Randomized Trial

Tapentadol Immediate Release Versus Oxycodone Immediate Release for Treatment of Acute Low Back Pain

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Background: Tapentadol has demonstrated analgesic efficacy across a range of pain conditions.

Objective: In a head-to-head study of up to 10 days in duration, the analgesic efficacy and tolerability of tapentadol immediate release (IR) versus oxycodone IR using a flexible dosing regimen were compared in patients with acute low back pain (LBP) and associated radicular leg pain.

Study Design: Randomized (1:1), double-blind, parallel-group study (NCT00986180). Independent Ethics Committee/Institutional Review Board approval of the protocol was obtained.

Setting: Ninety US outpatient treatment centers.

Methods: Patients with moderate to severe, acute LBP received tapentadol IR (50, 75, or 100 mg) or oxycodone HCl IR (5, 10, or 15 mg) every 4 to 6 hours as needed for pain for up to 10 days. Patients reported current pain intensity twice daily (11-point numerical rating scale). The primary efficacy endpoint was the sum of pain intensity differences (SPID) over 120 hours for LBP. Tapentadol IR was considered non-inferior to oxycodone IR if the upper bound of the 95% confidence interval (CI) for the least-squares mean (LSM) difference in $SPID_{120}$ was less than 120. Secondary efficacy endpoints included 2-, 3-, and 10-day SPID for LBP; 2-, 3-, 5-, and 10-day SPID for index leg pain; 30% and 50% responder rates; patient and clinician global impressions of change; and patient satisfaction.

Results: The safety population included 645 patients, and the modified intent-to-treat population included 585 patients. In the tapentadol IR and oxycodone IR groups, respectively, 86.3% (277/321) and 82.7% (268/324) of patients completed the study. The most common reason for study withdrawal in both treatment groups was adverse events (tapentadol IR, 6.5% [21/321]; oxycodone IR, 7.1% [23/324]). The LSM (standard error) $SPID_{120}$ for LBP was 264.6 (11.43) for tapentadol IR (n = 287) and 264.0 (11.22) for oxycodone IR (n = 298). The 95% CI for the LSM difference was –32.1 to 30.9; therefore, tapentadol IR was non-inferior to oxycodone IR for relief of LBP. No significant differences were observed between tapentadol IR and oxycodone IR for other SPID endpoints or for responder rates. At the end of the study, in the tapentadol IR and oxycodone IR treatment groups, respectively, approximately two-thirds of patients (66.2% vs 66.2%) and clinicians (67.9% vs 66.6%) rated patients' overall condition as "very much improved" or "much improved," and more than 75% of patients (79.3% vs 78.9%) were "very satisfied" or "somewhat satisfied" with their treatment. In the tapentadol IR and oxycodone IR groups, respectively, 52.3% (168/321) and 58.0% (188/324) of patients reported at least one treatment-emergent adverse event (TEAE); the most common (≥ 10%) TEAEs were vomiting (15.9% vs 24.7%), nausea (15.9% vs 20.7%), and dizziness (11.8% vs 10.5%). Vomiting (odds ratio [95% CI], 1.74 [1.17 - 2.57]) and constipation (3.43 [1.45 - 8.11]) were significantly more likely to occur in the oxycodone IR treatment group. Two (0.6%) patients in the tapentadol IR group and 3 (0.9%) patients in the oxycodone IR group experienced treatment-emergent serious adverse events.

Limitations: Strict patient monitoring is generally not representative of real-world medical practice; consequently, higher incidences of TEAEs may have been reported than would be expected in a typical practice setting; it is anticipated that this bias would be similar for both treatment groups.

Conclusions: This head-to-head study demonstrated that tapentadol IR had comparable analgesic efficacy and overall safety to that of oxycodone IR for the relief of moderate to severe, acute LBP and associated radicular leg pain when using flexible dosing regimens that reflect typical use in clinical practice; however, tapentadol IR demonstrated a better gastrointestinal tolerability profile, particularly for the common opioid-related TEAEs of vomiting and constipation.

Clinical Trial Registration: NCT00986180

Key words: Tapentadol, oxycodone, acute low back pain, radicular leg pain, neuropathic pain, flexible dosing, radiculopathy, gastrointestinal tolerability

Acute low back pain (LBP) is the most commonly reported type of pain in the United States (1,2). It is estimated that 70% to 80% of adults will experience an episode of acute or chronic LBP at least once during their lifetime (3,4). In approximately 1% to 10% of the population, acute LBP is associated with lumbosacral radiculopathy (5). This type of pain is typically caused by mechanical compression of nerve roots by herniated or bulging intervertebral discs, spondylosis, and/or inflammation in adjacent structures (6,7).

