

Original Research Article

Effectiveness and Safety of Once-Daily Extended-Release Hydrocodone in Individuals Previously Receiving Immediate-Release Oxycodone for Chronic Pain

Joseph Pergolizzi, MD,* Maribeth Kowalski, PharmD,[†] and Ellie He, PhD[†]

*Naples Anesthesia and Physician Associates, Naples, Florida; [†]Purdue Pharma L.P., Stamford, Connecticut, USA

Correspondence to: Ellie He, PhD, Purdue Pharma L.P., One Stamford Forum, 201 Tresser Boulevard, Stamford, CT 06901, USA. Tel: 203-588-7108; Fax: 203-588-6423; Email: ellie.he@pharma.com.

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Abstract

Objectives. This study evaluated the safety and effectiveness of a once-daily, single-entity, extended-release hydrocodone bitartrate (HYD) among patients with chronic noncancer and non-neuropathic pain who required opioid rotation from a previous analgesic regimen that primarily consisted of immediate-release (IR) oxycodone.

Methods. Post hoc analyses of a primary study that assessed HYD 20 to 120 mg over a 52-week period are presented. The primary study included a dose titration period (up to 45 days), a 52-week maintenance period, and an optional taper period (up to 14 days).

Results. Relative to baseline, mean “average pain over the last 24 hours” declined by 1.9 points at the end of the titration period and by 2.6 points at the end of the maintenance period. Additionally, interference and severity of pain as measured by the Brief Pain Inventory–Short Form decreased by 2.3 and 1.9 points, respectively, during the maintenance period. The use of supplemental opioid analgesics decreased. Most patients remained on a stable HYD dose throughout the maintenance period. Most patients indicated satisfaction with HYD and considered it convenient and easy to use. HYD demonstrated a safety profile typical of μ opioids; nausea, constipation, vomiting, and dizziness were the most frequently reported opioid-related adverse events during the study.

Conclusions. In patients with chronic pain who received HYD over a 52-week period, treatment was generally well tolerated and provided effective analgesia among those who rotated from a pain regimen primarily consisting of IR oxycodone.

Key Words. Pain; Hydrocodone Bitartrate; Oxycodone; Long-term Opioid

Introduction

Chronic pain is a widely prevalent condition estimated to affect approximately 100 million adults in the United States, resulting in annual costs upwards of \$560 to \$635 billion [1,2]. Opioids, including immediate-release (IR) oxycodone, are prescribed for the management of moderate to severe chronic noncancer pain that is refractory to other analgesics such as acetaminophen and nonsteroidal anti-inflammatory drugs [3–5]. Patients have variable response to opioids, and therefore some opioids may not be optimal for certain patients [6,7]. Opioid rotation, which involves the administration of an alternative opioid as a replacement to current opioid

therapy, is a frequently employed strategy intended to provide effective pain management [6,7]. The decision to implement opioid rotation is based on interindividual variability in sensitivity to opioid analgesics as a result of interaction between genetic and environmental factors and differential receptor-binding and metabolic profiles of various opioids [7,8]. Rotation to extended-release (ER) formulations of opioids offers certain advantages [9]. First, ER formulations provide sustained analgesia over prolonged durations [9,10]. In addition, ER formulations are associated with a reduced pill burden, which may improve treatment compliance [9,11]. Finally, rotation to an ER opioid may also enable patients to obtain adequate analgesia with tolerable adverse events (AEs) at the lowest possible opioid dose [8].

HYD (Hysingla ER, Purdue Pharma L.P., Stamford, CT, USA) is a single-entity, once-daily, ER hydrocodone bitartrate tablet that was approved in 2014 in the United States for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which other treatment options are inadequate [12]. HYD is formulated with physicochemical properties intended to make the tablet more difficult to manipulate for misuse and abuse. A randomized, double-blind, placebo-controlled trial demonstrated that HYD was effective at providing analgesia among opioid-experienced patients with moderate to severe chronic low back pain over a 12-week duration [13]. In a 52-week study, HYD was found to provide effective pain relief and was well tolerated among patients with moderate to severe chronic noncancer and non-neuropathic pain [14]. This paper reports the results of a post hoc analysis of the 52-week study, which examined a subset of patients with chronic noncancer and non-neuropathic pain who rotated from IR oxycodone to HYD following enrollment.

Methods

Study Design

The primary study (NCT01400139) was approved by a central institutional review board prior to initiation and was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice Guidelines [14]. All patients provided signed informed consent prior to enrollment.

The primary, open-label study was conducted at 88 sites in the United States. It evaluated the long-term safety and effectiveness of once-daily 20, 40, 60, 80, and 120 mg HYD in 922 patients with moderate to severe chronic noncancer and non-neuropathic pain [14]. This post hoc analysis evaluated the safety and effectiveness of HYD in a subset of patients receiving IR oxycodone as their primary prestudy analgesic regimen who then switched to once-daily HYD. Detailed methods for this study have been previously described [14] and are presented in brief here.

