Review

Renata Zajączkowska[1], Wojciech Leppert[2, 3], Jerzy Wordliczek[4]

[1]Department of Emergency Medicine and Intensive Care, Collegium Medicum, University of Rzeszów, Rzeszów, Poland
[2]Chair of Palliative Medicine, Institute of Medical Sciences, Collegium Medicum, University of Zielona Góra, Zielona Góra, Poland
[3]University Clinical Hospital in Poznań, Poland
[4]Outpatient Pain Clinic, Department of Pain Study and Treatment, Collegium Medicum, Jagiellonian University, Kraków, Poland

# Progress in pain management with opioid analgesics: focus on tapentadol, cebranopadol, and oxycodone with naloxone

## Abstract

Opioids are the strongest analgesics available in medicine and they are used when non-opioid analgesics are ineffective. However, they may cause side effects that may limit their use and therapeutic effect. Therefore, newer opioids with limited adverse effects while preserving analgesic efficacy may have a prominent role in the pharmacotherapy of patients with severe pain intensity. This narrative review focuses on three opioids (tapentadol, cebranopadol, and oxycodone/naloxone) that display different pharmacodynamic and pharmacokinetic properties compared to widely used opioids with the provision of effective analgesia and fewer adverse effects. It highlights a need for an individual and tailored approach to address patient needs regarding management of patients with pain and minimizing adverse effects which ultimately preserves possible highest patients and caregivers quality of life.

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**Keywords:** cebranopadol, opioid analgesics, oxycodone/naloxone, pain, tapentadol

## Introduction

Opioids are drugs with an established position in the treatment of patients with severe pain intensity [1]. However, opioid use in clinical practice may be limited by their adverse effects [2]. Therefore, new opioids are being investigated, which display similar efficacy to widely used opioid analgesics with less intense and fewer adverse effects [3]. Since most of the side effects of opioids result from activation of $\mu$-opioid receptors (MOR), a good option may be the use of opioids with complex mechanisms of action, which combine activation of MOR and descending antinociceptive pathways through inhibition of

**Address for correspondence:**
Renata Zajączkowska
Department of Emergency Medicine and Intensive Care, Collegium Medicum, University of Rzeszów, Rejtana 16c, 35–959 Rzeszów, Poland
e-mail: rzajaczkowska@ur.edu.pl

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norepinephrine reuptake (NRI) — tapentadol [4] or activation of nociceptin/orphanin receptors (NOP) (cebranopadol) [5]. To reduce the intensity and incidence of opioid-induced bowel dysfunction (OIBD), a combination of one formulation of opioid receptor agonist (prolonged release oxycodone) with an antagonist (prolonged release naloxone), in which the latter decreases the intensity of OIBD without impairing analgesic effect (PR oxycodone/PR naloxone) was elaborated [6].

## Methods

This narrative review focuses on pharmacodynamic and pharmacokinetic properties along with the clinical application of three opioids: tapentadol, cebranopadol, and oxycodone/naloxone. A literature search was conducted in the following databases: PubMed, Google Scholar, and Cochrane, with the terms: "tapentadol", "cebranopadol", "oxycodone/naloxone", "chronic pain", and "cancer pain" for the period until December 2024.

## Tapentadol

### Pharmacodynamics

Tapentadol is a drug classified as a strong opioid, which represents a new class of drugs known as $\mu$-opioid receptor agonist and norepinephrine reuptake inhibitor (MOR-NRI). Its mechanism of action is complex and consists of agonist effects on MOR and NRI [4, 7, 8] (Fig. 1). The affinity of tapentadol for MOR is 50 times lower compared to morphine. Despite this, as experimental studies show, its analgesic effect is only 3 times lower than morphine. Such a strong analgesic effect of tapentadol, despite its relatively weak affinity to MOR, is the result of the synergism of its two mechanisms of action i.e. influence on MOR and the descending noradrenergic antinociceptive system [7]. Experimental and clinical studies confirm the effectiveness of tapentadol in the treatment of acute and chronic pain of various types, including somatic, visceral, and neuropathic pain [8]. It is suggested that the agonist effect on MOR is largely responsible for the effectiveness of tapentadol in acute pain treatment, and inhibition of norepinephrine reuptake for the effectiveness of tapentadol in chronic pain, including neuropathic pain [9].

