drug administration. At each sampling time point, a 3- to 4-mL venous blood sample was collected by venipuncture or indwelling catheter into a tube containing potassium ethylene diamine tetra acetic acid, inverted slowly 6 to 8 times and placed on water/ice (approximately 4 °C). Blood samples were centrifuged (1500 g, approximately 15 minutes, 4 °C) within 60 minutes of collection to separate the plasma. Plasma samples were stored at –30 °C to –20 °C in an upright position.

Concentrations of hydrocodone and its metabolite hydromorphone were determined in human plasma samples by Pharmaceutical Product Development (Richmond, VA) using a validated high-performance liquid chromatography method with tandem mass spectrometric detection. The validated quantifiable range

was 0.100 to 100 ng/mL for hydrocodone and 0.050 to 50.0 ng/mL for hydromorphone.

The following pharmacokinetic parameters for hydrocodone and hydromorphone were calculated for each active treatment using noncompartmental analysis: maximum plasma drug concentration (C_{max}; by inspection and without interpolation), time to C_{max} (t_{max}; by inspection), area under the plasma concentration-time curve (AUC) from 0 to 0.75 hours after study drug administration ($AUC_{0–0.75}$; closest sampling time to median t_{max} for hydrocodone IR), AUC from 0 to 4 hours (AUC_{0-4}; closest sampling time to median t_{max} for finely crushed hydrocodone ER), AUC from 0 to 7 hours ($AUC_{0–7}$; closest sampling time to median t_{max} for intact hydrocodone ER), AUC from time 0 to the time of the last measurable drug concentration ($AUC_{0–t}$), AUC from time 0 to infinity ($AUC_{0–\infty}$), apparent plasma terminal elimination rate constant (λ_z), elimination half-life ($t_{1/2}$), abuse quotient (calculated as C_{max}/t_{max}), and percent extrapolation (calculated as 100 x $[AUC_{0–\infty} – AUC_{0–t}]/AUC_{0–\infty}$).

Safety

Safety and tolerability were assessed by monitoring adverse events (AEs), clinical laboratory test results, vital sign measurements, ECG and physical examination findings, oxyhemoglobin saturation (SpO_2) measurements, and concomitant medication use.

Statistical Analysis

A minimum of 32 evaluable subjects completing the double-blind, crossover treatment phase of the study provides 90% power to detect a difference of 12 to 20 points on a 100-mm VAS scale between a pair of treatments, based on a two-sided paired *t*-test with statistical significance of $P = 0.05$. The within-subject standard deviation (SD) was estimated based on two previous abuse liability studies [11,23].

Descriptive statistics were calculated to summarize pharmacodynamic parameters for each treatment. Continuous and ordinal categorical pharmacodynamic parameters were analyzed using a mixed effects analysis of variance (ANOVA) model with study drug, treatment sequence, and period as fixed effects and subject as a random effect. Comparisons between pairs of treatments were made using the least-squares means estimated from the ANOVA. For the primary pharmacodynamic measure, the comparison between hydrocodone IR and placebo was assessed first to ensure the validity of the measure. If the treatment difference was significant at an alpha level of 0.05, the comparison between hydrocodone IR and intact hydrocodone ER was made. If that treatment difference also was significant at an alpha level of 0.05, the comparison between hydrocodone IR and crushed hydrocodone ER was made.

A post hoc analysis of the completer analysis set was conducted and included a responder analysis using the percent reduction in the peak "at the moment" drug liking for the ER formulations relative to IR for individual subjects. This analysis evaluated the proportion of participants who had ≥30% reductions and ≥50% reductions in "at the moment" drug liking with intact and finely crushed hydrocodone ER vs. hydrocodone IR.

Descriptive statistics were calculated to summarize pharmacokinetic parameters for each treatment. Exploratory analyses were done using graphics to assess the relationship between plasma concentration and the effect of hydrocodone treatment on pharmacodynamic variables over time.

The pharmacodynamic and pharmacokinetic analysis sets included subjects with adequate pharmacodynamic and pharmacokinetic data, respectively, from the treatment phase to contribute to at least one planned comparison. The post hoc analyses of the completer analysis set included data from all subjects who completed all visits of the treatment phase. The safety analysis set for the treatment phase included all subjects who received one or more doses of study medication.

Results

Subjects

Of the 195 subjects screened, 100 were enrolled into the qualification phase and 49 were randomized into the treatment phase, received at least one dose of study drug, and were evaluable for safety (Figure 1). A total of 45 subjects were evaluable for pharmacodynamic measures and 43 were evaluable for pharmacokinetic analyses. Randomized subjects were predominantly male (80%) and white (94%), and had a median (range) age of 23 (18–43) years and a median (range) body mass index of 23.8 (19.5–32.6) kg/m^2.

Primary Pharmacodynamic Measure of Drug Liking

Mean (SD) E_{max} "at the moment" drug liking scores over 72 hours are presented in Figure 2. Significantly lower mean E_{max} for "at the moment" drug liking was observed after administration of intact and finely crushed hydrocodone ER compared with hydrocodone IR (53.9 and 66.9 vs. 85.2, respectively; $P < 0.001$). Post hoc analysis showed that the mean E_{max} of "at the moment" drug liking for intact hydrocodone ER was not significantly different from that of placebo (53.9 vs. 53.2; $P = 0.640$); however, the E_{max} for finely crushed hydrocodone ER was significantly different from that of placebo (66.9 vs. 53.2; $P < 0.001$). "At the moment" drug liking E_{max} was also significantly different after administration of intact hydrocodone ER compared with finely crushed hydrocodone ER (53.9 vs. 66.9; $P < 0.001$).

Post hoc analysis of the completer analysis set showed similar results, with the exception of "at the moment" drug liking for intact hydrocodone ER vs. placebo

