Gastrointestinal Tolerability of Tapentadol Extended Release in Patients With Chronic Low Back Pain: Results of a Randomized, Double-blind, Active- and Placebo-controlled Phase 3 Study

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ABSTRACT

Objective: To assess the efficacy and safety, including gastrointestinal tolerability, of tapentadol extended release (ER) for managing moderate to severe chronic low back pain.

Design: Patients were randomized to receive controlled, adjustable, twice-daily doses of tapentadol ER (100-250 mg), oxycodone HCl controlled release (CR; 20-50 mg), or placebo over a 12-week maintenance period. The maintenance period was preceded by a 3-week titration period to establish an optimal, stable dose that balanced efficacy and tolerability.

Setting: Clinical research facilities in the United States, Australia, and Canada.

Participants: Adult patients with moderate to severe chronic low back pain.

Main Outcome Measures: The primary efficacy endpoints were the change in average pain intensity (11-point numerical rating scale; 0 = "no pain" to 10 = "pain as bad as you can imagine") from baseline to Week 12 of the maintenance period or through the entire 12-week maintenance period. The last observation carried forward was used for imputing missing values. Treatment-emergent adverse events (TEAEs) were recorded.

Results: Patients (intent-to-treat population, n = 958) had significantly greater improvements in average pain intensity from baseline with tapentadol ER and oxycodone CR than with placebo at Week 12 of the maintenance period (least squares mean difference vs placebo: tapentadol ER, –0.8, P <0.001; oxycodone CR, –0.9, P <0.001) and throughout the 12-week maintenance period (tapentadol ER, –0.7, P <0.001; oxycodone CR, –0.8, P <0.001). In the placebo, tapentadol ER, and oxycodone CR groups, 59.6%, 75.5%, and 84.8% of patients, respectively, reported at least 1 TEAE; 26.3%, 43.7%, and 61.9% reported gastrointestinal-related TEAEs. Incidences of gastrointestinal-related TEAEs leading to study discontinuation were 1.3% in the placebo group, 5.3% in the tapentadol ER group, and 18.3% in the oxycodone CR group. In patients who reported TEAEs of nausea, vomiting, and constipation, the mean percentage of days that these TEAEs occurred was numerically lower in the placebo and tapentadol ER groups than in the oxycodone CR group (nausea, 20.6%, 24.7%, and 38.6%; vomiting, 13.1%, 14.9%, and 24.0%; constipation, 32.4%, 47.6%, and 51.3%, respectively).

Conclusions: Tapentadol ER (100-250 mg bid) provided effective analgesia for moderate to severe chronic low back pain compared with placebo and had improved gastrointestinal tolerability as reflected by lower frequencies of and fewer study discontinuations due to TEAEs than oxycodone HCl CR (20-50 mg bid).

INTRODUCTION

- The utility of pure μ-opioid analgesics for the management of chronic pain is limited by the occurrence of adverse effects such as nausea, vomiting, and constipation[1]
  - Opioid-induced constipation is particularly problematic for patients with chronic pain because, unlike other common opioid-related adverse effects, constipation rarely improves over time[2]
  - These adverse effects often cause patients to discontinue opioid therapy, leading to disruption of pain relief[3]
- Tapentadol is an oral analgesic with 2 mechanisms of action, μ-opioid receptor agonism and norepinephrine reuptake inhibition[4,5]
- The immediate-release formulation of tapentadol is approved in the United States for the relief of moderate to severe acute pain in patients 18 years or older
  - Results of phase 3 studies in acute postoperative pain[6] and pain due to end-stage joint disease[7] have shown that tapentadol immediate release (IR; 50, 75, or 100 mg every 4-6 hours) provides pain relief similar to that provided by oxycodone HCl IR (10 or 15 mg every 4-6 hours), but with fewer discontinuations from treatment due to adverse events (AEs) and with improved gastrointestinal tolerability
- Immediate-release and prolonged-release formulations of tapentadol have been submitted for approval in Europe

OBJECTIVE

- To evaluate the efficacy and gastrointestinal tolerability of orally administered tapentadol extended release (ER) 100 to 250 mg bid over 15 weeks in patients experiencing moderate to severe chronic low back pain

