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Randomized Trial

Dose Conversion Between Tapentadol Immediate and Extended Release for Low Back Pain

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Background: Tapentadol, a novel, centrally acting analgesic with 2 mechanisms of action (μ-opioid receptor agonism and norepinephrine reuptake inhibition), has been developed in an immediate-release (IR) and an extended-release (ER) formulation. Determination of the safety and equianalgesic ratios for conversion between formulations is important for physicians with patients taking tapentadol IR who may want to switch to tapentadol ER, or vice versa, for any reason.

Objectives: To test whether the total daily dose (TDD) of tapentadol IR may be directly converted into a comparable TDD of tapentadol ER, and vice versa, with equivalent efficacy and comparable safety.

Study Design: Randomized, double-blind, 2-period (2 weeks each) crossover study.

Setting: Study centers (N = 13) in the United States.

Methods: Patients with moderate to severe chronic low back pain received tapentadol IR 50, 75, or 100 mg every 4 or 6 hours (maximum TDD, 500 mg) during the 3-week open-label period to identify an optimal, stable dose of tapentadol IR for each patient. Patients were then randomized in a 1:1 ratio to receive, during the first 2-week double-blind period, either the optimal dose of tapentadol IR identified during the open-label period or a TDD of tapentadol ER (100, 150, 200, or 250 mg bid) that was as close as possible to the TDD of tapentadol IR from the open-label period. During a subsequent, 2-week double-blind period, patients received whichever formulation was not received during the first double-blind period. The primary endpoint was the mean average daily pain intensity (on an 11-point numerical rating scale) during the last 3 days of each double-blind treatment period. If the 95% confidence intervals (CIs) of the least squares mean difference between formulations were within the range of –2 to 2, the formulations were considered equivalent.

Results: Of the 88 patients who were randomized, 72 completed both double-blind treatments, and 60 were included in the per-protocol analysis. The mean (standard deviation [SD]) pain intensity score decreased from 7.3 (1.19) pre-treatment to 4.2 (2.13) after 3 weeks of open-label treatment with tapentadol IR and remained constant throughout double-blind treatment (3.9 or 4.0 each week) for both formulations. The mean (SD) of the average pain intensity scores over the last 3 days of double-blind treatment was 3.9 (2.17) with tapentadol IR and 4.0 (2.29) with tapentadol ER, for an estimated difference of 0.1 (95% CI, –0.09 to 0.28). For both tapentadol IR and tapentadol ER, the median TDD administered was 300.0 mg, and acetaminophen was used by 39.5% and 45.2% of patients, respectively. The incidence of treatment-emergent adverse events during double-blind treatment was similar between the tapentadol IR and tapentadol ER groups.

Limitations: Use of rescue medication theoretically could have influenced pain measurements, but in practice, pain measurements did not differ between treatments.

Conclusions: Approximately equivalent TDDs of tapentadol IR and tapentadol ER provided equivalent analgesic efficacy for the relief of moderate to severe chronic low back pain and were similarly well tolerated, allowing for direct conversion between the 2 formulations.

Key words: Chronic low back pain, conversion, efficacy, equivalence, extended release, immediate release, opioid, safety, tapentadol

Clinical Trial Registration: NCT00594516

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Low back pain is a common worldwide health problem (1). Estimates based on national survey data suggest that more than 26% of US adults experienced low back pain that lasted at least one day during the past 3 months (2), and lifetime prevalence rates of low back pain in Western societies are more than 70% (3). Sustained-release opioid formulations are often used to manage chronic low back pain, particularly for patients who have failed to respond to other therapies (4).

Tapentadol is an orally administered, centrally acting analgesic with 2 mechanisms of action, μ-opioid receptor agonism and norepinephrine reuptake inhibition (5). Tapentadol has been developed in an immediate-release (IR) and an extended-release (ER) formulation. Tapentadol IR has shown clinical efficacy in trials for the relief of postoperative bunionectomy pain (6-8), end-stage degenerative joint disease pain (9), and lower back pain and pain associated with osteoarthritis of the hip or knee (10). In the latter trial (10), flexible dosing of tapentadol IR (50 or 100 mg every 4 to 6 hours) over a 90-day treatment period provided pain relief similar to that provided by oxycodone HCl IR (10 or 15 mg every 4 to 6 hours). In this and other multiple-dose studies evaluating the efficacy and safety of tapentadol IR (6-10), the total daily dose (TDD) of tapentadol IR ranged from 300 to 600 mg. Tapentadol ER has shown efficacy in clinical trials for the relief of moderate to severe chronic low back pain (11,12), osteoarthritis knee pain (13), and painful diabetic peripheral neuropathy (14). In the low back pain (11,12) and osteoarthritis trials (13), tapentadol ER (100-250 mg bid) given over a 15-week period provided pain relief similar to that provided by oxycodone HCl controlled release (20 – 50 mg bid). In these studies (11-14), the TDD of tapentadol ER ranged from 200 to 500 mg. Results of several comparative studies (6-10,15,16) have shown that tapentadol is well tolerated and associated with a more favorable gastrointestinal tolerability profile than oxycodone, as evidenced by lower incidences of nausea and/or vomiting and constipation, and lower odds of experiencing nausea and/or vomiting or constipation.