There are no uniformly accepted guidelines for the management of lumbosacral radicular pain (8); however, opioid analgesics have demonstrated efficacy for the management of moderate to severe, acute LBP (1). Opioids provide rapid analgesia for a range of different pain conditions, but analgesics that act primarily through μ-opioid receptor agonism are associated with gastrointestinal and central nervous system side effects that can cause discomfort, distress, and poor patient adherence to treatment (9-11).

Tapentadol is a centrally acting analgesic with μ-opioid receptor agonist and norepinephrine reuptake inhibitor activities (12). Tapentadol immediate release (IR) is effective for the relief of moderate to severe, acute pain in adults and has been evaluated in patients with postsurgical (13,14) and osteoarthritis pain (15). Doses of tapentadol IR 50 and 75 mg were equianalgesic with oxycodone HCl IR 10 mg in patients with end-stage joint disease, but at these doses, tapentadol IR had a better gastrointestinal tolerability profile (16).

The current study of up to 10 days in duration provides a head-to-head comparison of the efficacy and tolerability of flexible dosing regimens of tapentadol IR versus oxycodone IR for the relief of moderate to severe, acute pain in patients with LBP and associated radicular leg pain. The primary clinical hypothesis was that tapentadol IR would be non-inferior to oxycodone IR for the relief of acute LBP based on the sum of pain intensity differences (SPID) over 120 hours (ie, 5 days).

Methods

Participants

This study enrolled men and women 18 years of age or older with a clinical diagnosis of acute LBP with associated radicular leg pain, with onset no more than 30 days prior to screening.

Eligible patients had moderate to severe, acute LBP at baseline (score ≥ 5 on an 11-point numerical rating scale [NRS]; 0 = "no pain," 10 = "pain as bad as you can imagine") and radicular leg pain on at least one side. Clinical presentation was consistent with Category 3 (acute LBP and pain radiating below the knee), Category 4 (Category 3 criteria and neurologic findings suggestive of lumbosacral radiculopathy [ie, ≥ 2 abnormal findings: unilateral abnormality in muscle strength, deep tendon reflex, or sensation in a dermatomal pattern]), or Category 6 (Category 4 criteria and evidence of nerve root compression on imaging) of the Quebec Task Force Classification for Spinal Disorders (QTFC) algorithm (17).

The leg affected with pain radiating below the knee was designated as the "index" leg; however, patients with bilateral distal leg pain were eligible for the study. In these cases, if no neurologic signs were present at screening, the leg with greater pain intensity was designated the "index" leg. If neurologic signs were present, the leg with neurologic signs was designated the "index" leg. Patients with neurologic signs in both legs were not eligible for the study.

Patients were excluded if they had a history of cervical, thoracic, or lumbosacral pain for ≥ 50% of the time in the year prior to screening; had a history of any LBP episode, except the current acute episode, within 3 months prior to screening that was greater than mild in pain intensity, was associated with disability, or required treatment with an opioid analgesic; had acute LBP caused by a serious or malignant condition; underwent spinal surgery in the year prior to screening or had a history of more than one spinal surgery; had a history of severe lumbar spinal stenosis, fibromyalgia, or ankylosing spondylitis; or had a history of epilepsy or recurrent seizures.

Patients who required supplemental pain medication or experienced intolerable or treatment-limiting side effects were discontinued from the study and treated at the investigator's discretion.

Interventions

This randomized, outpatient, double-blind, multicenter, parallel-group study (ClinicalTrials.gov Identifier: NCT00986180) consisted of a one-day screening/randomization phase and a 10-day double-blind treatment phase. Independent Ethics Committee and Institutional Review Board approvals were obtained for the study protocol. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practices, and applicable regulatory requirements. All patients provided written informed consent.

At baseline, eligible patients were stratified based on QTFC, with Stratum I defined as patients with a clinical presentation consistent with QTFC Category 3 and Stratum II defined as patients with a clinical presentation consistent with QTFC Category 4 or 6. An interactive voice response system (IVRS) ensured investigator and patient blinding to treatment assignment by randomly assigning patients to treatment using a computer-generated randomization schedule.

Within each stratum, patients were randomized in a 1:1 ratio to receive tapentadol IR (50, 75, or 100 mg) or oxycodone HCl IR (5, 10, or 15 mg) every 4 to 6 hours as needed for pain. To further assist with the maintenance of blinding, study drug capsules were identical in appearance.

On Day 1 of the double-blind treatment phase, patients began treatment in the evening with the lowest possible dose of study drug (ie, tapentadol IR 50 mg or oxycodone HCl IR 5 mg). Thereafter, patients could adjust the dose as needed to achieve meaningful pain relief with acceptable tolerability. Patients were given instructions for upward and downward dose titrations and limitations of no more than 600 mg of tapentadol IR or 90 mg of oxycodone HCl IR per day (according to treatment assignment).

