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Efficacy and Safety of Tapentadol Extended Release Compared with Oxycodone Controlled Release for the Management of Moderate to Severe Chronic Pain Related to Osteoarthritis of the Knee

A Randomized, Double-Blind, Placebo- and Active-Controlled Phase III Study

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Abstract

Background: Tapentadol is a novel, centrally acting analgesic with μ-opioid receptor agonist and norepinephrine reuptake inhibitor activity.

Objective: To evaluate the efficacy and safety of tapentadol extended release (ER) compared with oxycodone controlled release (CR) for management of moderate to severe chronic osteoarthritis-related knee pain.

Methods: This was a randomized, double-blind, active- and placebo-controlled, parallel-arm, multicentre, phase III study during which patients received tapentadol ER, oxycodone CR or placebo for a 3-week titration period followed by a 12-week maintenance period. The study was carried out at sites in Australia, Canada, New Zealand and the US. A total of 1030 patients with chronic osteoarthritis-related knee pain were randomized to receive tapentadol ER 100–250 mg twice daily, oxycodone HCl CR 20–50 mg twice daily or placebo. Primary endpoints (as determined prior to initiation of the study) were the changes from baseline in average daily pain intensity (rated by patients on an 11-point numerical rating scale) over the last week of maintenance and over the entire 12-week maintenance period; last observation carried forward was used to impute missing values after early treatment discontinuation.

Results: Efficacy and safety were evaluated for 1023 patients. Tapentadol ER significantly reduced average pain intensity from baseline to week 12 of the maintenance period versus placebo (least squares mean [LSM] difference [95% CI], –0.7 [–1.04, –0.33]), and throughout the maintenance period (–0.7 [–1.00, –0.33]). Oxycodone CR significantly reduced average pain intensity from baseline throughout the maintenance period versus placebo (LSM difference [95% CI], –0.3 [–0.67, –0.00]) but not at week 12 (–0.3 [–0.68, 0.02]). A significantly higher percentage of patients achieved ≥50% improvement in pain intensity in the tapentadol ER group (32.0% [110/344]) compared with the placebo group (24.3% [82/337]; p = 0.027), indicating a clinically significant improvement in pain intensity, while a significantly lower percentage of patients achieved ≥50% improvement in pain intensity in the oxycodone CR group (17.3% [59/342]; p = 0.023 vs placebo). In the placebo, tapentadol ER and oxycodone CR groups, respectively, 61.1% (206/337), 75.9% (261/344) and 87.4% (299/342) of patients reported at least one treatment-emergent adverse event (TEAE); incidences of gastrointestinal-related TEAEs were 26.1% (88/337), 43.0% (148/344) and 67.3% (230/342).

Conclusion: Treatment with tapentadol ER 100–250 mg twice daily or oxycodone HCl CR 20–50 mg twice daily was effective for the management of moderate to severe chronic osteoarthritis-related knee pain, with substantially lower incidences of gastrointestinal-related TEAEs associated with treatment with tapentadol ER than with oxycodone CR.

[Trial registration number: NCT00421928 (ClinicalTrials.gov Identifier)]

Introduction

Osteoarthritis is one of the most common causes of disability and pain among older adults,[1] with osteoarthritis pain affecting as many as one in every four adults over 65 years of age worldwide.[2] Current guidelines recommend paracetamol (acetaminophen), cyclo-oxygenase-2 inhibitors, oral NSAIDs, topical NSAIDs and opioid analgesics as options for the management of chronic osteoarthritis pain.[3] Although chronic pain associated with osteoarthritis is often managed with NSAIDs, paracetamol and aspirin (acetylsalicylic acid),[4,5] these agents may be contraindicated because of associated hepatotoxicity, renal toxicity, cardiovascular adverse effects and gastrointestinal adverse effects.[6-8] Opioid analgesics such as oxycodone and morphine have demonstrated efficacy in the management of moderate to severe pain.[9-13] However, the adverse effect profile of μ-opioid receptor agonists includes gastrointestinal symptoms, CNS symptoms and pruritus, all of which may significantly impact treatment compliance.[9,10,14-16]

The tolerability profile of an analgesic is an important consideration for the effective management of chronic pain and may influence decisions of patients and physicians with regard to compliance.[6-10,14-16] The adverse effects associated with opioids used to manage chronic pain,[17] including gastrointestinal-related and nervous system adverse effects and pruritus,[15] often necessitate lowering the dosage (and compromising analgesic efficacy), leading to treatment discontinuation. Opioid-induced constipation is particularly troublesome because unlike many other opioid-related adverse effects, tolerance to constipation rarely develops. Additional therapy with stool softeners and/or laxatives is often necessary to manage this problem; however, half of patients

using stool softeners and/or laxatives for this purpose are refractory to these treatments.[18]

Tapentadol is a centrally acting analgesic with two mechanisms of action, μ-opioid receptor agonism and norepinephrine reuptake inhibition.[19] It has been previously reported that enhancing monoaminergic transmission is effective for the relief of chronic pain;[20] however, studies have indicated that norepinephrine reuptake inhibition is more effective at producing analgesia than serotonin reuptake inhibition.[21] Preclinical studies have shown that norepinephrine reuptake inhibition can also augment the analgesia induced by morphine.[22] Hence, the noradrenergic reuptake inhibition combined with the μ-opioid receptor agonism produced by tapentadol may enhance its analgesic effects.[19,23]

An extended-release (ER) formulation of tapentadol has been developed for the management of chronic pain. This study evaluated the efficacy and tolerability of controlled, adjustable dosing of tapentadol ER compared with oxycodone controlled release (CR) for the management of moderate to severe chronic osteoarthritis knee pain.

Patients and Methods

Patients

The eligible population included men and women ≥40 years of age with a diagnosis of osteoarthritis of the knee according to American College of Rheumatology criteria,[24] functional capacity class I-III, and pain at the reference joint requiring the use of analgesics (non-opioids or opioids at doses equivalent to ≤160 mg oral morphine/day) for ≥3 months prior to screening. A patient-rated 11-point numerical rating scale (NRS; 0 = no pain, 10 = pain as bad as you can imagine) was used to assess pain intensity twice daily. Patients were dissatisfied with their current analgesic therapy and had an average baseline pain intensity NRS score of ≥5 during the 3 days preceding randomization. All patients provided written informed consent.

