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Review Article

Tapentadol, an opioid as a strategy for the treatment of chronic pain? A narrative review

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ABSTRACT

Chronic pain affects approximately 30 % of the world population. Tapentadol can be an analgesic option for patients who do not respond adequately to commonly used opioids. This study reviewed the general aspects of Tapentadol pain treatment and its possible association with increased oxidative stress, as well as the benefits of its association with antioxidant substances. The search was carried out in the Medline (Pubmed), Scopus, Web of Science, and Google academic databases, including studies since the registration of the drug in 2008. The selected articles were those related to the use of Tapentadol for chronic moderate to severe pain, but not cancer-related pain, in adults and the elderly. Tapentadol is a μ opioid receptors agonist and inhibits noradrenaline reuptake. Although Tapentadol causes fewer adverse effects than other conventional opioids, studies have shown the induction of oxidative stress by this drug, but without having elucidated the mechanisms.

1. Introduction

According to the World Health Organization (WHO), chronic pain affects 30 % of the population.[1] It is one of the main causes of absence from work and retirement due to illness, as it limits physical functions, simple day-to-day activities, and interpersonal relationships, significantly interfering in people's quality of life[1–3] Furthermore, pain is a serious public health problem and leads to an economic burden of medical expenses, lost wages, and reduced productivity.[3,4]

Usually, chronic pain is caused by some diseases, such as osteoarthritis, rheumatoid arthritis, osteoporosis, low back pain, and fibromyalgia. However, pain of any etiology that remains for more than three months can be considered chronic, if it is not directly related to neoplasms.[3] It can be classified as nociceptive or neuropathic: nociceptive pain arises due to tissue injury or inflammation and neuropathic pain occurs due to a dysfunction of the nervous system, which may be in the brain, spinal cord, or peripheral nerves, being common to appear in the form of burning, needling, or tingling.[2]

Furthermore, chronic pain induces neuroinflammation, neuroplasticity and neurodegeneration, which can extend and increase the pain signal. Pain information is relayed

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from one neuron to another, creating a persistent "memory" of an aggressive event and neuronal hyperexcitability. Therefore, its intensity increases, so that pain does not depend only on an injury to organs or tissues, but on a complex change in the sensory processing of the nervous system.[5,6] In addition, pain is perceived by brain circuits linked to emotions, so it may be related to depression and be the cause and consequence of it. Thus, some myalgias improve with the use of antidepressant medications, or with measures that act on the emotional state and response to stress.[7]

Several pharmacological treatments have been used to control or try to prevent the spread of the pain signal. However, they cause many adverse effects that impair adherence to treatment. Moreover, most chronic pain patients also report that severe pain is not adequately controlled by prescribed medications, which exacerbates the negative impacts of this condition. Therefore, the search for safe and effective drugs to treat severe chronic pain is one of the multiple challenges in pain management.[2,3]

Tapentadol is an opioid analgesic similar to tramadol and has been used effectively to treat pain.[6–8] This drug has a high affinity for opioid receptors, in addition to acting to inhibit the reuptake of NA (nor epinephrine).[2,6,9,10] The Tapentadol therapeutic profile allows for a more potent action, with greater tolerability by the patient, reducing the emergence of respiratory, gastrointestinal and endocrine disorders[11,12], being mainly nausea and vomiting, which have higher incidences with opioids such as Tramadol or Oxycodone.[13–16] In contrast, studies indicate that Tapentadol can imbalance the antioxidant system, leading to an increase in reactive oxygen species (ROS), which can favor the emergence of various pathologies or even increased pain.[17–19] Therefore it is essential to know the drug better so that possible undesirable effects are detected.

Thus, the focus of this review is to address the main mechanisms involved in Tapentadol action and its side effects. In addition, we focus on the possible oxidative process that may occur with chronic use of this drug and whether the use of antioxidant compounds can reverse or help prevent this process, as observed in studies with other opioids.