### Pharmacokinetics

Tapentadol is an active drug and for its analgesic activity does not require metabolic activation. The bioavailability of tapentadol after oral administration is estimated at 32%. The degree of binding of tapentadol to plasma proteins is relatively low (20%), which determines the low potential of tapentadol to displace other drugs from their protein bindings and cause adverse effects. The risk of drug–drug interactions with tapentadol is low. It does not activate or inhibit CYP 450 enzymes [10]. No drug interactions have been reported when tapentadol was administered with drugs that may affect glucuronidation (paracetamol, naproxen, and aspirin) [11] as well as those that affect tapentadol absorption (omeprazole, metoclopramide,

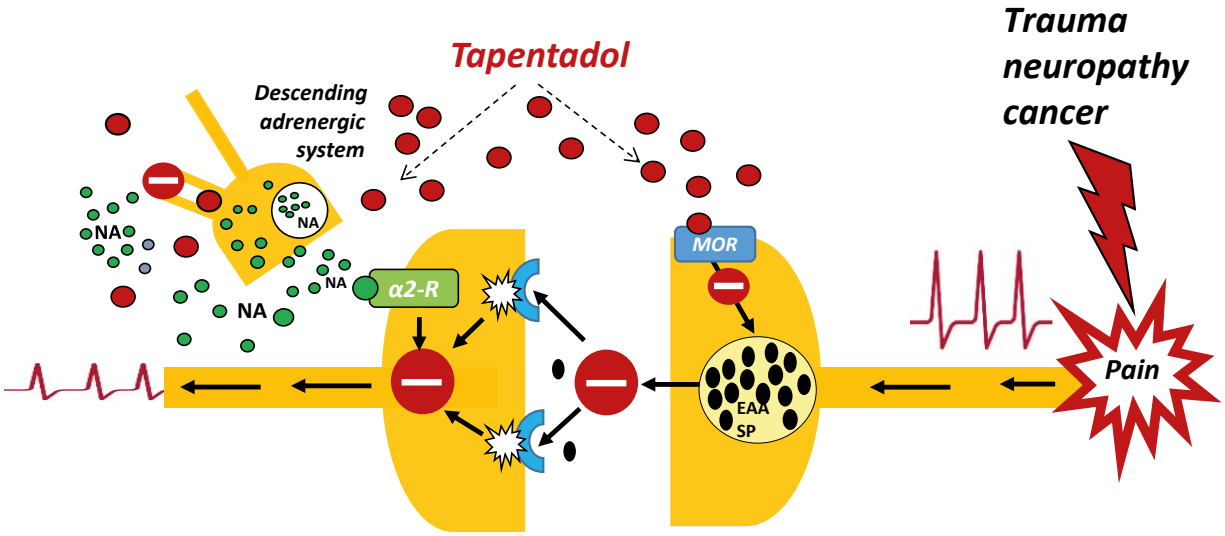


**Figure 1.** Mechanism of action of tapentadol. Tapentadol provides analgesia through two mechanisms of action: MOR agonism and NRI; NRI increases levels of NA, which in turn leads to analgesia through activation of α2-R; α2-R — inhibitors alpha-2 adrenergic receptors; EAA — excitatory amino acids; MOR — $\mu$-opioid receptor; NA — noradrenaline; NRI — noradrenaline reuptake inhibition; SP — substance P

probenecid) [12, 13]. However, the use of tapentadol with drugs or substances that have central nervous system (CNS) depressant effects such as benzodiazepines, antipsychotics, phenothiazines, or alcohol may cause additive effects and increase the intensity of CNS depression symptoms [14]. Due to the noradrenergic mechanism of action of tapentadol, administration of tapentadol with monoamine oxidase (MAO) inhibitors within 14 days is contraindicated because of the risk of cardiovascular events, especially hypertension [14].