Exclusion criteria included the presence of clinically significant or unstable medical or psychiatric disease, requirement for painful procedures (e.g. surgery) during the study that could influence efficacy or safety assessments, and history of substance abuse, epilepsy/seizure disorder, stroke/transient ischaemic attack, malignancy (preceding 2 years), HIV infection, chronic hepatitis B or C, uncontrolled hypertension (systolic blood pressure >160 mmHg and/or diastolic blood pressure >95 mmHg), severe renal impairment (creatinine clearance <60 mL/min), moderate or severe hepatic impairment, ALT or AST concentrations >3 times the upper limit of normal, and hypersensitivity to study medications or their excipients. Patients with conditions potentially influencing the assessment of osteoarthritis pain (anatomical deformities, fibromyalgia, gout or infectious or autoimmune diseases affecting the knee) were excluded. The use of concomitant analgesics (except allowed doses of paracetamol) was prohibited during the study. Neuroleptics, tricyclic antidepressants, anticonvulsants, antiparkinsonian drugs and serotonin-norepinephrine reuptake inhibitors were prohibited within 14 days prior to screening and during the study because their use could confound efficacy or safety assessments. Medications other than those listed above, such as selective serotonin reuptake inhibitors, were allowed for patients with diagnosed, controlled psychiatric or neurological conditions (e.g. major depressive disorder) if taken at a stable dose for ≥3 months prior to randomization. Monoamine oxidase inhibitors were prohibited within 14 days prior to screening and during the study. Corticosteroids were prohibited during the trial and within 4 weeks to 6 months prior to screening, depending on the route of administration.

Patients were recruited at 87 sites in the US, 15 sites in Canada, six sites in New Zealand and four sites in Australia.

Study Methodology

This study (ClinicalTrials.gov Identifier: NCT00421928) was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice. The protocol was reviewed and approved by institutional review boards at participating study centres.

This randomized, double-blind, active- and placebo-controlled, parallel-arm, multicentre, phase III study consisted of five periods: screening (≤14 days), washout (3–7 days, during which patients were to discontinue all analgesic medication), titration (3 weeks), maintenance (12 weeks) and follow-up (14 days after last intake of study medication). The double-blind treatment period included the 3-week titration period and the 12-week maintenance period.

After the washout period, eligible patients were randomized 1 : 1 : 1 to receive twice-daily, controlled, adjustable, oral doses of tapentadol ER 100–250 mg, oxycodone HCl CR 20–50 mg or placebo. This 5 : 1 dosing ratio was determined based on results of preclinical studies,[19,23] which found that the dose equivalency of tapentadol to morphine was approximately 2.5 : 1,[23] and oxycodone is approximately twice as potent as morphine.[25] Randomization was based on a computer-generated randomization list, balanced using permuted blocks, and stratified by study site. Randomization was implemented through an interactive voice response system (IVRS) to dispense blinded study medication. Placebo tablets and capsules (one for each active treatment) were used to maintain blinded treatments. Investigators were not provided with the randomization codes, and the schedule was maintained with the IVRS. The blinding was not broken until all patients had completed the trial, except in the case of a suspected unexpected serious adverse reaction or if emergency treatment required knowledge of a patient's treatment status.

Active treatments started with twice-daily doses of tapentadol ER 50 mg or oxycodone HCl CR 10 mg. After the first 3 days, doses were increased to tapentadol ER 100 mg twice daily or oxycodone HCl CR 20 mg twice daily; these were the minimum doses for the remainder of the study. At 3-day intervals, patients could increase their doses in consultation with a study investigator in twice-daily increments of tapentadol ER 50 mg or oxycodone HCl CR 10 mg (maximum twice-daily doses: tapentadol ER 250 mg, oxycodone HCl CR 50 mg); downward titration was possible in twice-daily decrements of tapentadol ER 50 mg or oxycodone HCl CR 10 mg without a time restriction. All doses were taken in the morning and evening. Paracetamol (≤1000 mg/day) could be taken up to 3 days before the conclusion of the titration period. The oxycodone CR dosages were selected based on prescribing information for OxyContin® (Purdue Pharma L.P., Stamford, CT, USA)[25] and anticipated equianalgesic potency to the selected tapentadol ER dose range. The titration schedule was designed to initiate treatment at the lowest dose, as recommended in US prescribing information for OxyContin®; doses were then adjusted to reach the optimal dose (in terms of pain relief and tolerability) within the allowed therapeutic dose range during the 3-week titration period.

After the 3-week titration period, patients entered the 12-week maintenance period. During this period, patients were encouraged to remain on a steady dose of study medication but could request additional dose adjustments to maintain their optimal balance between pain relief and tolerability. Additional analgesic medication was not allowed during the maintenance period (except paracetamol ≤1000 mg/day; maximum, 3 consecutive days) when deemed necessary for the relief of pain unrelated to the index joint osteoarthritis pain.

Study visits were scheduled at weeks 1, 2 and 3 of the titration period; at weeks 1, 2, 3, 5, 7, 9 and 11 of the maintenance period; and at week 13 of the maintenance period (end of treatment visit). Patients rated their pain twice daily (morning and evening) using the NRS; results were recorded in an electronic diary. The Western Ontario and McMaster Universities (WOMAC) Index of Osteoarthritis Questionnaire[26] (24 questions concerning pain, disability and joint stiffness) was completed by patients at baseline; at weeks 1, 3, 5, 7, 9 and 11 of the maintenance period; and at the end of treatment visit. The Patient Global Impression of Change (PGIC), a measure of perceived change in overall health status (1 = very much improved, 7 = very much worse),[27] was completed at weeks 5 and 9 of the maintenance period and at the end of treatment visit. The EuroQol-5 Dimension (EQ-5D)[28] and the Short Form-36 (SF-36) Health Survey,[29] which evaluate health outcomes and physical, social and

mental well-being, were administered at baseline; at weeks 1, 5 and 9 of the maintenance period; and at the end of treatment visit. A responder analysis was conducted to determine the percentages of patients achieving ≥30% and ≥50% improvement in average pain intensity from baseline to week 12 of the maintenance period (patients discontinuing study medication prior to week 12 were considered non-responders).

