Expert Opinion

Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled Phase III study

Robert Buynak, Douglas Y Shapiro, Akiko Okamoto, Ilse Van Hove, Christine Rauschkolb, Achim Steup, Bernd Lange, Claudia Lange & Mila Etropolski[†]

[†] *Tapentadol Chronic Pain Program, Johnson & Johnson Pharmaceutical Research & Development, Titusville, New Jersey, USA*

Objective: To evaluate the efficacy and safety of tapentadol extended release (ER) for the management of moderate to severe chronic low back pain.

Research design: Patients (N = 981) were randomized 1:1:1 to receive tapentadol ER 100 – 250 mg b.i.d., oxycodone HCl controlled release (CR) 20 – 50 mg b.i.d., or placebo over 15 weeks (3-week titration period, 12-week maintenance period).

Main outcome measures: Efficacy was assessed as change from baseline in average pain intensity (11-point NRS) at week 12 of the maintenance period and throughout the maintenance period; last observation carried forward was used to impute missing pain scores. Adverse events (AEs) were monitored throughout the study.

Results: Tapentadol ER significantly reduced average pain intensity versus placebo at week 12 (least squares mean difference vs placebo [95% confidence interval], -0.8 [-1.22, -0.47]; $p < 0.001$) and throughout the maintenance period (-0.7 [-1.06,-0.35]; $p < 0.001$). Oxycodone CR significantly reduced average pain intensity versus placebo at week 12 (-0.9 [-1.24,-0.49]; $p < 0.001$) and throughout the maintenance period (-0.8 [-1.16,-0.46]; $p < 0.001$). Tapentadol ER was associated with a lower incidence of treatment-emergent AEs (TEAEs) than oxycodone CR. Gastrointestinal TEAEs, including constipation, nausea, and vomiting, were among the most commonly reported TEAEs (placebo, 26.3%; tapentadol ER, 43.7%; oxycodone CR, 61.9%). The odds of experiencing constipation or the composite of nausea and/or vomiting were significantly lower with tapentadol ER than with oxycodone CR (both $p < 0.001$).

Conclusions: Tapentadol ER (100 – 250 mg b.i.d.) effectively relieved moderate to severe chronic low back pain over 15 weeks and had better gastrointestinal tolerability than oxycodone HCl CR (20 – 50 mg b.i.d.).

Keywords: analgesic, chronic pain, low back pain, opioid, oxycodone, tapentadol

Expert Opin. Pharmacother. (2010) ***11****(11):1787-1804*

informa
healthcare

10.1517/14656566.2010.497720 © 2010 Informa UK Ltd ISSN 1465-6566

1. Introduction

Low back pain is a common chronic pain condition worldwide [1]; in the United States alone, it affects approximately 26% of adults [2]. Chronic low back pain, which often requires long-term analgesic therapy, has been used as a model in previous clinical trials of extended-release (ER) opioid formulations [3-9]. Results of these studies [3-9] have shown that opioids provide adequate relief of chronic low back pain, and recent clinical guidelines [10,11] recommend opioid therapy for the management of chronic low back pain, especially in patients who have failed to respond to other therapies [12]; however, most of the data supporting the moderate efficacy and functional improvements provided by opioids for patients with chronic non-cancer pain are from short-term clinical trials [13], and there is a lack of high-quality evidence supporting the efficacy of long-term opioid therapy for chronic non-cancer pain, including low back pain [10]. In addition, the use of opioid analgesics for the long-term management of chronic pain is limited by the occurrence of adverse events, which may cause patients to discontinue therapy [14,15].

Gastrointestinal adverse effects are among the most commonly reported side effects in patients taking opioid analgesics. For example, in several randomized trials that evaluated the tolerability of opioids for the relief of chronic pain [3,9,16], the incidence of nausea ranged from 13 – 42%; vomiting, 6 – 23%; and constipation, 23 – 71%. Tolerance to opioid-induced nausea and vomiting typically develops within the first week of therapy [17], but constipation rarely improves with continued opioid use [18], and prophylactic laxative therapy often fails to adequately resolve opioid-induced constipation [19-22]. In a survey [19] of patients taking both daily opioids and laxatives, constipation was reported by 81% of patients, more than half of whom reported that opioid-induced constipation had a negative impact on their quality of life. Of the surveyed patients, 33% had missed doses, decreased usage, or stopped using opioids to relieve opioid-induced constipation [19].

Tapentadol is a novel, centrally acting analgesic with two mechanisms of action: μ-opioid receptor agonism and norepinephrine reuptake inhibition [23,24]. Tapentadol ER is being developed for the management of moderate to severe chronic pain. Previous studies with an immediate-release (IR) formulation of tapentadol in doses of 50, 75, or 100 mg administered every 4 – 6 h reported similar efficacy for the relief of osteoarthritis pain [25] and postoperative pain following bunionectomy [26-28], with an improved gastrointestinal tolerability profile compared with oxycodone HCl IR (10 or 15 mg every 4 – 6 h). The objective of the current study was to evaluate the efficacy and safety of controlled, adjustable doses of tapentadol ER (100 – 250 mg b.i.d.) over 15 weeks of treatment for the management of moderate to severe chronic low back pain.

2. Patients and methods

2.1 Patient population

Men and women aged ≥ 18 years, with a history of non-malignant low back pain for ≥ 3 months prior to the study, were eligible for enrollment. Patients were required to have been taking analgesics for low back pain for ≥ 3 months prior to screening, to be dissatisfied with their current treatment, and to have a baseline pain intensity of ≥ 5 on an 11-point numerical rating scale (NRS; 0 = 'no pain' and 10 = 'pain as bad as you can imagine') after a 3- to 7-day washout period of all previous analgesics. For patients taking opioid analgesics, daily doses of opioids had to be equivalent to ≤ 160 mg of oral morphine.

Patients who were currently participating in another clinical study or who had previously participated in other tapentadol studies were excluded from the study. Neuroleptics, tricyclic antidepressants, anticonvulsants, antiparkinsonian drugs, and serotonin norepinephrine reuptake inhibitors were prohibited within 14 days prior to the screening visit and during the study because their use could confound efficacy assessments; use of monoamine oxidase inhibitors was also prohibited within 14 days prior to the screening visit and during the study. However, patients with diagnosed psychiatric or neurologic conditions (such as major depressive disorder) could participate if they were treated with medications not listed above, such as selective serotonin reuptake inhibitors, at a controlled, stable dose for ≥ 3 months prior to randomization.

Corticosteroids were also prohibited during the trial and within the following timelines prior to screening: oral, within 4 weeks; intramuscular- or soft tissue–administered, within 8 weeks; intra-articular, within 3 months; and depot-injected, within 6 months. The use of concomitant analgesics, with the exception of allowed doses of acetaminophen (see *Treatment schedule*), was prohibited during the study. Transcutaneous Electrical Nerve Stimulation, acupuncture, physical therapy, packs, massages, and other interventional adjunctive therapy were permitted during the study if patients started the treatment ≥ 14 days prior to enrollment and continued on the same regimen during the study. Other reasons for exclusion were the presence of a clinically significant medical or psychiatric disease, requirement for painful procedures (such as surgery) during the study that could influence efficacy or safety assessments, surgery in the low back area within 3 months of screening, history of substance abuse (including alcohol), epilepsy/seizure disorder, stroke/transient ischemic attack, HIV, chronic hepatitis B or C, malignancy (preceding 2 years), uncontrolled hypertension (systolic blood pressure > 160 mmHg and/or diastolic blood pressure > 95 mmHg), severe renal impairment, moderate or severe hepatic impairment, abnormal baseline laboratory values that might affect patient safety, and hypersensitivity to the study medications or their excipients. Patients with conditions potentially influencing the self-assessment of low

back pain (anatomical deformities, fibromyalgia, gout, or infectious or autoimmune diseases) were also excluded.

2.2 Study design

This was a prospective, randomized, double-blind, active- and placebo-controlled, multicenter, Phase III study (ClinicalTrials.gov identifier: NCT00449176) in patients with moderate to severe chronic low back pain conducted at sites in the United States (85 sites), Canada (15 sites), and Australia (3 sites). Patients were randomized in a 1:1:1 ratio to receive controlled, adjustable doses of tapentadol ER (100 – 250 mg b.i.d.), oxycodone HCl controlled release (CR; 20 – 50 mg b.i.d.), or placebo b.i.d. Randomization of patients to treatment was based on a computer-generated randomization list, balanced by randomly permuted blocks, and stratified by study site. Randomization was implemented through an interactive voice response system (IVRS) that assigned patients to blinded study medication. Placebo tablets and capsules (one for each active treatment) were used to maintain the blind in this double-blind, double-dummy design. Investigators were not provided with the randomization codes and the schedule was maintained with the IVRS. The blind was not broken until all patients completed the trial and the database was locked. The study consisted of a screening period, a washout period, a 15-week treatment period that included a 3-week, double-blind titration period followed by a 12-week, double-blind maintenance period, and a follow-up period. Follow-up consisted of a visit 4 days after the end of treatment and a post-study telephone call. Patients who completed the study were given the option to continue treatment in an open-label extension study.

2.3 Ethical practices

The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practices [29], and the protocol and amendments were approved by institutional review boards. All patients provided written informed consent prior to enrollment.

2.4 Treatment schedule

During the titration period, active treatment started with tapentadol ER 50 mg b.i.d. or oxycodone HCl CR 10 mg b.i.d. After 3 days, doses were increased to tapentadol ER 100 mg b.i.d. or oxycodone HCl CR 20 mg b.i.d.; these were the minimum doses allowed for the remainder of the study. At a minimum of 3-day intervals, upward dose titration was allowed in increments of tapentadol ER 50 mg b.i.d. or oxycodone HCl CR 10 mg b.i.d.; downward titration was allowed in decrements of tapentadol ER 50 mg b.i.d. or oxycodone HCl CR 10 mg b.i.d. without any time restriction, but doses were not allowed to fall below the minimum doses. Under the supervision of a physician, patients were permitted to adjust their doses to reach an optimal dose, defined as meaningful pain relief with acceptable side effects. The highest tested doses were tapentadol ER 250 mg b.i.d. or oxycodone HCl CR 50 mg b.i.d. Patients were encouraged to attempt to maintain a steady dose level during the 12-week maintenance period; however, if needed, the dose could be adjusted up or down under the supervision of a physician to achieve optimal therapeutic effect. During the titration period, acetaminophen was permitted (≤ 1000 mg/day, as needed) as rescue medication except for the last 3 days of this period, when stability of the optimal dose of study medication was to be achieved. During the maintenance period, additional analgesic medication was not allowed unless deemed necessary for reasons unrelated to low back pain; and then, only acetaminophen (≤ 1000 mg/day) was allowed, for a maximum of 3 consecutive days.

2.5 Efficacy evaluations

To comply with diverse global regulatory requirements, this study had two different primary efficacy endpoints: change from baseline in mean pain intensity at week 12 of the maintenance period (week 15 of the study; US primary endpoint) or change from baseline in mean pain intensity over the entire 12-week maintenance period (European Union and other regions' primary endpoint). Average pain intensity in the previous 12 h was assessed twice daily on an 11-point NRS. The primary endpoint for health authorities in one region was considered a secondary endpoint for health authorities in the other region.

