REVIEW

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Comparison of pharmacotherapeutic analgesic response and safety profile of tapentadol with other opioids

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Tapentadol is a unique opioid analgesic due to its dual mechanism of action. Compared to other opioids with a classical mechanism of action, its analgesic potential is not far behind them, and its advantages are: a better safety profile in terms of a lower potential for drug-drug interactions and a lower potential for causing adverse events, and it is safe to use in sensitive populations. Tapentadol in the form of a immediate release formulation is an adequate drug of choice for achieving a pharmacotherapeutic analgesic response in acute pain conditions, while in the form of a extended release formulation it is an adequate pharmacotherapeutic analgesic solution for chronic pain syndromes of various etiology. Due to the specificity of the mechanism of action, tapentadol adequately relieves both pain components – nociceptive and neuropathic, and has an indication area for mixed pain syndrome as well. Based on this, the need for the use of co-analgesics is reduced, and thus the incidence of possible interactions and adverse events is reduced.

1. Introduction

Tapentadol (3-dimethylamino-1-ethyl-2-methyl-propyl-phenol hydrochloride) is a newer opioid analgesic. In addition to classic μ-opioid receptor agonism, tapentadol also acts by inhibiting the reuptake of noradrenaline, and in this way it is realized that there are two synergistic mechanisms of action in one molecule, which results in a reduction of incoming pain signals and an increase in descending inhibition of pain (Takahara et al. 2021; Fig.).

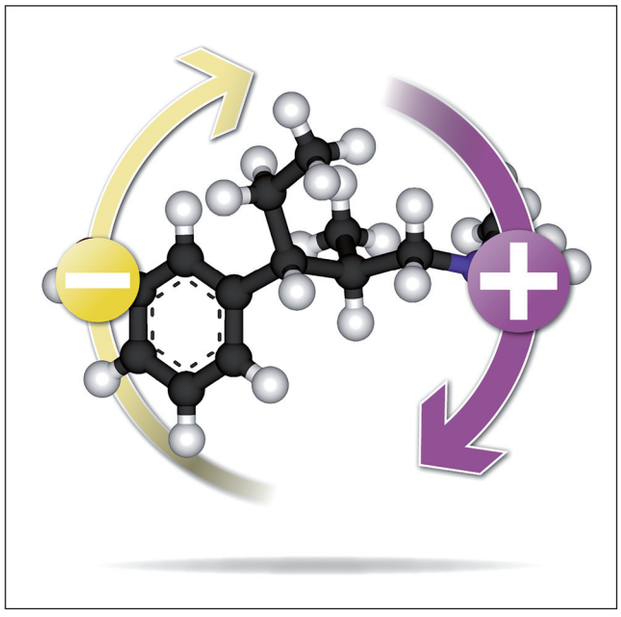

Fig.: Tapentadol formula showing its dual mechanism of action.

It was initially approved by the US Food and Drug Administration in November 2008 for the treatment of moderate to severe acute pain in adult patients, and in August 2011 for chronic pain in the extended release (ER) form in the same population. Due to its limited protein binding capacity, absence of active metabolites, and absence of significant induction or inhibition of microsomal enzymes, tapentadol has limited potential for drug-drug interactions allowing it to be well tolerated and effective in the treatment of moderate to severe acute and chronic pain. Because of its dual mechanism of action, tapentadol is a good option in the treatment of both nociceptive and neuropathic pain (Zajączkowska et al. 2018).

Traditional opioids produce their analgesic effects primarily through one mechanism – the activation of μ-opioid receptors (MOR). In contrast, the newer potent analgesic tapentadol produces its analgesic effect *via* two separate and complementary analgesic mechanisms, only one of which is a μ-opioid. The study by Raffa et al. applied standard drug receptor theory and new techniques to *in vitro* and *in vivo* data to estimate in several different ways the μ-load of tapentadol (% contribution of the opioid component to the magnitude of the adverse effect relative to the pure/classic μ-opioid and equianalgesia) in respiratory depression and constipation, and then the results were compared with clinical evidence. The estimate is remarkably consistent across approaches and indicates that the μ-loading of tapentadol is ≤ 40% (relative to pure MOR agonists, which have, by definition, a μ-loading of 100%) (Raffa et al. 2018).

