Pain Medicine 2016; 17: 820–831
doi: 10.1093/pm/pnv004

OXFORD

Intranasal Abuse Potential, Pharmacokinetics, and Safety of Once-Daily, Single-Entity, Extended-Release Hydrocodone (HYD) in Recreational Opioid Users

Stephen C. Harris, MD,* Alessandra Cipriano, MSHS,* Salvatore V. Colucci, MS,* Ram P. Kapil, PhD,* Pierre Geoffroy, MDCM,† Talar Hopyan, PhD,† and Naama Levy-Cooperman, PhD†

*Purdue Pharma L.P., Stamford, Connecticut, USA;
†INC Research Toronto, Toronto, Ontario, Canada

Correspondence to: Stephen C. Harris, MD, Executive Medical Director, Clinical Pharmacology and Clinical Pharmacokinetics, Purdue Pharma L.P., One Stamford Forum, Stamford, CT 06901-3431, USA. Tel: 203-588-7592; Fax: 203-588-6659; E-mail: stephen.harris@pharma.com.

Funding sources: This study was wholly funded by Purdue Pharma L.P. (Stamford, CT).

Disclosure: This study was sponsored by Purdue Pharma L.P., and was conducted by INC Research, Toronto. SC Harris, A Cipriano, SV Colucci, and RP Kapil are employees of Purdue Pharma L.P. P Geoffrey and T Hopyan are full-time employees of INC Research Toronto. N Levy-Cooperman was a full-time employee of INC Research Toronto at the time the study was conducted.

Abstract

Objectives. A once-daily, extended-release hydrocodone bitartrate tablet with abuse-deterrent properties (Hysingla ER® [HYD]) is available for the treatment of chronic pain in appropriate patients. This study evaluated the intranasal abuse potential and pharmacokinetics of HYD coarse and fine particles vs hydrocodone powder or placebo.

Design. Single-center, double-blind, positive- and placebo-controlled, randomized, four-treatment crossover study.

Subjects. Healthy adult, nondependent, recreational opioid users with a history of intranasal abuse.

Methods. During four treatment periods, subjects (N = 31) received hydrocodone powder 60 mg, HYD coarse particles 60 mg, HYD fine particles 60 mg, or placebo, with five-to-seven-day washouts between treatments. Measures over 36 hours post-dose included drug-liking and willingness to take drug again, assessed using visual analog scales (VASs), pupillometry, intranasal irritation, and pharmacokinetics.

Results. Insufflation of both HYD coarse and fine particles led to lower "At this Moment" Drug Liking VAS peak values compared with hydrocodone powder, but higher values compared with placebo ($P < 0.001$ for all comparisons). Similar results were observed for Overall Drug Liking VAS, Take Drug Again VAS, and Subjective Drug Value. Compared with hydrocodone, insufflation of HYD particles led to reduced miosis and increased nasal irritation. Mean hydrocodone C_{max} following insufflation of HYD coarse particles, HYD fine particles, and hydrocodone powder was 27.5, 36.5, and 105.8 ng/mL, respectively; median T_{max} was $\geq$2-fold longer with either HYD particle size than hydrocodone powder; and (C_{max}/T_{max}) was 9.5, 13.4, and 82.0 ng/mL/h, respectively. Safety was consistent with that of opioid agonists.

Conclusions. HYD demonstrated reduced intranasal abuse potential compared with hydrocodone powder.

Key Words. Hydrocodone; HYD; Abuse Potential; Abuse Deterrent; Pain

Introduction

Prescription opioid analgesics are an important component of modern pain management for many appropriately selected patients suffering from chronic pain. Hydrocodone is a semisynthetic opioid that produces

analgesic activity primarily via mu receptor agonism [1]. Immediate release (IR) hydrocodone in combination with acetaminophen is the most commonly prescribed opioid medication in the United States [2,3]. Until recently, hydrocodone was available only in IR combination products with hydrocodone doses of 5, 7.5, or 10 mg in combination with up to 325 mg acetaminophen or up to 200 mg of ibuprofen. For these IR combination products, the total daily hydrocodone dose is limited to 20–60 mg due primarily to the risk of hepatotoxicity for acetaminophen combination products [4,5] and toxic gastrointestinal effects for other nonopioid components. Single-entity, extended-release (ER) opioids provide another treatment option for patients with pain by addressing the toxicity of the nonopioid component of IR hydrocodone combination products and offering less frequent dosing [6,7].

The abuse and misuse of prescription opioids in the United States is itself a significant medical and public health problem affecting multiple aspects of life and greatly impacting the health care system [8,9]. Of the prescription opioids, IR hydrocodone in combination with acetaminophen is among the most widely abused drugs [10–12], and its misuse rose by 107% between 2004 and 2011 [13]. Prescription opioid abuse primarily involves oral, intranasal, and intravenous routes of administration. Opioid abuse frequently consists of taking more than the recommended dose of intact dosage forms using the intended route of administration; however, abusers often choose to manipulate opioid dosage forms (particle size reduction and/or opioid extraction) to defeat the control of opioid release and/or facilitate administration by oral, intranasal, or intravenous routes [10,11,14]. Development of opioid formulations with abuse-deterrent properties [8,14–17] is one approach in the overall strategy to minimize the abuse and misuse of prescription opioids while preserving their analgesic benefits for patients. The real-world impact of opioid formulations with abuse-deterrent properties on patterns of drug misuse and abuse is being evaluated as more of these products are approved and marketed. Recent experience with products with abuse-deterrent properties suggests that these products may reduce the abuse of prescription opioids by certain methods and routes of administration [18,19].

HYD (Hysingla ER®, Purdue Pharma L.P., Stamford, CT) is a single-entity, once-daily, extended-release, hydrocodone bitartrate tablet with abuse-deterrent properties [20]. The US Food and Drug Administration (FDA) has approved HYD for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment for which other treatment options are inadequate. HYD tablets contain no nonopioid analgesic component (e.g., acetaminophen) and are formulated in multiple strengths (20–120 mg) for prescribers to tailor daily dosage to meet individual patient needs. HYD is formulated using RESISTEC™, a proprietary extended-release solid oral dosage formulation platform. RESISTEC uses a unique combination of polymer and processing that confers tablet hardness and imparts viscosity when dissolved in aqueous solutions.

The objectives of this study were to evaluate the abuse potential of HYD in healthy, nondependent recreational opioid users relative to hydrocodone powder (positive control) and placebo, and to assess the safety and pharmacokinetic (PK) profile of manipulated HYD when administered intranasally. Two methods of HYD tablet manipulation were studied. Reproducible reduction of HYD tablets to fine particles required specialized equipment, while reduction of HYD tablets to coarse particles could be achieved using manual implements and is more likely to be representative of real-world manipulations of HYD.

