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Clinical Trials Study

Efficacy of Tapentadol ER for Managing Moderate to Severe Chronic Pain

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Background: Chronic non–cancer-related pain affects a large proportion of the adult population and is often difficult to manage effectively. Although opioid analgesics have been used to relieve chronic pain of different etiologies, opioids are associated with a range of side effects that may reduce patient quality of life and lead to reduced compliance with treatment.Tapentadol is a centrally acting analgesic with 2 mechanisms of action, μ-opioid receptor agonism and norepinephrine reuptake inhibition, that is available in an extended-release formulation for the management of chronic pain.

Objective: To review the efficacy of tapentadol extended release (ER) for the management of moderate to severe chronic nociceptive and neuropathic pain.

Methods: Efficacy results are summarized for four 15-week phase 3 studies of tapentadol ER in patients with moderate to severe chronic osteoarthritis knee pain (2 studies; ClinicalTrials.gov Identifiers: NCT00421928 and NCT00486811), low back pain (NCT00449176), and pain related to diabetic peripheral neuropathy (DPN; NCT00455520); a one-year phase 3 study of tapentadol ER in patients with moderate to severe chronic osteoarthritis pain or low back pain (NCT00361504); and a pooled analysis of data from the 15-week studies in patients with osteoarthritis knee pain or low back pain. A summary of the comparative tolerability for tapentadol ER and the active comparator used in these studies, oxycodone controlled release (CR), is provided.

Results: Results of these studies showed that tapentadol ER (100 - 250 mg bid) was effective for the management of moderate to severe chronic osteoarthritis knee pain, low back pain, and pain related to DPN. Tapentadol ER (100 - 250 mg bid) has been shown to provide comparable pain relief to oxycodone HCl CR (20 - 50 mg bid) for chronic osteoarthritis knee pain and low back pain over up to one year of treatment. Tapentadol ER (100 - 250 mg bid) was associated with an improved tolerability profile, particularly gastrointestinal tolerability profile, and with lower rates of treatment discontinuations and adverse event-related discontinuations compared with oxycodone HCl CR (50 - 250 mg bid) over up to one year of treatment in patients with osteoarthritis knee pain and low back pain.

Limitations: Differences in the design and duration of these phase 3 studies may limit comparisons of the efficacy results; nevertheless, this summary of efficacy results demonstrates the broad efficacy of tapentadol ER for different types of nociceptive and neuropathic pain.

Conclusions: Tapentadol ER (100 - 250 mg bid) is effective for moderate to severe osteoarthritis pain, low back pain, and pain related to DPN and provides efficacy similar to that of oxycodone HCl CR (20 - 50 mg bid) for patients with osteoarthritis and low back pain. Tapentadol ER treatment has been associated with better gastrointestinal tolerability and compliance with therapy than oxycodone CR, which suggests that tapentadol ER may be a better option for the long-term management of chronic pain.

Key words: Chronic pain, tapentadol ER, osteoarthritis pain, low back pain, diabetic peripheral neuropathy, oxycodone CR, opioid, analgesic

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Chronic non–cancer-related pain affects approximately 30% to 41% of adults worldwide (1-3), and is often associated with decreased physical functioning and reduced quality of life (3-6). Chronic pain involves complex interactions between biological, psychological, social, and cultural factors, which complicate its diagnosis and management (7-9). The management of chronic pain is particularly challenging because of the long-term course of therapy and the variability in pain etiology and individual response to treatment (4).

Chronic pain can be classified as nociceptive, neuropathic, inflammatory, or dysfunctional or may be mixed, having characteristics of multiple pain types (10). Although their causes and clinical presentation are distinctive, the mechanisms by which these types of pain arise may overlap, and a patient may experience chronic pain with aspects of more than one type of pain (11). For example, low back pain, which is one of the most common types of non–cancer-related chronic pain, is typically considered a nociceptive type of pain (2,4,12) but often has a neuropathic component (13-15). Chronic pain with a neuropathic component is often challenging to manage with current treatment options, including opioid analgesics (16,17). Combination therapy with drugs with different mechanisms of action is often necessary to address both the nociceptive and neuropathic components of chronic pain (17).

Pharmacotherapy, including non-opioid and opioid analgesics, is an important cornerstone in the multimodal management of chronic pain (18-21). Opioids have been used to manage both nociceptive and neuropathic chronic pain conditions but are associated with side effects that may limit their usefulness in long-term therapy (22). Specifically, gastrointestinal side effects, which are the most commonly reported side effects associated with chronic opioid therapy, may be particularly problematic for patients with chronic pain, with nausea occurring in 6% to 42% of patients, vomiting in 8% to 33% of patients, and constipation in 3.1% to 95% of patients (23). While vomiting and nausea are typically more problematic at the start of therapy, opioid-induced constipation often does not improve over the course of treatment and is refractory to standard treatment options (24). A 2010 Internet-based survey of 618 patients found that nausea and vomiting were rated as 2 of the most important side effects to avoid; patients indicated that they were willing to accept a reduction in pain relief to lower the incidence of these side effects (25). Opioid-induced side effects, particularly gastrointestinal side effects, may be severe enough that patients decrease their doses or even discontinue therapy, resulting in inadequate pain control (26,27). Peripherally acting μ-opioid receptor antagonists, such as methylnaltrexone or alvimopan, and oral μ-opioid receptor antagonists with limited systemic absorption, such as naloxone, may be used to prevent or reverse the gastrointestinal side effects associated with opioid therapy. Mu-opioid receptor antagonists have been shown to be effective and well tolerated for treating opioid-induced gastrointestinal side effects, including constipation (28-30).

Tapentadol represents a new class of centrally acting analgesic, the μ-opioid receptor agonist-norepinephrine reuptake inhibitor (MOR-NRI) (31), with analgesic activity that results from the contribution of both mechanisms of action (32,33). An extended-release formulation of tapentadol (tapentadol extended release [ER]; tapentadol prolonged release [PR] in Europe) has been approved in the United States for the management of moderate to severe chronic pain and neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adult patients requiring continuous, around-the-clock opioid therapy over an extended period of time (34) and in Europe for the management of severe chronic pain in adult patients who can only achieve adequate analgesia with opioid therapy (35). The tolerability and efficacy of tapentadol ER have been demonstrated for the management of both nociceptive and neuropathic types of chronic pain (36-39). The purpose of this review is to summarize efficacy results from individual phase 3 studies in patients with osteoarthritis knee pain (36,39), low back pain (37,39), and pain related to DPN (40), along with results from a pooled analysis (38) of 3 individual phase 3 studies of similar design.

