

# Role of Tapentadol Immediate Release (Nucynta) in the Management Of Moderate-to-Severe Pain



Bazhena Fidman, PharmD Candidate, and Anna Nogid, BS, PharmD, BCPS

## INTRODUCTION

Widespread in the U.S., pain is associated with significant adverse economic, clinical, and quality-of-life outcomes: from 15% to 20% of patients in the U.S. experience acute pain, up to 75% of patients experience pain after surgery, and 68 million people have chronic pain each year.<sup>1,2</sup> Uncontrolled pain is the leading cause of disability; it may also delay patient recovery from surgery, increase risk of life-threatening events (such as deep-vein thrombosis or myocardial infarction), and lead to the development of chronic pain.<sup>1</sup> For back pain alone, total health care expenditures in 2004 and 2005 were estimated at \$85 billion to \$100 billion.<sup>3</sup>

Current pharmacological treatment options commonly used for moderate-to-severe pain include anticonvulsants, antidepressants, nonsteroidal anti-inflammatory agents (NSAIDs), tramadol (Ultram, PriCara), and opioids. Anticonvulsants and antidepressants are associated with intolerable adverse effects (AEs) and numerous drug interactions, and successful analgesia is achieved in only 50% of patients with neuropathic pain.<sup>2</sup> NSAIDs are effective for managing chronic pain, but their use is limited by their gastrointestinal (GI) and cardio-

vascular toxicity, adverse renal effects, and an increased risk of bleeding. Opioids are highly effective for acute and chronic pain, but their use is limited by nausea, vomiting, constipation, and sedation, as well as the possibility of addiction or dependence. Tramadol is an attractive alternative to opioids, but it is subject to genetic polymorphism because it is metabolized by cytochrome P-450 (CYP) 2D6, has a neurotoxic metabolite, and may predispose patients to serotonin syndrome.<sup>4</sup>

Despite the availability of these numerous options, pain continues to be undertreated,<sup>2</sup> indicating a need for a potent analgesic with a low side-effect profile. Tapentadol HCl immediate release (IR) (Nucynta, PriCara), a centrally acting analgesic, was approved by the FDA on November 20, 2008, for the relief of moderate-to-severe acute pain. A long-acting formulation is being investigated.

## PHARMACOLOGY

Tapentadol produces its pharmacological effect by mu-opioid agonism and norepinephrine reuptake inhibition<sup>5,6</sup> and is highly selective for the mu-opioid receptor. By comparison, the drug's binding to the kappa-opioid receptor and delta-opioid receptor is 10-fold less potent, and binding to the ORL1 receptor is 1,000-fold less potent. Tolerance is possible but appears to be delayed.<sup>6</sup>

## PHARMACOKINETICS

Tapentadol is rapidly absorbed, with a maximum serum concentration ( $C_{max}$ ) typically observed between 1.25 and 1.5 hours.<sup>7</sup> Dose-proportional increases in the  $C_{max}$  and area-under-the-curve (AUC) values of tapentadol have been observed above the 50- to 150-mg dose range, suggesting linear pharmacokinetics. Tapentadol's AUC and  $C_{max}$  are increased by 25% and 16%, respectively, following a high-fat, high-calorie meal.

The mean absolute bioavailability after

a single dose is 32% as a result of the medication's extensive first-pass metabolism. Tapentadol is widely distributed throughout the body, with a volume of distribution of approximately 540 liters.<sup>5</sup> Plasma binding is low and has been reported at approximately 20%.<sup>8</sup>

Tapentadol is primarily and extensively (70%) metabolized via glucuronidation by the UGT1A9 and UGT2B7 enzymes to inactive metabolites. Phase 1 metabolites include *N*-desmethyl tapentadol (13%) as a result of metabolism by CYP 2C9 and 2C19, and hydroxytapentadol (2%), as a result of metabolism by CYP 2D6, which are further metabolized by conjugation.<sup>7</sup> The metabolites of tapentadol do not contribute to the drug's analgesic activity.<sup>5</sup>

Tapentadol is excreted primarily by the renal system (99%); 69% is excreted in the form of conjugates, 27% as other metabolites, and 3% as unchanged drug. Fecal clearance accounts for 1% of tapentadol's elimination.