Both formulations of tapentadol are effective for the management of moderate to severe pain (7-11,13, 14). In various clinical scenarios, it may be advisable for a patient's treatment to be converted from the IR to the ER formulation, or vice versa. The current study was designed to determine the equianalgesic ratios for conversion between the IR and ER formulations of tapentadol and to test whether the TDD of tapentadol IR may be directly converted into a comparable TDD of tapentadol ER, and vice versa, with equivalent efficacy and comparable safety.

Methods

Participants

Participants, screened at 13 US sites, were men and women at least 18 years of age with moderate to severe chronic low back pain of nonmalignant origin requiring analgesic treatment for at least 3 months before screening who were dissatisfied with their current therapy.

Eligible patients had normal or clinically insignificant results on physical examination, medical history, vital signs, and 12-lead electrocardiograms, and were healthy based on clinical laboratory tests performed at screening. Women were postmenopausal, surgically sterile, or had a negative pregnancy test at screening; if sexually active, women were required to use an effective method of birth control. Patients who had been taking opioids for low back pain were to have a TDD equivalent to no more than 160 mg of oral morphine.

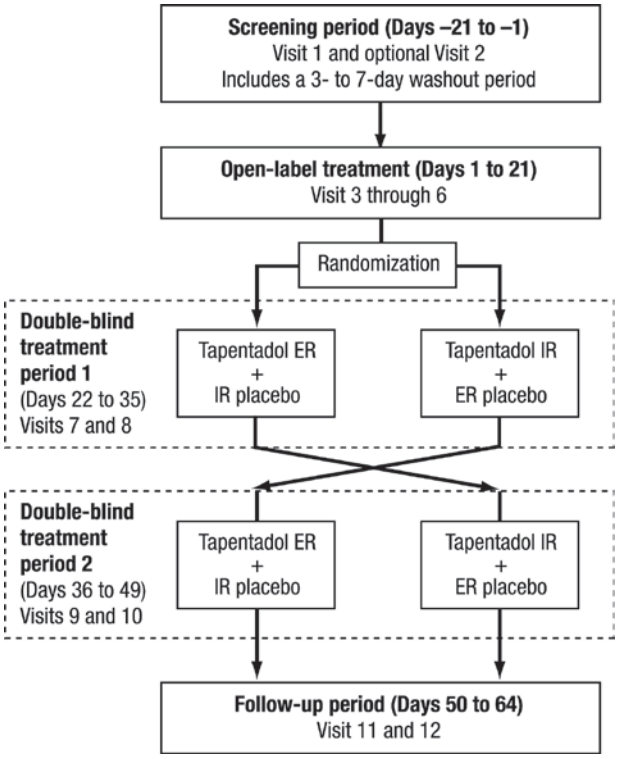
Patients were excluded if they had a history of malignancy (within the past 2 years, with the exception of basal cell carcinoma), seizure disorder or epilepsy, chronic hepatitis B or C or human immunodeficiency virus infection, or active hepatitis B or C within the past 3 months; had uncontrolled hypertension; had any scheduled surgery or painful procedure during the study that would affect efficacy or safety assessments; had surgery in the low back area within 3 months of screening; had significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, metabolic, neurologic, or psychiatric disorders, or any other clinically significant disease that could affect efficacy or safety assessments or compromise patient safety; had moderately or severely impaired hepatic function; or had severely impaired renal function at screening. All patients provided informed consent indicating that they understood the purpose and procedures of the study.