Secondary efficacy evaluations included the percentages of patients who responded with ≥ 30 and ≥ 50% reduction in pain intensity at week 12 of the maintenance period, the distribution of responders, the patient's global impression of change (PGIC), the Brief Pain Inventory (BPI) questionnaire [30], the Short Form-36 health survey (SF-36) [31], the EuroQol-5 Dimension (EQ-5D) health questionnaire [32,33], and a sleep questionnaire [34]. For the PGIC, which was assessed twice during the maintenance period and once at the end of study treatment, patients completed the following statement: 'Since I began trial treatment, my overall status is:' with a response from 1 to 7 (1 = 'very much improved' to 7 = 'very much worse'). The BPI, which was assessed at baseline, at weeks 1, 3, 5, 7, 9, and 11 of the maintenance period, and at the end of study treatment, is a questionnaire that assesses pain intensity (pain subscale score) and the degree to which pain interferes with patient functioning (pain interference subscale score) and also provides a total score. The SF-36, which was completed at baseline, at weeks 1, 5, and 9 of the maintenance period, and at the end of study treatment, evaluates eight dimensions of health (physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health) on a scale from 0 to 100 (0 = 'poor health'; 100 = 'good health'). The EQ-5D, which was completed at baseline, at weeks 1, 5, and 9 of the maintenance period, and at the end of study treatment, measures health status in five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each of which has three possible

responses ('no problems,' 'some problems,' and 'extreme problems'). The sleep questionnaire was completed once per week by each patient during the double-blind maintenance period and evaluated sleep latency, time slept, number of awakenings, and sleep quality during the preceding night.

2.6 Safety and tolerability evaluations

Safety was assessed throughout the study using adverse event reporting, findings from clinical laboratory testing (completed at screening and at the end of study treatment), physical examinations (completed at baseline and at the end of study treatment), vital signs (completed at screening, at baseline, at each clinic visit during treatment, at the end of study treatment, and at follow-up visit 1), and 12-lead electrocardiograms (ECGs; completed at screening, at weeks 1, 5, and 9 of the maintenance period, at the end of study treatment, and at follow-up visit 1). Additional safety assessments included the Patient Assessment of Constipation Symptoms (PAC-SYM) questionnaire (completed at baseline and at the end of study treatment) and the Clinical Opiate Withdrawal Scale (COWS) questionnaire [35] (completed by physicians at the follow-up visit for patients who did not enter the open-label study).

2.7 Statistical analyses

Assuming a mean treatment group difference of -0.7 with a standard deviation of 2.7 in the change from baseline in pain intensity on an 11-point NRS, it was estimated that 314 patients in each treatment group would provide 90% power to show a significant difference between tapentadol ER and placebo at $\alpha = 0.05$; thus, 942 patients needed to be enrolled and randomly assigned to treatment. Randomization was computer-generated, balanced by randomly permuted blocks and stratified by study center, and implemented through an IVRS.

The safety and intent-to-treat (ITT) populations were defined as all patients who were randomized and who took at least one dose of study medication. The primary efficacy analysis used linear interpolation to impute intermittent missing pain scores and the last observation carried forward (LOCF) method to impute missing pain scores after early discontinuation. Both active treatments were compared with placebo using an analysis of covariance (ANCOVA) model that included treatment and pooled analysis center as factors and baseline pain intensity score as a covariate. Treatment effects were estimated based on the least squares mean difference from placebo. To assess the robustness of the primary efficacy results, sensitivity analyses were performed using other imputation methods. These more conservative imputation methods included the baseline observation carried forward (BOCF); the worst observation carried forward (WOCF); the placebo mean imputation (PMI), which used the mean of all available pain intensity scores for all patients who received placebo and completed treatment for a given day to impute missing values following discontinuation and which used the observed mean pain intensity for all patients who received placebo at missing time points to impute intermittent missing pain scores; and the modified BOCF (a combination of LOCF and BOCF), which used the LOCF to impute missing pain intensity values for patients with a 'much improved' or 'very much improved' rating on the PGIC at the last post-baseline assessment and the BOCF to impute missing values for patients with any other PGIC rating or no PGIC assessment.

Responder rates for patients achieving ≥ 30 or $\geq 50\%$ improvement in pain intensity from baseline and PGIC assessments were compared between the active treatment groups and the placebo group using the Cochran–Mantel–Haenszel test with a p value for pairwise differences calculated at the 5% significance level. Patients who discontinued early from treatment were considered non-responders for the analysis of responders showing ≥ 30 and $\geq 50\%$ improvements. The distributions of percentage of improvement in pain score at week 12 of the maintenance period and the time to treatment discontinuation due to lack of efficacy were estimated using Kaplan–Meier methods and compared between treatment groups using the log-rank test.

Scores for the BPI, SF-36, and EQ-5D surveys were analyzed using ANCOVA models for each score with treatment and pooled analysis center as factors, baseline value as a covariate, and LOCF for imputation of missing values; two-sided p values were calculated at the 5% significance level. For the sleep questionnaire, quality of sleep was assessed on a nominal scale with four categories ('excellent,' 'good,' 'fair,' and 'poor'), and a frequency distribution of responses was presented at each visit by treatment group. Quality of sleep for patients in the active treatment groups was compared with placebo using the Cochran–Mantel–Haenszel test and LOCF for imputation.

Odds ratios and corresponding 95% CIs for nausea, vomiting, and constipation were determined by comparing both active treatment groups with placebo. For the PAC-SYM questionnaire, the change from baseline to week 12 was compared between active treatments using an ANCOVA model with treatment and pooled analysis center as factors and baseline score as a covariate; treatment differences were presented as p values calculated at the 5% significance level. Kaplan–Meier methods were used to determine the distribution of the time to onset of treatment-emergent adverse events (TEAEs) leading to discontinuation, and pairwise comparisons were performed using the log-rank test. For patients who completed the study or discontinued, the time to the onset of the first TEAE leading to discontinuation was replaced with the day of completion or discontinuation. COWS scores were calculated by adding individual scores from each question; the total scores for each time point were compared between treatment groups using an analysis of variance model with treatment and pooled analysis center as factors. COWS scores were summarized for questionnaires completed 1 day after the last intake of study medication, ≥ 2 to < 5 days after

the last intake of study medication, and ≥ 5 days after the last intake of study medication. Total possible COWS scores ranged from 0 to 48, with a higher score indicating more severe opioid withdrawal; scores were categorized as no (< 5), mild (5 – 12), moderate (13 – 24), moderately severe (25 – 36), or severe (> 36) withdrawal for patients who did not resume taking opioid analgesics following study discontinuation. The number and percentage of patients in each of the withdrawal categories were summarized, and the distribution of categorical results was compared between treatment groups using the Cochran–Mantel–Haenszel test.

3. Results

3.1 Patients

This study was conducted from 21 February 2007 to 12 March 2008. A total of 981 patients were randomized to receive placebo (n = 326), tapentadol ER (n = 321), or oxycodone CR (n = 334; **Figure 1**). Data were excluded for 14 of these patients who were randomized but who did not take study medication and for two patients who were randomized twice. Thus, 965 patients received at least one dose of study medication and were evaluable for safety. The ITT population consisted of 958 patients who were randomized to placebo (n = 317), tapentadol ER (n = 315), or oxycodone CR (n = 326). Seven patients at study sites with major audit findings were excluded from the ITT analysis prior to unblinding.

The percentage of patients who completed the study in the placebo, tapentadol ER, and oxycodone CR groups was 47.6% (152/319), 52.2% (166/318), and 40.5% (133/328), respectively. The distribution of time to treatment discontinuation based on the Kaplan–Meier estimate in the tapentadol ER group was significantly different from that in the oxycodone CR group ($p < 0.001$) but was not significantly different from that in the placebo group ($p = 0.309$; **Figure 2**), showing that treatment discontinuation occurred later with tapentadol ER (median 118 days) than with oxycodone CR (median 62 days). The primary reasons for treatment discontinuation were adverse events (placebo, 4.7% [15/319]; tapentadol ER, 16.7% [53/318]; oxycodone CR, 32.3% [106/328]) in the two active treatment groups and lack of efficacy (placebo, 20.7% [66/319]; tapentadol ER, 5.7% [18/318]; oxycodone CR, 2.7% [9/328]) in the placebo group.

Demographic and baseline characteristics were similar between treatment groups (**Table 1**); most patients in the safety population were white (73.3% [707/965]), female (57.9% [559/965]), and aged < 65 years (84.6% [816/965]). The mean (standard deviation [SD]) baseline pain intensity score was 7.5 (1.29), with 88.5% (848/959) of patients reporting severe pain (a score of ≥ 6) at baseline. The duration of time that patients experienced chronic low back pain prior to the study ranged from 6 months to 66 years. Opioid analgesics were taken by 53.4% (515/965) of patients in the safety population during the 3 months prior to screening.

3.2 Treatment exposure

The median treatment duration (defined as the time on study medication, not including zero-dose days) during the 15-week double-blind treatment period was longer in the placebo (102 days) and tapentadol ER (103 days) groups than in the oxycodone CR (62 days) group; this is consistent with the higher percentages of patients who entered the maintenance period in the placebo and tapentadol ER groups (66.1% [211/319] and 73.9% [235/318], respectively) than in the oxycodone CR group (60.7% [199/328]).

The group average of the individual mean (SD) total daily dose (TDD) during the 15-week double-blind treatment period was 313.2 (116.07) mg of tapentadol ER and 53.0 (23.39) mg of oxycodone HCl CR. Increases in the average value of the mean (SD) TDD from the first to the last 2 weeks of the maintenance period were approximately 10% in both the tapentadol ER (a change from 357.2 [120.42] to 393.2 [117.39] mg) and oxycodone HCl CR (a change from 67.4 [21.92] to 74.5 [21.50] mg) groups. The median of the individual modal (most frequently used) TDD during the 12-week maintenance period was 400 mg in the tapentadol ER group and 80 mg in the oxycodone HCl CR group. A high TDD (defined as ≥ 400 mg tapentadol ER or ≥ 80 mg oxycodone HCl CR) was maintained for ≥ 10 weeks by 33.2% (78/235) of patients in the tapentadol ER group and by 26.6% (53/199) of patients in the oxycodone CR group.

