Original Article

Can a Controlled-Release Oral Dose Form of Oxycodone Be Used as Readily as an Immediate-Release Form for the Purpose of Titrating to Stable Pain Control?

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Abstract

Two separate trials compared controlled-release (CR) oral oxycodone (administered every 12 hours) with immediate-release (IR) oxycodone (4 times a day) to determine whether patients with chronic pain could be titrated to stable pain control as readily with the CR as with the IR formulation. In one study, 48 patients with cancer pain were randomized to open-label titration with either CR or IR oxycodone (maximum dose, 400 mg/day) for a period of up to 21 days. In a study of similar design, 57 patients with low back pain were titrated with either CR or IR oxycodone (maximum dose, 80 mg/day) for a period of up to 10 days. The majority of patients in both studies were converted to oxycodone from other opioid analgesics. Results of both studies showed no difference between CR and IR oxycodone with respect to both the percentage of patients achieving stable pain control, the time to achieve stable pain control, and the degree of pain control achieved. Among cancer patients, 85% achieved stable analgesia, 92% with the CR formulation and 79% with the IR formulation. Among noncancer patients, 91% achieved stable pain control, 87% with the CR formulation and 96% with the IR formulation. The most commonly reported adverse effects in both studies were similar for the two formulations and were those anticipated with opioids: nausea, vomiting, constipation, somnolence, dizziness, and pruritus. Nausea and vomiting were the most frequently cited reasons for treatment discontinuations. These studies suggest that dose titration can be accomplished as readily with oral CR oxycodone as with IR oxycodone in patients with chronic, moderate to severe pain. J Pain Symptom Manage 1999;18:271–279. *© U.S. Cancer Pain Relief Committee, 1999.*

Key Words

Oxycodone, controlled-release formulation, immediate-release formulation, titration, dose conversion, cancer pain, low back pain

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Introduction

Guidelines for the use of opioid drugs in the management of chronic, moderate to severe pain recommend provision of around-the-clock analgesics and titration of the dose to an optimal level. The optimal dose should provide stable pain relief with an acceptable level of side effects.[1,2] For chronic pain syndromes, the goal of therapy is to provide sustained, around-the-clock analgesia, including prevention of breakthrough pain.

Pharmacotherapy for moderate to severe pain often begins with a nonopioid analgesic and progresses to fixed-dose opioid combinations (for example, hydrocodone or oxycodone combined with acetaminophen).[3] These agents are appropriate for management of moderate pain with an episodic pattern but are not suitable for more severe, continuous pain or the use of higher doses because upward dose titration is constrained by the analgesic ceiling effect and potential toxicities of the nonopioid component. Adjunctive therapies, such as amphetamines, antihistamines, and antiemetics, can enhance the effectiveness of the fixed-dose opioid combinations by ameliorating dose-limiting side effects. As such, adjuvants are an important component of fixed-dose regimens. For the management of moderate to severe continuous pain, pure opioid agonists are suitable because they have no analgesic ceiling effect and can be titrated upward until an acceptable balance is reached between analgesia and side effects. Single-entity opioids allow further individualization of therapy by separating the titration of nonopioid analgesics, which are often the platform of analgesic therapy upon which opioids are added.[2] For around-the clock analgesia, controlled-release (CR) opioid formulations offer the advantage of a convenient dosing schedule.

Morphine is the traditional choice for opioid agonists, and CR oral morphine has been a mainstay of therapy for chronic, moderate to severe cancer pain for more than a decade.[4–6] Oxycodone is a semisynthetic opioid agonist with potent dose-dependent analgesic properties. It is available in immediate-release (IR) formulations and has been widely used in fixed combinations with acetaminophen or aspirin. Oxycodone is also available in a single-entity CR formulation for the treatment of moderate to severe pain using a 12-hourly dosing regimen. CR oxycodone has been shown to be as effective as CR morphine in the treatment of chronic cancer pain.[7–9]