Tapentadol has a good pharmacological profile with low interaction and addiction potential as well as low tolerance development. It is not a prodrug, so its effectiveness does not depend on metabolic activation. Metabolizing tapentadol does not result in the creation of active metabolites, so there is no risk of potential toxicity due to their accumulation. After oral administration, approximately 70% of the dose is excreted in the urine in the form of conjugated forms (55% glucuronide and 15% tapentadol sulfate). Uridine diphosphate glucuronyl transferase (UGT) is the main enzyme involved in the glucuronidation of this drug (mainly UGT1A6, UGT1A9

and UGT2B7 isoforms). Tapentadol is further metabolized to N-desmethyl tapentadol (13%) by CYP2C9 and CYP2C19 and to hydroxy tapentadol (2%) by CYP2D6, which is then metabolized by conjugation (Muriel et al. 2024). None of the metabolites contribute to the analgesic activity of tapentadol. *In vitro* studies did not show any potential of tapentadol for either induction or inhibition of cytochrome P450 enzymes. Therefore, it is unlikely that clinically relevant interactions mediated by the cytochrome P450 system may occur when this drug is administered. Based on this, the minimum interaction potential of this drug with all drugs that are metabolized through the cytochrome P450 system is based (Cascella et al. 2018). The use of tapentadol in special (risky) patient populations includes suspension of its administration in patients with severe kidney and liver damage, dose reduction in moderate liver damage, dose adjustment is not required in elderly patients, while due to the lack of studies, its use is not recommended in pediatrics population as well as pregnant and lactating women (Coluzzi et al. 2020).

It has been proven that tapentadol should be prescribed to oncology patients for a longer period of time and in a stronger dosage regimen in order to obtain an adequate pharmacotherapeutic response. Tapantadol is the drug of choice for neuropathic cancer pain that is refractory to standard first-line opioid therapy with classic μ opioid agonists. It is an opioid analgesic that achieves an adequate therapeutic response in oncology patients and with a satisfactory safety profile (Homma et al. 2020). It is also an effective pharmacotherapeutic solution for patients who were previously on opioid therapy and in whom it is necessary to apply the rotation of the previous opioid to another opioid, e.g. tapentadol precisely because of its good safety profile (Sazuka and Koitabashi 2020).

2. Comparasion with other opioids – safety profile and adverse events

Some opioid interactions with other drugs can lead to an increase in intrasynaptic serotonin levels, so opioid analgesics are known as drugs responsible for serotonin toxicity if co-administered with serotonergic drugs such as: monoamine oxidase (MAO) inhibitors, selective serotonin reuptake inhibitors (SSRI), selective serotonin and noradrenaline reuptake inhibitors (SNRI) and tricyclic antidepressants (TCA). The most serious consequence of this interaction is the so-called serotonin syndrome. Research was conducted on experimental models including 5HT-receptors, serotonin transporter (SERT) and knockout mice. Synthetic opioids – tramadol, meperidine, methadone, tapentadol, dextromethorphan inhibited SERT, while fentanyl, morphine and hydromorphone did not. The interaction of fentanyl with 5-HT1 receptors as well as meperidine, methadone and fentanyl with 5HT-2 receptors was discovered (Baldo 2018).

The combined mechanism of action of tapentadol was expected to improve the therapeutic utility of opioid analgesics, particularly in the treatment of neuropathic pain conditions. Adding a noradrenergic mechanism of action should not only increase the analgesic effect of tapentadol, but also produce an opioid-sparing effect and reduce the risk of opioid-induced adverse events. μ-opioid receptor agonists differ in their intrinsic activity (the amount of receptor occupancy to induce a certain level of response) (Caputi et al. 2019). The US Food and Drug Administration approved ER tapentadol in November 2008 for the treatment of acute moderate to severe pain in adults and in August 2012 for the treatment of diabetic neuropathy pain. Examining the potential for abuse, tapentadol was found to be less likely to be abused than most other analgesics (Butler et al. 2015). Tapentadol is considered to have a reduced risk of obtaining prescriptions from multiple physicians and a lower risk of abuse and diversion than oxycodone (Schug and Goddard 2014).

