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CME

Controlled-release oxycodone for pain in diabetic neuropathy

A randomized controlled trial

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Abstract—*Background and objective:* Opioid treatment has played a limited role in the management of diabetic neuropathy, in part because of concerns about the responsiveness of neuropathic pain to opioid treatment. This controlled study evaluated the efficacy and safety of controlled-release (CR) oxycodone in subjects with moderate to severe pain due to diabetic neuropathy. *Methods:* This multicenter, randomized, double-blind, placebo-controlled, parallel-group study included 159 subjects with moderate to severe pain due to diabetic neuropathy. Treatment began with either one 10-mg tablet of CR oxycodone (n = 82) or identical placebo (n = 77) every 12 hours. Doses could be increased every 3 days to a maximum of 6 tablets (60 mg CR oxycodone) every 12 hours. Treatment lasted up to 6 weeks. The primary efficacy variable was overall average daily pain intensity during study days 28 to 42. *Results:* At an average (SD) dose of 37 (21) mg per day (range 10 to 99 mg/d), CR oxycodone provided more analgesia than placebo ($p = 0.002$) in the intent-to-treat cohort. From days 28 to 42, overall average daily pain intensity (least squares mean ±SE), rated in subject diaries on a numeric scale of 0 (no pain) to 10 (pain as bad as you can imagine), was 4.1 ± 0.3 in subjects given CR oxycodone and 5.3 ± 0.3 in placebo-treated subjects. Overall, 80 (96%) of 82 subjects given CR oxycodone and 52 (68%) of 77 subjects who received placebo reported adverse events. The most common adverse events in the CR oxycodone group were opioid related. *Conclusions:* In this 6-week trial, CR oxycodone was effective for the treatment of moderate to severe pain due to diabetic neuropathy. Adverse events were typical of opioid-related side effects.

NEUROLOGY 2003;60:927–934

Diabetic neuropathy is a heterogeneous set of disorders caused by many factors that injure sensory or sensorimotor nerves.[1] The mechanisms are complex and involve pathology of both myelinated and unmyelinated fibers.[2] The most common subtype of neuropathy is a symmetrical length-dependent neuropathy associated with injury to sensory, motor, and autonomic nerve fibers.[3] Patients with these disorders experience

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Supported by a grant from Purdue Pharma L.P. Purdue Pharma L.P. provided an educational grant and fees for educational services rendered to the Department of Pain Medicine and Palliative Care, Beth Israel Medical Center, New York, NY, chaired by Dr. Portenoy.

Received May 8, 2002. Accepted in final form January 8, 2003.

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pain, dysesthesias, and uncomfortable paresthesias, particularly involving the lower extremities. The morbidities related to diabetic neuropathy can have a profound adverse impact on an individual's day-to-day functioning and well-being. The reported prevalence of neuropathy in patients with diabetes varies widely depending on the criteria used.[1] In the Rochester Diabetic Neuropathy Study, 61% of diabetic patients showed some form of diabetic neuropathy after extensive neurologic evaluation, and 48% had diabetic polyneuropathy.[4] Others report a prevalence of 16%.[5] The prevalence of pain associated with diabetic neuropathy is poorly documented. Some authors report that less than 10% of diabetic patients in a clinic setting experienced pain.[6] In another study, however, pain was reported by 32% of a sample of non–insulin-dependent diabetics.[7]

Pharmacotherapy is a mainstay approach in the management of pain in patients with diabetic neuropathy.[8,9] Although controlled studies support the use of tricyclic antidepressants,[10-16] selective serotonin reuptake inhibitors,[17-19] anticonvulsants,[20,21] and a number of other drugs, such as ion channel blockers[22,23] and topical agents,[24,25] therapy remains unsatisfactory for many patients.

Opioids may be effective for pain in diabetic neuropathy; however, data are very limited, and findings must be extrapolated from experience with other types of neuropathic pain or from trials of related drugs. A controlled study showed that oxycodone, a pure μ-agonist, is effective in treating pain associated with postherpetic neuralgia.[26] Tramadol, a centrally acting analgesic with opioid activity, also relieved pain and allodynia in patients with chronic painful polyneuropathy and was effective in painful diabetic neuropathy in randomized, double-blind, controlled trials.[27,28]

The goal of the current study was to determine the efficacy and safety of CR oxycodone for the treatment of moderate to severe persistent pain associated with diabetic neuropathy.

Methods. The study was conducted according to the Declaration of Helsinki and was approved by institutional review boards at each of 15 sites in the United States. All subjects provided written informed consent. The design was a multicenter, randomized, double-blind, placebo-controlled, parallel-group comparison of CR oxycodone and placebo. There was an initial washout/screening phase of 3 to 7 days followed by a 42-day, double-blind treatment phase.