METHODS

Patients

- Main inclusion criteria
  - Men and non-pregnant, non-lactating women at least 18 years of age diagnosed with non-malignant low back pain for at least 3 months
  - Mean baseline score for average pain in the previous 12 hours of at least 5 on an 11-point numerical rating scale (NRS; 0 = "no pain" to 10 = "pain as bad as you can imagine") on pain assessments conducted twice daily over the 72 hours prior to randomization
  - Receiving analgesic treatment for low back pain for at least 3 months prior to screening
    - If receiving opioid therapy, taking daily doses equivalent to 160 mg or less of oral morphine
  - Dissatisfaction with current therapy
- Main exclusion criteria
  - History of alcohol or drug abuse
  - History of chronic hepatitis B or C or human immunodeficiency virus
  - Lifelong history of seizure disorder or epilepsy; traumatic brain injury, stroke, transient ischemic attack, or brain neoplasm within the past year; or a history of malignancy within the past 2 years, with the exception of successfully treated basal cell carcinoma
  - Clinically relevant history of hypersensitivity, allergy, or contraindication to oxycodone or acetaminophen (or their ingredients)
  - Uncontrolled hypertension
  - Moderate or severe hepatic impairment or severe renal impairment
  - Surgery or other painful procedure scheduled during the study or surgery in the low back area within 3 months prior to screening
  - Significant disease, including unstable cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurologic, psychiatric, or metabolic disturbances, or other conditions, such as anatomic deformities, significant skin conditions, or fibromyalgia, that could compromise efficacy and safety evaluations
- Concomitant analgesic use, with the exception of allowed doses of acetaminophen, was prohibited during the study
- The following medications were prohibited during the study and within 14 days prior to screening: neuroleptics, monoamine oxidase inhibitors, anticonvulsants, antiparkinsonian drugs, tricyclic antidepressants, and serotonin norepinephrine reuptake inhibitors (SNRIs)
  - SNRIs, neuroleptics, anticonvulsants, antiparkinsonian drugs, and tricyclic antidepressants were prohibited because their analgesic effects could confound the primary assessment of analgesic efficacy
  - Medications other than those listed above, such as selective serotonin reuptake inhibitors, were permitted as concomitant medications for patients with diagnosed psychiatric or neurologic conditions requiring treatment (eg, major depressive disorder) if patients were on a controlled, stable dose for at least 3 months prior to randomization
- Systemic steroid therapy was prohibited during the study and within 4 weeks to 6 months prior to screening, depending on the route of administration

Study Design

- This was a randomized, multicenter, double-blind, active- and placebo-controlled phase 3 trial
- The trial included a screening period (up to 14 days), a washout period (3-7 days) during which patients discontinued all prior analgesic medication and no analgesic medication was permitted, a titration period (3 weeks), a maintenance period (12 weeks), and a follow-up period (up to 14 days)
  - During the first week of the titration period, patients were allocated randomly in a 1:1:1 ratio to receive placebo bid, tapentadol ER 50 mg bid, or oxycodone HCl controlled release (CR) 10 mg bid for the first 3 days; doses were increased to tapentadol ER 100 mg bid or oxycodone HCl CR 20 mg bid for the next 4 days
    - For the remainder of the titration period, doses could be increased in increments of tapentadol ER 50 mg bid or oxycodone HCl CR 10 mg bid (maximum doses: tapentadol ER 250 mg bid and oxycodone HCl CR 50 mg bid) over 3-day intervals; doses could be titrated downward to minimum doses of tapentadol ER 100 mg bid or oxycodone HCl CR 20 mg bid with no time restriction. The aim was to find an optimal dose balancing efficacy and tolerability for each individual
    - During the titration period, up to 1,000 mg per day of acetaminophen was allowed as additional analgesia except for the last 3 days of that period
  - During the maintenance period, doses could be adjusted under a physician's supervision to maintain optimal therapeutic benefit; however, adjustments were to be kept to a minimum, and no additional analgesic medication for low back pain was permitted

Study Evaluations

- Efficacy was evaluated as the change from baseline in average pain intensity at Week 12 of the maintenance period and as the change from baseline in average pain intensity over the entire 12-week maintenance period
- Pain intensity was measured twice daily (in the morning and in the evening) on an 11-point NRS to indicate the level of average pain experienced over the previous 12 hours
- AEs and discontinuations were monitored and documented throughout the study

