

# Tapentadol extended release in the management of peripheral diabetic neuropathic pain

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**Abstract:** Tapentadol, a  $\mu$ -opioid agonist and norepinephrine reuptake inhibitor, has been found to be an effective medication for a wide variety of chronic pain conditions, including back pain, cancer-related pain, and arthritic pain. It has also been found to have fewer gastrointestinal side effects than more traditional opioid-based therapies. More recently, tapentadol extended release has been demonstrated to be effective in the management of painful diabetic neuropathy, an often debilitating condition affecting approximately one-third of all patients with diabetes. This review highlights the most up-to-date basic and clinical studies by focusing on the mechanisms of action of tapentadol and its clinical efficacy, especially with regard to painful diabetic neuropathy.

**Keywords:** chronic pain, neuropathic pain, pharmacology, analgesia, pain management

## Introduction to the management issues associated with the painful diabetic neuropathy (PDNP) in adults

### PDNP

PDNP, which affects approximately one-third of all patients with diabetes, has wide implications on the quality of life and general health of affected patients. Neuropathic pain, defined as pain caused by a lesion or disease of the somatosensory nervous system,<sup>1</sup> is not a result of a nociceptive source or a particular stimulus. Commonly, slight injuries produce pain that is seemingly disproportionate to any potential tissue damage (hyperalgesia), and will encompass an area broader than where the insult was inflicted.<sup>2</sup> Although the exact mechanism of neuropathic pain still has not been elucidated, it is believed that myelinated fiber density is diminished because of the release of proinflammatory cytokines in response to nerve damage.<sup>3</sup> Recently, glial cells, including astrocytes and microglia, have been implicated in neuropathic pain because they form close connections with neurons.<sup>4</sup> Growing evidence also supports the role of central sensitization in the pathophysiology of neuropathic pain. That is, increased sensitivity at the dorsal horn at the level of the spinal cord results from afferents acquiring synaptic efficiency, which causes lower pain thresholds and increased excitability within the ascending system of the pain pathway.<sup>5</sup>

The pathophysiology of neuropathic pain involves the restorative and inflammatory processes that are triggered once injury occurs and cause a hyperexcitable state that is associated with peripheral sensitization. In the normal host, inflammation will abate as the injury mends. However, in an altered milieu (as is observed in diabetes) or with persistent damaging triggers, nociception continues because of recurrent stimulation. Sensitization and stimulation of nociceptors, both of which can be caused by numerous factors, effectively lower neuronal thresholds of action potentials and promote

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peripheral sensitization. These factors include inflammatory mediators that are discharged from nociceptive terminals, including substance P and the calcitonin gene-related peptide. These mediators promote vascular permeability, which causes local edema and the leakage of growth factors, prostaglandins, cytokines, and bradykinin. It is thought that the multifactorial dependence of various substances on producing nociceptive sensitization may explain why there is no single comprehensively effective drug.<sup>6</sup>

Hyperalgesia, or the perception of pain which is disproportionate to the damage sustained by the peripheral pain fibers, is classified as either primary or secondary. Primary hyperalgesia accompanies injury to tissue as an outcome of peripheral nociceptor sensitization. In contrast, secondary hyperalgesia is found in the neighboring intact tissue because of the sensitization of the central nervous system. It is thought that this sensation can be attributed to either the extension of the receptive fields of damaged nerves, or by transmission of excitatory signals that spread through neighboring uninjured nerve fibers (ie, ephaptic transmission).<sup>6</sup>

Discharges of ectopic origin can lead to perceived pain that is spontaneous in nature. This pain can stem from undamaged neighboring fibers, the dorsal root ganglion, or along other points of the damaged nerve.<sup>7</sup> Allodynia, or perceived pain that is produced by a stimulus that is normally not painful, may result from reduced neuronal thresholds and can be characterized as either thermal or mechanical in nature.<sup>6</sup>

Within the ascending track in the sensory nervous system, nociceptive signals are transmitted as action potentials from A $\delta$  and C nociceptors to second and third order neurons situated in the spinal cord's dorsal horn. These neural signals are crucial in forming the excitatory signal that follows any noxious stimulus. They are transmitted to portions of the brain that are responsible for processing the sensory components of pain. Additionally, there are corresponding projections to limbic regions of the brain that are involved in processing these signals to generate the perceived element of pain.<sup>5</sup>

The descending pathway consists of the response signals traveling to the dorsal horn of the spinal cord via the rostral ventromedial medulla and the periaqueductal grey of the midbrain. In the dorsal horn, endogenous ligands, including serotonin, noradrenaline, and other neurotransmitters, are released and are bound by presynaptic receptors located on primary afferent fibers and are bound to postsynaptic receptors located on transmission neurons of the spinal cord. These receptors function to mediate and regulate the influx of transmittance of noxious signals. This top-down transmission pathway allows the brain to regulate signals of pain at

anatomically lower (spinal) levels.<sup>5</sup> Noxious stimuli that are processed by the limbic system result in either the excitation or the inhibition of the processing of the pain through the “on” or “off” cells within the portion of the descending pathway constituted by the rostral ventromedial medulla.<sup>8</sup>

