ORIGINAL ARTICLE

Sustained Safety and Efficacy of Once-Daily Hydromorphone Extended-Release (OROS® hydromorphone ER) Compared with Twice-Daily Oxycodone Controlled-Release Over 52 Weeks in Patients with Moderate to Severe Chronic Noncancer Pain

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■ **Abstract:** Once-daily hydromorphone extended-release (OROS® hydromorphone ER) and oxycodone controlled-release (CR) are semisynthetic, ER opioid analgesics with established efficacy. An open-label, randomized, 24-week, parallel group, flexible-dose study demonstrated noninferiority of OROS hydromorphone ER vs. twice-daily oxycodone CR in patients with chronic noncancer pain. In total, 112 patients were enrolled in a 28-week, open-label extension study; 60 patients received OROS hydromorphone ER and 52 received oxycodone CR. The primary efficacy measure was the change from baseline to Weeks 38 and 52 in Brief Pain Inventory item ''pain right now.'' Global assessments of efficacy, dosing convenience, and tolerability were secondary endpoints. Mean change in ''pain right now'' from baseline to Week 38 was −3.0 (OROS hydromorphone ER) vs. −2.8 (oxycodone CR), and from baseline to Week 52 was

−2.9 vs. −2.8; these changes were similar to the changes in the core phase (−2.1 vs. −2.1). Similar improvements were demonstrated for secondary assessments, including pain, pain interference, and quality of life. At Week 52, global assessment of efficacy was rated as ''very good'' or ''good'' by the majority of patients (OROS hydromorphone ER, 91.7%; oxycodone CR, 86.5%). More patients in the OROS hydromorphone ER group (35.0% vs. 21.2%) assessed mode of drug intake as ''very convenient.'' The majority of patients receiving OROS hydromorphone ER (88.3%) and oxycodone CR (88.5%) rated tolerability as ''good'' or ''very good'' at Week 52; few patients discontinued treatment because of an adverse event (1.6% vs. 0.4%, respectively). The effectiveness of OROS hydromorphone ER and oxycodone CR was maintained through 1 year. ■

Key Words: chronic pain, long-term safety, sustained efficacy, OROS, hydromorphone extended-release

INTRODUCTION

In the United States, approximately 14% of persons experience chronic pain,[1,2] defined as pain that persists beyond the expected period of healing and for extended periods of time.[3] Additionally, about 19% of adult Europeans experience moderate or severe chronic pain.[4] In addition to the physical burden, chronic pain can affect numerous aspects of patients' lives, substantially impacting overall quality of life.[5] Chronic pain can also affect sleep, as patients may experience difficulty falling and staying asleep or may have less restful sleep.[6] Wakefulness is often affected as well, as opioid-induced sedation is a possible adverse effect of chronic opioid therapy.[7] The overall objective of pharmacological pain management is to improve quality of life by balancing acceptable efficacy and tolerability.[8] When other interventions have proved unsuccessful for the management of chronic pain, opioid analgesics may be an appropriate treatment option.[9] The American Pain Society and American Academy of Pain Medicine agree that opioids can be effective for carefully selected and monitored patients with chronic noncancer pain.[9] Use of opioid analgesics for the treatment of chronic noncancer pain is also supported by guidelines issued by the European Federation of Chapters of the International Association for the Study of Pain.[10]

Once-daily hydromorphone extended-release (OROS® hydromorphone ER) and twice-daily oxycodone controlled-release (CR) are semisynthetic, ER opioid analgesics with established efficacy.[11,12] Hydromorphone is a potent oral opioid analgesic, with approximately 4:1 to 8:1 morphine:hydromorphone equianalgesic potency.[13] Hydromorphone has been used extensively in the treatment of chronic pain.[14,15] Originally available as an immediate-release formulation, hydromorphone is now available as an ER formulation (OROS® hydromorphone ER).[16] Oxycodone CR is approximately twice as potent as morphine and is also used extensively in the treatment of chronic pain.[12,17] A recently published open-label, randomized, 24-week, flexible-dose study demonstrated noninferiority of OROS hydromorphone ER vs. oxycodone CR for the treatment of chronic noncancer pain.[18] The objective of this report was to evaluate results from the 28-week extension phase of this study, which was designed to determine the sustained safety and efficacy of OROS hydromorphone ER and oxycodone CR in patients with chronic noncancer pain.

METHODS

This was an open-label, international, multicenter, randomized (1:1), comparative, parallel-group noninferiority study with a 28-week extension phase in which patients received treatment through 52 weeks (clinicaltrials.gov identifier: NCT00261495). The results of the 24-week, open-label study have been published elsewhere.[18] Of the 64 centers that participated in the core phase, 20 participated in the extension; many centers withdrew for administrative reasons. Written informed consent was obtained at the screening visit in accordance with the principles of the Declaration of Helsinki. All centers had review board approval.