Once nonopioid medications are insufficient for controlling pain, many physicians start opioid therapy with an IR formulation, which they titrate to stable pain control before switching to a CR formulation for maintenance therapy.[1] However, certain long-acting opioid forms exhibit a rapid absorption and prompt onset of action that make them suitable for titration. For example, methadone is rapidly absorbed and distributed in tissue, while its long half-life accounts for its prolonged duration of action. Fainsinger and colleagues[10] reviewed a number of studies in which methadone was as effective as short-acting morphine in titrating patients to stable pain relief in acute and chronic pain settings, despite broad individual differences in elimination kinetics. In two other randomized, double-blind studies,[11,12] patients with moderate to severe and severe chronic pain, mostly due to cancer, were as successfully titrated to stable pain control with CR oral morphine sulfate tablets (MS Contin; Purdue Frederick Company, Norwalk, Connecticut) given twice daily as with oral IR morphine sulfate solution given six times daily.

The absorption profile of CR oral oxycodone suggests that it may likewise be used for titration to stable pain control as readily as the IR oxycodone form.[13–15] With the CR formulation, 38% of the available dose is rapidly absorbed ($t_{1/2\ abs}$ = 37 minutes)[14] providing onset of analgesia within 1 hour in postsurgical patients.[15] The median time to onset of pain relief in the postsurgical setting was 46 minutes with 30 mg CR oxycodone and 41 minutes with the IR formulation[15]—a difference that is clinically insignificant in the chronic pain setting. At the same time, the controlled absorption of the remainder of the CR oxycodone dose ($t_{1/2\ abs}$ = 6.2 hours for 62% of the dose) [14] resulted in a significantly longer duration of pain relief than that provided by the IR formulation ($P < 0.05$).[15]

We conducted two multicenter investigations to determine if patients with chronic moderate to severe pain can be brought to stable pain control as readily with CR oral oxycodone as with the IR formulation. The two formulations were compared in patients with chronic pain of malignant and nonmalignant

origin with respect to the percentage of patients achieving stable pain control, the time to stable pain control, degree of pain control achieved, and side effects reported during titration.

Methods

Patient Population

Patients eligible for entry into the two studies were at least 18 years of age and had stable, chronic pain not adequately controlled by prior analgesic therapy with or without opioids. Patients with cancer participated in one study; patients who had chronic, moderate to severe low back pain, despite analgesic therapy, participated in the second study. Low back pain was due to intervertebral disc disease, nerve root entrapment, spondylolisthesis, osteoarthritis, or other similar nonmalignant conditions. (These patients are referred to hereafter as "noncancer patients.") Among patients who were receiving nonopioid analgesic therapy, the dosing regimen was stabilized at least 1 week before the initiation of study medication and remained stable for the duration of the studies. Patients excluded from the studies included individuals with an allergy or contraindication to opioid therapy; patients with a history of substance abuse; patients receiving an opioid analgesic that could not be discontinued; cancer patients prescribed oral oxycodone at a total dose of more than 400 mg/day; and noncancer patients prescribed oral oxycodone at a total dose of more than 80 mg/day. The studies were approved by the institutional review boards (IRB) of the 10 participating study sites. All patients entered in the studies gave written informed consent.

Titration Procedure and Assessments

Patients in both studies were randomized to open-label titration with either oral CR oxycodone tablets (OxyContin; Purdue Pharma L.P., Norwalk, Connecticut), administered every 12 hours, or oral IR oxycodone tablets, administered four times daily. For opioid-naive patients, the starting dose of CR and IR oral oxycodone was 20 mg/day. However, most patients (94% cancer patients and 88% noncancer patients) were converted to the study drug from a variety of fixed-combination or single-entity opioid therapies. For these patients, the starting dose was based on the prior 3 days of analgesic therapy. Dose conversion factors used to calculate the oxycodone starting dose were based on reports of equianalgesic doses obtained from well-controlled, single-agent, relative potency studies[16–18] and are listed in Table 1.