## Clinical presentation of PDNP

Patients with PDNP often present with symmetrical pain in the lower extremities that progresses proximally. The pain is unprovoked by any external stimulus and is described as a painful numbness, burning, or a stabbing sensation in the “stocking and glove” distribution.<sup>9</sup> In an Israeli study, the predominant locations of pain were the head (13%), the limbs (17%), and the back (32%).<sup>10</sup> Of the patients with neuropathic pain associated with type II diabetes mellitus, 73.6% described having pain for longer than a year. These patients also recounted that the nature of the pain was continuous, would worsen in the evenings, and would affect day-to-day activities and mood. Of these patients, 61.4% described a tingling or stabbing of the skin that accompanied the pain, and 55% experienced numbness or were hypersensitive to stimuli.<sup>11</sup>

PDNP is often categorized into three discrete categories: muscular pain, dysesthetic pain, and paresthetic pain. Muscular pain is often described as one that is deep and dull and stems from the neuropathy of large fibers. In contrast, dysesthetic and paresthetic pains derive from neuropathy of small fibers. Dysesthetic pain is often perceived as a prickling or burning sensation, whereas paresthetic pain is sensed as “pins and needles”.<sup>12</sup>

## Challenges in the management of PDNP

The lack of effective treatments to manage PDNP contributes to its high burden, especially among patients with chronic pain. This can be contrasted with the numerous effective treatment modalities used to manage nociceptive pain. In general, adjuvants that are used to manage neuropathic pain only have a minimal therapeutic effect and are only beneficial in only a small portion of affected patients. The underlying problem is the lack of understanding of the exact pathological mechanisms associated with neuropathic pain.<sup>13</sup>

Peripheral neuropathy is a complex disease process that is often associated with conditions that promote further damage to nerve endings, such as chemotherapy, zoster infection, thiamine and B<sub>12</sub> deficiencies, HIV, hypothyroidism, systemic lupus erythematosus, Lyme disease, and, of course, diabetes.<sup>9</sup> In addition, it is important to note that diabetic neuropathy affects not only sensory nerves, which

has implications for PDNP, but affects a wide variety of components of the nervous system. Motor nerves, including cranial nerves and autonomic nerves, can be affected as well.<sup>14</sup> Other conditions in which neuropathic pain persists include radiating lower back pain and postherpetic neuralgia. Currently, the medications available for targeting such pain include gabapentin, pregabalin, mixed serotonin and noradrenaline reuptake inhibitors, anticonvulsants, tricyclic antidepressants, and opioids. Unfortunately, many of these treatment options are conservatively prescribed and have restricted effectiveness because of severe side effects at the necessary dosages.<sup>5</sup>

One of the most frequent side effects accompanying long-term opioid treatment is constipation,<sup>15</sup> which is prone to be more persistent with long-term treatment.<sup>16–19</sup> Opioid usage is also often accompanied by various gastrointestinal side effects, including nausea and vomiting that is usually transitory. Two US surveys of patients undergoing opioid treatment for pain (both acute and chronic) demonstrated that greater than 50% of patients experienced constipation.<sup>20</sup> Difficulties in the management of pain arise when prescribed opioids produce side effects that are best addressed by reducing dosages to substandard levels or by terminating therapy with the drug.<sup>19</sup>

Within the first week of opioid therapy, opioid-related vomiting and nausea usually stops because enough tolerance has been built,<sup>21</sup> but constipation seldom improves with prolonged opioid use.<sup>22</sup> Furthermore, regular prophylactic laxative therapy does not effectively relieve opioid-usage induced constipation.<sup>23–26</sup> In one survey of patients taking concomitant daily laxatives and opioids, 33% of the patients reported decreasing dosages, missing doses, or stopping the consumption of opioids to mitigate opioid-induced constipation.<sup>23</sup>

There are three types of opiate receptors that have been acknowledged to affect gastrointestinal functions in humans. These receptors are classified as G-protein-coupled receptors that work via inhibition of adenylate cyclase and thereby effectively diminish the release of acetylcholine and neuronal excitability. These receptors include:  $\mu$ -receptors,  $\delta$ -receptors, and  $\kappa$ -receptors, which have an overall inhibitory effect on the cell.<sup>27</sup>

The management of analgesia by opioid administration occurs via the ability to bind to  $\mu$ -opioid receptors in the central system. However, gastrointestinal tract side effects become problematic because of the lack of selectivity of the opioids centrally; this leads to agonism of  $\mu$ -opioid receptors in the periphery, including those in the gastrointestinal tract. Within the gastrointestinal tract, there is an abundance of