The apparent half-life of tapentadol following oral administration is 3.93 hours, and more than 95% of the drug is excreted within 24 hours of dosing.<sup>7</sup> The total tapentadol clearance is  $1,530 \pm 177$  mL/minute.<sup>5</sup>

The pharmacokinetic properties of tapentadol do not appear to be affected by renal impairment. Moderate hepatic impairment results in decreased metabolism of tapentadol, resulting in higher exposures and serum tapentadol levels. The pharmacokinetic parameters of tapentadol have not been evaluated in patients with severe hepatic impairment.<sup>5</sup>

## CLINICAL TRIALS

### Phase 2 Trials

Stegmann et al.<sup>9</sup>

Stegmann and associates conducted a randomized, double-blind, phase 2 study to assess the efficacy and tolerability of multiple doses of tapentadol for the relief of acute pain following orthopedic sur-

Bazhena Fidman is a student at Arnold & Marie Schwartz College of Pharmacy and Health Sciences, Long Island University, in Brooklyn, New York. Dr. Nogid is Associate Professor of Pharmacy Practice at the Arnold & Marie Schwartz College of Pharmacy, Long Island University; and a Critical Care Pharmacist at Brookdale University Hospital and Medical Center in Brooklyn. Drug Forecast is a regular column coordinated by Alan Caspi, PhD, PharmD, MBA, President of Caspi & Associates in New York, New York.

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gery. Patients (n = 269) between 18 and 65 years of age who underwent a unilateral first metatarsal bunionectomy were included in the study if they experienced postoperative pain of greater or equal to 4 on an 11-point numeric rating scale (NRS) (where 0 = no pain and 10 = the worst pain imaginable) and an increase in pain of greater or equal to 1 point within nine hours after anesthesia was discontinued on the first postoperative day.

Patients with moderate-to-severe postoperative pain received tapentadol 50 mg (n = 67), tapentadol IR 100 mg (n = 68), oxycodone HCl IR 10 mg (OxyContin, Purdue) (n = 67), or placebo (n = 67). The study drug was administered every four to six hours over a 72-hour period starting one day after surgery (evaluation day 2). The primary efficacy endpoint was the sum of pain intensity over 24 hours (SPI<sub>24</sub>) on the second day after randomization (evaluation day 3). Pain intensity was measured with the use of the verbal rating scale (VRS) and the NRS.

Compared with placebo, tapentadol treatment resulted in a significant decrease in pain intensity, as reported by patients, on the third evaluation day with mean SPI<sub>24</sub> (VRS) scores of 33.6 for tapentadol 50 mg, 29.2 for tapentadol 100 mg, 35.7 for oxycodone, and 41.9 for placebo (*P* < 0.05 for placebo vs. tapentadol). Tapentadol also resulted in lower SPI<sub>24</sub> (VRS) scores, compared with placebo, on evaluation days 2 and 4. A statistically significant decrease in mean SPI<sub>24</sub> (NRS) scores for both tapentadol groups, compared with the placebo group, was noted on evaluation days 2, 3, and 4.

Tapentadol 50 mg resulted in a significant decrease in total pain relief after 24 hours (TOTPAR<sub>24</sub>) on evaluation day 2, compared with placebo. Tapentadol 100 mg resulted in a significant decrease in TOTPAR<sub>24</sub>, compared with placebo, on all evaluation days.

In addition, 61.4% of patients in the tapentadol 50-mg group, 86.4% of patients in the tapentadol 100-mg group, 74.2% of patients in the oxycodone group, and 45.4% of patients in the placebo group rated the study medication as good, very good, or excellent at controlling their pain on study day 3. More placebo patients (98.5%) required the study medication compared with those receiving tapentadol 50 mg (80.6%), tapentadol 100 mg (76.5%), and oxycodone (80.6%).