Patients

Patients aged ≥ 18 years with chronic noncancer pain (defined as pain occurring ≥ 20 days/month for > 3 months) who required continuous opioid therapy were enrolled. Chronic pain conditions included low back, musculoskeletal, and neuropathic pain and other conditions. The study included opioid-naïve patients, patients receiving treatment with weak opioids, patients taking ≤ 60 mg oral morphine or an equivalent of another strong opioid, and those patients using transdermal fentanyl 25 mcg/hour or transdermal buprenorphine 35 mcg/hour. Patients provided written consent to continue treatment for 28 weeks.

Patients whose previous hydromorphone or oxycodone therapy was unsuccessful and patients with known hypersensitivity to either drug were excluded.

Patients with a history of significant cardiac, nervous system, or gastrointestinal conditions, moderate-to-severe hepatic impairment, severe renal impairment, or hereditary problems of galactose intolerance, Lapp lactase deficiency, or glucose-galactose malabsorption were excluded. Women who were pregnant or breastfeeding were excluded.

Study Design and Treatments

Patients were enrolled for treatment from Week 0 to Week 56, with Weeks 53 to 56 included for a follow-up visit. The last dose of study medication was administered during Week 52. Primary and secondary efficacy measures were assessed at Weeks 38 and 52 in the extension study. In the core phase of the study, treatment was initiated with 8 mg OROS hydromorphone ER once daily or 10 mg oxycodone CR twice daily, followed by individual titration over 4 weeks to a maximum daily dose of 32 mg or 80 mg, respectively.

Use of supplemental analgesics (acetaminophen, up to 2 g/d) was permitted but was not documented in patient diaries. Investigators were permitted to administer bisacodyl 5 mg twice daily to prevent constipation. If patients remained symptom-free, investigators could decrease the dosage or discontinue bisacodyl. Anti-emetics could also be prescribed at the discretion of the investigators.

Most concomitant medications were allowed if they had been initiated ≥ 2 weeks prior to study inclusion and were maintained at a stable or reduced dosage. Concomitant medications not permitted during the study included other opioid analgesics; neuroleptics, excluding haloperidol or droperidol, up to 2 mg/day for ≤ 30 days during the course of the study to treat nausea and/or vomiting; hypnotics, excluding short-acting hypnotics taken for ≤ 30 days during the course of the study; sympathomimetic drugs; monoamine oxidase inhibitors; and tetrabenazines.

Efficacy Measures

The primary efficacy measure was the change in Brief Pain Inventory (BPI) pain severity item "pain right now" from baseline to Weeks 38 and 52. Scores range from 0 to 10, with lower values representing less pain. The BPI includes other measures of pain intensity, as well as interference with function. Secondary efficacy endpoints included BPI items "pain at its worst," "pain relief," and individual pain-interference items. Pain interference assesses the impact of pain on several areas of physical and emotional functioning. Global assessments of efficacy, tolerability, and convenience of the study drug were performed at Week 52.

Sleep was assessed using the BPI sleep interference item and the Medical Outcomes Study (MOS). The MOS assesses several aspects of sleep, including quality, disturbance, and somnolence. Lower MOS sleep subscales scores indicated better sleep quality. Patients were given a Short Form-36 (SF-36) questionnaire to assess quality of life at Weeks 38 and 52. The SF-36 scale is used to assess physical, emotional, and social functioning and includes a mental health index and a measure of general health perception. SF-36 scores range from 0 to 100, with a high score indicating better quality of life.

Safety Evaluations

Adverse events (AEs) were assessed from the administration of the first through the last dose of medication. A global assessment of tolerability was performed at Week 52.

Statistical Analysis

Demographic and baseline characteristics were analyzed for the per protocol (PP), intent-to-treat (ITT), and safety populations. Primary and selected secondary endpoint analyses were performed in the PP population, defined as all patients included in the ITT population who did not violate any major protocol. Efficacy analyses were performed in the ITT population, defined as randomized patients who received ≥ 1 dose of the study medication and had ≥ 1 postbaseline efficacy assessment. Safety analyses were performed in the safety population, defined as all randomized patients who received ≥ 1 dose of the study medication.

Summary statistics are presented by way of *n,* mean, and standard error of the mean (SEM) for continuous variables and by way of group frequencies and percentages for categorical variables. Percentages were calculated using the total number of patients in each treatment group. Summary statistics for the values observed at each visit are presented for all efficacy endpoints described as change from baseline. Analysis of observed cases was carried out for the primary endpoint and selected secondary efficacy endpoints. Testing for noninferiority between treatments with respect

to the primary endpoint, that of change in BPI "pain right now" from baseline, was conducted in a confirmatory sense. If a patient recorded an early termination visit, the early termination date was used as the end date of that last visit interval.