The pharmacokinetics of tapentadol is linear and dose-dependent. It is metabolized in the liver to inactive metabolites, including N-desmethyltapentadol and hydroxytapentadol. 99% of the dose of tapentadol is eliminated by the kidneys in the conjugated form, in the form of inactive metabolites, or as an unchanged drug. The remaining 1% of the tapentadol dose is excreted in stool [8]. Consideration should be given when using tapentadol in patients with impaired hepatic function. These patients should be carefully treated with reduced doses of tapentadol adjusted to the severity of liver dysfunction. In patients with severe hepatic insufficiency, tapentadol should not be used [15–17]. It is not necessary to reduce the dose of tapentadol in patients with mild or moderate renal dysfunction, but due to the lack of clinical trials in patients with advanced renal insufficiency, tapentadol is not recommended in this group of patients [14].

### Indications and dosing

The indications for tapentadol use include severe pain intensity in adults and children older than 6 years, which can be adequately controlled only with opioid analgesics. The dose of tapentadol should be selected individually, depending on the intensity of pain, treatment tolerance, and the patient's somatic condition, including liver and kidney function. The starting dose of tapentadol IR is 50 mg every 4–6 hours and tapentadol PR 50 mg every 12 hours. In case of strong intensity of pain or rotation from other opioids, higher initial doses of tapentadol may be required. Titration of the drug should be continued until adequate pain relief or adverse reactions occur. The recommended maximum daily dose of tapentadol IR is 600 mg and tapentadol PR is 500 mg per day [18]. An abrupt discontinuation of tapentadol may lead to the development of withdrawal symptoms. In order to avoid them, it is recommended to gradually reduce the tapentadol dose [8, 18].

### Clinical efficacy and tolerability

Many studies have been conducted to evaluate the effectiveness and tolerability of tapentadol in the treatment of various acute pain syndromes (e.g. acute postoperative pain after dental, orthopedic, and abdominal surgery) [19–22]. There are also many studies available in the literature assessing the effectiveness and safety of tapentadol in the treatment of chronic pain (osteoarthritis, chronic low back pain, musculoskeletal pain) [16, 23–27]. Because of the synergism of its two mechanisms of action i.e. influence on MOR and NRI, tapentadol appears to be a promising therapeutic option in the treatment of neuropathic pain [28–32]. Good results were also observed in the treatment of patients with cancer-related pain [33–40].

Tapentadol is a drug with a good safety profile. Trials comparing tapentadol with other opioids (primarily oxycodone and oxycodone with naloxone) have found fewer gastrointestinal adverse events (nausea, vomiting, constipation), a good safety profile for the cardiovascular system, and a lower incidence of treatment cessation due to unacceptable side effects. The most common side effects accompanying tapentadol therapy are nausea, vomiting, and constipation, but these occur less frequently and are less intense compared to morphine and oxycodone [41–44]. Tapentadol, compared to other opioids, has a lower potential for endocrine disturbances, dependence, and addiction. Tapentadol is less likely to induce addiction than other opioids. Likewise, tolerance to analgesic effects of tapentadol develops more slowly than in the case of other opioids [18, 45]. Tapentadol may be more suitable than hydromorphone, oxycodone, and fentanyl for G-allele carriers due to MOR-NRI properties and low susceptibility to OPRM1 A118G polymorphism [46].

## Cebranopadol

### Pharmacodynamics

Nociceptin/orphanin (N/O) phenylalanine (F) glutamine (Q) peptide (N/OFQ) is an endogenous agonist of the NOP receptor. It differs from traditional opioid peptides in terms of its binding properties. While at the molecular and cellular levels, N/OFQ works similarly to opioids, its pharmacological effects are not necessarily the same as, and sometimes even counteract those of opioids [5, 47, 48]. Cebranopadol is a new, powerful, and first-of-its-kind analgesic that affects the CNS by targeting both nociceptin/orphanin FQ peptide (NOP) and opioid receptors [49–51] (Fig. 2). Cebranopadol was shown to bind strongly to both NOP and opioid receptors, especially to human NOP and MOR, with inhibitory constants in the subnanomolar range. Its binding affinity for the human KOR was *ca.* 3–4 times lower, while for the human DOR it was *ca.* 20−26 times lower compared to MOR [50]. Since NOP and opioid receptor agonists affect pain through different but related mechanisms,