Methods

Efficacy results of the following individual phase 3 studies are summarized in this review: three 15 week, randomized, double-blind studies of similar design of tapentadol ER (100 - 250 mg bid) compared with placebo and oxycodone HCl CR (20 - 50 mg bid) in patients with moderate to severe chronic osteoarthritis knee pain (36) (2 studies; ClinicalTrials.gov Identifiers: NCT00421928 and NCT00486811) or low back pain (37) (NCT00449176); a 15-week, randomized-withdrawal study of tapentadol ER (100 - 250 mg bid) compared with placebo in patients with moderate to severe chronic pain related to DPN (40) (NCT00455520); and a one-year, randomized, open-label study of tapentadol

ER (100 - 250 mg bid) compared with oxycodone HCl CR (20 - 50 mg bid) in patients with osteoarthritis pain or low back pain (39) (NCT00361504). Efficacy results from a pooled analysis (38) of data from the three 15-week studies in patients with osteoarthritis knee pain or low back pain are also summarized in this article, along with a comparison of the tolerability of tapentadol ER and oxycodone CR.

Efficacy of Tapentadol ER for the Management of Chronic Osteoarthritis Pain and Low Back Pain

The general designs of the three 15-week, chronic osteoarthritis and low back pain studies are summarized in Table 1. Data from those 3 studies have also been pooled for efficacy analyses (38).

Chronic Osteoarthritis Knee Pain

In a double-blind, phase 3 study in patients with osteoarthritis knee pain (referred to as osteoarthritis study 1 in this review) (36), patients were randomized in a 1:1:1 ratio to receive placebo, tapentadol ER (100 - 250 mg bid), or oxycodone HCl CR (20 - 50 mg bid). Patients received study medication during a 15-week, double-blind treatment period (3-week titration period and 12-week maintenance period) (36). During the maintenance period, patients attempted to maintain a steady dose but were permitted to adjust their doses (under the supervision of a physician) to maintain an optimal balance of pain reduction and tolerability(36). Details of the study design have been published previously (36). Demographic and baseline characteristics for the 1,023 patients (safety and efficacy [intent-to-treat (ITT)] population) who received at least one dose of study drug during the double-blind treatment period are presented in Table 2.

To accommodate diverse global regulatory requirements, the following 2 primary endpoints were evaluated: the change in pain intensity (11-point numerical rating scale [NRS]; 0 = no pain to 10 = pain as bad as you can imagine) from baseline to Week 12 of the maintenance period (United States health authority primary endpoint) and the change in pain intensity from baseline for the overall maintenance period (European and other health authorities' primary endpoint) (36). The last observation carried forward (LOCF) was

Table 1. *Study Design for Randomized, Phase 3 Studies of Tapentadol ER in Patients with Moderate to Severe Chronic Pain.*

	Study characteristics
Osteoarthritis knee pain (36) (Osteoarthritis study 1; NCT00421928) (N = 1,023)	Patients with moderate to severe chronic OA knee pain 3-week, double-blind titration to an optimal dose in terms of pain relief and tolerability, followed by a 12-week, double-blind, controlled dose adjustment maintenance period Placebo, tapentadol ER (100 - 250 mg bid), or oxycodone HCl CR (20 - 50 mg bid)
Osteoarthritis knee pain (Osteoarthritis study 2; NCT00486811) (N = 987)	Patients with moderate to severe chronic OA knee pain 3-week, double-blind titration to an optimal dose in terms of pain relief and tolerability, followed by a 12-week, double-blind, controlled dose adjustment maintenance period Placebo, tapentadol ER (100 - 250 mg bid), or oxycodone HCl CR (20 - 50 mg bid)
Low back pain (37) (NCT0049176) (N = 965)	Patients with moderate to severe chronic low back pain 3-week, double-blind titration to an optimal dose in terms of pain relief and tolerability, followed by a 12-week, double-blind, controlled dose adjustment maintenance period Placebo, tapentadol ER (100 - 250 mg bid), or oxycodone HCl CR (20 - 50 mg bid)
One-year safety (low back pain or OA hip or knee pain) (39) (NCT00361504) (N = 1,117)	Patients with moderate to severe chronic OA hip or knee pain or low back pain One-week, open-label titration period, followed by an open-label, controlled dose adjustment maintenance period of up to 51 weeks Placebo, tapentadol ER (100 - 250 mg bid), or oxycodone HCl CR (20-50 mg bid)
DPN pain (40) (NCT00455520) (N = 588)	Patients with moderate to severe chronic pain related to DPN 3-week, open-label titration period with tapentadol ER, followed by a 12-week maintenance period in which patients who tolerated the drug and had an initial treatment effect (≥ 1-point improvement in pain intensity on an 11-point NRS) were randomized to placebo or the optimal dose of tapentadol ER determined during titration Placebo or tapentadol ER (100 - 250 mg bid, with a supplemental 25 mg/day allowed during the maintenance period[a])

ER, extended release; CR, controlled release; OA, osteoarthritis; DPN, diabetic peripheral neuropathy; NRS, numerical rating scale.
[a]Two doses of tapentadol ER 25 mg per day were allowed during the first 4 days of the maintenance period as supplemental analgesia, and a single 25-mg dose was allowed for the remainder of the maintenance period.

