

# Around-the-Clock, Controlled-Release Oxycodone Therapy for Osteoarthritis-Related Pain

## Placebo-Controlled Trial and Long-term Evaluation

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**Background:** Although opioid analgesics have well-defined efficacy and safety in treatment of chronic cancer pain, further research is needed to define their role in treatment of chronic noncancer pain.

**Objective:** To evaluate the effects of controlled-release oxycodone (OxyContin tablets) treatment on pain and function and its safety vs placebo and in long-term use in patients with moderate to severe osteoarthritis pain.

**Methods:** One hundred thirty-three patients experiencing persistent osteoarthritis-related pain for at least 1 month were randomized to double-blind treatment with placebo (n = 45) or 10 mg (n = 44) or 20 mg (n = 44) of controlled-release oxycodone every 12 hours for 14 days. One hundred six patients enrolled in an open-label, 6-month extension trial; treatment for an additional 12 months was optional.

**Results:** Use of controlled-release oxycodone, 20 mg, was superior ( $P < .05$ ) to placebo in reducing pain inten-

sity and the interference of pain with mood, sleep, and enjoyment of life. During long-term treatment, the mean dose remained stable at approximately 40 mg/d after titration, and pain intensity was stable. Fifty-eight patients completed 6 months of treatment, 41 completed 12 months, and 15 completed 18 months. Common opioid side effects were reported, several of which decreased in duration as therapy continued.

**Conclusions:** Around-the-clock controlled-release oxycodone therapy seemed to be effective and safe for patients with chronic, moderate to severe, osteoarthritis-related pain. Effective analgesia was accompanied by a reduction in the interference of pain with mood, sleep, and enjoyment of life. Analgesia was maintained during long-term treatment, and the daily dose remained stable after titration. Typical opioid side effects were reported during short- and long-term therapy.

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**O**STEARTHRTIS IS one of the most common joint disorders, with radiographic evidence of the disease present in most of the population by age 65 years and in 80% of the population by age 75 years.<sup>1</sup> Pain associated with osteoarthritis contributes substantially to disability<sup>2</sup> and has a negative impact on motor function, sleep, and mood.<sup>3</sup> Thus, control of pain is an important goal of therapy.<sup>4,5</sup> Frequently prescribed oral analgesics include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), combinations of an opioid with aspirin or acetaminophen, and tramadol hydrochloride.<sup>2,6</sup> Use of nonopioid analgesics to treat moderate to severe osteoarthritis pain is limited by a ceiling effect for analgesia<sup>7</sup> and potential toxic effects at high doses,<sup>8,9</sup> with gastrointestinal tract, hepatic, and renal side effects of NSAID

use of particular concern in elderly patients.<sup>9,10</sup>

The need to find effective strategies for managing chronic, moderate to severe noncancer pain has led to the reappraisal of opioids for this use. The favorable experience with long-term administration of centrally acting opioid analgesics to treat cancer pain<sup>11-13</sup> suggests that opioid treatment would be effective in noncancer pain as well. However, the clinical literature regarding long-term use of opioids for the management of chronic noncancer pain is contradictory. Some studies,<sup>14-19</sup> usually from populations at multidisciplinary pain clinics, have associated opioid use with functional impairment, increased pain, central nervous system (CNS) toxic effects, and drug abuse. Other studies<sup>20-25</sup> describe favorable experiences with opioid use in some patients, including effective analgesia, no CNS toxic effects, im-

## PATIENTS AND METHODS

One hundred thirty-three adults with persistent osteoarthritis-related pain for at least 1 month and moderate or severe pain at baseline were enrolled in the placebo-controlled trial. The diagnosis of osteoarthritis was confirmed by the following criteria: (1) at least a 3-month history of 2 or more of the following clinical signs—pain aggravated by motion and at least partly relieved by rest, limitation of the range of motion, stiffness with inactivity, bony tenderness on pressure, bony swelling, and joint fluid analysis consistent with osteoarthritis if effusion was present; and (2) at least 1 of the following radiographic findings—osteophytes, joint space narrowing, subchondral bony sclerosis, or bony cysts. Patients with severe organ dysfunction were excluded, as were those with a history of drug or alcohol abuse. Patients taking NSAIDs could continue their use if the dose had been stable for 1 month at the maximum dose tolerated by or effective for the patient and if the dose would not be changed. Use of other analgesics was prohibited throughout the study, and use of opioid analgesics was discontinued at study entry. One hundred six patients who had participated in the placebo-controlled trial were enrolled in the long-term, open-label extension trial. Each of the 7 participating rheumatology clinics obtained institutional review board approval before each study was initiated, and written informed consent was obtained from each patient before enrollment into either trial.

### STUDY DESIGN

#### Placebo-Controlled Trial

At baseline, patients were randomly assigned to 1 of 3 double-blind treatment groups: placebo or 10 mg or 20 mg of CR oxycodone every 12 hours (q12h). Each patient received 2 bottles, each containing identical placebo or 10-mg CR oxycodone tablets (OxyContin tablets; Purdue Pharma LP, Norwalk, Conn). The treatment was concealed in a tear-off portion of the label, which was stapled to the patient's

case report form, and the masked status was maintained until the study database was complete and prepared for analysis. One tablet was taken from each bottle at 8 AM and 8 PM daily for 14 days. Dose titration and use of rescue analgesia were prohibited.