Antiepileptic drugs, tricyclic antidepressants, selective serotonin reuptake inhibitors, and serotonin norepinephrine reuptake inhibitors were permitted during the study for patients who had been taking these medications at a stable dose for at least 30 days before Day 1 for conditions other than LBP. Patients were permitted to take non-steroidal anti-inflammatory drugs, muscle relaxants, and topical analgesic formulations during the study for any condition (including acute back pain) if they had been taking a stable daily dose for at least 7 days prior to Day 1. Patients were permitted to take aspirin (≤ 325 mg/day) for cardiovascular prophylaxis if the dose had been stable for at least 30 days prior to Day 1, and acetaminophen (≤ 2 pills/day) was permitted as needed for the treatment of pain other than acute LBP. The concomitant use of all other analgesic medications was prohibited.

Outcomes

Patients called an IVRS to complete a current LBP and index leg pain intensity assessment (11-point NRS) immediately before taking the first dose of study drug. Patients then reported their current pain intensity using the 11-point NRS and pain relief using a 5-point pain relief scale for LBP and for index leg pain twice daily (each morning and evening via the IVRS). At baseline and on Day 10, patients used an 11-point NRS to complete the Brief Pain Inventory-Short Form (BPI-SF; rating of pain intensity at the time of completing the questionnaire [right now], on average, and at its worst and least over the past 24 hours) (18) and the Short-Form McGill Pain Questionnaire-2 (SF-MPQ-2; 22-question evaluation of symptoms and treatment response with subscales of continuous pain, intermittent pain, predominantly neuropathic pain, and affective descriptors) (19). At the end of the study, patients completed the patient global impression of change (PGIC) and clinicians completed the clinician global impression of change (CGIC); these single-question assessments measured improvement compared with baseline using a 7-point scale (1 = "very much improved" and 7 = "very much worse"). On Day 5 and at the end-of-study visit, patients answered the question, "How satisfied or dissatisfied are you with the overall performance of your study pain medication?" on a 7-point scale (1 = "very satisfied" and 7 = "very dissatisfied").

Safety was assessed based on reported incidences of adverse events (AEs), serious AEs, and AEs leading to discontinuation. A serious AE was defined as any AE that required inpatient hospitalization or prolongation of an existing hospitalization, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, was life-threatening, or resulted in death.

Statistical Methods

Efficacy assessments were performed using the modified intent-to-treat (mITT) population, which was defined as all patients who took at least one dose of the study drug and had a baseline LBP intensity score of ≥ 5 (11-point NRS). The primary efficacy endpoint was $SPID_{120}$ for LBP starting from the time of first administration of the study drug. $SPID_{120}$ was calculated as the weighted sum of the pain intensity difference (difference between baseline and average pain intensity since the last assessment) collected over 120 hours for acute LBP starting from the time of the first dose of the study drug. Baseline pain intensity was the current pain intensity recorded by the patient immediately prior to the first dose of the study drug. The last observation carried forward imputation method was applied for any patient who discontinued treatment prior to 120 hours. Intermittent missing pain scores were imputed using linear interpolation. As the primary analysis, $SPID_{120}$ was analyzed with an analysis of covariance

(ANCOVA) model using patients from both strata, with stratum, treatment, and treatment by stratum as factors and baseline pain intensity score as a covariate. Tapentadol IR would be considered non-inferior to oxycodone IR if the upper bound of the 2-sided 95% confidence interval (CI) for the least-squares mean (LSM) difference (oxycodone IR – tapentadol IR) in $SPID_{120}$ was less than a pre-specified non-inferiority margin of 10% of the entire range of possible $SPID_{120}$ values (ie, 120 out of a maximum of 1,200, which corresponds to a mean difference in pain intensity of one on the NRS for the 120-hour period).

The study was originally designed with $SPID_{72}$ for LBP as the primary efficacy endpoint; however, in an approved protocol amendment that was implemented prior to locking the database and unblinding data, the primary efficacy endpoint was changed to $SPID_{120}$ for LBP because accumulating evidence suggested that a longer treatment duration would be needed to demonstrate clinically relevant analgesic efficacy in patients with acute LBP that had associated radicular leg pain.

Sample size was determined using the non-inferiority margin of 10% of the entire possible range for the $SPID_{120}$ LBP primary endpoint (chosen based on results of other completed trials of tapentadol IR for acute pain) (13-15) (NCT00814580; NCT00771758). The standard deviation (SD) for $SPID_{120}$ was estimated at 230 based on previous findings (15). Based on this common SD and non-inferiority margin, 79 patients in the tapentadol IR and in the oxycodone IR group in each stratum would have 90% power to demonstrate non-inferiority of tapentadol IR compared with oxycodone IR for $SPID_{120}$ with a one-sided significance level of 0.025. Thus, enrollment of 158 patients in each stratum was required. Based on the advanced enrollment status when the protocol amendment was approved, the sample size was not changed from the original sample size determination, which required 326 patients to be randomized to each stratum to achieve 292 patients in the mITT population. Thus, approximately 652 patients were to be enrolled in the study. Using this sample size, it was possible to compare treatments in each stratum and for both strata combined.