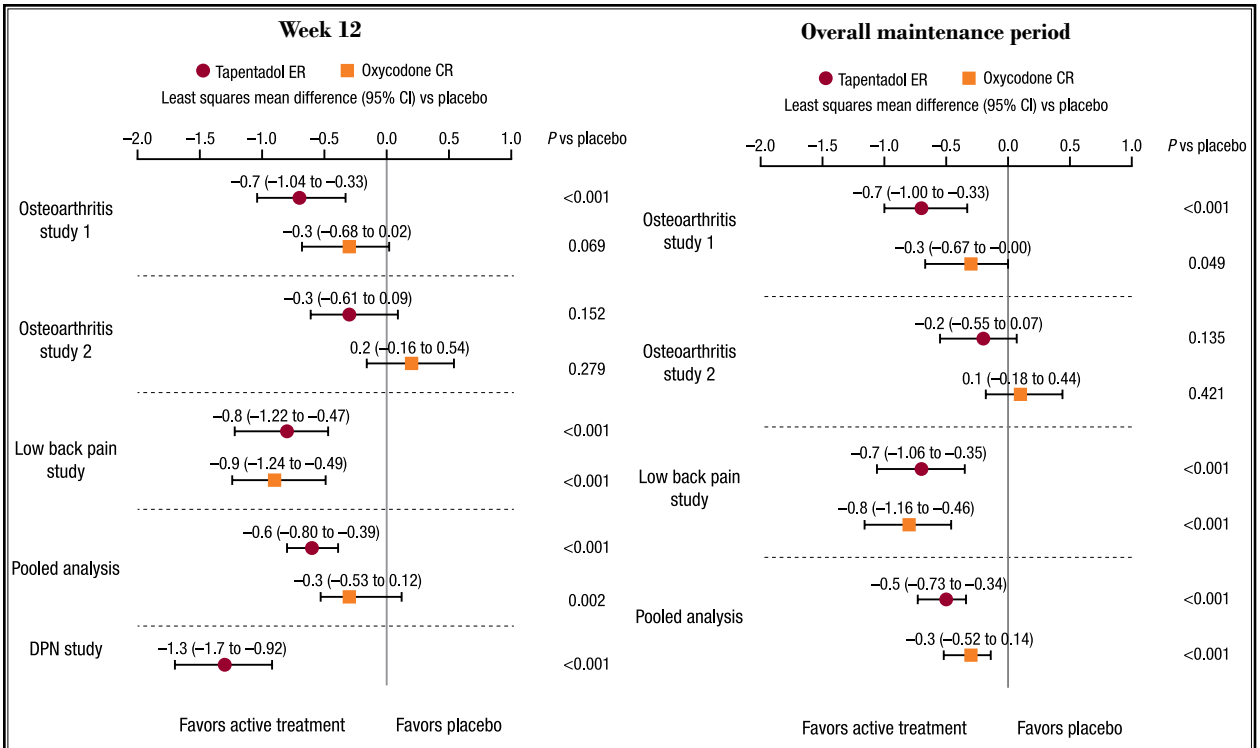
Table 2. *Baseline and Demographic Characteristics (Safety Populations)*

Characteristic	Osteoarthritis study 1 (36) (N = 1,023)	Osteoarthritis study 2 (N = 987)	Low back pain study (37) (N = 965)	Pooled analysis (38) (N = 2,968)[a]	One-year safety study (39) (N = 1,117)	DPN study (40) (N = 389)[b]
Age						
Mean (SD), y	58.3 (9.85)	62.1 (9.26)	49.9 (13.83)	56.8 (12.21)	57.0 (12.38)	60.2 (10.62)
< 65 y, n (%)	758 (74.1)	599 (60.7)	816 (84.6)	2,168 (73.0)	805 (72.1)	256 (65.8)
≥ 65 y, n (%)	265 (25.9)	388 (39.3)	149 (15.4)	800 (27.0)	312 (27.9)	133 (34.2)
Gender, n (%)						
Male	405 (39.6)	280 (28.4)	406 (42.1)	1,088 (36.7)	477 (42.7)	235 (60.4)
Female	618 (60.4)	707 (71.6)	559 (57.9)	1,880 (63.3)	640 (57.3)	154 (39.6)
Race, n (%)						
White	772 (75.5)	980 (99.3)	707 (73.3)	2,453 (82.6)	995 (89.1)	272 (69.9)
Black	132 (12.9)	2 (0.2)	167 (17.3)	300 (10.1)	73 (6.5)	45 (11.6)
Hispanic	78 (7.6)	1 (0.1)	60 (6.2)	139 (4.7)	30 (2.7)	62 (15.9)
Other	41 (4.0)	4 (0.4)	31 (3.2)	76 (2.6)	19 (1.7)	10 (2.6)
Baseline pain intensity score[c,d]						
Mean (SD)	7.3 (1.31)	7.3 (1.10)	7.5 (1.29)	7.4 (1.24)	7.6 (1.55)	7.3 (1.41)
Baseline pain intensity category,[c,d,e] n (%)						
Mild or none	2 (0.2)	0	0	2 (0.1)	0	2 (0.5)
Moderate	168 (16.4)	109 (11.1)	110 (11.5)	385 (13.0)	118 (10.6)	74 (19.0)
Severe	852 (83.4)	877 (88.9)	848 (88.5)	2,572 (86.9)	999 (89.4)	310 (79.7)

DPN, diabetic peripheral neuropathy; SD, standard deviation; NRS, numerical rating scale.
[a]Efficacy (intent-to-treat) population. [b]Characteristics of the double-blind safety population are presented. [c]Osteoarthritis study 1, n = 1,022; osteoarthritis study 2, n = 986; low back pain study, n = 958; pooled analysis, n = 2,959; one-year safety study, n = 1,117; DPN study, n = 386. [d]Baseline pain intensity score is the mean of the average pain intensity during the last 72 hours prior to randomization. For the DPN study, the baseline pain intensity before the start of the open-label titration is presented. [e]Mild pain intensity was defined as an NRS score > 0 to < 4; moderate pain intensity, ≥ 4 to < 6; severe pain intensity, ≥ 6.

used for imputing missing pain intensity values in the event of early discontinuation for both endpoints (36). Treatment with tapentadol ER resulted in significant decreases in pain intensity from baseline compared with placebo for both primary endpoints ($P < 0.001$ for both comparisons; Fig. 1) (36). In contrast, treatment with oxycodone CR resulted in a significant reduction in pain intensity compared with placebo for the overall maintenance period ($P = 0.049$), but not at Week 12 of the maintenance period ($P = 0.069$; Fig. 1) (36).

Responder rates were analyzed using the percentage improvement in pain intensity from baseline at Week 12 of the maintenance period; patients who worsened or discontinued early were considered non-responders (36). The distribution of responder rates at Week 12 of the maintenance period was not significantly different between tapentadol ER and placebo; however, a significant difference was observed between oxycodone CR and placebo, in favor of placebo ($P = 0.0022$). A significantly higher percentage of patients in the tapentadol ER group achieved a clinically significant improvement in pain intensity (≥ 50%) (41,42) from baseline at Week 12 of the maintenance period compared with placebo ($P = 0.027$), while a significantly lower percentage of patients in the oxycodone CR group achieved a clinically significant improvement in pain intensity compared with placebo ($P = 0.023$; Table 3) (36). There was no significant difference in the percentage of patients who achieved at least a 30% response between the tapentadol ER and placebo groups ($P = 0.058$); however, a significantly lower percentage of patients achieved at least a 30% improvement in pain intensity in the oxycodone CR group than in the placebo group ($P = 0.002$; Table 3) (36). Compared with placebo, significantly greater improvements on the patient global impression of change (PGIC) from baseline to the end of treatment (using the LOCF for imputation of missing values) were observed with both tapentadol ER ($P < 0.001$) and oxycodone CR ($P = 0.018$) (36). The percentages of patients in each treatment group with



CI, confidence interval; ITT, intent-to-treat; LOCF, last observation carried forward; ER, extended release; CR, controlled release; DPN, diabetic peripheral neuropathy.