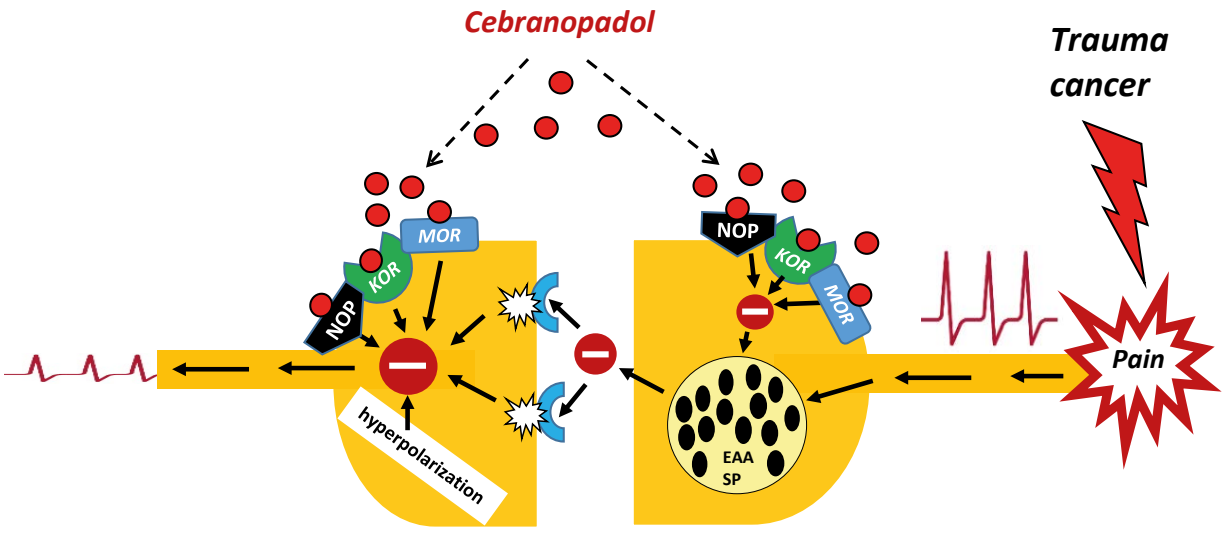


**Figure 2.** Mechanism of action of cebranopadol. Cebranopadol, as an agonist of the MOR and KOR opioid receptors, by inducing the closure of ion channels for calcium ions, inhibits the release of pronociceptive neurotransmitters — EAA and SP. While, postsynaptic stimulation of the opioid receptor KOR induces the opening of ion channels for potassium ions causing hyperpolarisation of neurons. Moreover at the molecular level, cebranopadol actions at the NOP receptor results in inhibition of adenylate cyclase, increase in K+ conductance (which leads to hyperpolarization in neuronal cells) and inhibition of $Ca^{2+}$ conductance leading to inhibition of release of pronociceptive neurotransmitters; EAA — excitatory amino acids; MOR — $\mu$-opioid receptor; KOR — kappa-opioid receptor; NOP — nociceptin/orphanin FQ peptide receptor; SP — substance P

a combination of both may offer more effective pain relief with fewer side effects compared to traditional opioids [49]. It should be born in mind that while "strong" opioids provide effective pain relief, their potential to cause tolerance to analgesia and physical dependence could restrict their usefulness in clinical settings in the long-term treatment. What is significant in this context is that the activation of NOP receptors mitigates the development of tolerance, addiction, and physical dependence caused by MOR agonists in rodent models [52–54].

