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## ORIGINAL ARTICLE

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# Long-term Safety and Tolerability of Tapentadol Extended Release for the Management of Chronic Low Back Pain or Osteoarthritis Pain

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### ■ Abstract

**Background:** Tapentadol is a novel, centrally acting analgesic with 2 mechanisms of action:  $\mu$ -opioid receptor agonism and norepinephrine reuptake inhibition. This randomized,

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open-label phase 3 study (ClinicalTrials.gov Identifier: NCT00361504) assessed the long-term safety and tolerability of tapentadol extended release (ER) in patients with chronic knee or hip osteoarthritis pain or low back pain.

**Methods:** Patients were randomized 4:1 to receive controlled, adjustable, oral, twice-daily doses of tapentadol ER (100 to 250 mg) or oxycodone HCl controlled release (CR; 20 to 50 mg) for up to 1 year. Efficacy evaluations included assessments at each study visit of average pain intensity (11-point numerical rating scale) over the preceding 24 hours. Treatment-emergent adverse events (TEAEs) and discontinuations were monitored throughout the study.

**Results:** A total of 1,117 patients received at least 1 dose of study drug. Mean (standard error) pain intensity scores in the tapentadol ER and oxycodone CR groups, respectively, were 7.6 (0.05) and 7.6 (0.11) at baseline and decreased to 4.4 (0.09) and 4.5 (0.17) at endpoint. The overall incidence of TEAEs was 85.7% in the tapentadol ER group and 90.6% in

the oxycodone CR group. In the tapentadol ER and oxycodone CR groups, respectively, TEAEs led to discontinuation in 22.1% and 36.8% of patients; gastrointestinal TEAEs led to discontinuation in 8.6% and 21.5% of patients.

**Conclusion:** Tapentadol ER (100 to 250 mg bid) was associated with better gastrointestinal tolerability than oxycodone HCl CR (20 to 50 mg bid) and provided sustainable relief of moderate to severe chronic knee or hip osteoarthritis or low back pain for up to 1 year. ■

**Key Words:** analgesics, opioid, low back pain

## INTRODUCTION

Chronic pain affects between 5% and 33% of patients in primary care settings<sup>1</sup> and may be associated with an increased incidence of anxiety and depression,<sup>2</sup> sleep disturbances, decreased physical functioning, and decreased quality of life.<sup>3</sup> In addition, chronic pain has been associated with a significant economic burden related to medical expenses, lost wages, and reduced productivity.<sup>3</sup> Opioids have been used for the management of chronic pain conditions,<sup>4-6</sup> including osteoarthritis<sup>7,8</sup> and low back pain.<sup>8</sup> However,  $\mu$ -opioid receptor agonists, including morphine and oxycodone, are associated with a number of side effects.<sup>9</sup> These side effects may reduce physicians' willingness to prescribe opioids for chronic pain<sup>10</sup> and may cause patients to stop taking their medication,<sup>5</sup> potentially resulting in undertreatment of their pain.

Tapentadol is a novel, centrally acting analgesic with 2 mechanisms of action:  $\mu$ -opioid receptor agonism and norepinephrine reuptake inhibition.<sup>11,12</sup> The analgesic effects of tapentadol are independent of metabolic activation. Orally administered tapentadol is cleared primarily by hepatic glucuronidation, and its major metabolite, tapentadol-*O*-glucuronide, has no clinically relevant analgesic activity at any binding sites.<sup>11</sup> Tapentadol does not undergo significant metabolism by cytochrome P450, and thus, is not prone to the drug-drug interactions and interindividual analgesic variability observed for many drugs metabolized by cytochrome P450.<sup>13-15</sup> Results of phase 3 clinical trials have demonstrated the safety and efficacy of tapentadol immediate release (IR) in patients with postoperative pain (bunionectomy)<sup>16,17</sup> and osteoarthritis pain related to end-stage joint disease.<sup>18</sup> In addition, the long-term tolerability of tapentadol IR was shown in patients with low back or osteoarthritis-related hip or knee pain treated with tapentadol IR (50 or 100 mg every 4 to 6 hours) for up to 90 days.<sup>19</sup> The current study assessed the long-term safety of tapentadol extended release (ER) for up to 1

year for the management of moderate to severe chronic low back pain or pain related to osteoarthritis of the knee or hip.

## PATIENTS AND METHODS

This randomized, multicenter, parallel-group, open-label, active-controlled phase 3 study (ClinicalTrials.gov Identifier: NCT00361504) was designed to assess the long-term safety profile of tapentadol ER for the management of chronic pain. The study protocol and amendments were reviewed and approved by independent ethics committees and institutional review boards. The study was conducted in accordance with Good Clinical Practice guidelines and Declaration of Helsinki principles. Patients were recruited at 53 study sites in North America and 36 sites in Europe.

### Inclusion Criteria

Men and nonpregnant, nonlactating women 18 years or older with a clinical diagnosis of moderate to severe knee or hip osteoarthritis pain or low back pain of nonmalignant origin, with at least a 3-month history of pain prior to screening, and who were dissatisfied with their current analgesic therapy were eligible to participate in this study. Patients were required to have a pain intensity score of at least 4 on an 11-point numerical rating scale (NRS) at baseline following a 3- to 7-day washout of all prior analgesic treatments.

