

# Tapentadol hydrochloride: A novel analgesic

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## ABSTRACT

Tapentadol is a novel, centrally acting analgesic with dual mechanism of action, combining mu-opioid receptor agonism with noradrenaline reuptake inhibition in the same molecule. It has an improved side effect profile when compared to opioids and nonsteroidal anti-inflammatory drugs. The dual mechanism of action makes Tapentadol a useful analgesic to treat acute, chronic, and neuropathic pain.

**Key words:** Nonsteroidal anti-inflammatory drugs, opioids, tapentadol hydrochloride

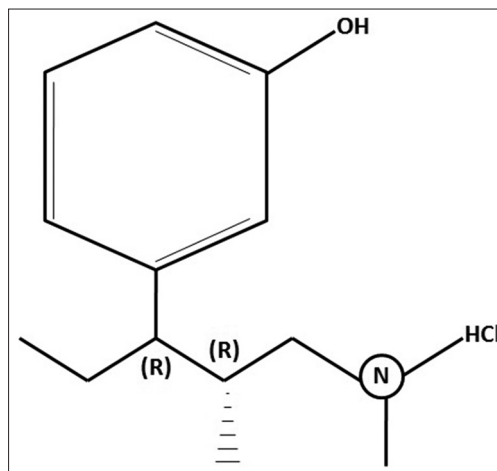
## INTRODUCTION

Pain is a disorder that everyone experiences and is often difficult to treat. Current drug treatment options for management of pain include opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and paracetamol.<sup>[1]</sup> NSAIDs are limited by ceiling effect and are appropriate for relief of mild to moderate pain.<sup>[1]</sup> NSAIDs are contraindicated in patients with acid peptic disease, renal impairment, and bleeding tendency.<sup>[2]</sup> COX-2 inhibiting NSAIDs overcome some of these side effects,<sup>[3]</sup> but some of them increase the risk of cardiovascular side effects, including MI.<sup>[4]</sup> Opioids are considered as gold standard for treatment of moderate to severe pain. However, opioids are underutilised, as doctors may be reluctant to prescribe them and patients may be reluctant to take them due to potential risk of adverse effects, abuse, tolerance, withdrawal, and liability.<sup>[5]</sup> Suboptimal use of opioids can lead to unrelieved pain, which can lead to poor patient outcome and potentially life-threatening complications.<sup>[5]</sup> Analgesics having similar effectiveness with improved compliance in comparison to opioids are valuable additions to the analgesic armamentarium.<sup>[6]</sup> One


strategy aimed at improving the compliance of mu-opioid receptor (MOR) agonists is to combine MOR agonism with monoamine reuptake inhibition. Tapentadol is a novel, next generation, centrally acting analgesic with dual mechanism of action that offers analgesic efficacy that is similar to that provided by a pure MOR agonist, but with an improved side-effect profile.<sup>[7]</sup> Literature search for the article was done using PubMed and Google Scholar using the terms "Tapentadol," "extended release," and "immediate release."

## CHEMISTRY

Tapentadol (3-((1R,2R)-3-(dimethylamino)-1-ethyl-2-methylpropyl) phenol hydrochloride) is a non-racemic molecule [Figure 1]. The molecular formula of Tapentadol



**Figure 1:** Chemical structure of Tapentadol

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is C<sub>14</sub>H<sub>23</sub>NO.HCl. It was first synthesized in USA and marketed by Ortho-McNeil-Janssen Pharmaceuticals; its trade name was Nucynta.

## PHARMACODYNAMICS

Tapentadol provides analgesia through two mechanisms of action, i.e., MOR agonism and noradrenaline reuptake inhibition (NRI).<sup>[8,9]</sup> It binds to MOR selectively, with a more than or equal to ten-fold affinity compared with delta- and kappa- opioid receptors. The affinity of Tapentadol for MOR is 44-fold lower than that of morphine.<sup>[10]</sup> NRI increases levels of noradrenaline (NA), which in turn leads to analgesia through activation of inhibitory alpha-2 receptors. This dual mechanism of action contributes to its opioid sparing effects.<sup>[5,11]</sup> Tapentadol is also a weak serotonin reuptake inhibitor, but this action does not contribute to its analgesic effect.<sup>[12]</sup> The analgesic potency of Tapentadol is only 2-3 times lower than that of morphine, despite its lower affinity of binding to MOR; this is due to additional noradrenergic mechanism of action of the drug.<sup>[10,13]</sup>

## PHARMACOKINETICS

### Absorption

Tapentadol is rapidly absorbed; oral bioavailability after single dose administration is 32% due to extensive first pass metabolism. Plasma steady-state concentration is achieved in 25-30 h when the drug is administered orally every 6 h.<sup>[13]</sup>

### Distribution

Tapentadol is widely distributed throughout the body. Following intravenous (IV) administration, the volume of distribution is 540±98 L. Only 20% of the drug is bound to plasma proteins.