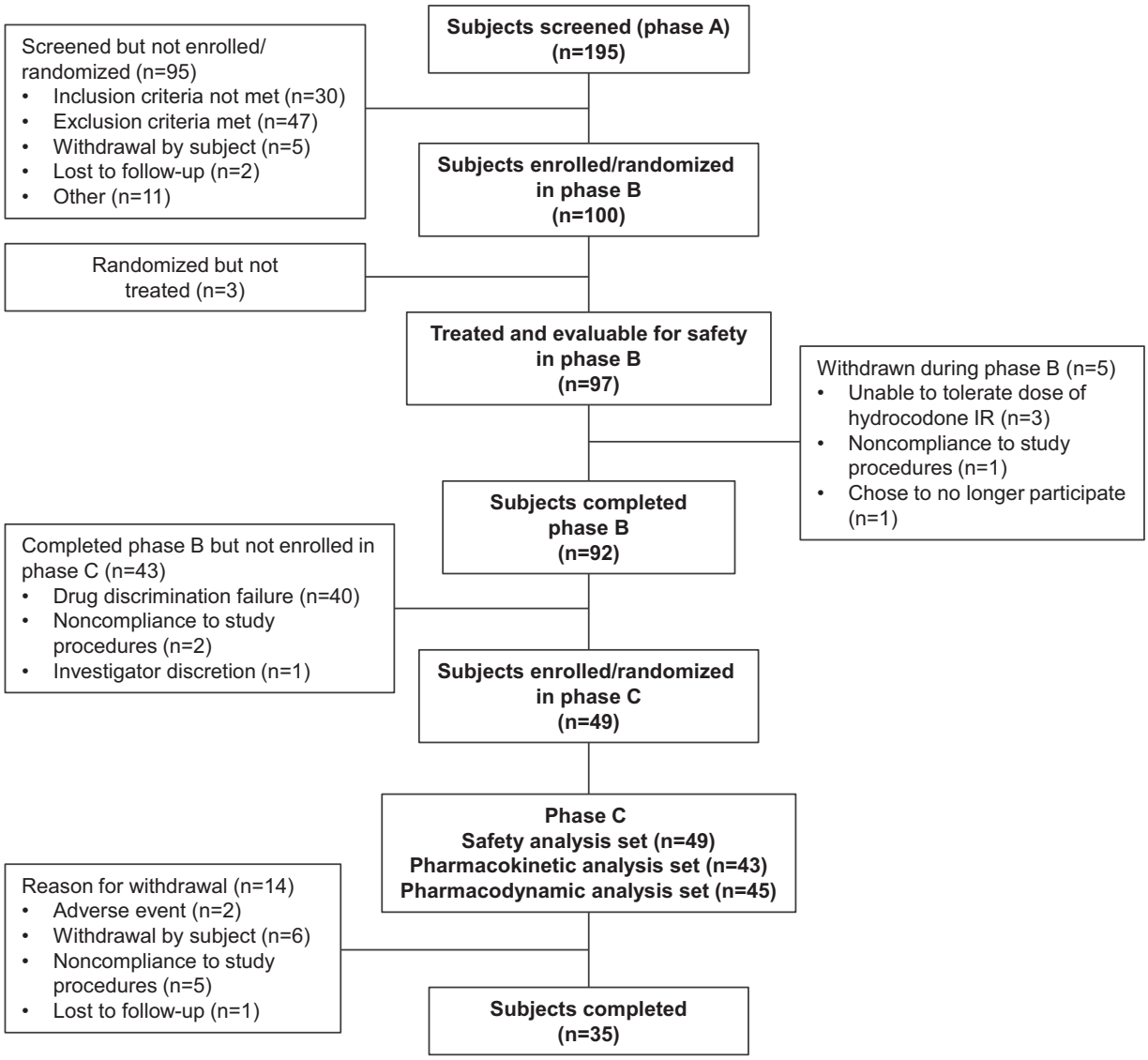

Figure 1 Subject disposition.

IR=immediate release; phase A=screening; phase B=crossover qualification phase; phase C=randomized, double-blind, crossover treatment phase.

(Wilcoxon signed-rank test; $P = 0.029$), although median values were the same for both treatments (51.0). The results of the post hoc responder analysis (using the completer analysis set) demonstrated that for the E_{max} of "at the moment" drug liking, 94% of subjects showed $\geq$30% reductions with intact hydrocodone ER compared with hydrocodone IR, while 88% of subjects showed $\geq$50% reduction. When finely crushed hydrocodone ER was compared with the intact hydrocodone IR, approximately 68% of subjects showed a >30% reduction in E_{max} and 58% of subjects showed a >50% reduction in E_{max}.

Mean "at the moment" drug liking over time for each treatment is presented in Figure 3A. After administration of hydrocodone IR, "at the moment" drug liking scores were in the "liking" range (>50) of the scale from 0.75 to 8.0 hours after administration, then they returned to just above neutral (50) by 12 hours after administration. After administration of the finely crushed hydrocodone ER tablet, a slower rise to a lower peak in drug liking was observed. Liking scores were generally higher than baseline from 1.25 to 8 hours after administration; however, only a small increase in mean scores was observed (approximately 10 points). "At the moment" drug liking

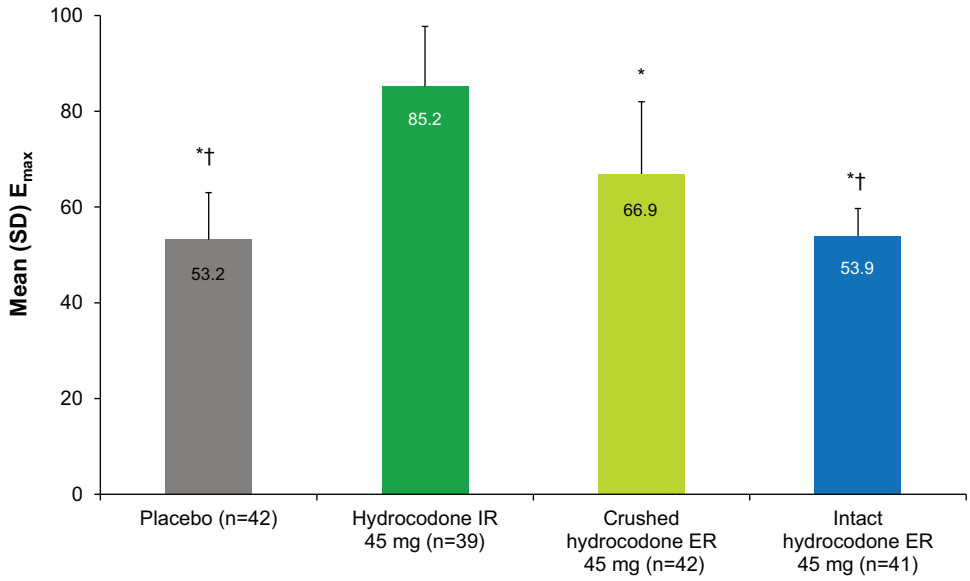

Figure 2 Maximum effect (E_{max}) of "at the moment" drug liking. *$P < 0.001$ vs. hydrocodone IR. †$P < 0.001$ vs. crushed hydrocodone ER. ER = extended release; IR = immediate release; SD = standard deviation.

scores following administration of placebo and intact hydrocodone ER had very similar profiles, showing little change across time points and hovering around neutral.

Overall Drug Liking VAS

The Overall Drug Liking VAS, administered at 24 hours post dose, reflects drug liking over a full 24-hour period after study drug administration. Findings for Overall Drug Liking were comparable to those for "at the moment" drug liking (Table 2). The hydrocodone IR Overall Drug Liking score was significantly higher than the scores for placebo ($P < 0.001$) and both intact and finely crushed hydrocodone ER ($P < 0.001$). Intact hydrocodone ER was not associated with higher Overall Drug Liking VAS mean scores compared with placebo ($P = 0.672$); however, the finely crushed hydrocodone ER mean scores were significantly higher than the placebo scores ($P = 0.013$). Overall Drug Liking was also significantly lower following administration of intact hydrocodone ER than following administration of finely crushed hydrocodone ER ($P = 0.004$).