Two-, 3-, and 10-day SPID for LBP and 2-, 3-, 5-, and 10-day SPID for index leg pain were analyzed using the same ANCOVA model used for the primary $SPID_{120}$ LBP analysis. Responder analyses were conducted to determine the percentage of patients who achieved meaningful analgesia (defined as $\geq$ 30% or $\geq$ 50% reduction in pain intensity from baseline) in LBP and index leg pain at Days 3, 5, and 10; if a patient discontinued for any reason by Day 3, 5, or 10, the baseline observation carried forward was used to impute missing values and the patient was considered a non-responder. The Cochran-Mantel-Haenszel test with stratum as a controlling factor was used for between–treatment-group comparisons.

Mean changes in BPI-SF and SF-MPQ-2 scores were summarized descriptively and compared between treatment groups. PGIC and CGIC were summarized descriptively and between-group differences were analyzed using the Cochran-Mantel-Haenszel test.

Tolerability was assessed using AE rates for all patients who were randomized and received at least one dose of the study drug. Treatment-emergent AEs (TEAEs) were coded using the *Medical Dictionary for Regulatory Activities* (MedDRA), version 11.1. Incidences of all reported TEAEs were summarized descriptively. In addition, odds ratios (defined as the ratio of the odds for patients randomized to oxycodone IR to tapentadol IR) were calculated for the specific TEAEs of nausea, vomiting, constipation, and pruritus.

Results

Participant Flow

The study was conducted from September 29, 2009, to December 16, 2010. The safety population included 645 patients, and the mITT population included 585 patients. Patient demographic and baseline characteristics are summarized in Table 1. The percentage of male patients was higher in the tapentadol IR group (53.7% [154/287]) than in the oxycodone IR group (46.3% [138/298]); all other characteristics were similar between treatment groups.

In the tapentadol IR and oxycodone IR groups, respectively, 86.3% (277/321) and 82.7% (268/324) of patients completed the study. Patient disposition is shown in Fig. 1. The most common reason for study withdrawal in both treatment groups was AEs (tapentadol IR, 6.5% [21/321]; oxycodone IR, 7.1% [23/324]).

Treatment Exposure

Patients took tapentadol IR and oxycodone IR for a mean of 9.4 days and 9.1 days, respectively. Dosing quintiles are presented in Table 2.

During the study, 72.0% (231/321) of patients in the tapentadol IR group and 66.7% (216/324) of patients in the oxycodone IR group took concomitant medications. In the tapentadol IR and oxycodone IR groups, respectively, 11.5% (37/321) and 10.8% (35/324) of patients

took ibuprofen, 8.1% (26/321) and 6.5% (21/324) of patients took acetaminophen, 4.4% (14/321) and 7.4% (24/324) of patients took acetylsalicylic acid, and 4.0% (13/321) and 3.1% (10/324) of patients took mefenamic acid.

Outcomes

Sum of Pain Intensity Differences

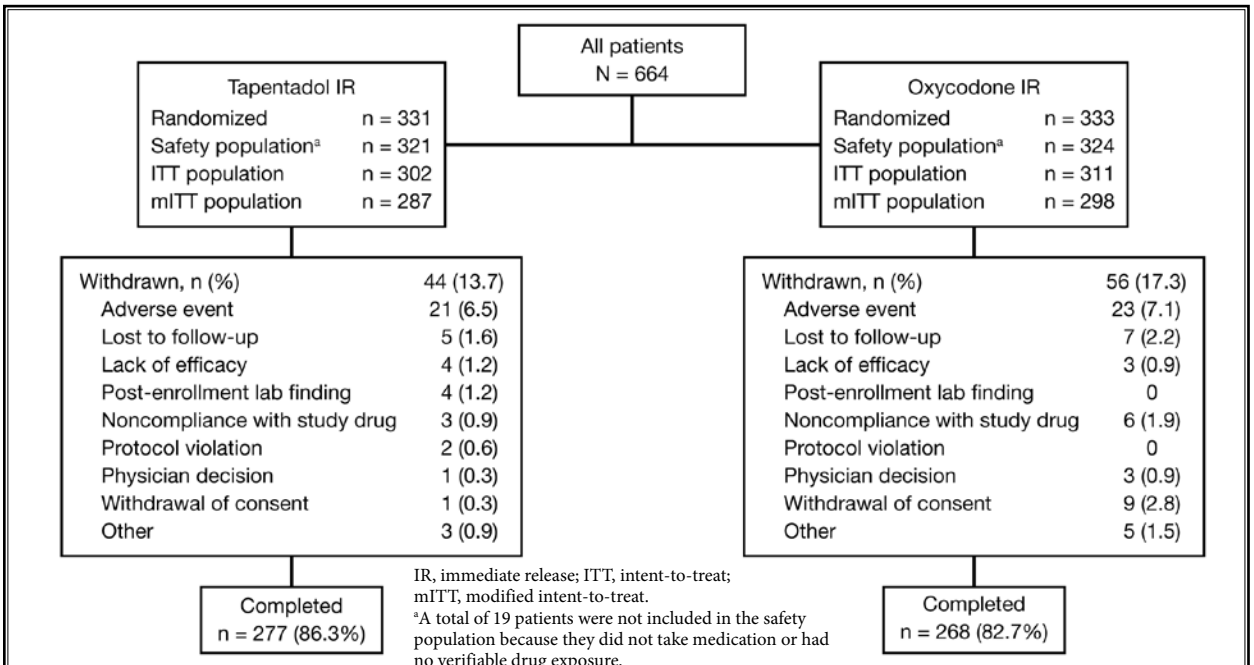
Results for SPID for LBP are summarized in Figure 2A. For the mITT population, the LSM (standard error [SE]) $SPID_{120}$ was 264.6 (11.43) for tapentadol IR and 264.0 (11.22) for oxycodone IR (95% CI for LSM difference, –32.1 to 30.9; 2-tailed $P = 0.9703$). Because the upper limit of the 95% CI was less than 120, the analgesic efficacy of tapentadol IR treatment was non-inferior to oxycodone IR treatment for LBP and thus, the primary clinical hypothesis was confirmed.