Therefore an active literature search was performed using the terms "Tapentadol and chronic pain", "Tapentadol and oxidative stress", "Tapentadol and antioxidants", and "Tapentadol and clinical studies". The search was carried out in the Medline (Pubmed), Scopus, Web of Science, and Google scholar databases, with no data and language restriction. In addition, filters were not used. The search was carried out on December 16, 2022. The selected articles were those dealing with the use of Tapentadol for chronic moderate to severe pain, unrelated to cancer pain, encompassing only use in adults (more than 18 years old), and the elderly (more than 60 years old). The analysis of the information began with the title and abstract, and later, if the article met the inclusion criteria, general analysis was carried out.

2. Discussion

2.1. Chronic pain and opioids

Chronic pain treatment is based on the WHO Analgesic Scale. Non-opioid analgesics, followed by selective COX-2 (cyclooxygenase) inhibitors and non-steroidal anti-inflammatory drugs are used to treat low-intensity pain. Opioids, such as morphine and oxycodone, can be combined with other analgesics for moderate to severe pain when other medications are not adequate to promote analgesia.[3,20,21] Adjuvant analgesics such as antidepressants or anticonvulsants are also used.[20]

Although opioids are potent analgesics, their prescription for the treatment of chronic pain should be cautious due to adverse effects and the risk of developing tolerance.[21] Nausea, vomiting, constipation, and drowsiness are common adverse effects that lead to the use of inadequate doses or discontinuation of therapy, which compromises the efficiency of the treatment.[2,5] Determining the correct dose of co-administered analgesics to optimize the efficacy and tolerability of pain management is a major clinical challenge, as many patients find it difficult to adhere to multiple medications. Thus, the use of only one safe and effective drug, covering the various pathophysiological mechanisms of pain, would be ideal for long-term treatment. Therefore, the implementation of safer drugs with fewer adverse effects becomes essential. In this context, Tapentadol has been studied as a promising alternative in the treatment of chronic pain.[2]

2.2. Tapentadol

Tapentadol was approved by the FDA (Food and Drug Administration) in November 2008 and since then, its immediate-release formulation has been marketed in the United States for the treatment of moderate to severe acute pain. The extended-release version has been used since 2011 for the treatment of moderate to severe chronic pain.[6–8] In Europe, the commercialization of immediate and extended-release formulations was approved in 2010 by the EMA (European Medicines Agency).[6] The extended-release formulation is indicated for patients with chronic pain who require long-term analgesic treatment, as it allows a frequent dose with better pain management.[2]

This opioid analgesic is structurally similar to tramadol, but more potent and better tolerated.[2,6] Its dual mechanism of action provides analgesia similar to potent narcotic analgesics such as oxycodone and morphine, however, it shows a lower incidence of side effects.[2,4,6]

In preclinical studies, the affinity of Tapentadol to μ opioid receptor was found to be approximately 50 times

lower than that of morphine, but the in vivo analgesic potency of Tapentadol was only two to three times lower than that of morphine in rat models, suggesting that Tapentadol may have weaker μ-receptor related side effects than classical opioids at equianalgesic doses.[22] Its chronic use was associated with a low incidence of constipation, showing a better gastrointestinal tolerability profile than oxycodone, tramadol, fentanyl, morphine, hydromorphone, buprenorphine, and oxymorphone.[17]

Tapentadol may also be an analgesic option for patients who do not respond adequately to commonly used opioids, due to genetic disposition (weak CYP450 (cytochrome)) metabolizers, as it does not depend on metabolism to produce its therapeutic effects.[2,6,17,23] Its inactive metabolites do not exert activities on opioid receptors or synapse reuptake systems, in addition to not demonstrating induction or significant inhibition of CYP 450. Therefore, it does not cause clinically relevant changes in pharmacokinetic properties when administered with other drugs such as omeprazole and metoclopramine.[6]