Adverse events (AEs) were monitored throughout the study and for 10–14 days after last administration of study medication. Treatment-emergent AEs (TEAEs) were those occurring between initiation of study medication and ≤3 days after discontinuation of study medication. The Patient Assessment of Constipation Symptoms (PAC-SYM),[30] a patient-rated, validated, 12-item questionnaire that measures severity of constipation-related symptoms over a 2-week period in patients using opioids to manage chronic pain, was administered at baseline and at the end of study treatment. The PAC-SYM contains three subscales (stool, abdominal and rectal symptoms), with responses rated on a 5-point scale (0 = absence of symptoms, 4 = very severe symptoms). The Clinical Opiate Withdrawal Scale (COWS),[31] a clinician-rated 11-item scale that evaluates various components of opioid withdrawal, was administered after cessation of study medication at the follow-up visit to all patients who discontinued prematurely and to those who did not enter the open-label extension of this study. The Subjective Opiate Withdrawal Scale (SOWS)[32] was also used to assess subjectively reported symptoms consistent with opioid withdrawal in English-speaking patients at US sites throughout the 4 days after treatment discontinuation.

The primary null hypothesis was that the tapentadol ER group would be no different from the placebo group with respect to the primary efficacy endpoint. In the US, the primary endpoint was change from baseline in average pain intensity at week 12 of the maintenance period. For European and other health authorities, the primary endpoint was change from baseline in average pain intensity over the entire 12-week maintenance period. The primary endpoint for one health authority was considered a secondary endpoint for the other.

Statistical Analyses

All analyses were performed using SAS® version 9 (SAS Institute Inc., Cary, NC, USA). Sample size calculation was based upon an assumed mean (standard deviation [SD]) treatment difference between tapentadol ER and placebo of –0.7 (2.7) on the 11-point NRS. To detect a statistically significant difference between tapentadol ER and placebo with 90% power at $\alpha = 0.05$, it was estimated that 314 patients per treatment group were required. The intent-to-treat (ITT) population (used for all efficacy and safety analyses) included all patients who were randomized and took one or more doses of study medication.

For the primary endpoint, an analysis of covariance (ANCOVA) model with treatment and pooled analysis centre as factors and baseline pain intensity score as a covariate was applied. The treatment effect of tapentadol ER versus placebo was estimated based on the least squares mean (LSM) of the difference. p-Values (5% significance level) and 95% confidence intervals (CIs) were calculated. Last observation carried forward was applied to impute missing pain measurements in the event of early discontinuation.

To analyse response rates, the percentage improvement from baseline in pain intensity at week 12 of the maintenance period was calculated for each patient. Patients who worsened or discontinued early were considered non-responders. The overall distribution of responder rates was compared between treatment groups using a log-rank test. Responder rates for patients achieving ≥30% and ≥50% improvement were compared using the Cochran-Mantel-Haenszel test, with p-values for pairwise differences between treatment arms. Changes from baseline in WOMAC scores were summarized with descriptive statistics and analysed with a repeated-measures ANCOVA model, with timepoint as the repeated factor, treatment and pooled analysis centre as factors, and baseline value as a covariate. Changes from baseline in weighted EQ-5D, SF-36 and PAC-SYM scores were summarized with

descriptive statistics and analysed with an ANCOVA model, with treatment and pooled analysis centres as factors, and baseline value as a covariate; endpoint data for these measures were reported. PGIC assessments were analysed using the Cochran-Mantel-Haenszel test. Last observation carried forward was applied to impute missing scores in the event of early discontinuation for the PGIC, the weighted EQ-5D index and visual analogue scale scores, and all SF-36 dimension and summary scores. No multiplicity adjustments were performed for efficacy analyses, which were evaluated for statistical significance at $p = 0.05$.

Descriptive statistics of study medication exposure included maximum and minimum total daily dose (TDD), mean TDD and modal (most frequently used) TDD. Summary descriptive statistics were calculated for baseline and demographic variables and for the incidence of TEAEs. The event rate for the composite of nausea and/or vomiting and for constipation was compared between the active treatment groups using the Cochran-Mantel-Haenszel test. The time to first onset of TEAEs leading to study discontinuation was estimated with Kaplan-Meier methods and compared with a log-rank test. For COWS, the total score (sum of 11 items; possible score of 0–48) was used to classify the severity of opioid withdrawal (<5, no withdrawal; 5–12, mild withdrawal; 13–24, moderate withdrawal; 25–36, moderately severe withdrawal; >36, severe withdrawal) for patients who did not use opioids following discontinuation. The number and percentage of patients in each opioid withdrawal category were summarized by treatment group and by the number of days (≥2 to <5 or ≥5 days) after last intake of study medication that the COWS was assessed. For SOWS, the total score (sum of 15 items; possible score of 0–60, with a score of 60 indicating extremely severe opioid withdrawal) was used to measure patients' self-reported symptoms consistent with 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 US study sites who did not use opioids following discontinuation.

Results

Patient Disposition and Demographic Characteristics

This study was conducted from 7 February 2007 through 4 June 2008. A total of 1030 patients were randomized (figure 1). Six patients received no study medication, and one was erroneously enrolled twice, leaving 1023 patients in the ITT population. In the placebo, tapentadol ER and oxycodone CR groups, respectively, 61.4% (207/337), 57.3% (197/344) and 35.4% (121/342) of patients completed the 15-week double-blind treatment period. The most common reason for discontinuation during double-blind treatment was lack of efficacy in the placebo group (16.6% [56/337]) and AEs in the tapentadol ER and oxycodone CR groups (19.2% [66/344] and 43.0% [147/342], respectively). Demographic and baseline characteristics were balanced across groups (table I).

Treatment Exposure

The group average (SD) of the individual mean TDDs during the entire 15-week double-blind treatment period was 299.3 (107.16) mg for tapentadol ER (n = 344) and 48.2 (23.94) mg for oxycodone HCl CR (n = 341). During the 12-week maintenance period, the group average of the individual mean TDDs remained stable at approximately 350 mg for tapentadol ER and approximately 70 mg for oxycodone HCl CR. The median modal TDD during the maintenance period was 400 mg for tapentadol ER (n = 264) and 80 mg for oxycodone HCl CR (n = 173). The median percentage of time patients spent on the modal dose in the tapentadol ER and oxycodone CR groups, respectively, was 95.3% and 94.0%.