RESULTS

Patient Disposition

Overall, 112 patients (40.4%) who completed the 24-week core phase of the study were enrolled in the 28-week open-label extension phase (Figure 1). Sixty patients had been receiving OROS hydromorphone ER (maximal daily dosage, 32 mg) and 52 had been receiving oxycodone CR (maximal daily dosage, 80 mg). Fifteen patients (13.4%) discontinued treatment during the extension phase; of these, 5 (4.5%) discontinued due to AEs and 6 (5.4%) due to other reasons (eg, dispensing of study medication not according to the protocol).

Patients in the extension phase had a mean duration of exposure of 371.0 days (OROS hydromorphone ER) and 380.5 days (oxycodone CR). Mean dose and distribution of patients at the end of titration, maintenance, and extension phases are described in Table 1. At Week 52, the mean daily doses of OROS hydromorphone ER and oxycodone CR were 17.1 mg and 44.6 mg, respectively. The mean equianalgesic dose ratio of OROS hydromorphone ER to oxycodone CR was approximately 2.5:1.

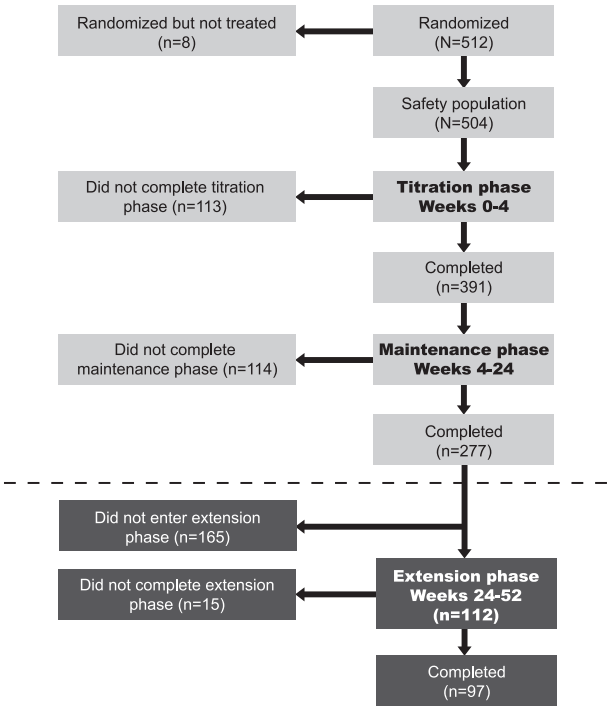

Figure 1. Study design.

Demographics and Baseline Characteristics

Patients who entered the extension phase tended to have lower pain severity, greater pain relief, and greater improvements in sleep quality compared with those who did not continue past Week 24.[18]

In the extension phase, the OROS hydromorphone ER and oxycodone CR treatment groups were comparable with regard to demographics (Table 2), disease-related baseline characteristics, and medical histories. The most common underlying diseases were chronic low back pain (59.8%), musculoskeletal pain (23.2%), and neuropathic pain (9.8%). Fourteen patients (23.3%) randomized to receive OROS hydromorphone

Table 1. Mean Dose and Distribution of Study Treatment at Week 4, Week 24, and Week 52 in Patients Who Enrolled in the Extension Phase

	OROS Hydromorphone ER (*n* = 60)			Oxycodone CR (*n* = 52)		
Study Period	Mean Dose (mg)	Dose per Day (mg)	*n* (%)	Mean Dose (mg)	Dose per Day (mg)	*n* (%)
Week 4, end of titration phase	16.1	8	19 (31.7)	40.4	20	15 (28.8)
		16	31 (51.7)		40	29 (55.8)
		32	10 (16.7)		80	8 (15.4)
Week 24, end of maintenance phase	17.5	8	19 (31.7)	43.5	20	11 (21.2)
		16	26 (43.3)		40	31 (59.6)
		32	15 (25.0)		80	10 (19.2)
Week 52, end of extension phase	17.1	8	20 (33.3)	44.6	20	10 (19.2)
		16	26 (43.3)		40	31 (59.6)
		32	14 (23.3)		80	11 (21.2)

CR, controlled release; ER, extended release; OROS, oral osmotic drug delivery system.

Table 2. Demographic Characteristics

Characteristic	OROS Hydromorphone ER (*n* = 60)	Oxycodone CR (*n* = 52)	Total (*N* = 112)
Age (years), mean (SD)	58.4 (10.1)	57.9 (12.3)	58.1 (11.1)
Gender, *n* (%)			
Female	33 (55.0)	27 (51.9)	60 (53.6)
Race, *n* (%)			
Caucasian	60 (100.0)	52 (100.0)	112 (100.0)
Country, *n* (%)			
Czech Republic	21 (35.0)	8 (15.4)	29 (25.9)
Germany	18 (30.0)	18 (34.6)	36 (32.1)
Poland	19 (31.7)	21 (40.4)	40 (35.7)
Slovakia	2 (3.3)	5 (9.6)	7 (6.3)

CR, controlled release; ER, extended release; OROS, oral osmotic drug delivery system; SD, standard deviation.