The most common AEs included nausea, dizziness, somnolence, vomiting, headache, generalized pruritus, hyperhidrosis, constipation, and feeling hot. Tapentadol 50 mg was associated with lower rates of nausea, dizziness, and constipation and a similar rate of somnolence, compared with oxycodone IR 10 mg. Statistical analysis for differences in AEs was not performed.

In this trial, tapentadol IR was effective and safe for the relief of acute postoperative pain following bunionectomy.

#### Kleinert et al.<sup>10</sup>

Kleinert and colleagues conducted a randomized, double-blind, placebo-controlled trial to assess the efficacy and tolerability of tapentadol, compared with morphine, ibuprofen, and placebo, in patients with moderate-to-severe postoperative dental pain. Patients (n = 400) were between 18 and 45 years of age who had undergone extraction of the mandibular third molar with bone removal because of impaction and pain within six hours after surgery. The patients received a single oral dose of tapentadol 25, 50, 75, 100, or 200 mg; morphine sulfate 60 mg; ibuprofen 400 mg; or placebo. The primary efficacy endpoint was mean total pain relief over eight hours (TOTPAR<sub>8</sub>). Secondary efficacy endpoints were total pain relief over four hours (TOTPAR<sub>4</sub>) and the time to onset of analgesia.

Mean TOTPAR<sub>8</sub> scores were significantly higher with placebo than with tapentadol 75 mg, 100 mg, 200 mg; morphine; and ibuprofen. Similar findings were noted for mean TOTPAR<sub>4</sub> scores for those receiving tapentadol 50 mg, 75 mg, 100 mg, 200 mg, morphine, and ibuprofen.

Pain-intensity difference scores increased in a dose-proportional manner, with peak differences noted at two hours and decreasing gradually thereafter. The percentages of patients rating study medication as good, very good, or excellent were 22%, 28%, 35%, 50%, and 68% for tapentadol 25 mg, 50 mg, 75 mg, 100 mg, and 200 mg, respectively; 55% for methadone; and 12% for placebo. The percentages of patients experiencing a 50% reduction in pain were 32.7% for tapentadol 25 mg, 46% for tapentadol 50 mg and 75 mg, 64.6% for tapentadol 100 mg, 87.8% for tapentadol 200 mg, 64.7% for mor-

phine, 76.5% for ibuprofen, and 25.1% for placebo. The onset of effect appeared to be more rapid for the 200-mg dose of tapentadol, compared with morphine (0.7 vs. 1.2 hours).

The most commonly reported AEs were dizziness, nausea, vomiting, and somnolence, as follows:

- The incidence of AEs was lowest with ibuprofen and placebo.
- The incidence of nausea and vomiting appeared to be lower with all doses of tapentadol when compared with morphine.
- The incidence of dizziness was lower with tapentadol 100 mg or less, compared with placebo.
- The incidence of dizziness with tapentadol 200 mg was similar to that with morphine.
- The incidence of somnolence was higher with tapentadol 200 mg and morphine.

Differences in safety findings between study groups were not statistically significant.

These results suggest that tapentadol was effective and well tolerated for managing moderate-to-severe pain after dental procedures. The efficacy of tapentadol 100 mg and 200 mg was comparable to that of morphine and ibuprofen. Tapentadol had a more rapid onset of analgesic effect and resulted in patient satisfaction similar to that of morphine and ibuprofen.

In summary, the safety profile of tapentadol 100 mg and 200 mg was similar to that of morphine, with a potentially lower incidence of AEs when doses of tapentadol were less than 100 mg.