Efficacy

The change from baseline in average pain intensity throughout the study is shown in figure 2. Significant pain relief was achieved with tapentadol ER versus placebo based on the primary efficacy endpoints. The LSM difference (95% CI) versus placebo was –0.7 (–1.04, –0.33) at week 12

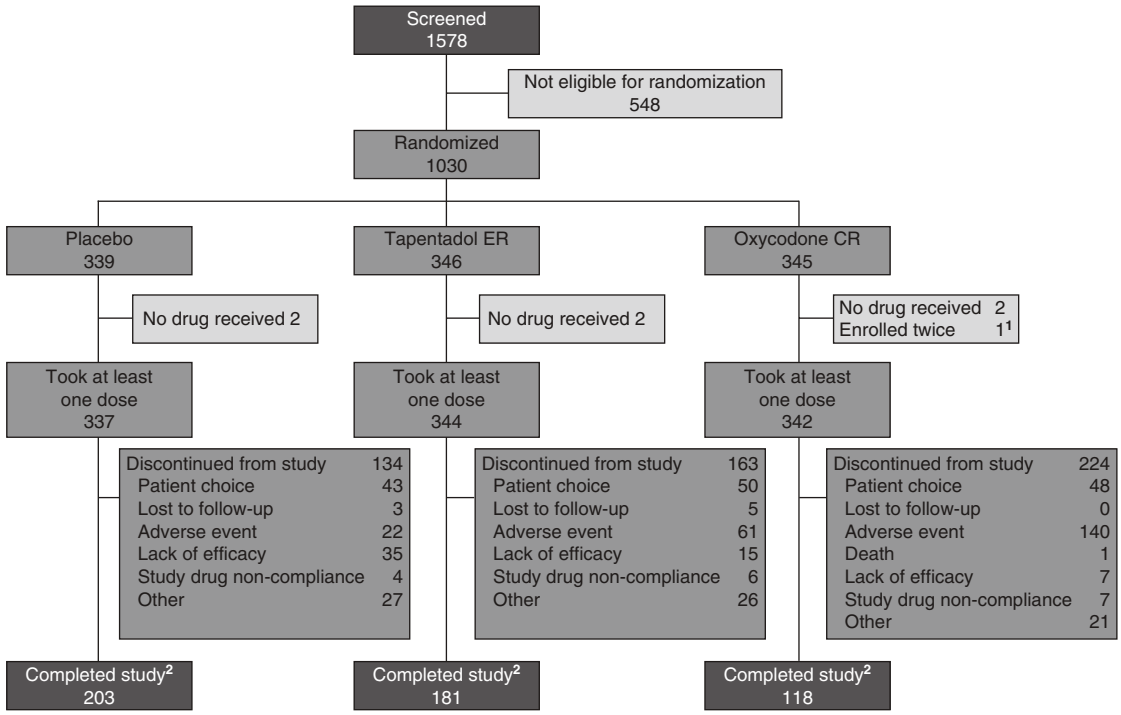


Fig. 1. Patient disposition. **1** One patient who received oxycodone CR was enrolled twice; only the second randomization was included in the analysis, as the patient did not receive study medication during the first randomization. **2** Includes patients who were enrolled in the open-label extension who completed all follow-up visits in the current study. **CR** = controlled release; **ER** = extended release.

of the maintenance period and –0.7 (–1.00, –0.33) for the overall maintenance period.

With oxycodone CR, average pain intensity was reduced significantly compared with placebo from baseline for the overall maintenance period (LSM difference vs placebo, –0.3; 95% CI [–0.67, 0.00]), but was not statistically significantly lower at week 12 of the maintenance period (–0.3 [–0.68, 0.02]).

The percentage of patients who achieved ≥30% reduction from baseline in average pain intensity at week 12 of the maintenance period was not significantly different between tapentadol ER and placebo (43.0% [148/344] vs 35.9% [121/337]; p = 0.058), but was significantly lower for oxycodone CR compared with placebo (24.9% [85/342] vs 35.9% [121/337]; p = 0.002). Treatment with tapentadol ER resulted in a significantly higher percentage of patients achieving ≥50% reduction in average pain intensity from baseline at week 12 of the maintenance period compared with placebo (32.0% [110/344] vs 24.3% [82/337]; p = 0.027). In contrast, treatment with oxycodone CR resulted in a significantly lower percentage of patients achieving ≥50% reduction in average pain intensity from baseline at week 12 of the maintenance period compared with placebo (17.3% [59/342] vs 24.3% [82/337]; p = 0.023). These responder analyses were affected by the higher percentage of patients who discontinued treatment (mostly due to AEs) in the oxycodone CR group (64.6% [221/342]) than in the tapentadol ER (42.7% [147/344]) or placebo (38.6% [130/337]) groups. Pairwise comparisons of the active treatment groups to placebo were affected by the definition of patients who discontinued as non-responders.

Estimated mean changes from baseline to week 12 of the maintenance period in WOMAC subscale scores and WOMAC global score are presented in table II. Tapentadol ER was significantly better than placebo at week 12 on the WOMAC

Table I. Baseline and demographic characteristics (safety analysis population)

Characteristic	Placebo (n = 337)	Tapentadol ER (n = 344)	Oxycodone CR (n = 342)
Age, y			
Mean (SD)	58.2 (9.15)	58.4 (10.09)	58.2 (10.29)
Age group, n (%)			
<65 y	260 (77.2)	249 (72.4)	249 (72.8)
≥65 y	77 (22.8)	95 (27.6)	93 (27.2)
Sex, n (%)			
Male	137 (40.7)	128 (37.2)	140 (40.9)
Female	200 (59.3)	216 (62.8)	202 (59.1)
Ethnicity, n (%)			
White	267 (79.2)	260 (75.6)	245 (71.6)
Black	38 (11.3)	49 (14.2)	45 (13.2)
Hispanic	20 (5.9)	21 (6.1)	37 (10.8)
Other	12 (3.6)	14 (4.1)	15 (4.4)
Body weight, kg			
Mean (SD)	100.28 (26.720)	94.80 (23.664)	97.43 (24.445)
Body mass index, kg/m^2			
Mean (SD)	35.08 (9.329)	33.61 (7.967)	34.16 (8.185)
Baseline pain intensity category,[a,b] n (%)			
Mild	0	2 (0.6)	0
Moderate	61 (18.2)	49 (14.2)	58 (17.0)
Severe	275 (81.8)	293 (85.2)	284 (83.0)

a Group average of individual mean daily pain scores on an 11-point NRS over 72 hours prior to randomization.

b Mild pain intensity was defined as a rating of 1 to <4 on the NRS; moderate was defined as a rating of ≥4 to <6; and severe was defined as a rating of ≥6.

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

global scale and on the pain and physical functioning subscales.