### Metabolism and elimination

Tapentadol is extensively metabolised to inactive metabolites (97% of the administered dose). The major pathway of metabolism is conjugation with glucuronic acid to produce glucuronides; tapentadol-O-glucuronide is the major metabolite.<sup>[14,15]</sup> It is also metabolised to N-desmethyl tapentadol by CYP2C9 and CYP2C19 and to hydroxyl tapentadol by CYP2D6, which are further metabolised by conjugation. CYP enzymes do not play a major role in metabolism. None of the metabolites contribute to its analgesic action.<sup>[16]</sup> Tapentadol does not inhibit or induce the activity of any of the CYP isoforms.<sup>[14]</sup>

Tapentadol follows first-order elimination kinetics. Tapentadol and its metabolites are excreted almost exclusively (99%) via the kidneys. Half life is 4 h. The total clearance is 1530±177 ml/min.

## Dosage and formulation

Tapentadol is available as 50, 75, and 100 mg oral tablets. Maximum dosage is 600-700 mg in divided doses every 4-6 h.<sup>[17]</sup> In India, it is marketed under the trade names Vorth TP (Glenmark Pharmaceuticals), Tydol (Ranbaxy Laboratories Ltd.), and Dolproxyvon (Wockhardt Ltd.). It can be administered with or without food. Tapentadol is available as immediate-release (IR) and extended-release (ER) formulations. A study has been published regarding the conversion of Tapentadol IR to ER, which suggests that a direct milligram to milligram conversion on a total daily dose basis is appropriate.<sup>[18]</sup> The IV formulation is presently under clinical trials and its use is not yet approved.

## Special group

Safety of tapentadol in pregnant, lactating women, and pediatric patients <18 years of age is not yet established. It is not recommended for use in patients with severe renal impairment. Tapentadol should be used with caution and reduced dosage in patients with moderate hepatic impairment and is not recommended for use in severe hepatic impairment.<sup>[19]</sup> It is advisable to start with lower range of recommended doses in elderly patients.

## Drug interactions

Tapentadol has low protein binding, displacement reactions are unlikely.<sup>[13]</sup> Tapentadol has a low potential for pharmacokinetic drug-drug interactions.<sup>[11]</sup> No significant change in plasma concentration of tapentadol was observed when it was administered with paracetamol, naproxen, or aspirin.<sup>[20]</sup> There are no drug interactions between Tapentadol and metoclopramide and between omeprazole and probenecid.<sup>[21-23]</sup> Patients receiving other opioids, general anesthetics, phenothiazines, sedative-hypnotics, or other CNS depressants like alcohol along with Tapentadol may have additional CNS depression that may manifest as respiratory depression, hypotension, or profound sedation.<sup>[24]</sup>

## Contraindications

Patients with impaired pulmonary function (acute bronchial asthma, significant respiratory depression) in unmonitored settings or in the absence of resuscitative equipment

- Paralytic ileus
- Current or recent (within 14 days) use of MAOIs due to potential increase in NA levels, which may cause adverse cardiovascular events<sup>[24]</sup>

## Indications

- Moderate to severe acute pain
- Chronic pain
- Neuropathic pain

The efficacy of Tapentadol for relief of moderate to severe acute pain has been evaluated in three randomized, double blind, phase three studies.<sup>[6,25,26]</sup> In one of the postoperative pain study, patients received Tapentadol 50 or 75 mg, oxycodone 10 mg, or placebo every 4-6 h for 72 h following bunionectomy;<sup>[25]</sup> in the other postoperative pain study, patients received Tapentadol 50, 75 or 100 mg, oxycodone 15 mg, or placebo every 4-6 h for 72 h post-bunionectomy.<sup>[6]</sup> In both studies, improvements in pain intensity were observed with Tapentadol that were similar to that observed with oxycodone based on pain intensity measurements on the numerical rating scale (NRS). In a study on postsurgical dental pain, patients undergoing third molar extraction were randomized to receive single doses of Tapentadol (50, 75, 100, or 200 mg), morphine 60 mg, ibuprofen 400 mg, or placebo. The results of the study showed that single doses of Tapentadol 75 mg or higher effectively reduced pain in a dose-related fashion and were well-tolerated relative to morphine.<sup>[26]</sup>