Fig. 1. *Least squares mean differences (95% CI) versus placebo in the change from baseline in average pain intensity to A) Week 12 and B) for the overall maintenance period (ITT populations; LOCF).*

a rating of "very much improved" or "much improved" on the PGIC are summarized in Fig. 2.

Treatment with tapentadol ER also resulted in significant improvements in quality of life and function measures compared with placebo for patients with moderate to severe osteoarthritis knee pain (36). With tapentadol ER treatment, significant improvements compared with placebo were observed from baseline to Week 12 in Western Ontario and McMaster Universities (43) (WOMAC) Index of Osteoarthritis Questionnaire pain ($P < 0.001$) and physical function ($P = 0.006$) subscale scores (stiffness subscale, $P = 0.053$) and the WOMAC global score ($P = 0.005$) (36). Treatment with oxycodone CR resulted in significant improvements compared with placebo from baseline to the end of treatment in the WOMAC physical function subscale score ($P = 0.019$) and in the WOMAC global score ($P = 0.038$), but not in the pain ($P = 0.051$) or stiffness ($P = 0.321$) subscale scores (36). Significant improvements were also observed from baseline to the end of treatment with tapentadol ER compared with placebo in the EuroQol-5 Dimension (44) (EQ-5D) health status index score ($P = 0.004$) and Short Form-36 (45) (SF-36) physical functioning, role-physical, bodily pain, and physical component summary scores ($P \leq 0.05$ for all comparisons; Table 4) (36). The difference between oxycodone CR and placebo in the change from baseline to the end of treatment in the EQ-5D health status index score failed to reach statistical significance ($P = 0.449$); significant differences between oxycodone CR and placebo in favor of placebo were observed for the change from baseline to the end of treatment in the SF-36 vitality, social functioning, role-emotional, mental health, and mental component summary scores ($P \leq 0.008$ for all comparisons; Table 4) (36).

A separate randomized, double-blind, phase 3 study of similar design (N = 987; referred to as osteoarthritis study 2 in this review) was conducted in patients with moderate to severe chronic osteoarthritis knee pain. Demographic and baseline characteristics of patients who received at least one dose of study medication (N = 987; safety and ITT population) are presented in Table 2.

Table 3. *Responder Rates Based on at Least 30% and at Least 50% Improvements in Average Pain Intensity (ITT Populations)*[a]

Responder rate	Placebo	Tapentadol ER	Oxycodone CR
Osteoarthritis study 1 (36)			
N	337	344	342
≥ 30% improvement, n (%)	121 (35.9)	148 (43.0)	85 (24.9)[b]
≥ 50% improvement, n (%)	82 (24.3)	110 (32.0)[c]	59 (17.3)[d]
Osteoarthritis study 2			
N	337	319	331
≥ 30% improvement, n (%)	138 (40.9)	131 (41.1)	86 (26.0)[e]
≥ 50% improvement, n (%)	91 (27.0)	99 (31.0)	73 (22.1)
Low back pain study (37)			
N	317	315	326
≥ 30% improvement, n (%)	86 (27.1)	125 (39.7)[f]	99 (30.4)
≥ 50% improvement, n (%)	60 (18.9)	85 (27.0)[c]	76 (23.3)
Pooled analysis (38)			
N	991	978	999
≥ 30% improvement, n (%)	345 (34.8)	404 (41.3)[f]	270 (27.0)[e]
≥ 50% improvement, n (%)	233 (23.5)	294 (30.1)[c]	208 (20.8)
DPN study (40)[g]			
N	192	196	-----
≥ 30% improvement, n (%)	81 (42.2)	105 (53.6)[c]	-----
≥ 50% improvement, n (%)	53 (27.6)	74 (37.8)[c]	-----

ITT, intent-to-treat; ER, extended release; CR, controlled release; DPN, diabetic peripheral neuropathy. [a]All patients who discontinued from the studies prematurely were considered to be non-responders. [b]$P = 0.002$ versus placebo (in favor of placebo). [c]$P < 0.05$ versus placebo. [d]$P = 0.023$ versus placebo (in favor of placebo). [e]$P < 0.001$ versus placebo (in favor of placebo). [f]$P < 0.001$ versus placebo. [g]Oxycodone CR was not included in the DPN study.

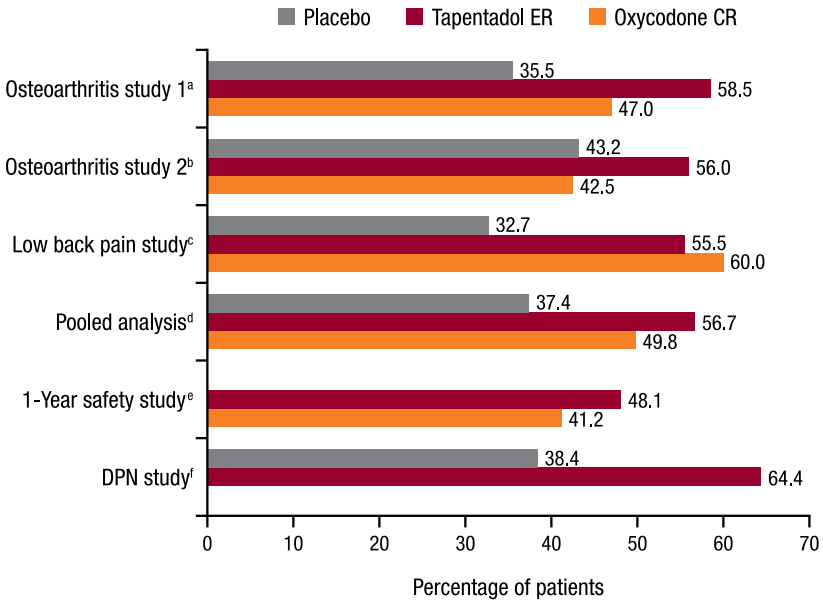


Fig. 2. *Ratings of "very much improved" or "much improved" on the PGIC at endpoint (ITT populations).*

PGIC, Patient Global Impression of Change; ITT, intent-to-treat; ER, extended release; CR, controlled release; DPN, diabetic peripheral neuropathy. [a]Placebo, n = 273; tapentadol ER, n = 258; oxycodone CR, n = 200. [b]Placebo, n = 294; tapentadol ER, n = 248; oxycodone CR, n = 212. [c]Placebo, n = 245; tapentadol ER, n = 236; oxycodone CR, n = 210. [d]Placebo, n = 812; tapentadol ER, n = 742; oxycodone CR, n = 622. [e]Tapentadol ER, n = 819; oxycodone CR, n = 177. [f]Placebo, n = 177; tapentadol ER, n = 180.