For the mITT population in Stratum I, the LSM (SE) $SPID_{120}$ for LBP was 268.9 (15.75) for tapentadol IR (n = 143) and 272.7 (15.53) for oxycodone IR (n = 147; 95% CI for LSM difference, –39.7 to 47.4; 2-tailed $P = 0.8613$). For the mITT population in Stratum II, the LSM (SE) $SPID_{120}$ was 260.5 (16.60) for tapentadol IR (n = 144) and 255.1 (16.21) for oxycodone IR (n = 151; 95% CI for LSM difference, –51.1 to 40.3; 2-tailed $P = 0.8158$).

Table 1. *Demographic and baseline characteristics of the Modified Intent-to-Treat Population.*

	Tapentadol IR (n = 287)	Oxycodone IR (n = 298)
Age, y		
Mean (SD)	45.1 (13.90)	44.9 (14.39)
Range	19 – 80	18 – 82
Race, n (%)		
White	202 (70.4)	207 (69.5)
Black or African American	67 (23.3)	75 (25.2)
Asian	9 (3.1)	6 (2.0)
American Indian or Alaskan Native	2 (0.7)	3 (1.0)
Other	5 (1.7)	5 (1.7)
Multiple	2 (0.7)	1 (0.3)
Not reported	0	1 (0.3)
Gender, n (%)		
Male	154 (53.7)	138 (46.3)
Female	133 (46.3)	160 (53.7)
Body mass index, kg/m²		
Mean (SD)	30.9 (8.73)	30.3 (8.48)
Baseline LBP intensity[a]		
Mean (SD)	7.4 (1.36)	7.3 (1.31)
Baseline index leg pain intensity[a]		
Mean (SD)	6.4 (2.07)	6.3 (2.02)

IR, immediate release; SD, standard deviation; LBP, low back pain. [a]Based on the 11-point numerical rating scale where 0 = "no pain" and 10 = "pain as bad as you can imagine." Baseline pain intensity score was the first pain score recorded by the patient in the interactive voice response system prior to the first dose of study drug.



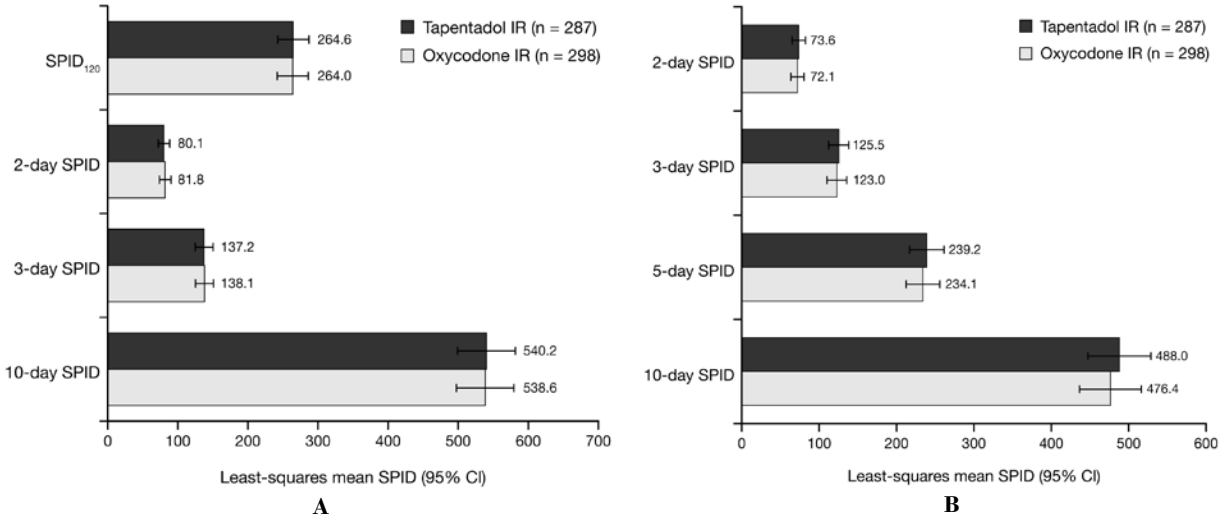
IR, immediate release; ITT, intent-to-treat; mITT, modified intent-to-treat.
[a]A total of 19 patients were not included in the safety population because they did not take medication or had no verifiable drug exposure.