Theoretically, the unique pharmacodynamic and pharmacokinetic properties of both buprenorphine and tapentadol with reduced risk of developing tolerance, opioid abuse, diversion and fewer hormonal changes compared to "classic opioids" make these opioids more attractive than other opioids in long-term opioid therapy. However, in the absence of clinical trials, the evidence supporting the method used for transdermal conversion of buprenorphine to tapentadol is weak (Miclescu 2016).

The theoretical advantage of tapentadol is to provide synergistic analgesic activities, which may reduce the need for opioid escalation. The advantage is its potential as a possible new agent in neuropathic pain. Preclinical models confirm analgesic properties in acute pain and neuropathic pain models, but with less potency than morphine. Tapentadol has minimal CYP450 interactions that limit the potential for drug interactions. Data from clinical trials in humans for the indication of non-malignant pain indicate a lower potency than classic opioids, which has been confirmed in oncology patients as well as those with neuropathic pain (Prommer 2010).

Tapentadol has a good tolerability profile. Trials comparing tapentadol with other opioids (primarily oxycodone) have found fewer gastrointestinal adverse events (nausea, vomiting, constipation), a lower incidence of discontinuation, and a good cardiovascular safety profile. The most common side effects associated with tapentadol therapy are: nausea, vomiting and constipation, but they are less frequent and less pronounced than those caused by morphine or oxycodone. In a study involving 1,117 chronic pain patients with severe degenerative arthritis or chronic low back pain, they were treated for 51 weeks with tapentadol or oxycodone. Tapentadol offers effective analgesia and significantly lower rates of constipation compared with oxycodone (22.6% vs. 38.6%), nausea (18.15 vs. 33.2%), and vomiting (7% vs. 13.5%). A significantly lower rate of discontinuation due to unacceptable gastrointestinal adverse events was also reported with tapentadol (8.6%) compared with oxycodone (21.5%) (Wild et al. 2010; Riemsma et al 2011).

Studies have shown no adverse events of tapentadol on heart function or blood pressure (Biondi et al. 2011). No ECG changes affecting the QT interval or significant changes in blood pressure were noted in hypertensive patients (Biondi et al. 2014).

Thanks to its dual – opioid and non-opioid – mechanism of action, tapentadol disrupts the functioning of the endocrine system and the hypothalamus-pituitary-gonadal axis to a lesser extent than other opioids. This is confirmed by the results of three randomized, placebo-controlled studies involving healthy volunteers and patients with osteoarthritis. In these studies, tapentadol lowered testosterone and gonadotropin (LH/FSH) levels to a significantly lower extent than oxycodone or morphine, while tapentadol-induced hormonal dysregulation, which is known to lead to serious consequences such as: reduced fertility, weight loss and muscle strength, osteoporosis, fatigue, or depression, was minimal compared to other pure opioid receptor agonists (Eichenbaum et al. 2015).

Tapentadol is less likely to be addictive than other opioids. Moreover, tolerance to the drug develops more slowly than with other opioids. Clinical studies in which tapentadol was administered to patients for up to 90 days gave few examples of withdrawal symptoms after abrupt discontinuation, and even if they did occur, they were classified as benign (Pergolizzi et al. 2012).

The risk of suicidal thoughts and suicide is higher in patients with chronic pain. The use of substances with pronounced effects on the monoaminergic system is associated with an increased risk of suicide in patients suffering from depression, especially at the beginning of treatment. Data obtained from clinical trials and postmarketing reports of tapentadol did not provide evidence of a similar increased risk (Hoy 2012).