Measures of Balance of Effects

Measures of the balance of drug effects included E_{min} and AUEC for "at the moment" drug liking and scores on the TDAA and PVAQ (Table 2). E_{min} for "at the moment" drug liking was comparable across treatments; there were no significant differences. AUEC for "at the moment" drug liking was significantly lower after administration of intact hydrocodone ER compared with hydrocodone IR (3544 vs. 3860; $P < 0.001$) and finely crushed hydrocodone ER (3544 vs. 3803; $P = 0.005$). No significant differences were observed after administration of finely crushed hydrocodone ER compared with hydrocodone IR (3803 vs. 3860; $P = 0.442$).

The TDAA assesses a subject's willingness or desire to take the drug again. Subjects were significantly less likely to want to take intact or finely crushed hydrocodone ER again compared with hydrocodone IR (TDAA 46.4 and 58.7 vs. 75.2; $P < 0.001$). Subjects were also significantly less likely to want to take intact hydrocodone ER compared with finely crushed hydrocodone ER (46.4 vs. 58.7; $P = 0.004$). Willingness to take drug again was comparable after administration of intact hydrocodone ER and placebo (46.4 vs. 47.2; statistical comparison not conducted).

The PVAQ assesses how much a subject would be willing to pay for the drug. Subjects were willing to pay significantly more for hydrocodone IR compared with intact or finely crushed hydrocodone ER (12.1 vs. 2.3 or 7.3; $P < 0.001$). Subjects were also willing to pay significantly more for finely crushed hydrocodone ER compared with intact hydrocodone ER (7.3 vs. 2.3; $P < 0.001$). Willingness to pay for the drug was comparable after administration of intact hydrocodone ER and placebo (2.3 vs. 0.7; statistical comparison not conducted).

Measures of Positive and Negative Effects

Measures of the positive effects of the drug included E_{max} and AUEC for the DLEQ question about "good drug effects" and the morphine-benzedrine group (MBG) subscale of the ARCI (Table 2). Mean DLEQ "good drug effects" scores rose sharply within the first 1.25 hours for hydrocodone IR; a slightly delayed and

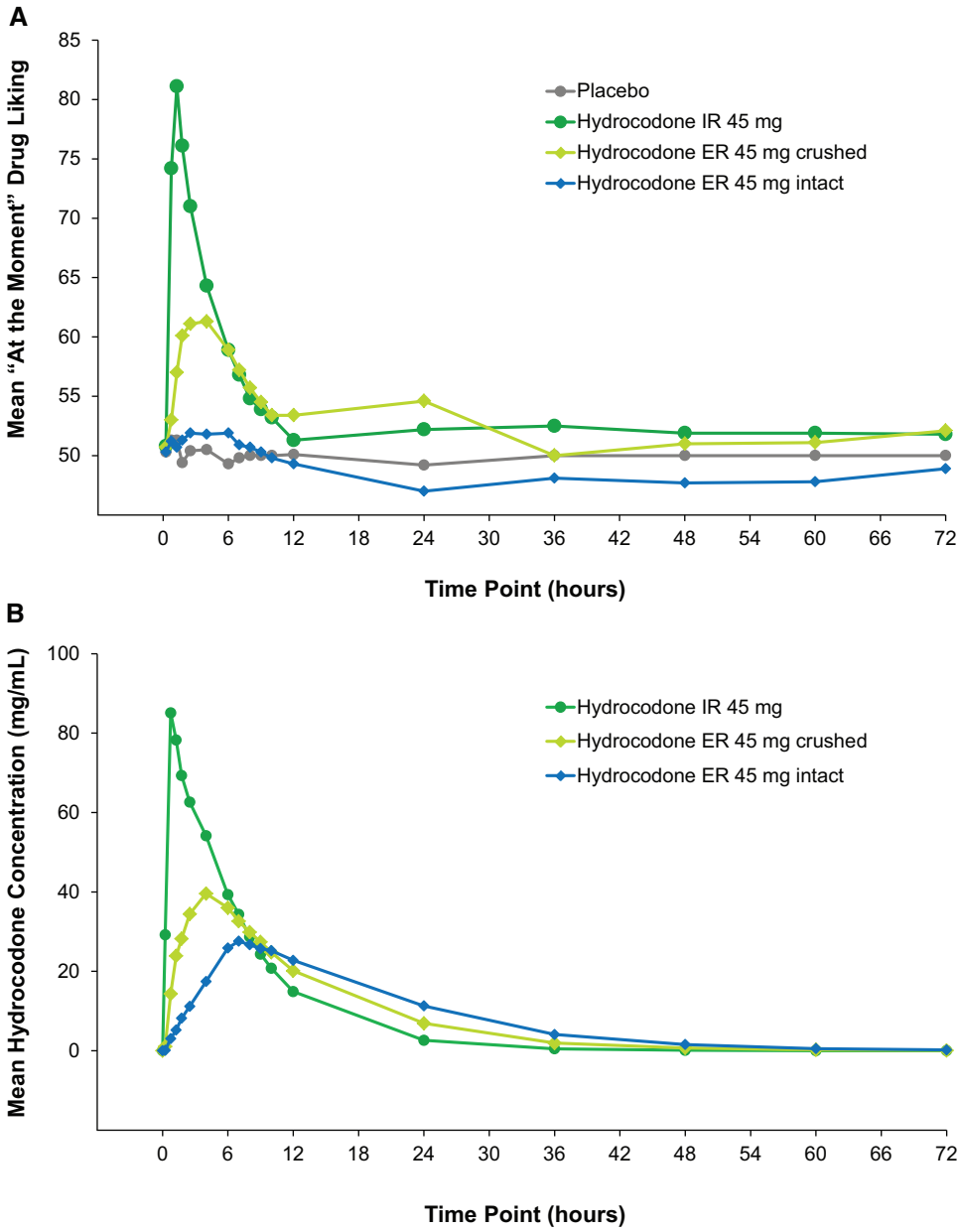

Figure 3 (A) Mean "at the moment" drug liking over time assessed by the Drug Liking and Effects Questionnaire (0–72 hours) and (B) mean plasma concentration over time (0–72 hours). ER = extended release; IR = immediate release.

smaller rise was seen with finely crushed hydrocodone ER. The "good drug effects" for these two treatments resolved by 12 hours. Profiles for intact hydrocodone ER and placebo were similar (Figure 4). E_{max} for "good drug effects" was significantly lower after administration of intact and finely crushed hydrocodone ER compared with hydrocodone IR (11.0 and 33.2 vs. 72.8; $P < 0.001$). AUEC for "good drug effects" was significantly lower after administration of intact and finely crushed hydrocodone ER tablet compared with hydrocodone IR (71 and 204 vs. 318; $P < 0.001$ and $P = 0.002$, respectively). E_{max} (11.0 vs. 33.2, respectively) and AUEC (71 vs. 204) were also significantly lower after administration of intact hydrocodone ER compared with finely crushed hydrocodone ER ($P < 0.001$). E_{max} values for DLEQ "good drug effects" were comparable after administration of intact hydrocodone ER and placebo (11.0 vs. 8.7; statistical comparison not conducted); AUEC values were numerically higher for intact hydrocodone ER vs. placebo (71 vs. 40; statistical comparison not conducted).

