A Randomized Withdrawal, Placebo-Controlled Study Evaluating the Efficacy and Tolerability of Tapentadol Extended Release in Patients With Chronic Painful Diabetic Peripheral Neuropathy

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OBJECTIVE

This study evaluated the efficacy and tolerability of tapentadol extended release (ER) for the management of chronic pain associated with diabetic peripheral neuropathy (DPN).

RESEARCH DESIGN AND METHODS

Adults with moderate to severe DPN pain were titrated to tapentadol ER 100–250 mg bid during a 3-week open-label period; patients with ≥1-point reduction in pain intensity (11-point numerical rating scale) at end of titration were randomized to receive placebo or tapentadol ER (optimal dose from titration) for 12 weeks (double-blind, fixed-dose maintenance phase). The primary end point was mean change in average pain intensity from the start to week 12 (last observation carried forward [LOCF]) of the double-blind maintenance phase.

RESULTS

A total of 358 patients completed the titration period; 318 patients (placebo, *n* = 152; tapentadol ER, *n* = 166) were randomized and received one or more doses of double-blind study medication. Mean (SD) pain intensity (observed case) was 7.33 (1.30) at the start and 4.16 (2.12) at week 3 of the open-label titration period (mean [SD] change, –3.22 [1.97]). The mean (SD) change in pain intensity (LOCF) from start of double-blind treatment to week 12 was as follows: placebo, 1.30 (2.43); tapentadol ER, 0.28 (2.04; least squares mean difference, –0.95 [95% CI –1.42 to –0.49]; *P* < 0.001). Treatment-emergent adverse events (≥10%) in the tapentadol ER group during the double-blind maintenance phase were nausea (21.1%) and vomiting (12.7%).

CONCLUSIONS

Tapentadol ER (100–250 mg bid) was effective and well tolerated for the management of moderate to severe chronic pain associated with DPN.

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Pain is a prominent and distressing symptom associated with diabetic peripheral neuropathy (DPN) (1,2). Chronic DPN pain affects up to 25% of all patients with diabetes but is frequently underdiagnosed and undertreated, in part because of the limitations of currently available therapies (1). In randomized clinical trials evaluating the efficacy of pharmacologic agents approved for the management of DPN pain, no more than half of patients have reported clinically meaningful pain relief (2,3).

Tapentadol is a novel, centrally acting analgesic with two mechanisms of action in a single molecule, μ-opioid receptor agonism and norepinephrine reuptake inhibition (4). Both mechanisms of action are well established for providing pain control and affect different types of pain; this is distinct from any opioid or approved single-acting agent (5–7). Tapentadol extended release (ER) is approved globally for the management of chronic pain (moderate to severe in the U.S.; severe in Europe) and neuropathic pain associated with DPN in the U.S. A previously conducted, randomized withdrawal, placebo-controlled trial demonstrated that tapentadol ER was effective and well tolerated for the management of painful DPN (8).

Here we report the results of a second randomized withdrawal, parallel-group, placebo-controlled, phase 3 study of tapentadol ER for the management of chronic neuropathic pain associated with DPN (ClinicalTrials.gov identifier NCT01041859).

RESEARCH DESIGN AND METHODS

Patient Population

This study enrolled adults ≥18 years of age with type 1 or 2 diabetes; chronic painful DPN for ≥6 months; and pain at screening. Eligible patients were required to have an optimized diabetic regimen for ≥3 months prior to screening consisting of diet, oral hypoglycemic, or insulin therapy; ≥3-month history of analgesic use for painful DPN and dissatisfaction with current analgesic treatment (if patients were taking an opioid, a dose equivalent of oral morphine ≤160 mg/day was required); and a mean pain intensity score of ≥5 on a Likert-type 11-point numerical rating scale (NRS; 0 = "no pain" and 10 = "pain as bad as you can imagine") calculated from twice-daily pain assessments during a 3-day pain intensity pretreatment evaluation period after a 5-day washout of previous analgesic medications.

Patients were excluded if they had a history of the following: alcohol and/or drug abuse; a condition other than painful DPN that could confound the assessment/self-evaluation of pain (e.g., fibromyalgia or inflammation [e.g., rheumatoid arthritis or ankylosing spondylitis]); a significant disorder (e.g., pulmonary, gastrointestinal, endocrine, or psychiatric) that could affect study assessments or compromise safety; moderate to severe hepatic impairment or severely impaired renal function; seizure disorder or epilepsy; traumatic brain injury, stroke, transient ischemic attack, or brain neoplasm within the past year; malignancy within the past 2 years (other than successfully treated basal cell carcinoma); extensive diabetic foot ulcers; limb amputation; or Charcot neuroarthropathy.

The use of any analgesic except study drug or permitted rescue medication was prohibited throughout the study. Neuroleptics, serotonin-norepinephrine reuptake inhibitors, anticonvulsants, and antiparkinsonian drugs were prohibited during the study and within 14 days before screening because their use could confound the primary assessment of analgesic efficacy. Use of selective serotonin reuptake inhibitors was allowed if patients were on a stable dose for ≥3 months before screening.