Subjects. A total of 159 adults with a history of stable diabetes mellitus and a glycosylated hemoglobin (HbA_{1C}) level of ≤11% were randomized and received at least one dose of study medication.

Subjects had painful symmetrical distal polyneuropathy documented by neurologic evaluation using the Einstein Focused Neurologic Assessment (J.C. Arezzo and H.H. Schaumburg, written communication, April 1999). Investigators trained in this procedure assigned an overall clinical impression scored on a four-point categorical scale to assessments of distal sensory function, distal muscle strength, and select reflexes. Distal sensory function was examined bilaterally at three standardized sites on the lower limbs (base of great toe, anterior malleolus, and head of fibula) using the following stimuli and instruments: light touch (Semmes-Weinstein monofilaments); temperature (cold only; metal thermal rod); and sharp (pin). Distal muscle strength (finger spread, great toe extension, ankle dorsiflexion) and deep tendon reflexes (biceps brachii, quadriceps femoris, and Achilles) also were assessed bilaterally.

Candidates for the study were required to have a pain syndrome consistent with painful symmetrical distal polyneuropathy; a history of pain in both feet (defined as an average pain intensity score of ≥5 on a numeric scale of 0 to 10) for more than half the day for at least 3 months prior to enrollment; and at least moderate pain in the absence of any opioid analgesic therapy for 3 days before receiving the study treatment. All prestudy opioid drugs were discontinued before administration of study medication.

Subjects were excluded from participation if they had 1) unstable or poorly controlled diabetes; 2) chronic pain unrelated to diabetic neuropathy; 3) a history of substance or alcohol abuse within the past 10 years; 4) serum creatinine levels ≥2.5 mg/dL; 5) hepatic dysfunction ≥3 times the upper limit of normal; 6) a history of active cancer, excluding basal cell carcinoma of the skin, in the past 3 years; 7) hypersensitivity to oxycodone or opioids; 8) rapidly escalating pain or recent neurologic deficit within the previous month; 9) a total of more than three doses per day of a short-acting opioid formulation in the preceding 2 weeks; 10) treatment with any long-acting opioid formulation; 11) autonomic neuropathy or gastrointestinal dysfunction that could compromise drug absorption or increase the risk from therapy; or 12) a need for elective surgery involving preoperative or postoperative analgesics or anesthetics during the study period. Women were excluded if they were pregnant or breast-feeding.

Treatment assignment. Prior to study start, subjects were assigned to treatment using a randomization schedule with permuted blocks of size 4 which was generated by the sponsor with SAS software (SAS Institute, Cary, NC). The schedule was used to package and label the study medication shipped to the investigative sites. The randomized treatment assignment was executed by the site staff, who assigned subject numbers in ascending sequence as subjects qualified for randomization. Site staff dispensed the blinded medication. Sealed randomization information was provided to the sites if needed for an emergency. Sealed copies of the randomization schedule also were placed in locked sponsor files. Unblinding took place according to a standard procedure after the database was locked and the analysis plan, including evaluability determination, finalized.

Procedures. Subjects were screened 3 to 7 days prior to entering the treatment phase. During the screening visit, a history was taken, subjects had a general physical and neurologic examination, and blood was sampled for HbA_{1C}, and renal and liver function tests. Subjects discontinued all opioid therapy at least 3 days before starting any study medication. Outpatient visits were scheduled on days 0 (start of treatment), 14, 28, and 42 (or at the time of discontinuation from study therapy) of the double-blind treatment phase.

Subjects received CR oxycodone (OxyContin; Purdue Pharma L.P., Stamford, CT) or an identical placebo tablet every 12 hours during the treatment phase of the study. Dosing began with one tablet of CR oxycodone (10 mg) or matching placebo. Subjects could increase the dose by one 10-mg tablet of CR oxycodone or placebo in the morning and one 10-mg tablet in the evening. Upward titration could occur every 3 days up to a maximum dose of 6 tablets (60 mg CR oxycodone) twice daily. No opioid rescue was allowed. If a subject developed unacceptable side effects, the dose could be decreased to the previous acceptable level. A medication compliance worksheet was completed at each study visit. Treatment lasted up to 6 weeks. After the end of the study, a final 1-week taper was optional.

Medications taken for diabetes control as well as adjuvant pain medications were continued at the same stable prestudy dose. Except for study medications, no other opioid analgesics were permitted. Other nonopioid analgesics, such as nonsteroidal anti-inflammatory drugs or acetaminophen, taken at a stable dose for ≥3 weeks before the study could be continued at the same prestudy dose. Stable dosing of concomitant medications was documented at each study visit.