Table 4. *EQ-5D Health Status Index and SF-36 Summary Scores (ITT Populations)*

	Tapentadol ER		Oxycodone CR	
Week 12 endpoint[a]	**LSMD vs placebo (SE)**	***P* vs placebo**	**LSMD vs placebo (SE)**	***P* vs placebo**
Osteoarthritis study 1 (36)				
EQ-5D health status index	0.1 (0.02)	0.004	– 0.0 (0.02)	0.449
SF-36 physical component summary	2.8 (0.61)	< 0.001	0.3 (0.61)	0.675
SF-36 mental component summary	– 1.1 (0.66)	0.089	– 3.0 (0.67)	< 0.001
Osteoarthritis study 2				
EQ-5D health status index	0.0 (0.02)	0.114	– 0.0 (0.02)	0.031[b]
SF-36 physical component summary	0.8 (0.63)	0.235	– 0.7 (0.63)	0.266
SF-36 mental component summary	– 0.7 (0.72)	0.342	– 1.9 (0.71)	0.006[b]
Low back pain study (37)				
EQ-5D health status index	0.0 (0.02)	0.020	0.1 (0.02)	0.019
SF-36 physical component summary	2.3 (0.65)	< 0.001	2.3 (0.65)	< 0.001
SF-36 mental component summary	0.1 (0.70)	0.901	– 0.7 (0.69)	0.285
Pooled analysis (38)				
EQ-5D health status index	0.0 (0.01)	< 0.001	– 0.0 (0.01)	0.867
SF-36 physical component summary	1.9 (0.37)	< 0.001	0.6 (0.36)	0.108
SF-36 mental component summary	– 0.6 (0.40)	0.167	– 1.9 (0.40)	< 0.001

EQ-5D, EuroQoL-5 Dimension; SF-36, Short-Form 36; ITT, intent-to-treat; ER, extended release; CR, controlled release; LSMD, least squares mean difference; SE, standard error. [a]LOCF used for imputing missing values. [b]In favor of placebo.

As in the previously described osteoarthritis study (36), 2 primary endpoints were evaluated to accommodate diverse global regulatory requirements. Reductions in average pain intensity (11-point NRS) were numerically larger in the tapentadol ER group than in the placebo or oxycodone CR groups from baseline to Week 12 of the maintenance period and from baseline for the overall maintenance period (using the LOCF for imputing missing pain intensity assessments), but reductions at both endpoints did not reach statistical significance (Week 12, $P = 0.152$; overall maintenance period, $P = 0.135$; Fig. 1). Reductions in average pain intensity from baseline to Week 12 and for the overall maintenance period were also not significantly different between oxycodone CR and placebo (Week 12, $P = 0.279$; overall maintenance period, $P = 0.421$; Fig. 1). Because the difference between the active comparator oxycodone CR and placebo was not statistically significant for either primary endpoint, this study must be considered a failed trial (46); hence, the lack of a statistically significant difference between tapentadol ER and placebo in the primary endpoint is not interpretable. In contrast to these pain intensity results, an analysis of the time to treatment discontinuation due to a lack of efficacy showed that patients in the placebo group discontinued treatment earlier because of a lack of efficacy than patients in the tapentadol ER or oxycodone CR groups ($P \leq 0.027$ for both comparisons).

Similar to the results observed in osteoarthritis study 1, no significant difference was observed in the distribution of responder rates at Week 12 of the maintenance period between the tapentadol ER and placebo groups in osteoarthritis study 2; however, a significant difference was observed between the oxycodone CR and placebo groups, in favor of placebo ($P = 0.017$). The percentage of patients with at least a 30% improvement in pain intensity from baseline to Week 12 of the maintenance period was not significantly different between the tapentadol ER and placebo groups, but a significantly higher percentage of patients in the placebo group than in the oxycodone CR group achieved at least a 30% improvement in pain intensity ($P < 0.001$; Table 3). No significant differences were observed between the tapentadol ER and oxycodone CR groups and the placebo group in the percentage of patients with at least a 50% improvement in pain intensity (Table 3). In addition, significantly greater improvements were observed on the PGIC compared with placebo from baseline to the end of treatment (using the LOCF for imputation of missing values) in the tapentadol ER group ($P = 0.015$), but not in the oxycodone CR group ($P = 0.204$). Ratings of "very much improved" or "much

improved" were reported by a similar percentage of patients in the placebo and oxycodone CR groups and by a numerically higher percentage of patients in the tapentadol ER group (Fig. 2).

No significant differences were observed between tapentadol ER and placebo in the EQ-5D health status index or in any of the SF-36 scores, except for the mental health score ($P = 0.041$, in favor of placebo; Table 4). Significant differences were observed between oxycodone CR and placebo in the EQ-5D health status index and in the SF-36 role-physical, general health, vitality, social functioning, mental health, and mental component summary scores ($P \leq 0.049$ for all comparisons, all in favor of placebo; Table 4).

Chronic Low Back Pain

A randomized (1:1:1), double-blind, phase 3 study evaluated the efficacy of tapentadol ER (100 - 250 mg bid) compared with placebo and oxycodone HCl CR (20 - 50 mg bid) for the management of moderate to severe low back pain (37). This study, like the studies (36) in patients with osteoarthritis knee pain, consisted of a 3-week titration period and a 12-week maintenance period, during which patients attempted to maintain a steady dose but were permitted to make adjustments under the supervision of a physician (37). Details of this study have been published previously (37). Demographic and baseline characteristics for patients who received at least one dose of study drug (safety population, n = 965; ITT population, n = 958) are presented in Table 2 (37).

As with the previously described osteoarthritis studies (36), 2 primary endpoints were evaluated in this study to accommodate global regulatory requirements (37). Treatment with tapentadol ER resulted in significant improvements in pain intensity (11-point NRS; LOCF used for imputing missing pain intensity assessments) compared with placebo from baseline to Week 12 and over the entire maintenance period ($P < 0.001$ for both comparisons; Fig. 1) (37). Significant reductions in pain intensity from baseline compared with placebo were also seen with oxycodone CR for both primary endpoints ($P < 0.001$ for both comparisons; Fig. 1) (37).