Each day, patients rated night, morning, afternoon, and evening pain intensity using a 4-point categorical scale (0 indicates none; 1, slight; 2, moderate; and 3, severe). This scale is the most widely used,<sup>28</sup> is simple for patients to use, is a valid indicator of pain intensity, and correlates well with other measures of pain intensity.<sup>29</sup> Patients also evaluated quality of sleep using a 5-point scale from 1 (very poor) to 5 (excellent).

At baseline, week 1, and week 2, patients completed the Brief Pain Inventory,<sup>30</sup> rating their worst, least, and average pain "in the last 24 hours" and pain "right now" using a numerical scale from 0 (no pain) to 10 (pain as bad as you can imagine). Numerical scales were used to rate interference of pain (0 indicates does not interfere; 10, completely interferes) on key functional activities and emotions: general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life.<sup>31</sup> Patients also completed an activities and lifestyle questionnaire in which they rated their ability to perform 8 daily activities (dress yourself, get in and out of bed, lift cup or glass to mouth, walk outdoors, wash and dry entire body, bend down, turn faucets, and get in and out of the car) using a 4-point categorical scale from 1 (without any difficulty) to 4 (unable to do) (modified from Pincus et al<sup>32</sup>).

Adverse experiences spontaneously reported by patients or observed by the investigators were recorded at each visit. All patients underwent baseline and end-of-study laboratory evaluations and physical examinations, during which vital signs were recorded.

#### Long-term Extension Trial

Patients who had participated in the placebo-controlled trial were eligible for an open-label 6-month extension trial. Two optional 6-month extension trials were added by protocol amendments, providing a maximum possible duration of

proved performance in some cases, and only infrequent instances of abuse, when opioid analgesics were included as part of a comprehensive, individualized pain management program.

Few blind, placebo-controlled clinical trials have evaluated the efficacy of opioid therapy in chronic noncancer pain. One double-blind, 7-day, placebo-controlled crossover study<sup>26</sup> (with subsequent 19-week open evaluation) found that controlled-release (CR) codeine administration reduced pain and pain-related disability in patients with chronic nonmalignant pain, 43.3% of whom had rheumatic pain. Another randomized, double-blind, 9-week crossover study<sup>27</sup> compared CR morphine sulfate therapy with active placebo use in patients with treatment-resistant chronic regional soft tissue or musculoskeletal pain. Opioid therapy reduced pain intensity but with no functional or psychological improvement. No impairment of cognitive function and no drug-seeking behaviors were observed. Thus, results of these 2 double-blind, placebo-controlled trials supported the

analgesic effect of opioid use in chronic nonmalignant pain but did not focus on long-term effectiveness and safety.

The present studies were undertaken to assess the effectiveness of an oral CR formulation of the opioid oxycodone for the short- and long-term treatment of moderate to severe pain associated with osteoarthritis. A randomized, double-blind, parallel-group study compared the analgesic efficacy, effect on function, and safety of 2 dose levels of CR oxycodone with placebo. An open-label extension trial assessed analgesic effectiveness, need for dose adjustments, effect on function, and safety during long-term treatment with CR oxycodone.

## RESULTS

### PLACEBO-CONTROLLED TRIAL

Patients with moderate to severe osteoarthritis-related pain were randomized to double-blind treatment with pla-

18 months. All patients received CR oxycodone tablets q12h at approximately 8 AM and 8 PM. The minimum dose was 10 mg q12h, and the dose was titrated until adequate pain control was achieved with an acceptable level of side effects. The q12h doses could be titrated symmetrically (ie, same dose in the morning and in the evening) or asymmetrically (ie, higher dose in the morning or in the evening), depending on the patient's need for pain control during the day.

Clinic visits were scheduled at baseline and at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, 56, 64, and 72. Patients were contacted by telephone daily during the first week of the trial, once a week until week 24, then when considered necessary by the investigator. The continuing need for opioid analgesia therapy was assessed by means of scheduled respite from opioid therapy, which began at the end of the clinic visits at weeks 4, 8, 16, 24, 48, and 64. Patients resumed CR oxycodone treatment if they reported that their pain intensity was unacceptable. Pain intensity, quality of sleep, and the number of night awakenings due to pain were assessed at baseline and at weeks 2, 4, 8, 16, 24, 32, 40, 48, 56, 64, and 72. The activities and lifestyle questionnaire was administered at baseline and at weeks 4, 24, 32, 40, 48, 56, 64, and 72. All adverse events spontaneously reported by patients or observed by the investigators were recorded. Physical examinations (including vital signs) and laboratory evaluations were performed at baseline and at the end of the study for each patient. After the last visit, the investigators telephoned the patients daily until the patient reported unacceptable moderate to severe pain. The patient was then instructed to resume therapy prescribed by his or her physician.