This study comprised a screening period (up to 14 days), an open-label dose titration period (up to 45 days), an open-label 12-month maintenance period, and an optional taper period (up to 14 days). Patients underwent a complete assessment at an initial screening visit and recorded their pain scores during the remainder of the screening period. If the results from all screening visit assessments indicated eligibility, patients entered the dose titration period, during which all long-acting or controlled-release opioid analgesics were discontinued, and patients began HYD at a dose (20 mg, 40 mg, 60 mg, or 80 mg) that was approximately 50% to 75% of their incoming daily opioid regimen. Hydrocodone equivalent opioid daily doses were calculated using previously published conversion factors [12]. Supplemental short-acting opioids and nonopioid analgesics were permitted throughout the study.

During the dose titration period, HYD dose adjustments were made as deemed necessary by the investigator until a stable dose was achieved (i.e., a dose with adequate pain control and acceptable tolerability for at least seven days). Subsequently, patients who entered the maintenance period continued HYD treatment for 12 months. HYD dose adjustments were permitted during the maintenance period, if necessary.

Patients receiving HYD doses of 40 mg or higher at the end of the study (or early discontinuation) could enter the taper period, during which patients converted to a nonopioid analgesic regimen after their HYD doses were gradually decreased by 50% to 75%.

Patients

Patients eligible for the primary study were at least 18 years of age and had moderate to severe chronic noncancer and non-neuropathic pain lasting several hours daily for at least three months prior to screening. Patient pain was either controlled (i.e., patients were receiving a stable analgesic regimen equivalent to 0 to 120 mg/d of oxycodone with an “average pain over the last 14 days” score of 4 or lower at the screening visit) or uncontrolled (i.e., patients were receiving a stable analgesic regimen equivalent to 0 to 100 mg/d of oxycodone and an “average pain over the last 14 days” score of 5 or higher at the screening visit).

All patients included in this post hoc analysis were receiving IR oxycodone as their primary prestudy analgesic regimen, either alone or in combination with other opioids or other nonopioid analgesics. Female patients could not be pregnant or lactating, and they had to be willing to use contraception during the study.

Assessments

The “average pain over the last 24 hours” score (measured on an 11-point numerical rating scale [NRS], where 0 = no pain and 10 = pain as bad as you can imagine) was recorded by patients at approximately 8 PM daily in

diaries during the screening, dose titration, and maintenance periods. "Pain right now" scores (measured on the same 11-point NRS) were recorded by patients into their diaries immediately prior to daily HYD dosing and at approximately 8 PM every evening during the dose titration period and the first three months of the maintenance period. The Brief Pain Inventory–Short Form (BPI-SF), which assessed pain severity and pain interference on daily functions (with lower scores representing less pain severity and pain interference), was administered immediately prior to dosing, at the initiation of HYD treatment, at the end of the dose titration period, and at four-week intervals throughout the maintenance period. The Treatment Satisfaction Questionnaire compared patients' experiences with HYD with their prestudy regimen and was completed by patients after they received one month of maintenance treatment. Safety evaluations included reported AEs, clinical laboratory values (complete blood count with differential, urinalysis, and blood chemistry panel), vital signs, electrocardiograms (ECGs), and physical exams.

Statistical Analysis

All patients who received at least one dose of HYD during the study and who used IR oxycodone as their primary prestudy analgesic regimen were included in this post hoc analysis (i.e., the safety population). Mean pain intensity, as measured by the weekly mean "average pain over the last 24 hours" score, was summarized at baseline, at the end of the dose titration period, and weekly during the maintenance period. Changes from baseline in patients' pain severity and pain interference, as measured by patient responses to the BPI, were summarized by period (dose titration period and maintenance period). Associated 95% confidence intervals (CIs) were calculated for the mean and the mean change from baseline for applicable variables. Safety evaluations, including AEs, clinical laboratory tests, vital sign measurements, and ECG findings, were previously summarized for the overall study [14].

Results

Patient Characteristics and Disposition

This post hoc analysis identified a total of 97 patients who primarily received IR oxycodone prior to switching to HYD in the primary study evaluating the long-term safety and effectiveness of once-daily HYD [13]. The majority of these patients were younger than age 65 years (88%), female (62%), and white (84%) (Table 1). The mean age of patients included in this analysis was 51.4 years, and their mean body mass index was 31.0 kg/m². Patients in this subpopulation presented with moderate to severe levels of pain, recording a mean screening "average pain over the last 24 hours" score of 6.5 (standard deviation [SD] = 1.4). At screening, the most common pain etiologies were back pain (59 patients, 61%) and osteoarthritis (37 patients, 38%) (Table 2).

Table 1 Summary of demography and baseline characteristics for patients switching from IR oxycodone

Variable	Total N = 97
Age (mean ± SD), y	51.4 ± 11.96
Age group, No. (%)	
<65 y	85 (88)
≥65 y	12 (12)
Sex, No. (%)	
Male	37 (38)
Female	60 (62)
Race, No. (%)	
White	81 (84)
Black or African American	14 (14)
Native Hawaiian or other Pacific Islander	1 (1)
Asian	0
American Indian or Alaska Native	1 (1)
Other	0
BMI (mean ± SD), kg/m ²	31.0 ± 7.0
Time since first diagnosis of primary pain condition (mean ± SD), mo	131.4 ± 113.3
Baseline pain* (mean ± SD)	
Screening average pain score over last 14 d	6.7 ± 1.6
Baseline mean average pain over last 24 h [†]	6.5 ± 1.4

Percentages are based on N.