3.3 Efficacy

Average pain intensity scores over time are shown in **Figure 3**. Throughout the 3-week titration period and the 12-week maintenance period, average pain intensity scores improved for both the tapentadol ER and oxycodone CR groups relative to placebo. Pain relief was consistent during the maintenance period. Tapentadol ER significantly reduced mean pain intensity compared with placebo at week 12 and throughout the entire maintenance period using the LOCF method for imputation of missing values. The mean (SD) change in pain intensity from baseline to week 12 was -2.9 (2.66) for tapentadol ER and -2.1 (2.33) for placebo (least squares mean difference [LSMD] vs placebo [95% CI], -0.8 [-1.22 to -0.47]; $p < 0.001$). The mean (SD) change in pain intensity from baseline over the entire maintenance period was -2.8 (2.50) for tapentadol ER and -2.1 (2.20) for placebo (LSMD vs placebo [95% CI], -0.7 [-1.06 to -0.35]; $p < 0.001$). Significant reductions in mean pain intensity were also observed for the oxycodone CR group compared with the placebo group at week 12 (-2.9 [2.52] vs -2.1 [2.33]; LSMD vs placebo [95% CI], -0.9 [-1.24 to -0.49]; $p < 0.001$) and over the entire maintenance period (-2.9 [2.36] vs -2.1 [2.20]; LSMD vs placebo [95% CI], -0.8 [-1.16 to -0.46]; $p < 0.001$). Reductions in mean pain intensity were significantly greater with tapentadol ER than with placebo at week 12 of the maintenance period both for patients with moderate baseline pain intensity (LSMD vs placebo

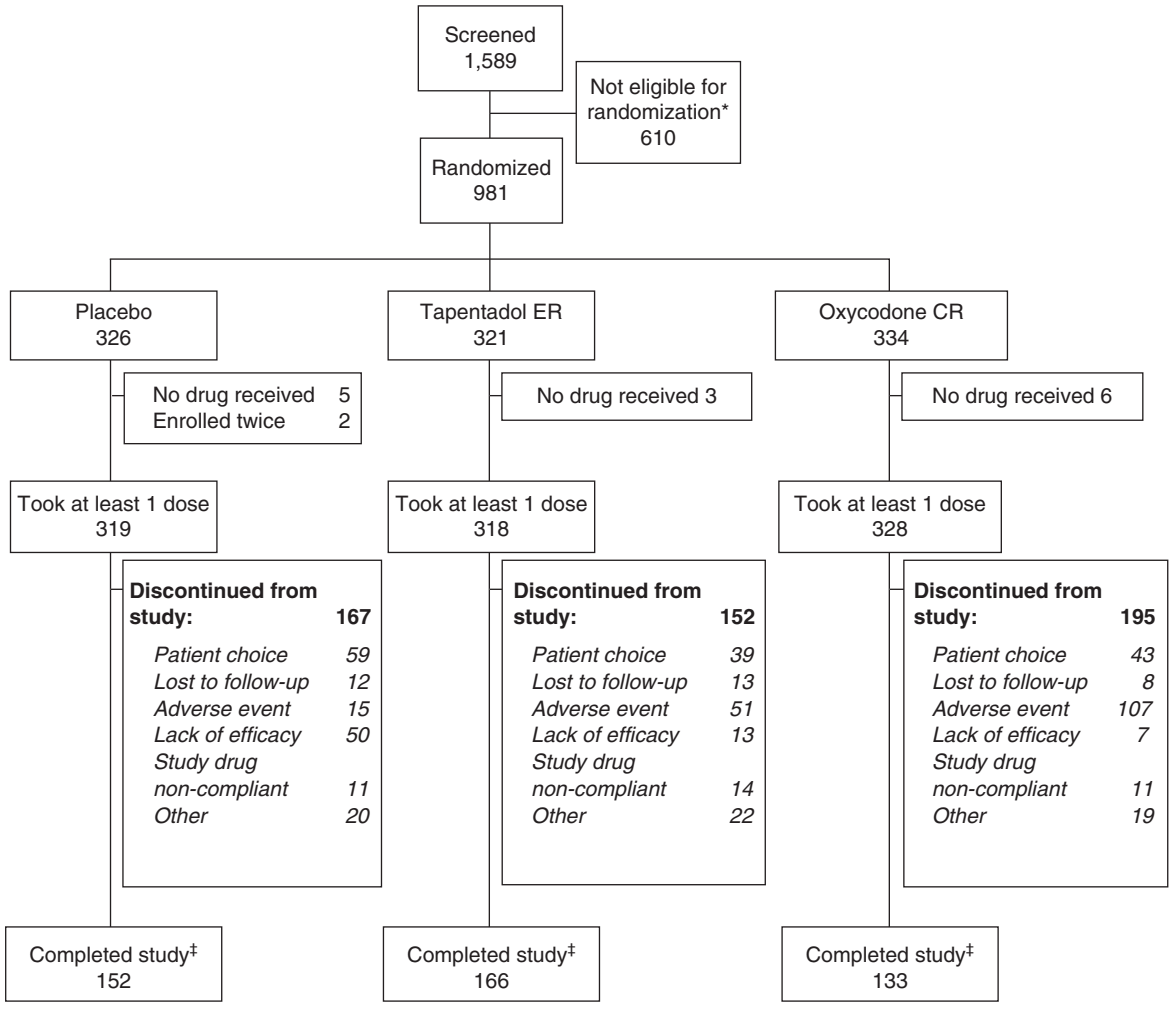


Figure 1. Patient disposition.

*Includes patients who were randomized in error, but did not take study drug.

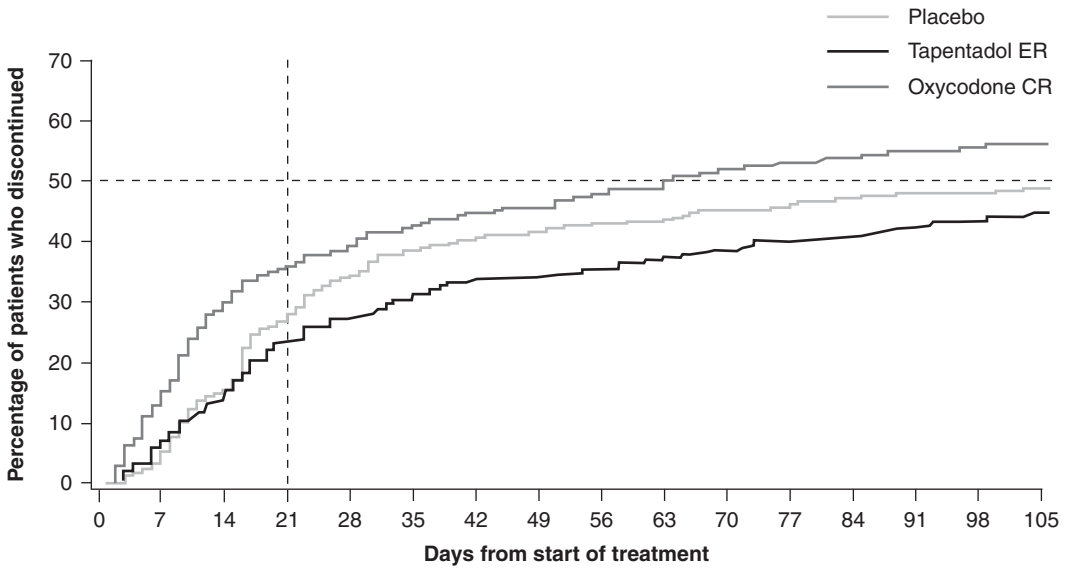
‡Includes all patients who were enrolled in an open-label extension study or completed all follow-up visits for the current study.

CR: Controlled release; ER: Extended release.

[95% CI], -1.8 [-3.15, -0.48]; p = 0.009) and for patients with severe baseline pain intensity (-0.8 [-1.23, -0.41]; p < 0.001). Significantly greater reductions in mean pain intensity with tapentadol ER compared with placebo were also observed for the overall maintenance period in patients with moderate baseline pain intensity (LSMD vs placebo [95% CI], -1.4 [-2.70, -0.16]; p = 0.028) and severe baseline pain intensity (-0.7 [-1.08, -0.31]; p < 0.001). Reductions in mean pain intensity were also significantly greater with oxycodone CR than with placebo for patients with moderate and severe baseline pain intensity at both week 12 of the maintenance period (moderate, LSMD vs placebo [95% CI], -1.5 [-2.63, -0.29]; p = 0.015; severe, -0.8 [-1.21, -0.40]; p < 0.001) and for the overall maintenance period (moderate, -1.2 [-2.28, -0.06]; p = 0.039; severe, -0.8 [-1.16, -0.40]; p < 0.001).

Sensitivity analyses of the primary efficacy endpoints showed that tapentadol ER significantly reduced average pain intensity compared with placebo at both week 12 of the maintenance period and for the overall maintenance period using more conservative imputation methods ($p \leq 0.003$ for all comparisons; **Figure 4**). Oxycodone CR significantly reduced average pain intensity compared with placebo for the overall maintenance period using all imputation methods (all $p \leq 0.023$; **Figure 4**). Oxycodone CR also significantly reduced average pain intensity compared with placebo at week 12 of the maintenance period using the PMI (p = 0.002) and modified BOCF (p = 0.003), but not BOCF (p = 0.216) or WOCF (p = 0.152; **Figure 4**), probably reflecting the higher rate of discontinuation observed with oxycodone CR.

The overall distribution of responders at week 12 of the maintenance period was significantly different between the tapentadol ER group and the placebo group (p = 0.004), with a higher percentage of patients showing improvements



Number of patients remaining in DB phase without an event

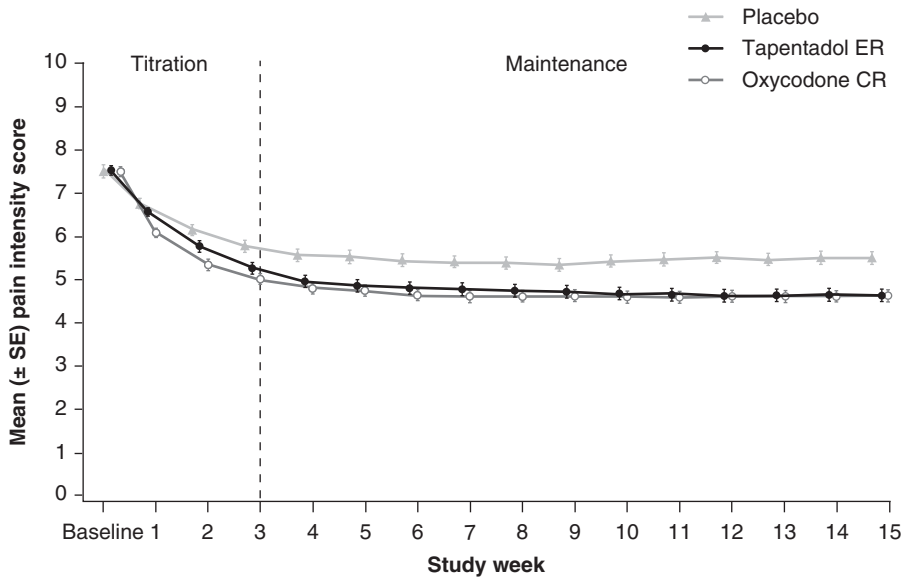
Placebo	319	294	264	226	207	195	188	184	182	179	175	171	168	167	162	121
Tapentadol ER	318	291	263	242	230	218	211	209	205	200	194	190	187	182	177	125
Oxycodone CR	328	272	224	208	195	187	181	178	169	162	157	154	151	148	145	99

Figure 2. Time to treatment discontinuation (safety analysis population).
CR: Controlled release; DB: Double-blind; ER: Extended release.

