

# Tapentadol: A Review of Experimental Pharmacology Studies, Clinical Trials, and Recent Findings

Fahad S Alshehri 

Department of Pharmacology and Toxicology, College of Pharmacy, Umm Al-Qura University, Makkah, Saudi Arabia

Correspondence: Fahad S Alshehri, Department of Pharmacology and Toxicology, College of Pharmacy, Umm Al-Qura University, Makkah, 24382, Saudi Arabia, Email fsshehri@uqu.edu.sa

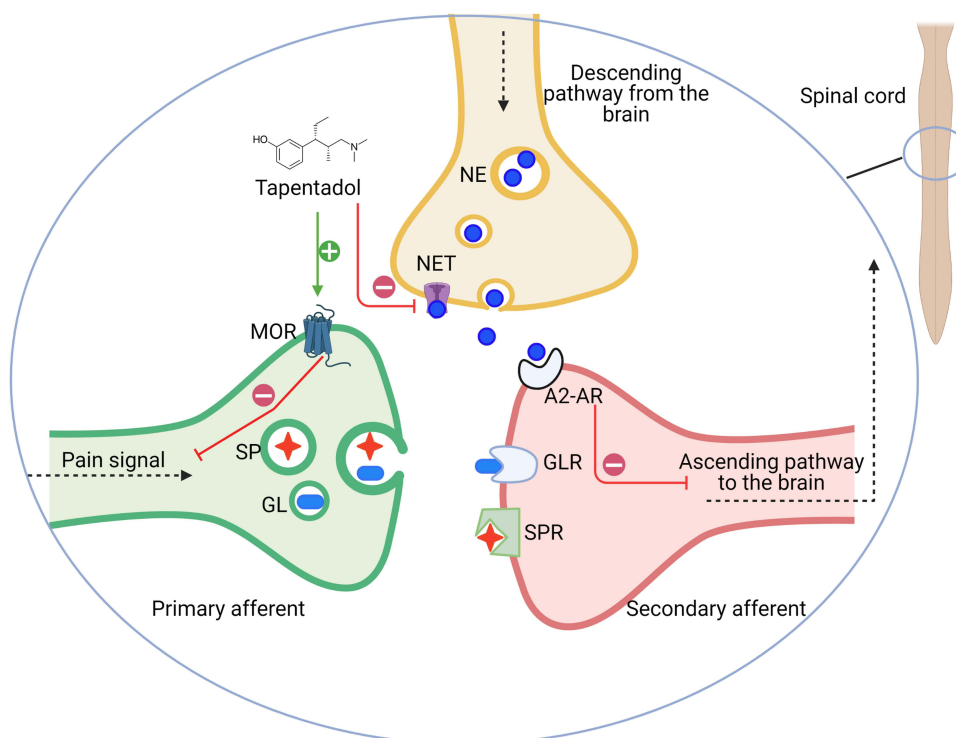
**Abstract:** Tapentadol is an analgesic compound that acts centrally to attenuate pain. Previous studies have shown that tapentadol has dual mechanisms of action as a mu-opioid receptor agonist and noradrenaline re-uptake inhibition. Therefore, tapentadol provides a great advantage over classic opioids in pain management from nociceptive to neuropathic. Cumulative evidence from in vitro data suggests that tapentadol effect of norepinephrine re-uptake could be a new target that overcomes other classic opioids in chronic neuropathic pain. Compared to tramadol and other opioids, tapentadol is associated with fewer adverse effects than tramadol. Tapentadol is a new alternative to treat acute, chronic, and neuropathic pain. Thus, this review article was focused on understanding the studies that led to the development of tapentadol as a novel analgesic drug and its advantages over conventional opioids. Thus, tapentadol is a good alternative with fewer adverse effects and is available for human use.