ER and 9 patients (17.3%) randomized to receive oxycodone CR were opioid naïve at the start of the core phase of the study; 46 (76.7%) and 43 (82.7%) patients in each group, respectively, had received prior weak opioid therapy (eg, codeine, dihydrocodeine, or tramadol). The majority of patients included in this extension phase were taking ≥ 5 concomitant medications (65% in the OROS hydromorphone ER group and 67.3% in the oxycodone CR group). Almost all patients were taking ≥ 1 concomitant medication (98.3% in the OROS hydromorphone ER group and 98.1% in the oxycodone CR group).

Efficacy

Among patients receiving OROS hydromorphone ER, mean (SEM) overall pain severity decreased from 6.3 (0.1) at baseline to 3.9 (0.2) at Week 52. In patients receiving oxycodone CR, pain severity decreased from 6.5 (0.2) at baseline to 4.0 (0.2) at Week 52.

Primary Efficacy Measure

Mean (SEM) change in BPI item "pain right now" from baseline to Week 38 was −3.0 (0.3) for OROS hydromorphone ER vs. −2.8 (0.3) for oxycodone CR, and from baseline to Week 52 was −2.9 (0.3) for OROS hydromorphone ER vs. −2.8 (0.3) for oxycodone CR (Figure 2A). In the OROS hydromorphone ER group, mean (SEM) "pain right now" decreased over time from 6.8 (0.2) at baseline to 3.9 (0.3) at Week 52. Similarly, in the oxycodone CR group, mean (SEM) "pain right now" decreased from 6.9 (0.2) at baseline to 4.1 (0.3) at Week 52.

Secondary Efficacy Measures

At baseline, mean (SEM) "pain at its worst" score was 8.1 (0.2) in both the OROS hydromorphone ER and oxycodone CR groups (Figure 2B). At Week 52, mean (SEM) "pain at its worst" score was 5.3 (0.3) and 5.7 (0.3) in the OROS hydromorphone ER and oxycodone CR groups, respectively. In the OROS hydromorphone ER group, mean (SEM) "pain at its least" decreased from 4.5 (0.2) at baseline to 2.6 (0.2) at Week 52 (Figure 2C). In the oxycodone CR group, "pain at its least" decreased from 4.8 (0.3) at baseline to 2.4 (0.2) at Week 52.

Mean (SEM) pain interference scores at baseline, Week 24, Week 38, and Week 52 for the OROS hydromorphone ER group were 6.6 (0.24), 4.2 (0.3), 3.9 (0.3), and 4.2 (0.3), respectively. In the oxycodone CR group, mean scores were slightly higher overall: baseline (7.0 [0.3]), Week 24 (4.3 [0.2]), Week 38 (4.7 [0.3]), and Week 52 (4.4 [0.3]). Similar findings were observed in both treatment groups when pain interference with general activity (Figure 3A), walking ability (Figure 3B),

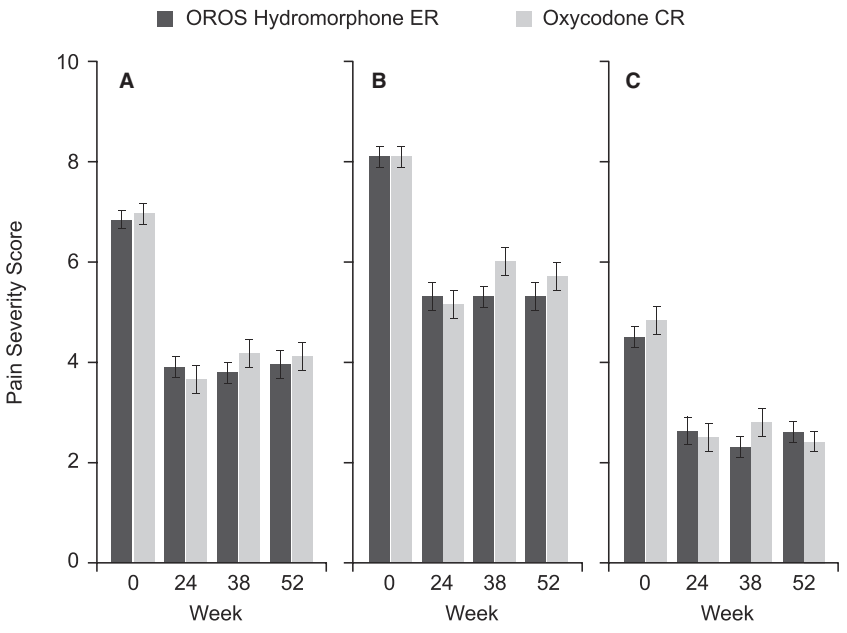

Figure 2. Mean (SEM) Brief Pain Inventory pain severity scores for (A) "pain right now", (B) "pain at its worst", and (C) "pain at its least". A decrease in pain severity score indicates less pain. Dark bars represent OROS hydromorphone extended-release, and light bars represent oxycodone controlled-release. OROS, oral osmotic drug delivery system; SEM, standard error of the mean.