### Phase 3 Studies

#### Daniels et al.<sup>11</sup>

Daniels and coworkers conducted a randomized, double-blind, and placebo- and active-controlled study to evaluate the efficacy of tapentadol following a bunionectomy in patients with moderate-to-severe pain. Patients (N = 603) received tapentadol 50, 75, or 100 mg; oxycodone IR 15 mg; or placebo every four to six hours for three days following the procedure. The primary endpoint was the sum of pain-intensity difference (SPID) over 48 hours (SPID<sub>48</sub>). Secondary endpoints included the SPID over a period of

12, 24, and 72 hours (SPID<sub>12</sub>, SPID<sub>24</sub>, and SPID<sub>72</sub>, respectively); total pain relief; use of rescue medication; overall impression of change; and perceived onset of action of the medication.

Patients receiving tapentadol (regardless of the dose) and oxycodone showed a statistically significant decrease in pain intensity, as evidenced by a decrease in SPID<sub>48</sub>, when compared with placebo. Higher doses of tapentadol were associated with higher levels of pain relief. A similar decrease in pain intensity was noted in SPID<sub>12</sub>, SPID<sub>24</sub>, and SPID<sub>72</sub>. The proportion of patients achieving pain reduction of at least 30% to 50% was significantly higher in the active-treatment patients compared with patients assigned to receive placebo. A reduction in pain intensity of 50% or greater was noted in 30% of the placebo patients, in 56.7% to 70.3% of patients assigned to tapentadol, and in 72.8% of patients receiving oxycodone ( $P < 0.001$  vs. placebo). The percentage of patients requiring rescue medication was 49% in the placebo group, 10% to 19% in the tapentadol groups, and 9% in the oxycodone group. Patients receiving tapentadol also attained pain relief more quickly than those receiving placebo ( $P \leq 0.005$ ).

The incidence of AEs was 70% with tapentadol 50 mg; 75% with tapentadol 75 mg; 85% with tapentadol 100 mg; 87% with oxycodone IR 15 mg; and 41% with placebo. The most common AEs observed were nausea, vomiting, constipation, dizziness, and somnolence. The incidence of GI effects was lower with tapentadol compared with oxycodone. The incidence of somnolence was similar for tapentadol 100 mg and oxycodone and lower with tapentadol 50 mg and 75 mg compared with oxycodone. The difference in AEs between the tapentadol and oxycodone groups was statistically significant.

Thus, multiple doses of tapentadol significantly reduced acute, postsurgical pain when compared with placebo. Furthermore, tapentadol 100 mg had efficacy comparable to that of oxycodone IR 15 mg. Tapentadol provided effective analgesia and a potentially superior GI tolerability profile compared with oxycodone.

#### Daniels et al.<sup>12</sup>

Another randomized, double-blind,

active- and placebo-controlled, parallel-group multicenter trial was conducted to evaluate the safety and efficacy of tapentadol for acute postsurgical pain. Patients ( $n = 901$ ) received tapentadol 50 mg, tapentadol 75 mg, oxycodone 10 mg, and placebo. The primary efficacy endpoint was SPID<sub>48</sub>. The primary safety endpoint was the incidence of treatment-emergent AEs of nausea and/or vomiting.

Patients receiving tapentadol and oxycodone reported statistically significant reductions in pain intensity compared with those receiving placebo, based on SPID<sub>48</sub>. A similar trend in reduced pain intensity was noted at 12, 24, and 72 hours with tapentadol and oxycodone, compared with placebo ( $P < 0.001$ ).

An additional analysis showed that analgesic efficacy of both doses of tapentadol was non-inferior to that of oxycodone. The proportion of patients with a reduction of 50% or more in pain intensity was 64.7% for tapentadol 50 mg ( $P = 0.009$  vs. placebo), 64% for tapentadol 75 mg ( $P = 0.12$  vs. placebo), 64.4% for oxycodone ( $P = 0.010$  vs. placebo), and 47.8% for placebo. More placebo patients (23.2%) required rescue medications compared with the oxycodone group (3.2%), patients receiving tapentadol 75 mg (1.4%), and those receiving tapentadol 50 mg (6.2%).