**Keywords:** opioids, chronic pain, neuropathic pain, clinical trials

## Introduction

Opioids have been used for a long time to treat acute pain, chronic pain, post-surgical pain, and cancer pain.<sup>1–3</sup> Opioids have also been used as cough suppressants and antidiarrheals.<sup>4,5</sup> Although opioids have great pain-relieving properties, they also have short- and long-term adverse effects, mostly involving the central nervous system. Short-term effects include nausea, vomiting, respiratory depression, mood swings, and difficulty in urination, while long-term effects include hyperalgesia, delirium, and seizures. Therefore, opioids, such as morphine, develop tolerance and lose effectiveness in chronic pain, especially in neuropathic and inflammatory types of chronic pain.<sup>6,7</sup> The existence of neuropathic pain is a major burden for patients. Various factors, including diabetic complications, vitamin B12, folate deficiencies, and certain inflammatory and idiopathic conditions, can cause it. Chronic idiopathic disease (eg, complex regional pain syndrome) is a chronic and painful disorder affecting patient life quality. The syndrome is triggered by severe traumatic injury of the soft tissues, including the surrounding nerves, possibly due to autonomic dysfunction, neurogenic inflammation, and neuroplasticity. These diseases require continuous treatment with pain relief medications, and in most cases, these medications are required for life. Thus, administering opioids for a long time can cause adverse effects and increase the chances of abuse and addiction.

The search for compounds that produce better analgesia for chronic pain treatment started with the synthesis of tramadol. Morphine is a potent analgesic. However, it is associated with major adverse effects such as respiratory depression and dependence. On the other hand, tramadol analgesic potency is less than morphine (10 times); however, it is favored over morphine due to its safety profile. Tramadol is considered safe and does not cause respiratory depression and dependence compared to morphine.<sup>8</sup> Therefore, tramadol's mechanism of action on MOR could be the reason for its better patient tolerability. Tramadol is a weak mu-opioid receptor (MOR) agonist and has serotonin (5HT) and norepinephrine (NE) reuptake inhibitory activity<sup>9</sup> (Figure 1). However, tramadol-induced analgesia is problematic due to its reliance on active metabolites. Tramadol is metabolized by cytochrome P450 2D6 (CYP2D6),<sup>10</sup> a polymorphic enzyme, which results in different degrees of analgesia in patients with different polymorphisms.



**Figure 1** Suggested tapentadol analgesic mechanism of action. A dual-function on the mu-opioids receptor (MOR) and norepinephrine reuptake transporter (NET). Alpha 2-adrenoreceptor (A2-AR), substance P receptor (SPR), and Glutamate receptor (GLR).

The idea of selective monoamine inhibitors was further investigated, and studies found that NE reuptake inhibitors produce more potent analgesia than 5HT reuptake inhibitors.<sup>11–13</sup> Thus, through chemical synthesis procedures, a new compound was found to exhibit a dual mechanism of action as a MOR agonist, and a NE reuptake inhibitor called 3-[(1R,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl] phenol hydrochloride (tapentadol HCl) was found to exhibit a dual mechanism of action as a MOR agonist and an NE reuptake inhibitor. In this review, we describe the preclinical and clinical studies leading up to the widespread use of tapentadol as an effective drug for pain management. The discovery of the involvement of 5HT and NE in pain circuitry<sup>14</sup> provided new insight into tramadol's mechanism of action as an atypical opioid namely that it works through 5HT and NE signaling pathways to mediate pain management. Tapentadol has a mechanism of action similar to tramadol. It targets MOR and NE reuptake but is not limited by the same features associated with tramadol's metabolism.<sup>15</sup>

Neurogenesis is the process of creating new neurons, and the hippocampus is the area of the brain responsible for memory, learning, and emotion.<sup>16</sup> During adulthood, the hippocampus creates new neurons, which help to improve learning and memory, regulate mood, and manage stress.<sup>17</sup> In the human brain, hippocampal neurogenesis is a process that occurs only during adulthood.<sup>17</sup> The impact of chronic pain on hippocampal neurogenesis and behavioral consequences has been hypothesized to be mediated by tumor necrosis factor receptor 1.<sup>18</sup> This receptor regulates tumor necrosis factor signaling at the molecular, cellular, and behavioral levels.<sup>18,19</sup> This is because opiates have been shown to affect the hippocampus, which is responsible for learning and memory.<sup>20</sup> Thus, it is hypothesized that the interventions of opiates could lead to a reduction in hippocampal neurogenesis, which could have long-term implications on cognition.<sup>21</sup>

5HT positively modulates hippocampal neurogenesis, according to literature reports.<sup>22,23</sup> Since opiates can cause a reduction in hippocampal neurogenesis, it is believed that interventions that increase the levels of 5HT in the hippocampus might counteract the effects of opiate use, potentially leading to improved cognitive outcomes.<sup>24,25</sup> Depletion of 5-HT reduced both the proliferation and survival of adult-generated neurons in the hippocampus.<sup>26</sup> The findings suggest that 5-HT plays an essential role in regulating the proliferation and survival of adult-generated neurons in the

hippocampus.<sup>26</sup> Furthermore, the beneficial effects of tapentadol treatment on the hippocampus indicate that tapentadol may modulate 5-HT and NE levels, which could lead to increased neurogenesis in the hippocampus.<sup>27</sup>