normal work activity (Figure 3C), and sleep (Figure 3D) was evaluated. Additionally, for emotional domains measured by pain interference scores (ie, mood [Figure 4A], relationships with others [Figure 4B], and enjoyment of life [Figure 4C]), improvements were sustained over time in both treatment groups.

According to the SF-36 questionnaire, mean (SEM) scores for pain index at baseline were 20.6 (1.6) in the OROS hydromorphone ER group and 16.4 (1.6) in the oxycodone CR group. At Week 52, pain index scores improved to 46.0 (3.6) and 41.9 (2.9) in the OROS hydromorphone ER and oxycodone CR groups,

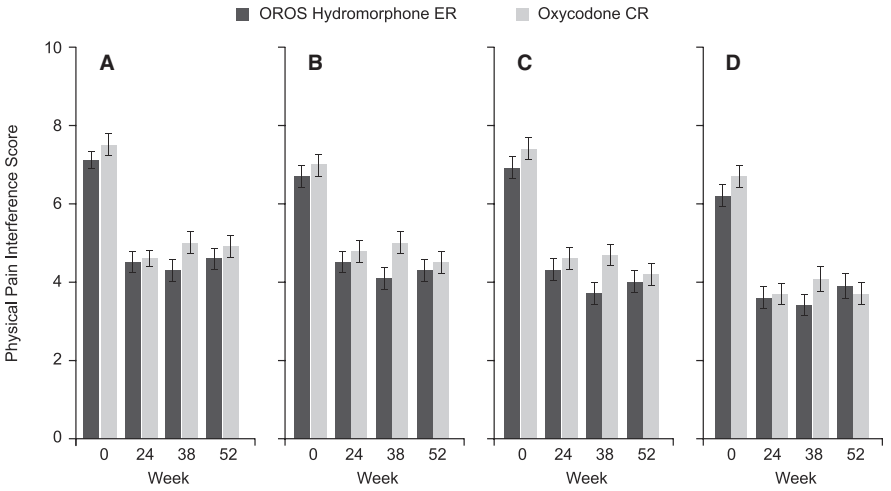

Figure 3. Mean (SEM) Brief Pain Inventory physical pain interference scores for general activity (A), walking ability (B), normal work activity (C), and sleep (D). A decrease in pain interference score indicates less interference. Dark bars represent OROS hydromorphone extended-release, and light bars represent oxycodone controlled-release. OROS, oral osmotic drug delivery system; SEM, standard error of the mean.

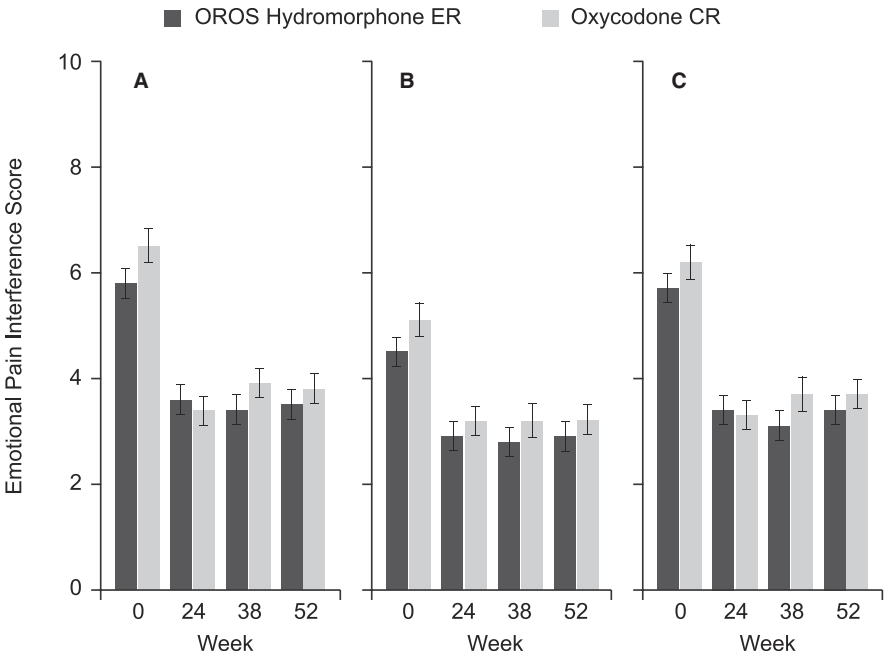

Figure 4. Mean (SEM) Brief Pain Inventory emotional pain interference scores for mood (A), relationships with others (B), and enjoyment of life (C). A decrease in pain interference score indicates less interference. Dark bars represent OROS hydromorphone extended-release, and light bars represent oxycodone controlled-release. OROS, oral osmotic drug delivery system; SEM, standard error of the mean.