Methods

Subject Eligibility

Study subjects were healthy, moderately experienced opioid users aged 18–55 years with a history of intranasal opioid abuse. Moderate experience was defined as opioid use for nontherapeutic purposes (i.e., for psychoactive effects) on at least 10 occasions in the previous year, with use of opioids ≥three times in the 12 weeks prior to screening, and ≥three occasions of intranasal opioid use for recreational abuse purposes in the past year. Subjects had a body mass index (BMI) of 18.0 kg/m^2–29.9 kg/m^2 and a weight of ≥50 kg. Subjects must have taken a dose of opioid equivalent to 40 mg hydrocodone or higher by any route of administration at least once in the past year. Negative urine drug screen results were required prior to administering the naloxone challenge and all subsequent treatments. Due to the long half-life of cannabinoids and benzodiazepines (and their metabolites), urine drug screen results for these molecules were required to be negative, stable, or decreasing during the study. Negative ethanol breath tests were required at screening and all subsequent visits.

Subjects were excluded if they had any clinically relevant findings in their medical history, including a history or presence of any significant illness, past or planned abdominal surgery, a history of hypotension, or a history of acute asthma or other obstructive airway disease. Subjects who consumed >20 cigarettes per day or were unable to abstain from smoking for at least 10 hours were excluded. Subjects who had a self-reported history of dependence within the previous two years, or who participated in a drug rehabilitation program at any time were also excluded. Subjects demonstrating drug/alcohol dependence as classified by Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) clinical interviews were also excluded.

Study Design

This study was conducted in 2013, in accordance with a 2013 FDA draft guidance on the evaluation of abuse-deterrent opioids [21]. This study remains consistent with the final version of that guidance, made available in April 2015 [22]. This was a single-center, double-blind,

positive- and placebo-controlled, randomized, four-treatment crossover study. The study protocol and its informed consent form were reviewed and approved by an institutional review board, and the study was conducted according to current Good Clinical Practice guidelines and all relevant parts of the United States Code of Federal Regulations Title 21. Prior to study entry, all subjects provided written informed consent. The study consisted of five phases: screening, dose selection, qualification, treatment, and follow-up (Figure 1). Following the screening phase, eligible subjects underwent a naloxone challenge to exclude subjects who were physically dependent on opioids.

Intranasal Hydrocodone Dose-Selection

Because the nasal bioavailability of hydrocodone was not known, a subset of subjects completed a dose selection phase to identify an appropriate intranasal dose of hydrocodone powder that would result in sufficient differentiation on a subjective measure of drug liking between placebo and hydrocodone in the study population. Doses of 40- or 60-mg hydrocodone powder and placebo were intranasally administered in a double-blind design in the dose selection phase. Subjects who participated in the dose-selection phase were not eligible to participate in the subsequent qualification and treatment phases of the main study.

Qualification Phase

In the qualification phase, eligible subjects self-administered 60 mg of hydrocodone powder and placebo powder intranasally in a double-blind crossover design, with an approximate 24-hour washout period between treatments. To qualify for the treatment phase, subjects were required to have acceptable responses to placebo and hydrocodone powder on visual analog scales (VASs; 0–100) for various subjective pharmacodynamic (PD) measures. Peak scores in response to hydrocodone powder had to be greater than placebo by defined increments for "At this Moment" Drug Liking VAS, a difference of $\geq$15 points, or 30%; Overall Drug Liking VAS, a difference of $\geq$10 points, or 20%; and Feeling High VAS, a difference of $\geq$30 points, or 30%. In addition, peak scores in response to hydrocodone powder needed to be $\geq$75 points for "At this Moment" Drug Liking VAS, $\geq$70 points for Overall Drug Liking VAS, and $\geq$40 points for Feeling High VAS. In addition, subjects were eligible to proceed to the treatment phase if they were able to tolerate hydrocodone based on

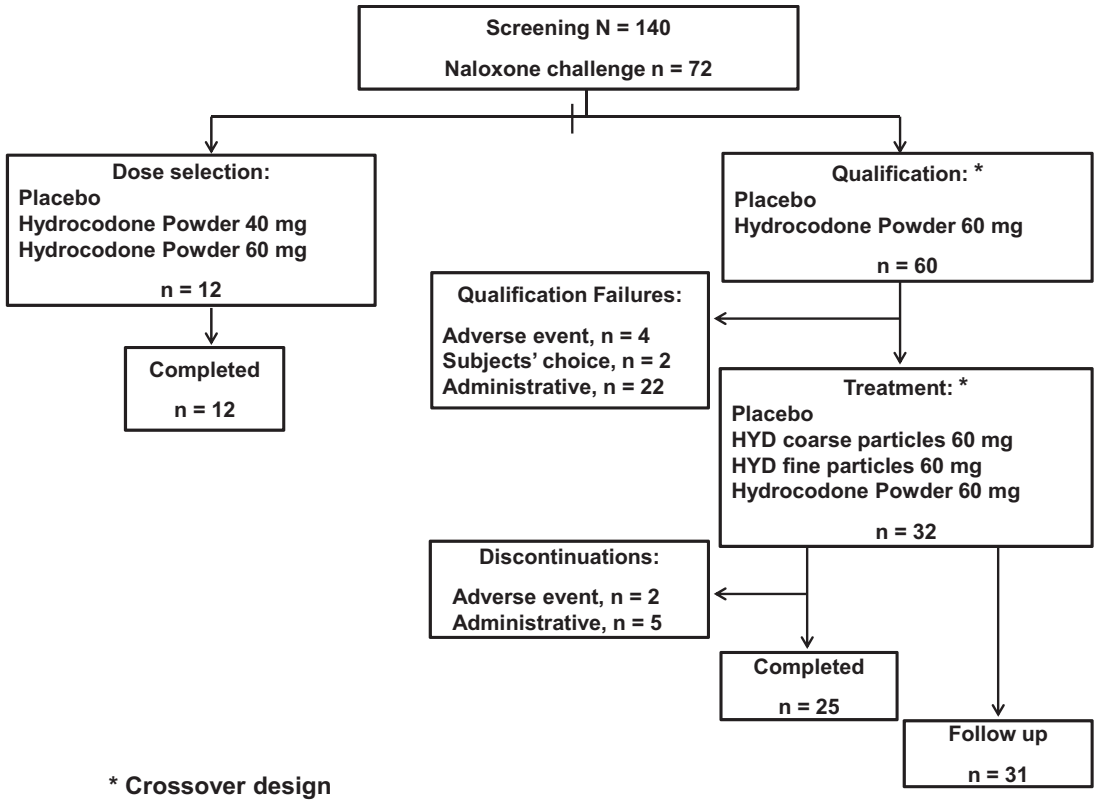

Figure 1 Study design.

available safety data and were judged by the clinical staff to be capable of successfully completing the study.

