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Pathophysiology and management of opioid-induced constipation: a narrative review

Abstract

Background: Treatment of chronic pain is among the primary tasks of palliative care. Among the most commonly prescribed analgesics are opioid agents. Opioids, in addition to being highly effective in controlling severe pain, have a high risk of adverse effects (AEs). The most common gastrointestinal AE is opioid-induced constipation (OIC).

Methods: A search through online databases was conducted including Google Scholar and PubMed and key information on the pathophysiology, epidemiology, diagnosis and current therapeutic options for OIC has been collected.

Results: The pathophysiology of OIC is primarily related to the direct action of opioids on opioid receptors located in the wall of the gastrointestinal tract. This leads to deregulation of the mechanisms responsible for the motor and secretory functions of the gastrointestinal tract. That results in impaired digestion and delayed intestinal transit, leading to the development of constipation. Opioid-induced constipation leads to a significant reduction in patients' quality of life and an increase in the cost of treatment and can lead to serious complications such as gastrointestinal perforation. Patients receiving palliative care due to their multiple burdens require a holistic diagnostic approach and thorough differential diagnosis of OIC. Among therapeutic approaches, we distinguish between non-specific methods related to lifestyle changes and laxatives, and cause-directed pharmacological methods related to the use of peripherally acting opioid receptor antagonists (PAMORA). The most commonly used PAMORA for the treatment of OIC include naloxegol, methylnaltrexone and naldemedine. Numerous clinical studies demonstrate the efficacy and high safety profile of PAMORA in the treatment of OIC.

Conclusions: Proper diagnosis of OIC among patients taking opioid drugs allows for the implementation of effective therapeutic measures. Appropriate treatment reduces the risk of OIC-related complications and leads to an increase in patients' quality of life.

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Keywords: opioid-induced constipation, palliative medicine, opioids, opioid receptor antagonists, pain, methylnaltrexone, naloxegol

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Introduction

The treatment of chronic pain is among the key issues of palliative medicine oriented toward improving the quality of life and comfort of patients with chronic and incurable diseases. The development of therapeutic methods allows patients receiving palliative care to live longer, and as a result, they take high doses of pain medication for long periods [1, 2]. For this reason, rational management of analgesic therapy that reduces the risk of adverse effects and counteracts the increase in tolerance to pharmacological agents has become extremely important [1–4]. Opioids are among the most commonly prescribed, strongest and most effective analgesics for chronic and severe pain, and their use has increased significantly in recent years [3, 5–8]. Their analgesic effect is primarily due to binding to opioid μ-receptors, although they also show the ability to bind to κ and δ receptors, which results in a different physiological effect [4]. The primary site of action for opioid drugs is the brain, brainstem, spinal cord, autonomic ganglia, as well as the enteric nervous system [4, 9].

The long-term use of opioid medications, multimorbidity and gradual increase in tolerance requiring the use of increased doses by palliative patients makes them a group particularly vulnerable to serious adverse effects such as sedation, opioid-induced respiratory depression, hyperalgesia and the risk of addiction [1–3]. Opioid drugs also exhibit adverse effects on the sensorimotor function of the gastrointestinal tract by acting on the enteric nervous system (ENS) [7]. This leads to a decrease in the natural activity of the ENS in the gastrointestinal tract, manifested as weakened peristaltic movements, delayed intestinal transit in both the small and large intestines, and increased fluid absorption [9, 10].

The term opioid-induced bowel dysfunction (OIBD) includes symptoms such as nausea vomiting, bloating, gastroesophageal reflux, abdominal pain and constipation [1, 7, 11, 12]. The most common subtype of OIBD is opioid-induced constipation (OIC), occurring in up to 87% of hospice patients taking opioid medications [1, 7]. According to the Rome IV criteria OIC is defined as new or worsening symptoms of constipation arising during the initiation, change or intensification of opioid treatment, accompanied by additional clinical symptoms such as a feeling of incomplete bowel movements and fewer than three spontaneous bowel movements per week. An additional condition for the diagnosis of OIC is the rare occurrence of loose stools without the use of laxatives [7].

The duration of opioid treatment is among the main factors in the development of OIC. It has been shown that the risk of OIC in patients taking opioids for more than 2 years is 10 times higher than in patients taking this treatment for less than 6 months [9]. Studies list OIC among factors that severely reduce patients' quality of life while indicating that the problem often goes undiagnosed [9, 13–18]. The purpose of this paper is to gather key information on the pathophysiology, clinical assessment of the patient's condition and possible treatments for OIC that may be useful in daily clinical practice.

Methods

A search through online databases was conducted — Google Scholar and PubMed. A variety of search terms and combinations of phrases was used, carefully selecting titles that included the following terms: "opioid-induced constipation", "opioids in palliative care", "palliative medicine", "opioid receptors", "PAMORA", "pathophysiology of opioid-induced constipation", "treatment of opioid-induced constipation", "lubiprostone", "naloxegol", "methylnaltrexone", "naldemedine" and "laxatives in opioid-induced constipation". In total, 198 articles were analysed, from which 54 articles have been selected as considered most relevant in this area. Any articles that were unrelated to the pathophysiology and treatment of opioid-induced constipation, as well as those which concerned mainly opioid-induced constipation in short-term opioid use have been eliminated. The selection of articles was based on the authors' experience through narrative review. When an article cited original papers, the authors decided to establish the original article as the source of information to emphasize the role of the research team in gaining knowledge. To maintain a high level of publication when selecting articles on therapeutic methods, the authors aimed to select recent reports published within the last 10 years. This ensured that the research focused and targeted toward a specific area of interest that was a target of the study and contains the most up-to-date knowledge.