#### STATISTICAL ANALYSIS

In the placebo-controlled trial, the primary efficacy variable was mean pain intensity calculated from patients' daily categorical scores. This was analyzed for the population of patients who took at least 4 doses of study medication, recorded at least 2 pain intensity evaluations, and complied with the protocol ( $n = 109$ ). For this analysis, missing

values were replaced by the last set of observations for that patient. For the remaining efficacy variables and all safety variables, all patients enrolled in the study ( $N = 133$ ) were included in the statistical analyses (intent to treat).

Baseline demographics were analyzed using a Cochran-Mantel-Haenszel test for categorical variables and analysis of variance (ANOVA) for continuous variables. An analysis of covariance (ANCOVA), with baseline pain intensity as a covariate, was used for weekly and overall pain intensity. Models encompassed treatment, study center, sex, age ( $<65$  or  $\geq 65$  years), and intervariable interactions. The Dunnett test was performed to compare active treatments with placebo, regardless of the significance level of the overall ANCOVA. The least significant difference test was used to compare the 2 active treatments if the overall ANCOVA was statistically significant. Activities and lifestyle questionnaire and Brief Pain Inventory responses were analyzed using either ANOVA or logistic regression, depending on the level of measurement of the variable. The dependent variables of the ANOVA were in terms of change from baseline. In all of the ANOVA and ANCOVA models, least squares means for the response variables were also calculated. The  $\chi^2$  test was performed to compare the difference between the active groups and the placebo group for discontinuations due to lack of efficacy and adverse events. Logistic regression was used to analyze treatment effects associated with adverse events. The model contained treatment, center, sex, and age.

In the long-term open-label trial, an overall trend analysis was performed from week 2 to the end of the study for pain intensity and "duration ratio" of the 4 most common opioid-related side effects (nausea, pruritus, somnolence, and constipation) using a mixed effects model with random intercept and slope. Duration ratio was calculated as the number of days the patient experienced the adverse event divided by the number of days the patient was treated with CR oxycodone, expressed as a percentage.

All statistical tests were 2 sided, with a significance level of  $P = .05$  for main effects and  $P = .10$  for interaction terms. Results are presented as mean (SE).

cebo ( $n = 45$ ) or 10 mg ( $n = 44$ ) or 20 mg ( $n = 44$ ) of CR oxycodone q12h (**Table 1**). There were no statistically significant differences among treatment groups in baseline characteristics. Most patients (73.7%) were women. The average age of patients was 62 years, and 42.9% were 65 years or older. The most common osteoarthritic sites were the spine or back (45.9%) and the knee (30.8%). Most patients had chronic disease, with an average duration of 9 years. Eighty-one patients (60.9%) had been taking opioid analgesics, which were discontinued before enrollment; 78 of these patients had been receiving fixed-combination products. Eighty-seven patients (65.4%) continued taking NSAIDs throughout the study.

Seventy patients (52.6%) discontinued study participation prematurely (**Figure 1**), 39 because of ineffective treatment and 28 because of adverse experiences (predominantly nausea, vomiting, and somnolence). The number of patients discontinuing for ineffective treatment was significantly lower in the active groups than in the placebo group: 22 in the placebo group, 12 in the

10-mg q12h group ( $P = .04$  vs placebo), and 5 in the 20-mg q12h group ( $P < .001$  vs placebo). The number of patients discontinuing for adverse events was significantly higher in the active groups than in the placebo group: 2 in the placebo group, 12 in the 10-mg q12h group ( $P = .009$  vs placebo), and 14 in the 20-mg q12h group ( $P = .004$  vs placebo). Of the remaining 3 patients who discontinued, all in the placebo group, 1 withdrew consent and 2 took analgesics prohibited by the protocol.

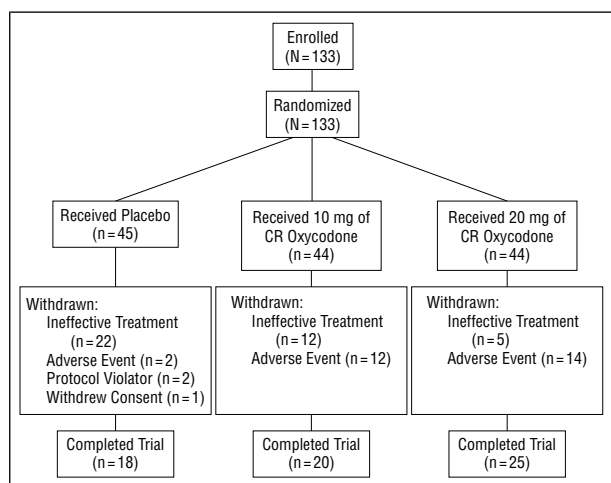
In many analgesic trials, a 20% average reduction in baseline pain intensity is considered clinically meaningful. Based on the 4-point categorical scale, use of 20 mg of CR oxycodone q12h attained this goal within 1 day, and use of 10 mg of CR oxycodone q12h attained this goal by day 2; the placebo group never achieved this reduction (**Figure 2**). The reduction in pain intensity with use of 20 mg of CR oxycodone q12h was prompt and sustained: taking 20 mg of CR oxycodone was more effective ( $P < .05$ ) in reducing mean pain intensity at weeks 1 and 2 and overall than was taking placebo or 10 mg of