### Exclusion Criteria

Patients meeting the following criteria were excluded from the study: lifelong history of seizure disorder or epilepsy; mild or moderate traumatic brain injury, stroke, transient ischemic attack, or brain neoplasm within 1 year of screening; severe traumatic brain injury within 15 years of screening; residual sequelae suggesting transient changes in consciousness; history of malignancy within 2 years of screening, with the exception of successfully treated basal cell carcinoma; history of alcohol or drug abuse; history of chronic hepatitis B or C or active hepatitis B or C within 3 months of screening; history of human immunodeficiency virus; a clinically relevant history of hypersensitivity, allergy, or contraindication to oxycodone or acetaminophen; or previous participation in this study or other studies of tapentadol. Patients who required major surgery during the study or who had surgery of the back or reference joint within 3 months of screening were also excluded. Patients with moderately or severely impaired hepatic function, severely impaired renal function, uncontrolled

hypertension, clinically significant disease that could affect efficacy or safety assessments, or significant pain associated with conditions other than osteoarthritis or low back pain were excluded.

### Study Methodology and Study Design

Patients were randomized in a 4:1 ratio to receive controlled, adjustable twice-daily doses of tapentadol ER (100 to 250 mg) or oxycodone HCl controlled release (CR; 20 to 50 mg). This study consisted of 5 phases: a screening period (up to 14 days from the signing of informed consent); a washout period (3 to 7 days prior to randomization); a 1-week titration period; a 51-week maintenance period; and a follow-up period, consisting of a visit 4 days post-treatment and a telephone call 10 to 14 days post-treatment. Patients were assigned to treatment based on a computer-generated randomization schedule; randomization was balanced using randomly permuted blocks and stratified by location (Europe or North America). Medication kits matching each patient's randomly assigned code were assigned using an interactive voice response system. Because this was an open-label study, the investigators were provided with the treatment assignment for each patient.

Patients received twice-daily oral doses of tapentadol ER 50 mg or oxycodone HCl CR 10 mg for the first 3 days of the titration period. Doses were increased to tapentadol ER 100 mg or oxycodone HCl CR 20 mg bid for the next 4 days; these were the minimum therapeutic doses used for the remainder of the study. Under the supervision of a study physician, patients could adjust their doses during the 51-week maintenance period to maintain an optimal balance of efficacy and tolerability. Doses could be titrated upward in twice-daily increments of tapentadol ER 50 mg or oxycodone HCl CR 10 mg at a minimum of 3-day intervals to a maximum therapeutic dose of tapentadol ER 250 mg bid or oxycodone HCl CR 50 mg bid. Downward titration was possible in twice-daily decrements of tapentadol ER 50 mg or oxycodone HCl CR 10 mg with no time restriction, but doses could not fall below the minimum therapeutic doses.

### Concomitant Medications

The use of analgesics other than the study drug and allowed amounts of selected analgesics was prohibited during the study. Nonsteroidal anti-inflammatory drugs (NSAIDs) could be used occasionally for fever or pain other than chronic pain (eg, toothache or headache pain) and acetylsalicylic acid (oral doses  $\leq 325$  mg/day)

could be used for cardiac prophylaxis. Acetaminophen ( $\leq 1,000$  mg/day) was permitted during the study for a maximum of 7 consecutive days and for no more than 14 out of 30 days. The use of neuroleptics and monoamine oxidase inhibitors was prohibited within 14 days of screening and during the study. The use of tricyclic antidepressants was prohibited within 14 days of screening and during the study, unless patients were on a stable dose exclusively for the management of pain. Corticosteroid use (with the exception of topical corticosteroids or those administered intranasally or by inhaler) was prohibited during the study and for 4 weeks to 6 months prior to screening, depending on the method of administration. Selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, benzodiazepines, antiparkinsonian drugs, anti-convulsants, and mood stabilizers (used as minor tranquilizers or hypnotics) were permitted if dosing was stable for at least 30 days prior to screening.

### Safety and Tolerability Evaluations

The primary objective of this study was to evaluate the safety of twice-daily doses of tapentadol ER (100 to 250 mg) over 1 year. Safety and tolerability assessments included adverse event (AE) reporting, vital signs measurements, physical examinations, clinical laboratory tests, serial electrocardiograms, Patient's Assessment of Constipation Symptoms (PAC-SYM),<sup>20</sup> the Clinical Opiate Withdrawal Scale (COWS),<sup>21</sup> and the Subjective Opiate Withdrawal Scale (SOWS)<sup>22,23</sup> questionnaires. AEs were recorded from the signing of informed consent through the follow-up period. All AEs were coded using the *Medical Dictionary for Regulatory Activities* (version 11.0) and summarized by system organ class and preferred term. Treatment-emergent AEs (TEAEs) were defined as AEs that initially occurred at the time of or after the first intake of study medication or as existing AEs that worsened in intensity during treatment. Serious TEAEs were defined as TEAEs that required hospitalization or resulted in prolongation of hospitalization, resulted in persistent or significant disability, were life threatening, resulted in death, or were considered otherwise medically important.

The PAC-SYM<sup>20</sup> was completed at baseline, twice during the treatment period, and at the end of study treatment. It is a validated 12-item questionnaire that assesses the severity of constipation symptoms in patients using opioids for the management of chronic pain using a 5-point scale (0 = "absence of symptoms" to 4 = "very severe symptoms"). Scores for individual

items on the PAC-SYM are summarized in 3 subscale scores (abdominal, rectal, and stool) and an overall score.

COWS questionnaires were scheduled to be completed by the investigators 4 days after treatment discontinuation. The COWS<sup>21</sup> is an 11-item scale based on questions and clinical observations rated by the investigator on a Likert-type scale (0 to 4 or 0 to 5, depending on the item). The severity of opioid withdrawal is categorized according to the sum of the 11 items (maximum score 48) as follows: no withdrawal, <5; mild withdrawal, 5 to 12; moderate withdrawal, 13 to 24; moderately severe withdrawal, 25 to 36; or severe withdrawal, >36. The SOWS questionnaire<sup>22,23</sup> is a 16-item, self-reported measure of perceived opioid withdrawal. An abbreviated 15-item version (deemed more appropriate for this study population) was used in this study. SOWS assessments were scored from 0 to 60, with a score of 60 indicating extremely severe opioid withdrawal. SOWS assessments were scheduled to be completed 24, 48, and 72 hours after the last dose of study medication by English-speaking patients enrolled at U.S. study sites only.