According to preclinical research findings, cebranopadol has a more favorable tolerance profile compared to other opioids, as it does not impact motor coordination or respiratory function even at doses that exceed the analgesic requirement [49]. Additionally, the activation of NOP receptors has been demonstrated to hinder the development of tolerance to analgesia, addiction, and physical dependence induced by MOR agonists in rodent models [50, 51]. Since cebranopadol has shown its efficacy in animal models of both nociceptive and neuropathic pain, it could be used to treat mixed pain conditions. Additionally, cebranopadol, a nonselective drug that affects multiple opioid receptors, may offer various benefits compared to selective agents or bivalent compounds. These advantages include targeting the pain pathway at several levels, a smaller molecular size that allows for better penetration into the CNS, and more predictable pharmacokinetics [48, 51]. The drug also has better respiratory safety [55] and lower potential for abuse when compared to traditional opioids, which could be beneficial in the treatment of chronic pain [56–59].

## Pharmacokinetics

Cebranopadol reaches its peak plasma concentration ($C_{max}$) 4–6 hours after oral intake, with a long half-life of 14–15 hours, and a terminal phase half-life lasting from 62 to 96 hours. Cebranopadol reaches a steady state in about 2 weeks with a 24-hour dosing interval. The drug shows dosage proportionality at steady state for doses ranging from 200 to 1600 $\mu$g. After giving patients the drug once a day for several days, an operational half-life of 24 h was found to be the relevant factor to describe the clinical pharmacokinetics of multiple doses of cebranopadol [60].

## Clinical efficacy

Early clinical trials indicate that cebranopadol is safe and effective in the treatment of patients with various pain conditions such as chronic osteoarthritis, diabetic peripheral neuropathy, acute postoperative pain, low back pain, and cancer-related pain [57–59, 61, 62]. Cebranopadol was analyzed in patients who had undergone bunionectomy surgery. A single dose of 400 $\mu$g and 600 $\mu$g of cebranopadol provided effective pain relief. In this study, cebranopadol was

compared to the opioid typically used in this setting, namely morphine. Both drugs provided sufficient pain relief for 24 hours, but cebranopadol was better tolerated and received a higher overall rating from patients. In the overall satisfaction survey, patients who were given cebranopadol were more content with their treatment compared to those who received morphine. It is important to mention that morphine started acting later than cebranopadol [59].

Eerdekens et al. [61] reported additional study results on the effectiveness, safety, and tolerance of cebranopadol in patients experiencing moderate to severe chronic pain intensity from diabetic peripheral neuropathy (DPN). Patients were given either a placebo, pregabalin 300 mg twice daily, or cebranopadol 100 $\mu$g, 300 $\mu$g, or 600 $\mu$g once daily. All doses of cebranopadol demonstrated a clinically significant difference in pain intensity compared to placebo. It was also shown that cebranopadol had a better analgesic effect at higher doses (600 $\mu$g) and was well tolerated in patients suffering from DPN-induced pain.

Christoph et al. [57] reported on the effectiveness of cebranopadol administered for 14 weeks to patients suffering from chronic low back pain both with and without a neuropathic pain component. Cebranopadol was given once a day at doses of 200, 400, or 600 $\mu$g. The treatment showed cebranopadol to be efficacious. Statistically significant and clinically relevant improvements compared with placebo were observed at all doses. In general, beneficial outcomes from cebranopadol treatment were seen regardless of whether a neuropathic pain component was present or not. Cebranopadol had a positive effect on sleep and functionality. In the maintenance period, treatment-dependent adverse events (dizziness, nausea, somnolence, vomiting, constipation, fatigue, headache, and hyperhidrosis) occurred in < 10% of study participants.

Cebranopadol showed a good safety and tolerance profile when administered to patients with chronic moderate-to-severe intensity of cancer-related pain for up to 26 weeks in doses ranging from 200 to 1000 $\mu$g once a day. Managing the intake and dose adjustment of cebranopadol was simple, leading to sufficient control of chronic cancer-related pain in this challenging patient group. Switching from morphine PR to cebranopadol was safe, well-received, and effective in terms of pain relief [62].

Eerdekens et al. [58] evaluated the analgesic effectiveness of cebranopadol in comparison to morphine PR in cancer patients experiencing moderate to severe pain intensity. A total of 126 patients received treatment for a maximum of 7 weeks. For the primary endpoint, noninferiority of cebranopadol with and superiority over morphine PR were demonstrated. Cebranopadol was effective, safe, and well tolerated in the dose range tested (200–1,000 $\mu$g) in patients suffering from chronic moderate-to-severe cancer-related pain intensity. Most used cebranopadol doses were ≤ 800 $\mu$g. Switching from another opioid to cebranopadol was found to be safe, well-tolerated, and effective.