At Week 12 of the maintenance period, a significant difference was observed in the distribution of responder rates between tapentadol ER and placebo, in favor of tapentadol ER ($P = 0.004$), while there was no significant difference in the distribution of responder rates between oxycodone CR and placebo ($P = 0.090$) (37). A significantly higher percentage of patients who received tapentadol ER had at least a 50% improvement in pain intensity at Week 12 of the maintenance period compared with placebo ($P = 0.016$), while there was no significant difference between the oxycodone CR and placebo groups ($P = 0.174$; Table 3) (37). A similar result was observed in the percentage of patients who achieved at least a 30% improvement in pain intensity. The percentage of patients who achieved at least a 30% improvement in pain intensity at Week 12 of the maintenance period was significantly higher in the tapentadol ER group than in the placebo group ($P< 0.001$), while the difference between the oxycodone CR and placebo groups was not significant ($P = 0.365$; Table 3) (37). At endpoint, PGIC ratings were significantly better following treatment with tapentadol ER or oxycodone CR compared with placebo ($P < 0.001$ for both comparisons) (37). The percentages of patients in each treatment group with a rating of "very much improved" or "much improved" on the PGIC are summarized in Fig. 2.

In addition to the previously described improvements in pain intensity, treatment with tapentadol ER was also associated with significant improvements in function and quality of life measures compared with placebo. Significant improvements from baseline to endpoint were observed in the Brief Pain Inventory (47) (BPI) pain interference subscale score, pain subscale score, and total score with tapentadol ER compared with placebo ($P < 0.001$ for all comparisons) (37). Significant improvements from baseline to Week 12 were also observed with tapentadol ER in the EQ-5D health status index ($P = 0.020$) and the SF-36 physical functioning, role-physical, bodily pain, vitality, and physical component summary scores ($P \leq 0.025$ for all comparisons; Table 4) (37). Significant improvements from baseline to Week 12 with oxycodone CR were observed in the EQ-5D health status index ($P = 0.019$) and in the SF-36 role-physical, bodily pain, and physical component summary scores ($P < 0.0001$ for all comparisons; Table 4) (37).

Chronic Osteoarthritis Knee Pain or Low Back Pain (Pooled Analysis)

A pooled analysis (38) of efficacy data (safety population, n = 2,974; ITT population, n = 2,968) was performed using results from the 3 previously described 15-week, randomized, double-blind studies of tapentadol ER (100 - 250 mg bid) compared with placebo and oxycodone HCl CR (20 - 50 mg bid) in patients with moderate to severe osteoarthritis knee pain (36) or low back pain (37). Demographic and baseline characteristics for the total pooled analysis population are summarized in Table 2.

Pain intensity (11-point NRS) was significantly reduced from baseline to Week 12 of the maintenance period (using the LOCF for imputing missing pain intensity values) compared with placebo with both tapentadol ER ($P < 0.001$) and oxycodone CR ($P = 0.002$; Fig. 1) (38). Compared with placebo, significant reductions in pain intensity from baseline were also observed for the overall maintenance period (using the LOCF for imputing missing pain intensity values) with both tapentadol ER and oxycodone CR ($P < 0.001$ for both comparisons; Fig. 1) (37). Further analyses demonstrated that the efficacy of tapentadol ER was non-inferior to that of oxycodone CR at both Week 12 and for the overall maintenance period (using LOCF for imputing missing pain intensity values), based on a 50% retention of the oxycodone CR analgesic effect ($P < 0.001$ for both comparisons) (37). Sensitivity analyses using different methods of imputation (baseline observation carried forward [BOCF], worst observation carried forward, modified BOCF, and placebo mean imputation) also showed that the efficacy of tapentadol ER was non-inferior to that of oxycodone CR for both primary endpoints ($P < 0.001$ for all comparisons) (38).

The distribution of responder rates (with patients who worsened or discontinued early considered non-responders) at Week 12 of the maintenance period was significantly better with tapentadol ER than with both placebo ($P = 0.006$) and oxycodone CR ($P < 0.001$) (38). In contrast, the distribution of responder rates at Week 12 was significantly better with placebo than with oxycodone CR ($P = 0.023$) (38). A significantly higher percentage of patients in the tapentadol ER group reported at least a 50% improvement in pain intensity from baseline to Week 12 of the maintenance period compared with both placebo and oxycodone CR ($P < 0.001$ for both comparisons; Table 3) (38). At least a 30% improvement in pain intensity from baseline to Week 12 of the maintenance period was also observed for a significantly higher percentage of patients in the tapentadol ER group than in the placebo group ($P = 0.003$) and oxycodone CR group ($P < 0.001$; Table 3). Ratings on the PGIC were significantly better in both the tapentadol ER and oxycodone CR groups compared with placebo ($P < 0.001$ for both comparisons), as well as in the tapentadol ER group compared with oxycodone CR ($P = 0.001$) (38). The percentages of patients in each treatment group with a rating of "very much improved" or "much improved" on the PGIC are summarized in Fig 2.

In this pooled analysis, significant improvements in quality of life measures were also observed with tapentadol ER treatment. Significant improvements from baseline to endpoint were observed in the EQ-5D health status index with tapentadol ER compared with both placebo and oxycodone CR ($P < 0.001$ for both comparisons) (38). Treatment with tapentadol ER was associated with significant improvements from baseline to endpoint in the SF-36 physical functioning, role-physical, bodily pain, vitality, and physical component summary scores compared with placebo ($P \leq 0.041$ for all comparisons; Table 4). Significant improvements from baseline to endpoint were also observed in all SF-36 scores with tapentadol ER compared with oxycodone CR ($P \leq 0.048$ for all comparisons), except the general health score for which the improvement observed with tapentadol ER compared with oxycodone CR failed to reach statistical significance ($P = 0.061$) (38).

Chronic Osteoarthritis or Low Back Pain (One-year Study)

An open-label, randomized (4:1), phase 3 study (39) evaluated the efficacy of treatment with tapentadol ER (100 - 250 mg bid) compared with oxycodone HCl CR (20 - 50 mg bid) for up to one year in patients (safety population, n = 1,121; ITT population, n = 1,095) with moderate to severe osteoarthritis pain or low back pain (39). The design of this study is summarized in Table 1. Demographic and baseline characteristics for all patients who received at least one dose of study drug are presented in Table 2. Following a one-week titration period, patients received tapentadol ER or oxycodone CR during a 51-week maintenance period. Patients were permitted to adjust their doses under the supervision of a physician throughout the study to maintain an optimal balance of efficacy and tolerability (39). Details of the design of this long-term safety study have been published (39).