Treatment Phase

Subjects who successfully completed the qualification phase were eligible to proceed to the treatment phase, with a ≥72-hour washout between the qualification and treatment phases. Subjects self-administered intranasal doses of the four study treatments in a double-blind, randomized, four-period, four-treatment crossover design. The four treatments were hydrocodone powder 60 mg, HYD coarse particles 60 mg, HYD fine particles 60 mg, or placebo.

Treatment administrations were separated by a washout period of five to seven days. The follow-up phase occurred between three and seven days after the last study drug administration. To help maintain blinding, all study treatments were dispensed in amber vials with a preinserted straw for intranasal administration.

Pharmacodynamic Measurements

During the treatment phase, PD assessments were collected over 36 hours following treatment administration. Subjects were asked to quantify treatment effects on either a 100-point bipolar (i.e., 50 = neutral response) or unipolar (i.e., 0 = no effect) VAS (Table 1). Bipolar measurements included "At this Moment" Drug Liking, Overall Drug Liking, and Drowsiness/Alertness. Unipolar measurements included Take Drug Again, Feeling High, Good Effects, Bad Effects, Feeling Sick, and Any Effects. The primary PD measures in this study were the "At this Moment" Drug Liking VAS and Feeling High VAS.

Table 1 Bipolar and unipolar visual analog scales

Category	Subjective Measure	VAS Type	0–100 mm VAS 0 50 100
Balance of Effects	"At this Moment" Drug Liking	Bipolar	At this moment, my liking for this drug is: Strong Disliking Neutral Strong Liking
	Overall Drug Liking		Overall, my liking for this drug is: Strong Disliking Neutral Strong Liking
	Take Drug Again	Unipolar	I would take this drug again: Definitely Not Definitely So
Positive Effects	Feeling High		I am feeling high: Definitely Not Definitely So
	Good Effects		I can feel good drug effects: Definitely Not Definitely So
Negative Effects	Bad Effects		I can feel bad drug effects: Definitely Not Definitely So
	Feeling Sick		I am feeling sick: Definitely Not Definitely So
Other Subjective Effects	Any Effects		I can feel any drug effect: Definitely Not Definitely So
Sedative Effects	Drowsiness/ Alertness	Bipolar	My mental state is: Very Drowsy Neither drowsy nor alert Very Alert

VAS = visual analog scale.

To estimate the subject's perception of drug value, a theoretical Subjective Drug Value (SDV) was determined by asking subjects to choose between receiving the same drug or a specified amount of money. Depending on the answer to each question, the subject was asked follow-up questions to ultimately determine the crossover monetary value (i.e., SDV) at which the subject was indifferent to choosing drug or choosing money. Pupil diameter, measured with an infrared digital pupillometer (NeurOptics Inc., Irvine, CA, USA), was included as an objective measure of opioid agonist effect.

Pharmacodynamic measures were assessed predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 13, 14, 15, 24, and 36 hours postdose. Global measures (Overall Drug Liking VAS, Take Drug Again VAS, and SDV) were assessed at 12 and 24 hours postdose.

Additional PD assessments included observer- and subject-rated assessment of nasal irritation. Observers rated any external nasal irritation, nasal congestion, or nasal discharge, and subjects rated any nasal burning, need to blow nose, nasal discharge, facial pain or pressure, or nasal congestion. Both observers and subjects used a six-point rating scale (0 = Not observed/No problem; 1 = Very Mild Problem; 2 = Mild/Slight Problem; 3 = Moderate Problem; 4 = Severe Problem; 5 = Very Severe Problem/"As Bad as Can Be"). Observer-rated intranasal irritation was measured predose and at 0.5, 1, 2, 3, 4, 6, 8, and 36 hours postdose. In addition, an ear, nose, and throat specialist conducted endoscopy and intranasal photography predose and 0.5 hours postdose, and assessed intranasal irritation using the observer-rated scale. Intranasal irritation was monitored and recorded by subjects predose and during the 36-hour postdose period, at the same timepoints as the other PD measures.

Mean maximum and minimum effect scores (E_{max} and E_{min}, respectively) were calculated for subjective PD measures (VAS assessments and observer- and subject-rated assessment of intranasal irritation), as appropriate. In addition, each subject was assessed for percent reduction in "At this Moment" Drug Liking VAS between HYD and hydrocodone powder as outlined in the recent FDA guidance [22]. For the objective measure of pupillometry, maximum pupil constriction (MPC) was measured.

Pharmacokinetic Measurements

During the treatment phase, blood samples were collected predose and at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 13, 14, 15, 24, and 36 hours after study drug administration. Plasma concentrations of hydrocodone were determined using high-performance liquid chromatography with tandem mass spectrometry. The lower limit of quantitation (LLOQ) for hydrocodone was 0.1 ng/mL.

Pharmacokinetic parameters for each subject were derived using a noncompartmental (model-independent) approach. For the analysis, actual blood sampling times were used. Pharmacokinetic parameters, including maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the concentration time curve to last quantifiable concentration (AUC_t), area under the concentration time curve from time zero to infinity (AUC_{inf}), terminal phase half-life ($t_{1/2}$), and the average rate of increase in plasma hydrocodone concentration between dosing and T_{max}, defined as the ratio of C_{max}/T_{max}, were calculated.

Safety Measurements

Safety was assessed by using recorded adverse events (AEs), clinical laboratory results, vital signs, physical examinations, and conventional 12-lead electrocardiograms. Adverse events were recorded from screening through follow-up. Adverse events were reported using the Medical Dictionary for Regulatory Activities (MedDRA) v16.0 system organ class and preferred terms.

Statistical Analysis

Pharmacodynamic analyses were performed on all subjects who completed all visits of the treatment phase and did not have any major protocol violations that would impact PD results. Most PD endpoints for the treatment phase were analyzed with a mixed-effect model for a crossover study. The model included treatment, period, sequence, and first-order carry-over effects as fixed effects, baseline (predose) measurements as covariates, where appropriate, and subject nested within treatment sequence as a random effect. Tests for nonnormality and homogeneity were conducted and nonparametric methods were employed, if necessary. Statistical comparisons included intranasal hydrocodone powder vs placebo (study validity), intranasal HYD (coarse and fine particles) vs hydrocodone powder, intranasal HYD (coarse and fine particles) vs placebo, and intranasal HYD coarse particles vs HYD fine particles.