### Efficacy Evaluations

Efficacy was assessed using patient ratings of their average pain intensity over the previous 24 hours on an 11-point NRS (0 = “no pain” to 10 = “pain as bad as you can imagine”) at each study visit. Additional efficacy assessments included separate patient and investigator global assessments of study medication and the patient global impression of change (PGIC). For the global assessments of study medication, patients and investigators rated their overall impression of the study drug on a scale from 0 to 4 (0 = “poor” to 4 = “excellent”) at each of the 16 study visits during the treatment period. The PGIC was assessed twice during the treatment period and at the end of study treatment. On the PGIC, patients completed the following statement: “Since I began my study treatment, my overall status is . . .” with a response from 1 to 7 (1 = “very much improved” to 7 = “very much worse”).

### Statistical Analysis

No formal sample size calculation was performed. It was assumed based on the screening failure and dropout rate from other phase 2 and 3 studies of tapentadol that 860 patients should be randomized to receive tapentadol ER and 215 patients should be randomized to receive oxycodone CR (based on the 4:1 randomization

ratio) to achieve a sample size of at least 300 patients exposed to tapentadol ER for at least 6 months and at least 100 patients exposed for at least 12 months, with a discontinuation rate of approximately 40% during the first month of the study and 10% every month thereafter. The safety population included all randomized patients who received at least 1 dose of study medication, and the intent-to-treat (ITT) population, which was used for all efficacy evaluations, included all randomized patients who received at least 1 dose of study medication and were not excluded because of major audit findings at their study site. Patients who completed the full treatment duration were considered to have completed randomized treatment.

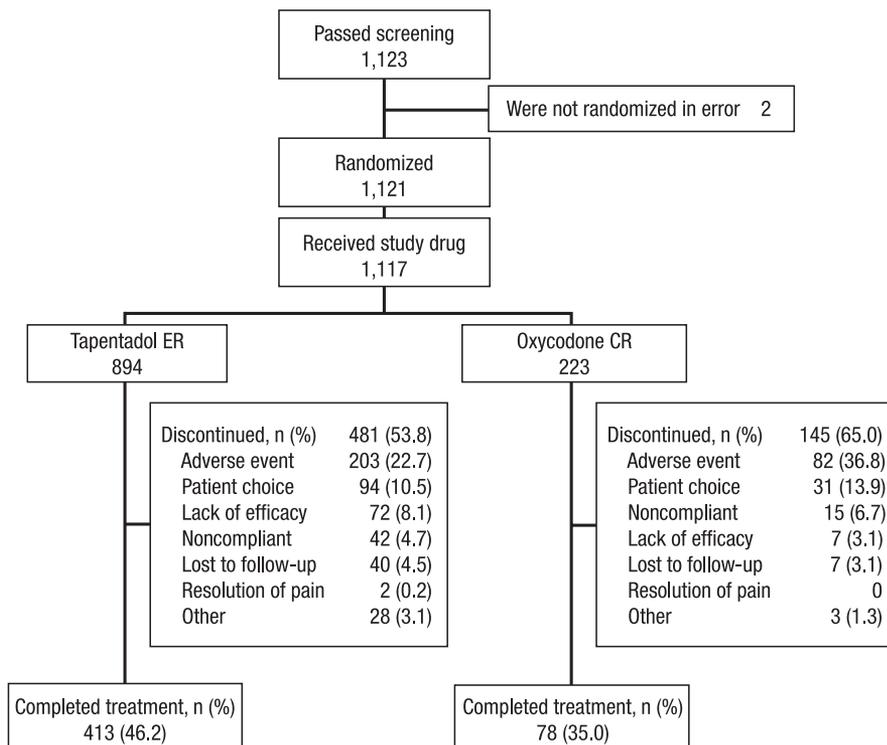
Exposure to study medication was summarized for the safety population and for patients who completed treatment using total daily dose (TDD) and duration of intake during the treatment period. Descriptive statistics were used to summarize TDDs. The distribution of time from the start of study drug exposure to discontinuation was summarized using Kaplan–Meier estimates; the log-rank test was used for comparison between treatment groups.

Summaries of TEAEs were presented by treatment group. The distribution of time to the first incidence of nausea, vomiting, or constipation was determined using Kaplan–Meier estimates; treatment groups were compared using the log-rank test. The distribution of time to onset of TEAEs leading to discontinuation was determined using Kaplan–Meier estimates; treatment groups were compared using the log-rank test.

For the PAC-SYM, overall scores and scores on the 3 subscales and 12 individual items were summarized by treatment group at each time point and at endpoint. Changes from baseline to endpoint were calculated and summarized descriptively.

The number and percentage of patients in each COWS category was summarized according to the time period in which the COWS assessment was completed following treatment discontinuation (1 day,  $\geq 2$  to 4 days, or  $\geq 5$  days). SOWS total scores were calculated by summing the scores of the 15 items. Summary statistics were provided at 1, 2, 3, 4, and 5 or more days after the last dose of study medication.

Descriptive statistics were used to summarize pain intensity scores, and the change from baseline in pain intensity was calculated at each time point and at endpoint; for the summaries at endpoint, the last observation carried forward was used for imputation of missing pain intensity values. Endpoint was defined as the last



**Figure 1.** Patient disposition (all patients). One patient who was randomized to tapentadol ER and was also randomized to oxycodone CR and was evaluated for treatment exposure for both tapentadol ER and oxycodone CR, but was excluded from the general oxycodone CR safety population. CR, controlled release; ER, extended release.

nonmissing measurement during the active treatment period. Frequency distribution and percentages of patients or investigators reporting each response were calculated for the patient and investigator global assessments of study medication and for the PGIC and were summarized for each treatment group.