## Preclinical Pharmacological Activities of Tapentadol

The binding of tapentadol to various receptors was assessed in a study in 2007.<sup>28</sup> To determine the binding of tapentadol to MOR, delta opioid receptor (DOR), and kappa opioid receptor (KOR), tapentadol was incubated with rat and human cellular membranes. The  $K_i$  values of tapentadol (an indicator of binding affinity) to rat receptors were 0.096  $\mu\text{M}$ , 0.97  $\mu\text{M}$ , and 0.91  $\mu\text{M}$  to MOR, DOR, and KOR, respectively. In addition, tapentadol bound to the human recombinant MOR with a  $K_i$  value of 0.16. Tapentadol was also tested for its reuptake inhibitor activity against NE in a rat synaptosomal reuptake assay. It was found that tapentadol inhibited NE reuptake with a  $K_i$  value of 0.48  $\mu\text{M}$ . Moreover, tapentadol was tested for reuptake inhibitor activity of 5HT and found to have a  $K_i$  value of 2.37  $\mu\text{M}$  in rat synaptosomes. In a binding assay to the human recombinant NE transporter, the  $K_i$  value was 8.80  $\mu\text{M}$  and to the human recombinant 5HT was 5.28  $\mu\text{M}$ . Tapentadol was further investigated with different receptors and transporters, such as muscarinic activity (rat M1) with a  $K_i$  value of 0.47  $\mu\text{M}$ ; however, tapentadol was weak in a muscarinic antagonist in a human embryonic kidney (HEK-293) cell assay. Other binding tests were performed for GABA and dopamine; however, no activity was found with tapentadol. In addition, the major tapentadol metabolite (tapentadol-o-glucuronide) has no analgesic activity. This is considered a major difference between tramadol and tapentadol in terms of pharmacogenetic variability found with tramadol. Therefore, it can be problematic in certain patients. To test the uptake of NE and 5HT after tapentadol treatment, synaptosomes were isolated from neuronal synaptic terminals by mild homogenization of neural tissue under isotonic conditions and subsequently fractionated using differential and density gradient centrifugation. In addition, tissues were obtained from the rat hypothalamus to test NE uptake and medulla oblongata and pons to test 5HT uptake.  $K_i$  values were 0.48  $\mu\text{M}$  and 2.37  $\mu\text{M}$  for NE and 5HT, respectively.<sup>28</sup> Thus, tapentadol showed more specificity and selectivity toward NE than 5HT.

Tapentadol was tested in rats to determine NE and 5HT inhibition effects. The microdialysis probes were inserted into the ventral hippocampus. Tapentadol increased extracellular NE levels higher than 5HT. In addition to testing tapentadol, responses to morphine (a standard opioid for analgesia) on NE and 5HT levels were also examined, but no increases in extracellular NE and 5HT levels were found.<sup>28</sup> Several behavioral studies have been conducted to investigate the analgesic action of tapentadol at different doses. Different procedures in non-human animals were conducted to simulate various pain etiologies. The hot-plate test was performed to assess the pain response in animals taking tapentadol, and the results were compared with those of morphine. In this test, mice were placed on a hot plate set to a temperature of 48 °C and the latency to jump was recorded. Latencies to jump were measured before and 30 minutes after the administration of tapentadol, allowing the drug time to produce its maximum effect. In rats, morphine was administered to compare the analgesic effect of tapentadol versus morphine. It was found that tapentadol was two to three times less potent than morphine, and the effective doses (ED50s) were 11.8 and 4.7 mg/kg, respectively.<sup>28</sup> Another study that used a diabetic animal model induced with streptozotocin. Tapentadol (0.1–1 mg/kg i.v.) attenuated heat-induced nociception in diabetic animals with more than 80% efficacy. In addition, tapentadol was effective against heat hyperalgesia, with a minimal effective dose of 0.32 mg/kg. On the other hand, control mice with normal blood glucose (nondiabetic) did not show anti-nociception with tapentadol using the maximum dose tested (1 mg/kg).<sup>29</sup>