Statistical Analyses

- Assuming a mean treatment group difference of –0.7 for the change from baseline in pain intensity with a standard deviation of 2.7, it was estimated that 314 patients per treatment group would provide 90% power to show a significant difference between the tapentadol ER group and the placebo group at $\alpha = 0.05$ for the primary efficacy endpoint
- The safety and intent-to-treat populations were defined as all patients who were randomized and received at least 1 dose of study drug
- Efficacy was evaluated using an analysis of covariance model with 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
  - Linear interpolation was used for the imputation of intermittent missing pain intensity scores; all other missing pain intensity values were imputed using the last observation carried forward
- Incidences of treatment-emergent AEs (TEAEs) were compared between the tapentadol ER and oxycodone CR treatment groups in a post hoc analysis of data from this study using the Cochran-Mantel-Haenszel test
- Among patients who experienced nausea, vomiting, and constipation, the mean percentage of days that patients experienced these TEAEs was calculated as follows: 100 • (number of days with the AE/number of days in the double-blind treatment period)

RESULTS

Patients

- 981 patients were randomly assigned to treatment
  - Of these, 965 received at least 1 dose of study drug and were included in the safety population
  - The efficacy analysis was performed using data from 958 patients; 23 patients from the randomized population were excluded because they did not receive the study drug, they were randomized twice, or there were major audit findings at their study site
  - Baseline and demographic characteristics were comparable across all treatment groups (**Table 1**)

Table 1. Baseline and Demographic Characteristics (Safety Population)

Characteristic	Placebo (n = 319)	Tapentadol ER (n = 318)	Oxycodone CR (n = 328)
Gender, n (%)			
Male	135 (42.3)	124 (39.0)	147 (44.8)
Female	184 (57.7)	194 (61.0)	181 (55.2)
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/ethnicity, n (%)[a]			
White	237 (74.3)	229 (72.0)	241 (73.5)
Black or African descent	50 (15.7)	62 (19.5)	55 (16.8)
Hispanic or Latino	21 (6.6)	18 (5.7)	21 (6.4)
Other	11 (3.4)	9 (2.8)	11 (3.3)
Body mass index,[b] kg/m^2			
Mean (SD)	31 (8.1)	32 (9.1)	31 (7.4)
Baseline pain intensity[c]			
Mean (SD)	7.6 (1.33)	7.5 (1.33)	7.5 (1.21)
Pain intensity category,[c,d] n (%)			
Moderate	42 (13.2)	35 (11.1)	33 (10.2)
Severe	276 (86.8)	280 (88.9)	292 (89.8)
Prior opioid use,[e] n (%)			
No	147 (46.1)	140 (44.0)	163 (49.7)
Yes	172 (53.9)	178 (56.0)	165 (50.3)

ER, extended release; CR, controlled release; SD, standard deviation; NRS, numerical rating scale.
[a]Percentages may not total 100.0% because of rounding.
[b]n = 316 for placebo; n = 317 for tapentadol ER; n = 328 for oxycodone CR.
[c]n = 318 for placebo; n = 315 for tapentadol ER; n = 325 for oxycodone CR.
[d]Moderate pain intensity, NRS ≥4 to <6; severe pain intensity, NRS ≥6.
[e]Defined as taking opioids during the 3 months prior to screening.

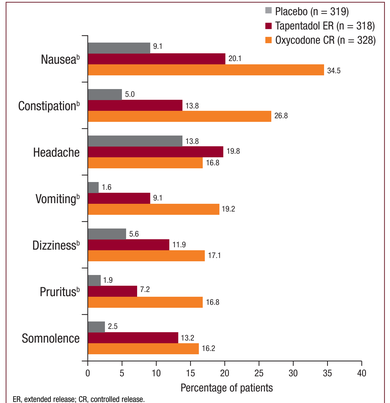
- The overall rate of treatment discontinuation during the double-blind treatment period was 49.5% in the placebo group, 45.9% in the tapentadol ER group, and 56.7% in the oxycodone CR group
  - The percentage of patients who discontinued treatment because of AEs was 4.7% in the placebo group, 16.7% in the tapentadol ER group, and 32.3% in the oxycodone CR group