Table 1. Patient demographic and baseline characteristics (safety population).

Characteristic	Placebo (n = 319)	Tapentadol ER (n = 318)	Oxycodone CR (n = 328)
Age, y			
Mean (SD)	50.4 (14.05)	49.4 (13.21)	50.0 (14.21)
Age category, n (%)			
< 65 y	264 (82.8)	279 (87.7)	273 (83.2)
≥ 65 y	55 (17.2)	39 (12.3)	55 (16.8)
*Race, n (%)**			
White	237 (74.3)	229 (72.0)	241 (73.5)
Black	50 (15.7)	62 (19.5)	55 (16.8)
Hispanic	21 (6.6)	18 (5.7)	21 (6.4)
Other	11 (3.4)	9 (2.8)	11 (3.4)
Gender, n (%)			
Male	135 (42.3)	124 (39.0)	147 (44.8)
Female	184 (57.7)	194 (61.0)	181 (55.2)
Body mass index, kg/m^2			
Mean (SD)	31.33 (8.143)	32.09 (9.121)	31.36 (7.449)
Baseline pain intensity score[‡]			
Mean (SD)	7.6 (1.33)	7.5 (1.33)	7.5 (1.21)
Baseline pain intensity category[§,¶], *n (%)*			
Moderate	42 (13.2)	35 (11.1)	33 (10.2)
Severe	276 (86.8)	280 (88.9)	292 (89.8)
Prior opioid use,[#] *n (%)*			
No	147 (46.1)	140 (44.0)	163 (49.7)
Yes	172 (53.9)	178 (56.0)	165 (50.3)

*Percentages may not total 100% because of rounding.
[‡]Baseline pain intensity score is the average of pain scores (11-point numerical rating scale) recorded over the 72 h prior to randomization.
[§]Placebo, n = 318; tapentadol ER, n = 315; oxycodone CR, n = 325.
[¶]Moderate pain intensity was defined as a baseline pain intensity score of ≥ 4 to < 6; severe pain intensity was defined as a baseline pain intensity score of ≥ 6.
[#]Prior opioid use was defined as taking opioid analgesics within 3 months of screening.
CR: Controlled release; ER: Extended release; SD: Standard deviation.



Number of patients remaining in the intent-to-treat population

Placebo	316	313	284	248	218	195	186	181	177	172	170	167	166	160	159	153
Tapentadol ER	312	313	284	255	232	223	212	204	201	197	191	184	183	178	172	168
Oxycodone CR	323	322	253	217	198	184	180	174	171	163	153	148	145	144	139	136

Figure 3. Average pain intensity scores over time (intent-to-treat population; last observation carried forward).
CR: Controlled release; ER: Extended release; SE: Standard error.

in pain scores in the tapentadol ER group than in the placebo group (**Figure 5**). The overall distribution of responders at week 12 in the oxycodone CR group was not significantly different from placebo ($p = 0.090$). At week 12, significantly higher percentages of patients taking tapentadol ER responded with ≥ 30% (39.7% [125/315]; $p < 0.001$) and ≥ 50% (27.0% [85/315]; $p = 0.016$) improvements in pain intensity from baseline compared with placebo (27.1% [86/317] and 18.9% [60/317], respectively). The percentage of patients in the oxycodone CR group with ≥ 30% (30.4% [99/326]; $p = 0.365$) and ≥ 50% (23.3% [76/326]; $p = 0.174$) improvements did not differ significantly from placebo.

At endpoint, there was a significant difference in PGIC ratings for both tapentadol ER ($p < 0.001$) and oxycodone CR ($p < 0.001$) compared with placebo. The percentage of patients who reported a rating of 'much improved' or 'very much improved' on the PGIC at endpoint was 32.7% (80/245) for placebo, 55.5% (131/236) for tapentadol ER, and 60.0% (126/210) for oxycodone CR.

On the BPI questionnaire, the percentage of patients with 'any pain today other than everyday kinds of pain' was similar across all treatment groups at baseline (placebo, 88.6% [280/316]; tapentadol ER, 85.6% [268/313]; and oxycodone CR, 86.1% [279/324]). At week 12, these percentages decreased to 80.7% (96/119) in the placebo group, 69.8% (88/126) in the tapentadol ER group, and 67.3% (70/104) in the oxycodone CR group. The percentage of patients who reported 'at least 50% pain relief during the past week' was similar for all three treatment groups at baseline (placebo, 23.4% [73/312]; tapentadol ER, 24.7% [77/312]; oxycodone CR, 20.9% [67/320]) and increased to 59.7% (71/119) in the placebo group, 75.4% (95/126) in the tapentadol ER group, and 80.0% (84/105) in the oxycodone CR group at week 12 of the maintenance period. Compared with placebo, both tapentadol ER and oxycodone CR showed significant reductions from baseline to endpoint in the BPI total score, the pain interference subscale score, and the pain subscale score (**Table 2**).

On the SF-36 questionnaire at week 12 of the maintenance period, the mean changes from baseline for four of eight measures (physical functioning, role-physical, bodily pain, and vitality) were significantly improved in the tapentadol ER group compared with the placebo group. In the oxycodone CR group, mean changes from baseline were significantly improved for role-physical and bodily pain scores compared with the placebo group. Treatment with both tapentadol ER and oxycodone CR significantly improved physical health status compared with placebo, as reflected by the physical component summary score (**Table 2**). The mean change from baseline to week 12 in the EQ-5D health status index was significantly greater in both the tapentadol ER group and the oxycodone CR group than in the placebo group, indicating an improvement in health status (**Table 2**).

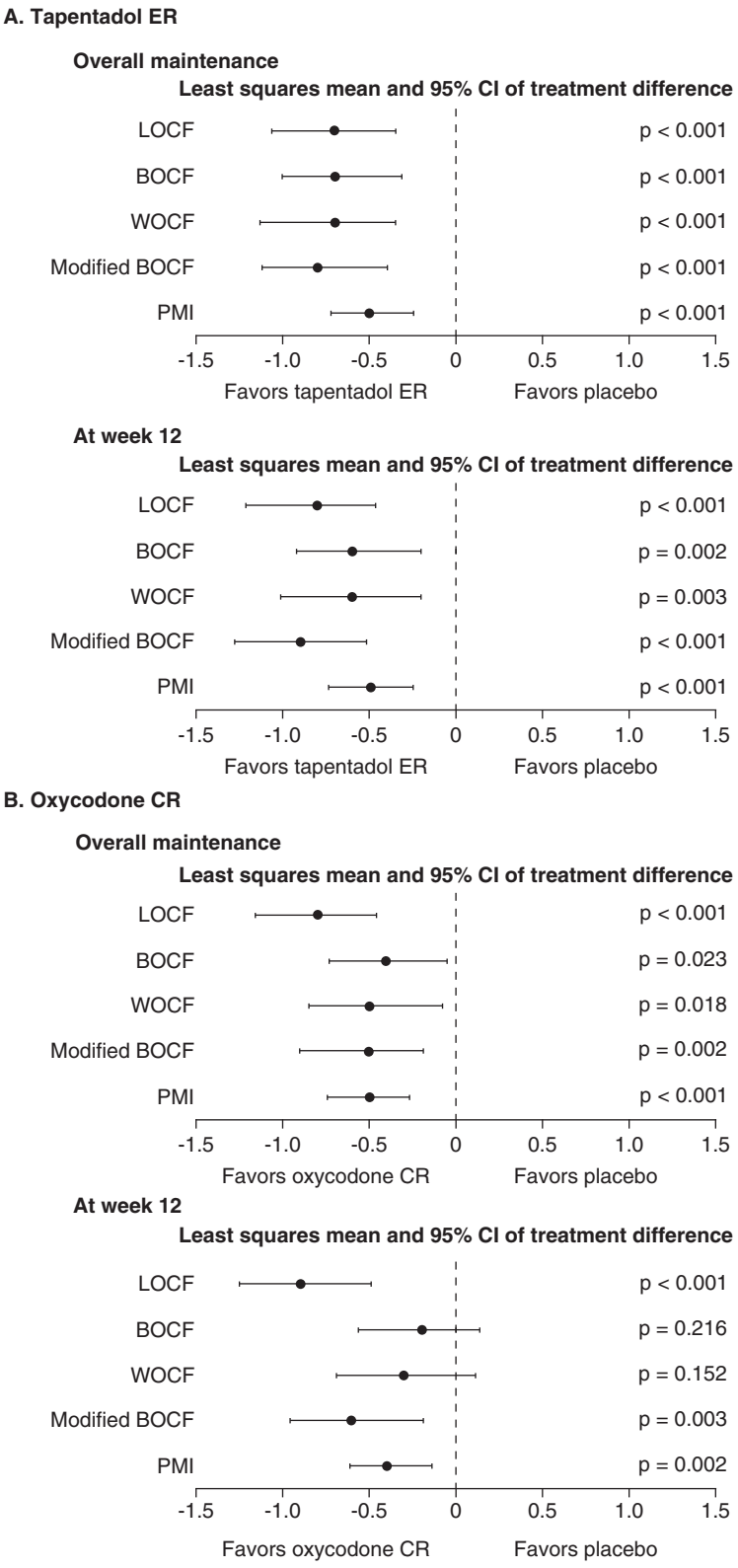


Figure 4. Sensitivity analyses of the primary efficacy endpoints for tapentadol ER (A) and oxycodone CR (B).

BOCF: Baseline observation carried forward; CI: Confidence interval; CR: Controlled release; ER: Extended release; LOCF: Last observation carried forward; PMI: Placebo mean imputation; WOCF: Worst observation carried forward.

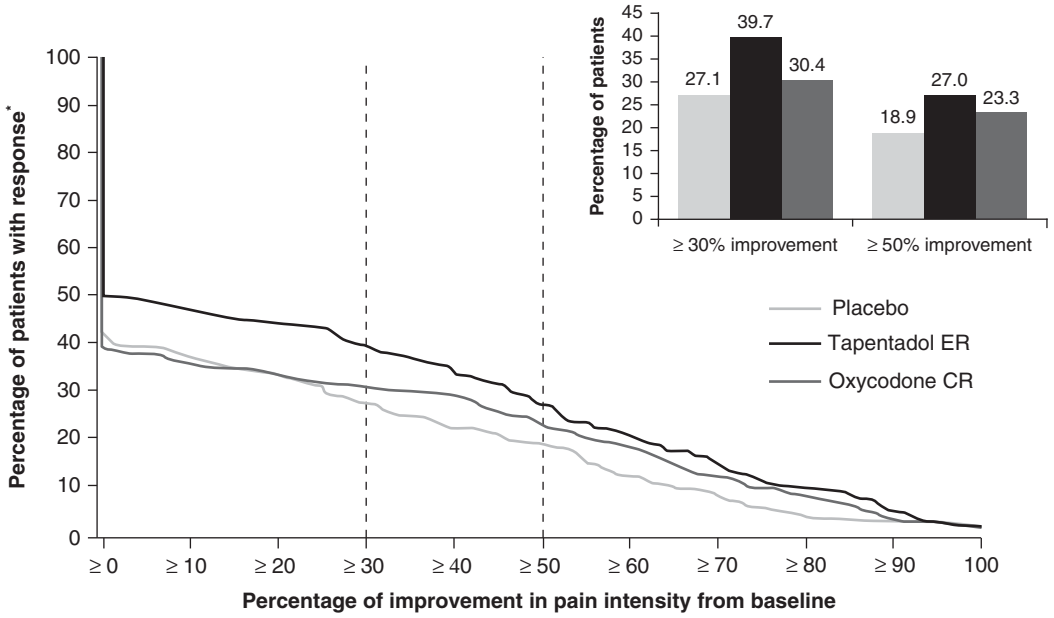


Figure 5. Distribution of the percentage improvement in pain intensity from baseline (intent-to-treat population).
Tapentadol ER vs placebo, p = 0.004; oxycodone CR vs placebo, p = 0.090.
*All patients who discontinued early were considered non-responders.
CR: Controlled release; ER: Extended release.