Mean (standard error) pain intensity scores (11-point NRS) in the tapentadol ER and oxycodone CR groups, respectively, decreased from 7.6 (0.04) and 7.6 (0.11) at baseline to 4.4 (0.09) and 4.5 (0.17) at endpoint (39). For tapentadol ER and oxycodone CR, respectively, ratings of "excellent," "very good," or "good" were reported on the global assessment of study medication by 75.1% and 72.3% of patients and 77.3% and 72.3% of investigators at the end of treatment (39). On the PGIC, a rating of "very much improved" or "much improved" was reported by 48.1% of patients who received tapentadol ER and 41.2% of patients who received oxycodone CR (Fig. 2) (39).

Efficacy of Tapentadol ER for the Management of Chronic Neuropathic Pain Associated with DPN

The efficacy of tapentadol ER has also been demonstrated in a neuropathic pain model (40). A randomized-withdrawal, placebo-controlled, phase 3 study evaluated the efficacy of tapentadol ER (100 - 250 mg bid) for the management of moderate to severe chronic pain associated with DPN (40). During an initial 3-week, open-label titration period, patients were titrated to their optimal dose of tapentadol ER (100 - 250 mg bid) in terms of pain reduction and tolerability (40). Patients who tolerated the study drug and had at least a one-point improvement in average pain intensity (11-point NRS) from pre-titration entered a 12-week, double-blind maintenance period and were randomized (1:1) to placebo or the optimal dose of tapentadol ER determined during the titration period (40). Full details of the study design have been published previously (40). Demographic and baseline characteristics for patients (double-blind safety and ITT population, n = 389) who were randomized to treatment in the double-blind maintenance period and received at least one dose of study drug are presented in Table 2.

From the start to the end of the 3-week, open-label titration period, when all patients received tapentadol ER, mean (SD) pain intensity decreased markedly, from 7.3 (1.43) at the start of the open-label titration period (n = 582) to 3.5 (1.89) at the start of the double-blind treatment period (n = 388) in the open-label safety population. Subsequently, over the course of the double-blind maintenance period, pain intensity worsened for patients randomized to placebo (n = 193), while improvements in pain intensity achieved during the open-label treatment period were maintained for patients randomized to continue on tapentadol ER (n = 196) (40). A significant difference in the change in pain intensity from the start of the maintenance period to Week 12 of the maintenance period was observed between placebo and tapentadol ER ($P < 0.001$; Fig. 1) (40). The distribution of responder rates (with patients who worsened or discontinued early considered non-responders) from pre-titration to Week 12 of the maintenance period was significantly different between tapentadol ER and placebo, in favor of tapentadol ER ($P = 0.032$) (40). From pre-titration to Week 12 of the maintenance period, a significantly higher percentage of patients in the tapentadol ER group compared with the placebo group experienced at least a 50% improvement in pain intensity ($P = 0.028$) and at least a 30% improvement in pain intensity ($P = 0.017$; Table 3) (40). At the end of the maintenance period, PGIC ratings were significantly better for patients who received tapentadol ER than for patients who received placebo ($P < 0.001$) (40). The percentages of patients in each treatment group with a rating of "very much improved" or "much improved" on the PGIC are summarized in Fig. 2.

Tolerability of Tapentadol ER Compared with Oxycodone CR

In studies (36,37,39) of tapentadol ER for the management of moderate to severe osteoarthritis pain or low back pain and in a pooled analysis (38) of data from these studies, the incidence of gastrointestinal disorders was lower in the tapentadol ER (100 - 250 mg bid) group than in the oxycodone HCl CR group (20 - 50 mg bid; Table 5). In osteoarthritis study 1 (36), significantly lower incidences of constipation and the composite of nausea and/or vomiting were observed in the tapentadol ER group than in the oxycodone CR group ($P < 0.001$ for both comparisons); in osteoarthritis study 2 and the low back pain study (37), the odds of experiencing either of these gastrointestinal treatment-emergent adverse events (TEAEs) was significantly lower with tapentadol ER than with oxycodone CR ($P < 0.001$ for all comparisons). In the pooled analysis (38), the incidences of the following gastrointestinal TEAEs were all significantly lower with tapentadol ER than with oxycodone CR: constipation, nausea, vomiting, and the composite of nausea and/or vomiting ($P < 0.001$ for all comparisons; Table 5). In the one-year study (39) in patients with chronic osteoarthritis or low back pain, incidences of constipation, nausea, and vomiting were numerically lower in the tapentadol ER group than in the oxycodone CR group, but these differences were not tested for statistical significance (Table 5).

Side effects commonly associated with opioid therapy, particularly gastrointestinal side effects, often lead patients to discontinue therapy (26,27). Rates of treatment discontinuations overall and treatment discontinuations due to adverse events (AEs) were lower with tapentadol ER (100 - 250 mg bid) than with oxycodone HCl CR (20 - 50 mg bid) in the 4 separate studies (36,37,39) in patients with osteoarthritis or low back pain and in the pooled analysis (38) of data from 3 of these studies. Across the individual studies and the pooled analysis(36-39), the incidence of treatment discontinuations overall ranged from 41.7% to 53.8% with tapentadol ER and from 59.5% to 65.0% with oxycodone CR. AEs were the most common reason for

discontinuation in both active treatment groups across all of these studies, and the percentages of patients discontinuing treatment because of AEs are summarized in Fig. 3 (36-39).

Both tapentadol ER and oxycodone CR have been associated with a low incidence of withdrawal following abrupt discontinuation of up to one year of treatment. In the one-year study that compared the efficacy and safety of tapentadol ER and oxycodone CR in patients with osteoarthritis pain or low back pain (39), the majority of patients had no opioid withdrawal in both the tapentadol ER group (77.6%) and the oxycodone CR group (72.7%), based on results from the Clinical Opiate Withdrawal Scale (COWS) questionnaire (48), which was completed 2 to 4 days after study drug discontinuation. All reported opioid withdrawal was mild or moderate. Results from a separate withdrawal questionnaire, the Subjective Opiate Withdrawal Scale (SOWS) (49), were consistent with the results of the COWS questionnaire (39). Similar results were observed in the three 15-week studies (36,37) of tapentadol ER and oxycodone CR for the management of moderate to severe chronic low back or osteoarthritis pain.

Discussion

The pharmacological management of chronic pain is often difficult because of the extended duration of therapy and differences between patients' responses to treatment (4). Chronic pain with a neuropathic component is particularly difficult to manage with currently available analgesics (16,17). Chronic pain management is further complicated by the range of side effects associated with opioids, which often lead to discontinuation of therapy.