Only ten studies were eligible for analysis in patients with severe pain (eight examined tapentadol and two trials compared buprenorphine patch versus placebo). For moderate and severe pain, 42 relevant trials were identified and indirect comparisons were made with transdermal buprenorphine, transdermal fentanyl, hydromorphone, morphine and oxycodone. Tapentadol, registred and applied only in oral form, showed statistically favorable results compared to oxycodone in terms of pain intensity, 30% and 50% pain relief, patient global impression of change (PGIC) and quality of life. Furthermore, some of the most important adverse events of chronic opioid treatment were significantly less frequent with tapentadol compared to oxycodone, ie. constipation, nausea and vomiting. Treatment discontinuations due to these adverse events were found to be significantly reduced with tapentadol. Tapentadol was superior for the primary outcome (pain intensity) to hydromorphone and morphine, while fentanyl and oxymorphone

showed trends in favor of these treatments. There are only oral formulations of tapentadol, so the ER oral formulation of tapentadol is compared with the fentanyl transdermal patch, which is also an ER formulation of a strong analgesic and has a similar indication area. Significantly fewer gastrointestinal adverse events were observed with oral tapentadol compared with fentanyl patch, hydromorphone, morphine, and oxymorphone, apparently leading to significantly reduced discontinuations (Riemsma et al. 2017).

Billeci et al. published a study evaluating the efficacy and tolerability of tapentadol ER in 54 patients with chronic cervical spine pain syndrome. The initial dose of tapentadol ER was 100 mg per day (ie, 50 mg every 12 hours), and then it was gradually increased according to the analgesic effect and tolerability of the therapy. The follow-up period was 12 weeks. The following parameters were evaluated: numerical rating scale (NRS) of pain intensity, DN4 score of the neuropathic pain component, neck disability index, range of motion of the cervical spine, sleep disturbance, Health Survey (PGI), side effects caused by opioids and need for other analgesics. Initial NRS pain intensity values were 6.8 at rest and 8.8 when moving. After 12 weeks of treatment, a significant reduction in pain scores was observed: by 5.1 at rest (ie at NRS 1.7) and by 5.8 at movement (ie at NRS 3.0). A significant reduction in pain intensity on NRS 4.7 at rest and on NRS 6.7 on movement (ie in both cases for NRS 2.1 points) was reported after the first week of taking tapentadol. Tapentadol was also shown to be effective in alleviating the neuropathic component of pain: initially, 70% of patients had a DN4 neuropathic score > 4, while after 12 weeks of treatment, this percentage dropped to 23%. Significant reductions were also found in the disability index – from 55.6 at baseline to 19.7 at the end of the 12-week follow-up period. Based on the patients' global impression of change, at the end of the 12-week follow-up, 90% of patients reported improvement, rating the treatment as good or very good. Tapentadol ER was a well-tolerated drug, but the most commonly observed adverse reactions were: nausea, vomiting, constipation, somnolence and dizziness. Their frequency was as follows: dizziness 13.7%, constipation 9.1%, nausea 7.8, drowsiness 7.8% and vomiting 3.8%. They were mild, and none of the patients discontinued the study due to opioid-induced side effects. During the 12-week follow-up period, there was a significant reduction in the demand for other adjuvant analgesics. After 4 weeks of the study, none of the patients received nonsteroidal anti-inflammatory drugs, steroids, or other opioids (Billeci and Coluzzi 2017).