$\mu$ -opioid receptors in the submucosa<sup>28</sup> and in the ileal mucosa, where they affect ion transport and balance.<sup>29</sup> The proximal colon and the stomach have the highest concentrated population of  $\kappa$ -opioid and  $\mu$ -opioid receptors.<sup>30</sup> As a consequence, patients undergoing opioid therapy will often experience a disruption in the propulsive motility of the gastrointestinal tract along with a disturbance of the migrating motor complex, a lengthening of the duration of gastrointestinal transit time, and a decrease in secretion of gastric fluids and intestinal ions.<sup>31</sup>

## Treatment options for PDNP

First and foremost, preventative measures are crucial to decrease the risks of the complications that accompany uncontrolled diabetes mellitus. Strict restriction of glycemic intake has been shown to help in the prevention of long-term complications. Other risk factors that should be addressed include obesity, smoking, heavy alcohol use, hyperlipidemia, hypertension, and vitamin B6 and B12 deficiency.<sup>12</sup>

At the time of this writing, the only antidepressants approved for the treatment of PDNP by the US Food and Drug Administration (FDA) are duloxetine and pregabalin, the latter of which is also the only anticonvulsant approved for PDNP by that agency.<sup>32</sup> However, other medications are used as well for this purpose.<sup>32</sup> Pure  $\mu$ -opioid agonists have shown an efficacy equivalent to that of pregabalin and gabapentin,<sup>17,33–38</sup> but they fall short as optimal treatment options because of inadequate tolerability and are therefore usually not considered as front-line analgesic options for neuropathic pain.<sup>18,39</sup> Because PDNP has a multifaceted pathophysiology, it often requires a multimodal approach to treatment.<sup>34</sup> Consequently, an analgesic that targets pain through a combination of mechanisms may potentially provide the most effective treatment for PDNP.<sup>40</sup> Historically, a wide variety of medications have been used to target PDNP including tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, antiepileptics, and opiates. Most recently, tapentadol has been studied extensively in the management of PDNP and has demonstrated not only clinical efficacy but also a better side effect profile.<sup>12</sup>

## Overview of the pharmacology, mode of action, pharmacokinetics of tapentadol extended release

### Overview

Tapentadol is an opioid analgesic that was developed relatively recently by Gruenthal, a pharmaceutical company in

Aachen, Germany, alongside Johnson & Johnson Pharmaceutical Research and Development.<sup>41</sup> Tapentadol is available in solution form or as an immediate-release (IR) tablet to target moderate to severe acute pain. It was approved by the FDA in 2009.<sup>42</sup> An extended-release (ER) film coated tablet for oral administration was approved by the FDA in 2011 for the relief of moderate to severe chronic pain and later to address diabetic neuropathy, which necessitates continuous administration of the drug for a prolonged period. Tapentadol is graded as a US Drug Enforcement Administration Schedule II medication.<sup>43</sup> It has also been approved in Europe to target severe chronic pain in adults who can only receive sufficient analgesia through opioids.<sup>44</sup> As of 2010, tapentadol IR and tapentadol ER were approved in 26 European countries.<sup>45</sup>

Tapentadol has two demonstrated modes of action: it is a weak  $\mu$ -opioid receptor agonist and it is a norepinephrine reuptake inhibitor. It represents a new class of centrally acting opioid analgesic, the  $\mu$ -opioid receptor agonist-norepinephrine reuptake inhibitor.<sup>46,47</sup> Stimulation of  $\mu$ -opioid receptors results in a diminution of relayed spinal pain and activity at the supraspinal levels via the descending pathway; this effect additionally reduces conduction of sensory signals. Furthermore, tapentadol's inhibitory effect on the reuptake of norepinephrine augments the inhibition of pain within the descending pathway, most possibly through  $\alpha 2$  adrenoreceptors.<sup>5</sup>

Because of tapentadol's weak affinity for the  $\mu$ -opioid receptor, there is a reduction in the common side effects that are associated with opioid use. Furthermore, its norepinephrine reuptake inhibiting ability lends to its efficacy as an analgesic drug.<sup>48</sup> This has also improved the efficacy of therapeutic opioid use in the treatment of neuropathic pain.<sup>49</sup> The dual action lends this drug the potential to diminish pain as a single drug functioning as a multimodal opioid – this could lessen the risk of any undesired drug-drug interactions.<sup>50</sup>

The manufacturer recommends an initial dose of 50 mg, 75 mg, or 100 mg every 4–6 hours on the basis of pain intensity. However, a second dose can be given 1 hour after the initial dose if it was found to be insufficient. The maximum daily dose is 600 mg.