Efficacy variables. The primary efficacy analysis was based on average daily pain intensity during the past 24 hours obtained during the study period from days 28 to 42. Pain intensity was rated in a daily diary using an 11-point scale ranging from 0 (no pain) to 10 (pain as bad as you can imagine). During the screening phase, subjects completed the diary for a minimum of 3 days

without opioid therapy and qualified for the study if they attained an average pain intensity score of ≥5. The daily diary also included 0 to 10 scales for current pain and worst pain; a 1 (not satisfied) to 6 (totally satisfied) scale for satisfaction with pain medication; and a 0 (poor sleep) to 10 (excellent sleep) scale for sleep quality. All scales were numeric.

Secondary end points included 1) scores recorded in the daily diary for average pain intensity from days 1 to 27, and for current and worst pain, satisfaction with pain medication, and sleep quality from days 1 to 42; 2) total and subscale scores calculated from the 14-item Brief Pain Inventory (BPI)[29] administered on days 0, 14, 28, and 42, or at study discontinuation; 3) scores for validated measures of psychological state (Rand Mental Health Inventory[30]), physical functioning (Sickness Impact Profile[31]), and general health status (SF-36 Health Survey[32]) obtained on days 0 and 42, or at discontinuation; 4) proportion of subjects who discontinued the study medication due to lack of efficacy; and 5) time to mild pain, number of days with mild pain, and proportion of days with mild pain.

Safety variables. The investigator asked about adverse events at each study visit, and reported events were graded for severity and probability of relationship to the study drug.

Statistical analyses. Based on an expected SD of 2.5 for the pain intensity score, 64 evaluable subjects per group were required to detect a difference between treatment groups of 1.25 on an 11-point scale with 80% power and a 5% level of significance. Planned enrollment was 160 subjects. The intent-to-treat (ITT) efficacy analysis included all subjects who received at least one dose of study medication. Because one subject was excluded due to double enrollment, the ITT efficacy analysis included 159 subjects. A per protocol cohort of 146 subjects was also defined; this cohort excluded 10 subjects from the CR oxycodone group and 4 from the placebo group because of protocol violations. Missing observations due to discontinuation were extrapolated by carrying forward values from the last observation immediately before discontinuation up to and including day 42. Intermittent missing data were not imputed.

The primary efficacy analysis used repeated measures analysis of covariance (ANCOVA) with day as the repeated factor to compare the average pain intensity during the past 24 hours recorded in the daily diary (from days 28 to 42) between treatment groups. The period between days 28 and 42 was selected to allow for an initial titration period. The null hypothesis postulated no overall treatment group effect from days 28 to 42. Baseline pain, center, treatment, study day, age group, sex, treatment by day, and treatment by center were included as effects in the ANCOVA. Baseline pain was included as a covariate because it was considered a prognostic variable. Secondary efficacy analyses used the same statistical model but included baseline measurements for the respective variables instead of baseline pain. Results of the ANCOVA analyses are reported as least squares means, i.e., group

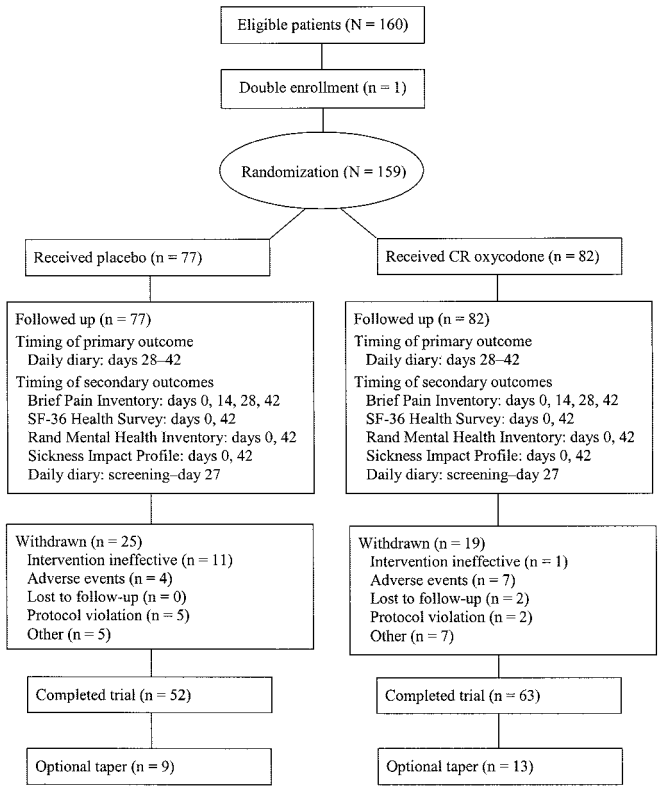

Figure 1. Flow diagram for subjects enrolled in the study.