Study Design

The randomized withdrawal, double-blind, parallel-group design was almost identical to that of the first study of tapentadol ER for the treatment of pain associated with DPN (8); however, this study used a new formulation of tapentadol ER that has a high mechanical strength conferred by use of a polyethylene oxide matrix and melt extrusion manufacturing process and that is less susceptible to breakage, splitting, crushing, or chewing than the conventional hypromellose-based formulation used in other phase 3 tapentadol ER studies (8–11). This new formulation of tapentadol ER (approved for the management of chronic pain in the U.S.) has a similar release profile to the conventional hypromellose-based formulation (12). This study also included the validated Neuropathic Pain Symptom Inventory (NPSI) as a neuropathic pain-specific efficacy instrument (13).

The study protocol was reviewed by an independent ethics committee or institutional review board at each institution. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practices, and applicable regulatory requirements. All patients provided written informed consent.

The initial open-label phase consisted of a 13-day screening period, 5-day washout period, 3-day pretitration pain intensity evaluation period, and a 3-week open-label titration period. Patients with a pretitration average pain intensity score ≥5 entered the open-label titration period and received tapentadol ER 50 mg bid for 3 days. Patients were titrated to their optimal dose in terms of pain intensity reduction and tolerability as previously described (8). Acetaminophen (≤2,000 mg/day) was allowed as additional analgesia during the 3-week open-label titration period, except during the last 4 days of that period.

Patients who tolerated tapentadol ER and had ≥1-point improvement in average pain intensity from the pretitration evaluation period to the last 3 days of the open-label titration period were randomly assigned (1:1) to receive tapentadol ER or placebo during a subsequent 12-week double-blind maintenance phase. Randomization was balanced using randomly permuted blocks and stratified by study site and the patient's tapentadol ER dose category (100–150 mg bid or 200–250 mg bid) at the end of titration. Patients were randomized to treatment based on a computer-generated schedule using an interactive voice response system. Tapentadol ER and placebo were identical in appearance and packaging.

Patients randomized to the tapentadol ER group continued taking their optimal dose of tapentadol ER as determined in the open-label titration period; this dose remained fixed throughout the double-blind phase. Patients randomized to the placebo group were down-titrated in a blinded fashion to tapentadol ER 100 mg bid for 3 days (to reduce the risk of withdrawal symptoms) before receiving placebo for the rest of the double-blind phase. In both treatment

groups, patients who needed additional analgesia could take supplemental tapentadol ER 25 mg bid during the first 4 days and once per day from day 5 onward. Follow-up evaluations were scheduled ~4 days (clinic visit) and 10–14 days (telephone contact) after the last intake of study drug.

Efficacy Evaluations

Average pain intensity over the last 12 h was recorded twice daily (11-point NRS). Daily pain intensity was calculated as the mean of average pain intensity scores in a 24-h period. Baseline pain intensity was the mean of daily pain intensity scores during the last 3 days before randomization. Weekly averages during the double-blind maintenance phase were the mean of daily pain intensities in each 7-day period starting from the first dose of double-blind study medication. The primary efficacy end point was the mean change in average pain intensity from baseline to week 12.

Secondary end points included the proportions of patients with ≥30 and ≥50% improvement in pain intensity from pretitration to week 12 of the double-blind maintenance phase; patient global impression of change (PGIC) (14–16) at the double-blind end point; and changes from the start of double-blind treatment to the double-blind end point in Brief Pain Inventory-Short Form (BPI-SF) (17) pain interference and pain intensity subscale scores, subscales of the NPSI (13,18), Short Form-36 (SF-36) Health Survey (19) subscales and summary scale, and the EuroQol 5-Dimension (EQ-5D) (20) health status index. The PGIC (16) is a single-question assessment ("Since I began trial treatment, my overall status is. . ."; responses, 1 = "very much improved" to 7 = "very much worse"). For the BPI-SF, patients use an 11-point NRS to rate their pain intensity at the time of completing the questionnaire (right now), on average, and at its worst and least over the past week. The NPSI (13,18) is a 12-item self-administered questionnaire that evaluates symptoms of neuropathic pain over the past 24 h (11-point NRS; 0 = "no symptoms" and 10 = "worst symptoms imaginable"). The SF-36 is a 36-item health status survey that includes eight subscales, each scored from 0 ("poor health") to 100 ("good health"); mental and physical component summary scores are calculated based on weighted combinations of the subscale scores. The EQ-5D is a measure of health status that includes five dimensions, each scored using one of three responses ("no problems," "some problems," or "extreme problems"); responses to individual dimensions are scored and combined to yield an overall EQ-5D health status index score (value of 1 indicates "full health").

Safety Evaluations

Safety was assessed based on adverse events (AEs), serious AEs, clinical laboratory tests, vital sign measurements, and 12-lead electrocardiograms. A treatment-emergent AE (TEAE) was defined as any AE that occurred after the first intake of study drug in a respective period or phase. Any AE that worsened in severity during the open-label titration period or double-blind maintenance period was considered a new TEAE.

Opioid withdrawal was assessed using the Clinical Opiate Withdrawal Scale (COWS) questionnaire (21), administered at predefined time points during the first 2 weeks of the double-blind maintenance phase and at the follow-up clinic visit 4 days after study drug discontinuation. Total possible scores for the 11-item COWS assessment range from <5 = no withdrawal to >36 = severe withdrawal.