Fig. 1. *Patient disposition.*

Table 2. *Quintiles for average daily dose in active treatment groups (safety population).*

Quintile	Tapentadol IR (n = 321)		Oxycodone IR (n = 324)	
	No. of patients[a]	Range of average daily doses, mg	No. of patients[a]	Range of average daily doses, mg
1	64	30.0 – 147.7	67	4.5 – 14.4
2	64	150.0 – 217.5	62	14.6 – 25.6
3	65	220.5 – 306.3	66	26.7 – 38.3
4	65	308.3 – 436.4	65	38.6 – 59.5
5	63	440.0 – 1,542.5	64	59.6 – 180.0

IR, immediate release.
[a]The number of patients could differ between quintiles if more than one patient had the same average daily dose at the minimum or maximum of the range in a given quintile.



SPID, sum of pain intensity differences; IR, immediate release; CI, confidence interval.

Fig. 2. *Summary of least-squares mean SPID results for (A) low back pain and (B) index leg pain (modified intent-to-treat population).*

No statistically significant differences were observed between the tapentadol IR and oxycodone IR treatment groups for mean 2-, 3-, or 10-day SPID for LBP (Fig. 2A) or for mean 2-, 3-, 5-, or 10-day SPID for index leg pain (Fig. 2B).

Between-group differences in $SPID_{120}$ values for index leg pain were not statistically significant in either stratum (Table 3). This study was not powered to demonstrate statistically significant differences in analgesic efficacy for leg pain within each stratum. However, in Stratum II, a numerical trend suggests a greater analgesic response for leg pain in the tapentadol IR group versus the oxycodone IR group for patients with lumbosacral radiculopathy (P <0.072).

Responder Rates

Responder rates for at least a 30% and at least a 50% improvement in LBP intensity and in index leg pain intensity at 3, 5, and 10 days were similar between treatment groups (Table 4). By Day 10, roughly 60% of patients in both treatment groups had at least a 30% reduction in LBP intensity and in index leg pain intensity, and more than 45% of patients in both treatment groups had at least a 50% reduction in LBP intensity and in index leg pain intensity.

BPI-SF and SF-MPQ-2

BPI-SF results are summarized in Table 5. Mean changes from baseline to Day 10 for "worst pain," "least

Table 3. *$SPID_{120}$ Results for Index Leg Pain (mITT Population).*

	Stratum I[a]		Stratum II[b]	
	Tapentadol IR (n = 143)	**Oxycodone IR (n = 147)**	**Tapentadol IR (n = 144)**	**Oxycodone IR (n = 151)**
Mean (SD) $SPID_{120}$	219.3 (179.96)	255.8 (198.16)	263.8 (218.56)	207.5 (226.58)
LSM (95% CI)	220.5 (191.5, 249.6)	254.6 (225.9, 283.2)	257.2 (223.5, 290.8)	213.9 (181.0, 246.8)
2-tailed *P* value[c]	0.1017		0.0718	

$SPID_{120}$, sum of pain intensity differences at 120 hours; mITT, modified intent-to-treat; IR, immediate release; SD, standard deviation; LSM, least-squares mean; CI, confidence interval; QTFC, Quebec Task Force Classification for Spinal Disorders.
[a]Clinical presentation consistent with QTFC Category 3 (acute low back pain and pain radiating below the knee).
[b]Clinical presentation consistent with QTFC Category 4 (Category 3 criteria and neurologic findings suggestive of lumbosacral radiculopathy [ie, at least 2 abnormal findings: unilateral abnormality in muscle strength, deep tendon reflex, or sensation in a dermatomal pattern]) or Category 6 (Category 4 criteria and evidence of nerve root compression on imaging).
[c]Oxycodone IR – tapentadol IR.