BMI = body mass index; IR = immediate release; N = number of patients in the safety population; No. = number of patients with data.

*Pain was recorded on an 11-point numerical rating scale where 0 = no pain, and 10 = pain as bad as you can imagine.

†The baseline mean "average pain over the last 24 hours" was defined as the mean value of the daily "average pain over the last 24 hours" scores recorded during the screening period.

At screening, patients included in this analysis received an average daily dose of 41.4 mg (SD = 28.5) oxycodone. The opioid analgesics used at baseline included oxycodone/acetaminophen combination therapy (66 patients, 68%) and single-entity oxycodone (35 patients, 36%). Patients in this analysis may have also been receiving other IR opioids prior to baseline.

A majority of patients (67 patients, 69%) included in this subgroup also received nonopioid regimens prior to the start of the study. In addition to the 68% of patients who were receiving APAP as part of combination therapy with oxycodone, the most frequently used nonopioid concomitant medications were ibuprofen

Table 2 Summary of coded medical history terms reported in $\geq 10\%$ of patients (by preferred term) who switched from IR oxycodone

MedDRA system organ class Preferred term	Safety population (N = 97) No. (%)
At least 1 preferred term	97 (100)
Gastrointestinal disorders	59 (61)
Gastroesophageal reflux disease	35 (36)
Constipation	24 (25)
Immune system disorders	35 (36)
Seasonal allergy	19 (20)
Drug hypersensitivity	17 (18)
Infections and infestations	36 (37)
Appendicitis	13 (13)
Tonsillitis	10 (10)
Metabolism and nutrition disorders	50 (52)
Hyperlipidemia	16 (16)
Hypercholesterolemia	15 (15)
Type 2 diabetes mellitus	13 (13)
Obesity	11 (11)
Musculoskeletal and connective tissue disorders	91 (94)
Back pain	59 (61)
Osteoarthritis	37 (38)
Intervertebral disc degeneration	25 (26)
Muscle spasms	23 (24)
Intervertebral disc protrusion	18 (19)
Arthralgia	17 (18)
Spinal osteoarthritis	15 (15)
Musculoskeletal pain	10 (10)
Neck pain	10 (10)
Nervous system disorders	42 (43)
Migraine	16 (16)
Headache	10 (10)
Psychiatric disorders	57 (59)
Anxiety	31 (32)
Insomnia	30 (31)
Depression	29 (30)
Respiratory, thoracic, and mediastinal disorders	28 (29)
Asthma	14 (14)
Surgical and medical procedures	75 (77)
Hysterectomy	20 (21)
Appendectomy	16 (16)
Cholecystectomy	13 (13)
Female sterilization	13 (13)
Tonsillectomy	11 (11)
Knee arthroplasty	10 (10)
Vascular disorders	46 (47)
Hypertension	42 (43)

Percentages are based on N. Multiple entries for an individual under the same body system/preferred term are counted once.

IR = immediate release; MedDRA = Medical Dictionary for Regulatory Activities, version 16.0; N = number of patients in the safety population; No. = number of patients with data.

Table 3 Summary of nonopioid medications used for pain by $\geq 5\%$ of patients prior to baseline for patients switching from IR oxycodone

MedDRA system organ class Preferred term	Safety population (N = 97) No. (%)
Any prior nonopioid medication or therapy	67 (69)
Ibuprofen	14 (14)
Carisoprodol	12 (12)
Cyclobenzaprine	11 (11)
Gabapentin	7 (7)
Naproxen	7 (7)
Duloxetine	6 (6)
Fluoxetine	6 (6)
Paracetamol/acetaminophen	5 (5)
Tizanidine	5 (5)
Trazodone	5 (5)

IR = immediate release; MedDRA = Medical Dictionary for Regulatory Activities, version 16.0; N = number of patients in the safety population; No. = number of patients with data.

(14 patients, 14%), carisoprodol (12 patients, 12%), and cyclobenzaprine (11 patients, 11%) (Table 3).

A total of 75 patients (77%) achieved a stable HYD dose during the dose titration period and entered the maintenance period (Table 4). Of these patients, 42 (56%) completed the study and 33 (44%) discontinued treatment. The most common reason for treatment discontinuation during the overall treatment period was AEs (15 patients, 15%) (Table 4). Other common reasons for treatment discontinuation during the overall treatment period included patient's choice (11 patients, 11%), lack of therapeutic effect (eight patients, 8%), administrative reasons (eight patients, 8%), and loss to follow-up (seven patients, 7%). Three (3%) patients each discontinued treatment due to suspected or confirmed study drug diversion or did not qualify for the maintenance period.