Neuroleptics, monoamine oxidase inhibitors, serotonin norepinephrine reuptake inhibitors, tricyclic antidepressants, anticonvulsants, and antiparkinsonian drugs were prohibited within 14 days before the screening visit and during the study. Patients with diagnosed psychiatric or neurologic disorders requiring treatment could participate in the study if they were treated with medications other than those listed above (e.g., selective serotonin reuptake inhibitors) if they were on a controlled, stable dose for at least 3 months before the screening visit.

Interventions

This was a randomized, double-blind, multicenter, 2-period crossover study. The study contained a screening period (≤ 21 days, during the last 3 – 7 days of which all prior analgesic medication was discontinued); an open-label, flexible-dose tapentadol IR treatment period (21 days); 2 randomized double-blind, fixed-dose treatment crossover periods (14 days each); and a follow-up period (10 –14 days; Fig. 1). The study protocol was reviewed by an Institutional Review Board, and the study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practices, and applicable regulatory requirements.

Average pain intensity during the previous 12 hours was assessed twice daily during the last 3 days of the screening period with an 11-point numerical rating scale (NRS; 0 = "no pain" to 10 = "pain as bad as you can imagine"); this measure was recorded as baseline pain. A mean baseline score of at least 5 was designated as moderate to severe pain and was required for patients to enter the open-label period. The purpose of the open-label period was to define an optimal, stable dose of tapentadol IR that provided meaningful analgesia with tolerable side effects, as defined by each patient. For the first 24 hours of the open-label period, each patient took one over-encapsulated tablet of tapentadol IR 50 mg every 6 hours. Thereafter, dose increases at one-day intervals (to tapentadol IR 75 mg or 100 mg every 4 or 6 hours) were permitted as needed in consultation with the investigator. The maximum allowed TDD was 500 mg.



ER, extended release; IR, immediate release

Fig. 1. *Study design*.

The optimal, stable dose of tapentadol IR identified for each patient during the open-label period was used in the double-blind treatment period. The dose of tapentadol ER administered to each patient in the double-blind period was identical or approximately equivalent to the TDD of tapentadol IR from the open-label period (e.g., a TDD of tapentadol IR 450 mg was rounded to tapentadol ER 500 mg). Tapentadol ER tablets are available in 5 strengths (50 [for titration], 100, 150, 200, and 250 mg). The matching or approximately equivalent TDD of tapentadol ER was divided into 2 equal doses per day and administered twice daily at approximately 12-hour intervals. The first double-blind treatment period began with random assignment of patients to a treatment sequence, taking IR tablets in the first double-blind period followed by ER tablets in the second period, or vice-versa. The second double-blind treatment period ended on the day after the last dose of study medication was administered. There was no washout separating the 2 double-blind, crossover periods. A follow-up visit was scheduled 4 days after the last dose of study medication, and a follow-up phone call was scheduled 10 to 14 days after the last dose to record any adverse events (AEs). Acetaminophen was permitted as rescue medication during all treatment periods (≤ 2,000 mg/day).

Objectives

The objective of this trial was to test whether the TDD of tapentadol IR may be directly converted into a comparable TDD of tapentadol ER, and vice versa, with equivalent efficacy and comparable safety.

Outcomes

The primary efficacy endpoint was average daily pain intensity assessed during the last 3 days of each double-blind treatment period. Pain intensity evaluations (using the 11-point NRS) were completed twice daily, once in the morning and once in the evening, with the question, "What has your average pain level been for the past 12 hours?" Secondary efficacy end-

points were the TDD for tapentadol IR and tapentadol ER, number of patients requiring rescue medication, and duration of rescue medication use.

Safety evaluations included AE reporting, clinical laboratory tests, electrocardiograms, vital signs, and physical examinations. AEs and concomitant therapies were monitored from the time the informed consent form was signed through the final visit; deaths and other serious AE summaries included events up to 30 days after the last dose of study medication. Baseline values for clinical laboratory tests, vital signs, and electrocardiograms were defined as the last evaluation before the initial administration of study medication. At the end of the second double-blind treatment period, AEs, concomitant therapy, and vital signs were recorded, and a 12-lead electrocardiogram was measured.

Sample Size

Based on the assumptions that the true difference between the 2 formulations was 0 and that the standard deviation (SD) of the difference was 4, it was estimated that a total of 45 patients would be required to achieve at least 90% power to enable the 95% confidence interval (CI) for the treatment difference to be contained within the range -2 to 2. Assuming that approximately 60% of those who entered the open-label treatment period would be randomized and included in the per-protocol (PP) population, it was estimated that approximately 75 patients would be required to enter the open-label treatment period.