AEs occurred in 68% of patients receiving tapentadol 50 mg, in 75% of patients receiving tapentadol 75 mg, in 83% of patients receiving oxycodone, and in 51% of patients in the placebo group. The most commonly reported AEs were nausea, vomiting, constipation, dizziness, and somnolence. The number of AEs was lower with tapentadol 50 mg than with placebo. The percentage of patients receiving tapentadol 50 mg who reported nausea or vomiting was significantly lower (35%) compared with the oxycodone group (59%) ( $P < 0.001$ ).

In summary, tapentadol was more effective than placebo and was non-inferior to oxycodone for managing acute pain. It was also associated with a potentially lower incidence of GI adverse effects.

#### Hartrick et al.<sup>13</sup>

Hartrick and colleagues conducted a randomized, double-blind study to evaluate the efficacy and tolerability of 10 days of treatment with tapentadol 50 mg

and 75 mg, oxycodone 10 mg, and placebo for patients with poorly controlled pain associated with osteoarthritis of the hip or knee. Patients were asked to discontinue the use of products containing opioids before the study run-in period. The use of non-opioid analgesics at a steady dose was allowed. The investigators used the numeric rating scale (NRS) for pain intensity, the NRS for pain relief, and the Patient Global Impression of Change (PGI-C) for assessment of pain and measurement of the primary efficacy outcomes.

The investigators randomly assigned 674 patients to treatment; 659 patients were included in the efficacy analysis and 666 patients were included in the safety analysis. Administration of tapentadol 50 mg, tapentadol 75 mg, and oxycodone resulted in a statistically significant decrease in pain intensity, compared with placebo, at days 2, 5, and 10. The percentage of patients with a decrease in pain intensity of at least 30% at day 5 was 43% for tapentadol 50 mg ( $P = 0.028$  vs. placebo), 41% for tapentadol 75 mg ( $P = 0.033$  vs. placebo), 40% for oxycodone 10 mg, and 30% for placebo.

Significantly more patients who received oxycodone discontinued treatment, compared with patients receiving tapentadol 50 mg (35% vs. 18%, respectively;  $P < 0.001$ ). AEs, particularly GI and neurological effects, were the primary reason for discontinuing the study drug in 13% of the tapentadol 50-mg group, 18% of the tapentadol 100-mg group, 30% of the oxycodone group, and 4% of the placebo group.

The most common AEs were dizziness, nausea, vomiting, somnolence, constipation, pruritus, and fatigue. The number of AEs was lower for both doses of tapentadol compared with oxycodone.

#### Hale et al.<sup>14</sup>

Hale et al. conducted a randomized, double-blind, active-control, parallel-group multicenter trial to evaluate the long-term tolerability and safety of tapentadol in patients with low back pain or osteoarthritis. Patients ( $n = 878$ ) with a pain-intensity score of at least 4 on an 11-point NRS while taking non-opioid analgesics received tapentadol 50 or 100 mg every four to six hours ( $n = 679$ ), as needed, or oxycodone 10 or 15 mg every four to six hours ( $n = 170$ ), as

needed, for a total of 90 days. The use of non-opioid analgesics at a stable dose was allowed, but the use of opioid rescue medication was not permitted.

During the study period, AEs were reported by 76.3% of the tapentadol patients and by 82.9% of the oxycodone patients. The most common AEs were GI events (44.2% for tapentadol vs. 63.5% for oxycodone), central nervous system (CNS) events (36.7% for tapentadol vs. 37.1% for oxycodone), and pruritus (4.3% for tapentadol vs. 11.8% for oxycodone).

Of those patients in the tapentadol group, 42% discontinued the study drug early, compared with 49% of patients in the oxycodone IR group; 21% of patients receiving tapentadol and 31% of the oxycodone patients discontinued the drug secondary to AEs. There were no differences in pain-intensity scores between the tapentadol group (4.9) and the oxycodone group (5.2).