The tail-flick test is a standard test for assessing pain in animals.<sup>30</sup> In this test, the animal's tail is placed on a hot plate, and the latency to a tail flick is recorded. In a set of experiments testing the effects of morphine and tapentadol on the tail-flick assay, a baseline measure was obtained before administration 20, 40, and 60 min after administering the drug, with a cut-off of 12s to prevent tissue damage. The analgesic effect of tapentadol was twice that of morphine.<sup>28</sup> Another study showed that tapentadol given intrathecally could increase nociceptive thresholds in rats' tail-flick tests. Tapentadol was given at three doses, 30, 50, and 100  $\mu\text{g}/\text{rat}$ , showing a slightly increased nociceptive threshold. The maximum antinociceptive response was reported at 15 min and then reduced gradually, reaching the baseline after 90 min.<sup>31</sup>

Mustard oil, among other compounds, has been used to induce visceral pain and acute colitis.<sup>32–34</sup> Mustard oil is administered rectally in mice, and pain behavior is scored based on time spent licking the abdomen, stretching, backward

movement, and flank muscle contraction. The animals were divided into three groups, control, tapentadol, and morphine. In the beginning, baseline testing was performed to measure pain-like behavior and was recorded for 20 min for all groups. Afterward, mustard oil was administered rectally after which behavioral changes were observed for another 20 min for all groups.<sup>28</sup> Finally, mustard oil-induced visceral pain was measured in the morphine group and compared tapentadol group. Tapentadol inhibited most visceral pain with ED50s of 1.5 mg/kg i.v.; however, morphine was more potent than tapentadol in alleviating the visceral pain with lower ED50s of 1.0 mg/kg i.v.

The writhing model is induced by a 0.02% solution of phenylquinone (i.p. 0.35 mL).<sup>35</sup> After injection, signs such as stretching and contraction of the abdomen are observed for 20 min. In one study. The antagonistic effect of naloxone was examined at different doses given 10 min before tapentadol or morphine treatment. It was found that tapentadol was less effective when pretreated with naloxone at different doses and was less sensitive than morphine in the writhing response to phenylquinone. The tapentadol dose required to produce an analgesic effect was 3.16 mg/kg i.v. as compared to morphine 0.681 mg/kg i.v.<sup>28</sup>

The chronic constriction injury model of neuropathic pain is performed by exposing the sciatic nerve at the mid-thigh and surrounding it with 4 loose ligatures.<sup>36</sup> Cold allodynia was tested in mice using a cold plate at 4 °C for 30 min before administering tapentadol or morphine to the animal.<sup>28</sup> The authors found that both tapentadol and morphine prevented cold allodynia. However, the ED50 of tapentadol was 13 mg/kg i.p. compared to the ED50 of morphine, 7.1 mg/kg i.p. In addition, tapentadol did not produce tolerance in animals until the 23rd day of continuous treatment with 6.81 mg/kg, but at the same dose of morphine, tolerance occurred after only 10 days of treatment.

## Clinical Trials

Up to 2022, only three interventional clinical studies were complete in Phase 4 were registered at clinicaltrials.gov database using “tapentadol” (Table 1). Tapentadol and tapentadol/pregabalin were comparable clinically and statistically. It was reported that patients who received either of tapentadol or tapentadol/pregabalin experienced significant improvements in neuropathic pain and quality of life measures. Also, compared to strong opioids and anticonvulsants, tapentadol/pregabalin monotherapy showed good tolerability. It was also reported that there was a significant decrease in the incidence of dizziness and/or somnolence with tapentadol/pregabalin as compared with tapentadol prolonged release or pregabalin alone.<sup>37</sup> Moreover, pain intensity and quality-of-life measures significantly improved in neuropathic patients. Tapentadol prolonged release 300 mg/day demonstrated more remarkable improvement in low back pain patients with a neuropathic component.<sup>38</sup> There was no difference between tapentadol prolonged release and oxycodone/naloxone prolonged release in terms of safety. There was a significant reduction in pain intensity with tapentadol prolonged release compared to oxycodone/naloxone prolonged release. In comparison with oxycodone/naloxone prolonged release, tapentadol prolonged release significantly improved pain DETECT and Neuropathic Pain Symptom Inventory scores. Also, clinical relevance and statistical significance indicated that tapentadol prolonged release was more effective than oxycodone/naloxone prolonged release. This is in comparison to oxycodone/naloxone prolonged release. Tapentadol prolonged release may be considered a first-line treatment option in treating severe chronic low back pain with a neuropathic component.<sup>39</sup> On the other hand, only three observational clinical studies were complete, with results registered at clinicaltrials.gov database using “tapentadol” (Supplementary Table 1).<sup>40–45</sup>