Given its relatively weaker  $\mu$ -opioid receptor affinity, tapentadol is believed to have less dependence and abuse potential than more traditional opioids. One rat model study did demonstrate the development of dependence to the anti-allodynic effects of tapentadol.<sup>47</sup> In one comparative study, when the Clinical Opiate Withdrawal Scale was used, subjects taking tapentadol were found to be less likely to have withdrawal symptoms than subjects taking oxycodone (17% versus 29%);

however, no differences were found between the two medications when the Subjective Opiate Withdrawal Scale was used.<sup>51</sup> A recent retrospective cohort study has demonstrated the risk of receiving an abuse diagnosis with tapentadol to be lower than the risk with oxycodone.<sup>52</sup>

## Chemical structure

Tapentadol is made up of two chiral carbon atoms, and thereby exists as four stereoisomers. It is a pure enantiomer; analgesic activity is provided only by the S, S (left handed configuration) and R, R (right handed configuration) isomers – the diastereoisomers are not active forms.<sup>53</sup> The dimethylaminomethyl component of tapentadol is responsible for its activity with the  $\mu$ -opioid receptor.<sup>54</sup> When demethylated, the resulting derivatives of the compound,  $\text{CH}_2\text{NH}_2$  and  $\text{CH}_2\text{-NH}(\text{CH}_3)$ , are devoid of any substantial analgesic activity.<sup>55,56</sup>

## Tapentadol ER

Tapentadol ER is supplied in tablets of varying doses of tapentadol hydrochloride at 58.24 mg, 116.48 mg, 174.72 mg, 232.96 mg, and 291.20 mg. These increments respectively correspond to 50 mg, 100 mg, 150 mg, 200 mg, and 250 mg of free-base tapentadol. Aside from the active ingredient, tapentadol HCl, the tablets contain the following inactive ingredients: polyethylene oxide, polyethylene glycol, hypromellose, and alpha-tocopherol. The film coating of the tablets contains polyvinyl alcohol, polyethylene glycol, talc, titanium dioxide, and yellow iron oxide for 150 mg tablets, and Food, Drug, and Cosmetics (FD&C) Blue #2 for the 100 mg, 150 mg, 200 mg, and 250 mg tablets. The printing ink is made up of shellac glaze, propylene glycol, and titanium dioxide for the 250 mg strength, and black iron oxide for the 50 mg, 100 mg, 150 mg, and 200 mg strengths.<sup>42</sup>

Tapentadol IR is available in three doses (50 mg, 75 mg, and 100 mg) given every 4–6 hours, whereas tapentadol ER is given twice a day. The formulations for IR are bioequivalent to ER and thereby allow for easy 1:1 conversions of doses.<sup>57</sup> The maximum daily dose of tapentadol ER is designated as 500 mg for every 24 hours, whereas that of IR is 600 mg for every 24 hours aside from the first day of therapy, on which a maximum dose of 700 mg is permitted to deliver a loading analgesic dose.<sup>58</sup>

## Metabolism

The drug reaches maximum serum concentrations between 3 and 6 hours after administration. It has been observed to maintain concentrations at a steady-state following the third dose, which is given 24 hours following the first two

administrations of the daily multiple doses. Furthermore, the most marginal levels of accumulation were observed with 250 mg doses given every 12 hours.<sup>42</sup>

Tapentadol does not require metabolic activation and does not have any active metabolites. Approximately 97% of the substance is metabolized in humans, predominantly through the Phase 2 pathways – only a small share of the compound goes through Phase 1 oxidative pathways. The favored metabolic pathway of tapentadol yields glucuronides after conjugation with glucuronic acid. After oral administration, tapentadol undergoes sulfation and direct glucuronidation (15% sulfate, 55% O-glucuronide); roughly 70% of the final products are excreted in urine as conjugated end-products.<sup>42</sup> Tapentadol undergoes glucuronidation via UGT2B7 and UGT1A9.<sup>59</sup> About 13% of tapentadol is also metabolized to N-desmethyl tapentadol via CYP2C19 and CYP2C9, and approximately 2% to hydroxyl tapentadol via CYP2D6, both of which are further conjugated. The main metabolite of tapentadol, tapentadol-O-glucuronide, does not activate synaptosomal reuptake systems, opioid receptors, or any other binding sites.<sup>47</sup> Approximately 3% of the compound is excreted in urine as an unmetabolized, unaltered drug.<sup>42</sup>

Considering what is presently understood about the pathways of metabolism of this drug, it is thought to be unlikely to have its clinical applications complicated by drug-drug interactions. Studies have shown that this drug does not induce production of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2E1, or CYP3A4 at any concentration.<sup>60</sup> Moreover, no autoinduction in fresh human hepatocytes was observed, suggesting that tapentadol is not likely to affect the metabolism of concurrently managed drugs that are metabolized via the CYP pathway.<sup>60</sup> Furthermore, because the plasma protein binding is low, it is unlikely that tapentadol would cause clinically significant displacement of concomitantly administered drugs. These two factors together make tapentadol highly unlikely to exhibit clinically significant drug-drug interactions with drugs affected by CYP or plasma protein-binding activity at usual plasma concentrations.<sup>60</sup>

Both tapentadol and its metabolites are eliminated almost entirely via the kidneys (99%). Following oral administration, the drug has a half-life averaging roughly 5 hours. The total clearance of the drug is  $1,603 \pm 227$  mL/min.<sup>42</sup>