2.3. Pharmacodynamic

Opioids are agonists of one or more of the three major opioid receptors: μ, δ (Delta), and k (Kappa) opioid receptors. These receptors are transmembrane and G protein-coupled and are located along the pain pathways in the central nervous system. The activation of these receptors inhibits transmission, decreasing the release of presynaptic neurotransmitters and hyperpolarization of postsynaptic neurons.[2,21,24]

The μ opioid receptors can be found in the amygdala and nucleus accumbens and are responsible for the state of euphoria and reward, in addition to their agonists promoting a powerful analgesic effect.[25,26] Tapentadol has up to ten times greater affinity to μ compared to δ and k opioid receptors[14] In vitro studies have shown that the affinity of Tapentadol to μ is considerably lower than that of classic opioids such as morphine.[5,27]

Tapentadol produces the analgesic effect, acting both in the descending and ascending path of pain.[28] The μ effect of Tapentadol blocks ascending pain signals in the spinal cord, activating the descending inhibition of supraspinal projections, while the increase in the concentration of NA leads to descending inhibition of this pathway.[12] This evidence is confirmed by Kogel et al.[29] who observed that knockout mice with genetic μ deletion showed a partial decrease in the analgesic efficacy of Tapentadol. Another study by Meske et al.[30] quantified the NA concentration in the cerebrospinal fluid of rats with spinal nerve ligation or sham surgery, which received morphine, Tapentadol and duloxetine, intraperitoneally. Tapentadol has shown a significant increase in spinal NA, relating to its clinical efficacy in analgesia. Schröder et al.[31] suggest, in studies with rodents, that analgesia produced by Tapentadol in acute nociceptive pain is due to its μ agonism, while in chronic neuropathic pain, it is due to noradrenaline reuptake inhibition (NRI).

By blocking NA reuptake, Tapentadol increases the level of this neurotransmitter in spinal synapses and interrupts pain signaling by activating adrenoreceptors in postsynaptic spinal nociceptive neurons. In vivo and in vitro studies show that Tapentadol restores the descending inhibitory control of pain.[28]

Tapentadol still has a greater inhibitory effect on NA reuptake, which can reach approximately 450 %, while in relation to serotonin levels, this is around 150 %. *In vitro* and *in vivo* studies using Wister rats, showed that this effect is due to greater inhibition of NA transporters compared to serotonin.[32] With minimal serotoninergic activity, Tapentadol proves to be tolerable for chronic therapy since the activity of serotoninergic pathways is analgesic and stimulates vomiting.[32,33]

Moreover, Tramadol is the drug with the greatest similarity with the mechanism of action of Tapentadol, but it has serotoninergic properties, and the presence of enantiomers with different actions reduces its synergism of activity.[13] Serotonin syndrome is characterized by excessive activation of central and peripheral serotoninergic receptors, with neuro-excitatory characteristics.[34] There is only a theoretical relationship between the occurrence of this syndrome and the administration of Tapentadol, since the evidence in the literature was insufficient.[27] Currently, no additional mechanisms are observed to be involved in the analgesic action of Tapentadol, as the spinal application of opioid receptors and selective antagonists of adrenergic receptors completely reversed the inhibitory effects of Tapentadol.[28]

In relation to undesirable effects, in general this drug is well tolerable, with reduced unwanted respiratory, gastrointestinal, and endocrine effects related to the adverse effects of opioids.[11,12,35] Therefore, patients who use Tapentadol are less likely to develop an adverse effect and discontinue treatment than those who are treated with other opioids, such as buprenorphine, oxymorphone, oxycodone, hydromorphone, and morphine.[36]

Studies associate adverse effects to Tapentadol such as: abdominal pain, electrolyte anormality, atrial fibrillation, suspension, tremor, miosis, hypotension, convulsions, tachycardia, hypertension, delirium, hallucination, convulsion, respiratory depression, reaching coma and death. The most common are vomiting, dizziness, headache, and drowsiness.[37] As mentioned above, Tapentadol promotes less activation of μ receptors compared to classic opioids, eliminating a lower incidence of unwanted effects. However, most adverse reactions observed with the use of this drug are related to the wide expression of the μ in different devices and organs.[35]