PGIC results are summarized in figure 3. In the placebo, tapentadol ER and oxycodone CR groups, respectively, 8.4% (23/273), 20.2% (52/258) and 13.5% (27/200) of patients reported that their overall status was 'very much improved'; 27.1% (74/273), 38.4% (99/258) and 33.5% (67/200) of patients reported that their overall status was 'much improved'; and 23.4% (64/273), 20.9% (54/258) and 26.5% (53/200) of patients reported that their overall status was 'minimally improved' from baseline to end of treatment. The percentage of patients who reported that there was 'no change' in their overall status from baseline to end of treatment was 24.2% (66/273) in the placebo group, 12.8% (33/258) in the tapentadol ER group and 9.5% (19/200) in the oxycodone CR group. In the placebo, tapentadol ER and oxycodone CR groups, respectively, 11.0% (30/273), 3.1% (8/258) and 10.0% (20/200) of patients reported that their overall status was 'minimally worse'; 4.0% (11/273), 3.9% (10/258) and 6.5% (13/200) of patients reported that their overall status was 'much worse'; and 1.8% (5/273), 0.8% (2/258) and 0.5% (1/200) of patients reported that their overall status was 'very much worse' from baseline to the end of treatment. Improvements in PGIC scores were statistically significant compared with placebo for both active treatment groups (tapentadol ER, $p < 0.001$; oxycodone CR, $p = 0.018$).

Changes from baseline to end of treatment in health outcomes measured by the EQ-5D and SF-36 are summarized in tables III and IV, respectively. Scores on the EQ-5D health status index, a subcomponent of the EQ-5D, improved significantly with tapentadol ER compared with

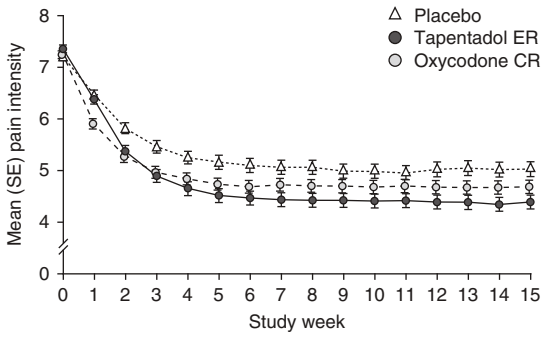


Fig. 2. Mean (SE) pain intensity scores over time using last observation carried forward (intent-to-treat population). **CR** = controlled release; **ER** = extended release; **SE** = standard error.

placebo (p = 0.004). There was no significant difference between oxycodone CR and placebo in EQ-5D health status index scores. Tapentadol ER showed statistically significant improvements from baseline to end of treatment compared with placebo on the SF-36 'physical functioning', 'role-physical', 'bodily pain' and 'physical component summary' subscale scores. In contrast, significant differences in favour of placebo were shown for comparisons of oxycodone CR and placebo for changes from baseline to end of treatment in the SF-36 'role-physical', 'vitality', 'social functioning', 'role-emotional', 'mental health' and 'mental component summary' subscale scores.

Safety

The incidence of TEAEs was 61.1% (206/337) with placebo, 75.9% (261/344) with tapentadol ER and 87.4% (299/342) with oxycodone CR. The most common (≥10% in any group) TEAEs in the active treatment groups were nausea, constipation, vomiting, dizziness, headache, somnolence, fatigue and pruritus (table V). Most were mild or moderate in intensity. Incidences of constipation and the composite of nausea and/or vomiting were significantly lower in the tapentadol ER group than in the oxycodone CR group (constipation, 18.9% [65/344] vs 36.8% [126/342]; p < 0.001; nausea and/or vomiting, 22.7% [78/344] vs 40.6% [139/342]; p < 0.001).

Table II. Estimated changes in Western Ontario and McMaster Universities (WOMAC) Index of Osteoarthritis Questionnaire subscale and global scores from baseline to week 12 based on a mixed effects model (intent-to-treat analysis population)

Measure	Placebo (n = 158)	Tapentadol ER (n = 149)	Oxycodone CR (n = 92)
Pain subscale			
LSM change (SE)	−0.88 (0.055)	−1.16 (0.055)	−1.05 (0.070)
LSMD vs placebo (95% CI)		−0.27 (−0.422, −0.126)	−0.17 (−0.338, 0.000)
p-Value		<0.001	0.051
Physical function subscale[a]			
LSM change (SE)	−0.83 (0.055)	−1.04 (0.055)	−1.04 (0.070)
LSMD vs placebo (95% CI)		−0.21 (−0.357, −0.060)	−0.20 (−0.373, −0.034)
p-Value		0.006	0.019
Stiffness subscale			
LSM change (SE)	−1.00 (0.063)	−1.17 (0.063)	−1.10 (0.080)
LSMD vs placebo (95% CI)		−0.17 (−0.337, 0.002)	−0.10 (−0.292, 0.096)
p-Value		0.053	0.321
Global WOMAC score[a]			
LSM change (SE)	−0.91 (0.054)	−1.12 (0.054)	−1.08 (0.068)
LSMD vs placebo (95% CI)		−0.21 (−0.357, −0.065)	−0.18 (−0.343, −0.010)
p-Value		0.0047	0.0381

a n = 158 for placebo; n = 148 for tapentadol ER; n = 92 for oxycodone CR.

CI = confidence interval; **CR** = controlled release; **ER** = extended release; **LSM** = least squares mean; **LSMD** = LSM difference; **SE** = standard error.

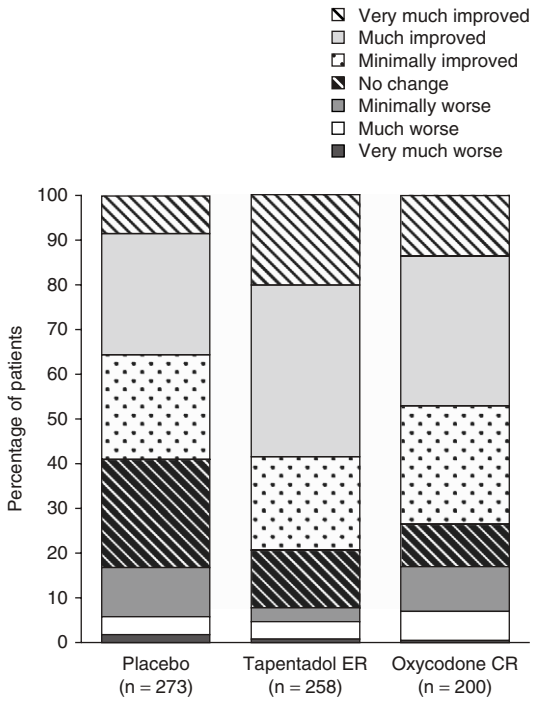


Fig. 3. Patient global impression of change at endpoint (intent-to-treat population). **CR** = controlled release; **ER** = extended release.