Efficacy for short-term use in chronic inflammatory pain was examined in patients with end-stage degenerative joint disease over a period of 10 days, while awaiting knee or hip replacement surgery in a double-blind placebo controlled trial; Tapentadol 50 mg and 75 mg and oxycodone 10 mg produced significant reductions in pain intensity as compared with placebo and Tapentadol was not inferior to oxycodone.<sup>[27]</sup> In a recent analysis of pooled data from three phase three studies in patients with chronic osteoarthritis knee or low back pain evaluating the efficacy and tolerability of Tapentadol in comparison with placebo and oxycodone showed that Tapentadol (100-250 mg, twice daily) provided efficacy that was similar to that by oxycodone (20-50 mg, twice daily) with a superior gastrointestinal tolerability profile and fewer treatment discontinuations.<sup>[28,29]</sup> A phase three trial in patients with painful diabetic peripheral neuropathy showed the efficacy of Tapentadol in neuropathic pain.<sup>[30]</sup> NRI action of Tapentadol makes it especially useful in neuropathic pain.<sup>[5]</sup>

## COMPARISON WITH TRAMADOL

Tramadol is the other analgesic with dual mechanism of action. Hence, it would be pertinent to compare both the drugs. Tapentadol has several advantages in comparison with Tramadol.<sup>[31]</sup> The comparison of both the drugs is summarised in Table 1.

Lesser incidence of nausea and vomiting has been reported with Tapentadol as compared to that by tramadol because Tapentadol is a weak inhibitor of serotonin reuptake, whereas tramadol is a potent inhibitor.

## LIMITATIONS OF TAPENTADOL IN COMPARISON TO TRAMADOL

At present IV/IM formulation of Tapentadol is not approved for use, hence in situations where the patient is fasting Tapentadol cannot be used. Tramadol can be administered through various routes like oral IV, IM, suppository, and epidural, whereas Tapentadol can only be administered oral. Tapentadol is more expensive when compared to tramadol or other opioids. A cost-effectiveness analysis comparing Tapentadol and oxycodone for acute pain suggested that increased direct drug costs are offset by reductions in expenses incurred due to treatment of adverse effects, treatment discontinuation, and conversion to alternate opioids.<sup>[32]</sup>

## SAFETY AND TOLERABILITY

Opioids are commonly associated with side effects like nausea, vomiting, constipation, dizziness, headache, somnolence, and pruritis. These adverse effects may be dose limiting and are often severe enough for patients to discontinue therapy.<sup>[33-35]</sup> The tolerability of Tapentadol has been evaluated in trials in which patients with acute pain received multiple oral doses. The most common adverse effects noted with Tapentadol were nausea, vomiting,

**Table 1: Comparison of tapentadol and tramadol**

Feature	Tapentadol	Tramadol	Advantage
Opioid activity	Potent opioid	Weak opioid	Better analgesia with tapentadol
Additional action	Inhibition of NA reuptake and weak inhibition of serotonin reuptake	Inhibition of reuptake of serotonin and NA	Improved side-effect profile of tapentadol
Active metabolite	Active drug	Prodrug; active metabolite is O-desmethyl-tramadol	Early onset of action with tapentadol
Onset of action	32 min	Within 60 min	Early onset of action with Tapentadol
Drug interactions	Lack of CYP 450 interaction	Metabolised by CYP 450 enzymes	Minimal risk of adverse drug interactions with tapentadol
Interindividual variation	Lack of CYP interaction	Primarily metabolised by CYP450 isoenzyme 2D6; poor metabolisers may not get satisfactory analgesia with usual doses of tramadol	No inter-individual variation with tapentadol

constipation, dizziness, somnolence, headache, and pruritis;<sup>[6,25,27-29]</sup> these effects are typical of a MOR agonist. The incidence of these adverse effects has been reported to be lesser with Tapentadol in comparison to that by opioids like morphine and oxycodone; this can possibly be due to lower affinity of Tapentadol for MOR in comparison to other opioids.<sup>[26]</sup> Tapentadol does not cause significant respiratory depression. Studies have shown that abrupt discontinuation of the drug after long-term therapy does not cause opioid-like withdrawal symptoms and, even if they do occur, these symptoms are mild. Long-term therapy was not associated with clinically significant changes in laboratory values (including hepatic and renal parameters), vital signs, or Electrocardiography findings.<sup>[24,29]</sup>

## CONCLUSION

Tapentadol is the first FDA approved (November 2008)<sup>[36]</sup> centrally acting analgesic with MOR agonist and NRI actions. This dual mode of action is responsible for its opioid sparing effect, which contributes to reduction in some of the typical opioid related adverse effects and may result in improved compliance.<sup>[28]</sup> This combination of potent analgesia and tolerability may provide a substantial improvement over current pain relief regimens and would be a valuable addition to the analgesic armamentarium.<sup>[8]</sup> Tapentadol has not yet been studied in cancer pain. Given the limited number of published studies, the side-effect profile, and pharmacoeconomic impact will need to be confirmed in further studies.

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