Statistical Analyses

Based on results of the first phase 3 study of tapentadol ER for painful DPN (8), it was estimated that 144 patients per treatment group at randomization would provide 90% power to show a statistically significant difference of 1.0 point between tapentadol ER and placebo at $\alpha = 0.05$; therefore, it was planned to enroll 455 patients in the open-label titration period to ensure that ≥300 patients would be randomized to double-blind treatment (150 patients per treatment group).

Efficacy was assessed for the intent-to-treat population, which included all randomized patients who received one or more doses of study drug during the double-blind maintenance phase. The primary efficacy end point was evaluated with an ANCOVA model that included treatment, pooled analysis site, and dose category (100–150 or 200–250 mg bid) at the end of open-label titration as factors and baseline average pain intensity at the start of double-blind treatment as a covariate. Treatment effects were estimated based on the least squares means of the changes from baseline. The 95% CI and *P* value were presented for tapentadol ER compared with placebo; tests for efficacy were two sided and conducted at a 0.05 level of significance. The primary efficacy analysis used the last observation carried forward (LOCF) to impute missing values after discontinuation. Sensitivity analyses of the primary end point were conducted using other imputation methods (including baseline observation carried forward, worst observation carried forward, placebo mean imputation, and modified baseline observation carried forward) and observed cases (described previously for other tapentadol ER studies) (8,10). In light of a recent report from the National Academy of Sciences presenting limitations of single-imputation methods (e.g., LOCF) in chronic pain trials (22), an additional post hoc sensitivity analysis was performed. This longitudinal analysis used all observed-case data in a mixed model repeated measures analysis to evaluate the change in average pain intensity from the start of the double-blind maintenance period to the week 12 double-blind end point.

Responder rates were calculated at week 12 of the double-blind phase for the percentage change in average pain intensity from the start of the open-label phase using the following equation: 100 × (average pain intensity during week 12 [observed cases] − average pain intensity at the start of open label)/(average pain intensity at the start of open label). Patients whose pain intensity worsened or who discontinued during treatment were assigned a value of zero, and patients with no change in pain intensity were assigned a nominal value close to zero (0.00001); these patients were considered to be nonresponders. Between-group differences for responder rates (≥30 and ≥50% improvement) and PGIC were compared with the Cochran-Mantel-Haenszel test controlling for pooled analysis site and dose category at the end of open-label treatment. For analyses of BPI-SF, NPSI, SF-36, and EQ-5D, the double-blind end point was defined as the last available measurement during the double-blind

maintenance phase. The changes from the start of open-label titration to double-blind end point in BPI-SF scores and from the start of the double-blind period to double-blind end point in NPSI scores, SF-36 subscale and summary scales, and the EQ-5D health status index were evaluated using an ANCOVA model similar to that used for analysis of the primary efficacy end point. Safety assessments were performed on the open-label and double-blind safety populations (patients who received one or more doses of open-label and double-blind treatment, respectively). TEAEs were coded using the *Medical Dictionary for Regulatory Activities* (MedDRA), version 13.1.

Post hoc analyses were performed to evaluate the change in average pain intensity from the start of the double-blind maintenance period to the week 12 double-blind end point for the subgroup of patients who used supplemental tapentadol ER (25 mg) during double-blind treatment compared with those patients who did not.

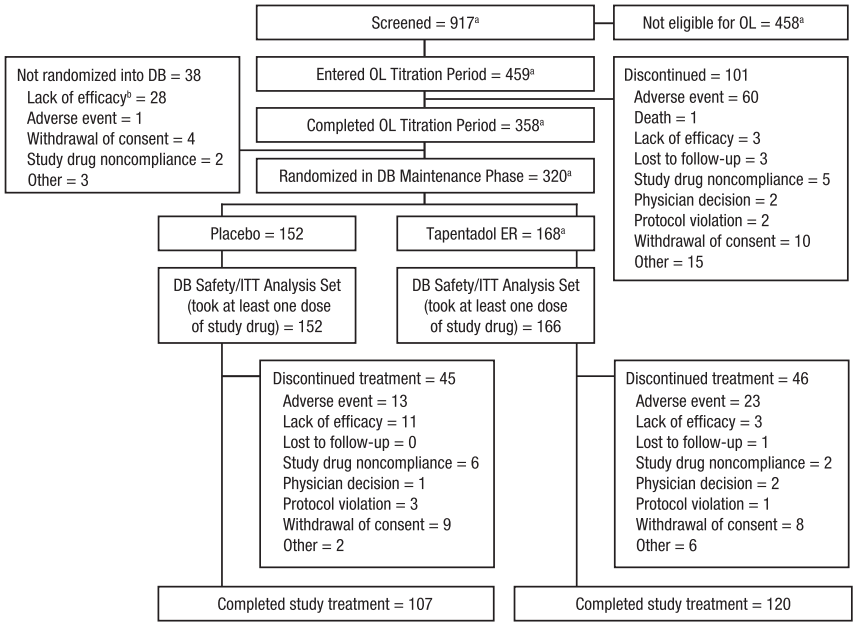

Figure 1—Patient disposition. DB, double blind; ITT, intent to treat; OL, open label. [a]Does not include patients who entered the study twice (one screen failure on first entry, one randomly assigned to tapentadol ER twice); [b]includes patients who did not achieve a ≥1-point improvement in pain intensity from the start to the end of the open-label titration period.