**Table 1. Characteristics of 133 Patients Enrolled in the Placebo-Controlled Trial\***

Characteristic	Placebo Group (n = 45)	CR Oxycodone q12h Group	
		10 mg (n = 44)	20 mg (n = 44)
Sex, M/F	10/35	13/31	12/32
Age, y			
Mean (SE)	62 (2)	62 (2)	63 (2)
Range	32-85	38-81	41-90
<65, No. (%)	27 (60)	25 (57)	24 (55)
≥65, No. (%)	18 (40)	19 (43)	20 (45)
Baseline pain intensity, mean (SE)†	2.4 (0.1)	2.5 (0.1)	2.4 (0.1)
Osteoarthritis site, No. (%)			
Spine or back	17 (38)	24 (55)	20 (45)
Knee	18 (40)	9 (20)	14 (32)
Other	10 (22)	11 (25)	10 (23)
Duration of disease, mean (SE)	10 (1)	9 (2)	8 (1)

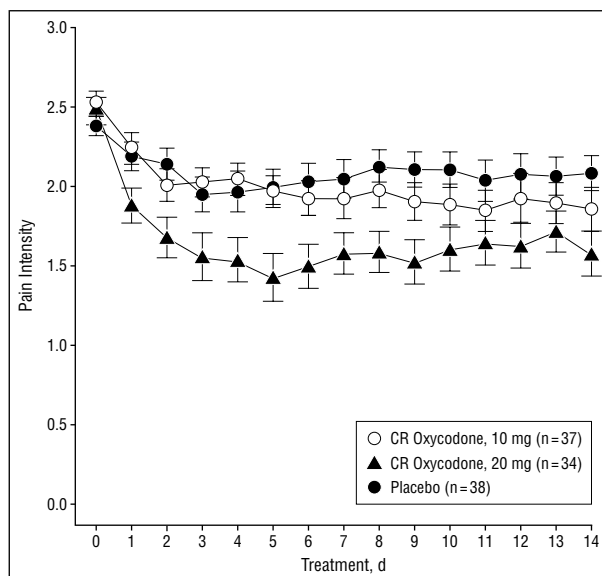
\*CR indicates controlled release; q12h, every 12 hours.

†Categorical scale (0 indicates none; 1, slight; 2, moderate; and 3, severe); average of morning, noon, evening, and night assessments.



**Figure 1.** Disposition of patients enrolled in the double-blind, placebo-controlled trial of controlled-release (CR) oxycodone, 10 and 20 mg, every 12 hours.

CR oxycodone. Overall mean scores showed little difference in night, morning, afternoon, or evening pain assessments, demonstrating continuous stable pain control over 24 hours. The mean scores for each time of day differed by a maximum of 0.1 U in the placebo group and 0.2 U in the 2 CR oxycodone groups. There were no significant center × treatment interactions. Baseline pain intensity was significant, but sex and age were not significant factors among the 3 treatment groups. At weeks 1 and 2, the Brief Pain Inventory assessments of pain intensity showed that use of 20 mg of CR oxycodone q12h was significantly more effective than placebo use ( $P < .05$ ) in improvement from baseline for pain right now and for worst and average pain in the last 24 hours. At week 2, use of the 20-mg dose was significantly more effective than was use of placebo for least pain in the last 24 hours