Calculation of percent reduction of "At this Moment" drug liking VAS E_{max} of HYD coarse or HYD fine particles compared with hydrocodone powder used the following formula (where C = control, hydrocodone powder; T = test drugs HYD, coarse or fine particles; P = placebo):

This method is consistent with the 2015 FDA guidance [22].

$$\%\,reduction = \begin{cases} \dfrac{C-T}{C-50} \times \left(1 - \dfrac{P-50}{50}\right) \times 100\%, & if\ P > 55; \\ \dfrac{C-T}{C-50} \times 100\% & if\ P \geq 55; \end{cases}$$

Pharmacokinetic analyses were performed on all subjects who were randomized, received study drug, and had at least one valid PK parameter. Plasma

concentrations of hydrocodone and PK parameters were summarized using descriptive statistics (mean, median, standard deviation [SD], range [min, max], and % coefficient of variation). All subjects who received ≥1 dose of study drug during the treatment phase were included in the safety analysis. Descriptive statistics were calculated for demographics and baseline characteristics. Safety results were summarized as the number and percentage of subjects who experienced ≥1 adverse events.

Based on previous experience with oxycodone, a sample size of 24 completed subjects had greater than 95% power to detect a significant difference between intranasal hydrocodone powder and placebo on both the "At this Moment" Drug Liking VAS and Feeling High VAS. Statistical analyses were performed using Statistical Analysis System (SAS®, version 9.3) using a Microsoft Windows 2008 x64-bit R2 operating system.

Results

Disposition and Subject Characteristics

During enrollment, 140 subjects were screened and 72 were eligible to proceed. Of these, 12 subjects completed the dose-selection phase, and the remaining 60 subjects participated in the qualification phase. Thirty-two of the subjects who met the qualification criteria were randomized to the treatment phase. Of these, one subject was withdrawn prior to receiving any study drug due to bradycardia and presyncope, one subject discontinued from the treatment phase after dosing due to ventricular tachycardia (n = 1), and five subjects discontinued for administrative reasons (e.g., for a logistical, nonmedical reason). The ventricular tachycardia treatment emergent AE resolved less than 1 minute after onset without intervention and was assessed as mild and possibly related to study drug. A follow-up ECG was normal. Twenty-five subjects completed all four treatment periods (Figure 1).

Overall, the mean age (SD; range) was 38.9 (10.21; 21–54) years. Subjects were primarily white (64.5%), male (90.3%), and had a mean BMI (SD; range) of 25.3 kg/m^2 (2.42; 20.6–29.9). All subjects had previous experience with recreational opioid use. Subjects also reported experience with cannabinoids (77.4%), stimulants (71%), hallucinogens (38.7%), depressants (16.1%), and dissociative anesthetics (12.9%).

Intranasal Hydrocodone Dose-selection Phase

Both 40- and 60-mg intranasal doses of hydrocodone powder (positive control) were safe and well tolerated; however, only the 60-mg dose elicited sufficient levels of discrimination vs placebo in opioid-experienced abusers and thus was selected for the qualification and treatment phases.

Qualification Phase

During the qualification phase, peak VAS scores (mean [SD]) for hydrocodone powder 60 mg compared with placebo for "At this Moment" Drug Liking were 97.0 (6.8) vs 50.6 (0.5), where 100 = strong liking; 50 = neutral; 0 = strong disliking. Corresponding scores for Feeling High VAS were 97.8 (4.9) vs 2.3 (10.2), respectively, where 100 = maximum high feeling and 0 = no high feeling.

Treatment Phase

Pharmacodynamic Parameters

Subjective Measures

Study validity was confirmed as hydrocodone powder showed significantly higher mean "At this Moment" Drug Liking VAS E_{max} compared with placebo (90.4 vs 50.6, respectively; $P < 0.001$). Both HYD treatments (coarse and fine particles) showed significantly lower mean "At this Moment" Drug Liking VAS E_{max} values compared with hydrocodone powder ($P < 0.001$) but significantly higher E_{max} values compared with placebo ($P < 0.001$). Mean "At this Moment" Drug Liking VAS scores were highest 1 hour after hydrocodone powder administration and remained in the "liking" range (> 50 on the bipolar VAS) through eight hours postdose, before returning to near neutral or 50 on the VAS (Figure 2A). For both HYD coarse and HYD fine particle treatments, "At this Moment" Drug Liking VAS scores minimally increased (< 10 points) between one and four hours postdose, while placebo scores remained around neutral throughout the sampling period.

An analysis of the percent reduction for HYD coarse and HYD fine particles relative to hydrocodone powder for each subject for "At this Moment" Drug Liking VAS E_{max} values is shown in Figure 2B. Compared with hydrocodone powder, 68%, 64%, and 44% of subjects showed a reduction in "At this Moment" Drug Liking VAS E_{max} of at least 30%, 50%, and 90%, respectively, following administration of HYD coarse particles. Compared with hydrocodone powder, 72%, 64%, and 36% of subjects showed a reduction in Drug Liking VAS E_{max} of at least 30%, 50%, and 90%, respectively, following administration of HYD fine particles.

Hydrocodone powder Feeling High VAS scores were markedly higher than placebo (mean E_{max} 93.3 vs 6.3, respectively) (Figure 2C). HYD fine or HYD coarse particles led to significantly lower E_{max} values compared with hydrocodone powder ($P < 0.001$ for both comparisons) and significantly higher E_{max} values than placebo ($P \leq 0.001$ for both comparisons).

Both HYD coarse and HYD fine particles had significantly lower VAS E_{max} scores than hydrocodone powder for "At this Moment" Drug Liking, Feeling High, Good Effects, and Any Effects ($P < 0.001$; Table 2). In addition, the Bad