Tapentadol ER was also associated with lower incidences of somnolence and pruritus than oxycodone CR.

TEAEs led to study discontinuation in 6.5% (22/337), 19.2% (66/344) and 42.7% (146/342) of patients in the placebo, tapentadol ER and oxycodone CR groups, respectively. Gastrointestinal-related TEAEs were the most common TEAEs associated with study discontinuation in both active treatment groups (figure 4).

A Kaplan-Meier plot of time to first onset of TEAEs leading to discontinuation is shown in figure 5. The time to first onset of TEAEs leading to discontinuation was significantly shorter in both active treatment groups than in the placebo group ($p < 0.001$ for both) and significantly longer for patients treated with tapentadol ER than with oxycodone CR ($p < 0.001$). These results are consistent with the finding that a high percentage of patients in the oxycodone CR group discontinued treatment early because of AEs. During the titration period, discontinuations due to AEs were reported by 3.9% (13/337), 10.8% (37/344) and 36.3% (124/342) of patients in the placebo, tapentadol ER and oxycodone CR groups, respectively.

During double-blind treatment (titration and/or maintenance periods) and within 30 days of the last dose of study medication, 20 patients experienced serious AEs (placebo, n = 6 [1.8%]; tapentadol ER, n = 4 [1.2%]; oxycodone CR, n = 10 [2.9%]). One patient died because of a myocardial

Table III. Outcomes measured on the EuroQol-5 Dimension questionnaire (intent-to-treat analysis population)

Outcome	Placebo (n = 337)	Tapentadol ER (n = 344)	Oxycodone CR (n = 342)
Patients reporting 'no problem at study end' (%)			
Mobility	16.3	25.0	16.7
Self-care	75.1	81.1	80.1
Usual activities	26.1	33.7	27.2
Pain/discomfort[a]	5.6	9.0	4.7
Anxiety/depression	71.8	70.9	69.6
Health status index (change from baseline to endpoint)			
Mean change (SE)	0.1 (0.02)	0.2 (0.02)	0.1 (0.02)
LSM	0.12	0.17	0.11
LSMD vs placebo (SE) [95% CI]		0.05 (0.02) [0.02, 0.09]	–0.01 (0.02) [–0.05, 0.02]
p-Value		0.004	0.449

a Placebo, n = 336; tapentadol ER, n = 344; oxycodone CR, n = 342.

CI = confidence interval; **CR** = controlled release; **ER** = extended release; **LSM** = least squares mean; **LSMD** = LSM difference; **SE** = standard error.

Table IV. Change from baseline to end of treatment in SF-36 scores (intent-to-treat analysis population)

Measure	Placebo (n = 337)	Tapentadol ER (n = 344)	Oxycodone CR (n = 342)
Physical functioning[a]			
LSM change from baseline	5.4	10.7	7.3
LSMD vs placebo (SE) [95% CI]		5.3 (1.43) [2.49, 8.10]	1.8 (1.43) [−0.98, 4.65]
p-Value		<0.001	0.200
Role-physical			
LSM change from baseline	12.1	18.0	6.8
LSMD vs placebo (SE) [95% CI]		5.9 (2.69) [0.60, 11.16]	−5.3 (2.69) [−10.58, −0.00]
p-Value		0.029	0.050
Bodily pain			
LSM change from baseline	13.1	18.6	11.6
LSMD vs placebo (SE) [95% CI]		5.5 (1.50) [2.54, 8.43]	−1.6 (1.50) [−4.51, 1.38]
p-Value		<0.001	0.297
General health			
LSM change from baseline	1.7	2.4	0.9
LSMD vs placebo (SE) [95% CI]		0.7 (0.86) [−0.98, 2.40]	−0.8 (0.86) [−2.48, 0.90]
p-Value		0.407	0.361
Vitality			
LSM change from baseline	6.8	8.6	1.3
LSMD vs placebo (SE) [95% CI]		1.8 (1.28) [−0.74, 4.26]	−5.5 (1.28) [−8.04, −3.04]
p-Value		0.168	<0.001
Social functioning			
LSM change from baseline	7.0	9.7	2.7
LSMD vs placebo (SE) [95% CI]		2.8 (1.62) [−0.42, 5.94]	−4.3 (1.62) [−7.51, −1.15]
p-Value		0.089	0.008
Role-emotional			
LSM change from baseline	7.8	4.8	0.1
LSMD vs placebo (SE) [95% CI]		−3.1 (2.66) [−8.28, 2.15]	−7.7 (2.66) [−12.96, −2.52]
p-Value		0.248	0.004
Mental health			
LSM change from baseline	3.5	2.3	−0.1
LSMD vs placebo (SE) [95% CI]		−1.2 (1.07) [−3.26, 0.92]	−3.5 (1.07) [−5.63, −1.44]
p-Value		0.270	<0.001
Mental component summary			
LSM change from baseline	2.0	0.9	−1.0
LSMD vs placebo (SE) [95% CI]		−1.1 (0.66) [−2.44, 0.17]	−3.0 (0.67) [−4.34, −1.72]
p-Value		0.089	<0.001
Physical component summary			
LSM change from baseline	3.5	6.2	3.7
LSMD vs placebo (SE) [95% CI]		2.8 (0.61) [1.56, 3.95]	0.3 (0.61) [−0.94, 1.45]
p-Value		<0.001	0.675

a Placebo, n = 337; tapentadol ER, n = 343; oxycodone CR, n = 341.

CI = confidence interval; **CR** = controlled release; **ER** = extended release; **LSM** = least squares mean; **LSMD** = LSM difference; **SE** = standard error; **SF-36** = Short Form-36 Health Survey.