Table 1 *Subject characteristics: ITT cohort*

Characteristic	Placebo, n = 77	CR oxycodone, n = 82	Total, n = 159
Male, n (%)	38 (49.4)	45 (54.9)	83 (52.2)
White, n (%)	62 (80.5)	72 (87.8)	134 (84.3)
Age, y, mean (SD)	58.8 (12.4)	59.0 (10.2)	58.9 (11.3)
Screening HbA_{1C}, %, mean (SD)	7.9 (1.5)	7.6 (1.4)	7.8 (1.4)
Baseline pain intensity, mean (SD)*	6.8 (1.3)	6.9 (1.4)	6.9 (1.4)
Prior or concomitant medications			
Opioid analgesics, n (%)	7 (9.1)	12 (14.6)	19 (11.9)
Nonopioid analgesics, n (%)	61 (79.2)	72 (87.8)	133 (83.6)
Adjuvant pain medications, n (%)	47 (61.0)	47 (57.3)	94 (59.1)
Anticonvulsants†	10 (13.0)	14 (17.1)	24 (15.1)
Tricyclic antidepressants‡	17 (22.1)	18 (22.0)	35 (22.0)
Other antidepressants	10 (13.0)	16 (19.5)	26 (16.4)
Benzodiazepines	6 (7.8)	9 (11.0)	15 (9.4)
Other adjuvants	19 (24.7)	20 (24.4)	39 (24.5)
Diabetes medications, n (%)	74 (96.1)	75 (91.5)	149 (93.7)

* 0 (no pain) to 10 (pain as bad as you can imagine).
† Twenty-two (92%) of 24 subjects who took anticonvulsants were taking gabapentin (mean baseline dose, 445 mg).
‡ Twenty-seven (77%) of 35 subjects who took tricyclic antidepressants were taking amitriptyline (mean baseline dose, 47 mg).

Table 2 *Neurologic assessment at baseline: ITT cohort**

Neurologic assessment	Overall clinical impression†	Placebo, n = 77	CR oxycodone, n = 82	Total, n = 159
Distal sensory function‡				
Light touch	Normal	9 (11.7)	4 (4.9)	13 (8.2)
	Mild	7 (9.1)	9 (11.0)	16 (10.1)
	Moderate	38 (49.4)	35 (42.7)	73 (45.9)
	Severe	23 (29.9)	34 (41.5)	57 (35.8)
Temperature (cold only)	Normal	11 (14.3)	9 (11.0)	20 (12.6)
	Mild	12 (15.6)	14 (17.1)	26 (16.4)
	Moderate	29 (37.7)	31 (37.8)	60 (37.7)
	Severe	25 (32.5)	28 (34.1)	53 (33.3)
Sharp (pin)	Normal	12 (15.6)	5 (6.1)	17 (10.7)
	Mild	11 (14.3)	16 (19.5)	27 (17.0)
	Moderate	33 (42.9)	35 (42.7)	68 (42.8)
	Severe	21 (27.3)	26 (31.7)	47 (29.6)
Muscle strength	Normal	51 (66.2)	60 (73.2)	111 (69.8)
	Mild	17 (22.1)	19 (23.2)	36 (22.6)
	Moderate	8 (10.4)	3 (3.7)	11 (6.9)
	Severe	1 (1.3)	0	1 (<1%)
Reflexes	Normal	17 (22.1)	10 (12.2)	27 (17.0)
	Mild	19 (24.7)	19 (23.2)	38 (23.9)
	Moderate	30 (39.0)	38 (46.3)	68 (42.8)
	Severe	11 (14.3)	15 (18.3)	26 (16.4)

Values are n (%).

* Einstein Focused Neurologic Assessment.
† Rated on a four-point categorical scale. Scores for bilateral sites combined.
‡ Tested on the dorsal surface of the great toe, anterior malleolus, and head of fibula.

means adjusted for covariates and other terms in the statistical model.

Time to mild pain was estimated using the Kaplan-Meier method, and the two treatments were compared by the log-rank test. The Wilcoxon test was used to compare treatment differences in the number and proportion of days with mild pain. Adverse events were classified by COSTART term and body system, and tabulated by treatment group. Fisher's exact test was used to compare discontinuation rates and the incidence of adverse events between treatment groups. All statistical tests were two-tailed at the 0.05 level of significance.

Results. Figure 1 shows a flow diagram for all subjects who entered the trial. A total of 160 subjects were enrolled at 15 sites and received at least one dose of study medication. One subject was enrolled twice (nonoverlapping periods of study enrollment); only the information from the first period of study enrollment was included in the ITT analysis. Both the ITT and safety analyses included 159 randomized subjects: 82 received CR oxycodone and 77 received placebo every 12 hours. Monitoring confirmed that the blind was not broken at the sites.