## Pharmacokinetics

Tapentadol has been calculated to have a  $K_i$  of  $0.5 \mu\text{M}$  in rat synaptosomal norepinephrine reuptake assays and  $0.1 \mu\text{M}$  in  $\mu$ -opioid receptor binding assays.<sup>47</sup> These characteristics indicate that tapentadol's  $\mu$ -opioid receptor has an affinity

that is 50 times lower than that of morphine. Levels of affinity at other types of opioid receptors, including that of the ORL1 receptor, the  $\delta$ -opioid receptor, and the  $\kappa$ -opioid receptor, are at least one order of magnitude less than at the  $\mu$ -opioid receptor.<sup>47</sup>

## Efficacy studies that include comparative studies

Tapentadol has demonstrated clinical efficacy in improving pain scores in patients with a wide variety of painful disease states, such as chronic back pain, cancer pain, and PDNP. Because of tapentadol's distinct pharmacology and mode of action, studies have been able to demonstrate not only improved gastrointestinal side effect profiles, but also better adherence and less tolerance potential. Much of the most recently available data suggests that tapentadol may have particular clinical utility in the management of PDNP.

Tapentadol's modest affinity for the  $\mu$ -opioid receptor and the drug's opioid-sparing effects, which are caused by its norepinephrine reuptake inhibitory characteristic, imply that the drug should generate fewer side effects than morphine and other conventional  $\mu$ -opioid receptor agonists at equianalgesic dosages. In a study that compared the side effects of morphine with those of tapentadol in ferrets, it was found that tapentadol caused much less frequent vomiting and shorter durations of vomiting. In addition, the dosage that was needed to elicit these responses was 100 times smaller for morphine than for tapentadol. These data demonstrate that tapentadol is a weaker contributor to gastrointestinal side effects than morphine.<sup>46</sup>

Studies have observed that tapentadol ER is an effective analgesic to target moderate to severe chronic osteoarthritis-related knee pain. Treatment using tapentadol ER yielded a lower occurrence of gastrointestinal side effect disorders in a comparative study against oxycodone controlled-release (CR), which is an opioid agonist commonly prescribed for this population.<sup>61</sup> A follow-up study demonstrated significantly higher at-work productivity in patients with osteoarthritic chronic moderate to severe pain who were taking tapentadol ER than in subjects who were taking oxycodone CR or a placebo.<sup>62</sup> Similarly, another study of patients taking a placebo, tapentadol ER, or oxycodone CR for either lower back pain or osteoarthritis found that those on tapentadol ER had greater work productivity than those on oxycodone CR. The measurements of increased productivity included fewer absences and a decrease in overall loss of work productivity.<sup>45</sup>

Clinical trials in patients suffering from chronic lower back pain similarly found that tapentadol offered fewer

occurrences of adverse side effects than did oxycodone within equivalent doses.<sup>63</sup> A recent study demonstrated significantly greater improvements in pain intensity measures for patients with severe chronic osteoarthritis knee pain who had previously responded to World Health Organization Step III therapy and who were later treated with tapentadol ER (50–250 mg twice daily) than patients who were treated with step III opioids. Interestingly, the improvements observed in pain intensity scores in the tapentadol ER group were accompanied with improvements in anxiety and depression, function, quality-of-life, and health status.<sup>64</sup>

Tapentadol's synergistic mechanism of activity as both a  $\mu$ -opioid receptor agonist and a norepinephrine reuptake inhibitor has also other demonstrated advantages. The time required for patients to develop tolerance is longer with tapentadol than morphine. In fact, it was shown that tolerance to morphine developed 2.5 times more rapidly than to tapentadol.<sup>47</sup> Furthermore, tapentadol's characteristic dual mechanism leads to a smaller adverse event (AE) profile than that of other opioids.<sup>58</sup>

Polypharmacy is an area of concern particularly in elderly patients who commonly take more than ten medications. Particular sensitivity among the elderly population to AEs leads to poor compliance, greater risks of drug-drug interactions, and duplication of treatments.<sup>65</sup> Thus, treatment options that offer combined multiple modes of action at low doses in a single medication confer significant opioid-sparing advantages to the elderly patient population in that these patients experience greater relief from pain while simultaneously experiencing fewer AEs.<sup>66</sup> Indeed, in practice, the clinical grouping of a monoamine reuptake inhibitor with an opioid agonist seems to minimize AEs and improve pain management.<sup>47,67–69</sup> The first pharmacological drug that was available to provide these dual actions within a single medication was tramadol. Tapentadol was developed to overcome the impediments to tramadol's effectiveness.<sup>47</sup>