## Tapentadol Use for Neuropathic Pain

The term “neuropathic pain” is defined as “pain caused by a lesion or disease which affects the somatosensory system”.<sup>46</sup> This type of pain is caused by damage to the nervous system, which can affect how the brain interprets bodily sensations.<sup>47</sup> As a result, pain signals may be sent to the brain even when there is no physical injury, leading to chronic pain. For example, nerves can become damaged or irritated due to various factors, including injury, infection, autoimmune diseases, and certain medications.<sup>47</sup> When this happens, the nerve fibers can become hypersensitive and send pain signals to the brain without physical injury. This can cause chronic pain that can be difficult to treat. There are many potential causes of neuropathic pain, including peripheral neuropathies, spinal cord injuries, and brain lesions.<sup>48</sup> The signs and symptoms of neuropathic pain are often characterized by sensory losses (eg, hypoesthesia and hypoalgesia)

**Table 1** Interventional Clinical Studies for Tapentadol That Have Completed Phase 4

#	Study Title	Study Arms	Intervention/Treatment	Conditions	Primary Outcome Measures	Publications Resulted from the Study
1	Comparison of Increasing Doses of Tapentadol Versus A Combination of Tapentadol and Pregabalin	<p>Experimental: Tapentadol Prolonged Release Tapentadol Prolonged Release (100–500 mg per day) Oral administration twice daily</p> <p>Active Comparator: Tapentadol Prolonged Release with Pregabalin Tapentadol Prolonged Release (100–300 mg per day) with Pregabalin (150–300 mg per day) Both administered orally twice a day</p>	<p>Drug: Tapentadol Prolonged Release 100–500 mg per day orally twice daily for a maximum of 12 weeks</p> <p>Drug: Tapentadol Prolonged Release open label maintenance 100–400 mg per day Tapentadol Prolonged Release orally administered twice daily</p> <p>Drug: Tapentadol Prolonged Release with Pregabalin Tapentadol Prolonged Release 100–300 mg per day with Pregabalin 150–300 mg per day orally twice daily for a maximum of 12 weeks</p> <p>Drug: Tapentadol Prolonged Release open label maintenance 100–400 mg per day Tapentadol Prolonged Release orally administered twice daily</p>	Low Back Pain Neuropathic Pain	<p>Change in the Average Pain Intensity Score for the Overall Low Back Pain on an 11-point Numeric Rating Scale (NRS-3) [Time Frame: Randomization (Day 22); Final Evaluation Visit (Day 77)]</p> <p>The primary endpoint is defined as the comparison of tapentadol prolonged release (PR) 300 mg plus 200 mg per day and the combination of tapentadol PR 300 mg per day and pregabalin 300 mg per day regarding the change in NRS-3 pain intensity scores (recalled average pain intensity score during the last 3 days on 11-point NRS, where 0 is the no pain and 10 is pain as bad as you can imagine) from the randomization visit to the final evaluation visit.</p> <p>Theoretically a maximum decrease of –10 and an increase of +4 in the pain intensity would have been possible. A negative sign indicates a decrease in pain intensity from the start of treatment. The higher the absolute values, the greater the change since the start of treatment (Baseline visit)</p>	[37,38]
2	Comparison of the Effects of Tapentadol and Oxycodone on Gastrointestinal and Colonic Transit in Humans	<p>Active Comparator: Tapentadol (75 mg tapentadol tid)</p> <p>Active Comparator: Oxycodone (5 mg oxycodone tid)</p> <p>Placebo Comparator: Placebo Placebo tid</p>	<p>Drug: Tapentadol Subjects received tapentadol immediate release formulation, 75 mg three times per day (tid) for 48 hours. Other Name: Tapentadol brand name: Nucynta</p> <p>Drug: Oxycodone Subjects received oxycodone immediate release formulation, 5 mg three times per day (tid) for 48 hours. Other Names: Dazidox ETH-Oxydose Endocodone Oxecta Oxy IR Oxycontin Oxyfast Percolone Roxicodone</p> <p>Drug: Placebo Subjects received placebo three times per day (tid) for 48 hours.</p>	Effects of 2 Mu-opiates on Gastrointestinal Transit	<p>1. Colonic Transit, Geometric Center at 24 Hours [Time Frame: 24 hours]</p> <p>The scintigraphic method is used to measure colonic transit. An isotope is adsorbed on activated charcoal particles and delivered to the colon in a delayed release capsule. Anterior and posterior gamma images are taken hourly. The geometric center (GC) is the weighted average of counts in the different colonic regions. The scale ranges from 1 to 5; a high GC implies faster colonic transit, a GC of 1 implies all isotope is in the ascending colon, and a GC of 5 implies all isotope is in the stool.</p> <p>2. Gastric Emptying Half-time (t1/2) at 24 Hours [Time Frame: 24 hours]</p>	NON