Randomization

To be eligible for randomization to double-blind treatment, patients had to remain on the same optimal, stable dose and frequency of tapentadol IR during the last 3 days of the open-label period.

Sequence Generation

Randomization was carried out with a permuted block method and an Interactive Voice Response System (IVRS) and was stratified by study center and optimal stable dose level achieved in the open-label period.

Allocation Concealment

Investigators were not provided with the randomization codes.

Implementation

Randomization numbers were assigned only at the time of randomization after phoning into the IVRS. The IVRS assigned a unique randomization number that dictated the treatment sequence for each patient. Patients were assigned randomly in a 1:1 ratio to tapentadol IR followed by tapentadol ER or to tapentadol ER followed by tapentadol IR. Each time a study drug was dispensed, the IVRS assigned study drug kits that matched the treatment based on the treatment sequence to which the patient had been randomly assigned.

Blinding (Masking)

For patients receiving tapentadol IR during double-blind treatment, placebo ER tablets were used to maintain double-dummy blinding of the study. For patients receiving tapentadol ER during double-blind treatment, placebo IR capsules were used, and placebo ER tablets were included on the blister card to have dosing up to 4 or 6 times daily.

Statistical Methods

The primary efficacy analysis was performed on the per protocol (PP) data analysis set, which included all patients who were randomized to double-blind treatment, received at least one dose of study medication, had no major protocol deviation, and met the following pre-specified inclusion criteria: availability of pain intensity data for the primary analysis time period, a stable dose over the last 3 days of open-label treatment, and stable and consistent study medication intake during the primary efficacy analysis period. The primary comparisons were the mean values of average daily pain intensity scores during the last 3 days of each double-blind treatment period while a patient was receiving tapentadol IR and while the same patient was receiving tapentadol ER. The values were analyzed with a 2-period crossover analysis of variance model that included treatment, period, and patient (fitted as a fixed effect).

The equivalence of tapentadol ER and tapentadol IR was assessed with Schuirmann's 2 one-sided t test. If the 95% CIs of the least squares mean difference between the formulations during the last 3 days of double-blind treatment were within the equivalence range of - 2 to 2, the formulations were considered equivalent. This predefined margin of difference was based on the value used in a similar, previously published study (17). It was observed during the study that a patient might have received medication from both double-blind periods on the last day of the first double-blind period; therefore, the last day of each double-blind period was not used in the primary endpoint analysis. Also, some

patients met the per-protocol definition but may have had different treatment durations for the 2 treatment periods. In order to assess the robustness of the primary analysis, the following sensitivity analyses using various definitions of average pain score on the last 3 days of treatment were performed: an analysis that included the last day of treatment in the 3 days to be used in the averaging of pain intensity scores, an analysis that excluded the last day of treatment in the 3 days to be used in the averaging of pain intensity scores and included patients with a pain score on Day 6 or later in both treatment periods, and an analysis that excluded the last day of treatment in the 3 days to be used in the averaging of pain intensity scores and included patients with a pain score for only one of the double-blind treatment periods.