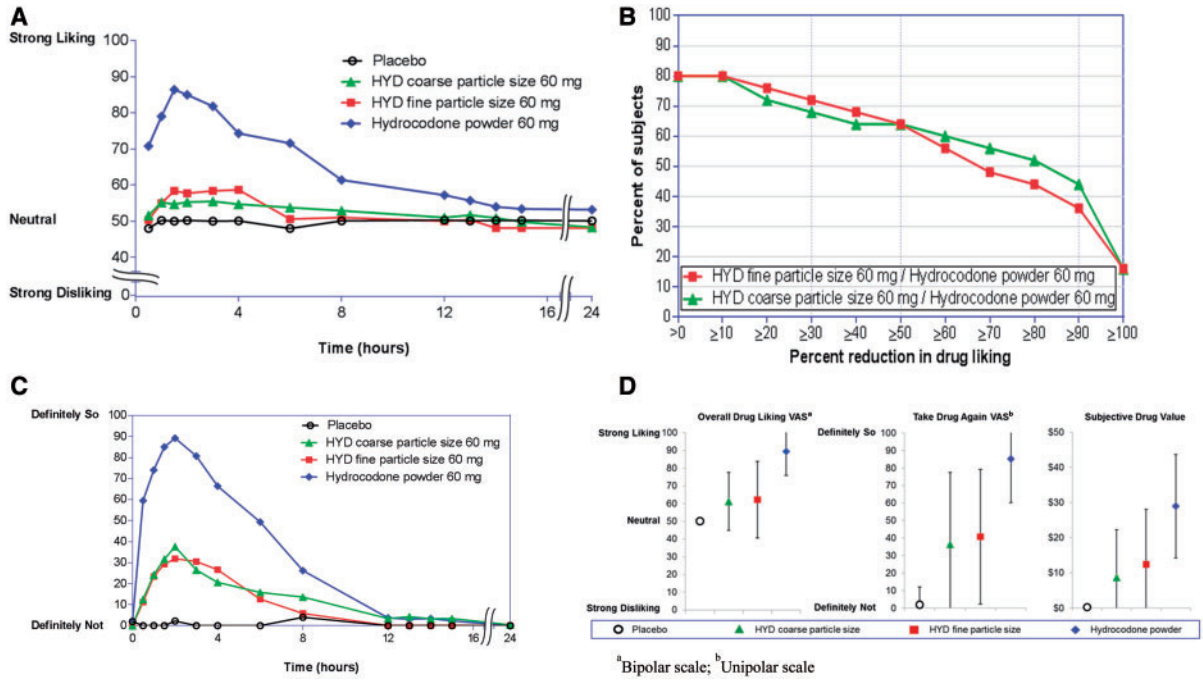

Figure 2 Subjective measures. (A) Mean VAS scores for "At this Moment" Drug Liking. Drug liking was measured on a bipolar scale with values ranging from 0 to 100 where 0 represents maximum disliking, 100 represents maximum liking, and 50 represents a neutral response of neither like nor dislike. (B) Percent reduction plot of "At this Moment" drug liking VAS E_{max} HYD coarse/fine particle size compared with hydrocodone powder. (C) Mean VAS scores for Feeling High. Subjects rated the statement "I am feeling high" on a unipolar scale of 0–100 where 0 represents definitely not and 100 represents definitely so. (D) Mean (standard deviation) E_{max} scores for Overall Drug Liking VAS, Take Drug Again VAS, and Subjective Drug Value; E_{max} = maximum effect; HYD = hydrocodone bitartrate once-daily tablet; VAS = visual analog scale.

Effects VAS E_{max} for HYD fine particles was significantly lower than for hydrocodone powder ($P = 0.037$), while the Drowsiness/Alertness VAS E_{min} for HYD fine particles was significantly higher than for hydrocodone powder ($P = 0.011$), indicating less drowsiness.

Mean Overall Drug Liking VAS, Take Drug Again VAS, and SDV E_{max} scores were significantly higher for hydrocodone powder compared with HYD coarse particles, HYD fine particles, and placebo ($P < 0.001$ for all) (Figure 2D). There were no significant differences in E_{max} for these global measures between HYD coarse and HYD fine particles. Mean Overall Drug Liking VAS, Take Drug Again VAS, and SDV scores for each treatment at 12 and 24 hours are shown in Table 3.

Pupillometry

Maximum pupil constriction was greater for hydrocodone powder than HYD coarse or HYD fine particles (Figure 3). The mean (SD) MPC values were 0.88 (0.62), 1.55 (0.86), 1.43 (0.72), and 2.52 (0.86) mm for placebo, HYD coarse particles, HYD fine particles, and hydrocodone powder, respectively ($P < 0.001$ comparing HYD coarse and HYD fine particles vs hydrocodone powder).

Intranasal Tolerability

Subject-rated intranasal irritation mean and median E_{max} scores for hydrocodone powder were low and similar to placebo. Insufflation of either HYD coarse or HYD fine particles led to significantly higher E_{max} scores compared with hydrocodone powder ($P \leq 0.049$) for the subject-rated assessments of need to blow nose, runny nose/nasal discharge, facial pain/pressure, and nasal congestion. Insufflation of either HYD coarse or fine particles led to significantly higher E_{max} scores compared with placebo ($P \leq 0.014$) for need to blow nose, runny nose/nasal discharge, nasal congestion, and burning subscales. A significant difference from placebo in the E_{max} for facial pain/pressure was seen only with HYD coarse particles ($P = 0.032$).

Similar to the subject-rated scores, E_{max} scores for observer-rated intranasal irritation were relatively low following administration of hydrocodone powder and placebo. However, insufflation of hydrocodone powder was associated with significantly higher E_{max} compared with placebo for nasal irritation ($P = 0.034$). Insufflation of either HYD coarse or HYD fine particles led to significantly higher E_{max} values on all observer-rated measures compared with hydrocodone powder and placebo ($P < 0.001$

Table 2 Primary and secondary pharmacodynamics measures

	Placebo (N = 25)	HYD coarse particles 60 mg (N = 25)	HYD fine particles 60 mg (N = 25)	Hydrocodone powder 60 mg (N = 25)	*P* value[a] vs hydrocodone powder: HYD coarse particles	*P* value[a] vs hydrocodone powder: HYD fine particles
"At this moment" drug liking, E_{max}						
Mean (SD)	50.6 (0.5)	65.4 (18.4)	66.8 (18.4)	90.4 (13.2)	<0.001	<0.001
Median	51.0	56.0	61.0	100.0		
Feeling high, E_{max}						
Mean (SD)	6.3 (16.4)	44.1 (42.8)	38.8 (41.5)	93.3 (15.3)	<0.001	<0.001
Median	0.0	50.0	16.0	100.0		
Good effects, E_{max}						
Mean (SD)	4.7 (13.9)	47.5 (44.8)	38.5 (40.1)	94.8 (13.8)	<0.001	<0.001
Median	0.0	61.0	15.0	100		
Bad effects, E_{max}						
Mean (SD)	4.2 (14.1)	9.9 (20.3)	9.1 (23.1)	27.0 (42.1)	0.115	0.037
Median	0.0	0.0	0.0	1.0		
Feeling sick, E_{max}						
Mean (SD)	7.0 (22.0)	11.1 (23.8)	5.1 (15.8)	19.4 (34.0)	NS	NS
Median	0.0	0.0	0.0	0.0		
Any effects, E_{max}						
Mean (SD)	2.0 (9.4)	44.3 (44.0)	39.4 (41.2)	93.0 (15.7)	<0.001	<0.001
Median	0.0	22.0	17.0	100		
Drowsiness/alertness, E_{min}						
Mean (SD)	48.8 (19.3)	33.6 (19.0)	39.9 (23.6)	25.9 (22.6)	0.560	0.011
Median	50.0	42.0	44.0	29.0		

E_{max} = maximum effect; E_{min} = minimum effect; HYD = hydrocodone bitartrate once-daily tablet; NS = not significant; SD = standard deviation; VAS = visual analog scale.

[a]Pairwise comparisons were only presented if the treatment effect *P* value was significant. For most measures, overall treatment effect was assessed using Friedman's test. Pairwise treatment comparisons were assessed using the Wilcoxon sign-rank test on the within-subject differences. Drowsiness/Alertness *P* values were estimated based on the least squares mean difference and corresponding 95% confidence intervals.

for all). In addition, nasal administration of HYD fine particles was associated with significantly higher E_{max} values compared with HYD coarse particles for nasal congestion and irritation ($P \leq 0.034$), but not for discharge.