HYD Effectiveness

The mean score for "average pain over the last 24 hours" declined from 6.5 to 4.6 during the course of the titration period and remained consistent throughout the maintenance period (ranging from 3.8 to 4.2) (Figure 1). Relative to baseline levels, mean pain severity and pain interference with daily function as assessed by BPI were lower by 1.5 and 1.7 points, respectively, at the end of dose titration period. At the end of the maintenance period, the mean reductions from baseline in pain severity and pain interference with daily function were 1.9 and 2.3, respectively (Table 5). In addition, mean "pain right now" scores were comparable at the

Table 4 Summary of patient disposition and reasons for discontinuation

	Dose titration period (6–7 wk) (N = 97) No. (%)	Maintenance period (52 wk) (N = 75) No. (%)	Overall treatment period (58–59 wk) (N = 97) No. (%)
Completed period on HYD	75 (77)	42 (56)	42 (43)
Discontinued study	22 (23)	33 (44)	55 (57)
Reason for discontinuation			
Adverse event	8 (8)	7 (9)	15 (15)
Patient’s choice	4 (4)	7 (9)	11 (11)
Lost to follow-up	0	7 (9)	7 (7)
Lack of therapeutic effect	4 (4)	4 (5)	8 (8)
Confirmed or suspected diversion	0	3 (4)	3 (3)
Administrative*	3 (3)	5 (7)	8 (8)
Did not qualify for maintenance period†	3 (3)	NA	3 (3)

HYD = hydrocodone bitartrate.

*Patient discontinued from the study early for any logistical, nonmedical reason that was associated with either the study site or sponsor.

†Patient completed all the open-label dose titration period dosing and procedures but did not meet all the entry criteria for the maintenance period.

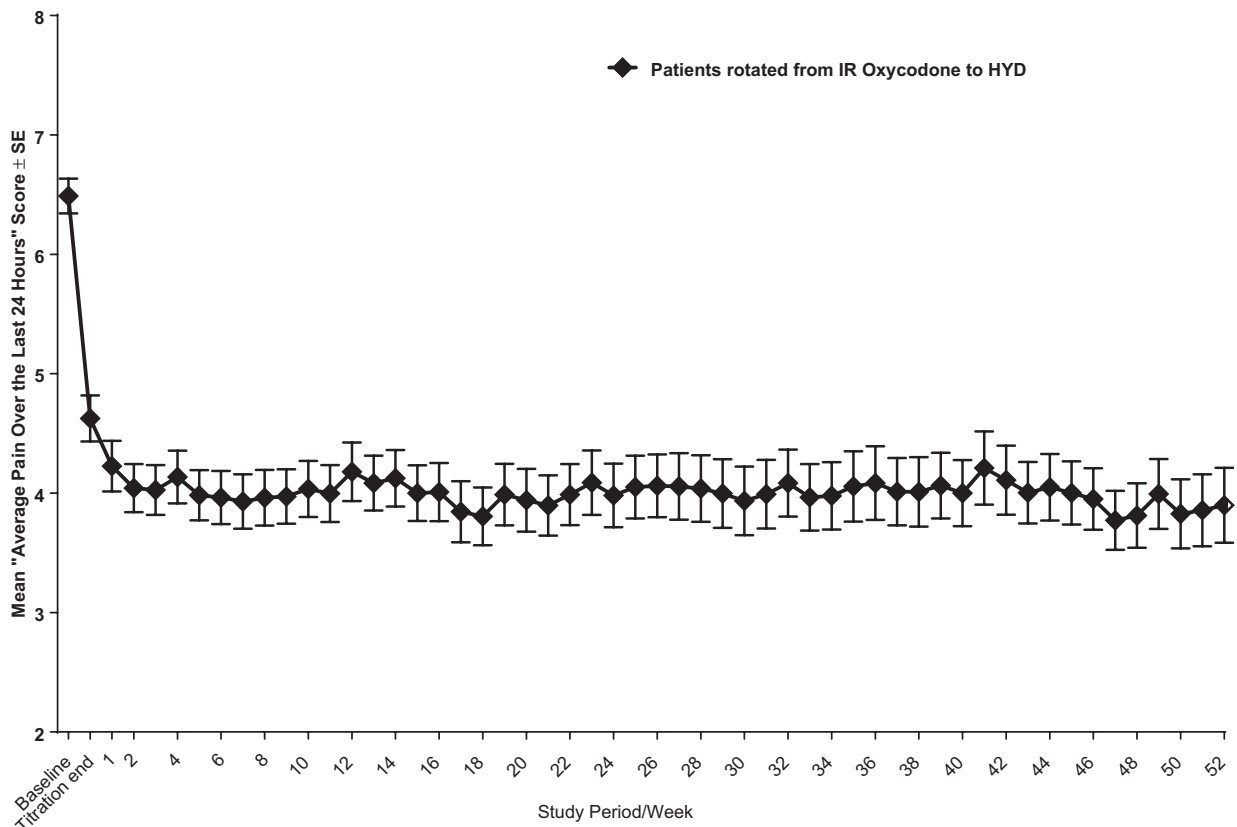


Figure 1 Mean “average pain over the last 24 hours.” Ns at baseline, titration end, and weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52 were, respectively, 96, 97, 61, 63, 63, 61, 59, 58, 55, 54, 49, 50, 48, 45, 43. IR = immediate release; HYD = hydrocodone bitartrate; SE = standard error.

time of HYD dosing (4.0, SD = 1.6, 95% CI = 3.67–4.42, N = 75 patients), at 12 hours postdose (4.0, SD = 1.6, 95% CI = 3.54–4.39, N = 60 patients), and on average over the 24-hour dosing interval (4.0, SD = 1.7, 95% CI = 3.64–4.40, N = 75 patients) (Figure 2).