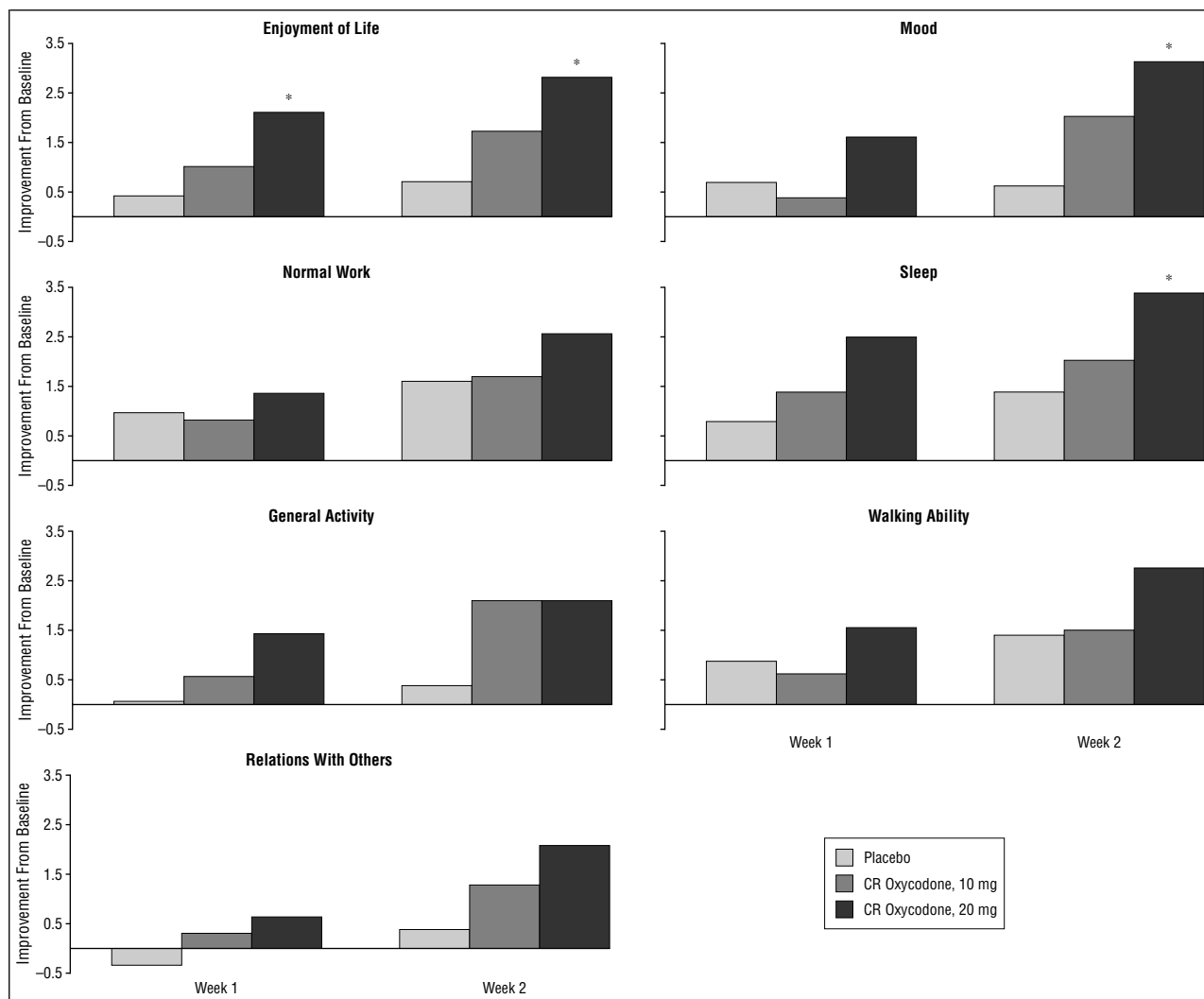
**Figure 2.** Daily mean pain intensity (0 indicates none; 1, slight; 2, moderate; and 3, severe) during 14-day double-blind treatment. CR indicates controlled release. Error bars represent SE.

and use of the 10-mg dose for worst and least pain in the last 24 hours.

The 20-mg CR oxycodone group showed significant ( $P < .05$ ) mean improvements from baseline in mitigating the interference of pain on mood, sleep, and enjoyment of life (**Figure 3**). Interference of pain on walking ability, general activity, normal work, and relations with others showed some improvement from baseline but did not reach statistical significance. The 10-mg CR oxycodone group showed larger improvements from baseline than did the placebo group for pain and function, but differences were not statistically significant.

At baseline, activities and lifestyle questionnaire scores ranged from 1.1 (0.1) to 2.3 (0.1) on the 4-point scale. Thus, most patients were able to perform daily activities “without any difficulty” or “with some difficulty.” Treatment with 10 or 20 mg of CR oxycodone q12h did not result in increased impairment in the performance of these functions and did not improve performance. Quality of sleep was significantly better in patients receiving 20 mg of CR oxycodone q12h than in those receiving placebo at week 1 and overall ( $P < .05$ ).

Eighty-seven (65.4%) of 133 patients reported at least 1 treatment-related adverse experience during the study; the most common were known opioid-related side effects (**Table 2**). Common gastrointestinal events seemed to be dose related, whereas no dose relationship was apparent for CNS events. Using a logistic regression model, there were no significant differences in these adverse events between men and women. In patients 65 years and older vs those younger than 65 years, only somnolence was significantly more prevalent in elderly patients ( $P = .02$ ). No adverse events were life threatening. There were no clinically significant safety observations concerning physical examination results, laboratory findings, or changes in vital signs.



**Figure 3.** Mean improvement from baseline in mitigating interference of pain with lifestyle (using the Brief Pain Inventory and a numerical scale from 0-10). CR indicates controlled release. Asterisk indicates  $P < .05$  better than placebo.

### LONG-TERM EXTENSION TRIAL

Twenty-six men and 80 women aged 32 to 88 years (mean, 62 years) enrolled in the long-term trial. Forty-five patients (42.5%) were 65 years or older. Seventy-three patients (68.9%) continued NSAID therapy during the long-term trial. Sixty patients (56.6%) discontinued treatment with CR oxycodone for the following reasons: adverse events (32 patients), ineffective treatment (8 patients), intercurrent illness (6 patients), withdrew consent (5 patients), lost to follow-up (3 patients), noncompliance (3 patients), no longer required opioid therapy (2 patients), and physician's advice (1 patient). The most common adverse events leading to discontinuation were constipation, nausea, pruritus, somnolence, and nervousness. One of the 3 noncompliant patients took more drug than prescribed. Thirty-one patients were required to discontinue treatment with CR oxycodone because the sponsoring company ended the study. At that time, 58 patients had completed 6 months of treatment, 41 had completed approximately 12 months (48 weeks), and 15 had completed 18 months. Analgesics used after study

completion were recorded for 48 patients, 46 of whom continued opioid therapy.