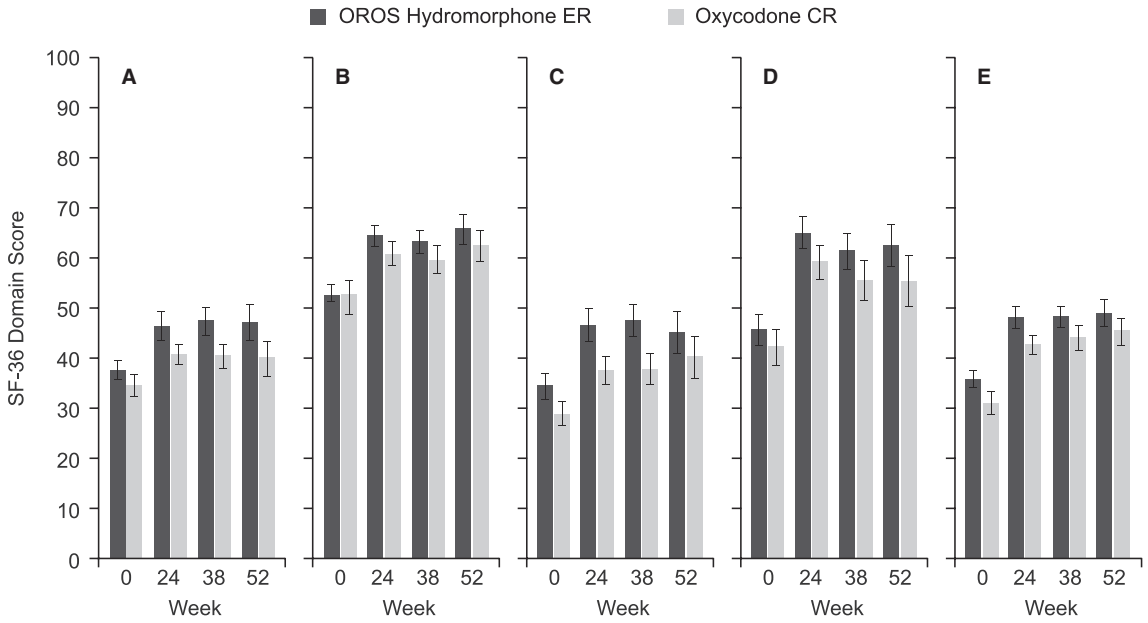

Figure 5. Change in quality of life according to mean (SEM) SF-36 domain scores for general health perception (A), mental health index (B), physical functioning (C), social functioning (D), and vitality (E). An increase in domain scores indicates an improvement in quality of life. Dark bars represent OROS hydromorphone extended-release, and light bars represent oxycodone controlled-release. OROS, oral osmotic drug delivery system; SEM, standard error of the mean.

respectively. Improvements were also demonstrated across all other domains in both treatment groups (ie, general health perception [Figure 5A], mental health index [Figure 5B], physical functioning [Figure 5C], social functioning [Figure 5D], and vitality [Figure 5E]) in both groups.

Sleep quality is summarized in Table 3. Improvement (mean change [SEM]) in sleep quality from baseline to Week 38 was −12.5 (2.7) for OROS hydromorphone ER vs. −12.4 (3.0) for oxycodone CR. Similarly, improvement in sleep quality (mean change [SEM]) from baseline to Week 52 was also comparable between treatment groups (−10.7 [2.4] for OROS hydromorphone ER vs. −11.5 [2.7] for oxycodone CR). Treatment with OROS hydromorphone ER was associated with substantially less somnolence than oxycodone CR. This was also true in the core phase of the study, where there was a significant difference ($P = 0.020$) for somnolence in the OROS hydromorphone ER group.[18]

At Week 52, the majority of patients rated the global assessment of efficacy as "very good" or "good" (OROS hydromorphone ER, $n = 55$ [91.7%]; oxycodone CR, $n = 45$ [86.5%]). More patients in the OROS hydromorphone ER group than in the oxycodone CR group assessed mode of drug intake as "very convenient" (21 [35.0%] vs. 11 [21.2%]). Ten (16.7%) and 15 (28.8%) patients receiving OROS hydromorphone ER and oxycodone CR, respectively, assessed mode of drug intake as "convenient."