Table 2 Mean (SD) scores on secondary pharmacodynamic measures of subjective drug effects by treatment

Secondary variables		Placebo (n = 42)	Hydrocodone 45 mg IR (n = 39)	Hydrocodone 45 mg ER crushed (n = 42)	Hydrocodone 45 mg ER intact (n = 41)
Overall drug liking VAS		51.1 (7.6)*†	75.0 (16.8)	59.0 (19.9)*	49.2 (11.0)*†
Measures of balance of effects	"At the moment" drug liking on DLEQ – E_{min}	45.3 (13.0)	46.8 (9.8)	46.6 (9.7)	46.2 (10.6)
	"At the moment" drug liking on DLEQ – AUEC	3595 (110)*	3860 (585)	3803 (592)	3544 (308)*†
	TDAA	47.2 (15.5)*	75.2 (17.3)	58.7 (21.5)*	46.4 (18.3)*†
	PVAQ	0.7 (3.4)*	12.1 (8.0)	7.3 (11.3)*	2.3 (4.8)*†
Measures of positive effects	Good drug effects on DLEQ – E_{max}	8.7 (21.9)*	72.8 (26.6)	33.2 (31.7)*	11.0 (16.3)*†
	Good drug effects on DLEQ – AUEC	40 (70)*	318 (256)	204 (293)*	71 (86)*†
	MBG scale – E_{max}	2.5 (3.2)*	8.6 (4.3)	5.7 (4.4)*	2.8 (2.8)*†
	MBG scale – AUEC	90 (88)*	135 (98)	118 (87)*	100 (101)*
Measures of negative effects	Bad drug effects on DLEQ – E_{max}	3.0 (11.8)*	16.7 (21.4)	12.6 (20.8)	5.5 (11.8)*†
	Bad drug effects on DLEQ – AUEC	30 (52)*	109 (149)	98 (209)	85 (202)
	LSD scale – E_{max}	4.0 (1.6)*	6.2 (2.1)	4.7 (1.7)*	4.4 (1.6)*
	LSD scale – AUEC	249 (52)	243 (61)	242 (54)	250 (60)
	Nausea on DLEQ – E_{max}	4.2 (16.1)*	14.7 (23.9)	11.1 (22.9)	9.0 (20.4)
	Nausea on DLEQ – AUEC	35 (58)	102 (157)	74 (156)	124 (354)
Measures of sedative effects	PCAG scale – E_{max}	4.7 (2.6)*	8.8 (2.6)	6.6 (2.6)*	5.4 (2.6)*†
	PCAG scale – AUEC	217 (66)*	238 (81)	245 (72)	242 (92)
	Drowsiness on DLEQ – E_{min}	45.8 (15.7)*	27.5 (15.3)	35.8 (15.4)*	44.0 (12.2)*†
	Drowsiness on DLEQ – AUEC	3675 (780)	3611 (475)	3569 (544)	3638 (523)
Measures of other drug effects	Any drug effects on DLEQ – E_{max}	9.6 (22.0)*	74.4 (24.5)	33.3 (30.0)*	12.0 (16.3)*†
	Any drug effects on DLEQ – AUEC	44 (75)*	355 (275)	231 (281)*	102 (181)*†
	Pupillometry – E_{min}	5.5 (0.9)*	3.2 (0.6)	4.0 (0.8)*	4.3 (0.8)*†

AUEC = area under the effect curve; DLEQ = Drug Liking and Effects Questionnaire; E_{max} = maximum effect; E_{min} = minimum effect; ER = extended release; IR = immediate release; LSD = lysergic acid diethylamide; MBG = morphine-benzedrine group; PCAG = pentobarbital, chlorpromazine, alcohol group; PVAQ = Price Value Assessment Questionnaire; TDAA = take drug again assessment; VAS = visual analog scale.

*$P < 0.05$ vs. hydrocodone IR.

†$P < 0.05$ vs. crushed hydrocodone ER.

The MBG subscale of the ARCI assesses positive subjective effects of drugs with true/false statements such as "I feel in complete harmony with the world and those about me" and "I would be happy all the time if I felt as I feel now." Significantly lower E_{max} (2.8 vs. 8.6; $P < 0.001$) and AUEC (100 vs. 135; $P < 0.001$) values for the MBG subscale were observed after administration of intact hydrocodone ER compared with hydrocodone IR. E_{max} (5.7 vs. 8.6; $P < 0.001$) and AUEC (118 vs. 135; $P = 0.026$) the MBG subscale were also significantly lower after administration of finely crushed hydrocodone ER compared with hydrocodone IR. Similarly, E_{max} for the MBG subscale was significantly lower for intact hydrocodone ER compared with finely crushed hydrocodone ER (2.8 vs. 5.7; $P < 0.001$), while AUEC was comparable between the treatments (100 vs. 118; $P = 0.138$). E_{max} and AUEC values for the MBG subscale were comparable after administration of intact hydrocodone ER

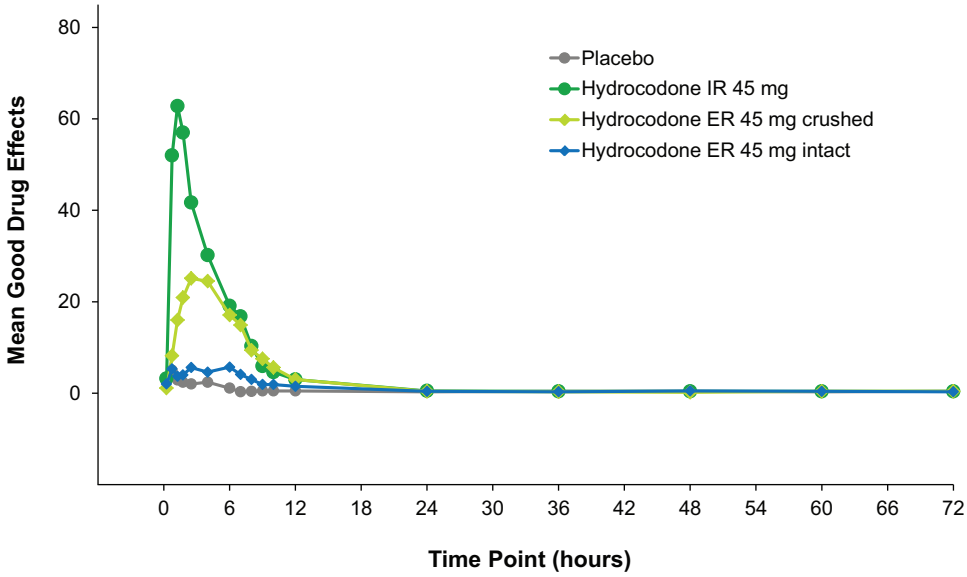

Figure 4 Mean Good Drug Effects over time assessed by the Drug Liking and Effects Questionnaire (0–72 hours). ER = extended release; IR = immediate release.