Baron et al. published a multicenter, randomized, controlled, open-label trial comparing the efficacy, safety and impact of tapentadol ER and oxycodone/naloxone ER. The study included 258 patients with severe (NRS > 6), chronic pain with a neuropathic component (PainDETECT score > 13), who had not previously used strong opioid analgesics. The study lasted 12 weeks and included a titration period of 3 weeks followed by a treatment period of 9 weeks. Initial doses were: tapentadol ER 50 mg twice daily, oxycodone/naloxone ER 10 mg + 5 mg twice daily. The maximum acceptable dose of tapentadol ER was 500 mg daily, while oxycodone/naloxone ER was 80 mg + 40 mg daily. In the treatment phase, the mean daily dose of tapentadol ER was 378.8 mg and oxycodone/naloxone ER 75.3 mg. Both tapentadol ER and oxycodone/naloxone ER significantly reduced mean pain. Intensity scores ranged from baseline values of 7.6 in both groups to 4.8 in the oxycodone/naloxone ER group, and 3.9 in the tapentadol ER group. Both drugs also significantly reduced neuropathic pain in the Pain DETECT and Neuropathic Pain Symptom Inventory (NPSI) questionnaires, while tapentadol ER significantly reduced mechanical and thermal allodynia, burning, stinging and the incidence of spontaneous pain exacerbations. A significant decrease was observed in relation to the total score in the Pain DETECT questionnaire. The NPSI questionnaire showed a significant increase in the proportion of pain-free patients from 1.6% to 14.4% in the oxycodone/naloxone ER group, and from 3.1% to 31.0% in the tapentadol ER group. Differences in the analgesic efficacy of oxycodone/naloxone ER and tapentadol ER in neuropathic pain are probably related to the different mechanisms of action of both drugs (taking into account the dual mechanism of action of tapentadol via opioid receptors and inhibition of noradrenaline reuptake). Comparison of tapentadol ER with oxycodone/naloxone ER showed similar rates of side effects such as: nausea, dry mouth, pruritus, excessive sweating, dizziness and headache, while significantly lower rates of constipation and vomiting were observed in the tapentadol ER group, both during the dose titration phase and maintenance. In the treatment phase, gastrointestinal symptoms led to study discontinuation in 14.6% of patients in the tapentadol ER group and 21.1% in the oxycodone/naloxone ER group. Significant improvements in SF-12, EK-5D, Hal's anxiety and depression scale (HADS) scores and sleep quality were observed in both groups (Baron et al. 2016).

Treatment with tapentadol increased colonic volume without leading to harder stools, possibly as a result of less absorption of water from the intestinal lumen. Oxycodone treatment also increased colonic volume, but at the same time increased stool dryness and gastrointestinal and central nervous system adverse events. The results confirm that tapentadol treatment may be better than oxycodone in terms of tolerability of pain treatment (Mark et al. 2021).

An Australian study examined the cost-effectiveness of immediate release (IR) tapentadol versus IR oxycodone and concluded that it was more cost-effective for the treatment of acute postoperative pain after major hip surgery (Wang et al. 2022). The results of another pharmacoeconomic evaluation promote the use of tapentadol compared with oxycodone/naloxone fixed combination in patients with musculoskeletal pain, confirming the results obtained in previous studies (Ruggeri et al. 2021).

The results of another study support the use of tapentadol in combination with ketoprofen (versus oxycodone/naloxone fixed combination) for the treatment of moderate-severe pain after major orthopedic surgery, given its efficacy in reducing pain intensity and its satisfactory tolerability (D'Amatoi et al. 2019).

An US study showed that tapentadol IR formulation has comparable analgesic efficacy and overall safety to oxycodone IR for the relief of moderate to severe, acute low back pain and associated radicular leg pain when using flexible dosing regimens that reflect typical clinical practice use. However, tapentadol IR showed a better gastrointestinal tolerability profile, especially for common opioid-related side effects such as vomiting and constipation (Biondi et al. 2013).

The efficacy of tapentadol ER was superior to oxycodone/naloxone ER based on clinical relevance and statistical significance in another phase 3b/4 study in patients with severe low back pain and a predominant neuropathic component. Tapentadol ER was associated with significantly greater improvements in neuropathic pain symptoms and global health status than oxycodone/naloxone ER and with a significantly better gastrointestinal tolerability profile. Tapentadol ER can be considered a first-line option for the management of severe chronic low back pain with a neuropathic pain component (Baron et al. 2016).

The efficacy and safety of tapentadol has also been evaluated in the oncology patient population. In a randomized, double-blind, multicenter phase III study, the efficacy and safety of tapentadol ER (100–250 mg twice daily) was compared with morphine ER (40–100 mg twice daily) and placebo in 496 patients with chronic NRS pain scores ≥ 5. During the two-week titration period, optimal doses that provide maximum efficacy and least side effects of tapentadol and morphine are established. These drugs were then prescribed for another 4 weeks. IR morphine in a single dose of 10 mg is approved as an emergency analgesic for breakthrough pain. The results of the study showed that tapentadol ER could be an effective analgesic whose efficacy was at least as good as the morphine used in the study. It was also well tolerated with a slightly lower incidence of gastrointestinal adverse events than morphine (Kress et al. 2014).