(Continued)

Table 1 (Continued).

#	Study Title	Study Arms	Intervention/Treatment	Conditions	Primary Outcome Measures	Publications Resulted from the Study
3	Tapentadol Prolonged Release (PR) Versus Oxycodone/Naloxone Prolonged Release in Severe Chronic Low Back Pain With a Neuropathic Component	Experimental: Tapentadol Prolonged Release (PR)	Drug: Tapentadol Prolonged Release All participants started with 50 mg tapentadol hydrochloride prolonged release (twice daily). The dose of tapentadol hydrochloride prolonged release will be adjusted in increments of 50 mg to a level that provided adequate analgesia. Titration will be after a minimum of 3 days on a dose. Participants are permitted a maximum dose of 250 mg twice a day (500 mg total daily dose). After titration participants will remain on the stable dose for 9 weeks.	<ul style="list-style-type: none"> <li>• Back Pain</li> <li>• Low Back Pain</li> <li>• Neuropathic Pain</li> </ul>	<p>1. Change in the Average Pain Intensity Score on an 11-point Numeric Rating Scale (NRS-3) [Time Frame: Baseline (Randomization Visit); End of Continuation Period (Week 12)] For this pain assessment, the participant indicated the level of average pain experienced over the previous 3 days on an 11-point Numeric Rating Scale (NRS-3) where a score of 0 indicated "no pain" and a score of 10 indicated "pain as bad as you can imagine". The value reported represents the change from the randomization visit (ie, the last 3 days in the washout period prior to Investigational Medicinal Product initiation and titration) to the end of the continuation period (ie, up to 9 weeks on the stable dose). The theoretical values range from -10 to 10. A negative sign indicates a decrease in pain from the start of treatment. The higher the absolute values, the greater the change since the start of treatment (Baseline Visit).</p> <p>2. Change in the Patient Assessment of Constipation Symptoms (PAC-SYM) Total Score [Time Frame: Baseline (Randomization Visit); End of Continuation Period (Week 12)] The Constipation Assessment (PAC-SYM) is a 12-item self-report questionnaire that assessed the severity of symptoms of constipation. Participants were asked "How severe have each of these symptoms been in the last two weeks?" eg "Pain in your stomach". There are 3 subscales: 4 questions on abdominal symptoms, 3 on rectal symptoms and 5 on stool symptoms. Responses were rated on a 5-point Likert scale ranging from 0 (absence of symptom) to 4 (very severe symptoms). If the changes in the overall or subscale scores are positive then there is a worsening in symptoms associated with constipation. The change in the assessment of constipation symptoms (PAC-SYM) total score from the Randomization Visit to the Final Evaluation Visit. The PAC-SYM overall score is the sum of scores of all non-missing items divided by the number of non-missing items (if at least 6 items were non-missing).</p>	[39]
		Active Comparator: Oxycodone/Naloxone Prolonged Release	Drug: Oxycodone/Naloxone Prolonged Release All participants start with 10 mg/5 mg oxycodone/naloxone (twice daily). The dose of oxycodone/naloxone may be adjusted in increments of 10mg/ 5 mg oxycodone/naloxone to a level that provide adequate analgesia. Titration will be after a minimum of 3 days on a dose. Participants will be permitted a maximum dose of 50 mg/ 20 mg oxycodone/naloxone twice daily a day (100 mg/40 mg total daily dose). After titration participants will remain on the stable dose for 9 weeks.			

and/or sensory gains (eg, tactile and mechanical allodynia).<sup>48</sup> Furthermore, the intensity of these symptoms can vary from person to person, ranging from mild to severe.