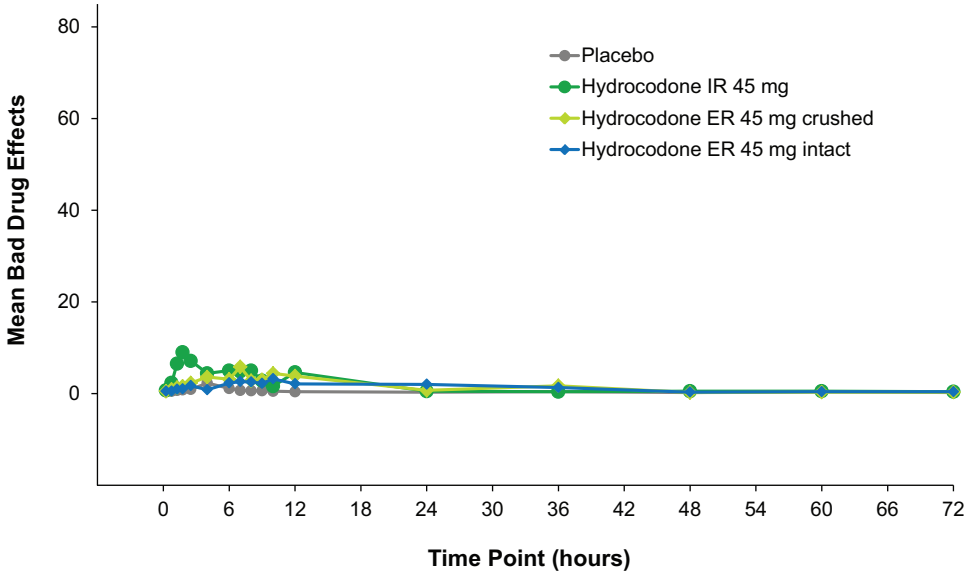

Figure 5 Mean Bad Drug Effects over time assessed by the Drug Liking Effects Questionnaire (0–72 hours). ER = extended release; IR = immediate release.

and placebo (E_{max}: 2.8 vs. 2.5; AUEC: 100 vs. 90; statistical comparison not conducted).

Measures of the negative effects of the drugs include the E_{max} and AUEC for DLEQ "bad drug effects" question, the Lysergic Acid Diethylamide (LSD) subscale of the ARCI, and DLEQ nausea question (Table 2). A small rise of short duration in DLEQ "bad drug effect" was seen during the first 1.75 hours for hydrocodone IR. Profiles for crushed and intact hydrocodone ER were similar to that for placebo (Figure 5). The E_{max} for DLEQ "bad drug effect" was significantly lower for intact hydrocodone ER compared with hydrocodone IR and finely crushed hydrocodone ER (5.5 vs. 16.7 and 12.6; $P = 0.002$ and $P = 0.036$, respectively); the E_{max} was not significantly different between finely crushed hydrocodone ER and hydrocodone IR (12.6 vs. 16.7; $P = 0.259$). AUEC values for "bad drug effects" were

comparable across hydrocodone treatments. The E_{max} values were comparable after administration of intact hydrocodone ER and placebo (5.5 vs. 3.0; statistical comparison not conducted); AUEC was numerically higher with intact hydrocodone ER vs. placebo (85 vs. 30; statistical comparison not conducted).

The LSD subscale of the ARCI assesses negative subjective effects of drugs with statements such as "I feel drowsy" and "I feel anxious and upset." Significantly lower E_{max} values for the LSD subscale of the ARCI were observed for intact and finely crushed hydrocodone ER compared with hydrocodone IR (4.4 and 4.7 vs. 6.2; $P < 0.001$); however, the AUEC for the LSD subscale was comparable across treatments, with no significant differences. There were no significant differences in the LSD subscale E_{max} or AUEC between intact hydrocodone ER and finely crushed hydrocodone ER ($P = 0.278$ and $P = 0.318$, respectively). The E_{max} and AUEC values for the LSD subscale were comparable after administration of intact hydrocodone ER and placebo (E_{max}: 4.4 vs. 4.0; AUEC: 250 vs. 249; statistical comparison not conducted).

There were no meaningful differences across hydrocodone treatments in E_{max} or AUEC for the DLEQ question assessing feelings of nausea.

Measures of Sedative Effects

Measures of the sedative effects of the drugs include the pentobarbital, chlorpromazine, alcohol group (PCAG) subscale E_{max} and AUEC and the E_{min} and AUEC for the DLEQ drowsiness question (Table 2). The PCAG subscale of the ARCI assesses subjective sedative effects of drugs with statements such as "I am not as active as usual" and "My head feels heavy." E_{max} values for the PCAG subscale were significantly lower after administration of intact and finely crushed hydrocodone ER compared with hydrocodone IR (5.4 and 6.6 vs. 8.8; $P < 0.001$). E_{max} was also significantly different between intact and finely crushed hydrocodone ER (5.4 vs. 6.6; $P = 0.008$). AUEC for the PCAG was comparable across hydrocodone treatments. The E_{max} and AUEC values for the PCAG subscale were comparable after administration of intact hydrocodone ER and placebo (E_{max}: 5.4 vs. 4.7; AUEC: 242 vs. 217; statistical comparison not conducted).

Based on E_{min} for the DLEQ question assessing feelings of drowsiness, subjects felt significantly less drowsy after administration of intact and finely crushed hydrocodone ER compared with hydrocodone IR (44.0 and 35.8 vs. 27.5; $P < 0.001$ and $P = 0.004$, respectively). E_{min} was also significantly different between intact and finely crushed hydrocodone ER (44.0 vs. 35.8; $P = 0.003$). AUEC for DLEQ drowsiness was comparable across treatments. E_{min} and AUEC values for the DLEQ drowsiness question were comparable after administration of intact hydrocodone ER and placebo (E_{max}: 44.0 vs. 45.8; AUEC: 3638 vs. 3675; statistical comparison not conducted).