In a study of 343 Japanese and Korean patients with chronic cancer pain (40% gastrointestinal tumors, 30% respiratory system tumors), the efficacy and safety of tapentadol ER was evaluated. The drug showed good analgesic properties comparable to those of oxycodone ER. Tapentadol is well tolerated with less potential for adverse events—both gastrointestinal symptoms (constipation, nausea, vomiting) and central nervous system symptoms (drowsiness, dizziness) compared to oxycodone (Imanaka et al. 2013).

Iatrogenically induced pain syndromes, including radiotherapy and chemotherapy, are sometimes unavoidable. In these cases, encouraging results were also obtained with tapentadol ER. For example, 30 patients with head or neck cancer suffering from postradiotherapy pain syndrome caused by mucositis received tapentadol in gradually increasing doses. 26 patients (86.7%) reported pain relief of at least 30%, while 23% (76.7%) reported pain relief of at least 50% (Mazzola et al. 2016). The literature also reports a case in which the combined administration of tapentadol 300 mg daily with pregabalin 300 mg daily provided effective pain control in severe peripheral polyneuropathy induced by oxaliplatin chemotherapy used in the treatment of colorectal cancer (Borja 2014).

In 2015, the Cochrane Database of Systematic Reviews published a review of studies in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE, evaluating the efficacy and safety of tapentadol ER in oncology patients. Given the mechanism of action of tapentadol and its effect on the noradrenergic system, its primary target group is likely to be patients with neuropathic pain or pain with a strong neuropathic component. Oncology patients are also likely to benefit from tapentadol due to the minimal risk of adverse interactions between tapentadol and chemotherapeutics. Tapentadol is less likely to cause dependence than other opioids, moreover, tolerance to this drug also evolves more slowly compared to other opioids. Good candidates for tapentadol treatment are patients on long-term pharmacotherapy, e.g. oncology patients in remission (Wiffen et al. 2015).

In elderly people with chronic pain of malignant etiology, tapentadol represents a better pharmacotherapeutic option than tramadol as a weak opioid due to a more adequate pharmacological profile of the adverse events it can cause and with a lower potential for causing serotonin syndrome (Veal and Peterson 2015).

A Japanese study examined the safety of tapentadol in cancer patients versus methadone, oxycodone, fentanyl, and hydromorphone. The results showed that the rate of discontinuation of therapy due to adverse events was the lowest in the group treated with tapentadol and proves that tapentadol could be an adequate therapeutic solution for oncological patients with neuropathy and those patients who have an increased risk of side effects of opioid therapy (Takemura et al. 2021).

Tapentadol was approved in Japan in March 2014. In a double-blind, randomized study compared with oxycodone, tapentadol showed relatively better tolerability. Advantages such as the absence of active metabolites and minimal drug interactions also facilitate the use of tapentadol in patients with comorbidities (Takagi and Aruga 2018). Also, its safety profile is incomparable with methadone and hydromorphone.

A recent study concluded that tapentadol is an adequate therapeutic choice for mixed malignant pain in oncology patients who are currently undergoing radiotherapy for bone metastatic changes, without the additional prescription of coanalgesics (Krtinic et al. 2023).

Tramadol and tapentadol are widely prescribed synthetic opioid analgesics. Both are metabolized in the liver and exhibit a dual mechanism of action as MOR agonists and noradrenaline reuptake inhibitors, making them important therapeutic options in the treatment of a wide range of acute and chronic pain situations. Unlike tapentadol, which has minimal serotonergic activity, tramadol poses some risk of causing serotonin syndrome, especially when administered together with SSRIs (Barbosa et al. 2016). Tramadol is a prodrug that mainly undergoes O and N demethylation mediated by the CYP450 isoenzyme complex. In turn, tapentadol is a centrally acting synthetic opioid with a characteristic mechanism of action as a moderate MOR agonist and strong noradrenaline reuptake inhibitor. Both mechanisms of action of tapentadol work synergistically to increase its effectiveness in a wide range of acute, chronic, nociceptive and neuropathic pain conditions. Its activity as a MOR agonist contributes most to analgesia in acute situations, inhibition of monoamine reuptake is more effective in the treatment of chronic pain. In addition to its clinical versatility, this mechanistic synergy gives tapentadol an "opioid-sparing" effect, as compared to other opioids, it requires lower doses to provide equivalent analgesia. This also implies a lower incidence and intensity of adverse events.