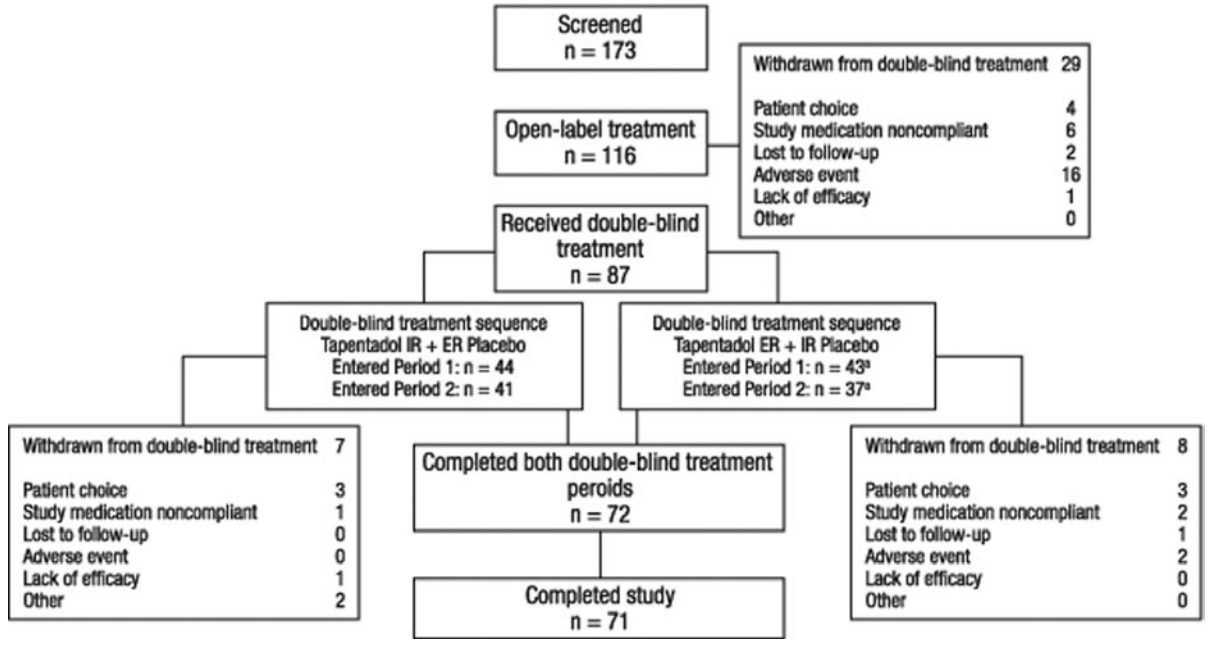
The safety analysis set was defined as all patients who took at least one dose of study medication. Safety data were summarized over all treatments combined and for each treatment period separately. Exposure to study drug was summarized for the safety analysis set based on TDD and days of study medication exposure. AEs were coded using the *Medical Dictionary for Regulatory Activities*, version 11. A treatment-emergent AE (TEAE) was defined as any AE with a first onset on or after the first day of intake of study medication or any AE with an onset before the first intake of study medication that worsened in intensity during either the open-label or the double-blind treatment periods.

Clinical laboratory data were analyzed at a central facility and summarized by the type of laboratory test (hematology, serum chemistry, serology, and urinalysis); summary statistics for the absolute values and change from pre-treatment were presented post-treatment with both treatment formulations pooled. Shifts in values between pre-treatment and post-treatment relative to normal were also summarized. Electrocardiogram findings and vital signs were summarized by parameter and time point, and descriptive statistics were calculated.

Results

Participant Flow

Of 116 patients who entered the open-label period, 88 patients were assigned randomly to treatment at the beginning of the first double-blind treatment period (44 to tapentadol IR followed by tapentadol ER and 44 to tapentadol ER followed by tapentadol IR; Fig.



ER, extended release; IR, immediate release.
aOne patient discontinued open-label treatment but was subsequently randomized. This patient did not take any double-blind medication.

Fig. 2. *Patient disposition.*

2). At least one dose of study medication was taken by 87 patients during the double-blind treatment periods. Most patients (n = 78) received both double-blind treatments, and 72 patients completed both double-blind treatments. The PP analysis set included 60 patients. The main reasons for exclusion from the PP analysis set were insufficient pain scores and missed doses on primary endpoint calculation days. Demographic and baseline characteristics of the PP population were similar between groups (Table 1).

Recruitment

The study was conducted from December 10, 2007, to April 28, 2008.

Outcomes

Treatment Exposure

At the end of the open-label period, 28 patients were receiving a high stable, optimal dose of tapentadol IR (TDD of 400 – 500 mg), and 32 patients were receiving a low stable, optimal dose of tapentadol IR (TDD of 200 – 300 mg) in the PP analysis set. The median treatment duration during the double-blind treatment periods was 14.0 days while patients were taking tapentadol IR and 14.0 days while they were taking tapentadol ER; the median TDD administered was 300.0 mg for both groups.

Table 1. *Demographic and pre-treatment (baseline) characteristics (PP analysis set).*