Patients randomized to receive the CR formulation of oxycodone were instructed to take a dose at 8 A.M. and 8 P.M. (± 1 hour each time). Patients receiving the IR formulation were instructed to take doses at 8 A.M., 2 P.M., 8 P.M., and bedtime (± 1 hour each time). The bedtime dose was to be taken at least 3 hours following the 8 P.M. dose. Supplemental analgesic was permitted as needed for control of breakthrough or incident pain and was provided in doses of 5 mg IR oxycodone (1 tablet) for patients titrated to 20 to 40 mg/day and 10 mg IR oxycodone (2 × 5 mg tablets) for patients titrated to 60 to 80 mg/day. For patients receiving doses greater than 80 mg/day, the supplemental analgesic dose was approximately 1/6 of the patient's total daily oxycodone dose rounded to the nearest 5 mg. Rescue medication was taken no more than once every 4 hours. All other opioid analgesics were prohibited. Besides nonopioid analgesic medications (discussed above), other medications necessary for patients' welfare were administered under the supervision of the investigator/physician.

Patients recorded pain intensity, adverse events, and study and rescue medication use in daily diaries. They rated pain intensity on a

Table 1
Multiplication Factors for Converting the Daily Dose of Prior Opioids to the Daily Dose of Oral Oxycodone[a]

Pre-study Opioid	Factor
Single-entity opioid	
Hydromorphone	4
Levorphanol	7.5
Meperidine	0.1
Methadone	1.5
Morphine	0.5
Oxycodone	
Opioid component of fixed-combination	
Codeine	0.15
Oxycodone	1
Hydrocodone	0.9

[a]Total daily dose of pre-study opioid (mg) × Factor = Total daily dose of oxycodone (mg).
Source: Refs. 16, 17.

four-point categorical (CAT) scale of 0, "none"; 1, "slight"; 2, "moderate"; and 3, "severe." Patients were contacted daily throughout the study in order to remind them to record their pain intensity and adverse events; these calls also allowed assessment of the need for dose titration. Pain intensity and adverse events were also assessed at the clinic visit at the end of the titration period.

The starting dose was titrated upward in each study to a limit of 400 mg/day for cancer patients and to 80 mg/day for noncancer patients. Among those who required titration, the dose was increased until patients rated their level of pain at an intensity of no greater than "slight" (1.5) on the CAT scale. The dose could be adjusted every 24 to 48 hours if necessary. Criteria for stable pain control were said to be met if pain was stabilized at 1.5 or below for 48 hours while patients were taking no more than two doses per day of supplemental analgesic. Time to stable pain control was recorded as zero for patients meeting the criteria for success in the first 48 hours (i.e., no titration was needed). Among cancer patients, titration was rated as successful if pain was stabilized within a maximum of 21 days; among noncancer patients, the time limit was 10 days.

Statistical Analyses

Baseline variables were assessed using the Cochran-Mantel-Haenszel chi-square test or Fisher's exact test. Treatment differences with respect to the percentage of patients successfully titrated to stable pain were evaluated using Fisher's exact test. Kaplan-Meier survival analysis techniques were used to assess time required to achieve stable pain control, and McNemar's test was used to analyze differences between oxycodone formulations with respect to the incidence of treatment-related adverse events. All statistical tests were two-sided, with a significance level of 0.05 for treatment effects.

Results

Patient Population

In one study, 50 patients with cancer pain were enrolled at five centers. Two patients withdrew before receiving any study medication. Thus, 48 cancer patients received at least one dose of oxycodone; 35 patients completed the titration period. Eight patients discontinued because of ineffective treatment or intercurrent illnesses, three patients discontinued because of adverse events, and two discontinued for other reasons. In the second study, 57 noncancer patients with chronic low back pain were enrolled at five centers. All patients received at least one dose of trial medication; 47 patients completed the titration period. Two noncancer patients discontinued after reaching the maximum allowed dose of 80 mg/day, and eight discontinued because of adverse events.

There were no significant differences in demographic variables between patients titrated with the CR versus IR formulations in either study (Table 2). In both studies, patients were predominantly white and female. Baseline pain intensity was comparable between CR and IR treatment groups. Among cancer patients, mean baseline pain intensity (± SE) was 1.8 ± 0.2 and 1.5 ± 0.2 for the CR and IR groups, respectively. Among noncancer patients, mean baseline pain intensity was 2.3 ± 0.1 and 2.4 ± 0.1 for the CR and IR groups, which was significantly greater than that seen in the cancer patients ($P = 0.0001$). Most patients (91%) reported taking one or more of a variety of single-entity and fixed-combination opioid-containing medications prior to entering the studies, including morphine, hydromorphone, propoxyphene, oxycodone/acetaminophen, propoxyphene/acetaminophen, hydrocodone/acetaminophen, hydrocodone/aspirin, pentazocine/naloxone, and fentanyl transdermal system.