Dose Adjustments

By the end of the titration period, the mean daily HYD dose for patients in this subgroup was 83.3 mg (SD = 33.4). This dose remained relatively stable throughout the maintenance period, with patients receiving an average daily dose of 89.4 mg (SD = 27.8) at the end of the maintenance period (Figure 3). HYD doses of 20, 40, 60, 80, and 120 mg were administered to one (1%), 15 (20%), 11 (15%), 17 (23%), and 31 (41%) patients, respectively, at the end of the maintenance period.

In total, 55 (57%) patients used concomitant opioid medications during this study. Oxycodone-containing products were used by 36 (37%) patients, while

single-entity oxycodone was concomitantly used by 15 (15%) patients. Other commonly used opioid formulations included hydrocodone/acetaminophen (10 patients, 10%), hydromorphone (five patients, 5%), morphine (five patients, 5%), tramadol (four patients, 4%), buprenorphine (one patient, 1%), and fentanyl (one patient, 1%). Relative to baseline levels (41.4, SD = 28.5), the mean daily dose of nonstudy opioids decreased substantially at the end of the titration period (7.0, SD = 17.3), and this decrease was sustained throughout the maintenance period (Figure 3). Supplemental nonopioid medications used for pain were used by 65 (67%) patients during the study, the most common of which were ibuprofen (17 patients, 18%), carisoprodol (11 patients, 11%), gabapentin (11 patients, 11%), cyclobenzaprine (nine patients, 9%), naproxen (eight patients, 8%), duloxetine (seven patients, 7%), acetaminophen (seven patients, 7%), fluoxetine (six patients, 6%), trazodone (six patients, 6%), amitriptyline (five patients, 5%), diclofenac (five patients, 5%), and sumatriptan (five patients, 5%).

The majority of patients (52 patients, 69%) did not require HYD dose adjustments during the maintenance period of the study (Figure 4). Dose increases to one level higher (e.g., HYD dose increase from 20 to 40 mg) and two levels higher (e.g., HYD dose increase from 20 to 60 mg) were required for 15 (20%) and five (7%) patients, respectively, while three (4%) patients received a dose decrease (Figure 4). Similar results were observed among patients who completed six months and 12 months of maintenance treatment.

Table 5 Brief Pain Inventory–Short Form

Mean Score	Baseline (N = 97)	Change from Baseline* (N = 75)
BPI	5.78	–2.10
BPI pain severity subscale	6.16	–1.91
BPI pain interference subscale	5.41	–2.29

BPI = Brief Pain Inventory.

*Change from baseline of overall maintenance average.

Treatment Satisfaction

Of the 75 patients who switched from IR oxycodone and entered the maintenance period, 59 (79%)

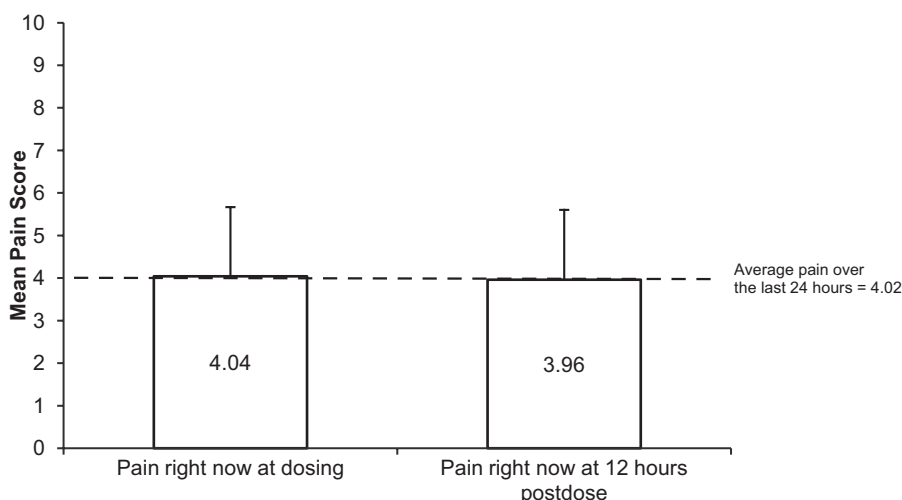


Figure 2 Mean “pain right now” scores recorded immediately prior to each daily dose and at 12 hours postdose and mean “average pain over the last 24 hours” score during the first three months of the maintenance period (dashed line). Error bars represent the standard deviation.