Characteristic	Tapentadol IR/ Tapentadol ER (n = 31)	Tapentadol ER/ Tapentadol IR (n = 29)	Total (n = 60)
Age, years			
Mean (SD)	53.2 (17.43)	54.7 (11.28)	53.9 (14.68)
Range	21 – 88	36 – 76	21 – 88
Age category, n (%)			
<65 years	23 (74.2)	21 (72.4)	44 (73.3)
≥65 years	8 (25.8)	8 (27.6)	16 (26.7)
Gender, n (%)			
Male	16 (51.6)	13 (44.8)	29 (48.3)
Female	15 (48.4)	16 (55.2)	31 (51.7)
Racial/ethnic group, n (%)			
White	23 (74.2)	22 (75.9)	45 (75.0)
Black	5 (16.1)	4 (13.8)	9 (15.0)
Hispanic	3 (9.7)	3 (10.3)	6 (10.0)
Weight, kg			
Mean (SD)	91.7 (18.71)	92.9 (24.81)	92.3 (21.69)
Range	61 – 127	51 – 140	51 – 140
Pre – treatment pain intensity, [a]			
Mean (SD)	7.1 (1.21)	7.5 (1.15)	7.3 (1.19)
Range	5 – 10	5 – 10	5 – 10
Pre – treatment pain intensity category, [a,b n] (%)			
Moderate	5 (16.1)	2 (6.9)	7 (11.7)
Severe	26 (83.9)	27 (93.1)	53 (88.3)
Prior opioid treatment, [c n] (%)			
No	17 (54.8)	8 (27.6)	25 (41.7)
Yes	14 (45.2)	21 (72.4)	35 (58.3)

PP, per protocol; IR, immediate release; ER, extended release; SD, standard deviation; NRS, numerical rating scale.
aDefined as mean pain score during the 3 days prior to the start of the open-label treatment period; measured on an 11-point NRS.
bModerate was defined as pain intensity of 4 to < 6 on the NRS; severe was defined as pain intensity ≥ 6 on the NRS.
cDefined as taking opioid analgesics during the 3 months prior to the screening visit.

Efficacy

The mean (SD) pain intensity score decreased from 7.3 (1.19) pre-treatment to 4.2 (2.13) after 3 weeks of open-label treatment with tapentadol IR, and it remained approximately constant at 3.9 or 4.0 each week during double-blind treatment for both the IR and ER formulations (Fig. 3). The mean (SD) of the average pain intensity scores over the last 3 days of treatment was 3.9 (2.17) when patients were receiving tapentadol IR and 4.0 (2.29) when patients were receiving tapentadol ER, and the estimated difference in these values (tapentadol ER – tapentadol IR) was 0.one (95% CI, -0.09 to 0.28). This 95% CI was well within the prespecified margin (–2 to 2), indicating that the efficacy of approximately equivalent TDDs of tapentadol ER and tapentadol IR was equivalent. The results of all 3 sensitivity analyses were consistent with the primary analysis with regard to the point estimate of the difference and with regard to the location and the width of the 95% CI for this difference.

There was a high correlation (0.95) between the 2 primary endpoint values for each patient (i.e., between the values when patients received both formulations of tapentadol; Fig. 4). For each patient, the primary endpoint values were numerically similar when the patient received tapentadol ER and tapentadol IR. Equivalence of endpoint values between the IR and ER formulations was found in both treatment sequence groups.

Rescue Medication

The percentage of patients who used acetaminophen during the double-blind treatment period was 39.5% (32/81) while patients received tapentadol IR and 45.2% (38/84) while patients received tapentadol ER; the mean (SD) duration of acetaminophen use was similar with both formulations (2.4 [4.19] days for tapentadol IR and 2.7 [4.19] days for tapentadol ER).

Adverse Events

The most common TEAEs (reported by > 10% of patients) in all treatment periods combined were dizziness (24.1% [28/116]), headache (16.4% [19/116]), somnolence (16.4% [19/116]), and nausea (13.8% [16/116]). Most TEAEs were of mild or moderate intensity. During double-blind treatment, the incidence of TEAEs was comparable between formulations (34.6% [28/81] with tapentadol IR and 33.3% [28/84] with tapentadol ER), and no TEAE was reported at an incidence of 5% or