On the sleep questionnaire, small median improvements from baseline in the number of hours slept during the night for each week of study treatment were observed in all three treatment groups, with numerically greater increases observed in the tapentadol ER group (increases of 0.3 to 1.0 h) and the oxycodone CR group (0.1 to 1.0 h) than the placebo group (0.0 to 0.5 h). Compared with placebo, the distribution of overall sleep quality ratings in the tapentadol ER group was significantly improved (p = 0.003) from baseline to endpoint; results were not statistically significant in the oxycodone CR group (p = 0.091 vs placebo).

3.4 Safety and tolerability

No clinically important treatment-related changes were observed in laboratory values, vital signs, or ECG findings. Overall, at least one TEAE was reported by 59.6% (190/319), 75.5% (240/318), and 84.8% (278/328) of patients in the placebo, tapentadol ER, and oxycodone CR groups, respectively (**Table 3**). The most common TEAEs (reported by > 10% of patients in any treatment group) were nausea, constipation, headache, vomiting, dizziness, pruritus, and somnolence. In the oxycodone CR group, the incidences of vomiting, constipation, and pruritus were approximately double those in the tapentadol ER group. The majority of TEAEs were of mild to moderate intensity across all treatment groups. Odds of experiencing constipation or the composite of nausea and/or vomiting were significantly (p < 0.001 for both comparisons) lower in the tapentadol ER group than in the oxycodone CR group.

The PAC-SYM measures the severity of constipation-related symptoms in patients using opioids for the control of chronic pain [36]. At endpoint, the mean (standard error [SE]) changes from baseline in the overall PAC-SYM score were lower in the placebo (-0.0 [0.04]) and the tapentadol ER (0.1 [0.05]) groups than in the oxycodone CR group (0.3 [0.07]). The mean (SE) changes from baseline at endpoint were also lower for patients in the placebo and tapentadol ER groups than for those in the oxycodone CR group in the overall abdominal (placebo, -0.1 [0.06]; tapentadol ER, 0.0 [0.06]; oxycodone CR, 0.1 [0.08]), rectal (placebo, 0.0 [0.04]; tapentadol ER, 0.1 [0.05]; oxycodone CR, 0.2 [0.07]), and stool (placebo, -0.0 [0.05]; tapentadol ER, 0.2 [0.07]; oxycodone CR, 0.5 [0.09]) subscale scores. The smaller change from baseline to endpoint observed with tapentadol ER treatment indicates that there was a smaller change in the severity or presence of constipation symptoms than with oxycodone CR treatment.

Among patients who reported a TEAE of constipation, the change in symptoms from baseline to study endpoint was significantly greater for patients who received oxycodone CR than for those who received tapentadol ER for the overall (p = 0.024) PAC-SYM score as well as for the overall abdominal (p = 0.037) and overall stool (p = 0.028) subsets of constipation symptoms. The significantly greater change observed with oxycodone CR indicates an increase in the presence and/or a worsening in the severity of constipation symptoms associated with oxycodone CR treatment compared with tapentadol ER treatment.

Table 2. Results of secondary efficacy endpoints at week 12 (intent-to-treat population).

Week 12 endpoint	Tapentadol ER		Oxycodone CR	
	LSMD vs placebo (SE)	p-value vs placebo	LSMD vs placebo (SE)	p-value vs placebo
*BPI**				
Total score	-0.7 (0.18)	< 0.001	-0.5 (0.17)	0.002
Pain interference subscale score	-0.7 (0.19)	< 0.001	-0.4 (0.19)	0.023
Pain subscale score	-0.8 (0.18)	< 0.001	-0.7 (0.17)	< 0.001
*SF-36**				
Physical functioning	4.1 (1.65)	0.013	2.6 (1.64)	0.119
Role-physical	9.9 (2.87)	< 0.001	9.4 (2.86)	< 0.001
Bodily pain	5.5 (1.56)	< 0.001	6.3 (1.54)	< 0.001
General health	-0.2 (1.00)	0.847	-0.0 (0.99)	0.962
Vitality	3.2 (1.43)	0.025	0.8 (1.42)	0.576
Social functioning	1.3 (1.65)	0.423	-0.5 (1.64)	0.743
Role-emotional	2.7 (2.77)	0.338	2.3 (2.76)	0.414
Mental health	0.5 (1.23)	0.667	-0.6 (1.22)	0.630
Physical component summary	2.3 (0.65)	< 0.001	2.3 (0.65)	< 0.001
Mental component summary	0.1 (0.70)	0.901	-0.7 (0.69)	0.285
*EQ-5D**				
Health status index	0.0 (0.02)	0.020	0.1 (0.02)	0.019

*Using last observation carried forward for imputation.

BPI: Brief Pain Inventory; CR: Controlled release; EQ-5D: EuroQol-5 Dimension; ER: Extended release; LSMD: Least squares mean difference; SE: Standard error; SF-36: Short Form-36.

No deaths occurred during the study. Serious TEAEs were reported by 0.9% (3/319) of patients in the placebo group, 2.2% (7/318) of patients in the tapentadol ER group, and 3.4% (11/328) of patients in the oxycodone CR group; no specific serious TEAE was reported by more than one patient per treatment group. All serious TEAEs in the placebo group were considered to be unlikely to be related to or not related to study drug. In the tapentadol ER group, there were three patients with serious TEAEs considered possibly related to study drug by the investigator and/or sponsor. One patient had a decreased level of consciousness, one had mental confusion, and one had atrial fibrillation; all other serious TEAEs were considered unlikely to be related to or not related to study drug. In the oxycodone CR group, two serious TEAEs, an incident of dizziness and an incident of dehydration, were considered possibly related to study drug by the investigator and/or sponsor, with all other serious TEAEs considered unlikely to be related to or not related to study drug.

In the placebo, tapentadol ER, and oxycodone CR groups, 4.4% (14/319), 16.7%, (53/318) and 31.7% (104/328) of patients, respectively, reported TEAEs that led to study discontinuation. Gastrointestinal and nervous system TEAEs were the most commonly reported TEAEs leading to study discontinuation, and a numerically lower percentage of patients in both the placebo and tapentadol ER groups than in the oxycodone CR group reported gastrointestinal (placebo, 1.3% [4/319]; tapentadol ER, 5.3% [17/318]; oxycodone CR, 18.3% [60/328]) and nervous system (placebo, 0.0% [0/319]; tapentadol ER, 6.9% [22/318]; oxycodone CR, 14.0% [46/328]) TEAEs leading to study discontinuation (**Figure 6**). The percentage of patients in the tapentadol ER group who reported the most common TEAEs leading to study discontinuation, including nausea, headache, constipation, dizziness, vomiting, and pruritus, was less than half the percentage of patients reporting these TEAEs in the oxycodone CR group (**Figure 6**). The time to onset of TEAEs leading to treatment discontinuation was significantly longer for patients in the tapentadol ER group than for those in the oxycodone CR group ($p < 0.001$; **Figure 7**).

Among patients who did not take opioids after the discontinuation of study medication, most (placebo, 89.8% [53/59]; tapentadol ER, 95.2% [59/62]; oxycodone CR, 91.1% [82/90]) patients with COWS assessments experienced no opioid withdrawal after abrupt discontinuation of treatment without tapering. Mild or moderate opioid withdrawal was observed in 10.2% (6/59) of patients in the placebo group, 4.8% (3/62) of patients in the tapentadol ER group, and 8.9% (8/90) of patients in the oxycodone CR group; no patient had moderately severe or severe opioid withdrawal in any treatment group. For COWS assessments performed ≥ 2 and < 5 days after study drug discontinuation in patients who did not take opioids after study discontinuation, there were no significant differences in mean COWS scores for tapentadol ER ($p = 0.977$) or oxycodone CR ($p = 0.807$) compared with placebo.

4. Discussion

Treatment with tapentadol ER 100 – 250 mg b.i.d. resulted in significantly better relief of chronic low back pain over 15 weeks than placebo administration. In addition, the distribution of responders at week 12 of the maintenance period was significantly different in the tapentadol ER group compared

Table 3. Incidence of treatment-emergent adverse events in ≥ 5% of patients in any treatment group (safety population).

System organ class, n (%)	Placebo (n = 319)	Tapentadol ER (n = 318)	Oxycodone CR (n = 328)
Patients with ≥ 1 TEAE	190 (59.6)	240 (75.5)	278 (84.8)
Gastrointestinal disorders	84 (26.3)	139 (43.7)	203 (61.9)
Nausea	29 (9.1)	64 (20.1)	113 (34.5)
Constipation	16 (5.0)	44 (13.8)	88 (26.8)
Vomiting	5 (1.6)	29 (9.1)	63 (19.2)
Dry mouth	7 (2.2)	26 (8.2)	12 (3.7)
Diarrhea	23 (7.2)	19 (6.0)	8 (2.4)
Dyspepsia	8 (2.5)	16 (5.0)	6 (1.8)
Nervous system disorders	72 (22.6)	126 (39.6)	147 (44.8)
Headache	44 (13.8)	63 (19.8)	55 (16.8)
Dizziness	18 (5.6)	38 (11.9)	56 (17.1)
Somnolence	8 (2.5)	42 (13.2)	53 (16.2)
General disorders	32 (10.0)	50 (15.7)	62 (18.9)
Fatigue	13 (4.1)	21 (6.6)	24 (7.3)
Psychiatric disorders	30 (9.4)	47 (14.8)	59 (18.0)
Insomnia	9 (2.8)	13 (4.1)	25 (7.6)
Skin and subcutaneous tissue disorders	17 (5.3)	45 (14.2)	91 (27.7)
Pruritus	6 (1.9)	23 (7.2)	55 (16.8)
Hyperhidrosis	0	12 (3.8)	17 (5.2)

CR: Controlled release; ER: Extended release; TEAE: Treatment-emergent adverse event.

with the placebo group, with a higher percentage of responders in the tapentadol ER group; a significantly higher percentage of patients in the tapentadol ER group achieved ≥ 30 and ≥ 50% improvements in pain intensity compared with the placebo group, indicating a clinically significant improvement in pain intensity with tapentadol ER [37]. The reduction in pain intensity observed with placebo treatment in the current study was also relatively high; however, such a marked response to placebo is not uncommon in studies of extended-release opioids for chronic pain [4,5,38]. Results of secondary efficacy analyses, including PGIC, BPI, SF-36, EQ-5D, and sleep surveys, support the results of the primary analyses and show a reduction in pain intensity and an improvement in functional and health status outcomes associated with treatment with tapentadol ER.