RESULTS

Patients

Between November 2009 and March 2011, 917 patients were screened at 80 sites (66 in the U.S. and 14 in Canada). In the open-label titration period, 459 patients received one or more doses of tapentadol ER and 358 (78%) patients completed this period (Fig. 1). A similar percentage of patients in the placebo and tapentadol ER groups discontinued double-blind treatment (placebo, 30% [45/152]; tapentadol ER, 28% [46/166]); the most common reason for discontinuation was AEs (placebo, 9% [13/152]; tapentadol ER, 14% [23/166]) (Fig. 1).

Demographic and baseline characteristics for the double-blind safety population were similar for both treatment groups and similar to characteristics of the open-label safety population (Supplementary Table 1). Mean (SD) age was 59.8 years (10.30) in the open-label safety population and 59.0 years (9.00) with placebo and 58.5 years (10.63) with tapentadol ER in the double-blind safety population. The mean (SD) duration of DPN in the open-label safety population was 238.3 weeks (285.10). At the start of open-label titration, 87.1% (400/459) of patients in the open-label safety population had severe pain (≥6 on the 11-point NRS; mean [SD] pain intensity, 7.3 [1.30]). At the end of open-label titration, mean (SD) pain intensity had decreased to 3.6 (1.99).

Efficacy

On average, pain score improvements achieved during the open-label titration period were maintained during the double-blind phase in patients randomized to tapentadol ER but diminished in patients randomized to placebo (Fig. 2). Using LOCF for imputation of missing values, the mean (SD) change in average pain intensity from the start of double-blind treatment (mean [SD] score at start: placebo, 3.53 [2.174]; tapentadol ER, 3.70 [1.781]) to week 12 of double-blind treatment (a positive value for the mean change indicates worsening of pain) was 1.30 (2.43) with placebo and 0.28 (2.04) with tapentadol ER (least squares mean difference for tapentadol ER minus placebo, −0.95 [95% CI −1.42 to −0.49]; $P < 0.001$ favoring tapentadol ER). Sensitivity analyses performed on the primary efficacy end point showed similar statistically significant differences favoring tapentadol ER versus placebo for all evaluated imputation methods ($P \leq 0.001$ for all imputation methods) (Supplementary Table 2). Results of the post hoc mixed model repeated measures analysis were consistent; the estimate of the difference in the change in average pain intensity from the start of double-blind treatment to week 12 of double-blind treatment between the tapentadol ER and placebo groups was −1.11 (95% CI −1.60 to −0.61; $P < 0.001$). From pretitration (baseline open label) to the last week of double-blind treatment, ≥30% improvement in pain intensity was observed in 45.4% (69/152) of patients in the placebo group and 55.4% (92/166) of patients in the tapentadol ER group ($P = 0.032$). At least a 50% improvement was observed in 28.9% (44/152) of patients in the placebo group and 40.4% (67/166) of patients in the tapentadol ER group ($P = 0.015$).

Supplementary Table 3 summarizes the results of post hoc analyses of average pain intensity and changes in pain intensity by use of supplemental tapentadol ER. In both treatment groups, numerically greater increases in pain intensity were observed from the start to week 12 of the double-blind treatment period for patients who took supplemental analgesia (mean [SD] change in pain intensity: placebo, 1.5 [2.53]; tapentadol ER, 0.4 [2.28]) than for those who did not (placebo, 0.7 [2.03]; tapentadol ER, 0.0 [1.52]).