In addition to improvement of opioid-induced gastrointestinal side effects, and perhaps largely because of it, administration of tapentadol ER seems to also lower the incidence of patient-initiated study discontinuation due to treatment-emergent AEs (TEAEs) more than oxycodone CR does. In one study, for example, 981 patients were randomized to receive tapentadol ER, oxycodone CR, or a placebo over 15 weeks, and the tapentadol group demonstrated a lower incidence of TEAEs, including constipation, nausea, and vomiting, than did the oxycodone group. As a result, tapentadol ER may offer a more tolerable and steady treatment to managing chronic pain.<sup>70</sup> Similarly, a pooled analysis

of three Phase III studies involving a total of 2,968 study participants demonstrated that tapentadol ER (100–250 mg twice daily) had a similar efficacy to oxycodone HCl CR (20–50 mg twice daily) for the management of chronic osteoarthritis knee and low back pain and that tapentadol ER had a superior gastrointestinal tolerability profile and fewer treatment discontinuations.<sup>71</sup>

The application of tapentadol ER to manage cancer pain was initially studied by Mercadante et al.<sup>72–75</sup> Only 7% of the patients in this cohort discontinued usage of tapentadol or showed poor compliance with its treatment; this finding suggests that tapentadol is a well-tolerated drug in cancer patients. Furthermore, the rate of discontinuation of tapentadol was less than that of other therapeutic opioids that had been formerly considered, including transdermal buprenorphine (15%), transdermal fentanyl (14%), and oral morphine (13%).<sup>72–75</sup> In a recent double-blind randomized controlled study of 236 patients with chronic malignant tumor-related cancer pain, tapentadol ER was compared to oxycodone CR in terms of analgesic efficacy and TEAEs. The study demonstrated that tapentadol ER provides analgesic efficacy that is not inferior to that of oxycodone in this particular patient population and, at the same time, results in a better gastrointestinal tolerability profile.<sup>76</sup> Another recent double-blind Phase III randomized placebo-controlled study that involved 496 patients with moderate to severe chronic malignant tumor-related pain compared tapentadol ER (100–250 mg administered twice a day) to morphine sulfate CR (40–100 mg administered twice a day). The study demonstrated tapentadol to be more effective than a placebo and that while tapentadol provides efficacy comparable to that of morphine, tapentadol has superior gastrointestinal tolerability.<sup>77</sup>

Another group of patients that appears to benefit from tapentadol ER is the group with chronic back pain with a neuropathic component. Baron et al studied the effects of 300 mg per day of tapentadol ER in patients with severe chronic low back pain with a neuropathic component; the study demonstrated significant improvements in pain intensity, neuropathic pain-related symptoms, and quality of life.<sup>78</sup> The same research group compared the effectiveness and tolerability of tapentadol ER monotherapy and tapentadol ER/pregabalin combination therapy in patients with chronic low back pain with a neuropathic component. The double-blind randomized trial demonstrated improved neuropathic pain scores and quality-of-life variables along with improved tolerability in both treatment groups. Interestingly, tapentadol alone was associated with a lower incidence of dizziness and somnolence than the combination of tapentadol ER and

pregabalin (16.9% versus 27.0%).<sup>78</sup> Tapentadol, therefore, appears to have particular clinical utility in treating chronic back pain with a neuropathic component.

Tapentadol ER has been associated with a more favorable side effect profile than traditional opioid medications, especially with regard to nausea and other gastrointestinal symptoms. Mercadante et al observed that patients who shifted therapy to morphine from tapentadol presented with more unfavorable side effects as measured by an increase in the distress score (predominantly attributed to vomiting and nausea) and the usage of antiemetic drugs.<sup>73</sup> On the other hand, subjects who converted from taking morphine to tapentadol showed no differences in the distress scores.<sup>73</sup> In a recent randomized trial in patients with chronic malignant tumor-related cancer pain on around-the-clock strong opioid therapy, the patients were randomized (1:1) to receive twice-daily treatment with tapentadol ER or morphine sustained release. In the tapentadol group, 84% maintained pain control after 1 week, whereas 98% did so in the morphine group. However, the tapentadol group exhibited a lower incidence of gastrointestinal side effects.<sup>79</sup>

## Tapentadol and PDNP

Numerous experiments have also been conducted that exclusively analyze the efficacy of tapentadol in the management of PDNP. A recent study has demonstrated that tapentadol potentiates descending pain inhibition in chronic pain patients with diabetic polyneuropathy. The study employed two experimental paradigms of endogenous pain modulation: 1) conditioned pain modulation, an experimental measure of endogenous pain inhibition that gates incoming pain signals as a consequence of a preceding painful stimulus; and 2) offset analgesia, a test in which a large amount of analgesia becomes apparent upon a slight decrease in noxious heat stimulation. Twenty-four patients with diabetic polyneuropathy were randomized to receive daily treatment with tapentadol ER or placebo for 4 weeks. At the conclusion of the study period, tapentadol ER demonstrated significant pain relief that coincided with enhanced conditioned pain modulation responses. No effect of tapentadol was observed in the responses to offset analgesia. Additionally, relief of diabetic neuropathic pain was also greater in patients treated with tapentadol than in those treated with placebo ( $P=0.028$ ). Thus, the specific effects of tapentadol on diabetic neuropathic pain may be mediated by the potentiation of descending inhibitory pain pathways.<sup>80</sup>