Tapentadol is also advantageous in that it is an analgesic independent of metabolic activation. Also, the relative contributions of MOR activation and noradrenaline reuptake inhibition are invariant throughout its biotransformation. In addition, tapentadol undergoes mainly glucuronidation reactions. While CYP450 enzymes are extremely polymorphic, with significant potential impact on tramadol metabolism, safety and efficacy, UGTs have no genetic variability. In fact, only the CYP2D6 phenotype currently appears to be clinically relevant to tramadol treatment. Thus, compared to tramadol, tapentadol reduces interindividual variability due to genetic polymorphisms and has a lower probability of drug-drug interactions (Roulet et al. 2021).

Noradrenaline inhibition combined with moderate opioid agonist activity results in fewer gastrointestinal adverse events compared to equianalgesic doses of oxycodone. Because it has no active metabolites and minimal protein binding, tapentadol provides improved tolerability with less potential for pharmacokinetic drug-drug interactions or accumulation with impaired renal or hepatic function compared to oxycodone. IR tapentadol is currently approved by the US FDA for moderate to severe acute pain in adults (Hartrick 2010).

Chronic pain is multifactorial and this approach ignores the fact that different causative mechanisms may be involved. The presence of more than one causative mechanism means that chronic pain can rarely be controlled by a single agent. Therefore, combining drugs with different analgesic effects increases the likelihood of interrupting the pain signal, but this is often associated with an increased risk of drug/drug interactions and increased adverse events. Tapentadol combines μ-opioid receptor agonism and noradrenaline reuptake inhibition in a single molecule, with both mechanisms contributing to its analgesic effects. Preclinical studies have shown that μ-opioid agonism is primarily responsible for analgesia in acute pain, while noradrenaline reuptake inhibition is more important in chronic pain. In clinical trials in patients with chronic pain, the efficacy of tapentadol was similar to that of oxycodone, but produced significantly fewer gastrointestinal adverse events and discontinuations. Pain relief remained stable during the one-year safety study. Thus, tapentadol may be able to overcome some of the limitations of currently available analgesics for the treatment of chronic pain (Pergolizzi et al. 2012).

3. Conclusion

Based on all of the above, it is clear that tapentadol is the drug of choice both for acute pain conditions (in the form of a IR formulation) and for the treatment of chronic pain syndromes in a pharmaceutical formulation with ER with the achievement of an adequate analgesic response and a minimum of adverse events of therapy compared to classical opioids and that it could be pharmacotherapeutic solution for mixed pain syndromes.

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Table 1: Properties of extended release formulation of tapentadol

Administration and dosage (Deeks 2018)	
Administation route	Oral
Dose	100-500mg
Administation frequency	Twice daily
Pharmacokinetic profile	
Plasma protein binding	20%
Time to maximum serum concentration	3-6h
Mean terminal half-life	4-5h
Mean total clearance	1530-1603 ml/min
Biotransformation	
None of the metabolites contribute to analgesic efficacy.	
Most frequent adverse events	
Nausea	Somnolence
Constipation	Dizziness

Table 2: Propreties of immediate release formulation of tapentadol

Administration and dosage (Chang et al. 2016)	
Administation route	Oral
Dose	50-700 mg
Administation frequency	4-6 times daily
Pharmacokinetic profile	
Plasma protein binding	20%
Time to maximum serum concentration	1.25 h
Distribution volume	540 +/- 98 L
Mean total clearance	1530 +/- 177 ml/min
Biotransformation	
None of the metabolites contribute to analgesic efficacy.	
Most frequent adverse events	
Nausea	Somnolence
Constipation	Dizziness