Table 4. *Responders Based on Percentage Change From Baseline in Low Back Pain and Index Leg Pain Intensity (mITT Population).*

Percentage change from baseline in pain intensity, n (%)	Tapentadol IR (n = 287)	Oxycodone IR (n = 298)	*P* value
Low back pain			
Day 3			
≥ 30% reduction	135 (47.0)	135 (45.3)	0.6786
≥ 50% reduction	81 (28.2)	76 (25.5)	0.4618
Day 5			
≥ 30% reduction	154 (53.7)	166 (55.7)	0.6157
≥ 50% reduction	98 (34.1)	94 (31.5)	0.5071
Day 10			
≥ 30% reduction	177 (61.7)	177 (59.4)	0.5769
≥ 50% reduction	130 (45.3)	137 (46.0)	0.8645
Index leg pain			
Day 3			
≥ 30% reduction	140 (48.8)	143 (48.0)	0.8567
≥ 50% reduction	90 (31.4)	97 (32.6)	0.7442
Day 5			
≥ 30% reduction	159 (55.4)	170 (57.0)	0.6789
≥ 50% reduction	110 (38.3)	111 (37.2)	0.7981
Day 10			
≥ 30% reduction	170 (59.2)	173 (58.1)	0.7799
≥ 50% reduction	135 (47.0)	142 (47.7)	0.8728

mITT, modified intent-to-treat; IR, immediate release.

pain," "pain on average," and "pain right now" were not significantly different between treatment groups (*P* >0.05). On average, patients who received either tapentadol IR or oxycodone IR experienced at least a 3.5-point improvement in "worst pain" and "pain right now" and at least a 2.8-point improvement in "least pain" and "pain on average" from baseline to Day 10.

No between–treatment-group differences were observed for tapentadol IR versus oxycodone IR for mean changes from baseline to Day 10 in SF-MPQ-2 subscale

Table 5. *Mean (SD) Brief Pain Inventory-short form scores*[a].

Item	Tapentadol IR (n = 302)	Oxycodone IR (n = 311)
Worst pain in the past 24 hours		
Baseline	8.4 (1.21)	8.3 (1.29)
Day 10/last visit	4.7 (2.49)	4.6 (2.65)
Change from baseline to Day 10	−3.6 (2.49)	−3.7 (2.66)
Least pain in the past 24 hours		
Baseline	5.6 (1.93)	5.7 (1.94)
Day 10/last visit	2.8 (2.13)	2.9 (2.35)
Change from baseline to Day 10	−2.9 (2.47)	−2.8 (2.60)
Pain on average		
Baseline	7.0 (1.40)	7.0 (1.38)
Day 10/last visit	4.0 (2.17)	3.9 (2.41)
Change from baseline to Day 10	−3.0 (2.34)	−3.0 (2.42)
Pain right now		
Baseline	7.0 (1.55)	7.0 (1.54)
Day 10/last visit	3.5 (2.38)	3.4 (2.55)
Change from baseline to Day 10	−3.5 (2.53)	−3.6 (2.65)

SD, standard deviation; IR, immediate release.
[a]A score of 0 = "no pain" and a score of 10 = "pain as bad as you can imagine."

Table 6. *Treatment-emergent adverse events reported by ≥5% of patients treated with Tapentadol IR or Oxycodone IR (safety population)*.

Type of TEAE, n (%)	Tapentadol IR (n = 321)	Oxycodone IR (n = 324)
No. of patients with ≥ 1 TEAE	168 (52.3)	188 (58.0)
Gastrointestinal disorders	94 (29.3)	140 (43.2)
Vomiting	51 (15.9)	80 (24.7)
Nausea	51 (15.9)	67 (20.7)
Constipation	7 (2.2)	23 (7.1)
Nervous system disorders	70 (21.8)	78 (24.1)
Dizziness	38 (11.8)	34 (10.5)
Somnolence	26 (8.1)	22 (6.8)
Headache	14 (4.4)	20 (6.2)
Skin and subcutaneous tissue disorders	31 (9.7)	32 (9.9)
Pruritus	27 (8.4)	26 (8.0)

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

or total scores (all P >0.05). The greatest difference in mean (SD) change from baseline between tapentadol IR and oxycodone IR was observed in Stratum II for the neuropathic pain subscale at Day 10 (–2.1 [2.13] vs –1.6 [1.96]; P = 0.0755).

PGIC, CGIC, and Patient Satisfaction

PGIC results showed that approximately two-thirds of patients rated their overall condition as "very much improved" or "much improved" in both the tapentadol IR (66.2% [200/302]) and oxycodone IR (66.2% [206/311]) treatment groups. Similarly, about two-thirds of clinicians rated their patients' conditions as "very much improved" or "much improved" in both treatment groups (tapentadol IR, 67.9% [205/302]; oxycodone IR, 66.6% [207/311]). Less than 2% of patients and clinicians in both treatment groups rated conditions as "minimally worse," "much worse," or "very much worse."