Steigerwald, Ilona et al evaluated patients with severe chronic low back pain accompanied by neuropathic pain using tapentadol prolonged release (PR).<sup>49</sup> There was an open-label study of tapentadol PR (100–500 mg/day) administered to patients over the course of five weeks of titration and a subsequent seven week maintenance period.<sup>49</sup> For instance, when compared to a placebo, tapentadol PR reduced pain intensity and improved physical functioning in patients with severe chronic low back pain with neuropathic pain. The neuropathic pain symptoms of chronic low back pain patients were significantly reduced with tapentadol PR treatment, with decreased pain attacks and spontaneous pain duration.<sup>49</sup> There was, however, a greater risk of neuropathic pain with lower tapentadol doses.<sup>49</sup>

A retrospective study by Coluzzi et al evaluated 25 patients with multiple myeloma treated with tapentadol (200–300 mg/kg) for moderate-to-intense pain.<sup>50</sup> As assessed by (Douleur Neuropathique en 4 Questions) DN4, 18 patients (70%) had neuropathic pain during pretreatment assessment.<sup>50</sup> The DN4 scores improved by up to 0.41% from baseline to week 12 of treatment on tapentadol. Additionally, there was a decrease in the number of patients with neuropathic pain, while the quality of life was improved across all domains of the Short Form 36 Health Survey Questionnaire (SF-36).<sup>50</sup> These results showed a positive impact on patients' lives, highlighting the effectiveness of the treatment.

It was reported that Freo et al conducted a retrospective analysis of 96 patients with moderate-to-severe intensity chronic musculoskeletal pain (low back pain and neck pain).<sup>51</sup> They concluded that there was a significant reduction in pain intensity after applying a combination of physical therapy and medication. In addition to standard pain questionnaires, cognitive tests were administered to patients to determine and monitor potential side effects related to their cognitive function. Age is associated with a decrease in the incidence of probable neuropathic pain. This is likely because as people age, their nervous system becomes less sensitive to pain, and they develop more effective coping mechanisms.<sup>52</sup> Therefore, cognitive tests assessed whether the treatments adversely affected the patient's cognitive functioning. Freo et al reported that 42% of patients aged 65 and younger, 35% aged 65 to 75, 18% aged 75 to 85, and 18% over 85 had neuropathic pain at pretreatment.<sup>51</sup> The mean pain Detect questionnaire score significantly declined in all age groups after six months of treatment (mean daily dose 200–300 mg/day).<sup>51</sup> The study reported that probable neuropathic pain decreased from around 17 to 7.2, in patients younger than 65, from 12 to 6.5 in patients 65 and 75 years, and from 10 and 6.2 in patients 75 to 85 and older.<sup>51</sup> No further impairment was observed during treatment despite a general decline in neuropsychological performance with age. Overall, the results indicate that the treatment effectively reduced pain, regardless of the age of the patients.

In a cohort study, they conducted on 30 opioid-naïve head and neck cancer patients with pain due to painful mucositis as part of intensity-modulated radiation therapy with or without cisplatin with either a definitive or an adjuvant intent, Mazellola et al evaluated tapentadol PR's effectiveness and tolerability profile.<sup>53</sup> An initial dosage of 50 mg of tapentadol PR twice daily was given; the dosage could be increased according to the severity of the pain.<sup>53</sup> This is a common practice in pain management because it allows the dosage to be tailored to the individual's needs.<sup>54</sup> Tapentadol PR is a long-acting opioid medication that can relieve sustained pain for up to 12 hours. The patient can maintain effective pain control with minimal side effects by starting with a low dosage and increasing it as needed. There was a 90-day observation period after the start of antineoplastic treatment: tapentadol PR was administered to 25% of patients 22 days after the initiation of antineoplastic treatment.<sup>53</sup> The pain intensity decreased by 30% in 26 patients (86.7%) and 50% in 23 patients (76.7%) after 39 days.<sup>53</sup> Overall, the treatment was effective in decreasing pain levels for the majority of patients.