The active comparator in this study, oxycodone HCl CR 20 – 50 mg b.i.d., also provided significant pain relief compared with placebo. However, the distribution of responders at week 12 and the percentages of patients achieving ≥ 30 and ≥ 50% improvements in pain intensity scores in the oxycodone CR group did not differ significantly from placebo. These results may have been affected by the higher percentage of patients in the oxycodone CR group who discontinued treatment during the titration and maintenance periods than in the tapentadol ER and placebo groups, because all patients who discontinued were considered non-responders.

In this study, the mean dose of tapentadol ER was relatively stable throughout the maintenance period, indicating that patients maintained adequate pain relief without any substantial increase in doses of tapentadol ER over 12 weeks of therapy. Similar dose stability was shown over 1 year of treatment in a randomized, open-label, Phase III study [39] of tapentadol ER (100 – 250 mg b.i.d.) in patients with moderate to severe chronic low back pain or osteoarthritis pain. In the current study as well as in previous prospective, randomized controlled trials of tapentadol ER, a dose equivalency of approximately 5:1 has been shown for tapentadol ER to oxycodone CR [40,41].

The results of other secondary efficacy analyses were generally similar between tapentadol ER and oxycodone CR. Although efficacy was not compared directly between tapentadol ER and oxycodone CR in this study, the data suggest that tapentadol ER provided analgesic efficacy that is similar to that of oxycodone CR for the management of moderate to severe chronic low back pain. The results of these efficacy analyses are consistent with those of Phase III studies of tapentadol IR, which showed that tapentadol IR provided efficacy that was similar to that provided by oxycodone IR in patients with moderate to severe low back pain or osteoarthritis hip or knee pain [42], postoperative pain following bunionectomy [28], and pain resulting from end-stage joint disease [25].

In the current study, the safety profile of tapentadol ER was consistent with the profile expected for centrally acting analgesics with μ-opioid activity, but tapentadol ER had improved gastrointestinal tolerability, as indicated by numerically lower incidences of constipation, nausea, and vomiting, as well as numerically lower incidences of dizziness and pruritus, compared with oxycodone CR. Moreover, results of the PAC-SYM questionnaire indicated that tapentadol ER

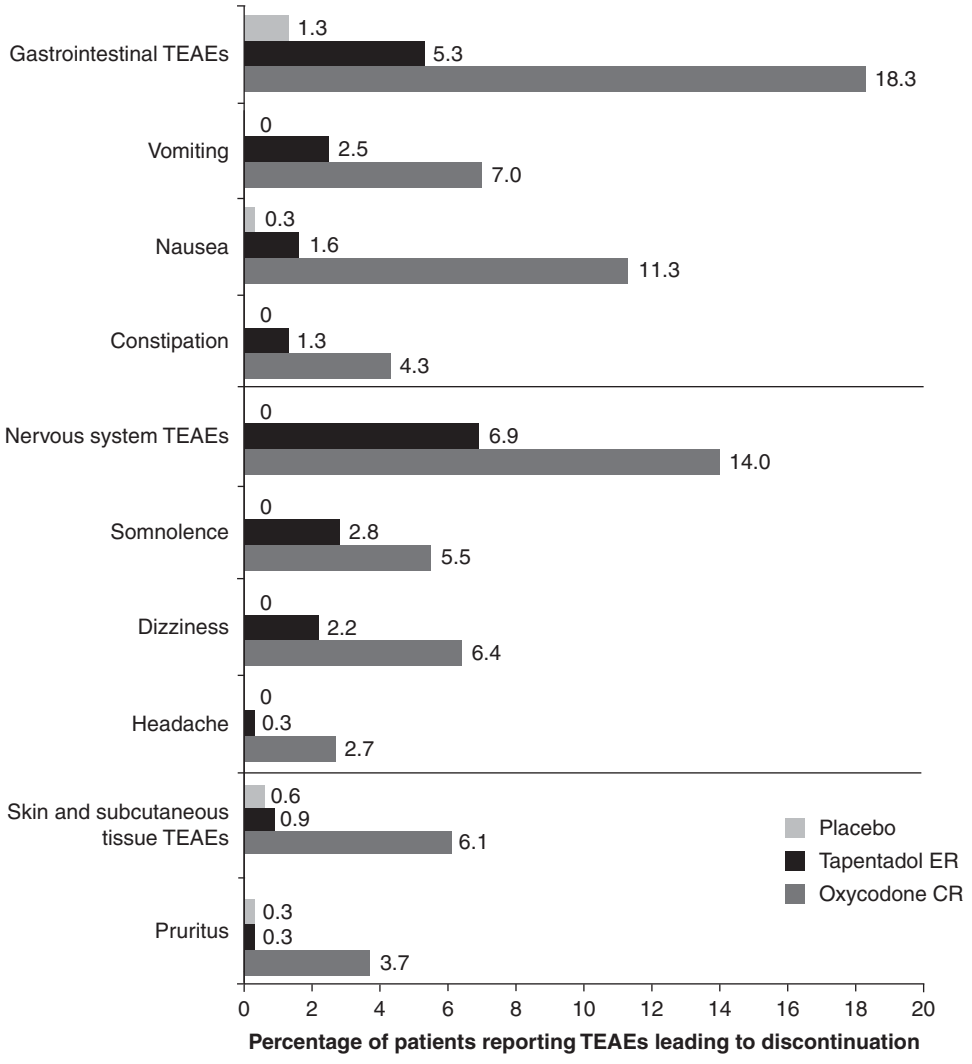


Figure 6. Incidence of TEAEs (in ≥ 2% of patients) leading to study discontinuation (safety population)*.

*Percentages are based on number of patients experiencing ≥ 1 event, not the number of events. Patients could report more than 1 TEAE as their reason for discontinuation.

CR: Controlled release; ER: Extended release; TEAE: Treatment-emergent adverse event.

treatment was associated with a significantly smaller increase in the severity of constipation symptoms than oxycodone CR among patients reporting constipation as a TEAE, in addition to the lower incidence of constipation observed with tapentadol ER treatment than with oxycodone CR treatment. Tapentadol ER was associated with a numerically lower incidence of TEAEs leading to discontinuation than oxycodone CR. Specifically, the percentage of patients in the tapentadol ER group who reported gastrointestinal TEAEs (nausea, vomiting, and constipation), nervous system TEAEs (dizziness and somnolence), and pruritus leading to discontinuation was approximately half the percentage of patients who reported discontinuing because of these TEAEs in the oxycodone CR group. COWS assessments in patients not taking opioids after the last intake of study drug showed that tapentadol ER treatment was associated with low incidences of mild or moderate opioid withdrawal, with symptom scores similar to those observed in the placebo group. The majority of patients who received tapentadol ER (95.2%) experienced no withdrawal, and no patients experienced moderately severe or severe withdrawal.

These results are supported by previous studies of the immediate-release formulation of tapentadol, which had an improved gastrointestinal tolerability profile, lower incidences of pruritus, and lower rates of study discontinuation relative to oxycodone IR and was associated with a low incidence of opioid withdrawal [25,27,28,42]. In a randomized, double-blind, Phase III study [25] comparing tapentadol IR and oxycodone IR for the relief of pain related to end-stage joint disease, both studied doses of tapentadol IR (50 and 75 mg, every 4 – 6 h) were found to

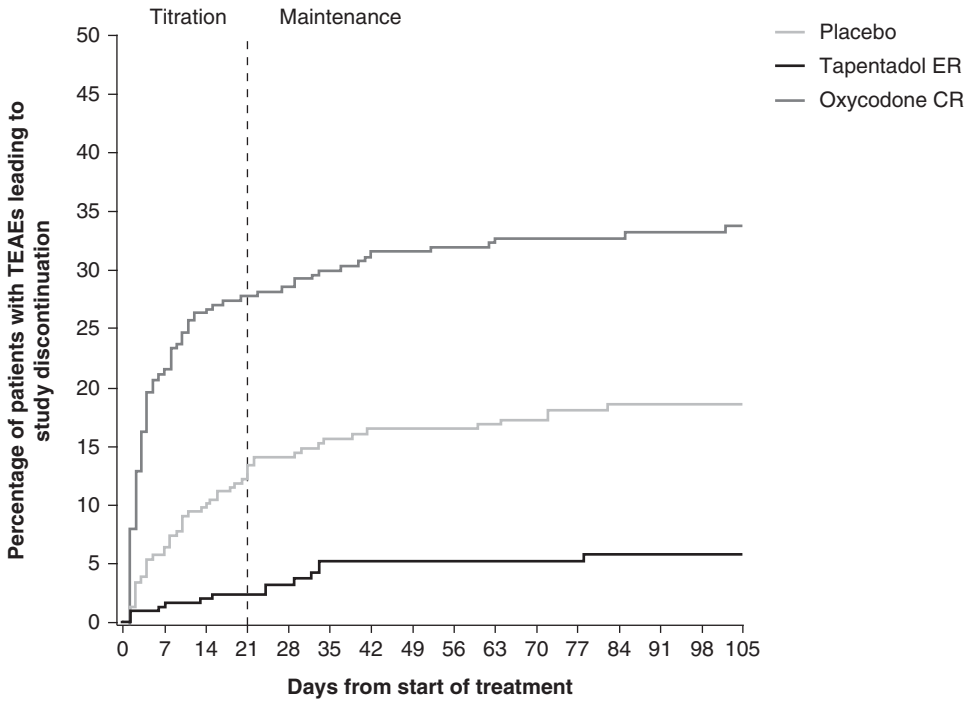


Figure 7. Distribution of time to onset of TEAEs leading to treatment discontinuation (safety population).
CR: Controlled release; DB: Double-blind; ER: Extended release; TEAE: Treatment-emergent adverse event.

have noninferior efficacy compared with oxycodone HCl IR 10 mg (every 4 – 6 h), but were associated with significantly lower incidences of select gastrointestinal TEAEs, including nausea, vomiting, and constipation (nominal $p < 0.001$ for all comparisons). In a *post hoc* analysis of data from that study [25], tapentadol IR 50 mg was also associated with a significantly lower incidence of treatment discontinuations for any reason than oxycodone HCl IR 10 mg ($p < 0.001$).