## Prolonged release oxycodone with prolonged release naloxone

Opioid-induced bowel dysfunction (OIBD) is a common gastrointestinal tract adverse effect (AE) caused by opioids. Targeted treatment includes the administration of a combination of prolonged-release (PR) oxycodone with PR naloxone (OXN) in one tablet. A combination of oxycodone with naloxone in one preparation provides an analgesic effect with limited AE on the function of the gastrointestinal tract. The systemic availability of naloxone after oral administration of PR formulation is very low — approximately 2% in patients with normal liver and renal function. Restrictions of the use of OXN include a maximum daily dose of 160 mg/80 mg of PR oxycodone and PR naloxone, normal liver function, right portal circulation, and normal renal function, which are necessary to minimize the risk of significant systemic availability of naloxone and occurrence of opioid withdrawal syndrome [6, 63].

### Pharmacodynamics

Oxycodone is a step 3 World Health Organization (WHO) analgesic ladder opioid, a semisynthetic thebaine derivative. It binds to MOR and KOR [64]. Naloxone is an opioid receptor antagonist, a semisynthetic morphine derivative. It acts on MOR, KOR, and DOR. Due to the higher affinity for opioid receptors, naloxone displaces opioid analgesics from their receptors. For this reason, naloxone is used parenterally to treat opioid overdose, primarily to reverse opioid-induced respiratory depression. Orally administered naloxone alleviates or eliminates the adverse effects of opioids on the gastrointestinal tract, especially opioid-induced constipation (OIC) and OIBD, and improves bowel function [63] (Fig. 3).

OXN is a combination of PR oxycodone and PR naloxone in a 2:1 ratio. This optimal ratio of oxycodone to naloxone was determined in a study, which showed that a combination of PR oxycodone and PR naloxone in a 2:1 ratio provides effective analgesia and improvement of bowel function in patients with chronic pain of severe intensity [65] and a good tolerance of the treatment [66]. There is a clinically observed difference