Supplementary Fig. 1 presents PGIC results at double-blind end point. The

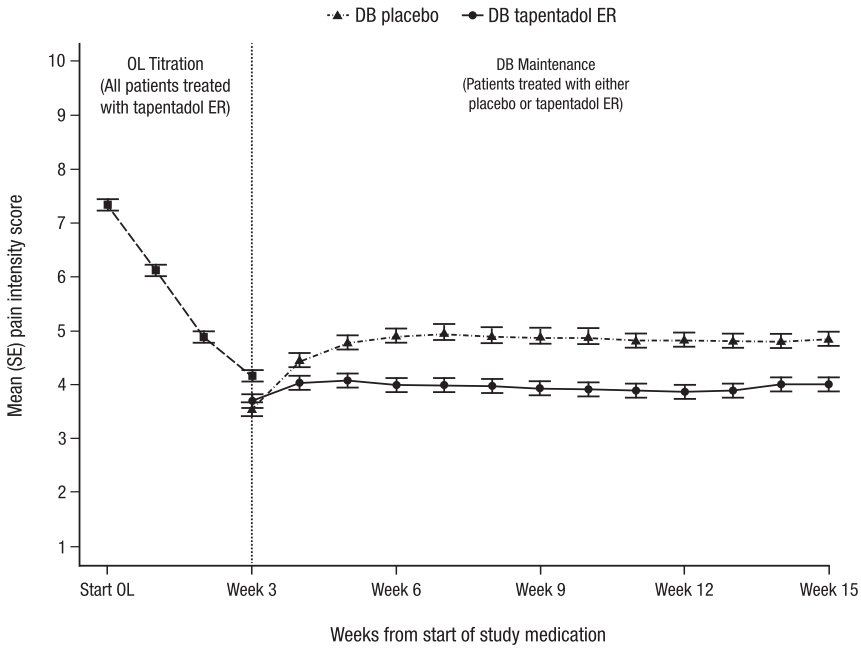

Figure 2—Weekly mean (SE) average pain intensity scores. DB, double blind; OL, open label. Values for the OL titration period are observed cases; values for the DB maintenance phase are based on the LOCF.

distribution of PGIC scores was significantly different at the end point between treatment groups ($P < 0.001$); 45.3% (63/139) of patients in the placebo group reported their PGIC status as "very much improved" or "much improved" compared with 66.0% (99/150) of patients in the tapentadol ER group.

Supplementary Table 4 summarizes BPI-SF results from the start of open-label titration to double-blind end point. From the start of the double-blind maintenance phase to double-blind end point, mean (SD) BPI-SF pain interference scores increased (worsened) in the placebo group and decreased (improved) in the tapentadol ER group ($P = 0.003$ favoring tapentadol ER); mean (SD) BPI-SF pain intensity subscale scores increased in the placebo group and to a lesser extent in the tapentadol ER group ($P < 0.001$ favoring tapentadol ER).

At double-blind end point, statistically significant differences in changes from the start of double-blind maintenance were observed between tapentadol ER and placebo for all NPSI subscales and the total score ($P \leq 0.015$ for all scores, favoring tapentadol ER) (Table 1). The distribution of the reported duration of spontaneous pain in the past 24 h was significantly different between treatment groups at double-blind end point ($P = 0.012$ in favor of tapentadol ER) (Supplementary Fig. 2). The distribution of pain attack frequency was not significantly different between treatment groups ($P = 0.349$).

Significant differences in mean changes from start of the double-blind phase to end point of the double-blind maintenance phase were observed between the tapentadol ER and placebo groups in favor of tapentadol ER in the SF-36 role-physical and bodily pain subscale scores and the physical component summary score ($P \leq 0.004$ for all) (Supplementary Table 5). A significant difference was observed between the tapentadol ER and placebo groups in favor of tapentadol ER in the mean (SD) change from the start of double-blind treatment (mean [SD] score at start: placebo, 0.71 [0.16]; tapentadol ER, 0.70 [0.14]) to double-blind end point in the EQ-5D health status index (mean [SD] change: placebo, −0.10 [0.26]; tapentadol ER, 0.00 [0.20; least squares mean difference for tapentadol ER minus placebo, 0.10 (95% CI 0.05–0.15); $P < 0.001$]).

Safety and Tolerability

In the open-label safety population, 76.0% (349/459) of patients reported one or more TEAEs. TEAEs reported by ≥5% of patients in the open-label titration period ($n = 459$) were nausea (24.4%), dizziness (17.0%), constipation (11.8%), somnolence (10.7%), vomiting (10%), headache (9.6%), fatigue (9.6%), dry mouth (8.7%), pruritus (7.4%), and diarrhea (5.2%). In the double-blind safety population, 61.2% (93/152) of patients in the placebo group and 79.5% (132/166) of patients in the tapentadol ER group reported one or more TEAEs. Table 2 presents the most frequently reported TEAEs (≥5% in either group). Throughout the study, most TEAEs were mild or moderate in intensity.

Treatment-emergent serious AEs were reported for 2.4% (11/459) of patients in the open-label titration period. Serious AEs reported by more than one patient included chest pain ($n = 3$) and dehydration ($n = 2$); one patient reported both of these AEs. In the double-blind maintenance phase, treatment-emergent serious AEs were reported by 5.9% (9/152) of patients with placebo and 4.8% (8/166) of patients with tapentadol ER; coronary artery disease was the only serious AE reported by more than one patient in either treatment group ($n = 2$, placebo). One patient died of myocardial ischemia while taking tapentadol ER 150 mg bid in the open-label titration period (assessed by investigator as doubtfully related to study drug; suspected cause of death, atherosclerotic coronary artery disease). The patient

Table 1—NPSI total score and subscale score results (intent-to-treat population): DB maintenance phase[a]