Measures of Other Effects

Measures of other drug effects include E_{max} and AUEC for the DLEQ question about feeling "any drug effect" and pupil diameter E_{min} (Table 2). Mean "any drug effect" scores rose sharply within the first 1.25 hours with hydrocodone IR; a smaller rise was seen with finely crushed hydrocodone ER for the first 2.5 hours. The effects resolved by hour 12 for all treatments. Profiles for intact hydrocodone ER and placebo were similar (Figure 6). Subjects had significantly fewer feelings of any drug effect after administration of intact hydrocodone ER compared with hydrocodone IR (E_{max}: 12.0 vs. 74.4 [$P < 0.001$]; AUEC: 102 vs. 355 [$P < 0.001$]). After administration of finely crushed hydrocodone ER, feelings of any drug effect were significantly lower compared with hydrocodone IR based on E_{max} (33.3 vs. 74.4; $P < 0.001$) and AUEC (231 vs. 355; $P = 0.003$). Subjects also had significantly fewer feelings of any drug effect after administration of intact hydrocodone ER compared with finely crushed hydrocodone ER (E_{max}: 12.0 vs. 33.3 [$P < 0.001$]; AUEC: 102 vs. 231 [$P < 0.001$]). E_{max} values for "any drug effect" were comparable after administration of intact hydrocodone ER and placebo (12.0 vs. 9.6; statistical comparison not conducted). AUEC values were numerically higher for hydrocodone ER compared with placebo (102 vs. 44; statistical comparison not conducted).

Pupillometry was also performed to provide an objective measure of the physiologic effects of the treatments. Mean pupil diameter over 72 hours is shown in Figure 7. Mean E_{min} for pupil diameter measurements for hydrocodone IR, intact hydrocodone ER, and finely crushed hydrocodone ER were all lower than those for placebo (statistical comparison not conducted), validating the physiologic effect of hydrocodone. Mean E_{min} for pupil diameter measurements was significantly higher (i.e., pupils were less constricted) after administration of intact or finely crushed hydrocodone ER (4.3 and 4.0) than after administration of hydrocodone IR (3.2; $P < 0.001$). Pupils were also significantly less constricted after administration of intact hydrocodone ER compared with finely crushed hydrocodone ER (4.3 vs. 4.0; $P = 0.015$).

Pharmacokinetics

Mean plasma hydrocodone concentration-time profiles over 72 hours for intact hydrocodone ER compared with finely crushed hydrocodone ER and hydrocodone IR are shown in Figure 3B. The plasma concentration-time profile for each treatment resembled its corresponding profile for "at the moment" drug liking over time shown in Figure 3A.

Pharmacokinetic parameters for the study treatments are summarized in Table 3. C_{max} was lowest for intact hydrocodone ER (28.8 ng/mL). C_{max} for finely crushed hydrocodone ER (40.8 ng/mL) was 55% lower than that for hydrocodone IR (91.5 ng/mL). The rate of absorption of hydrocodone was slowest for intact

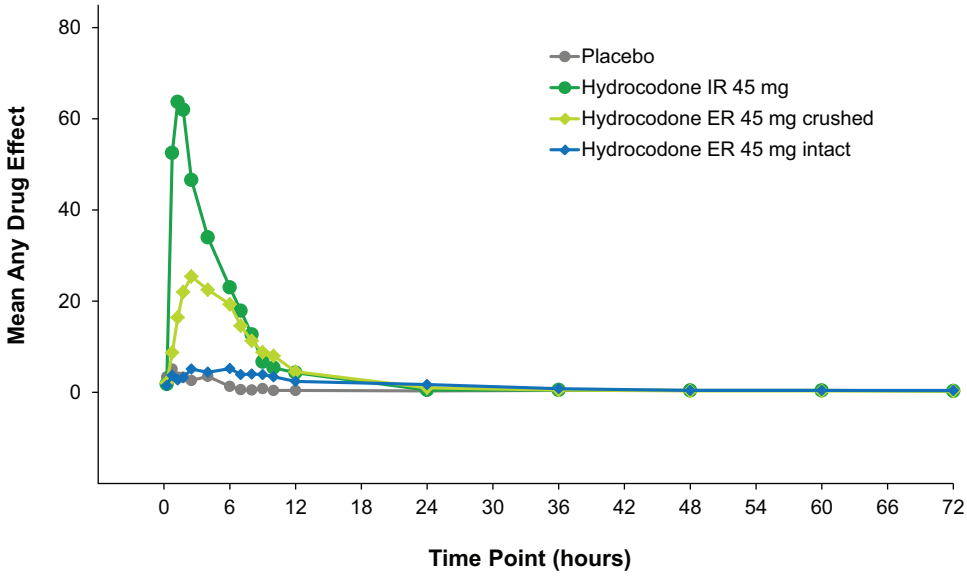

Figure 6 Mean Any Drug Effects over time assessed by the Drugs Liking Effects Questionnaire (0–72 hours). ER = extended release; IR = immediate release.

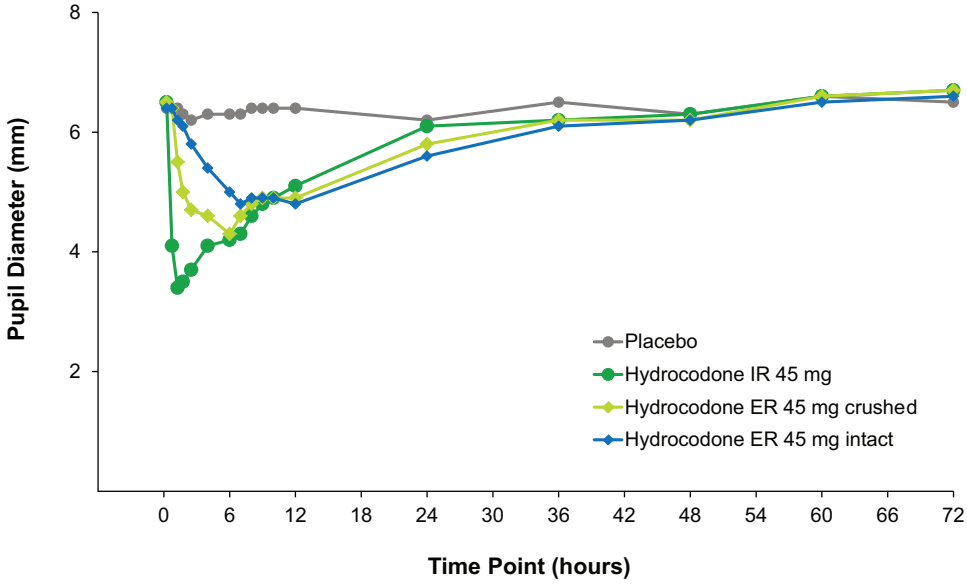

Figure 7 Mean pupil diameter over time (0–72 hours). ER = extended release; IR = immediate release.

hydrocodone ER, with a t_{max} of 7.1 hours, compared with the t_{max} for finely crushed hydrocodone ER (4.0 hours) and hydrocodone IR (0.8 hours). The decline from the peak plasma concentrations appeared to be monophasic for all three treatments, with mean $t_{1/2}$ of 8.0 hours for intact hydrocodone ER, 8.0 hours for finely crushed hydrocodone ER, and 5.1 hours for hydrocodone IR.