In a study that was conducted by Schwartz et al (2011) on diabetic patients who had suffered from diabetic neuropathic

pain for at least 6 months, tapentadol ER 100–250 mg administered twice a day was found to be well tolerated and also to improve experienced pain significantly more than a placebo.<sup>40</sup> From the beginning of the double-blind treatment to week 12, the average increase in mean pain intensity in the placebo group was 1.4. However, there was no change in the calculated mean pain intensity within this range in the group treated with tapentadol ER (0.0). There were no substantial differences between female and male patients for the average changes in mean pain intensity scores in the double-blind treatment from the beginning through week 12 of treatment in the tapentadol ER group. There were also no substantial differences in changes in the mean pain intensities between opioid-experienced and opioid-naive subjects within this group. Of the patients in this group, 65% reported an improvement of at least 30% in pain intensity, and 34.9% experienced an improvement of at least 50% in pain intensity.

Similar results were demonstrated in a recent randomized placebo-controlled Phase III study of the efficacy and tolerability of tapentadol ER in the management of chronic neuropathic pain associated with PDNP. This second study was similar in design to the one conducted by Schwartz et al in 2011, except this study used a new formulation of tapentadol ER that is approved in the US for the treatment of chronic pain. This new formulation of tapentadol has a high mechanical strength conferred by the use of a polyethylene oxide matrix and melt extrusion manufacturing process, and this formulation is less susceptible to breakage, splitting, crushing, or chewing than the conventional hypromellose-based formulation used in other Phase III tapentadol ER studies.<sup>81</sup> In the study, adults with moderate to severe diabetic neuropathic pain were titrated to tapentadol ER 100–250 mg twice a day during a 3-week open-label period; patients with  $\geq 1$ -point reduction in pain intensity at end of titration (number of patients [n]=318) received either a placebo or tapentadol ER (optimal dose from titration) for 12 weeks. After the 12-week period, the mean change in pain intensity from the start of double-blind treatment to week 12 was 1.30 in the placebo group and 0.28 in the tapentadol ER group. TEAEs ( $\geq 10\%$ ) in the tapentadol ER group during the double-blind maintenance phase were nausea (21.1%) and vomiting (12.7%); these findings demonstrate a similar tolerability profile to profiles from previous studies.<sup>81</sup>

Tapentadol ER has demonstrated acceptable tolerability and clinically efficacy in reduction of pain intensity in two recent clinical studies of patients with diabetic neuropathic pain. Diabetic neuropathic pain, which affects up to 25% of

all patients with diabetes, has proven to be a source of often debilitating pain in this population of patients. Tapentadol, a unique, centrally acting analgesic with both opioid receptor agonism and norepinephrine reuptake inhibition, appears to be well tolerated and efficacious in treating pain from PDNP.

## Safety and tolerability issues

The foremost concern regarding tapentadol in terms of safety is its effect on respiratory depression. Tapentadol causes depression of the respiratory system via its effect on the respiratory centers in the brainstem, and therefore the drug should not be administered to patients with severe respiratory illnesses. Furthermore, elderly and compromised patients with an underlying respiratory disease should refrain from taking this drug or take it in the lowest sufficient dose of effectiveness. The tablets must not be broken, smashed, or fragmented because of potentially fatal effects that can follow rapid absorption.<sup>82</sup>

Several studies have assessed the tolerability of tapentadol and compared it to that of conventional opioid therapy. In a large, randomized open-label Phase III study of patients with chronic knee or hip osteoarthritis pain or low back pain, patients were randomized to receive twice-daily doses of tapentadol ER (100–250 mg) or oxycodone HCl CR (20–50 mg) for up to 1 year. The incidences of several types of TAEAs were lower for the tapentadol group; these include constipation (22.6% versus 38.6%), nausea (18.1% versus 33.2%), vomiting (7% versus 13.5%), and dizziness (14.8% versus 19.3%). Furthermore, TAEAs led to discontinuation less frequently in the tapentadol group than in the oxycodone group (22.1% versus 36.8%). In a recent analysis of three randomized controlled trials, patients with hypertension who had been treated with tapentadol ER were found to have no clinically meaningful changes in blood pressure or heart rate.<sup>83</sup>

In a recent analysis of pooled data from four randomized controlled Phase III studies in over 4,000 patients with chronic osteoarthritis hip pain, knee pain, or low back pain, tapentadol ER (100–250 mg twice a day) demonstrated better gastrointestinal tolerability than did oxycodone CR. The analysis considered the overall incidence of gastrointestinal TAEAs, the incidence of moderate or severe gastrointestinal TAEAs, and the incidence of gastrointestinal TAEAs leading to discontinuation.<sup>84</sup> Therefore, while tapentadol has some of the same serious AEs as standard opioids do, such as respiratory depression, tapentadol is associated with fewer gastrointestinal symptoms and, for this reason, appears to be better tolerated than conventional opioid therapies.<sup>85</sup>