Table 3. Mean (SEM) Values of MOS Efficacy Parameters for OROS Hydromorphone ER and Oxycodone CR

Efficacy Measure Score, mean (SEM)	OROS Hydromorphone ER (n = 60)	Oxycodone CR (n = 52)
Sleep quality		
Baseline	48.1 (2.1)	51.9 (2.2)
Week 24	34.0 (2.7)	37.2 (2.4)
Week 38	35.4 (2.6)	40.3 (3.1)
Week 52	38.0 (2.7)	40.4 (2.3)
Sleep disturbance		
Baseline	53.4 (2.5)	60.8 (2.8)
Week 24	34.2 (3.0)	35.9 (3.1)
Week 38	36.1 (3.2)	42.5 (3.8)
Week 52	37.3 (3.2)	40.7 (3.0)
Sleep somnolence		
Baseline	40.9 (2.2)	39.9 (2.7)
Week 24	37.4 (2.2)	40.1 (3.0)
Week 38	32.8 (2.2)	41.4 (2.4)
Week 52	34.8 (2.5)	41.7 (2.8)

Lower scores indicate better sleep quality.
CR, controlled release; ER, extended release; MOS, Medical Outcomes Study; OROS, oral osmotic drug delivery system; SEM, standard error of the mean.

Safety

Overall, 42 patients receiving OROS hydromorphone ER (84%) and 43 receiving oxycodone CR (91%) reported

Table 4. Summary of Adverse Events During the Extension Phase

Variable	OROS Hydromorphone ER (*n* = 50)	Oxycodone CR (*n* = 47)	Total (*N* = 97)
Most common AEs, *n* (%)			
Nasopharyngitis	1 (2.0)	3 (6.4)	4 (4.1)
Vertigo	1 (2.0)	3 (6.4)	4 (4.1)
Weight decreased	3 (6.0)	1 (2.1)	4 (4.1)
Anorexia	3 (6.0)	0 (0)	3 (3.1)
Drug withdrawal syndrome	0 (0)	3 (6.4)	3 (3.1)
Hypertension	3 (6.0)	0 (0)	3 (3.1)
Nausea	1 (2.0)	2 (4.3)	3 (3.1)
AEs, *n* (%)			
Possibly related to study drug	10 (20.0)	4 (8.5)	14 (14.4)
Probably related to study drug	1 (2.0)	0 (0)	1 (1.0)
Very likely related to study drug	0 (0)	6 (12.8)	6 (6.2)
Resulted in withdrawal	4 (8.0)	1 (2.1)	5 (5.2)
Severity, *n* (%)			
Mild	14 (28.0)	7 (14.9)	21 (21.6)
Moderate	23 (46.0)	31 (66.0)	54 (55.7)
Severe	5 (10.0)	5 (10.6)	10 (10.3)

AE, adverse event; CR, controlled release; ER, extended release; OROS, oral osmotic drug delivery system.

AEs. The most commonly reported AEs were nasopharyngitis (4.1%), vertigo (4.1%), and weight decrease (4.1%) (Table 4). In total, investigators determined that 20.0% of AEs were possibly related to treatment with OROS hydromorphone ER, and 2.0% of AEs were probably related to this treatment. The majority of AEs (74%) in the OROS hydromorphone ER group were mild to moderate in severity. In the oxycodone CR group, investigators determined that 8.5% of AEs were possibly related to study medication, with 12.8% of AEs very likely related to study medication. The majority of AEs (80.9%) in the oxycodone CR group were mild to moderate in severity.

Serious AEs occurred in 6 patients (12%) receiving OROS hydromorphone ER and 4 patients (8.5%) receiving oxycodone CR. The most common serious AEs were gastrointestinal disorders (2 [2.1%]) and surgical and medical procedures (3 [3.1%]). No deaths occurred during the course of the study.

The majority of patients receiving OROS hydromorphone ER (88.3%) and oxycodone CR (88.5%) rated tolerability as "good" or "very good" at Week 52; few patients discontinued due to an AE (1.6% vs. 0.4%, respectively).

DISCUSSION

The objective of this study was to assess the long-term safety and efficacy of once-daily OROS hydromorphone ER compared with twice-daily oxycodone CR in patients with chronic noncancer pain. Patients who completed an initial open-label 24-week trial were allowed to continue in the 28-week open-label extension phase, resulting in up to 52 weeks of active treatment. Pain control was maintained in both groups for up to 1 year, with OROS hydromorphone ER demonstrating a similar efficacy and safety profile to oxycodone CR. Improvements in pain severity were observed across a number of outcome measures, including BPI items "pain right now," "pain at its worst," and "pain at its least." Sustained improvements were also observed for pain interference with functioning, quality of life, and indices of sleep. Overall, changes in efficacy endpoints from baseline to Week 38 and Week 52 were generally comparable to changes reported from baseline to the endpoint of the core phase (Week 24).[18] OROS hydromorphone ER and oxycodone CR were generally well tolerated for up to 1 year. These results extend the findings of previous short-term studies in patients with chronic noncancer and cancer pain,[18,19] and also long-term studies in patients with chronic cancer pain,[20] and demonstrate sustained efficacy and tolerability of both drugs through 1 year.