In relation to nausea and vomiting, studies show that the better tolerability of Tapentadol is related to its reduced opioid action, in addition to the minimal serotoninergic activity, but it is not related to NRI.[38] On the contrary, the reduction of physical dependence is closely linked to this second drug mechanism, despite the reduced opioid activity also presented.[13] Nausea and constipation with the use of Tapentadol is less frequent than with other opioids.[36,39,40] These data can be confirmed in animal models and in clinical studies. When Tapentadol was applied intraperitoneally in high doses, it led to a lower incidence of nausea in ferrets, whereas with the use of morphine in low doses, animals develop intense nausea. As for constipation, in mice in diarrhea models, the potency ratio to produce an analgesic action and constipation was more favorable to Tapentadol compared to morphine. These studies were confirmed in patients who were administered Tapentadol and oxycodone, demonstrating that the former produces less nausea, vomiting and constipation.[13,14,39] Regarding dependence, Tapentadol is less likely compared to other opioids.[40]

Classic opioids have adverse effects, such as respiratory depression and constipation related to analgesic effects, that is, they are one-dimensional and their therapeutic and adverse effects are due to μ agonism.[11] Respiratory depression is particularly important in centrally acting drugs as they can be fatal. It is associated with direct activation of opioid receptors on brainstem neurons. This condition has been reported in clinical trials with Tapentadol, being evidenced only in high dose administrations or in patients related to μ agonists, leading to discontinuation of treatment in only 15 % of cases[5,14,27,41] Channell et al.[37] identified in the literature at least four deaths associated with respiratory depression with the use of this analgesic. However, this adverse reaction may be related to the presence of previous respiratory problems.

Regarding other adverse reactions, Tapentadol minimally acts on the hypothalamic-pituitary-gonodal axis in a way that has a lower impact on the concentration of sex hormones than morphine or oxycodone.[42] The NRI activity of Tapentadol contributes so that no dysfunction in adult neurogenesis and other associated functions, such as memory, is observed, as this action neutralizes the adverse effect mediated by μ.[43] In a study developed by Biondi et al.[44] in hypertensive patients who used Tapentadol for chronic pain, no clinical changes in mean blood pressure and cardiac function were observed. According, Oh et al.[45] subtherapeutic and therapeutic doses of Tapentadol also did not change the QT/QTc interval in healthy subjects.

2.4. Clinical studies

Tapentadol has been shown to be effective and well tolerated in most chronic painful conditions.[46] In the recent observational and cross-sectional study by Barrachina et al.[47], Tapentadol was shown to have a lower MEDD (Morphine-Equivalent Daily Dose) (89 ± 88 mg/day) than oxycodone/naloxone (124 ± 109 mg/day), in addition to presenting fewer undesirable effects and better tolerability in patients with chronic pain not associated with cancer.

In a randomized clinical study with more than 900 patients after orthopedic surgery, Tapentadol IR (Immediate Release) 50 mg and 75 mg, placebo, and oxycodone IR 10 mg were compared in terms of effectiveness and safety in acute pain. These drugs were administered every 4-6 hours until 72 hours after surgery. Compared to placebo, Tapentadol was shown to significantly improve moderate and acute pain, whereas in relation to oxycodone, Tapentadol, at the two doses tested, did not show inferior effectiveness to this opioid. Regarding undesirable effects such as nausea and vomiting, Tapentadol had a significantly lower incidence.[39] Similarly, Taiwanese[48] and Korean[49] patients after bunionectomy when receiving Tapentadol IR 50 or 75 mg or placebo orally every 4-6 hours for a period of 72 hours, showed a reduction in the intensity of acute pain compared to placebo.