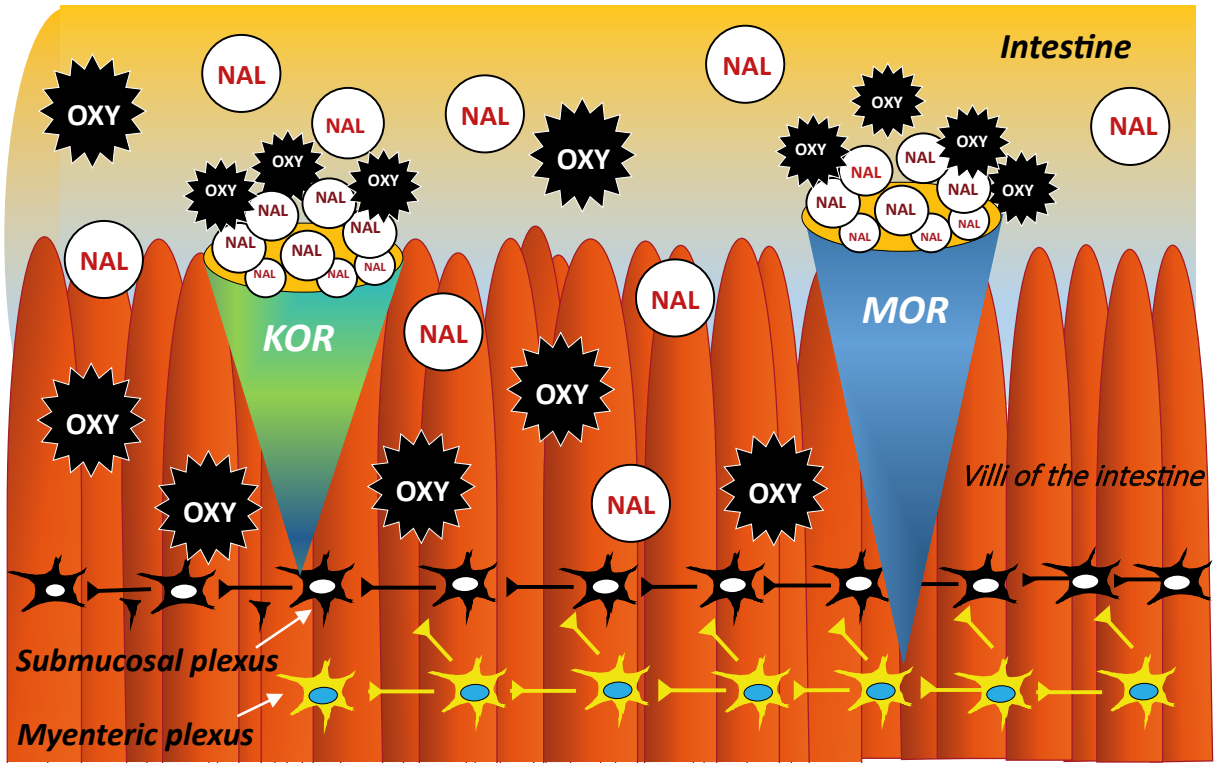


**Figure 3.** Mechanism of action of oxycodone/naloxone in the intestinal wall. Combination of oxycodone with naloxone in one preparation provides an analgesic effect with limited adverse effects on the function of the gastrointestinal tract. Mechanism of action of naloxone, which is a component of OXN, is to prevent binding or to displace oxycodone from opioid receptors located in the intestinal wall; KOR — kappa-opioid receptor; MOR — $\mu$-opioid receptor; NAL — naloxone; OXY — oxycodone

between the results of administration of immediate--release (IR) and PR formulations of naloxone in patients treated with opioid agonists. IR naloxone may attenuate analgesia or induce opioid withdrawal symptoms [67]. The PR naloxone formulation, thanks to the gradual release of naloxone, prevents the saturation of the hepatic enzyme system which is involved in naloxone metabolism and this mechanism reduces the risk of opioid antagonism [67].

## Pharmacokinetics

The bioavailability of oxycodone after oral administration is high (60–87%) and it binds mainly to albumin — approximately 45%. Oxycodone metabolism takes place mainly in the liver and small intestine, and its results are noroxycodone (via CYP3A4) and oxymorphone (via CYP2D6). Oxycodone and its metabolites are eliminated mainly in the urine and to a lesser extent in feces [68]. The maximum plasma concentration ($T_{max}$) is achieved within 25 minutes after oxycodone intravenous administration, 1.3 h after oral administration of IR formulations, and 2.6 h after the administration of PR formulations. The plasma half--life ($T_{1/2}$) of oxycodone is approximately 2–3 h after intravenous administration, 3 h after oral administration of IR formulations, and approximately 5 h after oral administration of PR formulations [64].

In contrast to oxycodone, the bioavailability of naloxone after oral administration is very low (less than 2%). Naloxone undergoes first-pass metabolism via glucuronidation in the liver to its main metabolite naloxone-3-glucuronide (NAL-3-G) [69]. After oral naloxone administration, $T_{max}$ of NAL-3-G is achieved within 60 minutes. $T_{1/2}$ of naloxone after oral administration of PR tablets is approximately 60 minutes and of NAL-3-G is approximately 8 h. Naloxone and its metabolites are eliminated in the urine. Because the effect of orally administered naloxone depends on normal liver function, OXN is not recommended in patients with significant liver dysfunction [70]. OXN should not be used in patients with renal failure, because in this group of patients, the level of naloxone may increase significantly. Because oxycodone is metabolized via the P450 system, especially CYP3A4 and CYP2D6, drugs inhibiting these enzymes should not be co-administered or used with caution when co-administered with oxycodone, because they may increase oxycodone plasma levels and cause overdose [68, 71]. The risk of drug interactions with naloxone is lower because it is metabolized through glucuronidation [67].