Efficacy

- Patients who received tapentadol ER or oxycodone CR reported statistically significant improvements in average pain intensity relative to placebo at Week 12 of the maintenance period and for the overall 12-week maintenance period
  - At Week 12 of the maintenance period, the least squares mean difference from placebo (95% confidence interval [CI]) was –0.8 (–1.22 to –0.47; P <0.001) for tapentadol ER and –0.9 (–1.24 to –0.49; P <0.001) for oxycodone CR
  - Over the entire 12-week maintenance period, the least squares mean difference from placebo (95% CI) was –0.7 (–1.06 to –0.35; P <0.001) for tapentadol ER and –0.8 (–1.16 to –0.46; P <0.001) for oxycodone CR

Safety

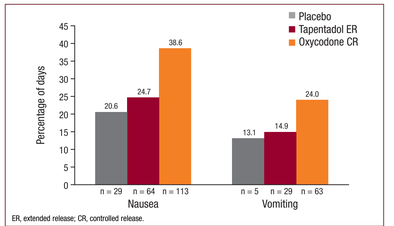
- The incidence of TEAEs was 59.6% in the placebo group, 75.5% in the tapentadol ER group, and 84.8% in the oxycodone CR group
- The most common TEAEs experienced by ≥10% of patients in any treatment group are provided in **Figure 1**
  - Patients who received tapentadol ER experienced a significantly lower incidence of nausea, vomiting, constipation, dizziness, and pruritus (all P <0.05) than patients who received oxycodone CR
  - Patients who received tapentadol ER experienced a numerically lower incidence of somnolence and a numerically higher incidence of headache than patients who received oxycodone CR
  - In the placebo, tapentadol ER, and oxycodone CR groups, respectively, 26.3%, 43.7%, and 61.9% of patients reported gastrointestinal-related TEAEs
  - The percentage of patients in the tapentadol ER group with TEAEs of constipation (13.8%) or the composite of nausea and/or vomiting (23.6%) was significantly lower than in the oxycodone CR group (26.8% and 40.5%, respectively; P <0.001 for both)



ER, extended release; CR, controlled release.
[a]Incidence is based on the number of patients experiencing at least 1 adverse event, not the number of events.
[b]P <0.05 for tapentadol ER versus oxycodone CR.

Figure 1. Treatment-emergent adverse events occurring in ≥10% of patients (safety population).[a]

- Among patients with TEAEs of nausea and/or vomiting, the mean percentage of days that these TEAEs occurred was numerically lower in the tapentadol ER group than in the oxycodone CR group (nausea: 20.6%, 24.7%, and 38.6%; vomiting: 13.1%, 14.9%, and 24.0%, respectively, for placebo, tapentadol ER, and oxycodone CR; **Figure 2**)



ER, extended release; CR, controlled release.

Figure 2. Mean percentage of days with nausea and/or vomiting (safety population).

- Among patients with a TEAE of constipation, the mean percentage of days that constipation occurred was numerically lower in the placebo (32.4%) and tapentadol ER (47.6%) groups than in the oxycodone CR group (51.3%)
- Incidences of gastrointestinal-related TEAEs that led to study discontinuation were 1.3% for placebo, 5.3% for tapentadol ER, and 18.3% for oxycodone CR
- During the treatment period and within 30 days of the last dose of study drug, the incidence of serious AEs was low among groups (0.9% in the placebo group, 2.2% in the tapentadol ER group, and 3.4% in the oxycodone CR group), and no deaths were reported
- No specific serious AE was reported by more than 1 patient per treatment group

CONCLUSIONS

- **Compared with placebo, tapentadol ER (100-250 mg bid) and oxycodone HCl CR (20-50 mg bid) provided effective relief of moderate to severe chronic low back pain**
- **Tapentadol ER (100-250 mg bid) had better gastrointestinal tolerability than oxycodone HCl CR (20-50 mg bid), with patients experiencing lower incidences of discontinuation due to gastrointestinal-related TEAEs and significantly lower incidences of constipation and the composite of nausea and/or vomiting**
  - **Among patients who experienced nausea, vomiting, and/or constipation, the mean percentage of days patients experienced these TEAEs was lower in the tapentadol ER group than in the oxycodone CR group**
- **The effective analgesia provided by tapentadol ER, combined with an improved gastrointestinal tolerability profile compared with oxycodone CR, offers a new therapeutic option for the management of moderate to severe chronic low back pain**

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