Pharmacokinetic Parameters

In contrast with HYD coarse and HYD fine particle doses, all subjects successfully insufflated 100% of hydrocodone powder and placebo doses. For HYD coarse and HYD fine particles, only 21% and 18% of subjects, respectively, were able to successfully insufflate 100% of the dose. The mean percent of dose insufflated was 54.3% and 65.2% for HYD coarse and fine particles, respectively.

Mean hydrocodone plasma concentration vs time profiles for the three active intranasal treatments are shown in Figure 4. The mean C_{max} was higher following hydrocodone powder (106 ng/mL) compared with HYD coarse (27.5 ng/mL) and HYD fine (36.5 ng/mL) particles (Table 4). The median T_{max} for HYD coarse and fine particles were 4.1 and 3.1 hours, respectively, compared with 1.6 hours for hydrocodone powder. Hydrocodone systemic exposure (mean AUC_{inf}) was decreased by 59% and 54% following administration of HYD coarse or fine particles, respectively, compared with hydrocodone powder insufflation. The mean C_{max}/T_{max} values following HYD coarse and HYD fine nasal administration were considerably lower (9.5 and 13.4 ng/mL/h, respectively) than that following hydrocodone powder administration (82.0 ng/mL/h) (Table 4).

Safety

Intranasal administration of the four study treatments was not associated with any serious AEs (Table 5). The incidence of treatment-related AEs was lowest in the HYD coarse particles group (64.3%), followed by the HYD fine particles (78.6%) and hydrocodone powder groups (96.3%). Following administration of placebo, only 7.4% of subjects experienced an AE. The majority of AEs was related to study drug and were generally mild in severity.

Table 3 Overall subjective drug effects at 12 and 24 hours

Pharmacodynamic measure	N	12 hours Mean (SD)	24 hours Mean (SD)
Overall drug liking VAS			
Placebo	25	50.2 (0.5)	50.0 (0.4)
HYD coarse 60 mg	25	60.8 (16.4)	52.8 (21.4)
HYD fine 60 mg	25	59.4 (24.4)	55.8 (22.5)
Hydrocodone powder 60 mg	25	88.2 (13.4)	83.4 (19.0)
Take drug again VAS			
Placebo	25	0.0 (0.0)	2.0 (10.0)
HYD coarse 60 mg	25	33.1 (40.2)	29.5 (38.3)
HYD fine 60 mg	25	36.4 (38.1)	34.6 (36.4)
Hydrocodone powder 60 mg	25	84.7 (25.1)	83.9 (25.6)
Subjective drug value ($)			
Placebo	25	0.25 (0.0)	0.25 (0.0)
HYD coarse 60 mg	25	7.8 (13.2)	7.4 (13.0)
HYD fine 60 mg	25	12.0 (15.7)	11.0 (15.8)
Hydrocodone powder 60 mg	25	27.7 (14.9)	27.8 (14.4)

HYD = hydrocodone bitartrate once-daily tablet; SD = standard deviation; VAS = 100 mm visual analog scale.

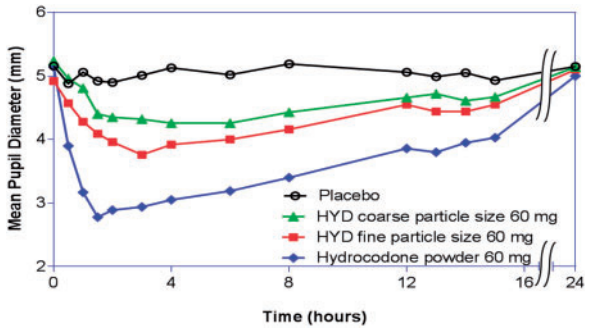

Figure 3 Pupillometry. HYD = hydrocodone bitartrate once-daily tablet.

Consistent with opioid agonists, euphoric mood and somnolence were the most common AEs across active treatments. Euphoric mood was most commonly reported following administration of hydrocodone powder (88.9%, 24 subjects), in addition to pruritus (55.6%, 15 subjects) and somnolence (25.9%, seven subjects). The most common AE for HYD coarse particles and HYD fine particles was nasal congestion (28.6% and 50%, respectively). The majority of subjects recovered from AEs with no action required, except for five subjects who were treated with concomitant paracetamol. One subject experienced mild ventricular tachycardia following administration of HYD coarse particles which led to discontinuation from the study. This AE resolved less than 1 minute after onset without intervention and was assessed as 'possibly related' to study drug. A follow-up ECG (approximately six days after the AE) was normal. There were no deaths in this study.

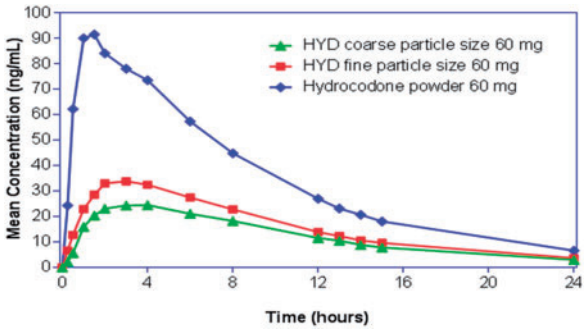

Figure 4 Mean plasma concentrations (ng/mL) of hydrocodone treatments. HYD = hydrocodone bitartrate once-daily tablet.

Discussion

Opioid analgesics serve an important role in the management of moderate-to-severe chronic pain; however, there is a widespread abuse and misuse in the United States and across the world [23,24]. Currently, there is an emphasis on the development of opioid formulations with abuse-deterrent properties to minimize abuse and misuse as part of a multifaceted approach to combating this public health problem. One category of formulations designed to deter abuse are those that incorporate physicochemical barriers which hinder chewing, crushing, cutting, and other physical manipulations, and inhibit extraction of the opioid in common solvents such as water or alcohol [22]. Interpretation of abuse potential results for different dosage form manipulations must take into account the time, effort, equipment, and knowledge required to produce the manipulated result.

To evaluate the effectiveness of various methods of physical manipulation of HYD tablets that abusers might employ, two manipulation methods were studied. One method of manipulation represented the FDA Guidance requirement for particle size reduction and the other represented real-world relevance. Due to the intrinsic hardness of HYD tablets, there were challenges in standardizing the manipulation methods in order to provide reproducible particle size reduction. Consistent with the FDA Guidance requirement, the HYD fine particle size treatment was included to represent the manipulation that would cause the highest release of the opioid and the highest plasma opioid concentrations. Reproducible production of fine particles from HYD tablets required the use of a laboratory-grade analytical mill, and consequently is not representative of a practical, real-world manipulation. Therefore, the HYD coarse-particle size treatment was included to represent greater real-world relevance. The coarse-particle size was prepared using a standardized method of manipulation involving manual implements that is more likely to be representative of real-world manipulations of HYD.