At the end of treatment, 66% of the tapentadol patients and 62% of the oxycodone patients reported their overall status as improved, suggesting that there was no difference in efficacy between the two study groups.

Although statistical analyses were not performed in this study, it appears that tapentadol was as effective as oxycodone in managing chronic pain and was associated with a lower risk of GI adverse events.

## SAFETY AND TOLERABILITY

The most commonly reported AEs of tapentadol therapy in clinical trials have been nausea, vomiting, dizziness, somnolence, pruritus, dry mouth, headache, and fatigue. The effects appear to be dose-related, with higher doses resulting in a higher potential for AEs.<sup>9-14</sup>

## CONTRAINDICATIONS AND PRECAUTIONS

Tapentadol is contraindicated in those patients with impaired pulmonary function and paralytic ileus. This medication should not be used in combination with monoamine oxidase (MAO) inhibitors or within 14 days of discontinuation of MAO inhibitors. It should be used with caution in patients with asthma, chronic obstructive pulmonary disease, cor pulmonale, severe obesity, sleep apnea, myxedema, kyphoscoliosis, CNS depression, seizures, or coma.

Tapentadol should not be prescribed for patients with head injury or increased intracranial pressure.<sup>5</sup>

## DOSAGE

The manufacturer recommends that tapentadol be initiated at a dose of 50 mg, 75 mg, or 100 mg, administered every four to six hours. The dose should then be tailored to each individual, based on the severity of pain and the patient's previous experience with similar drugs, to maintain adequate analgesia while avoiding unwanted effects of therapy. On the first day of dosing, the second dose may be administered one hour after the first dose. Doses greater than 700 mg on day 1 and 600 mg on subsequent days are not recommended.

Dose adjustments are not needed in patients with renal insufficiency or in those with mild hepatic impairment. In patients with moderate hepatic impairment, tapentadol should be initiated at a dose of 50 mg, with the interval between doses of at least eight hours. Tapentadol has not been studied in patients with severe liver impairment.<sup>5</sup>

## DRUG INTERACTIONS

Tapentadol has minimal potential for pharmacokinetic drug interactions because it does not undergo significant metabolism by the CYP 450 system. Tapentadol does not inhibit the activity of CYP 1A2, 2A6, 2C9, 2C19, 2E1, or 3A4, but it has been shown to inhibit CYP 2D6 to a limited extent.<sup>8</sup> Tapentadol does not induce CYP 1A2, 2D6, or 3A4 metabolism. Displacement interactions are unlikely as a result of the drug's low protein-binding properties.<sup>8</sup>

Administration of tapentadol concomitantly with acetaminophen, acetylsalicylic acid, and naproxen has not resulted in clinically relevant changes in tapentadol serum concentrations.<sup>15</sup> Co-administration of tapentadol with opioid analgesics, general anesthetics, phenothiazines, other tranquilizers, sedatives, hypnotics, or other CNS depressants may result in additive CNS depression. Administering tapentadol with serotonergic drugs such as selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), MAO inhibitors, and triptans may result in serotonin syndrome.<sup>5</sup>

## CONCLUSION

Tapentadol is a centrally acting analgesic with established efficacy in acute pain, chronic pain, neuropathic pain, and pain with an inflammatory origin. The drug follows linear pharmacokinetics, is absorbed rapidly, attains maximum concentrations quickly, and is excreted primarily by the renal system in the form of inactive metabolites. Tapentadol is not metabolized by the CYP 450 system to a significant extent, and it does not induce or inhibit CYP enzymes to a clinically significant effect, resulting in a low potential for drug interactions.

Adverse effects are primarily related to the CNS and GI tract and have been reported to occur less frequently than in patients treated with opioids. Tapentadol is an important addition to the armamentarium for the management of moderate-to-severe pain.

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