Long-term dose stability was assessed by comparing the mean percent change in the average weekly dose for the duration of the study for patients who completed the study, using weeks 5 to 8 as the baseline for comparison.

## RESULTS

### Patients

This study was conducted from November 14, 2006, to July 25, 2008. A total of 1,121 patients were randomized. The progression of patients through the study is shown in Figure 1. The safety population included 1,117 patients (tapentadol ER,  $n = 894$ ; oxycodone CR,  $n = 223$ ) and the ITT population included 1,095 patients (tapentadol ER,  $n = 876$ ; oxycodone CR,  $n = 219$ ). Demographic and baseline characteristics were similar in the 2 treatment groups (Table 1).

The percentages of patients who completed treatment in the tapentadol ER and oxycodone CR groups, respectively, were 46.2% (413/894) and 35.0% (78/223; Figure 1). The most common reason for treatment dis-

**Table 1. Demographic and Baseline Characteristics (Safety Population)**

Characteristic	Tapentadol ER ( $n = 894$ )	Oxycodone CR ( $n = 223$ )
Age, y		
Mean (SD)	56.8 (12.51)	58.1 (11.83)
Age category, $n$ (%)		
<65 y	649 (72.6)	156 (70.0)
≥65 y	245 (27.4)	67 (30.0)
Gender, $n$ (%)		
Female	515 (57.6)	125 (56.1)
Male	379 (42.4)	98 (43.9)
Race, $n$ (%)		
White	792 (88.6)	203 (91.0)
Black	60 (6.7)	13 (5.8)
Hispanic	26 (2.9)	4 (1.8)
Other	16 (1.8)	3 (1.3)
Body mass index,* kg/m <sup>2</sup>		
Mean (SD)	31.7 (7.88)	31.8 (6.81)
Pain intensity score <sup>†</sup>		
Mean (SD)	7.6 (1.54)	7.6 (1.62)
Pain intensity category, <sup>‡</sup> $n$ (%)		
Moderate	89 (10.0)	29 (13.0)
Severe	805 (90.0)	194 (87.0)
Prior opioid experience, <sup>§</sup> $n$ (%)		
No	421 (47.1)	111 (49.8)
Yes	473 (52.9)	112 (50.2)

\* Tapentadol ER,  $n = 890$ ; oxycodone CR,  $n = 221$ .

<sup>†</sup> Baseline pain intensity was the last pain intensity score (11-point NRS) recorded prior to randomization.

<sup>‡</sup> Moderate pain intensity is defined as a rating of 4 to <6 and severe is defined as a rating of ≥6 on an 11-point NRS.

<sup>§</sup> Prior opioid experience was defined as taking opioid analgesics during the 3 months prior to screening.

CR, controlled release; ER, extended release; NRS, numerical rating scale; SD, standard deviation.

continuation in both treatment groups was AEs (tapentadol ER, 22.7% [203/894]; oxycodone CR, 36.8% [82/223]). Based on Kaplan–Meier estimates, the time to treatment discontinuation was significantly longer with tapentadol ER than with oxycodone CR ( $P < 0.001$ ).

**Treatment Exposure**

Study medication was taken for at least 6 months by 54.5% (487/894) of patients in the tapentadol ER group and 41.1% (92/224) of patients in the oxycodone CR group and for at least 1 year by 25.4% (227/894) of patients in the tapentadol ER group and 19.6% (44/224) of patients in the oxycodone CR group. The median duration of treatment for the safety population was more than 4 times longer in the tapentadol ER group (268.0 [range, 1 to 385] days) than in the oxycodone CR group (59.0 [range, 1 to 384] days). The mean (standard deviation [SD]) TDDs for the safety population were tapentadol ER 326.7 (120.23) mg and oxycodone HCl CR 51.5 (26.89) mg. For patients who completed the study, the mean (SD) TDDs were tapentadol ER 380.5 (102.43) mg and oxycodone HCl CR 71.0 (22.89) mg.

**Concomitant Medications**

The percentage of patients taking concomitant medications other than analgesics was 89.4% in the tapentadol ER group and 88.3% in the oxycodone CR group. Commonly used concomitant medications (used by ≥5% of patients in either treatment group) included alprazolam, atenolol, atorvastatin calcium, bisacodyl, calcium, docusate sodium, esomeprazole magnesium, fish oil, hydrochlorothiazide, levothyroxine sodium, lisinopril, metformin, multivitamins, omeprazole, senna alexandrina, and simvastatin.

Additional non-opioid analgesics (including allowed doses of acetaminophen as rescue medication, NSAIDs for pain other than chronic pain, and acetylsalicylic acid for cardiac prophylaxis) were taken by 19.9% (178/894) of patients in the tapentadol ER group and 17.0% (38/223) of patients in the oxycodone CR group. In the tapentadol ER and oxycodone CR groups, respectively, 9.7% (87/894) and 11.2% (25/223) of patients took acetylsalicylic acid, and 6.0% (54/894) and 4.0% (9/223) of patients took acetaminophen. Other analgesics or co-analgesics that were used during the study were amitriptyline/amitriptyline HCl (tapentadol ER group, 2.2% [20/894]; oxycodone CR group, 3.1% [7/223]) and gabapentin (tapentadol ER group, 2.2% [20/894]; oxycodone CR group, 3.1% [7/223]).