	Placebo (n = 124)	Tapentadol ER (n = 137)
Evoked pain		
Mean (SD) score at start of DB phase	2.43 (2.18)	2.39 (2.23)
Mean (SD) change at DB end point	0.78 (2.64)	0.16 (2.15)
P value (minus placebo)[b]		0.015
Paresthesia/dysesthesia		
Mean (SD) score at start of DB phase	3.64 (2.69)	3.81 (2.53)
Mean (SD) change at DB end point	1.29 (2.95)	−0.01 (2.79)
P value (minus placebo)[b]		<0.001
Paroxysmal pain		
Mean (SD) score at start of DB phase	2.90 (2.42)	2.96 (2.32)
Mean (SD) change at DB end point	0.92 (3.02)	0.12 (2.53)
P value (minus placebo)[b]		0.009
Pressing pain		
Mean (SD) score at start of DB phase	2.44 (2.22)	2.50 (2.20)
Mean (SD) change at DB end point	1.03 (2.97)	0.15 (2.29)
P value (minus placebo)[b]		0.010
Burning pain		
Mean (SD) score at start of DB phase	3.11 (2.35)	3.09 (2.55)
Mean (SD) change at DB end point	1.27 (3.07)	0.26 (2.86)
P value (minus placebo)[b]		0.005
Total score		
Mean (SD) score at start of DB phase	28.35 (19.98)	28.82 (18.94)
Mean (SD) change at DB end point	10.10 (24.38)	1.26 (19.80)
P value (minus placebo)[b]		<0.001

DB, double blind. [a]Results are presented for all patients who had observations at both the start of the DB maintenance phase and at the end point of the DB maintenance phase. [b]Based on an ANCOVA model with treatment, pooled analysis site, and dose category as factors and value at the start of the DB maintenance phase as a covariate.

had a history of hypertension, hypercholesterolemia, and diabetes.

TEAEs led to discontinuation for 16.6% (76/459) of patients during the open-label phase, with only nausea (6.1% [28/459]) reported as a TEAE leading to discontinuation for ≥5% of patients. During the double-blind maintenance phase, TEAEs led to discontinuation for 7.9% (12/152) of patients in the placebo group and 11.4% (19/166) of patients in the tapentadol ER group. Nausea (placebo, 1.3% [2/152]; tapentadol ER, 3.6% [6/166]) was the only TEAE reported as leading to discontinuation for ≥2% of patients in either group.

Table 2—TEAEs reported by ≥5% of patients in the DB maintenance phase (DB safety population)[a]

AE, n (%)	Placebo (n = 152)	Tapentadol ER (n = 166)
Any AE	93 (61.2)	132 (79.5)
Gastrointestinal disorders		
Nausea	15 (9.9)	35 (21.1)
Vomiting	7 (4.6)	21 (12.7)
Diarrhea	10 (6.6)	11 (6.6)
Constipation	0	9 (5.4)
General disorders and administration site conditions		
Fatigue	1 (0.7)	12 (7.2)
Infections and infestations		
Nasopharyngitis	4 (2.6)	9 (5.4)
Nervous system disorders		
Dizziness	3 (2.0)	12 (7.2)
Somnolence	1 (0.7)	10 (6.0)
Headache	8 (5.3)	4 (2.4)
Psychiatric disorders		
Insomnia	4 (2.6)	9 (5.4)
Anxiety	8 (5.3)	8 (4.8)

DB, double blind. [a]Patients could report more than one AE.

There were no clinically important treatment-related changes observed in clinical laboratory values, vital signs, or electrocardiogram findings.

Based on COWS total scores, among patients who did not discontinue during week 1 of the double-blind maintenance phase (including patients who discontinued during or at the end of the open-label titration period) and who did not immediately start taking opioid medications, 95.5% (105/110) and 96.6% (113/117) of patients in the placebo and tapentadol ER groups, respectively, had no opioid withdrawal. All incidences of opioid withdrawal in the tapentadol ER group (4/117) were mild.

CONCLUSIONS

Treatment with tapentadol ER (100–250 mg bid) was associated with clinically meaningful reductions in pain intensity that were maintained over 12 weeks of double-blind treatment in patients who tolerated the drug and had an initial treatment effect during a 3-week open-label titration period. Although a 15-week treatment period represents a relatively short time when considering a potentially life-long pain disorder, a duration of at least 3 months is a U.S. Food and Drug Administration requirement for confirmatory trials in chronic pain, such as the present trial. Furthermore, these improvements in pain intensity were observed in patients with chronic neuropathic pain related to DPN that had been present for ≥6 months prior to study entry. These results confirm those of the earlier study evaluating the efficacy and tolerability of tapentadol ER for the management of moderate to severe chronic pain associated with DPN (8). The randomized withdrawal design allowed for an enriched enrollment that is representative of clinical practice, in which only patients who tolerate the drug and have a clinically meaningful initial response are candidates for long-term treatment. In the previous study of tapentadol ER in patients with painful DPN (8) and the current study, the extent of enrichment was minimal with regard to treatment effect, as

only a small number of patients (45 patients [7.6%] [8] and 28 patients [6.1%], respectively) discontinued the study at the end of titration because of a lack of efficacy or failed to achieve ≥1-point improvement in pain intensity during open-label titration.