Single-Entity Hydrocodone Among Users of Oxycodone

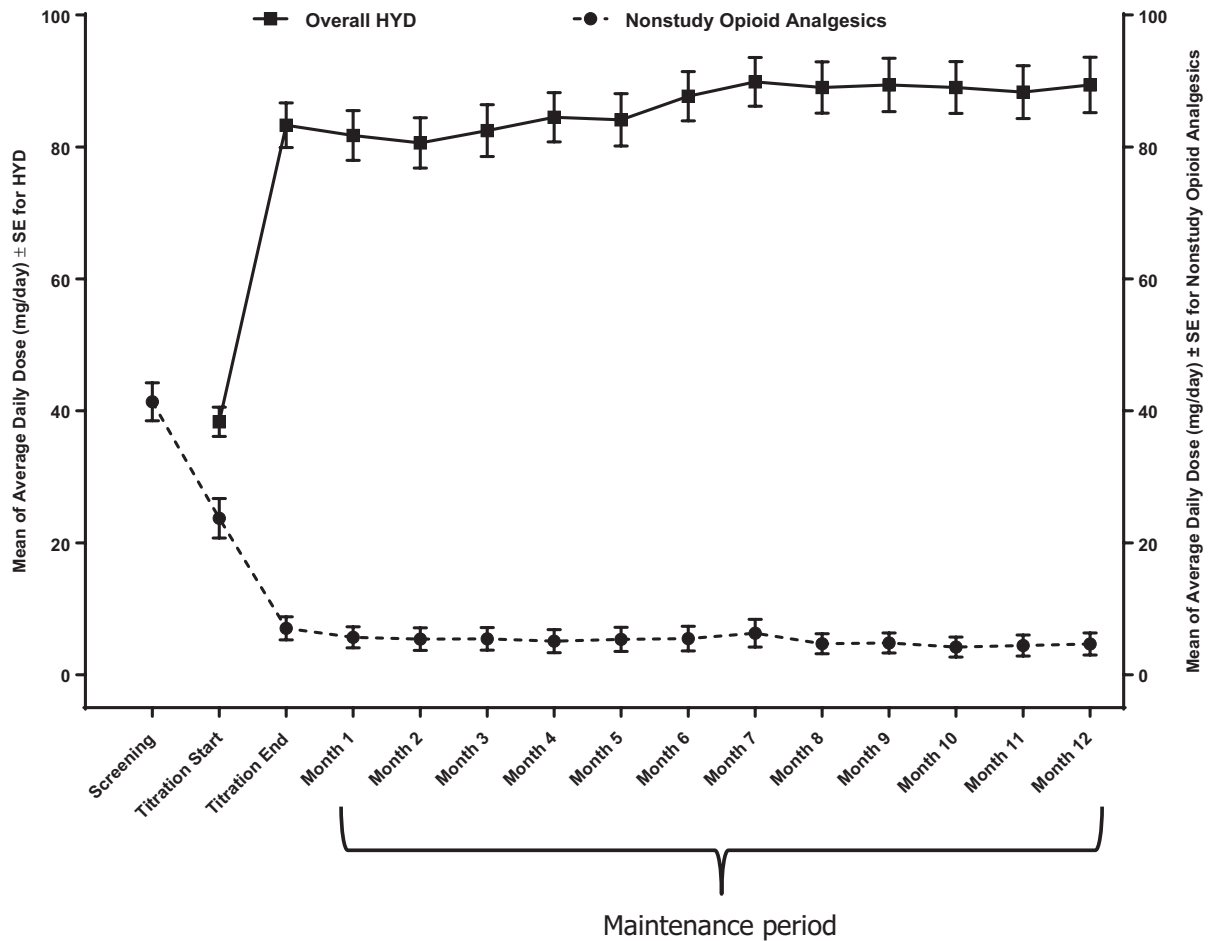


Figure 3 Average daily dose of HYD and supplemental opioids. For overall HYD, Ns from titration start through month 12 were 97, 97, 75, 67, 66, 63, 60, 59, 56, 53, 51, 50, 48, 44. For nonstudy opioid analgesics, Ns from screening through month 12 were 97, 97, 97, 75, 69, 66, 64, 62, 60, 58, 54, 54, 52, 49, 47. HYD = hydrocodone bitartrate.

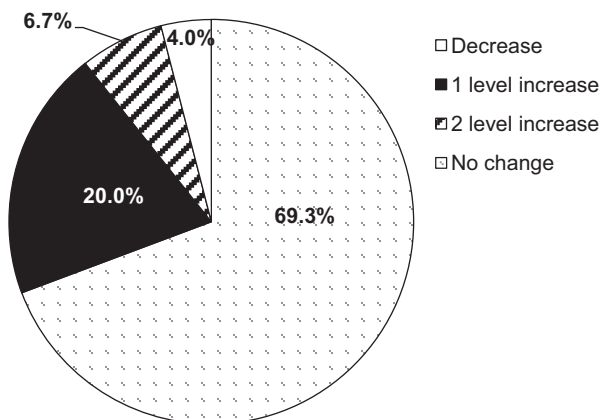


Figure 4 HYD dose adjustments during the maintenance period of the study. 1-level increase = a stepwise increase in HYD dose (e.g., HYD 80 mg to HYD 120 mg); HYD = hydrocodone bitartrate.

responded to the treatment satisfaction questionnaire. Ninety-two percent of these patients (54/59) reported satisfaction with HYD, and 93% (55/59) reported overall satisfaction with HYD for the management of pain (55/59) (Table 6). All patients found HYD easy and convenient to use and were satisfied with dosing frequency. Overall, 98% (58/59) of patients found the planning of HYD use to be easy.