**Safety and Tolerability**

Overall, 85.7% (766/894) of patients in the tapentadol ER group and 90.6% (202/223) of patients in the oxycodone CR group experienced at least 1 TEAE. The most common TEAEs (reported by >10% in either treatment group) included constipation, nausea, dizziness, somnolence, vomiting, headache, fatigue, and pruritus. The incidences of constipation (tapentadol ER, 22.6% [202/894]; oxycodone CR, 38.6% [86/223]), nausea (tapentadol ER, 18.1% [162/894]; oxycodone CR, 33.2% [74/223]), and vomiting (tapentadol ER, 7.0% [63/894]; oxycodone CR, 13.5% [30/223]) were lower in the tapentadol ER group than in the oxycodone CR group. The incidence of pruritus in the tapentadol ER group (5.4% [48/894]) was almost half that in the oxycodone CR group (10.3% [23/223]). The incidence of dizziness was also lower in the tapentadol ER group (14.8% [132/894]) than in the oxycodone CR group (19.3% [43/223]). The incidence of TEAEs reported by ≥5% of patients in either treatment group in the safety population is shown in Table 2. No clinically relevant treatment-related effects on laboratory values, vital sign measurements, or electrocardiogram parameters were observed during the study.

The distribution of time to first onset of TEAEs of nausea, vomiting, or constipation was significantly dif-

**Table 2. TEAEs Reported by at Least 5% of Patients in Either Treatment Group (Safety Population)\***

SOC or Preferred Term, n (%)	Tapentadol ER (n = 894)	Oxycodone CR (n = 223)
Gastrointestinal disorders	465 (52.0)	143 (64.1)
Constipation	202 (22.6)	86 (38.6)
Nausea	162 (18.1)	74 (33.2)
Vomiting	63 (7.0)	30 (13.5)
Dry mouth	81 (9.1)	10 (4.5)
Diarrhea	71 (7.9)	12 (5.4)
Nervous system disorders	406 (45.4)	89 (39.9)
Dizziness	132 (14.8)	43 (19.3)
Somnolence	133 (14.9)	25 (11.2)
Headache	119 (13.3)	17 (7.6)
Infections and infestations	261 (29.2)	51 (22.9)
Sinusitis	33 (3.7)	13 (5.8)
Nasopharyngitis	49 (5.5)	6 (2.7)
Psychiatric Disorders	192 (21.5)	30 (13.5)
Insomnia	60 (6.7)	9 (4.0)
General disorders and administration site conditions	184 (20.6)	43 (19.3)
Fatigue	87 (9.7)	23 (10.3)
Skin and subcutaneous tissue disorders	151 (16.9)	48 (21.5)
Pruritus	48 (5.4)	23 (10.3)

\* Incidence is based on the number of patients experiencing ≥1 TEAE, not the number of events. CR, controlled release; ER, extended release; SOC, system organ class; TEAE, treatment-emergent adverse event.

ferent between tapentadol ER and oxycodone CR (all  $P < 0.001$ ; Figure 2). The increase in the percentage of patients reporting a first TEAE of nausea, vomiting, or constipation was more rapid within the first 4 weeks in both treatment groups, then remained relatively steady for the remainder of the study. However, first TEAEs of nausea, vomiting, or constipation occurred earlier for patients in the oxycodone CR group than for those in the tapentadol ER group.

No deaths occurred during the study, and the incidence of serious TEAEs was low in both treatment groups (tapentadol ER, 5.5% [49/894]; oxycodone CR, 4.0% [9/223]). One patient in the tapentadol ER group experienced a serious TEAE of “drug withdrawal syndrome” 8 days after completion of the study medication that resolved 3 days later. In the tapentadol ER group, serious TEAEs that were considered by the investigator to be probably/likely related to study drug included abdominal pain, constipation, abdominal obstruction, hypoglycemia, dehydration, euphoric mood, visual disturbance, and overdose; each TEAE was reported by 1 patient. The patient in the tapentadol ER group who experienced the serious TEAEs of euphoric mood, visual disturbance, and overdose had a history of substance abuse that was not known at the time of enrollment.