A preliminary, dose-selection phase determined 60 mg of hydrocodone provided sufficient levels of

Table 4 Summary of mean hydrocodone pharmacokinetic parameters

Parameter	HYD coarse particles 60 mg (N = 27)[a]	HYD fine particles 60 mg (N = 27)	Hydrocodone powder 60 mg (N = 27)
AUC_{inf} (h*ng/mL)Mean (SD)	379 (289)	421 (211)	918 (304)
C_{max} (ng/mL)Mean (SD)	27.5 (24.9)	36.5 (18.4)	106 (37.2)
T_{max} (h)Median (range)	4.1 (0.25–13.1)	3.1 (1.1–8.1)	1.6 (0.63–6.1)
$t_{1/2}$ (h)Median (range)	5.7 (4.6–8.0)	5.9 (4.9–8.1)	6.0 (4.9–7.6)
C_{max}/T_{max} (ng/mL/h)Mean (SD)	9.5 (12.2)	13.4 (9.0)	82.0 (49.9)

n = 23 for $t_{1/2}$, AUC_{inf}.
AUC_{inf} = area under the plasma concentration vs time curve extrapolated to infinity; C_{max} = maximum plasma concentration; HYD = hydrocodone bitartrate once-daily tablet; SD = standard deviation; $t_{1/2}$ = terminal elimination half-life; T_{max} = time to maximum plasma concentration.

Table 5 Summary of adverse events

	Placebo (N = 27)	HYD coarse particles 60 mg (N = 28)	HYD fine particles 60 mg (N = 28)	Hydrocodone powder 60 mg (N = 27)
Preferred term	Number of subjects (%)			
Subjects reporting ≥1 AE	2 (7.4)	18 (64.3)	22 (78.6)	26 (96.3)
Euphoric mood	0	7 (25.0)	9 (32.1)	24 (88.9)
Pruritus	0	0	4 (14.3)	15 (55.6)
Somnolence	0	2 (7.1)	5 (17.9)	7 (25.9)
Nasal discomfort	0	1 (3.6)	0	3 (11.1)
Fatigue	0	0	0	2 (7.4)
Headache	0	6 (21.4)	2 (7.1)	2 (7.4)
Nasal congestion	0	8 (28.6)	14 (50.0)	2 (7.4)
Nausea	0	2 (7.1)	1 (3.6)	2 (7.4)
Rhinorrhoea	0	1 (3.6)	0	2 (7.4)
Dizziness	0	1 (3.6)	2 (7.1)	1 (3.7)
Nasal obstruction	0	2 (7.1)	2 (7.1)	0

AE = adverse event; HYD = hydrocodone bitartrate once-daily tablet.

discrimination vs placebo in non-dependent recreational opioid users and was the dose used during the qualification and treatment phases of this study. In the treatment phase, statistically significant differences between hydrocodone powder and placebo for the primary measures of "At this Moment" Drug Liking and Feeling High were observed, confirming the sensitivity of the measures and study validity. The physicochemical properties of HYD significantly reduced hydrocodone abuse potential when HYD was insufflated either as coarse or fine particles. This effect was demonstrated by significantly lower E_{max} for Drug Liking and Feeling High VAS. The Drug Liking reduction analysis, where a majority of subjects showed a reduction in drug liking for the HYD coarse and fine particles compared with hydrocodone powder, supports the comparisons of E_{max} scores. In addition, secondary measures of Balance of Effects (Overall Drug Liking VAS, Take Drug Again VAS, and SDV); Positive Effects (Good Effects VAS), Negative Effects (Bad Effects VAS), Sedative Effects (Drowsiness/Alertness VAS), and the Any Effects VAS also showed statistically significant differences between HYD coarse or fine particles and hydrocodone powder.

Consistent with these reductions in subjective effects, insufflation of HYD coarse or HYD fine particles produced opioid-induced pupil constriction that were significantly lower than those produced by hydrocodone powder. Subjects had greater difficulty insufflating both HYD treatments and reported greater nasal irritation in comparison with hydrocodone powder. Both HYD coarse and HYD fine particles had significantly higher E_{max} values for observer-rated assessments (nasal congestion, nasal irritation, and nasal discharge) and subject-rated assessments (need to blow nose, nasal discharge, facial pain, and nasal congestion) of intranasal irritation measures relative to hydrocodone powder.

The PK profile for insufflated HYD coarse and fine particles showed reduced C_{max} and delayed T_{max} in comparison with hydrocodone powder. Here, mean C_{max} of

HYD coarse and fine particle sizes was reduced by 75% and 66%, respectively, to that of hydrocodone powder, while median T_{max} was 158% and 96% longer, respectively. These differences may be associated with lower abuse potential, because the rate of increase (i.e., C_{max}/T_{max}) in opioid plasma concentrations affects response—the faster the increase in opioid plasma concentrations, the more likely it is to be abused [25]. In addition, compared with insufflated hydrocodone powder, overall exposure to hydrocodone was reduced by more than half following administration of HYD coarse or HYD fine particles. These PK results likely reflect, in part, the incomplete insufflation of manipulated HYD, which was for a common occurrence both HYD coarse and HYD fine particles but did not occur for hydrocodone powder. In addition, the slower onset of effects may reflect retention of some of the controlled-release properties of the formulation, despite physical manipulation of the HYD tablet.

Adverse events were generally mild in severity and consistent with those of opioids [26]. Intranasal administration of HYD coarse and fine particles produced lower rates of euphoric mood and somnolence compared with hydrocodone powder, but higher levels of nasal irritation, in agreement with the PD assessments.

This study does have limitations inherent to any assessment of a formulation with abuse-deterrent properties [27]. As this was carried out in a controlled, clinical environment, the abuse-deterrent potential in the real world cannot be directly determined. The relationships between reductions in abuse potential measured in controlled settings and reductions in abuse liability in real-world settings remain to be fully elucidated. Further, the complex socioeconomic factors that also affect abuse liability over time and across geographic space further complicate the direct translation of abuse potential reduction into expectations of real-world effects. Another limitation is that, although careful consideration was given to blinding study treatments (e.g., use of tinted vials with preinserted tubes for insufflation), it was not possible to completely prevent subjects from making certain comparisons between study treatments, thus potentially compromising the blinding and introducing bias.