### Clinical efficacy

Analgesic efficacy of OXN is similar to oxycodone, with improvement in bowel function and lower consumption of laxatives in patients with chronic non-malignant pain including low-back pain and neuropathic pain [72], in cancer patients with pain [73, 74], and in patients with acute pain, including postoperative pain [75–78]. OXN is a registered therapy for the management of severe pain intensity, which can only be adequately treated with opioid analgesics. OXN provides analgesia with limited oxycodone effect on bowel function. In this two-component formulation, oxycodone provides patients with adequate analgesia, and opioid antagonist naloxone is used to counteract OIC by blocking oxycodone's action on opioid receptors which are located in the myenteric and submucosal plexus of the gut wall.

OXN is a treatment option for patients with severe pain intensity who require a "strong" opioid and who have OIC. OXN may be administered to patients with pain unresponsive to opioids of the 2 step of the WHO analgesic ladder or to opioid-naive patients with moderate-to-severe pain who have OIC. OXN may also be effective in patients rotated from other step 3 opioids who suffer from severe pain intensity and OIC. It can also be used occasionally during therapy with other "strong" opioids [79]. OXN is also registered as a second-line drug for symptomatic treatment of patients with severe to very severe idiopathic restless legs syndrome after failure of dopaminergic therapy. The maximum total daily dose of OXN should not exceed 160 mg PR oxycodone/80 mg PR naloxone (80 mg/40 mg q 12 h) [79]. For patients requiring higher opioid doses, administration of supplemental PR oxycodone at the same time intervals should be considered, taking into account the maximum daily dose of 400 mg PR oxycodone. In the case of supplemental oxycodone dosing, the beneficial effect of naloxone on bowel function may be impaired [79].

Although the maximum registered total daily dose of OXN is 160 mg/80 mg, research shows that slightly higher daily doses of OXN 180 mg/90 mg may also be safe and effective [80]. However, Mercadante et al. [81] presented a case report of a cancer patient who was receiving increasing doses of oxycodone/naloxone combination (ratio 2:1) with an unexpected declining analgesia. The substitution with the same doses (240 mg/day) of regular PR oxycodone was effective in restoring adequate analgesia. Probably such a high dose of naloxone blocked the analgesic effect of oxycodone, which could occur if the dose of naloxone exceeds the capability of enzymes involved in naloxone metabolism. The portal vein thrombosis may also lead to an increase in the bioavailability of naloxone [82]. It should also be noted that renal impairment may lead to a significant increase in naloxone levels and ineffective analgesia along with a high risk of opioid withdrawal. Clinical practice suggests that lower doses (in the range of 10–30 mg naloxone per day) may be effective in preventing OIC.

OXN is cost-effective in the management of patients with moderate-to-severe pain and OIC compared to oxycodone alone [83–85] and slightly less cost-effective compared to tapentadol [29, 86, 87]. The European Society for Clinical Oncology (ESMO) [88] recommends the use of OXN for pain management in cancer patients and OIC. According to ESMO, a combination of an opioid and naloxone has been shown to reduce the risk of OIC through both open-label, phase II and III studies [89]. OXN may also be used for the management of patients with chronic non-cancer pain and OIC. The evidence from OXN studies conducted in patients with chronic non–malignant and cancer-related pain points to the role of OXN in the treatment of OIBD in patients who require opioid therapy for moderate-to-severe pain intensity [90–99]. OXN should be used early in the treatment of pain in patients requiring opioid analgesic administration, particularly in those predisposed to constipation [94, 97].

## Summary

Promising results of clinical studies with tapentadol, cebranopadol, and oxycodone with naloxone indicate the possibility of the improvement of analgesia and elimination or at least reduction of a significant burden associated with opioid-induced adverse effects [100]. Good knowledge of the characteristics of each of the drugs presented, allows for the introduction of personalized therapy, individually tailored to the needs of each patient. Such treatment may be especially important for those who need chronic administration of opioids. Effective treatment of pain with limited adverse effects allows the majority of patients with chronic severe pain to achieve optimal well-being and quality of life.

## Article information and declarations

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### *Author contributions*

All authors participated in the preparation of the manuscript.

## *Conflict of interest*

All authors declare that they have no conflicts of interest.


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None.

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