Table V. Treatment-emergent adverse events reported by ≥5% of patients (safety analysis population)[a]

Adverse event	Placebo (n = 337)	Tapentadol ER (n = 344)	Oxycodone CR (n = 342)
Gastrointestinal disorders	88 (26.1)	148 (43.0)	230 (67.3)
Constipation	22 (6.5)	65 (18.9)	126 (36.8)
Nausea	23 (6.8)	74 (21.5)	125 (36.5)
Vomiting	11 (3.3)	18 (5.2)	61 (17.8)
Dry mouth	8 (2.4)	22 (6.4)	15 (4.4)
Diarrhoea	20 (5.9)	16 (4.7)	17 (5.0)
Nervous system disorders	84 (24.9)	138 (40.1)	164 (48.0)
Somnolence	14 (4.2)	37 (10.8)	67 (19.6)
Dizziness	16 (4.7)	61 (17.7)	65 (19.0)
Headache	56 (16.6)	51 (14.8)	50 (14.6)
General and administration site disorders	37 (11.0)	65 (18.9)	66 (19.3)
Fatigue	15 (4.5)	37 (10.8)	35 (10.2)
Skin and subcutaneous disorders	12 (3.6)	50 (14.5)	71 (20.8)
Pruritus	4 (1.2)	24 (7.0)	43 (12.6)
Musculoskeletal and connective tissue disorders	59 (17.5)	36 (10.5)	36 (10.5)
Back pain	22 (6.5)	7 (2.0)	5 (1.5)
Arthralgia	17 (5.0)	10 (2.9)	6 (1.8)

a Data are given as n (%).

CR = controlled release; **ER** = extended release.

infarction 90 days after receiving the first dose of oxycodone CR; this patient had a history of morbid obesity, and the death was considered by the investigator to be unrelated to study medication.

Because the incidence of constipation was relatively low in the placebo group, statistical comparisons of PAC-SYM results were only performed between the active treatment groups at the end of the study. At the end of treatment, in the safety analysis population, the LSM change from baseline was significantly lower in the tapentadol ER group than the oxycodone CR group for the overall PAC-SYM score ($p < 0.001$) and the overall abdominal ($p < 0.001$), overall rectal ($p = 0.018$), and overall stool subscale scores ($p < 0.001$). The significantly greater change observed with oxycodone CR indicates a worsening of constipation symptoms with oxycodone CR treatment compared with tapentadol ER treatment.

Opioid withdrawal severity at treatment discontinuation was evaluated for patients who did not use opioids following discontinuation of study medication. COWS scores in all treatment groups for all time periods (placebo, n = 82; tapentadol ER, n = 106; oxycodone CR, n = 121) indicated that all patients who were evaluated had no, mild or moderate opioid withdrawal. For COWS assessments completed ≥2 days to <5 days after the last intake of study medication, 100% (23/23), 82.9% (29/35) and 86.5% (32/37) of patients in the placebo, tapentadol ER and oxycodone CR groups, respectively, experienced no opioid withdrawal, and 0% (0/23), 17.1% (6/35) and 13.5% (5/37), respectively, experienced mild opioid withdrawal. For COWS assessments completed ≥5 days after last intake of study medication, 91.5% (54/59), 98.6% (69/70) and 85.7% (72/84) of patients in the placebo, tapentadol ER and oxycodone CR groups, respectively, experienced no opioid withdrawal; 8.5% (5/59), 1.4% (1/70) and 11.9% (10/84) experienced mild opioid withdrawal; and 0% (0/59), 0% (0/70) and 2.4% (2/84) experienced moderate opioid withdrawal. In the subgroup of patients eligible for SOWS assessments, there were no statistically significant differences in LSM SOWS total scores in the tapentadol ER and placebo groups at 3, 4 or ≥5 days after the last dose of study drug.

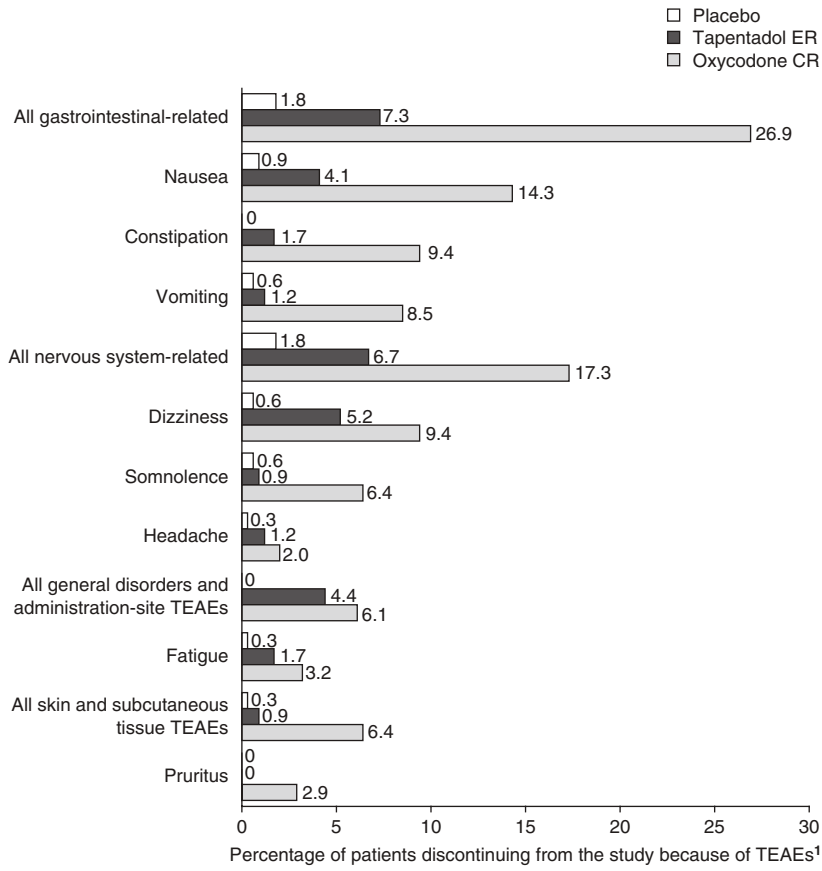


Fig. 4. Percentage of patients who discontinued from the study because of treatment-emergent adverse events (TEAEs) [safety analysis population]. **1** Incidence is based on the number of patients experiencing at least one adverse event, not the number of adverse events; patients could experience more than one adverse event leading to treatment discontinuation. **CR** = controlled release; **ER** = extended release.