Mean $AUC_{0-\infty}$ for intact and crushed hydrocodone ER was comparable (584 vs. 586 ng·h/mL), indicating that the full dose of hydrocodone ER was administered. Exposure before t_{max} for hydrocodone IR ($AUC_{0-0.75}$) and before t_{max} for intact hydrocodone ER (AUC_{0-7}) was greatest for hydrocodone IR. Mean $AUC_{0-0.75}$ and AUC_{0-7} for intact hydrocodone ER were 97% and 72% lower, respectively, than for hydrocodone IR. Mean $AUC_{0-0.75}$ for finely

Table 3 Mean (SD) pharmacokinetic parameters for hydrocodone by treatment

Variable	Hydrocodone 45 mg		
	IR (n = 39)	ER crushed (n = 41)	ER intact mg (n = 40)
C_{max} (ng/mL)	91.5 (16.8)	40.8 (10.2)	28.8 (6.1)
t_{max} (h)*	0.8 (0.3, 4.1)	4.0 (1.8, 7.0)	7.1 (6.1, 12.0)
$AUC_{0-\infty}$ (ng•h/mL)	625 (137)	586 (139)	584 (125)
$AUC_{0-0.75}$ (ng•h/mL)	29 (14)	3 (2)	1 (0)
AUC_{0-4} (ng•h/mL)	246 (43)	103 (25)	34 (9)
AUC_{0-7} (ng•h/mL)	377 (60)	212 (47)	104 (23)
AUC_{0-t} (ng•h/mL)	623 (136)	584 (139)	581 (125)
Extrapolation (%)†	0.3 (0.1)	0.4 (0.2)	0.6 (0.5)
λ_z (1/h)	0.1384 (0.0218)	0.0933 (0.0252)	0.0929 (0.0267)
$t_{1/2}$ (h)	5.1 (0.8)	8.0 (2.1)	8.0 (2.2)
Abuse quotient (ng/mL/h)‡	108.6 (58.8)	11.0 (4.0)	3.9 (1.1)

λ_z = apparent plasma terminal elimination rate constant; $AUC_{0-\infty}$ = area under the plasma drug concentration by time curve (AUC) from 0 to infinity; $AUC_{0-0.75}$ = AUC from 0 to 0.75 hours after study drug administration; C_{max} = maximum observed plasma drug concentration; AUC_{0-4} = AUC from 0 to 4 hours after study drug administration; AUC_{0-7} = AUC from 0 to 7 hours after study drug administration; AUC_{0-t} = AUC from time 0 to the time of the last measurable drug concentration; ER = extended-release; IR = immediate release; t_{max} = time to maximum observed plasma drug concentration.
*Values for t_{max} are median (range).
†Percent extrapolation: 100 x ($AUC_{0-\infty}$ – AUC_{0-t})/$AUC_{0-\infty}$.
‡Abuse quotient: C_{max}/t_{max}.

crushed hydrocodone ER was 86% lower than for hydrocodone IR. AUC_{0-4} (exposure before t_{max} for intact hydrocodone ER) was 57% lower for finely crushed hydrocodone ER than for hydrocodone IR.

The abuse quotient (calculated as C_{max}/t_{max}) for intact and finely crushed hydrocodone ER was 27-fold and 10-fold lower, respectively, than for hydrocodone IR, respectively.

Plasma concentrations of hydromorphone were approximately 1% of those of the parent drug hydrocodone for each treatment.

Safety and Tolerability

Subjects enrolled in this study were nondependent, recreational opioid users. No deaths or serious AEs were reported during the study; however, 1 patient died approximately 2.5 months after the final study drug administration of a self-inflicted gunshot wound. Two subjects discontinued from the study during the treatment phase owing to AEs after administration of intact hydrocodone ER (toothache [n = 1] and catheter site cellulitis [n = 1]). Both events resolved, and neither was considered to be related to hydrocodone administration.

During the qualification phase, at least one AE occurred in 6 (6%) subjects after administration of placebo and 65 (67%) subjects after administration of hydrocodone IR. AEs considered by the investigator to be treatment related were reported in 3 (3%) subjects after administration of placebo and in 61 (63%) subjects after administration of hydrocodone IR.

During the treatment phase, the overall incidence of AEs was lower after administration of intact hydrocodone ER (53%) compared with crushed hydrocodone ER (73%) and hydrocodone IR (79%). AEs reported for ≥5% of subjects in any treatment group are summarized in Table 4. Some of the more frequent AEs (pruritus generalized, pruritus, nausea, dizziness, and hiccups) seen in this study occurred less frequently after administration of intact hydrocodone ER compared with hydrocodone IR and crushed hydrocodone ER. Other AEs (abdominal pain upper, dyspepsia, and anxiety) occurred with a greater frequency after administration of intact hydrocodone ER. The majority of AEs were mild in severity and resolved.

No clinically relevant mean changes from baseline were noted for serum chemistry, hematology, or urinalysis assessments. There were no AEs reported regarding clinically significant laboratory test results. Overall, mean vital signs and SpO_2 values remained within normal ranges throughout the study. For those subjects with individual potentially clinically significant vital sign measurements, no correlation was detected between the potentially clinically significant changes in vital sign measurements and plasma hydrocodone concentrations. All clinically significant vital sign and SpO_2 measurements resolved without treatment, and there were no significant sequelae. No clinically meaningful changes in ECG or physical examination findings were reported during the course of the study.

Table 4 Adverse events occurring in ≥ 5% of subjects in any treatment group: Safety analysis set

		Hydrocodone 45 mg		
	Placebo (n = 43)	IR (n = 43)	ER crushed (n = 44)	ER intact (n = 43)
≥1 AE	10 (23)	34 (79)	32 (73)	23 (53)
Adverse events ≥ 5%				
Nausea	2 (5)	12 (28)	11 (25)	7 (16)
Headache	5 (12)	6 (14)	12 (27)	6 (14)
Generalized pruritus	1 (2)	14 (33)	15 (34)	5 (12)
Somnolence	1 (2)	5 (12)	3 (7)	3 (7)
Vomiting	0	5 (12)	3 (7)	3 (7)
Anxiety	0	0	1 (2)	3 (7)
Dizziness	1 (2)	4 (9)	4 (9)	2 (5)
Tinnitus	0	2 (5)	1 (2)	2 (5)
Upper abdominal pain	1 (2)	1 (2)	1 (2)	2 (5)
Photophobia	0	1 (2)	1 (2)	2 (5)
Nasopharyngitis	0	0	1 (2)	2 (5)
Dyspepsia	0	0	0	2 (5)
Catheter site pain	0	0	0	2 (5)
Oropharyngeal pain	0	0	0	2 (5)
Hiccups	0	3 (7)	4 (9)	1 (2)
Pruritus	0	14 (33)	2 (5)	1 (2)
Dry mouth	1 (2)	4 (9)	1 (2)	1 (2)
Laceration	0	2 (5)	1 (2)	0

ER = extended release; IR = immediate release.