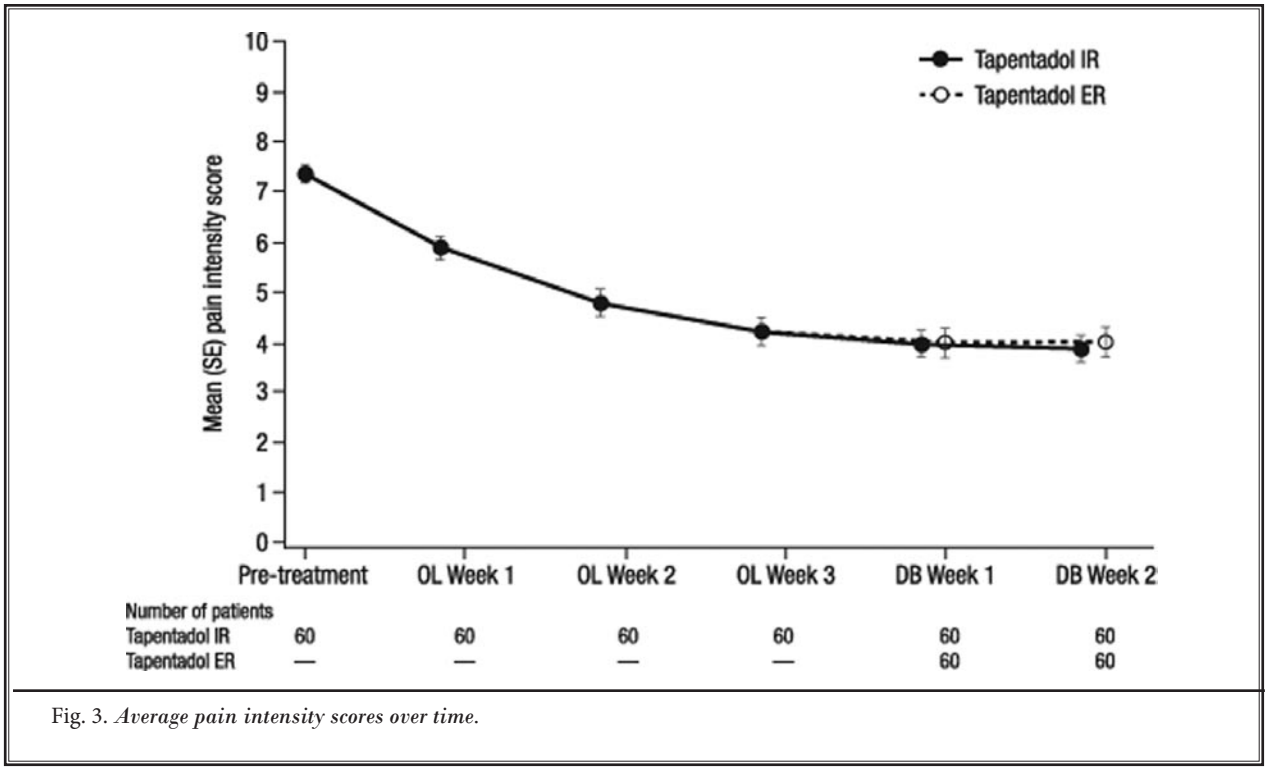
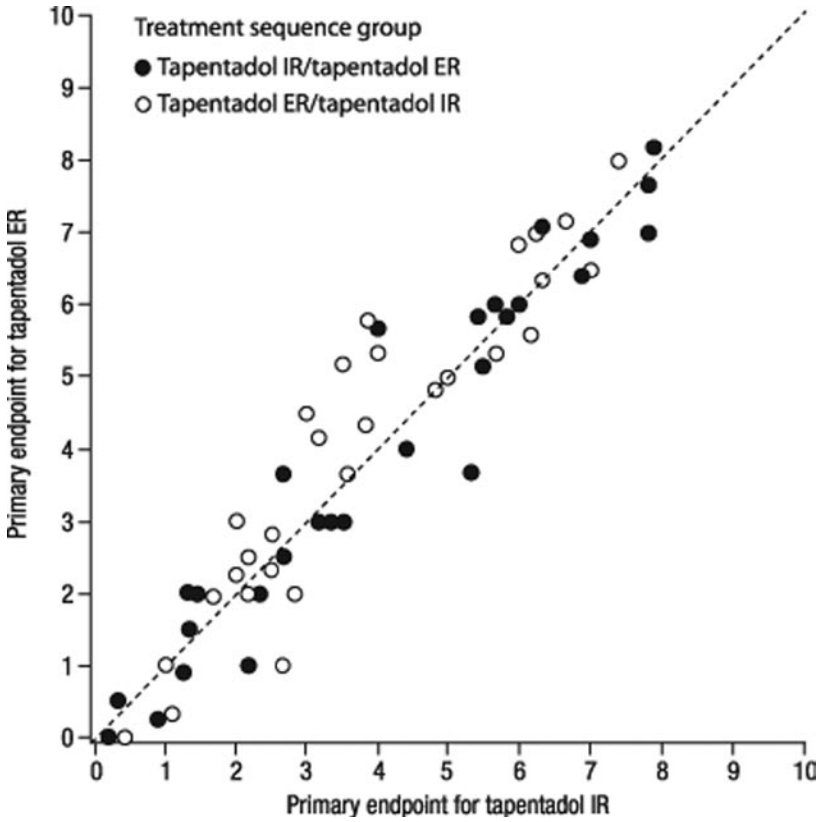


Fig. 3. *Average pain intensity scores over time.*



PP, per-protocol; ER, extended release; IR, immediat release.