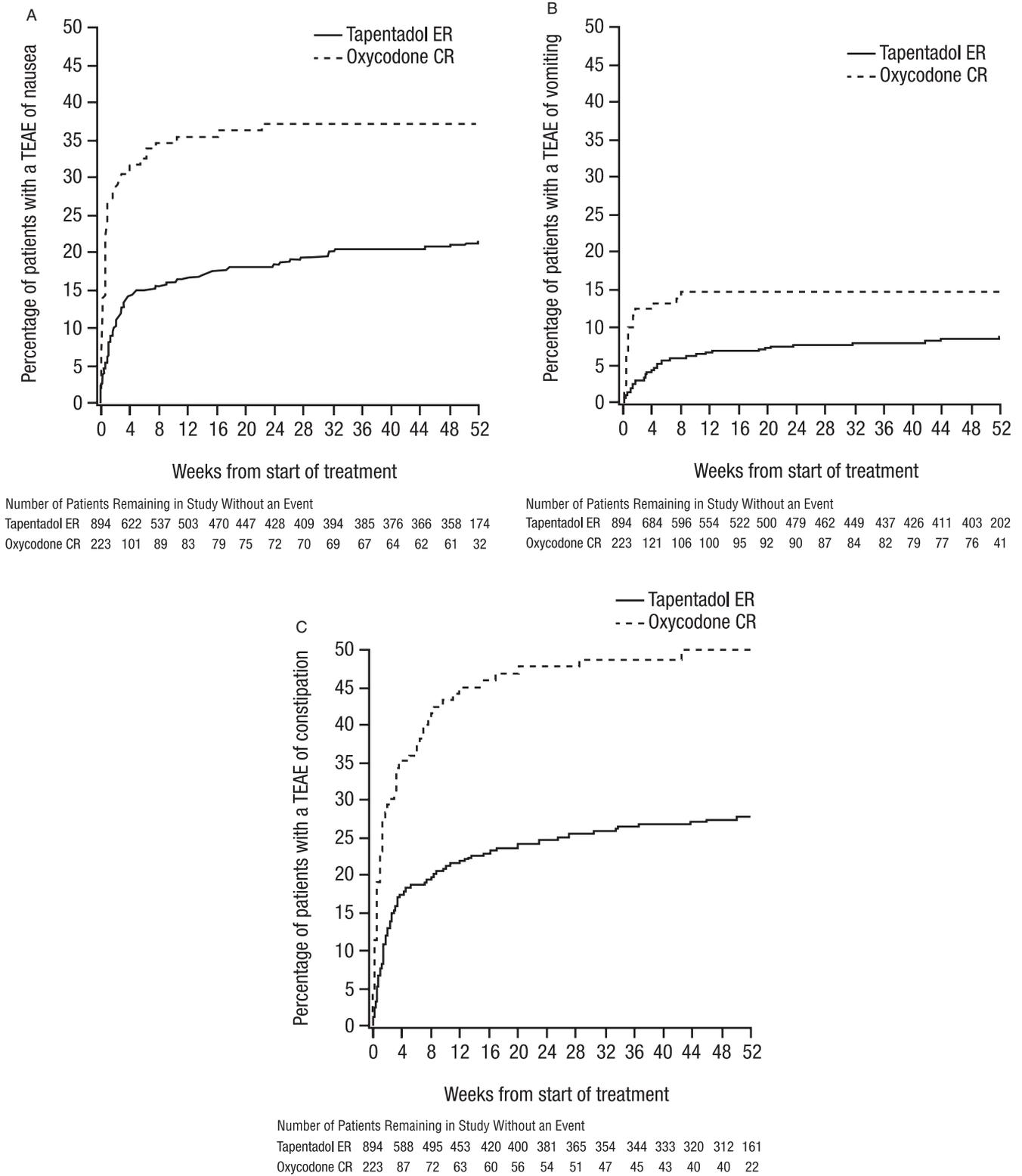
TEAEs led to study discontinuation in 22.1% (198/894) of patients in the tapentadol ER group and 36.8% (82/223) of patients in the oxycodone CR group. The incidence of gastrointestinal TEAEs, including nausea, vomiting, or constipation, that led to study discontinuation was lower in the tapentadol ER group (8.6% [77/894]) than in the oxycodone CR group (21.5% [48/223]). The incidence of the most common (reported by  $\geq 2\%$  of patients in either treatment group) TEAEs leading to study discontinuation is summarized in Figure 3. The distribution of time to onset of TEAEs leading to treatment discontinuation was significantly different between the tapentadol ER and the oxycodone CR groups ( $P < 0.001$ ); the onset of TEAEs leading to treatment discontinuation occurred later in the tapentadol ER group than in the oxycodone CR group.

Among patients who reported a TEAE of constipation, the mean (standard error [SE]) change from baseline to endpoint was lower for patients in the tapentadol ER group than for those in the oxycodone CR group for the overall PAC-SYM score (0.3 [0.05] and 0.5 [0.14], respectively), as well as for the overall rectal (0.2 [0.06] and 0.5 [0.14], respectively) and overall stool (0.4 [0.07] and 0.7 [0.17], respectively) subscale scores. The greater change in scores for overall constipation symptoms

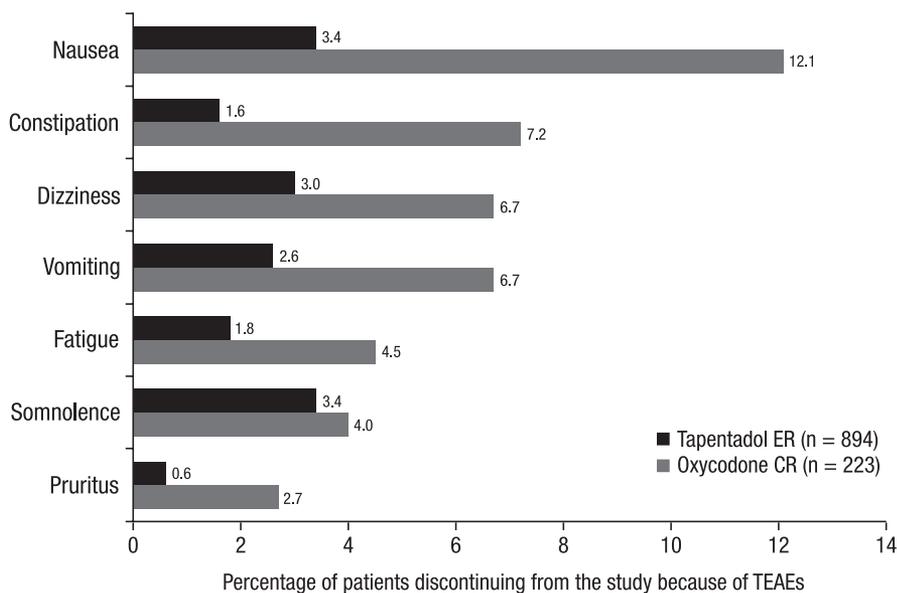
measured by the PAC-SYM, as well as for the rectal and stool subsets of constipation symptoms, with oxycodone CR indicates that the worsening of constipation symptoms for patients with constipation was more severe with oxycodone CR treatment than with tapentadol ER treatment.

Within 3 days of the last dose of study medication, 1.5% (13/894) of patients in the tapentadol ER group and 0.9% (2/223) of patients in the oxycodone CR group reported the TEAE “withdrawal syndrome.” TEAEs related to “withdrawal syndrome” were reported by the investigator as “withdrawal symptoms,” “withdrawal syndrome,” or related unspecified symptoms, such as anxiety, nausea, shivering agitation, tremor, tachycardia, or sweating. Additionally, 1.0% (9/894) of patients in the tapentadol ER group and 0.4% (1/223) of patients in the oxycodone CR group experienced the TEAE “drug withdrawal syndrome.” Of the patients who received tapentadol ER and reported either “withdrawal syndrome” or “drug withdrawal syndrome,” 8 patients had corresponding COWS assessments at the end of treatment that indicated mild opioid withdrawal and 3 patients had COWS assessments that indicated moderate opioid withdrawal. Nine of the patients who received tapentadol ER and reported “withdrawal syndrome” had corresponding COWS assessments that indicated no opioid withdrawal. One patient who received oxycodone CR and reported “withdrawal syndrome” or “drug withdrawal syndrome” had corresponding COWS data that showed mild opioid withdrawal.