In randomized, controlled studies (36-38,50), tapentadol ER (100 - 250 mg bid) has been shown to be efficacious for the management of moderate to severe chronic pain (36-38,50) in patients with osteoarthritis knee pain (36), low back pain (37), and neuropathic pain associated with DPN (40). Based on pooled results from 2 studies of patients with osteoarthritis pain and one study of patients with low back pain, tapentadol ER (100 - 250 mg bid) provided efficacy that was non-inferior to that provided by oxycodone HCl CR (20 - 50 mg bid), while the incidences of the common opioid-related gastrointestinal AEs of nausea, vomiting, constipation, and nausea or vomiting were significantly higher in the oxycodone CR group than in the tapentadol ER group (38). These results were supported by those of individual phase 3 studies (36,37,39) which showed similar reductions in

Table 5. *Incidence of Common Opioid-induced Gastrointestinal TEAEs with Tapentadol ER Versus Oxycodone CR (Safety Populations)*

TEAE, n (%)	Tapentadol ER	Oxycodone CR
Osteoarthritis study 1 (36)		
n	344	342
Gastrointestinal TEAEs	148 (43.0)	230 (67.3)
Nausea	74 (21.5)	125 (36.5)
Vomiting	18 (5.2)	61 (17.8)
Constipation	65 (18.9)[a]	126 (36.8)
Osteoarthritis study 2		
n	319	331
Gastrointestinal TEAEs	133 (41.7)	224 (67.7)
Nausea	65 (20.4)	124 (37.5)
Vomiting	33 (10.3)	86 (26.0)
Constipation	57 (17.9)	116 (35.0)
Low back pain study (37)		
n	318	328
Gastrointestinal TEAEs	139 (43.7)	203 (61.9)
Nausea	64 (20.1)	113 (34.5)
Vomiting	29 (9.1)	63 (19.2)
Constipation	44 (13.8)	88 (26.8)
Pooled analysis (38)		
n	980	1,001
Gastrointestinal TEAEs	420 (42.9)	657 (65.6)
Nausea	203 (20.7)[a]	362 (36.2)
Vomiting	80 (8.2)[a]	210 (21.0)
Constipation	166 (16.9)[a]	330 (33.0)
One-year Safety Study (39)		
n	894	223
Gastrointestinal TEAEs	465 (52.0)	143 (64.1)
Nausea	162 (18.1)	74 (33.2)
Vomiting	63 (7.0)	30 (13.5)
Constipation	202 (22.6)	86 (38.6)

TEAE, treatment-emergent adverse event; ER, extended release; CR, controlled release.

[a] $P < 0.001$ versus oxycodone CR.

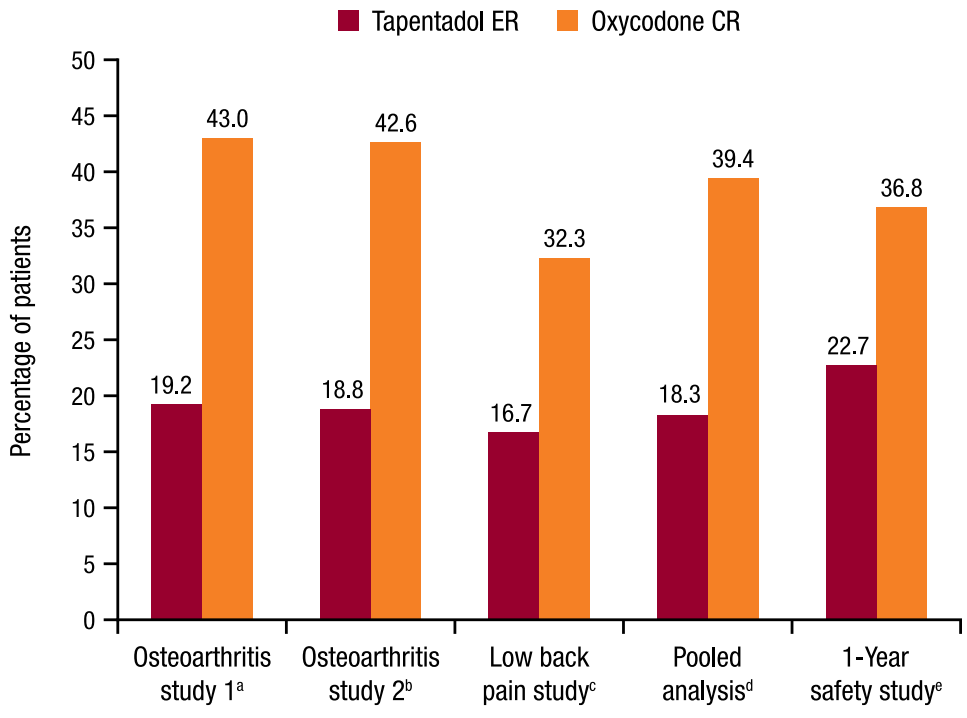


Fig. 3. *Incidences of treatment discontinuations related to AEs (safety populations).*
AE, adverse event; ER, extended release; CR, controlled release. [a]Tapentadol ER, n = 344; oxycodone CR, n = 342. [b]Tapentadol ER, n = 319; oxycodone CR, n = 331. [c]Tapentadol ER, n = 318; oxycodone CR, n = 328. [d]Tapentadol ER, n = 980; oxycodone CR, n = 1,001. [e]Tapentadol ER, n = 894; oxycodone CR, n = 223.

pain intensity for tapentadol ER (100 - 250 mg bid) and oxycodone HCl CR (20 - 50 mg bid) for up to one year of therapy with reduced incidences of gastrointestinal side effects for patients who received tapentadol ER. In addition, treatment discontinuations overall and discontinuations resulting from AEs were lower with tapentadol ER treatment than with oxycodone CR treatment for osteoarthritis or low back pain (36-39). Differences in the design and duration of these phase 3 studies may limit comparisons of the efficacy results; nevertheless, results from these studies support the broad efficacy of tapentadol ER for different types of nociceptive and neuropathic pain.

The 2 mechanisms of action of tapentadol ER, μ-opioid receptor agonism and norepinephrine reuptake inhibition (32,33), may contribute to the demonstrated efficacy of tapentadol ER for both nociceptive and neuropathic pain, as well as the reduction in incidences of common opioid-related gastrointestinal side effects with tapentadol ER compared with oxycodone CR. Taken together, these results indicate that tapentadol ER (100 - 250 mg bid) is effective and well tolerated for the management of moderate to severe chronic nociceptive pain of different etiologies and neuropathic pain related to DPN. Tapentadol ER (100 -250 mg bid) provides efficacy that is similar to that of oxycodone HCl CR (20 - 50 mg bid) for patients with osteoarthritis and low back pain while offering improved gastrointestinal tolerability and improved compliance with therapy, which may be particularly important for patients on long-term analgesic therapy for chronic pain.

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