Baseline characteristics, including control of diabetes (as measured by HbA_{1C} levels), were similar in both treatment groups (table 1). The study population consisted predominantly of white men and had a mean age of 59 years. On the 0 to 10 scale, the average daily pain intensity at baseline was 6.9 for the CR oxycodone group and 6.8 for the placebo group. While overall clinical impressions of neurologic status showed small treatment group differences (table 2), they were considered clinically unimportant. Twelve subjects who received CR oxycodone and seven of those given placebo had a history of opioid analgesic use. The majority had received nonopioid analgesics together with adjuvant pain medications (see table 1).

One hundred fifteen (72%) of 159 subjects completed the study. Of the 44 subjects (28%) who discontinued prematurely, 12 discontinued because of ineffective treatment and 11 because of adverse events. Of the 12 subjects discontinuing due to inadequate pain control, 1 was in the CR oxycodone group and 11 were in the placebo group ($p = 0.002$). Of the 11 subjects discontinuing due to adverse events, 7 were in the CR oxycodone group and 4 in the placebo group ($p = 0.536$). Eight (5 CR oxycodone and 3 placebo) of the 11 were considered to have events related to the study drug. Among the remaining subjects who discontinued prematurely, seven discontinued due to protocol violations (2 in the CR oxycodone group and 5 in the placebo group).

Overall, 17 subjects (10 CR oxycodone and 7 placebo) had protocol violations that justified exclusion from the per protocol cohort, discontinuation, or both. Fourteen of these subjects (10 CR oxycodone and 4 placebo) were excluded from the per protocol cohort; 11 of these exclusions (8 CR oxycodone and 3 placebo) were due to a baseline neurologic assessment score that was lower than the cutoff criterion. Two other exclusions were due to a change in the dose of gabapentin or nonopioid analgesic during the study.

Of the 82 subjects who received CR oxycodone, the average (SD) daily dose from days 1 to 14 was 29 (11) mg. The dose increased to 42 (27) mg by days 15 to 28 and remained at this level from days 29 to 42. Subjects with prior opioid use received a slightly higher average daily dose of CR oxycodone (48 ± 27 mg) than those who were opioid-naive (35 ± 19 mg). Although subjects were allowed to increase the dose to a maximum of 120 mg per day, the overall average daily dose of CR oxycodone was 37 (21) mg per day (range 10 to 99 mg/d), approximately one third of the

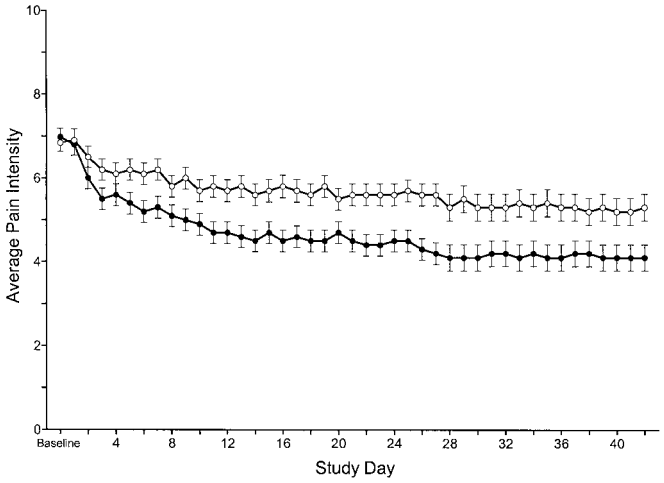

*Figure 2. Average pain intensity scores recorded in subject daily diaries from days 28 to 42 were reduced with the use of CR oxycodone (4.1 ± 0.3) compared with placebo (5.3 ± 0.3) (*p *= 0.002) in the ITT cohort. Scale ranges from 0 (none) to 10 (pain as bad as you can imagine). Values are expressed as least squares means (SE). —○— = Placebo; —●— = CR oxycodone.*

maximum. The overall average daily dose of placebo was 52 (25) mg per day (range 20 to 99 mg/d). The overall average daily dose of CR oxycodone was relatively unchanged when subjects with dose-limiting adverse events were excluded. Mean compliance, or the total number of tablets taken by each subject divided by the total number of tablets planned for each subject, was about 95% for each treatment group and ranged from 21% to 146% for subjects treated with CR oxycodone and from 26% to 166% for those given placebo.

Because subjects were not permitted by protocol to change the doses of concomitant medications during the study, few changes in the doses of nonopioid analgesics, adjuvant pain medications, or medications taken for the control of diabetes were recorded. Medication classes with dose changes included nonsteroidal anti-inflammatory drugs (1 placebo), anticonvulsants (2 CR oxycodone and 1 placebo), oral hypoglycemics (3 CR oxycodone and 1 placebo), and insulin products (3 placebo).