The dose of CR oxycodone became constant at approximately 40 (2) mg/d by week 16, ranging from 39 (2) to 41 (4) mg/d between weeks 16 and 72 (**Figure 4**). The highest percentage of patients, 65.1% (69/106), required dose titration at week 2. The dose was increased in all but 7 of these patients, and 67 patients required asymmetrical titration. After week 8, when 35.2% of patients required titration, the percentage declined from 9.5% to 21.3% per visit for the remainder of the trial. A higher percentage of patients required downward titration as the trial progressed. Thirty-nine patients (36.8% of those enrolled) were receiving asymmetrical doses at the time of completion or discontinuation, with 32 receiving a higher dose in the morning than in the evening.

Pain was controlled below a "moderate" level throughout the long-term trial, with no statistically significant trends from week 2 to the end of the trial. Pain intensity was 1.7 (0.1) at 6 months and ranged from 1.7 (0.1) to 1.9 (0.1) during weeks 32 to 72 (Figure 4). At the end of each scheduled respite, pain intensity rose to

**Table 2. Treatment-Related Adverse Experiences Reported by More Than 10% of 133 Patients During the Placebo-Controlled Trial\***

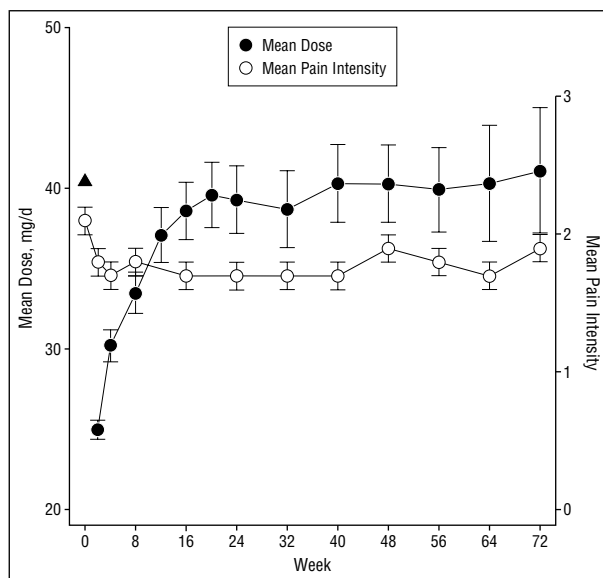
Adverse Experience	Placebo Group (n = 45)	CR Oxycodone q12h Group	
		10 mg (n = 44)	20 mg (n = 44)
Nausea	5 (11)	12 (27)	18 (41)
Constipation	3 (7)	10 (23)	14 (32)
Somnolence	2 (4)	11 (25)	12 (27)
Vomiting	3 (7)	5 (11)	10 (23)
Dizziness	4 (9)	13 (30)	9 (20)
Pruritus	1 (2)	8 (18)	7 (16)
Headache	3 (7)	4 (9)	5 (11)

\*Values are expressed as number (percentage) of patients. CR indicates controlled release; q12h, every 12 hours.

above moderate, with scores ranging from 2.3 (0.1) to 2.5 (0.2). These average scores were close to the mean score at baseline of the placebo-controlled trial (Table 1). More than 80% of patients rated their level of pain as unacceptable during each respite.

The activities and lifestyle questionnaire findings showed that patients were not highly impaired when they entered the long-term trial. They could perform activities of daily living “without any difficulty” or “with some difficulty.” At 6 months and for the remainder of the trial, there were small changes of 0.1 to 0.4 U on the 4-point scale, indicating that CR oxycodone therapy did not lead to a deterioration or an improvement in function. Patients rated quality of sleep as “fair” when they entered the long-term trial (3.1 [0.1]) and fair to “good” at 6 months (3.6 [0.1]). This was constant for the remainder of the trial, with scores ranging from 3.4 (0.2) to 3.7 (0.1). The number of night awakenings due to pain was 1.6 (0.2) at baseline, 0.7 (0.1) at 6 months, and 0.6 (0.2) to 1.4 (0.3) for the remainder of the trial.