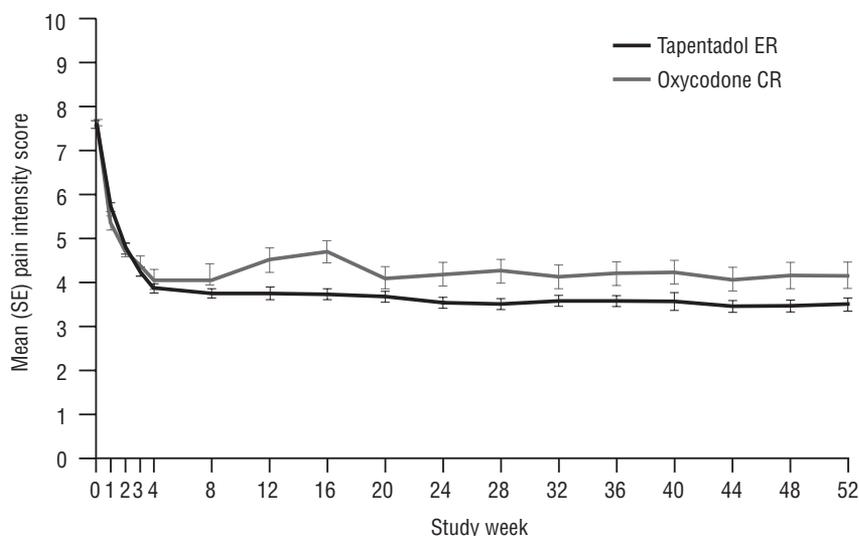
All COWS total scores during all time periods were less than 25, indicating that there was no moderately severe or severe withdrawal in either treatment group for patients who did not take opioids after the last dose of study medication. A total of 147 COWS assessments (tapentadol ER,  $n = 125$ ; oxycodone CR,  $n = 22$ ) were completed  $\geq 2$  to 4 days after treatment discontinuation for patients who did not take opioids following discontinuation. The majority (76.9% [113/147]) of these patients had no opioid withdrawal (tapentadol ER, 77.6% [97/125]; oxycodone CR, 72.7% [16/22]). In the tapentadol ER and oxycodone CR groups, respectively, 17.6% (22/125) and 22.7% (5/22) experienced mild opioid withdrawal, and 4.8% (6/125) and 4.5% (1/22) experienced moderate opioid withdrawal. A total of 216 patients (tapentadol ER,  $n = 166$ ; oxycodone CR,  $n = 50$ ) who did not take opioids after treatment discontinuation had COWS assessments  $\geq 5$  days after treatment discontinuation. Among these patients, in the



**Figure 2.** Distribution of time to the onset of first TEAE of (A) nausea, (B) vomiting, or (C) constipation (safety population). CR, controlled release; ER, extended release; TEAE, treatment-emergent adverse event.



**Figure 3.** Incidence of TEAEs leading to study discontinuation reported by at least 2% of patients (safety population). Patients could report more than one TEAE as their reason for discontinuation. CR, controlled release; ER, extended release; TEAE, treatment-emergent adverse event.



**Figure 4.** Mean (standard error [SE]) pain intensity over time (intent-to-treat population). Pain intensity was measured on an 11-point NRS. CR, controlled release; ER, extended release; NRS, numerical rating scale.

tapentadol ER and oxycodone CR groups, respectively, 88.0% (146/166) and 84.0% (42/50) experienced no opioid withdrawal, 10.8% (18/166) and 14.0% (7/50) experienced mild opioid withdrawal, and 1.2% (2/166) and 2.0% (1/50) experienced moderate opioid withdrawal.

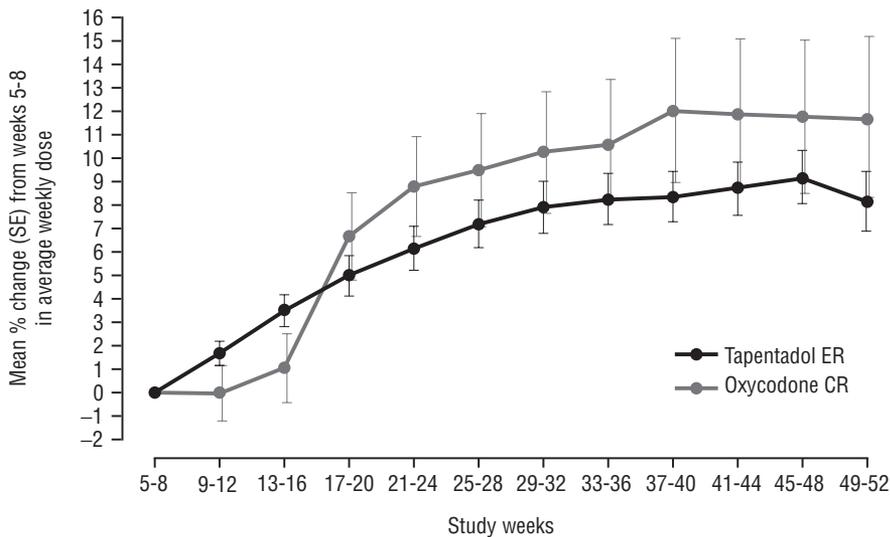
Of patients who did not take opioids after discontinuation of study medication, at least 1 SOWS assessment was obtained from 164 patients in the tapentadol ER group and from 46 patients in the oxycodone CR group. SOWS results were consistent with findings from the COWS assessments. Mean SOWS total scores from 2, 3, 4, and 5 or more days after discontinuation of study medication ranged from 6.9 to 9.5 for patients

treated with tapentadol ER and from 7.5 to 12.3 for patients treated with oxycodone CR.