Efficacy. In the ITT cohort, the efficacy analysis of the primary end point showed that CR oxycodone provided superior analgesia to placebo ($p = 0.002$) (figure 2). Least squares mean scores (SE) for overall average daily pain intensity from days 28 to 42 were 4.1 (0.3) for the CR oxycodone group and 5.3 (0.3) for the placebo group on a scale of 0 to 10. The primary efficacy results from the per protocol cohort confirmed these results: least squares mean scores (SE) for overall average daily pain intensity from days 28 to 42 in this cohort were 4.2 (0.3) for the CR oxycodone group and 5.3 (0.3) for the placebo group ($p = 0.009$). In the ITT cohort, a significant difference in average daily pain intensity between groups was first apparent by day 3. These differences were maintained throughout the treatment period (see figure 2). The period of sustained analgesia from days 28 to 42 coincided with a mean average daily CR oxycodone dose of 42 mg.

Analyses of the secondary efficacy variables obtained from the daily diary in the ITT cohort yielded similar results. CR oxycodone produced significant improvements in overall scores for average pain intensity from days 1 to 27 and for pain right now, worst pain, satisfaction with study medication, and sleep quality from days 1 to 42 (table 3). Significant improvements in all pain measurements (except worst pain) and in sleep quality were observed within 1 week of initiation of CR oxycodone therapy.

A comparison of BPI scores obtained at baseline and at the end of the study showed that 9 of 14 items (average pain intensity, pain right now, worst pain, least pain, pain relief, interference score, relations with other people, sleep, and enjoyment of life) were significant and improved in the CR oxycodone group compared with the placebo group (table 4). On the pain relief scale of 0% (no relief) to 100% (complete relief), mean scores at the final study visit were 53% for the CR oxycodone group compared with 37% for the placebo group ($p = 0.005$). No significant improvements occurred for the five remaining items of the BPI (physical function score, general activity, mood, walking ability, and normal work).

The median time to achieve mild pain (defined as an average pain intensity score of ≤4 on the 0 to 10 scale) was shorter for the CR oxycodone group (6 days) than for the placebo group (17 days) ($p = 0.017$). In addition, subjects treated with CR oxycodone had more days with mild pain: mean (SD) of 20.0 (16.6) days vs 12.5 (16.0) days for the placebo group ($p = 0.007$). Subjects who received CR oxycodone reported a higher mean (±SD) percentage of days with mild pain (47% ± 39%) compared with placebo-treated subjects (29% ± 37%) ($p = 0.006$).

No significant differences were observed between CR oxycodone and placebo groups in the physical functioning, general health, and mental health subscales of the SF-36 Health Survey or in the seven subscales of the Rand Mental Health Inventory. A significant difference in ambulation, a subscale of the Sickness Impact Profile, was observed between CR oxycodone and placebo groups at the final visit; however, the other 15 subscales of the Sickness Impact Profile showed no significant differences.

Safety. Safety was evaluated for all 159 randomized subjects. The incidence of adverse events was greater in the CR oxycodone

Table 3 *Least squares means (SE) of overall scores from subject daily diaries: ITT cohort*

		Placebo, n = 77		CR oxycodone, n = 82		
Variable	Study days	Postbaseline value	Change from baseline	Postbaseline value	Change from baseline	*p* Value*
Average pain intensity†	1–27	5.9 (0.23)	−1.0 (0.23)	4.9 (0.23)	−2.0 (0.23)	<0.001
Pain right now†	1–42	5.1 (0.26)	−1.1 (0.26)	4.1 (0.26)	−2.1 (−0.26)	0.002
Worst pain†	1–42	6.4 (0.26)	−1.3 (0.26)	5.4 (0.26)	−2.4 (0.26)	0.001
Satisfaction with study drug‡	1–42	2.4 (0.18)	NA§	3.4 (0.18)	NA	<0.001
Sleep quality‖	1–42	5.4 (0.24)	0.5 (0.24)	6.1 (0.24)	1.2 (0.24)	0.024

* ANCOVA with effects for baseline measurement, center, age group, sex, treatment, study day, treatment by day, and treatment by center.

† 0 (no pain) to 10 (pain as bad as you can imagine).

‡ 1 (not satisfied) to 6 (totally satisfied).

§ Because of the large number of missing baseline values, change from baseline omitted, and baseline satisfaction scores not included in ANCOVA.

‖ 0 (poor sleep) to 10 (excellent sleep).