Analyzing 258 patients with low back pain, the efficacy of Tapentadol (250 mg) was compared with oxycodone/naloxone (40 mg/20 mg) and a greater reduction in pain and greater gastrointestinal tolerability was observed.[50] These results corroborate the findings of Biondi et al.[51] with 585 patients with acute, moderate to severe pain, showing similar analgesic effectiveness to oxycodone. Biondi et al.[52] also demonstrated greater tolerability of this drug in elderly people aged 75 years and over, with a diagnosis of knee osteoarthritis or low back pain in relation to oxycodone.

In this sense, a study carried out in four countries (Australia, Canada, New Zealand, and the United States), involving 1030 patients with chronic knee pain derived from osteoarthritis, observed that the use of Tapentadol for 12 weeks showed better efficacy and lower incidence of undesirable effects comparable to oxycodone, thus presenting a better safety profile.[53] These data corroborate the studies by Lange (2017) carried out in the United States that found better efficacy and safety associated with Tapentadol. In addition, Tapentadol (100-250 mg) promoted improvement in pain and was well tolerated compared to placebo over three[54] and twelve weeks[55] in patients with diabetic peripheral neuropathy, being an alternative to this health problem.

Furthermore, patients who underwent the substitution of opioids by Tapentadol were followed in the study by Gálvez et al.[56] Tapentadol analgesia (50-250 mg twice daily) was compared to opioids such as oxycodone, buprenorphine, fentanyl, morphine, and hydromorphone and showed comparable pain relief. The main undesirable effects of opioids such as nausea and vomiting were reduced with the use of this analgesic.

In moderate to severe pain associated with malignant tumors, Tapentadol (100-250 mg) showed comparable efficacy to morphine (40-100 mg) over two weeks, but with fewer gastrointestinal undesirable effects.[57] In this same clinical condition, 233 Japanese and Korean patients who received Tapentadol (200 mg) showed efficacy comparable to another opioid, oxycodone (40 mg), and similarly a lower incidence of undesirable effects.[58]

2.5. Oxidative stress

In addition, recent evidence suggests that opioids can act directly on the antioxidant defense.[59] Toxicity studies show that chronic treatment for 21 days of rodents with morphine[60] and codeine[61] is able to decrease superoxide dismutase (SOD) and catalase (CAT) activities and increase malonaldehyde (MDA) in the brain of these animals.

Toxicity studies with acute doses of morphine have shown depletion of GSH (Glutathione Reductase) levels in the brain of rodents.[62] Codeine, in turn, in chronic use for six weeks to assess its toxicity, increased MDA, and myeloperoxidases and decreased GSH levels and SOD and CAT activities in liver tissues.[63] In humans, the use of buprenorphine and methadone decrease plasma levels of GSH and CAT and enhance MDA in patients on heroin maintenance therapy.[64]

In relation to tramadol, this compound can increase oxidative stress by regulation of dopamine levels with consequent release of hydrogen peroxide rodent brain mitochondria.[65] In studies of toxicity in which Wistar rats were subjected to doses of 40 or 200 mg/kg/day of tramadol for approximately one month, the opioids demonstrated a decrease in antioxidant enzymes and an increase in MDA levels in the brain and plasma of rodents. Furthermore, the association of antioxidants with tramadol such as thyme in the dose of 500 mg/kg for 30 days or fennel incorporated into rodent diets at concentrations of 10, 20 and 30 % for six weeks led to a reduction in these damages. The damage caused by Tapentadol to organs such as the brain, heart, and lungs of rodents is believed to be related to tramadol- like mechanisms.[18]

In this regard, chronic administration of Tapentadol in Wistar rats for 14 days at doses of 10, 25, and 50 mg/kg is related to changes in lipid peroxidation levels in the liver, kidney, heart, lung, liver, and brain of these animals.[66] Furthermore, Tapentadol induced an increase in protein oxidation due to the elevation of carbonyl groups in the liver, kidney[66], and brain[67] of these animals and a decrease in the total antioxidant capacity in the liver.[66]