Assessments of Titration

In both studies, the percentage of patients achieving stable analgesia was not significantly different between the CR and IR oxycodone treatment groups (Figure 1A). Among cancer patients, 41 (85%) of the 48 patients achieved stable analgesia, 22 (92%) who were treated with the CR formulation and 19 (79%) with the IR formulation ($P = 0.42$). Among noncancer patients, 52 (91%) of the 57 enrolled patients achieved stable analgesia, 26 (87%) receiving the CR formulation and 26 (96%) receiving the IR formulation ($P = 0.36$).

Of the seven cancer patients who did not achieve stable analgesia, four (two in each treatment arm) were unable to titrate to a therapeutic dose. Of these patients, two in the CR oxycodone arm discontinued while taking 80

Table 2
Demographic Characteristics of Patients Entering Titration

Patient characteristic	Cancer patients		Noncancer patients	
	CR oxycodone (n = 24)	IR oxycodone (n = 24)	CR oxycodone (n = 30)	IR oxycodone (n = 27)
Age (yr)				
Mean	60	61	56	56
Range	25, 77	39, 91	26, 84	28, 86
Race, n (%)				
White	22 (92)	20 (83)	28 (93)	22 (82)
Black	0 (0)	4 (17)	0 (0)	0 (0)
Hispanic	2 (8)	0 (0)	2 (7)	5 (19)
Sex, n (%)				
Male	8 (33)	13 (54)	11 (37)	15 (56)
Female	16 (67)	11 (46)	19 (63)	12 (44)
Patients taking pre-study opioids, n (%)				
Yes	23 (96)	22 (92)	25 (83)	23 (85)
No	1 (4)	2 (8)	5 (17)	4 (15)

mg/day and 100 mg/day, respectively. Both patients experienced increased sedation and somnolence. Two patients in the IR oxycodone treatment arm were unable to reach a therapeutic dose. One patient was receiving 60 mg/day and discontinued treatment after experiencing sedation. The other discontinued treatment while taking IR oxycodone 360 mg/day; the patient required a higher dose to reach stable analgesia but experienced unacceptable delirium with upward titration. Three other cancer patients who did not achieve stable analgesia (one in the CR and two in the IR treatment arm) discontinued because of adverse events, which are discussed below.

Of the five noncancer patients who did not achieve stable analgesia, one was titrated to the maximum 80 mg dose of CR oxycodone without stable pain control. Four experienced adverse effects (three receiving the CR formulation and one receiving the IR formulation) that precluded titration to stable control of pain. These adverse effects are discussed below.

Time to stable pain control was not significantly different in patients receiving the CR and IR formulations of oxycodone in either study (Figure 1B). Among cancer patients, the mean time to stable pain control (± SE) was 1.6 ± 0.4 days for patients receiving CR oxycodone and 1.7 ± 0.6 days for those receiving IR oxycodone (P = 0.51). Among noncancer patients, the mean time to stable pain control was 2.7 ± 0.5 days and 3.0 ± 0.4 days for those receiving the CR and IR formulations, respectively (P = 0.90).

In both studies, expeditious pain relief was achieved with a minimum of dose titration of either CR or IR oxycodone. Forty-one cancer patients (85% of the total) achieved stable pain control. Of these, nearly 60% required no dose titration. Fifty-two noncancer patients (91% of the total) achieved stable pain control. The mean number of dose adjustments (± SE) required to reach stable pain control in the noncancer study was 1.1 ± 0.2 and 1.7 ± 0.4 for those receiving the CR and IR formulations, respectively (P = 0.58).