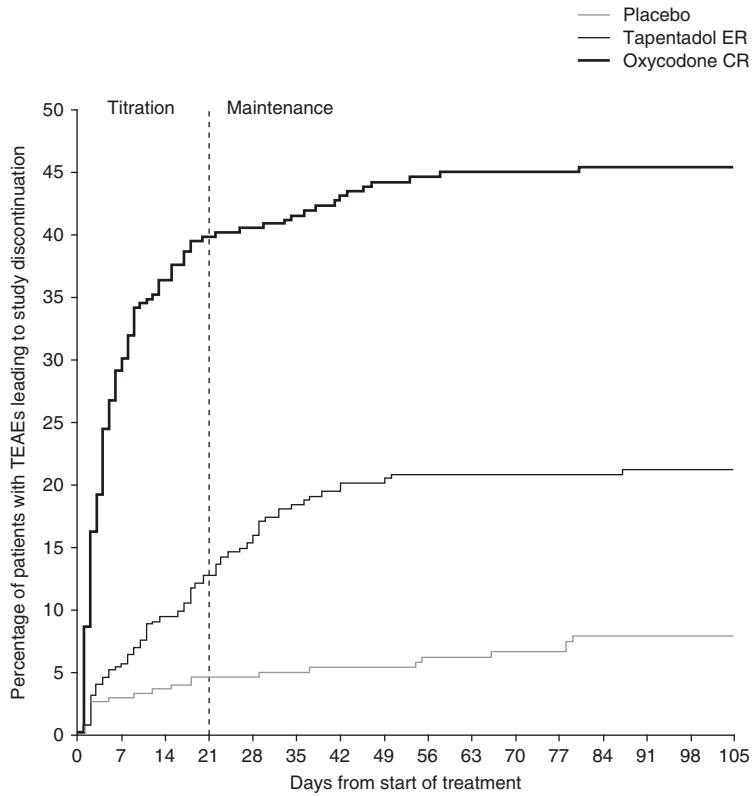
Discussion

The results of this trial showed that both tapentadol ER and oxycodone CR provided effective relief of moderate to severe osteoarthritis knee pain, as indicated by a significant reduction in average pain intensity compared with placebo from baseline for the overall maintenance period. Tapentadol ER was also associated with a significant reduction in average pain intensity from baseline compared with placebo at week 12 of the maintenance period, whereas oxycodone CR was not. In addition, the percentage of patients who achieved ≥50% reduction in average pain intensity from baseline to week 12 was significantly higher in the tapentadol ER group than in the placebo group, and the percentage of patients who achieved ≥30% reduction in average pain intensity from baseline to week 12 was numerically higher in the tapentadol ER group than in the placebo group. In contrast, the percentage of patients who achieved ≥30% or ≥50% reduction in average pain intensity from baseline to week 12 was significantly lower in the oxycodone CR group than in the placebo group. A reduction in pain intensity of ≥30% on an 11-point NRS is considered to reflect at least a moderate clinically relevant change in chronic pain,[27,33] while a ≥50% reduction in the intensity of chronic pain may reflect a more substantial

improvement in chronic pain.[27,33] Thus, treatment with tapentadol ER 100–250 mg twice daily was associated with a clinically significant decrease in pain intensity compared with placebo, based on widely accepted measures of clinically meaningful treatment differences.[27,33] Both tapentadol ER and oxycodone CR were also associated with statistically significant improvements in PGIC ratings at the end of treatment compared with placebo.

In addition to showing clinically meaningful improvements in pain intensity compared with placebo, tapentadol ER had a better tolerability profile than oxycodone CR, as shown by significantly lower incidences of nausea, vomiting and constipation. The observed incidences of pruritus and somnolence were also lower with tapentadol ER than with oxycodone CR, and fewer patients discontinued the study because of gastrointestinal-related TEAEs in the tapentadol ER group than in the oxycodone CR group.

The two mechanisms of action of tapentadol ER may explain the lower incidence of opioid-related AEs compared with oxycodone CR observed in this study. Specifically, adding a second mechanism of action, norepinephrine reuptake inhibition, to μ-opioid receptor agonism may produce an opioid-sparing effect; that is, analgesic efficacy



No. of patients remaining in the study without an event

Placebo	337	307	289	263	249	245	235	231	227	226	222	218	214	211	208	135
Tapentadol ER	344	314	285	265	246	236	224	217	212	209	204	203	202	198	198	139
Oxycodone CR	342	222	196	175	160	155	149	144	139	136	133	132	127	122	120	79

Fig. 5. Time to first onset of treatment-emergent adverse events (TEAEs) leading to discontinuation (safety analysis population). **CR** = controlled release; **ER** = extended release.

is preserved by the addition of norepinephrine reuptake inhibition but the incidence of adverse effects associated with μ-opioid receptor activation is reduced.[23,34] Like tapentadol, tramadol has both μ-opioid receptor agonist and norepinephrine reuptake inhibitor activity, but tramadol also exhibits serotonin reuptake inhibitor activity[35] and has low μ-opioid receptor activity relative to other opioid-type analgesics.[36] This serotonin reuptake inhibitor activity may be responsible for the proemetic effects of tramadol[37] and may account for the apparent difference in gastrointestinal tolerability between tapentadol ER and tramadol ER; tapentadol ER has been associated with lower incidences of nausea and constipation than tramadol ER in chronic pain trials.[38-42] In addition, unlike tapentadol (which has both mechanisms of action combined in a single molecule), tramadol is a racemic mixture and the μ-opioid receptor agonist and norepinephrine and serotonin reuptake inhibitor activities of tramadol are associated with the different enantiomers and metabolites of the compound.[43]

As with any clinical study, the limited sample size and restricted patient population (defined by inclusion and exclusion criteria) are possible limitations of this study. The sample size was calculated to satisfy the primary objective of assessing the analgesic efficacy of tapentadol ER compared with placebo. Further studies will be helpful to comprehensively evaluate the AE profile of tapentadol and to define the association between tolerability and compliance for tapentadol ER compared with pure opioid analgesics.

Conclusion

Treatment with tapentadol ER 100–250 mg twice daily for the management of moderate to severe chronic osteoarthritis knee pain showed robust analgesic efficacy compared with placebo and an improved tolerability profile compared with oxycodone HCl CR 20–50 mg bid at equianalgesic doses. In addition, the majority of patients who did not take opioid analgesics following discontinuation of tapentadol ER or oxycodone CR did not experience opioid withdrawal. The improved overall and gastrointestinal tolerability of tapentadol ER are clinically important findings, as tapentadol ER provided more consistent pain relief (because of the lower incidence of treatment discontinuations with tapentadol ER) with better tolerability than oxycodone CR, thus allowing patients to adhere to treatment for longer periods of time. Tapentadol may represent an improved alternative treatment option for the management of moderate to severe chronic osteoarthritis pain compared with μ-opioid receptor agonists such as oxycodone.

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