To date, there have been no adequately controlled studies of tapentadol used by women during pregnancy. A meta-analysis found no clear evidence of fetal or neonatal harm, but a possible increased rate of fetal loss has been reported when the drug is taken early in the pregnancy.<sup>86</sup> The same article states that it appears unlikely that maternal use during breastfeeding will cause harm to healthy-term infants. Without well controlled studies, the drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.<sup>87</sup>

## Compliance and cost

### Compliance

As important as the efficacy of the drug in question is its rate of compliance in the patient population, for offering a mechanistically effective treatment is unserviceable if the subjects do not consistently comply with the recommended administration or dosages. In a study conducted by Coluzzi and Ruggeri (2014) on patients experiencing musculoskeletal pain, researchers observed that the expected risk ratio (RR) of withdrawal from treatment because of AEs was significantly lower for tapentadol ER (RR 0.526; 95% CI 0.4656–0.607) than for CR oxycodone and for naloxone/oxycodone ER (RR 0.758; 95% CI 0.427–1.343).<sup>88</sup>

When administered to diabetic patients suffering from PDNP, the compliance rates for tapentadol ER were similar to those observed in previous studies.<sup>89,90</sup> Roughly 30% of the subjects terminated tapentadol ER treatment during the double-blind or open-label titration period, and about 30% of the subjects terminated treatment with placebo during the period of double-blind treatment. Moreover, the occurrence of AEs, including nausea and vomiting, that lead to the termination of treatment was comparable in this study (vomiting, 2.7%; nausea, 7.7%) to those in studies conducted on patients with chronic lower back pain<sup>70</sup> and to those in studies on patients with osteoarthritic pain.<sup>85</sup>

### Cost

The expenses that accumulate in the treatment of neuropathic pain are considerable. This presents dually as the loss caused by the decrease in work productivity and as the direct and indirect medical expenses. For instance, in a survey of patients in Europe with neuropathic pain, within the month preceding the survey, 19% of respondents had been to a physician three or more times, and 49% had visited a pain specialist. Patients suffering from neuropathic pain often were also treated for anxiety, sleep disorders, and depression.<sup>91–94</sup>

An aforementioned study calculated the projected average expense savings per year for each subject and found that



the mean savings were \$1,400 for oxycodone CR, \$1,510 for placebo, and \$1,960 for tapentadol ER.<sup>62</sup> Based on an annual salary figure of \$100,000, the estimated net savings were \$450 per subject with tapentadol ER and \$560 per subject with oxycodone CR treatment.<sup>62</sup> In effect, tapentadol can potentially offer patients a low-cost alternative to more commonplace opioids such as oxycodone.

In Spain, a similar study was conducted to compare the cost-effectiveness of tapentadol with transdermal fentanyl and morphine. Calculations confirmed the economic advantages of tapentadol over other available analgesic drugs; there is an estimated incremental cost-effectiveness ratio of €2,656 for morphine and €2,069 for transdermal fentanyl. Additionally, the likelihood of tapentadol being more cost-effective than these other drugs at the “willingness-to-pay threshold” between €20,000 and €30,000 per quality-adjusted life-year gained based on the National Spanish Health System surpassed 90%.<sup>95</sup>

A recent meta-analysis employed a Markov model to compare the cost effectiveness of tapentadol ER and oxycodone/naloxone ER for the treatment of musculoskeletal pain by indirect comparison with CR oxycodone. In this study both analgesics were shown to be more cost effective than CR oxycodone. Furthermore, in 65% of cases, tapentadol ER was not only less costly but also produced a gain in quality-adjusted life-years. The authors hypothesize that the superior cost effectiveness of tapentadol ER was likely related to the price, the lower incidence of AEs, and the lower discontinuation rate related to the AEs.<sup>88</sup>

## Conclusion

The growing numbers in preclinical and clinical data suggest tapentadol's efficacy in a wide array of patient populations and across numerous etiologies of traditionally difficult to manage pain. The outcomes of numerous studies portray the growing potential of tapentadol as a treatment modality that offers greater efficacy and tolerability than classical opioids. Several recent clinical trials have demonstrated improved outcomes in pain indices and quality of life measures of patients treated with tapentadol. Interestingly, the novel analgesic appears to be more tolerable in patients who have previously failed treatment with more conventional opioid therapy. Chronic pain due to PDNP appears to be particularly responsive to tapentadol; this finding is promising given the increased societal burden and recalcitrant nature of this pain. Emerging data also suggest that tapentadol is more cost-effective and has better tolerability and clinical outcomes than more conventional opioid-based therapies. There remains a need to further investigate the effectiveness of

tapentadol in comparison with currently available analgesic drugs so that in the future, treatments can be tailored to the individual patient.

## Disclosure

The authors report no conflicts of interest in this work.

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