## Pharmacokinetics of Tapentadol

In humans, tapentadol tablets are given orally, and the oral absorption is around 32% and not affected by stomach acidity or changes in gastric motility, unlike tramadol.<sup>55,56</sup> Tapentadol protein-binding in the plasma is lower by approximately 20% than tramadol, and it has a greater blood–brain barrier penetration.<sup>55,57</sup> One hour after oral administration, tapentadol reaches its maximum blood concentration and produces relief from chronic pain for approximately 4 to 6 hours.<sup>55</sup> Tapentadol is not metabolized extensively in the liver through Phase I metabolism.<sup>57</sup> However, Phase II is considered the major pathway for tapentadol metabolism, which undergoes glucuronidation.<sup>57</sup> Tapentadol is metabolized in the liver mainly via CYP450, including different isoenzymes such as CYP2C9, CYP2C19, and CYP2D.<sup>55</sup> After

metabolism, most tapentadol metabolites are excreted by the kidney (99%) in the urine.<sup>57,58</sup> Tapentadol has a lower potential for drug–drug interactions.<sup>59</sup> [Supplementary Table 2](#) shows the main pharmacokinetics parameters of tapentadol vs tramadol.

## Adverse Effects and Abuse Potential

Tapentadol produces different central and peripheral adverse effects as shown in ([Supplementary Table 2](#)). Peripherally, tapentadol may cause nausea and vomiting because of its effects on the gastrointestinal tract. Centrally, tapentadol may cause headaches, dizziness, and somnolence.<sup>60</sup> It is less likely to cause life-threatening situations associated with delirium, neuromuscular rigidity, and hyperthermia when combined with selective serotonin reuptake inhibitors (serotonin syndrome).<sup>61–63</sup> Serotonin syndrome is a potentially life-threatening condition caused by excess serotonin. SSRIs and other antidepressants, which increase serotonin levels, can cause it when combined with other medications. Symptoms include agitation, confusion, sweating, and seizures.<sup>64</sup>

Tramadol is generally regarded as having less dependency and abuse risk than potent opioids.<sup>65</sup> Extended-release forms of tramadol have even been proposed to replace opioids in doses up to 600 mg daily.<sup>66,67</sup> Since tramadol has fewer euphoric effects than opioids, it is less likely to be abused.<sup>68</sup> It also has a lower risk of dependency, as it does not cause the same physical dependence as opioids.<sup>68</sup> In addition, its extended-release form allows for a more gradual release of the drug, which reduces the risk of abuse. However, it has been confirmed in patients treated for acute pain following elective surgery that tramadol is associated with the same or even higher risk of abuse from acute to prolonged use as other short-acting opioids.<sup>69</sup> Despite this, its extended-release form still provides for a more gradual release of the drug, making it a viable option for those who wish to avoid a high risk of opioid dependency.

By marketing extended-release tablets that are difficult to crush and dissolve, the risk of diversion for non-medical purposes was considered when developing tapentadol.<sup>70,71</sup> This is because these tablets are harder to manipulate and less likely to be misused. Additionally, they are designed to be slowly released into the body, thus reducing the potential for abuse.<sup>72</sup> Reports have shown that immediate-release tablets have been used recreationally and abused by injecting crushed tablets, some of which caused death.<sup>73</sup> As a result of data obtained from a US prescription drug-monitoring system, a study concluded that tapentadol has a significantly higher abuse potential than tramadol.<sup>74</sup> However, its abuse potential is comparable to that of hydrocodone but is lower than that of other potent opioids (ie, morphine) after adjusting for prescription volume.<sup>74</sup> This suggests that tapentadol is a safer alternative to more potent opioids while still providing an effective pain management solution.

## Conclusion

Opioids have been the standard treatment for pain for a long time. Morphine specifically works by activating the MOR and relieving pain. However, chronic pain management is problematic, as some patients do not respond well to conventional opioids such as morphine. In addition, there is a great chance that conventional opioids develop tolerance and hyperalgesia with more extended use in patients with chronic pain. Thus, atypical opioids are suggested as a new alternative to reduce these adverse effects. Atypical opioids activate the MOR and act as a norepinephrine and serotonin reuptake inhibitor. Considering its favorable efficacy/side-effect ratio, tapentadol is a valuable option for treating nociceptive and neuropathic pain in patients with mixed pain. It has been found to have comparable efficacy to other opioid analgesics, with the added benefit of fewer adverse effects. This makes it an attractive option for treating both types of pain in patients with mixed pain, as it offers an effective pain relief option with fewer side effects. Specifically, tapentadol inhibits NA reuptake in chronic pain states, especially those associated with neuropathic pain, indicating that it differs from classical opioids in that it predominates over them. Tapentadol also differs from classical opioids in that it has a reduced incidence of some of the typical side effects associated with opioids, compared with equianalgesic doses of classical opioids.

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