Safety

Overall treatment-emergent AEs (TEAEs) occurred in 80% (78/97 patients) of the safety population included in this subanalysis, with the most frequent overall TEAEs ($\geq 10\%$) being nausea (15 patients, 15%), constipation (10 patients, 10%), vomiting (nine patients, 9%), and dizziness (nine patients). Opioid-related treatment-emergent AEs occurred in 52% (50/97 patients), with the most frequent opioid-related AEs being nausea (15 patients, 15%), constipation (10 patients, 10%), vomiting

Table 6 Treatment satisfaction questionnaire

Question number: Category answered	Total (N = 75) No. (%)
Q1: Satisfaction with study drug	59
Satisfied to extremely satisfied	54 (92)
Dissatisfied to extremely dissatisfied	5 (8)
Q2: Ease of study drug use to treat pain	59
Easy to extremely easy	59 (100)
Difficult to extremely difficult	0
Q3: Convenience of study drug to treat pain	59
Convenient to extremely convenient	59 (100)
Inconvenient to extremely inconvenient	0
Q4: Overall drug satisfaction managing pain	59
Satisfied to extremely satisfied	55 (93)
Dissatisfied to extremely dissatisfied	4 (7)
Q5: Satisfaction with frequency of use	59
Satisfied to extremely satisfied	59 (100)
Dissatisfied to extremely dissatisfied	0
Q6: Ease of planning study drug use	59
Easy to extremely easy	58 (98)
Difficult to extremely difficult	1 (2)

N = number of patients in the safety population entering the maintenance period; No. = number of patients with each individual response.

(nine patients, 9%), and dizziness (nine patients, 9%) (Table 7). In total, 15 patients (15%) discontinued this study due to AEs. During the titration period, eight patients (8%) who discontinued reported 16 AEs; three of these AEs were severe, of which one (dry mouth) was considered related to study drug. During the maintenance period, seven patients (9%) who discontinued experienced nine AEs. Two of these AEs were severe, of which one (impaired gastric emptying) was considered related to study drug.

Six serious AEs (SAEs) occurred in five patients. One patient who died during the study had three SAEs of profound metabolic acidosis and thrombocytopenic embolic purpura, which were considered to be unrelated to study drug. The other five patients were withdrawn from the study and recovered from their SAEs. SAEs of multiple drug overdose and gastroparesis occurred in one patient each and were considered probably related to study drug. SAEs of alcohol abuse and breast cancer occurred in one patient each and were considered unrelated to study drug.

Discussion

Although opioid therapy may be used for the treatment of chronic noncancer pain in appropriate patients [4,15], many patients appear not to achieve sufficient analgesia with their existing medication. Others experience intolerable AEs associated with their existing opioid treatment.

Table 7 Treatment-emergent opioid-related adverse events

MedDRA system organ class Preferred term*	Total switched from IR oxycodone (N = 97) No. (%)
Any TEAE	50 (52)
Gastrointestinal disorders	23 (24)
Nausea	15 (15)
Constipation	10 (10)
Vomiting	9 (9)
Dry mouth	1 (1)
General disorders and administration site conditions	10 (10)
Fatigue	7 (7)
Edema peripheral	3 (3)
Injury, poisoning, and procedural complications	4 (4)
Fall	4 (4)
Nervous system disorders	22 (23)
Dizziness	9 (9)
Somnolence	7 (7)
Headache	5 (5)
Sedation	3 (3)
Psychiatric disorders	6 (6)
Insomnia	6 (6)

IR = immediate release; MedDRA = Medical Dictionary for Regulatory Activities, version 16.0; TEAE = treatment-emergent adverse event.

*This table includes TEAEs occurring during any of the treatment periods; multiple occurrences of the same adverse event in one individual are counted only once.

Indeed, a study of patients with chronic noncancer pain demonstrated that only 36% of patients achieved effective therapy from their first prescribed opioid [16]. In contrast, 77% of patients in this post hoc analysis were successfully titrated to a maintenance dose, of which 56% were able to complete the 52-week maintenance period. This is comparable with the disposition of the primary study, in which 79% of patients were successfully titrated to a maintenance dose and 56% completed the 52-week maintenance period. Such patients may benefit from switching to a different opioid medication [6,7]. While studies have examined the effects of switching from oxycodone to other opioids (including ER oxycodone, methadone, and fentanyl) among patients with chronic cancer and noncancer pain) [7], to our knowledge there are currently no published data on the safety and effectiveness of the rotation from IR oxycodone, one of the most frequently prescribed opioid medications [17], to HYD in patients with chronic noncancer and non-neuropathic pain. This post hoc analysis assessed the long-term safety and effectiveness of HYD among patients with moderate to severe chronic

noncancer and non-neuropathic pain who were previously treated with an analgesic regimen that included IR oxycodone and required an opioid rotation.