### Efficacy

Baseline mean (SE) pain intensity scores in the tapentadol ER and oxycodone CR groups, respectively, were 7.6 (0.05) and 7.6 (0.11); at endpoint, mean (SE) pain intensity scores decreased to 4.4 (0.09) and 4.5 (0.17). Mean pain intensity over time is shown for the ITT population in Figure 4.

For both tapentadol ER and oxycodone CR, respectively, ratings on the global assessment of study medication of “excellent,” “very good,” or “good” were reported by the majority of patients (75.1% [616/820])



**Figure 5.** Mean percent change from weeks 5 to 8 in average weekly dose (patients who completed treatment; tapentadol ER,  $n = 412$ ; oxycodone CR,  $n = 78$ ). CR, controlled release; ER, extended release; SE, standard error.

and 72.3% [128/177]) and investigators (77.3% [635/821] and 72.3% [128/177]) at the end of treatment. The most commonly reported rating on the PGIC at the end of treatment was “much improved” for both the tapentadol ER (35.7% [292/819]) and oxycodone CR (32.8% [58/177]) groups. A rating of “very much improved” or “much improved” was reported by 48.1% (394/819) of patients in the tapentadol ER group and 41.2% (73/177) of patients in the oxycodone CR group.

#### Dose Stability and Tolerance

Among patients who completed trial treatment, the mean TDD of both tapentadol ER and oxycodone CR increased sharply during the first 4 weeks of the treatment period (dose titration), then remained approximately stable at tapentadol ER 390 mg and oxycodone HCl CR 74 mg for the remainder of the study. The mean percent change from weeks 5 to 8 in average weekly dose was numerically lower in the tapentadol ER group than in the oxycodone CR group from week 17 to the end of the study (Figure 5). Among patients who completed treatment, mean pain intensity scores decreased rapidly in both treatment groups during the first 4 weeks of the study then remained relatively stable from week 4 onward, with mean weekly pain intensity scores ranging from 3.5 to 3.9 in the tapentadol ER group and from 4.1 to 4.7 in the oxycodone CR group. Based on the relatively stable mean TDD and the stability of mean pain intensity scores there was no indication for acquired tolerance within the tested dose range of tapentadol ER in patients who completed the trial.

#### DISCUSSION

Extended-release opioid analgesics have been shown to provide relief for moderate to severe chronic pain, but are associated with high incidences of TEAEs and TEAE-related discontinuations;<sup>5,7,24–26</sup> of these, gastrointestinal TEAEs can be particularly bothersome and severe for many patients.<sup>9,27,28</sup> For example, constipation affects an estimated 40% to 95% of patients on long-term opioid therapy.<sup>27</sup> Opioid-induced constipation rarely improves with time<sup>27</sup> and can be difficult to manage with laxatives.<sup>29</sup> Improved tolerability, particularly gastrointestinal tolerability, is critical to improving patient compliance in long-term treatment situations.<sup>3,9</sup>

In this study, tapentadol ER was associated with a lower incidence of gastrointestinal AEs than oxycodone CR, including nausea, vomiting, and constipation, despite the fact that the median duration of treatment was substantially longer with tapentadol ER (268 days) than with oxycodone CR (59 days). In addition, the severity of constipation symptoms was lower with tapentadol ER treatment relative to oxycodone CR treatment. The favorable gastrointestinal tolerability profile observed for tapentadol ER over the 1-year treatment period may improve patient compliance with long-term analgesic treatment, as indicated by the reduction in TEAE-related discontinuations. The incidence of gastrointestinal TEAEs leading to discontinuation was approximately 2.5 times greater in the oxycodone CR group than in the tapentadol ER group, and the incidence of constipation leading to discontinuation was 4.5 times greater

in the oxycodone CR group than in the tapentadol ER group.

The favorable tolerability profile observed for tapentadol ER in 15-week studies in patients with moderate to severe low back,<sup>30</sup> osteoarthritis,<sup>31</sup> and neuropathic pain<sup>32</sup> was confirmed by the results of this 1-year trial, and the long-term use of tapentadol ER was not associated with any unexpected safety findings. One notable finding that was consistently observed in the 15-week studies of tapentadol ER that used oxycodone CR as an active comparator,<sup>30,31</sup> as well as in this 1-year study, was a lower incidence of pruritus associated with treatment with tapentadol ER than with oxycodone CR.

These results indicate that tapentadol ER (100 to 250 mg bid) relieved moderate to severe chronic low back pain or hip or knee osteoarthritis pain. The stability of both the mean of the average TDDs along with the steadiness of the analgesic scores over time throughout the study supports that there was no acquired tolerance associated with tapentadol ER treatment at the dose range tested for up to 1 year in this population. In addition, treatment with tapentadol ER was associated with a low incidence of opioid withdrawal following discontinuation of treatment and results from both COWS and SOWS assessments indicated a low risk of physical dependence for patients treated with tapentadol ER (100 to 250 mg bid). Furthermore, tapentadol ER was associated with a better tolerability profile than oxycodone HCl CR (20 to 50 mg bid), as indicated by the lower incidences of gastrointestinal TEAEs, dizziness, and pruritus and the lower rates of study discontinuations. The better side-effect profile and lower rate of study discontinuation may allow for improved treatment adherence and thereby permit the effective management of potentially undertreated chronic pain conditions such as low back and osteoarthritis pain.

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