The adverse experiences reported by more than 10% of patients during the long-term trial were those usually anticipated with use of opioid analgesics: constipation (55 patients), somnolence (32 patients), nausea (25 patients), pruritus (21 patients), nervousness (16 patients), headache (14 patients), and insomnia (14 patients). The duration ratio (calculated as the number of days a patient experienced the adverse event divided by the number of days the patient was treated with CR oxycodone, expressed as a percentage) for 4 typical opioid side effects—nausea, pruritus, somnolence, and constipation—decreased during the trial. This downward trend was statistically significant for all 4 adverse events ( $P < .001$ ) (Figure 5). Thirteen patients were hospitalized during the 18-month trial. In 8 of these patients, the investigator judged that the hospitalization was unrelated to CR oxycodone therapy. Five patients were hospitalized for adverse events in which a causal relationship to CR oxycodone use could not be ruled out, all of which resolved with treatment: 2 for abdominal pain, 1 for constipation, 1 for withdrawal symptoms, and 1 for a fall secondary to confusion and disorientation. The last patient was receiving many CNS-active medications. The

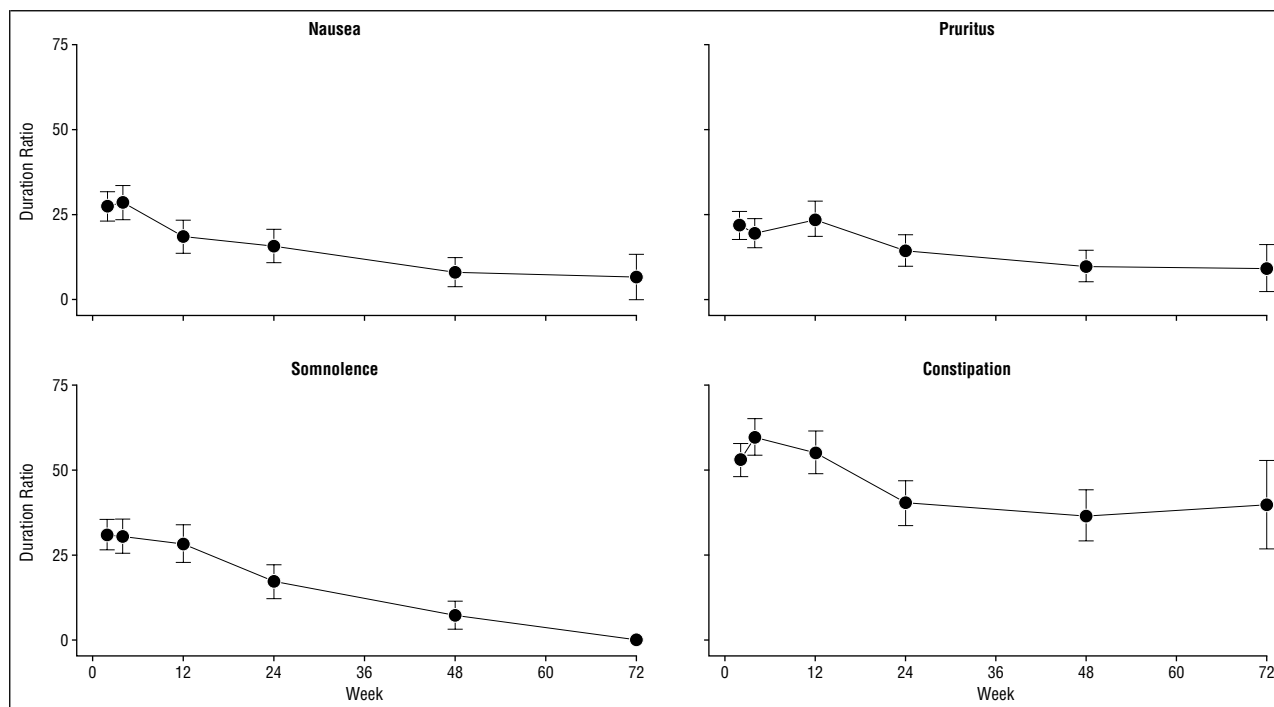


**Figure 4.** Daily dose of controlled-release oxycodone administered and pain intensity (0 indicates none; 1, slight; 2, moderate; and 3, severe) during the long-term trial. The black triangle indicates the baseline pain intensity lead-in. Error bars represent SE.

confusion and disorientation were attributed to doubling the dose of one of these medications (flurazepam hydrochloride) in the presence of other CNS-active medications, including CR oxycodone. The patient who was hospitalized with withdrawal symptoms had completed the study on the previous day and had been receiving CR oxycodone, 70 mg/d; symptoms resolved after 3 days. A second patient, who was receiving 60-mg/d CR oxycodone, experienced withdrawal symptoms after running out of study medication. The patient had not reported withdrawal symptoms during scheduled respites from doses of 30 or 40 mg/d. Withdrawal syndrome was not reported as an adverse event for any patient during scheduled respites. Adverse experiences reported by more than 10% of patients during the scheduled respites were nervousness (9 patients) and insomnia (8 patients). During the long-term trial, there were no clinically significant safety observations concerning physical examination results, laboratory findings, or changes in vital signs.