Discussion

Abuse liability studies can provide valuable information regarding the abuse potential of a drug in recreational drug users. Limiting abuse is particularly important with ER formulations, as they have an increase in total drug load that may increase the potential for abuse and the risk of overdose [24]. In this study, we evaluated the abuse potential of hydrocodone ER, a novel formulation of hydrocodone bitartrate formulated with CIMA® ADT to protect against rapid release of hydrocodone when tablets are comminuted and provide resistance against dose dumping when tablets are taken with alcohol. Abuse potential after oral administration was evaluated, as this route has been shown to be the most common route of administration in the abuse of hydrocodone products [16,17].

In this randomized, double-blind, placebo-controlled study in nondependent, recreational opioid users, significantly lower drug liking was observed after oral administration of intact hydrocodone ER compared with hydrocodone IR based on mean E_{max} "at the moment" drug liking over 72 hours (53.9 vs. 85.2; $P < 0.001$) and the Overall Drug Liking VAS 24 hours after study drug administration (49.2 vs. 75.0; $P < 0.001$). Although drug liking for finely crushed hydrocodone ER was significantly higher ($P \leq 0.004$) compared with that for intact hydrocodone ER, drug liking was significantly lower ($P < 0.001$) for finely crushed hydrocodone ER compared with that of hydrocodone IR (Table 1, Figure 2). The outcomes for secondary measures were consistent with these results, showing that positive, negative, and sedative drug effects were diminished with intact and finely crushed hydrocodone ER tablet compared with hydrocodone IR. Pupillometry assessments confirmed that the physiologic effects of intact or crushed hydrocodone ER were significantly lower compared with those of hydrocodone IR. Significant ($P < 0.05$) differences in drug liking were observed after administration of placebo vs. hydrocodone IR, confirming the validity of these study findings. Significant ($P < 0.05$) differences in drug liking were also observed for finely crushed hydrocodone ER but not intact hydrocodone ER compared with placebo, indicating a lack of liking for hydrocodone ER when administered intact as intended.

Reductions in drug liking with ER formulations of opioids (e.g., oxycodone, hydromorphone, morphine) over IR formulations have been observed in several studies evaluating abuse potential [23,25–27]. One study using methodology similar to that of the current study compared the abuse potential of 40 mg of IR oxycodone with 40 mg of an encapsulated, water insoluble, highly viscous ER oral formulation of oxycodone (Remoxy®, Pfizer Inc, New York, NY) [26]. Compared with peak

drug liking for IR oxycodone, peak drug liking was approximately 42% lower for whole ER oxycodone and 21% lower for chewed oxycodone ER ($P < 0.05$). In our study, peak drug liking was approximately 37% lower for intact hydrocodone ER and 21% lower for finely crushed hydrocodone ER than for hydrocodone IR ($P < 0.001$).

In a study by Webster et al evaluating the abuse potential of different formulations of oxycodone, drug liking was lower with the intact ER formulation of oxycodone than with IR oxycodone [25]. However, when the ER oxycodone tablet was crushed, drug-liking results resembled those seen with the IR oxycodone formulation [25]. A recently approved hydrocodone ER formulation with abuse-deterrent properties (Hysingla® ER, Purdue Pharma, Stamford, CT) was evaluated for oral abuse potential in a study that compared pharmacodynamic parameters following administration of intact and chewed ER drug and a hydrocodone IR solution [28]. Mean drug liking was significantly lower for both the intact and chewed ER drug compared with the hydrocodone IR solution. The present study used finely crushed tablets, which may provide a more rigorous standard for assessing abuse potential than chewing. The significantly lower drug liking with orally administered finely crushed hydrocodone ER compared with hydrocodone IR observed indicates that the CIMA® ADT platform employed in this ER formulation of hydrocodone may effectively reduce the potential for drug tampering and abuse. However, given that intact hydrocodone ER behaves much like placebo, there was a significant increase in most drug likeability and effect measures when comparing crushed to intact hydrocodone ER, suggesting that potential for abuse cannot be fully eliminated.

The pharmacokinetic properties of hydrocodone IR and hydrocodone ER (intact and crushed) were consistent with the known profile of hydrocodone IR products and hydrocodone ER in earlier studies [18–21]. Overall systemic exposure to hydrocodone was comparable between the treatments. The plasma concentration-time curves for intact hydrocodone ER, finely crushed hydrocodone ER, and hydrocodone IR resemble its corresponding "at the moment" drug liking over time profile. Hydrocodone ER retained some of its extended-release properties after being finely crushed, as shown by its lower C_{max} (55%), longer t_{max} (400%), and lower early absorption (90% during the first 0.75 hours and 58% during the first 4 hours) compared with those seen with hydrocodone IR.

Although this study was conducted prior to the FDA issuing recommendations on assessment of opioid abuse-deterrent potential, the design is consistent with these guidelines [4], as well as with previous studies of drug liking and abuse potential [11,23]. A crossover design was employed to control for within-subject variability, and subjects were required to have a history of recreational drug abuse for eligibility. Additionally, a qualification phase was implemented to ensure the study did not enroll a substantial percentage of nonresponders (patients not able to discriminate between active drug and placebo) [26,29]. Results from this abuse potential study are in line with results from in vitro manipulation and extraction studies and pharmacokinetic studies of hydrocodone ER, and confirm the abuse-deterrent properties of this hydrocodone ER formulation which limits rapid release of drug when finely crushed, significantly reducing drug-liking compared with hydrocodone IR. However, because these studies are typically conducted in controlled settings with small sample sizes, caution must be taken when generalizing these results to the at-risk population. A number of additional factors also may play an important role in the abuse of an opioid in the real-world setting, including cost, accessibility, mechanisms of abuse, and what other peers are abusing. As such, the FDA recommends phase IV, post-marketing studies to assess the abuse potential of a product in the community [4].

In this study, hydrocodone ER, orally administered intact or finely crushed, and hydrocodone IR were generally well tolerated in the healthy nondependent recreational opioid users. No new safety issues associated with the use of hydrocodone ER were observed. A lower overall incidence of AEs was observed with intact hydrocodone ER (53%) compared with hydrocodone IR (79%) and finely crushed hydrocodone ER (73%).

Conclusions

The abuse potential with oral use, the most common route of abuse for hydrocodone products, is significantly lower for intact and finely crushed hydrocodone ER tablets developed with CIMA Abuse-Deterrence Technology compared to hydrocodone IR in nondependent, recreational opioid users based on "at the moment" and Overall Drug Liking over 24 hours. Positive, negative, and sedative drug effects were also diminished with intact and finely crushed hydrocodone ER tablet compared with hydrocodone IR. When administered as intended (intact orally), liking scores for hydrocodone ER were similar to those for placebo. The time course of the "at the moment" drug liking profiles for each treatment mimicked its corresponding plasma concentration-time profile. Additionally, assessment of pharmacokinetic parameters for the finely crushed hydrocodone ER tablet showed that it retained some of its ER properties. The reduced dosing frequency and lower abuse potential of this hydrocodone ER tablet may provide a much needed alternative to currently available, combination hydrocodone IR products.

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