Table 4 *Least squares means (SE) of overall Brief Pain Inventory scores from days 14 to 42: ITT cohort*

Variable	Placebo, n = 77		CR oxycodone, n = 82		*p* Value*
	Postbaseline value	Change from baseline	Postbaseline value	Change from baseline	
Average pain intensity†	5.2 (0.28)	−1.5 (0.29)	4.2 (0.28)	−2.6 (0.28)	0.004
Pain right now†	4.4 (0.28)	−1.6 (0.29)	3.2 (0.28)	−2.8 (0.29)	<0.001
Worst pain†	6.2 (0.32)	−1.6 (0.33)	4.9 (0.32)	−2.9 (0.32)	0.001
Least pain†	4.0 (0.26)	−1.1 (0.26)	3.1 (0.25)	−1.9 (0.25)	0.004
Pain relief‡	36.9 (4.15)	17.5 (4.24)	55.8 (4.08)	37.2 (4.12)	<0.001
Interference score§	4.3 (0.27)	−1.8 (0.27)	3.5 (0.26)	−2.6 (0.26)	0.015
Physical function score‖	4.4 (0.28)	−1.9 (0.29)	3.8 (0.28)	−2.4 (0.28)	0.139
General activity¶	4.1 (0.29)	−1.8 (0.29)	3.5 (0.29)	−2.4 (0.29)	0.075
Mood¶	3.7 (0.32)	−2.1 (0.32)	3.2 (0.32)	−2.6 (0.31)	0.217
Walking ability¶	4.5 (0.32)	−2.0 (0.33)	4.2 (0.32)	−2.4 (0.33)	0.337
Normal work¶	4.4 (0.31)	−1.9 (0.32)	3.9 (0.31)	−2.4 (0.31)	0.237
Relations with other people¶	3.2 (0.27)	−1.3 (0.27)	2.4 (0.27)	−2.0 (0.27)	0.023
Sleep¶	5.3 (0.31)	−1.5 (0.32)	3.6 (0.32)	−3.3 (0.32)	<0.001
Enjoyment of life¶	4.6 (0.32)	−2.2 (0.32)	3.6 (0.31)	−3.2 (0.31)	0.016

* ANCOVA with effects for baseline measurement, center, age group, sex, treatment, study day, treatment by day, and treatment by center.
† 0 (no pain) to 10 (pain as bad as you can imagine).
‡ 0% (no relief) to 100% (complete relief).
§ Mean of general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life scores.
‖ Mean of general activity, walking ability, and normal work scores.
¶ 0 (pain does not interfere) to 10 (pain completely interferes).

group than in the placebo group. Overall, 80 (96%) of 82 subjects treated with CR oxycodone and 52 (68%) of 77 subjects who received placebo reported adverse events. Seventy-one (86%) of 82 subjects given CR oxycodone compared with 33 (43%) of 77 subjects given placebo reported adverse events that were considered related to the study drug by the investigator. The majority of adverse events in both groups were mild or moderate.

The most commonly reported adverse events in the CR oxycodone group were those usually associated with opioid use: constipation (35 subjects), somnolence (33 subjects), nausea (30 subjects), and dizziness (26 subjects) (table 5). The most common adverse events reported among placebo-treated subjects were headache (18 subjects), constipation (11 subjects), and dizziness (8 subjects). The most common adverse event leading to discontinuation was nausea (2 CR oxycodone and 1 placebo). Overall, 26 (32%) of 82 subjects treated with CR oxycodone and 10 (13%) of 77 subjects given placebo had adverse events that were dose limiting (i.e., dose reduced, dose interrupted, or dose discontinued).

During the study, one death occurred in the CR oxycodone group during the fifth week of dosing; the cause of death was acute renal failure unrelated to the study drug. Thirteen other serious adverse events were reported: four in the CR oxycodone group (flulike syndrome, hyperglycemia, hypoglycemia, and epistaxis) and nine in the placebo group (alcohol intoxication, ascites, chest pain, asthenia, nausea, diarrhea, vomiting, decreased body weight, and dyspnea). None of these adverse events was considered related to the study drug.

Table 5 *Most frequently reported (≥10% of subjects) adverse events*

Adverse events	Placebo, n = 77	CR oxycodone, n = 82	*p* Value*
Constipation	11 (14)	35 (42)	<0.001
Somnolence	1 (1)	33 (40)	<0.001
Nausea	6 (8)	30 (36)	<0.001
Dizziness	8 (10)	26 (32)	<0.001
Pruritus	6 (8)	20 (24)	0.005
Vomiting	2 (3)	17 (21)	<0.001
Dry mouth	2 (3)	13 (16)	0.005
Asthenia	5 (7)	12 (15)	0.125
Headache	18 (23)	9 (11)	0.055

Values are n (%).

* Fisher's exact test.