Consistent with FDA's 2015 guidance for industry on the development and assessment of abuse deterrent technologies [22], HYD has shown through premarketing studies that its abuse-deterrence properties are expected to reduce abuse of the drug by chewing and then taking orally, or by crushing and snorting or injecting [19]. Laboratory based in vitro manipulation and extraction studies (Category 1) demonstrated that HYD has physical and chemical properties that are expected to deter intranasal and intravenous abuse [19]. Clinical studies of abuse potential (Category 3), which include the present study as well as an oral abuse potential study, along with support from the in vitro studies, also indicate that HYD has physicochemical properties that are expected to reduce intranasal abuse and oral abuse when chewed [19]. However, abuse of HYD by the intravenous, intranasal, and oral routes is still possible. Ultimately, the full abuse-deterrent potential of HYD cannot be completely ascertained until the product is introduced into the market and long-term postmarketing epidemiologic studies are performed.

Conclusion

Based upon the pattern of responses on subjective measures of drug liking and intranasal irritation, the intranasal abuse potential of HYD, when manipulated to produce coarse or fine particles, is significantly reduced compared with the hydrocodone powder. The time course of subjective opioid effects was generally consistent with the time course of both objective opioid effects and systemic hydrocodone concentrations. Taken together, the results of the current study suggest that the physicochemical properties of HYD tablets provide barriers that deter the effective physical manipulation of HYD tablets for the purpose of insufflation in order to achieve a "high" or euphoric effect. Postmarketing studies of HYD are needed to assess the real-world abuse-deterrent effects of HYD.

Acknowledgments

This study was wholly funded by Purdue Pharma L.P. (Stamford, CT). Medical writing and editorial assistance were provided by Meryl Gersh, PhD, of QSci Communications, LLC (King of Prussia, PA), and funded by Purdue Pharma L.P.

References

1 Walsh SL, Nuzzo PA, Lofwall MR, Holtman JR, Jr. The relative abuse liability of oral oxycodone, hydrocodone and hydromorphone assessed in prescription opioid abusers. Drug Alcohol Depend 2008;98:191–202.

2 Drug Enforcement Administration. US Department of Justice. Drug Fact Sheet: Hydrocodone. Available at: www.justice.gov/dea/druginfo/drug_data_sheets/Hydrocodone.pdf (accessed August 20, 2014).

3 Von Korff M, Saunders K, Thomas Ray G, et al. De facto long-term opioid therapy for noncancer pain. Clin J Pain 2008;24:521–7.

4 US Food and Drug Administration. FDA Drug Safety Communication: Prescription Acetaminophen Products to be Limited to 325 mg Per Dosage Unit; Boxed Warning Will Highlight Potential for Severe Liver Failure. 2011. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm239821.htm (accessed August 20, 2014).

5 Ostapowicz G, Fontana RJ, Schiodt FV, et al. Results of a prospective study of acute liver failure

at 17 tertiary care centers in the United States. Ann Intern Med 2002;137:947–54.

6 Lee WM. Acetaminophen toxicity: Changing perceptions on a social/medical issue. Hepatology 2007;46: 966–70.

7 Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. Clin Ther 2001;23:1296–310.

8 Office of the National Drug Control Policy. Epidemic: Responding to America's Prescription Drug Abuse Crisis. Washington, DC: Executive Office of the President of the United States; 2011. Available at: http://www.whitehouse.gov/sites/default/files/ondcp/policy-and-research/rx_abuse_plan.pdf (accessed February 16, 2015).

9 Sehgal N, Manchikanti L, Smith HS. Prescription opioid abuse in chronic pain: A review of opioid abuse predictors and strategies to curb opioid abuse. Pain Physician 2012;15:ES67–92.

10 Butler SF, Black RA, Cassidy TA, Dailey TM, Budman SH. Abuse risks and routes of administration of different prescription opioid compounds and formulations. Harm Reduct J 2011;8:29.

11 Katz N, Dart RC, Bailey E, et al. Tampering with prescription opioids: Nature and extent of the problem, health consequences, and solutions. Am J Drug Alcohol Abuse 2011;37:205–17.

12 Drug Enforcement Agency, Office of Diversion Control, Drug and Chemical Evaluation Section: Hydrocodone (Trade Names: Vicodin, Lortab, Lorcet-HD, Hycodan, Vicoprofen). Available at: http://www.deadiversion.usdoj.gov/drug_chem_info/hydrocodone.pdf (accessed February 16, 2015).

13 Atluri S, Sudarshan G, Manchikanti L. Assessment of the trends in medical use and misuse of opioid analgesics from 2004 to 2011. Pain Physician 2014;17:E119–28.

14 Hays L, Kirsh KL, Passik SD. Seeking drug treatment for OxyContin abuse: A chart review of consecutive admissions to a substance abuse treatment facility in Kentucky. J Natl Compr Canc Netw 2003;1:423–8.

15 Raffa RB, Pergolizzi JV, Jr. Opioid formulations designed to resist/deter abuse. Drugs 2010; 70:1657–75.

16 Budman SH, Grimes Serrano JM, Butler SF. Can abuse deterrent formulations make a difference? Expectation and speculation. Harm Reduct J 2009;6:8.

17 Katz N. Abuse-deterrent opioid formulations: Are they a pipe dream? Curr Rheumatol Rep 2008;11–18.

18 Butler SF, Cassidy TA, Chilcoat H, et al. Abuse rates and routes of administration of reformulated extended-release oxycodone: Initial findings from a sentinel surveillance sample of individuals assessed for substance abuse treatment. J Pain 2013;14: 351–8.

19 Sellers EM, Perrino PJ, Colucci SV, Harris SC. Attractiveness of reformulated OxyContin(R) tablets: Assessing comparative preferences and tampering potential. J Psychopharmacol 2013;27:808–16.

20 HYSINGLA^{TM} ER (hydrocodone bitartrate) Extended Release Tablets for Oral Use, CII [package insert]. Purdue Pharma L. P., Stamford, CT, 2014.

21 Food and Drug Administration. US Department of Health and Human Services. Guidance for Industry: Abuse-Deterrent Opioids — Evaluation and Labeling. Draft Guidance; 2013. Available at: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm334807.htm (accessed October 13, 2015).

22 Food and Drug Administration. US Department of Health and Human Services. Guidance for Industry: Abuse-Deterrent Opioids — Evaluation And Labeling. Final guidance; 2015. Available at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm334743.pdf. [http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm334807.htm.] (accessed October 13, 2015).

23 Degenhardt L, Hall W. Extent of illicit drug use and dependence, and their contribution to the global burden of disease. Lancet 2012;379:55–70.

24 Degenhardt L, Whiteford HA, Ferrari AJ, et al. Global burden of disease attributable to illicit drug use and dependence: Findings from the Global Burden of Disease Study 2010. Lancet 2013;382:1564–74.

25 de Wit H, Bodker B, Ambre J. Rate of increase of plasma drug level influences subjective response in humans. Psychopharmacology 1992;107:352–8.

26 Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. Pain Physician 2008;11:S105–20.

27 Turk DC, O'Connor AB, Dworkin RH, et al. Research design considerations for clinical studies of abuse-deterrent opioid analgesics: IMMPACT recommendations. Pain 2012;153:1997–2008.