In a long-term, double-blind, Phase III safety study [42] comparing flexible doses of tapentadol IR and oxycodone IR for the relief of low back pain or osteoarthritis hip or knee pain over 90 days, tapentadol IR (50 – 100 mg every 4 – 6 h) provided pain relief similar to that provided by oxycodone HCl IR (10 – 15 mg every 4 – 6 h) based on pain intensity scores; however, patients treated with tapentadol IR were significantly less likely to report nausea, vomiting, and constipation than those treated with oxycodone IR (nominal $p < 0.001$ for all comparisons). The percentage of patients in that 90-day study [42] who experienced adverse events leading to discontinuation was lower in the tapentadol IR group (20.8%) than in the oxycodone IR group (30.6%). Additionally, according to the COWS assessment in that study [42], a significantly lower percentage of patients in the tapentadol IR group (17%) experienced opioid withdrawal, classified as mild or moderate in all cases, than in the oxycodone IR group (29%; $p < 0.05$). Across these studies [25-28,42], the incidence of pruritus was lower for patients treated with various doses of tapentadol IR than for those treated with oxycodone IR. In addition to the positive efficacy and tolerability results observed for tapentadol IR, tapentadol ER (100 – 250 mg b.i.d.) provided comparable pain relief to oxycodone HCl CR (20 – 50 mg b.i.d.) with improved tolerability (particularly gastrointestinal tolerability) compared with oxycodone CR in the 1-year study [39] in patients with chronic low back pain or osteoarthritis pain.

The favorable tolerability profile observed for tapentadol likely results from the combination of two mechanisms of action, μ-opioid receptor agonism and norepinephrine reuptake inhibition, in a single molecule [23]. Despite an approximately 50-fold lower affinity for the μ-opioid receptor compared with morphine, the analgesic potency of tapentadol is only two to three times less than that of morphine [24]. The contribution of norepinephrine reuptake inhibition to the analgesic activity of tapentadol seems to provide an opioid-sparing effect, reducing the activation of μ-opioid receptors and the incidence of associated side effects, while maintaining

analgesic efficacy [24,43]. The analgesic activity of tapentadol resides in a single parent molecule, and tapentadol has no active metabolites [23,24,44].

Tramadol and tapentadol are both centrally acting analgesics that exhibit μ-opioid receptor agonist and norepinephrine reuptake inhibitor activity; however, they are distinct in that tramadol also displays serotonin reuptake inhibitor activity [45] but has relatively low μ-opioid receptor activity compared with other opioid-type medications [46]. Tramadol is a World Health Organization (WHO) Step II analgesic (weak opioid) [47]; in previous studies [39,40] and in the current study, tapentadol ER was shown to have efficacy comparable to that of oxycodone CR, which is a WHO Step III analgesic (strong opioid) and is appropriate for the management of moderate to severe pain [48]. Unlike tapentadol, which combines its two mechanisms of action in a single molecule, tramadol exists as a racemic mixture, and the mechanisms of action of tramadol reside in different enantiomers and metabolites of the compound [49]. Approximately 40% of the analgesic effect of tramadol is provided by the active metabolite *O*-desmethyl-tramadol; therefore, unlike tapentadol, tramadol relies upon metabolic activation to achieve its full analgesic effect [49]. Based on the incidences of nausea and constipation observed in chronic pain studies with tramadol ER [50-52] and the incidences observed with tapentadol ER in both previous studies [39,53,54] and the current study, tapentadol ER appears to have a better gastrointestinal side-effect profile than tramadol ER, which may be due to the serotonin-mediated pro-emetic effects of tramadol [55].

Gastrointestinal adverse events, nervous system adverse events, and pruritus are among the most common side effects associated with opioid analgesics [14]. Previous studies have indicated that doctors tend not to prescribe opioids to avoid opioid-related side effects and discontinuation of treatment by patients [56,57]. Discontinuation from therapy due to the occurrence of adverse events leads to undermanaged chronic pain, which can increase patient discomfort, reduce patient quality of life, and lead to other deleterious consequences, including an increased risk of psychological disorders (most commonly depression or anxiety) [58], physical dysfunction, social isolation, sleep disturbance, and excessive fatigue [59,60]. The lower incidences of TEAEs, particularly gastrointestinal TEAEs, and the lower rates of treatment discontinuation observed with tapentadol ER treatment for the management of moderate to severe chronic low back pain may contribute to improved treatment compliance and more stable and effective pain relief compared with μ-opioid receptor agonists such as oxycodone CR. These improvements in tolerability may have contributed to the improvements in quality of life, health status, and physical functioning measures observed in the current study, which may be an important benefit for patients on long-term analgesic therapy for chronic pain.

Although the study duration was selected to correspond with currently accepted standards for chronic pain trials [61], the 3-month duration of the trial may not accurately represent the long-term course of treatment for a patient with chronic low back pain; however, as described previously, results of a 1-year study [39] have demonstrated that tapentadol ER provided efficacy comparable to that of oxycodone CR with an improved tolerability profile. In addition, the requirement for a 3-month history of chronic pain (a standard definition of chronic pain) prior to study enrollment may not be sufficient to show that treatment is effective and that pain reductions are not the result of natural history [61]; however, patients in the current study had experienced chronic low back pain for 6 months to 66 years.

Chronic low back pain is highly prevalent in Western societies [1]. Low back pain may have both nociceptive and neuropathic pain components [1,62,63]. In a meta-analysis [63] of data from three studies of 21,047 patients with chronic low back pain who consulted a physician, approximately one-third of these patients reported symptoms indicative of neuropathic pain. Results of that meta-analysis [63] also revealed that the percentage of patients with 'positive (neuropathic)' pain increased with increasing pain intensity, from < 10% for patients with the lowest grade of pain (pain intensity < 5 on an 11-point NRS and a functional performance score > 70) to just under 50% for patients with the highest pain intensity (≥ 5 on an 11-point NRS and a functional performance score ≤ 70). Unfortunately, neuropathic pain is often difficult to manage, with approximately 30% of patients failing to respond to therapy [64].

The two mechanisms of action of tapentadol, μ-opioid receptor agonism and norepinephrine reuptake inhibition, may make it a treatment option for the management of both nociceptive and neuropathic pain. Results of preclinical studies have shown that tapentadol was effective in models of both nociceptive and neuropathic pain [23]. In addition, results of a 12-week, randomized-withdrawal, Phase III study [54] in patients with moderate to severe neuropathic pain related to diabetic peripheral neuropathy have shown that tapentadol ER (100 – 250 mg b.i.d.) was well tolerated and effective compared with placebo. Thus, tapentadol ER may be an effective new treatment option for the management of moderate to severe pain with a neuropathic component, such as chronic low back pain.

5. Expert opinion and conclusion

Tapentadol ER administered in controlled, adjustable doses of 100 – 250 mg b.i.d. over 15 weeks was significantly more effective for the management of moderate to severe chronic low back pain than placebo, as indicated both by significant reductions in mean pain intensity and significantly higher percentages of patients with ≥ 30 and ≥ 50% improvements in pain intensity (which are considered clinically relevant outcomes [65]), and was generally well tolerated. Tapentadol ER had improved gastrointestinal tolerability and a lower incidence of study discontinuation due to TEAEs than

oxycodone CR at doses providing similar analgesic efficacy. Thus, tapentadol ER may contribute to more consistent and improved relief of chronic pain.

Acknowledgements

Data presented in this manuscript have been presented at the 134th Annual Meeting of the American Neurological Association (ANA), 11 – 14 October 2009, Baltimore, MD, USA; the Annual Scientific Meeting of the British Pain Society (BPS), 13 – 16 April 2010, Manchester, England; the 10th Annual Congress of the European League Against Rheumatism (EULAR), 10 – 13 June 2009, Copenhagen, Denmark; the 24th Annual Meeting of the North American Spine Society (NASS), 10 – 19 November 2009, San Francisco, CA, USA; the 28th Annual Scientific Meeting of the American Pain Society (APS), 7 – 9 May 2009, San Diego, CA, USA; the 6th Triennial Congress of the European Federation of IASP Chapters (EFIC), 9 – 12 September 2009, Lisbon, Portugal; the Proceedings of the American College of Rheumatology (ACR), 16 – 21 October 2009, Philadelphia, PA, USA; the Congress of the German Society for Pain Therapy (DGS), 18 – 20 March 2010, Frankfurt, Germany; the American Academy of Physical Medicine & Rehabilitation (AAPM&R), 22 – 25 October 2009, Austin, TX, USA; the National Conference on Pain for Frontline Practitioners (PAINWeek), 9 – 13 September 2009, Las Vegas, NV, USA; the 20th Annual Clinical Meeting of the American Academy of Pain Management (AAPM), 8 – 11 October 2009, Phoenix, AZ, USA; and the 2009 Fall Proceedings of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), 24 – 27 October 2009, Paris, France.

Declaration of interest

Editorial support for the writing of this manuscript was provided by Megan Knagge, PhD, of MedErgy, and was funded by Johnson & Johnson Pharmaceutical Research & Development L.L.C., and Global Development, Grünenthal GmbH, Aachen, Germany. R Buynak, who is not employed by Johnson & Johnson Pharmaceutical Services, L.L.C., or Grünenthal GmbH, was not compensated for this manuscript. Although writing assistance was provided, the authors retained full editorial control over the content of the manuscript. R Buynak received funding for study support from Johnson & Johnson Pharmaceutical Research & Development, L.L.C. DY Shapiro, A Okamoto, I Van Hove, C Rauschkolb and M Etropolski are Johnson & Johnson employees and shareholders. A Steup and B Lange are employees of Grünenthal GmbH. C Lange is a former employee of Grünenthal GmbH.

Bibliography

1. Freynhagen R, Baron R, Gockel U, Tolle TR. Paindetect: a new screening questionnaire to identify neuropathic components in patients with back pain. Curr Med Res Opin 2006;22:1911-20
2. Deyo RA, Mirza SK, Martin BI. Back pain prevalence and visit rates: estimates from US national surveys, 2002. Spine 2006;31:2724-7
3. Hale ME, Fleischmann R, Salzman R, et al. Efficacy and safety of controlled-release versus immediate-release oxycodone: randomized, double-blind evaluation in patients with chronic back pain. Clin J Pain 1999;15:179-83
4. Hale ME, Dvergsten C, Gimbel J. Efficacy and safety of oxymorphone extended release in chronic low back pain: results of a randomized, double-blind, placebo- and active-controlled phase III study. J Pain 2005;6:21-8
5. Hale ME, Ahdieh H, Ma T, Rauck R. Efficacy and safety of OPANA ER (oxymorphone extended release) for relief of moderate to severe chronic low back pain in opioid-experienced patients: a 12-week, randomized, double-blind, placebo-controlled study. J Pain 2007;8:175-84
6. Katz N, Rauck R, Ahdieh H, et al. A 12-week, randomized, placebo-controlled trial assessing the safety and efficacy of oxymorphone extended release for opioid-naive patients with chronic low back pain. Curr Med Res Opin 2007;23:117-28
7. Rauck RL, Bookbinder SA, Bunker TR, et al. A randomized, open-label, multicenter trial comparing once-a-day avinza (morphine sulfate extended-release capsules) versus twice-a-day oxycontin (oxycodone hydrochloride controlled-release tablets) for the treatment of chronic, moderate to severe low back pain: improved physical functioning in the action trial. J Opioid Manag 2007;3:35-43
8. Rauck RL, Bookbinder SA, Bunker TR, et al. The ACTION study: a randomized, open-label, multicenter trial comparing once-a-day extended-release morphine sulfate capsules (AVINZA®) to twice-a-day controlled-release oxycodone hydrochloride tablets (OxyContin®) for the treatment of chronic, moderate to severe low back pain. J Opioid Manag 2006;2:155-66
9. Roth SH, Fleischmann RM, Burch FX, et al. Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain: placebo-controlled trial and long-term evaluation. Arch Intern Med 2000;160:853-60
10. Chou R, Fanciullo GJ, Fine PG, et al. Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain. J Pain 2009;10:113-30
11. Bartleson JD. Evidence for and against the use of opioid analgesics for chronic nonmalignant low back pain: a review. Pain Med 2002;3:260-71
12. Schofferman J, Mazanec D. Evidence-informed management of chronic low back pain with opioid analgesics. Spine J 2008;8:185-94
13. Chou R, Ballantyne JC, Fanciullo GJ, et al. Research gaps on use of opioids for chronic noncancer pain: findings from a review of the evidence for an American