## COMMENT

Moderate to severe osteoarthritis pain is difficult to manage adequately with non-centrally acting analgesics. Acetaminophen and NSAIDs have an analgesic ceiling<sup>7</sup> and potential toxic effects at high doses.<sup>8,9</sup> Toxic effects associated with long-term use of high-dose NSAIDs are of particular concern in elderly patients,<sup>9,10</sup> the population most likely to experience osteoarthritis. As the population ages, the demand for effective analgesics for treatment of osteoarthritis pain is likely to increase. Opioid analgesic therapy might offer an alternative for patients whose pain cannot be controlled by use of weaker analgesics or in whom use of NSAIDs is contraindicated.<sup>33</sup> Although the benefits of long-term use of opioids for chronic noncancer pain is debated in the literature,<sup>14-19</sup> there is growing recognition that some patients



**Figure 5.** Mean duration ratio (calculated as the number of days the patient experienced the adverse event divided by number of days the patient was treated with controlled-release oxycodone, expressed as a percentage) of 4 opioid side effects during the long-term trial. Error bars represent SE.

achieve pain relief without deterioration in function when opioids are included as part of a comprehensive pain management program.<sup>20-25</sup>

Results of our clinical trials showed that CR oxycodone therapy provided clinically meaningful, sustained analgesia with a typical opioid side effect profile during short- and long-term treatment of moderate to severe osteoarthritis pain. Use of CR oxycodone at a dose of 20 mg q12h provided a clinically meaningful reduction in pain within 24 hours and was significantly more effective than placebo during the 2-week study. Improved analgesia was accompanied by significant reductions in the interference of pain with mood, sleep, and enjoyment of life and by significant improvement in quality of sleep. During long-term therapy, the mean dose of CR oxycodone stabilized at approximately 40 mg/d after an initial titration period, while analgesia was maintained throughout the trial. Scheduled respites supported the continuing need for opioid analgesia in these patients, with pain intensity returning to prestudy baseline levels when CR oxycodone therapy was discontinued. Patients' ability to conduct their daily activities was neither impaired nor improved during short- or long-term therapy with CR oxycodone. Our study population exhibited little functional impairment at baseline, leaving little room for treatment-related improvement.

Overall discontinuation rates were similar in the double-blind (52.6%) and long-term (56.6%) trials. The rate of discontinuation for ineffective treatment was related to the CR oxycodone dose; rates were similarly low in patients treated with 20 mg of CR oxycodone q12h in the placebo-controlled trial and in patients whose dose was individually titrated in the long-term trial (to an average dose of 40 mg/d). In contrast, discontinuation rates

for adverse events were similar across CR oxycodone groups, whether the dose was fixed or titrated and despite the differences in duration of therapy in the 2 trials. In a trial<sup>34</sup> of CR oxycodone therapy in cancer pain, discontinuations for ineffective treatment were lower when the dose was titrated compared with a fixed dose based on previous opioid use, whereas discontinuations for adverse events were similar whether the dose was titrated or fixed. Individual dose titration and careful patient monitoring, along with appropriate treatment of opioid-related side effects, are important components of the pain management program when opioids are used.<sup>33</sup>

During short- and long-term treatment with CR oxycodone, the most commonly reported adverse experiences were characteristic of opioid use. The duration of nausea, pruritus, and somnolence relative to CR oxycodone exposure decreased during the trial. Decreasing frequency of nausea and sedation has been reported<sup>11</sup> during long-term opioid therapy for cancer pain. The present study also showed a decreasing duration of constipation relative to CR oxycodone exposure, which likely reflects effective preventive therapy because experience in cancer pain indicates that constipation generally persists during long-term opioid therapy.<sup>11</sup> There were 2 reports of withdrawal symptoms after patients abruptly stopped taking CR oxycodone at doses of 60 or 70 mg/d. Withdrawal syndrome was not reported as an adverse event during scheduled respites, indicating that CR oxycodone at doses below 60 mg/d can be discontinued without tapering the dose if the patient's condition so warrants.

Results of our studies in patients with moderate to severe osteoarthritis pain support those of previous controlled trials<sup>26,27</sup> demonstrating the analgesic efficacy of CR opioids for treating chronic noncancer pain and pre-

vious clinical experience<sup>20-25</sup> demonstrating that some patients with noncancer pain benefit from the pain relief offered by opioids without a deterioration in function. Management of chronic osteoarthritis pain requires non-pharmacological and pharmacological approaches. When use of weaker analgesics is ineffective or contraindicated, use of opioid analgesics can be of benefit when they are incorporated into a multidisciplinary, individualized treatment program. Key components of such a program include patient screening, regular pain assessments, dose titration to an acceptable balance between analgesia and side effects, dosing scheduled by the clock, control of breakthrough pain, and ongoing management of side effects.<sup>33</sup> Within such a framework, patients with osteoarthritis can benefit from the analgesic effects of opioids and minimize their adverse effects.

In conclusion, around-the-clock CR oxycodone therapy seemed to be an effective and safe treatment modality for patients with chronic, moderate to severe pain associated with osteoarthritis. Effective analgesia was accompanied by a reduction in the interference of pain with mood, sleep, and enjoyment of life. Analgesia was maintained during long-term treatment, and the daily CR oxycodone dose remained stable after an initial titration period. Common opioid-related side effects were reported during CR oxycodone therapy, several of which decreased in duration as therapy continued. Patients' ability to function was not compromised during short- and long-term treatment with CR oxycodone.

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