The final mean daily doses are shown in Table 3. Among cancer patients completing the titration period, the mean daily dose of oxycodone (± SE) was 104 ± 20 mg of CR oxycodone and 113 ± 24 mg of IR oxycodone; among noncancer patients, daily doses were 41 ± 4 mg and 39 ± 4 mg, for those receiving the CR and IR formulations, respectively.

The majority of patients did not use a nonopioid analgesic during titration (68% of cancer patients and 60% of noncancer patients). For patients who were taking nonopioid analgesics, dosages remained stable throughout the study period. In cancer patients, concomitant therapy with a nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen did not significantly shorten the time to reach stable pain control compared with the time required by patients who were not taking these drugs (data not shown).

At the end of the titration period, pain assessments revealed a "slight" level of pain in those receiving the CR and IR formulations of

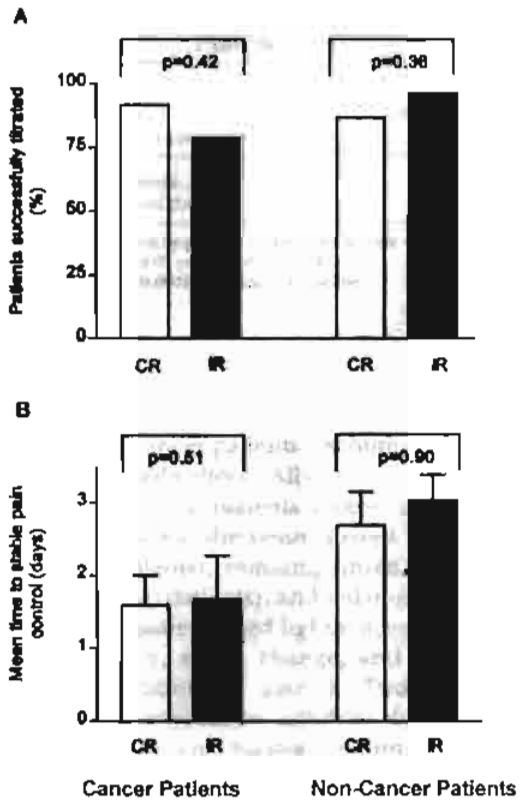

Fig. 1. (A) Percentage of patients successfully titrated with controlled-release (CR) oxycodone versus immediate-release (IR) oxycodone. (B) Mean time to stable pain control (days) in patients titrated with CR oxycodone versus IR oxycodone.

oxycodone (Table 4). Patients reported reductions in pain intensity from baseline despite use of pre-study opioid analgesics by the majority. At baseline, pain intensity was lower in cancer patients than in noncancer patients. Nevertheless, among cancer patients who completed the titration period, mean pain intensity (± SE) decreased from baseline by 0.7 ± 0.2 units (P = 0.01) in those treated with CR oxycodone and 0.3 ± 0.2 units in those treated with IR oxycodone (P = 0.14) Among noncancer patients completing titration, the mean decrease in pain intensity was greater than that in cancer patients (1.1 ± 0.2 units and 1.3 ± 0.2 units in patients treated with the CR the IR formulations, respectively). The decrease from baseline was significant for both treatment groups (P = 0.0001).

Tolerability of Study Medication

Treatment-related side effects occurring in greater than 10% of patients in at least one of the four treatment groups are presented in Table 5. Among both cancer and noncancer patients, there were no statistically significant differences between the CR and IR treatment groups with respect to the incidence of adverse effects. Most side effects reported during the titration period were mild or moderate (96% of reported adverse effects in the cancer study and 93% in the noncancer study).

Side effects most often involved the digestive and nervous systems. The most common were those anticipated with opioid therapy: nausea, vomiting, constipation, somnolence, dizziness, and pruritus. In both studies, more women than men reported nausea and vomiting, although the relatively small number of patients precluded statistical comparison of the genders. Among cancer patients, 30% of women and 19% of men complained of nausea during titration. In the noncancer study, 52% of women and 31% of men reported nausea. Among noncancer patients, women reported more cases of pruritus (42% versus 12%) but fewer headaches (10% versus 27%) than did men.