On Day 5, a higher percentage of patients in the tapentadol IR group indicated they were "very satisfied" with their treatment (37.4% [113/302]) compared with the oxycodone IR group (29.6% [92/311]; P = 0.0401). By the end of the study, similar percentages of patients in the tapentadol IR (48.3% [146/302]) and oxycodone IR (47.6% [148/311]) groups indicated they were "very satisfied" with their treatment (P = 0.4679). A small percentage of patients in the tapentadol IR and oxycodone IR groups indicated they were "very dissatisfied" with the study drug at both Day 5 (1.0% and 1.3%, respectively) and at end-of-study (3.3% and 4.2%, respectively).

Adverse Events

A total of 52.3% (168/321) of patients in the tapentadol IR group and 58.0% (188/324) of patients in the oxycodone IR group reported at least one TEAE. The majority of TEAEs were mild or moderate in intensity. Table 6 shows TEAEs reported by at least 5% of patients in either treatment group. Gastrointestinal TEAEs of vomiting and constipation were significantly more likely to occur in the oxycodone IR group than in the tapentadol IR group (odds ratio [95% CI] for vomiting, 1.74 [1.17 - 2.57]; for constipation, 3.43 [1.45 - 8.11]).

Two (0.6%) patients in the tapentadol IR group and 3 (0.9%) patients in the oxycodone IR group experienced treatment-emergent serious AEs. Neither of the events in the tapentadol IR group (back pain or metastatic lung cancer) was considered by the investigators to be related to the study drug. Two of the 3 events in the oxycodone IR group were considered probably (syncope) or possibly (convulsion) related to the study drug, and the remaining event (anxiety) was not considered related to the study drug. Twenty-one (6.5%) patients in the tapentadol IR group and 26 (8.0%) patients in the oxycodone IR group discontinued from the study because of TEAEs.

Discussion

This head-to-head study of up to 10 days in duration comparing flexible dosing regimens of tapentadol IR (50, 75, or 100 mg) versus oxycodone HCl IR (5, 10, or 15 mg) every 4 to 6 hours as needed for pain was designed to reflect usual analgesic use in clinical practice. Thus, comparing these oxycodone IR doses with the approved doses of tapentadol IR (50, 75, or 100 mg) (20) enables physicians to consider the results associated with tapentadol IR treatment within the context of results from an established and commonly prescribed Schedule II analgesic. Previous studies have shown that in patients with post-surgical pain, the analgesic efficacy of tapentadol IR 50 and 75 mg is non-inferior to that of oxycodone HCl IR 10 mg (13), and that tapentadol IR 100 mg and oxycodone HCl IR 15 mg provide equivalent analgesia (14).

For the dose ranges used in this study, tapentadol IR and oxycodone IR had comparable analgesic efficacy for the relief of moderate to severe, acute LBP and the associated radicular leg pain. Observed mean changes on the BPI-SF from baseline to Day 10 indicate that patients in both treatment groups achieved clinically meaningful reductions in pain intensity. With both treatments, the majority of patients and clinicians reported patients' conditions to be "much improved" or "very much improved" by the end of the study. At Day 5, the percentage of patients who were "very satisfied" with their treatment was 7.8% higher in the tapentadol IR group than in the oxycodone IR group, and by the end of the study, more than 75% of patients in both treatment groups indicated they were "somewhat satisfied" or "very satisfied" with their treatment.

Consistent with the results of previously completed studies of tapentadol IR or oxycodone IR for acute pain (13-16), this study demonstrated that the gastrointestinal tolerability profile of tapentadol IR is better than that of oxycodone IR when taken as needed for pain in a flexible dosing regimen; specifically, patients treated with tapentadol IR were significantly less likely to experience vomiting or constipation.

A limitation of this study may be the strict patient monitoring that was performed. Intensive patient monitoring is generally not representative of real-world medical practice. Consequently, higher incidences of TEAEs may have been reported than would be expected in a typical practice setting; however, this bias is anticipated to be similar for both treatment groups.

Conclusion

This head-to-head study of up to 10 days in duration demonstrated that tapentadol IR had comparable analgesic efficacy and overall safety to that of oxycodone IR for the relief of moderate to severe, acute LBP and associated radicular leg pain when using flexible dosing regimens that reflect typical use in clinical practice; however, tapentadol IR had a better gastrointestinal tolerability profile, particularly for the common opioid-related AEs of vomiting and constipation. Because this study was not powered to show statistically significant differences in analgesic efficacy for leg pain within each stratum, additional studies comparing treatment responses in patients with radicular leg pain (ie, pain with no neurologic deficit) versus lumbosacral radiculopathy (ie, pain with neurologic deficits) are warranted. Additional analyses are planned to further evaluate between-group differences based on enrollment stratum, outcome measures, and global assessments.

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