Pain Society and American Academy of Pain Medicine clinical practice guideline. J Pain 2009;10:147-59

14. Christo PJ. Opioid effectiveness and side effects in chronic pain. Anesthesiol Clin North America 2003;21:699-713
15. Moore RA, McQuay HJ. Prevalence of opioid adverse events in chronic non-malignant pain: systematic review of randomised trials of oral opioids. Arthritis Res Ther 2005;7:r1046-51
16. Caldwell JR, Hale ME, Boyd RE, et al. Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminophen added to nonsteroidal anti-inflammatory drugs: a double blind, randomized, multicenter, placebo controlled trial. J Rheumatol 1999;26:862-9
17. Nicholson B. Responsible prescribing of opioids for the management of chronic pain. Drugs 2003;63:17-32
18. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. Pain Physician 2008;11:s105-20
19. Bell TJ, Panchal SJ, Miaskowski C, et al. The prevalence, severity, and impact of opioid-induced bowel dysfunction: results of a US and European Patient Survey (PROBE 1). Pain Med 2009;10:35-42
20. Panchal SJ, Müller-Schwefe P, Wurzelmann JI. Opioid-induced bowel dysfunction: prevalence, pathophysiology and burden. Int J Clin Pract 2007;61:1181-7
21. Pappagallo M. Incidence, prevalence, and management of opioid bowel dysfunction. Am J Surg 2001;182:11s-8s
22. Thorpe DM. Management of opioid-induced constipation. Curr Pain Headache Rep 2001;5:237-40
23. Tzschentke TM, Christoph T, Kogel B, et al. (-)-(1*R*,2*R*)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride (tapentadol HCl): a novel μ-opioid receptor agonist/norepinephrine reuptake inhibitor with broad-spectrum analgesic properties. J Pharmacol Exp Ther 2007;323:265-76
24. Tzschentke TM, de Vry J, Terlinden R, et al. Tapentadol HCl. Drugs Future 2006;31:1053-61
25. Hartrick C, Van hove I, Stegmann J-U, et al. Efficacy and tolerability of tapentadol immediate release and oxycodone HCl immediate release in patients awaiting primary joint replacement surgery for end-stage joint disease: a 10-day, phase III, randomized, double-blind, active- and placebo-controlled study. Clin Ther 2009;31:260-71
26. Stegmann J-U, Weber H, Steup A, et al. The efficacy and tolerability of multiple-dose tapentadol immediate release for the relief of acute pain following orthopedic (bunionectomy) surgery. Curr Med Res Opin 2008;24:3185-96
27. Daniels SE, Upmalis D, Okamoto A, et al. A randomized, double-blind, phase III study comparing multiple doses of tapentadol IR, oxycodone IR, and placebo for postoperative (bunionectomy) pain. Curr Med Res Opin 2009;25:765-76
28. Daniels S, Casson E, Stegmann J-U, et al. A randomized, double-blind, placebo-controlled phase 3 study of the relative efficacy and tolerability of tapentadol IR and oxycodone IR for acute pain. Curr Med Res Opin 2009;25:1551-61
29. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Guidance for Industry. E6 Good Clinical Practice: Consolidated Guidance. Available from: http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm129515.pdf [Last accessed 4 May 2010]
30. Cleeland CS, Ryan KM. Pain assessment: global use of the brief pain inventory. Ann Acad Med Singapore 1994;23:129-38
31. Ware JE Jr, Donald Sherbourne C. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473-83
32. The EuroQol Group. EuroQol – a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-208
33. Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53-72
34. Haythornthwaite JA, Hegel MT, Kerns RD. Development of a sleep diary for chronic pain patients. J Pain Symptom Manage 1991;6:65-72
35. Wesson DR, Ling W. The clinical opiate withdrawal scale (COWS). J Psychoactive Drugs 2003;35:253-9
36. Slappendel R, Simpson K, Dubois D, Keininger DL. Validation of the PAC-SYM questionnaire for opioid-induced constipation in patients with chronic low back pain. Eur J Pain 2006;10:209-17
37. Farrar JT, Young JP Jr, Lamoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149-58
38. Matsumoto AK, Babul N, Ahdieh H. Oxymorphone extended-release tablets relieve moderate to severe pain and improve physical function in osteoarthritis: results of a randomized, double-blind, placebo- and active-controlled phase III trial. Pain Med 2005;6:357-66
39. Wild JE, Grond S, Kuperwasser B, et al. Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain. Pain Pract 2010; In press
40. Afilalo M, Kuperwasser B, Kelly K, et al. Efficacy and safety of tapentadol extended release (ER) for chronic pain due to osteoarthritis of the knee: results of a phase 3 study. Pain Pract 2009;9:159
41. Etropolski M, Shapiro DY, Okamoto A, et al. Efficacy and safety of tapentadol ER for diabetic peripheral neuropathic pain: results of a randomized-withdrawal, double-blind, placebo-controlled phase III study. Neurology 2009;72(Suppl 3):A217-8
42. Hale M, Upmalis D, Okamoto A, et al. Tolerability of tapentadol immediate release in patients with lower back pain or osteoarthritis of the hip or knee over 90 days: a randomized, double-blind study. Curr Med Res Opin 2009;25:1095-104
43. Tzschentke TM, Jahnel U, Kogel B, et al. Tapentadol hydrochloride: a next-generation, centrally acting analgesic with two mechanisms of action in a single molecule. Drugs Today (Barc) 2009;45:483-96
44. Terlinden R, Kogel B, Englberger W, Tzschentke T. In vitro and in vivo characterization of tapentadol

metabolites. Methods Find Exp Clin Pharmacol 2010;32:31-8

45. Minami K, Uezono Y, Ueta Y. Pharmacological aspects of the effects of tramadol on G-protein coupled receptors. J Pharmacol Sci 2007;103:253-60

46. Hennies HH, Friderichs E, Schneider J. Receptor binding, analgesic and antitussive potency of tramadol and other selected opioids. Arzneimittelforschung 1988;38:877-80

47. Radbruch L, Grond S, Lehmann KA. A risk-benefit assessment of tramadol in the management of pain. Drug Saf 1996;15:8-29

48. Dalton JA, Youngblood R. Clinical application of the World Health Organization analgesic ladder. J Intraven Nurs 2000;23:118-24

49. Reeves RR, Burke RS. Tramadol: basic pharmacology and emerging concepts. Drugs Today (Barc) 2008;44:827-36

50. Babul N, Noveck R, Chipman H, et al. Efficacy and safety of extended-release, once-daily tramadol in chronic pain: a randomized 12-week clinical trial in osteoarthritis of the knee. J Pain Symptom Manage 2004;28:59-71

51. Pascual ML, Fleming RR, Gana TJ, Vorsanger GJ. Open-label study of the safety and effectiveness of long-term therapy with extended-release tramadol in the management of chronic nonmalignant pain. Curr Med Res Opin 2007;23:2531-42

52. Vorsanger GJ, Xiang J, Gana TJ, et al. Extended-release tramadol (tramadol ER) in the treatment of chronic low back pain. J Opioid Manag 2008;4:87-97

53. Kelly K, Kuperwasser B, Okamoto A, et al. Efficacy and gastrointestinal tolerability of tapentadol extended release in a randomized, double-blind, placebo- and active-controlled study in patients with moderate-to-severe chronic osteoarthritis knee pain. Pain Pract 2009;9:161-2

54. Etropolski MS, Shapiro DY, Okamoto A, et al. Safety and tolerability of tapentadol extended release in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal phase 3 study. Diabetes 2009;58:a226-7

55. Barann M, Urban B, Stamer U, et al. Effects of tramadol and O-demethyl-tramadol on human 5-HT reuptake carriers and human 5-HT3A receptors: a possible mechanism for tramadol-induced early emesis. Eur J Pharmacol 2006;531:54-8

56. Arnold R. Why patients do not take their opioids. J Palliat Med 2004;7:716-7

57. Bhamb B, Brown D, Hariharan J, et al. Survey of select practice behaviors by primary care physicians on the use of opioids for chronic pain. Curr Med Res Opin 2006;22:1859-65

58. Gureje O, Von KM, Simon GE, Gater R. Persistent pain and well-being: a world health organization study in primary care. JAMA 1998;280:147-51

59. Becker N, Bondegaard TA, Olsen AK, et al. Pain epidemiology and health related quality of life in chronic non-malignant pain patients referred to a Danish multidisciplinary pain center. Pain 1997;73:393-400

60. Ashburn MA, Staats PS. Management of chronic pain. Lancet 1999;353:1865-9

61. Dworkin RH, Turk DC, Peirce-Sandner S, et al. Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. Pain 2010;149:177-93

62. Freynhagen R, Baron R. The evaluation of neuropathic components in low back pain. Curr Pain Headache Rep 2009;13:185-90

63. Schmidt CO, Schweikert B, Wenig CM, et al. Modelling the prevalence and cost of back pain with neuropathic components in the general population. Eur J Pain 2009;13:1030-5

64. Davis MP. What is new in neuropathic pain? Support Care Cancer 2007;15:363-72

65. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9:105-21

Affiliation

Robert Buynak[1], Douglas Y Shapiro[2], Akiko Okamoto[2], Ilse Van Hove[3], Christine Rauschkolb[2], Achim Steup[4], Bernd Lange[4], Claudia Lange[4] & Mila Etropolski[†5]

[†]Author for correspondence

[1]Northwest Indiana Center for Clinical Research, Indiana, USA

[2]Johnson & Johnson Pharmaceutical Research & Development, L.L.C., New Jersey, USA

[3]Johnson & Johnson Pharmaceutical Research & Development, Division of Janssen Pharmaceutica NV, Beerse, Belgium

[4]Grünenthal GmbH, Global Development, Aachen, Germany

[5]Tapentadol Chronic Pain Program, Johnson & Johnson Pharmaceutical Research & Development, L.L.C., CNS/Pain, 1125 Trenton-Harbourton Road, Titusville, NJ 08560, USA

Tel: +1 609 730 4537; Fax: +1 609 730 3538; E-mail: METropol@its.jnj.com