Overall, 91.7% of patients rated the efficacy of OROS hydromorphone ER as "very good" or "good." In the oxycodone CR group, 86.5% of patients rated the drug as "very good" or "good." More patients receiving OROS hydromorphone ER rated the mode of intake as "very convenient" (35.0% vs. 21.2%). The difference in global assessment of convenience between treatment groups may be a reflection of the once-daily dosing of OROS hydromorphone ER. Once-daily dosing may result in higher treatment compliance and fewer episodes of end-of-dose failure relative to formulations that require multiple daily doses. Once-daily dosing may also decrease overall pill burden, which is particularly important for chronic pain patients, who often take several concomitant medications.[21]

At Week 52, the mean weighted daily dose of oxycodone CR (44.6 mg) was ~2.5 times more than that of OROS hydromorphone ER (17.1 mg) and was similar to study medication doses at the end of the titration (Week 4) and core phases (Week 24). That neither treatment group required substantial increases in daily dosage after Week 4 suggests that no additional tolerance to analgesic effects of the opioids developed. The ratio of mean daily doses used in the present study

(2.5:1 for OROS hydromorphone ER:oxycodone CR) is consistent with the 5:1 equianalgesic dose ratio for morphine to hydromorphone from previous reports.[19,20,22]

OROS hydromorphone ER and oxycodone CR had comparable safety and tolerability profiles through 1 year. In total, 84% of patients receiving OROS hydromorphone ER and 91% receiving oxycodone CR experienced AEs during the extension phase. The most common AEs were nasopharyngitis (5.2%), vertigo (4.1%), and weight decrease (4.1%), which is in contrast to AEs reported in the core phase.[18] In the core phase, the most common AEs were typical of those associated with potent opioids (eg, nausea, constipation, vomiting, and fatigue).[18] It is important to note that only 40% of the patients who completed the core phase continued into the extension phase. The subgroup of patients who continued into the extension phase may have experienced more favorable tolerability of OROS hydromorphone ER or oxycodone CR than those who chose not to continue. For example, it is possible that those patients who experienced constipation even while taking constipation prophylaxis in the core phase of the study chose not to participate in the extension phase; this may have contributed to the low incidence of constipation reported in the extension phase (2.1%). Also, constipation and other gastrointestinal AEs were considered AEs in the extension phase only if they were new onset or worsened from the core phase. The results suggest that these AEs were well managed with long-term treatment. It is also possible that some tolerance developed to certain opioid-related AEs throughout the course of the study. However, tolerance to the analgesic effects did not appear to occur, as the daily opioid doses and reports of pain relief were quite stable. Furthermore, tolerance to opioid-mediated constipation is believed not to occur. The majority of AEs were considered to be mild-to-moderate in severity. Serious AEs occurred in 12% of patients receiving OROS hydromorphone ER and 8.5% of patients receiving oxycodone CR; no deaths were reported. The percentages of patients who rated tolerability as "very good" or "good" were 88.3% for OROS hydromorphone ER and 86.5% for oxycodone CR.

In the clinical setting, the practice of opioid rotation is often employed when treating patients with chronic pain.[8] Opioid rotation, a change in the opioid drug or route of administration with the goal of improving outcomes, has been shown to improve pain control and reduce toxicity.[8,23] Ideally, physicians will select opioids with established efficacy and tolerability. The present data, and that of other studies employing OROS hydromorphone ER and oxycodone CR, establish the efficacy and safety profile of both formulations in patients with chronic cancer and noncancer pain.[11,18–20,24–33]

There are several limitations of this study that may affect the generalizability of these findings. The open-label design, while including an active comparator, does not take into account the percentage of patients who may have improved with no active treatment. The fact that inferential statistics were not applied to the data represents another limitation. As the primary objective of the study was to assess the sustained safety of the opioid formulations, data were presented only in a descriptive fashion. Finally, the relatively low percentage of patients who completed the core phase of the study and continued into the extension study may represent a subset that experienced a particularly favorable tolerability and efficacy profile.

Overall, the results of this long-term, 28-week extension phase indicate that OROS hydromorphone ER and oxycodone CR are effective and well tolerated in patients with chronic noncancer pain. Changes in efficacy endpoints from baseline to Week 38 and to Week 52 were generally comparable to the changes from baseline to the endpoint of the core phase, indicating a consistent analgesic effect. The long-term safety, efficacy, and convenience of OROS hydromorphone ER may afford a rational treatment option in appropriate patients.

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