Fig. 4. *Scatter plot of the primary efficacy endpoint for tapentadol ER versus tapentadol IR by treatment sequence group (PP analysis set). Each data point represents the value for a single patient.*

greater with either formulation of tapentadol during the double-blind treatment period (Table 2). TEAEs led to discontinuation in 18 (15.5%; n = 116) patients overall, with 17 of these discontinuations occurring during the open-label period. TEAEs that led to discontinuation in more than one patient were dizziness (5/116), anxiety (2/116), and nausea (2/116).

There were no deaths during the study. Two serious TEAEs occurred. Both were considered by the investigator to be unrelated to the study drug. One patient who was not randomized to double-blind treatment reported worsening of chronic back pain during open-label treatment, and one patient reported fracture of the right hip during the second double-blind treatment period while receiving tapentadol ER. The hip fracture was the result of a trip-and-fall accident and was not syncopal in nature. The affected individual had a history of osteoporosis, degenerative disc disease, and left hip replacement.

No clinically relevant mean changes in laboratory or vital sign values were observed from pre-treatment to the end of the study. Of 116 patients who entered the open-label phase, the incidence of potentially clinically important abnormal laboratory results was low (3.4% [4/116]). No patient had post-treatment electrocardiogram QTc values higher than 500 ms based on any method for correcting the QT interval. Clinical laboratory, vital sign, and electrocardiogram findings were similar to those observed in other previously completed clinical studies of tapentadol (6-10).

Table 2. *TEAEs Reported by ≥2% of patients during the double-blind treatment period.*

Type of TEAE, n (%)	Tapentadol IR (n = 81)	Tapentadol ER (n = 84)
Patients with ≥ 1 TEAE	28 (34.6)	28 (33.3)
Infections and infestations	5 (6.2)	4 (4.8)
Gastroenteritis viral	2 (2.5)	0
Upper respiratory tract infection	2 (2.5)	1 (1.2)
Musculoskeletal and connective tissue disorders	4 (4.9)	5 (6.0)
Arthralgia	2 (2.5)	1 (1.2)
Pain in extremity	1 (1.2)	2 (2.4)
Nervous system disorders	4 (4.9)	7 (8.3)
Headache	2 (2.5)	4 (4.8)
Somnolence	2 (2.5)	1 (1.2)
Skin and subcutaneous tissue disorders	4 (4.9)	0
Rash	3 (3.7)	0
General disorders and administration site conditions	3 (3.7)	7 (8.3)
Pyrexia	2 (2.5)	4 (4.8)
Fatigue	0	3 (3.6)

TEAE, treatment-emergent adverse event; IR, immediate release; ER, extended release.

Discussion

Key Results

The results of this study show that the tapentadol IR and tapentadol ER formulations can be directly converted into equivalent or approximately equivalent TDDs (based on the available doses of each formulation) that provide equivalent efficacy and comparable safety for the relief of moderate to severe chronic low back pain. The primary analysis was supported by the results of 3 separate sensitivity analyses, illustrating that the conclusion of equivalence is robust. Both formulations were well tolerated, with a similar AE profile and incidence of TEAEs.

Interpretation

The equivalence limits of the present study were large at –2 to 2; however, if this study had used a much stricter equivalence margin of –0.28 to 0.28, representing 50% retention of the tapentadol ER effect as estimated by an 86% CI from a phase 3 trial of tapentadol ER in patients with chronic low back pain, equivalence could be concluded using a standard of evidence that exceeds that suggested by Rothmann and colleagues (18). Thus, based on the pain intensity scores recorded in the current study, the dosing equivalence between tapentadol ER and tapentadol IR is supported by the protocol-defined equivalence margin as well as by a much narrower demonstrated equivalence margin.

Generalizability

Several study designs (17,19,20) and modeling simulations (21) have been used to evaluate the conversion between IR and ER formulations of the same analgesic agent. The current study design was chosen because it represented the strongest design, consisting of an initial titration period, criteria for the identification of an optimal stable dose, 2 successive crossover periods, and a prespecified margin of difference for use in the statistical analysis.

Conclusion

Physicians can prescribe either the IR or the ER formulation of tapentadol to their patients with moderate to severe low back pain and could switch patients who had initiated treatment with tapentadol IR to tapentadol ER and vice versa, without compromising efficacy or safety.

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