In this study, supplemental tapentadol ER 25 mg bid (up to twice per day during the first 4 days, and once per day from day 5 onward) was permitted throughout the maintenance period in both treatment groups. Post hoc analyses of pain intensity by supplemental tapentadol ER use showed greater levels of pain intensity in all patients who took supplemental medication (both in the placebo and tapentadol ER treatment groups) at the beginning of the open-label titration period; at the beginning of the randomized, double-blind treatment period; and at the end of the double-blind treatment period. These results show that, as expected, patients with higher levels of pain intensity were the ones taking supplemental tapentadol ER. Nevertheless, at the end of the 12-week double-blind treatment period, patients who had received supplemental medication in the placebo group had higher levels of pain intensity than patients in the tapentadol ER group who had received supplemental medication, and the pain reduction in the tapentadol ER group was greater than that in the placebo group when compared with pain intensity scores at the beginning of the double-blind treatment period and at the beginning of the open-label titration period. Therefore, it appears that patients with higher pain intensity elected to receive the permitted supplemental medication, but, regardless of supplemental medication consumption, improvements in pain intensity were markedly better in the tapentadol ER group than in the placebo group. Pain intensity scores did not return to those observed prior to tapentadol PR treatment for patients who were randomized to placebo during the double-blind treatment period, regardless of supplemental analgesia intake. This retention of a degree of pain reduction during the double-blind period by placebo patients may have been, in part, due to a placebo response, which has been previously reported in studies of neuropathic pain (23). The use of supplemental tapentadol ER may have played a role in maintaining the open-label treatment effect in patients randomized to placebo; however, since the decision to use supplemental tapentadol ER was not a randomized decision, it is not possible to verify this proposition based on the data.

The efficacy measures used in this study are consistent with recommendations of the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) (14,15). The primary efficacy measures based on twice-daily average pain intensity assessments on the 11-point NRS are widely accepted measures of pain, especially when used with complementary assessments of responder analyses, PGIC, and BPI (14,15). In responder analyses, significantly higher percentages of patients in this study reported an individual improvement in pain intensity of ≥30 or ≥50% with tapentadol ER versus placebo ($P \leq 0.032$ for both), and results of patient-reported measures of functional interference (BPI), quality of life (SF-36 and EQ-5D), and PGIC were all significantly better with tapentadol ER versus placebo ($P \leq 0.05$ for all; consistent with the primary end point). Pregabalin, which has been recommended for the relief of painful DPN (24), has been associated with improvements in SF-36 scores and PGIC ratings in patients with painful DPN and postherpetic neuralgia (25).

Tapentadol ER was generally well tolerated, with a safety profile consistent with that of a centrally acting analgesic. No clinically important safety signals were observed with tapentadol ER compared with placebo, and the safety profile of the new formulation used in this study was similar to that of the hypromellose-based formulation used in other phase 3 tapentadol ER studies (8–11).

Population-based studies have shown that neuropathic pain is considered to be more severe than other types of pain (2,26). Central sensitization of intact nociceptors that share innervation networks with injured nerves can result in ongoing pain and hyperalgesia (27). Because of the potentially severe and multifactorial nature of neuropathic pain associated with DPN, patients may require treatment with multiple agents with complementary mechanisms of action (28,29). Although combination therapies are used for the management of neuropathic pain, the combination of two or more medications may burden patients with multiple side effects. Thus, current treatment guidelines generally focus on the use of single agents (1,24,30), even though patients treated with a single agent often do not achieve satisfactory pain relief (3).

Tapentadol ER may be beneficial for the relief of multifactorial neuropathic pain because it has two mechanisms of action, μ-opioid receptor agonism and norepinephrine reuptake inhibition, and may avoid the need for combination therapy. In the current study, tapentadol ER (100–250 mg bid) was associated with significantly greater improvements than placebo ($P \leq 0.05$ for all) in the total and subscale scores of the NPSI, a valid and sensitive tool for assessing the effects of treatment on neuropathic pain components (13); these results support the efficacy of tapentadol ER for the relief of neuropathic pain-specific symptoms. In separate, phase 3b studies of tapentadol ER (50–250 mg bid) for the management of moderate to severe chronic low back pain with or without a neuropathic pain component (based on the painDETECT questionnaire), improvements from baseline over the course of the study were observed not only in pain intensity but in measures of anxiety (31,32), depression (31,32), and sleep quality (31,32) for patients with a neuropathic pain component.

This is the second placebo-controlled trial using a randomized withdrawal design demonstrating that tapentadol ER (100–250 mg bid) is well tolerated and effective for the management of neuropathic pain associated with DPN in adults. The safety and tolerability profile of tapentadol ER was consistent with that of a centrally acting analgesic and similar to that observed in other phase 3 studies of tapentadol ER for the management of moderate to severe chronic pain.