Three cancer patients discontinued treatment because of adverse effects. One patient receiving the CR formulation withdrew after developing pruritus. Two patients receiving the IR formulation withdrew; one reported

Table 3
Final Mean Daily Doses of Oxycodone

Final daily dose (mg), mean (SE)			
Cancer patients		Noncancer patients	
CR oxycodone (n = 22)	IR oxycodone (n = 19)	CR oxycodone (n = 26)	IR oxycodone (n = 26)
	113 (24)	41 (4)	39 (4)

Table 4
Patients' Assessment of Pain Intensity at Baseline and the End of Titration

Pain Intensity,[a] mean (SE)	Cancer patients		Noncancer patients	
	CR oxycodone (n = 19)	IR oxycodone (n = 16)	CR oxycodone (n = 22)	IR oxycodone (n = 25)
Baseline	1.8 (0.2)[b]	1.4 (0.2)		2.4 (0.1)[c]
End of titration	1.1 (0.2)[b]	1.1 (0.1)		1.0 (0.2)[c]

[a]Rated by patients on categorical scale of 0, none; 1, slight; 2, moderate; 3, severe.
[b]P = 0.01 compared to baseline.
[c]P = 0.0001 compared to baseline.

confusion and irritability and the other reported anxiety.

Eight noncancer patients discontinued treatment due to side effects. All were receiving prestudy opioids. Six patients receiving CR oxycodone withdrew; the reasons cited were nausea (four patients), vomiting (three patients), headache (two patients), and sedation (two patients); one patient cited lightheadedness, dizziness, anxiety, mood change, and constipation, in addition to nausea. Two patients receiving IR oxycodone withdrew due to side effects; one reported nausea, vomiting, itching, and shakiness, and the other reported dizziness and confusion. As noted above, more women than men complained of nausea during titration, and the higher dropout rate in patients receiving the CR versus the IR formulation in the noncancer study may be due, in part, to the higher proportion of women randomized to titration with CR oxycodone (63%) compared with IR oxycodone (44%).

Discussion

In these two studies, which were performed as separate clinical trials, patients with chronic pain were titrated to stable analgesia with an oral CR oxycodone formulation as readily as with an oral IR formulation. CR oxycodone was statistically indistinguishable from IR oxycodone with respect to the percentage of patients achieving stable pain control, the time to stable pain control, and the degree of pain control achieved. The occurrence of adverse effects was also similar.

These results suggest that the convention of determining CR opioid dosages by first using IR formulations to titrate to stable pain[1] may be unnecessary when this formulation of oral CR oxycodone is used. The absorption profile of CR oxycodone may explain, in part, the ease of titration. CR oxycodone is characterized by an initial rapid absorption of 38% of the dose ($t_{1/2\,abs}$ = 37 minutes),[14] providing onset of analgesia within 1 hour in most patients.[15] The

Table 5
Most Frequently Reported Adverse Events Related to Study Medication[a]

Adverse event, n (%)	Cancer patients		Noncancer patients	
	CR oxycodone (n = 24)	IR oxycodone (n = 24)	CR oxycodone (n = 30)	IR oxycodone (n = 27)
Somnolence	9 (37)	7 (29)	8 (27)	10 (37)
Nausea	7 (29)	5 (21)	15 (50)	9 (33)
Vomiting	5 (21)	3 (12)	6 (20)	1 (4)
Postural hypotension	5 (21)	4 (17)	0 (0)	0 (0)
Constipation	4 (17)	9 (37)	9 (30)	10 (37)
Pruritus	4 (17)	0 (0)	9 (30)	7 (26)
Confusion	3 (12)	2 (8)	1 (3)	0 (0)
Dry mouth	3 (12)	1 (4)	0 (0)	3 (11)
Dizziness	2 (8)	0 (0)	9 (30)	6 (22)
Nervousness	2 (8)	4 (17)	0 (0)	2 (7)
Asthenia	2 (8)	1 (4)	2 (7)	3 (11)
Headache	1 (4)	1 (4)	4 (13)	7 (26)

[a]Events reported in greater than 10% of patients in at least one treatment group and judged by the investigator to be at least possibly, probably, or definitely related to study medication. Values are expressed as number of adverse events, with percentages in parentheses.