Studies using Wistar rats in acute exposure to a single dose of 10, 25, or 50 mg/kg decreased substances reactive to thiobarbituric acid (TBARS) levels in liver and kidney. However, the same studies revealed significant increases in protein carbonyl groups of these tissues, indicating an induction of oxidation at the protein level. Therefore, the decrease in TBARS levels may be related to a protective effect or up-regulation of enzymes, to prevent oxidative damage. Consequently, the role of this drug in the formation of oxidative stress cannot be ruled out.[18]

Additionally, a study with cultures of neuronal cells treated with a concentration of 100 μM (micromole) and 200 μM of Tapentadol demonstrated that this drug promotes a decrease in metabolic activity, mainly by decreasing ATP (Adenosine Triphosphate) levels, which is closely linked with enzymatic and metabolic changes.[17] Neuronal damage is observed through darker colored neurons and glial activation with microglial proliferation and the presence of inflammatory infiltrates in cardiac, pulmonary[18], and renal[68] tissue.

In this context, the antioxidant system is mainly formed by the enzymes SOD, CAT, and GPx (Glutathione Reductase), which together play an important role in maintaining the body's balance, neutralizing ROS and thus preventing tissue and cell damage. However, in situations of oxidative stress there is an increase in oxidizing compounds and dysregulation in the activities of these enzymes, leading to various damages.[69]

The presence of oxidative stress is detected in animals by the dosage of antioxidant enzymes and MDA, which is the main marker of lipid peroxidation, which is determined through the technique of reactive species to TBARS.[69] In humans, this detection occurs through biomarkers, which are indicators of normal and pathogenic biological processes or pharmacological response to a therapy.[70,71]

According to Gunn et al.[70], oxidative stress markers in humans correspond to pyroglutamate and ethylmalonic acid, and ethylmalonic acid, and mainly indicate glutathione depletion, deficiency of coenzyme Q10, Vitamin B12 and/or carnitine, respectively. Thus, high levels of pyroglutamate, for example, indicate that the cell is more susceptible to oxidative damage by reducing glutathione.

Vitamin B12 has several functions in the body, including the elimination of free radicals, as well as the preservation of glutathione. In this sense, its reduction becomes an important mechanism to identify a higher percentage of pro-oxidant compounds; and studies demonstrate that vitamin B12 supplementation leads to decreases in ROS, especially the superoxide anion.[72,73]

Additionally, Vecchiet et al.[19] observed that free radicals are associated with hyperalgesia, and therefore, the maintenance of glutathione levels is essential for the management of chronic pain. Thus, the monitoring of patients who use drugs that can increase ROS levels, such as Tapentadol, need monitoring, as do the associations with antioxidant compounds, which are substances capable of inhibiting or delaying the damage caused by oxidizing agents.[69]

Therefore further studies are needed to clarify the relationship of oxidative stress in the use of Tapentadol,

especially in chronic use. Thus, it would be crucial to associate the use of this drug concomitantly with antioxidants, as was done with tramadol, to determine whether the results found will be the same and whether the antioxidants will act to improve the inflammatory infiltrates found in the use of Tapentadol, since most antioxidant compounds also have anti-inflammatory activity.[69,72,74]

3. Conclusions

Tapentadol is a promising drug in the treatment of acute and chronic pain, as it has better tolerability of use by the patient. In addition, its dual mechanism of action allows the use of an effective monotherapy, facilitating medication adherence and making it safer, since the use of a single drug to promote analgesia can reduce the incidence of side effects.

However some issues need to be clarified, as biochemical abnormalities such as vitamin B12 deficiency can compromise the analgesic efficacy of drugs such as Tapentadol, leading to hyperalgesia or the need for concomitant supplementation of antioxidants to neutralize the production of free radicals and favor the action of this analgesic.

Thus, more studies need to be carried out to determine the safety of the chronic use of Tapentadol, as this drug simulates other drugs that lead to severe oxidative damage "in vivo". Given the possibility of harmful effects to the body with its use, the therapeutic follow-up of patients is essential in clinical practice.

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5. Conflict of Interest

None.

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