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References

1. Tesfaye S, Vileikyte L, Rayman G, et al.; on behalf of the Toronto Expert Panel on Diabetic Neuropathy. Painful diabetic peripheral neuropathy: consensus recommendations on diagnosis, assessment and management. Diabetes Metab Res Rev 2011;27:629–638
2. Vinik A. The approach to the management of the patient with neuropathic pain. J Clin Endocrinol Metab 2010;95:4802–4811
3. Dworkin RH, O'Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: an overview and literature update. Mayo Clin Proc 2010;85 (Suppl.):S3–S14
4. Tzschentke TM, Christoph T, Kögel B, et al. (-)-(1*R*,2*R*)-3-(3-dimethylamino-1-ethyl-2-methyl-propyl)-phenol hydrochloride (tapentadol HCl): a novel μ-opioid receptor agonist/norepinephrine reuptake inhibitor with broad-spectrum analgesic properties. J Pharmacol Exp Ther 2007;323:265–276
5. Lee YC, Chen PP. A review of SSRIs and SNRIs in neuropathic pain. Expert Opin Pharmacother 2010;11:2813–2825
6. Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. Pain Physician 2008;11 (Suppl.):S133–S153
7. Kroenke K, Krebs EE, Bair MJ. Pharmacotherapy of chronic pain: a synthesis of recommendations from systematic reviews. Gen Hosp Psychiatry 2009;31:206–219
8. Schwartz S, Etropolski M, Shapiro DY, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. Curr Med Res Opin 2011;27: 151–162
9. Afilalo M, Etropolski MS, Kuperwasser B, et al. Efficacy and safety of Tapentadol extended release compared with oxycodone controlled release for the management of moderate to severe chronic pain related to osteoarthritis of the knee: a randomized, double-blind, placebo- and active-controlled phase III study. Clin Drug Investig 2010;30:489–505
10. Buynak R, Shapiro DY, Okamoto A, et al. Efficacy and safety of tapentadol extended release for the management of chronic low back pain: results of a prospective, randomized, double-blind, placebo- and active-controlled Phase III study. Expert Opin Pharmacother 2010;11: 1787–1804
11. Wild JE, Grond S, Kuperwasser B, et al. Long-term safety and tolerability of tapentadol extended release for the management of chronic low back pain or osteoarthritis pain. Pain Pract 2010;10:416–427
12. Zannikos PN, Smit JW, Stahlberg H-J, Wenge B, Hillewaert VM, Etropolski MS. Pharmacokinetic evaluation of tapentadol extended-release tablets in healthy subjects. J Opioid Manag 2013;9: 291–300
13. Bouhassira D, Attal N, Fermanian J, et al. Development and validation of the Neuropathic Pain Symptom Inventory. Pain 2004;108:248–257
14. Dworkin RH, Turk DC, Farrar JT, et al.; IMMPACT. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain 2005;113:9–19
15. Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. J Pain 2008;9: 105–121
16. Guy W. *ECDEU Assessment Manual for Psychopharmacology*. Washington, DC, U.S. Govt. Printing Office, 1976 (DHEW publ. no. ADM 76-338)
17. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. Ann Acad Med Singapore 1994;23:129–138
18. Crawford B, Bouhassira D, Wong A, Dukes E. Conceptual adequacy of the neuropathic pain symptom inventory in six countries. Health Qual Life Outcomes 2008;6:62
19. Ware JE Jr, Snow KK, Kosinski M, Gandek B. *SF-36 Health Survey Manual and Interpretation Guide*. Boston, MA, The Health Institute, New England Medical Center, 1993
20. Brooks R. EuroQol: the current state of play. Health Policy 1996;37:53–72
21. Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs 2003;35:253–259
22. Panel on Handling Missing Data in Clinical Trials, Committee on National Statistics, Division of Behavioral and Social Sciences and Education. *The Prevention and Treatment of Missing Data in Clinical Trials*. Washington, DC, The National Academies Press, 2010
23. Quessy SN, Rowbotham MC. Placebo response in neuropathic pain trials. Pain 2008; 138:479–483
24. Bril V, England J, Franklin GM, et al.; American Academy of Neurology; American Association of Neuromuscular and Electrodiagnostic Medicine; American Academy of Physical Medicine and Rehabilitation. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation [published correction appears in Neurology 2011;77:603]. Neurology 2011;76: 1758–1765
25. Vinik A, Emir B, Cheung R, Whalen E. Relationship between pain relief and improvements in patient function/quality of life in patients with painful diabetic peripheral neuropathy or postherpetic neuralgia treated with pregabalin. Clin Ther 2013;35:612–623
26. Bouhassira D, Lantéri-Minet M, Attal N, Laurent B, Touboul C. Prevalence of chronic pain with neuropathic characteristics in the general population. Pain 2008;136:380–387
27. Campbell JN, Meyer RA. Mechanisms of neuropathic pain. Neuron 2006;52:77–92
28. Argoff CE, Backonja MM, Belgrade MJ, et al. Consensus guidelines: treatment planning and options. Diabetic peripheral neuropathic pain. Mayo Clin Proc 2006;81(Suppl.):S12–S25
29. American Society of Pain Educators. Diabetic peripheral neuropathic pain. Consensus guidelines for treatment. J Fam Pract 2006; 2006(Suppl.):1–19
30. Handelsman Y, Mechanick JI, Blonde L, et al.; AACE Task Force for Developing Diabetes Comprehensive Care Plan. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for developing a diabetes mellitus comprehensive care plan. Endocr Pract 2011;17(Suppl. 2):1–53
31. Gálvez R, Schäfer M, Hans G, Falke D, Steigerwald I. Tapentadol prolonged release versus strong opioids for severe, chronic low back pain: results of an open-label, phase 3b study. Adv Ther 2013;30:229–259
32. Steigerwald I, Müller M, Davies A, et al. Effectiveness and safety of tapentadol prolonged release for severe, chronic low back pain with or without a neuropathic pain component: results of an open-label, phase 3b study. Curr Med Res Opin 2012;28:911–936