Discussion. This study was conducted in a well-defined population of subjects with neuropathic pain related to diabetic neuropathy. The results demonstrated that CR oxycodone was significantly more effective than placebo for the primary efficacy variable—average pain intensity from days 28 to 42. Overall scores for average pain intensity from days 1 to 27, and for pain right now, worst pain, satisfaction with study medication, and sleep quality from days 1 to 42 were also significantly improved. In addition, subjects treated with CR oxycodone had more days with mild pain than placebo-treated subjects.

The study was powered appropriately and used a randomized, double-blind design to limit possible confounding or bias. While no measures were taken to blind investigators when subjects reported adverse events, the primary efficacy variable was based on subject diaries, so that it was probably not influ-

enced by the investigators; however, contact occurred between subjects and investigators on the day 28 study visit. While the subjects may have been influenced by changes in adverse event profiles, patients with diabetic neuropathy may experience constipation, nausea, and vomiting due to their underlying disease as well as to opioid side effects.

In this study, every effort was made to confirm that pain was related to the neuropathy. Any possible contribution of withdrawal symptoms from previous opioid analgesics to the total pain burden experienced by these subjects was minimal because few subjects (a total of 19) received opioids before the start of the study and, for those treated, opioid doses were low (highest dose, 10 mg hydrocodone per day). The generalizability of the results also is supported by the wide geographic distribution of the study centers across the United States and by the inclusion of a number of different practice settings, such as primary care, endocrinology, and neurology.

The time frame for the primary efficacy variable was days 28 to 42; the time frame for the secondary efficacy variable, average daily pain intensity, was days 1 to 27. Although the choice of these time frames was based on an assumed need for a 28-day titration period, the onset of pain reduction actually occurred within the first week of treatment and little titration was necessary.

Reduction in pain intensity was achieved with a relatively low average daily dose of CR oxycodone, which was one third of the maximum allowed in the study. The low dose attained during dose titration appeared to be due to sufficient efficacy rather than to poor tolerability because the average daily dose was relatively unchanged when subjects with dose-limiting adverse events were excluded. By protocol, the doses of nonopioid analgesics, adjuvant pain medications, and medications taken for control of diabetes were required to remain stable throughout the study, and few subjects changed their doses. As a result, concomitant medication use had little impact on the efficacy end points.

The adverse events reported during CR oxycodone therapy were similar to those observed in previous studies.[26,33] No significant difference occurred between CR oxycodone and placebo groups in the number of subjects discontinuing because of adverse events. Constipation occurs in diabetic patients with autonomic neuropathy and as a side effect of opioid therapy; the low incidence of severe constipation (1%) in this study was most likely a reflection of management with appropriate prophylactic laxative therapy.

Although opioid tolerance and physical dependence have been reported during chronic opioid therapy, neither phenomenon was demonstrated in this 42-day study. After the initial titration of CR oxycodone, there was no need for increasing doses to maintain the analgesic effect. Withdrawal symptoms also were not noted because most patients entered an extension trial and continued to receive CR oxycodone, and those who stopped the drug did so following a 1-week taper period after study completion. Tolerance and physical dependence must be anticipated during long-term opioid therapy but are seldom problems in the clinical setting. These phenomena are distinct from addiction (defined as compulsive use, loss of control over drug use, use despite harm, and craving), which also appears to be a very uncommon problem in patients with no history of drug abuse. Drug abuse was an exclusion criterion in this study, and no aberrant drug-related behavior was observed.

Studies examining opioid-related cognitive dysfunction in chronic nonmalignant pain are limited. A recent review[34] noted mixed results. Some authors report improvement[35] or lack of impairment[36,37] in cognitive status in parallel with pain relief, whereas others report significant cognitive and psychomotor impairment.[38] The use of long-term opioid therapy may have greater limitations in specific groups, such as the elderly. Decisions about the use of long-term opioid therapy should be taken with care because of the potential side effects.

The efficacy of CR oxycodone for moderate to severe pain due to diabetic neuropathy suggests that opioid therapy should be included among the therapeutic approaches used for this disorder. Subjects in this study had significant improvement in pain without intolerable adverse events or the need for increasing opioid doses. Other treatment strategies, including the use of tramadol, and nonopioid and adjuvant analgesics such as antidepressants and anticonvulsants, as well as nonpharmacologic therapies (e.g., psychological and rehabilitative approaches) also may be appropriate to comprehensively address the persistent pain and functional impairments of patients with this condition.[9] Therapy with a controlled-release opioid analgesic, such as CR oxycodone, requires careful patient selection, regular monitoring of outcomes, and use of techniques such as dose titration and management of side effects to optimize long-term effectiveness.

Acknowledgment

The authors thank Phyllis Clark (Clinical Trials Manager), Pinggao Zhang, PhD (Biostatistician), Michael Friedman, PhD (Biostatistician), and Daniel Bonzo, PhD (Biostatistician) for their contributions to this study and Susan Nick for writing assistance.

Appendix

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