Patients who rotated to HYD treatment presented with moderate to severe levels of pain at baseline as assessed by a mean “average pain over the last 24 hours” score. HYD treatment was efficacious, as evidenced by a decrease in the mean score for “average pain over the last 24 hours” by the end of the dose titration period. The reduction in pain scores was sustained throughout the 52-week maintenance period, with a total decrease of 2.6 points in mean “average pain over the last 24 hours” scores over the duration of the study. This greater than 2 point decrease in pain scores with HYD treatment exceeded the criteria for a minimum clinically important difference [18] and led to stable analgesia over a 52-week maintenance period. Additionally, patients reported lower pain severity and interference during the maintenance period, demonstrating that treatment with HYD was associated with clinically important pain relief (≥ 1 point decrease) and functional improvements in the daily activities of patients [19]. Furthermore, analgesia provided by HYD was stable throughout the 24-hour dosing interval as evidenced by mean “pain right now” scores that were similar at dosing, at 12 hours postdose, and over the 24-hour duration. Collectively, these data indicate that, among patients switching from oxycodone who continued to receive treatment during the 52-week period, once-daily HYD provided pain relief that was sustained over the 24-hour dosing interval, maintained over a 52-week period, and associated with functional improvements in daily living.

Importantly, opioid tolerance, a phenomenon reported with long-term opioid treatment when a particular dose fails over time to provide acceptable analgesia, thus necessitating dose escalation, [20,21] was not observed with HYD in this subanalysis. The majority of patients receiving HYD did not require dose adjustments during the maintenance period, while some patients were switched to a lower HYD dose and a dose increase of one or two levels was necessary in some patients. Only four patients (5%) discontinued due to lack of therapeutic effect. The mean daily dose of HYD administered during the maintenance period remained consistent. Notably, the use of supplemental opioid analgesics decreased from baseline levels to the end of the titration period, and this reduction persisted during the maintenance period. Finally, a survey of the 77% of patients who entered the maintenance period indicated that all patients found HYD convenient to use, while most patients were satisfied with the pain management of HYD.

Treatment with HYD was generally well tolerated among patients included in this analysis; a few patients discontinued HYD treatment due to AEs. This discontinuation rate was similar to or lower than rates reported for patients with chronic noncancer pain who received opioid treatment [13,14,22,23]. Most AEs leading to study

discontinuation were mild or moderate in severity. The types and rates of AEs observed in this post hoc analysis were comparable with those previously reported for opioid treatment among patients with noncancer pain [13,14,23]. A small proportion of patients (4%) experienced falls, which was similar to the findings of the primary study [14]. These falls were not associated with fractures or hospitalization.

The safety and efficacy results of this subanalysis are similar to the primary study results [14], as well as to a subanalysis of users of hydrocodone combination therapy [24]. Among patients who switched from hydrocodone combination therapy to HYD and completed treatment (N = 226), 43% discontinued treatment (16% for AEs and 6% for lack of therapeutic effect). Mean oxycodone equivalent dose at baseline was 48 mg, and patients experienced clinically important reductions in average pain scores, pain interference, and pain severity during the maintenance period while maintaining stable daily doses of HYD and marked reductions of supplemental nonstudy opioid analgesics.

The amount of opioid received by patients increased from 38.35 mg oxycodone equivalents at titration start to 83.30 mg at titration end. However, the dose adjustment appeared to have been appropriate because clinically relevant improvements in pain and function were seen throughout the 52-week maintenance period, patient satisfaction with HYD treatment was high, and the majority of patients required either no dose adjustment, an adjustment of one dosage level, or a dosage decrease. Additionally, discontinuation rates were similar in both the titration period and maintenance period for both lack of therapeutic effect (4% and 5%, respectively) and adverse events (8% and 9%, respectively). Furthermore, dose levels of nonstudy opioids analgesics decreased from 41.4 mg oxycodone equivalents at baseline to 7.0 mg at titration end. These results are similar to results seen in the primary study and subsequent post hoc analyses.

This study may be limited by the post hoc nature of the analysis, the small sample size evaluated (i.e., 97 patients out of 922 [11%] in the primary study [14]), and the open-label noncomparative study design. However, this post hoc analysis demonstrated that, among patients who continued to receive treatment over a 52-week period, HYD provided effective analgesia in patients with chronic pain who received prior treatment with IR oxycodone, with a safety profile similar to that expected of μ opioid agonists, as previously reported [14].

Conclusion

This post hoc analysis of an open-label study examined patients with chronic noncancer and non-neuropathic pain who switched from immediate-release oxycodone to extended-release once-daily hydrocodone (HYD). HYD was generally well tolerated. Many patients treated

with HYD experienced clinically important, long-term pain relief that was sustained throughout the day as well as over a 52-week period in this subgroup. HYD treatment resulted in clinically important functional improvements in the daily activities of these patients who were switched from IR oxycodone to HYD. A majority of these patients did not require HYD dose adjustments and were treated with a relatively constant HYD dose during the maintenance period. The use of supplemental IR opioids was lower at the end of the study compared with baseline levels among these patients. The safety profile of HYD in these patients was consistent with that seen with other μ opioid agonists. A majority of patients indicated satisfaction with the ease and convenience of HYD. This post hoc analysis demonstrated that, among patients who received treatment over a 52-week period, HYD was well tolerated and provided effective long-term analgesia to patients with pain that was insufficiently controlled by IR oxycodone.

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