initial phase is followed by slower absorption of the remaining 62% of the dose ($t_{1/2\ abs}$ = 6.2 hours)[14] for prolonged duration of analgesia. This biphasic absorption profile relies on the formulation's matrix carrier, which regulates the release of the drug while preserving oxycodone's intrinsic rapid absorption and short elimination half-life. The short elimination half-life of oxycodone permits prompt attainment of steady state, and concentration-time curves show no evidence of accumulation with repeated dosing.[13]

In previous trials of CR oxycodone in cancer pain, the time to achieve stable pain ranged from nearly 2 to 6 days. In one trial, the mean time to stable pain control was 2.8 days for patients titrated with CR oxycodone, which was similar to the 2.6 days required with titration of CR morphine.[7] A second trial comparing CR oxycodone and CR morphine reported a mean titration time of 6 days.[8] In the present studies, the time to stable pain control was shorter for cancer patients than for noncancer patients. However, pain was significantly greater at baseline in noncancer compared with cancer patients (mean baseline pain score, 2.3 ± 0.5 versus 1.6 ± 0.7 (± SE) units, respectively [$P < 0.0001$]), and therefore there was a larger treatment effect. While both cancer and noncancer patients completing titration achieved a similarly "slight" level of pain, the mean decrease in pain intensity was greater among noncancer patients compared with cancer patients. The poor pain control at baseline in the noncancer patients may account for longer time to achieve stable pain control in this group (mean time to stable pain control, 2.9 ± 0.3 days in noncancer patients versus 1.6 ± 0.4 days in the cancer group [$P = 0.007$]). The somewhat shorter time to stable pain control in cancer patients indicates that pain was better controlled at baseline and reflects published recommendations for aggressive upward dose titration to stable analgesia in the management of pain in this patient population.[3]

In our studies of both cancer and noncancer patients, titration to stable pain control with oral oxycodone resulted in important reductions in pain intensity despite the use of prestudy opioids by 94% of the cancer patients and 88% of the noncancer patients. In addition, most patients did not require a concomitant nonopioid analgesic. Pre-study therapies included single-entity opioids as well as fixed-dose combinations. Patients converting from pre-study opioids were provided with equianalgesic doses of oral oxycodone. Conversion ratios used to determine oxycodone doses were consistent with published recommendations based on well-controlled, single-dose studies.[16,17] Patients who had been receiving oral morphine prior to entry into the studies were converted to oral oxycodone at one-half the previous oral morphine dose. This conversion ratio is derived from the equianalgesic dose established in relative analgesic potency trials.[16–18] Although an oral dose ratio of 2:3 for oxycodone to morphine is sometimes recommended,[8] we found the more conservative 1:2 ratio to be also effective.

The appropriateness of conversion ratios used to determine oxycodone dosages was supported by study results showing the majority of patients required only minimal dose titration to achieve stable analgesia. Nearly 60% of the cancer patients achieved stable pain control with no dose titration. Noncancer patients generally required only one or two dose adjustments to reach stable control of pain. In each study, the mean effective daily dose of oxycodone (108 ± 16 mg for cancer patients and 40 ± 3 mg/day for noncancer patients) was within the maximum allowed by the protocols (400 mg and 80 mg for cancer and noncancer patients, respectively). Among patients from both studies, only one (1/105), a patient in the noncancer study, failed to achieve stable analgesia while titrated to the maximum allowed dose. However, because oxycodone is a pure opioid agonist, with no ceiling effect for analgesia, the total daily dose can be titrated to the level necessary for proper pain control.

Overall, no important differences emerged between the side-effect profiles of the CR and IR formulations of oxycodone. The most common adverse events in all treatment groups were typical opioid side effects. Six noncancer patients receiving the CR formulation and two receiving the IR formulation discontinued study medication because of side effects, with more than half citing nausea and vomiting as the cause.

The results of these two studies suggest that oral CR oxycodone can be used as readily as the IR formulation for titration to stable analgesia in patients with moderate to severe chronic pain due to cancer or nonmalignant

causes. The ability to titrate rapidly and effectively with oral CR oxycodone is related to the absorption profile of this formulation, which preserves the prompt onset of action and short half-life of oxycodone.

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