Pathophysiology of opioid-induced constipation

The extensive network of neuronal connections within the gastrointestinal tract, the largest outside the central nervous system, means that the gut can be considered a neurological organ. This is an extremely important aspect to consider when administering pharmacotherapy with neuroactive agents. Since many of the receptors and neurotransmitters found in the central nervous system are also found in the

ENS, it is to be expected that many neuroactive drugs with primary applications in other areas of medicine such as psychiatry, neurology, anaesthesiology or intensive care will also affect the enteric nervous system, leading to changes in its function [19, 20]. This has important clinical implications when administering analgesic opioid drugs to palliative care patients, as adverse effects can significantly reduce the balance of therapeutic benefits of using opioid drugs for pain management [1, 21, 22].

The opioidergic system has a significant impact on the physiology of the digestive system [16, 20]. Opioid μ, κ, σ receptors, which are G-protein-coupled receptors, are widely distributed throughout the gastrointestinal tract [5, 12, 14]. Endogenous opioid peptides such as enkephalins, endorphins and dynorphins by binding to opioid receptors can lead to internalization, coupling to inhibitory Gi/Go proteins, which have an activating or inhibitory effect on downstream transmission [7, 20]. Naturally occurring opioid peptides have an important regulatory function in the gastrointestinal tract, affecting the release of neurotransmitters that regulate its function [18–20]. Proper gastrointestinal motility depends on the proper balance of neurotransmitters/neuromediators released by excitatory and inhibitory neurons. Excitatory neurons release acetylcholine and tachykins, which lead to the contraction of longitudinal smooth muscle, while inhibitory neurons secrete nitric oxide and vasoactive intestinal peptide, leading to its relaxation [3, 5, 7, 20]. Exogenous opioid drugs disrupt this delicate balance of ENS neurotransmission by affecting the opioid receptors within the gastrointestinal tract [5, 23, 24]. They delay gastric emptying, increase pyloric tone and inhibit propulsive movements while increasing non-propulsive segmental contractions. In addition, they increase fluid absorption in both the small and large intestines, increase rectal sphincter muscle tension and impair its reflex relaxation in response to rectal filling [19–21, 25, 26]. Opioids are also responsible for disorders of secretory function of the stomach, gallbladder, pancreas and intestines leading to digestive disorders [25, 26]. The effects of opioids on the gastrointestinal tract are summarized in Table 1.

Table 1. A summary of the effects of opioids on the gastrointestinal tract

Site of action	Pharmacological action of opioids
Oesophagus	Dysmotility Achalasia
Stomach	Decreased gastric motility Increased pyloric tone Gastroparesis Decreased secretion Reflux
Gallbladder	Decreased biliary secretion
Pancreas	Decreased pancreatic secretion of bicarbonate
Sphincter of Oddi	Sphincter of Oddi dysfunction
Small intestine	Reduced propulsion Increased fluid absorption Small intestinal bacterial overgrowth Delayed transit
Large intestine	Decreased propulsion Increased non-propulsive contractions Increased fluid absorption Delayed transit
Anal sphincter	Increased anal sphincter tone Incomplete relaxation

The exact pathophysiology of OIC is most likely due to the direct action of opioids on μ opioid receptors located directly in the intestinal wall [1, 21, 27, 28]. Within the gastrointestinal tract, expression of opioid receptors occurs in myenteric and submucosal neurons, interstitial cells of Cajal, and immune cells located in the enteric lamina propria [5]. The effect on central receptors is probably less important, although it is also significant [16, 27]. The inhibitory effect of opioids on small intestinal peristalsis in the guinea pig is thought to be primarily due to the interruption of neural and neuroeffector transmission pathways in the enteric nervous system that regulate intestinal muscle activity [20]. Such action is due to the effects of opioid agonists on G-protein-coupled μ and σ receptors, leading to the closure of voltage-gated Ca^{2+} channels located on the presynaptic membrane of nerve endings [3, 5, 7]. Consequently, this leads to a reduction in the release of cyclic adenosine monophosphate (cAMP) and neurotransmitters. Opioid agonists also lead to the hyperpolarization of the postsynaptic membrane by opening K^+ channels, resulting in its hyperpolarization and a decrease in the excitability of postsynaptic neurons [5, 7, 25, 29]. Thus, collectively, opioids affect gastrointestinal function in a multifaceted manner by reducing neural excitability within the enteric nerves [7, 25]. This ultimately results in a disruption of the release of neurotransmitters that perform regulatory functions within the gastrointestinal tract, leading to its dyscoordination [20, 23].

In addition to their effects on gastrointestinal motility, opioids also lead to inhibition of the secretion of vasoactive intestinal peptide (VIP) by binding to the μ opioid receptor within the ENS. A decrease in its release results in decreased gallbladder and pancreatic secretion and dysregulation of intestinal fluid absorption. Inhibition of acetylcholine and VIP release

decreases the release of chloride and water into the intestinal lumen, resulting in a decrease in stool hydration, further predisposing to constipation [5, 7, 12, 23]. Thus, the pathophysiology of OIC is a complex phenomenon consisting of decreased stool hydration, impaired digestion and slowed intestinal transit.

The importance of developing opioid tolerance

An important factor in the development of OIC is the gradual increase in tolerance to opioid agents used in long-term analgesic therapy in palliative patients. It is related to the presence of the intracellular protein β arrestin-2, which, by binding to dephosphorylated G-protein-coupled receptors on the cell membrane, leads to receptor internalization and, consequently, desensitization [3, 5, 30]. This leads to the need for increased drug doses to achieve the intended analgesic effect, which can result in increased adverse effects, including gastrointestinal AE [3]. However, ENS differs from CNS in terms of the development of opioid tolerance. Unlike many other adverse effects, constipation does not tend to subside as a result of opioid tolerance development [1, 3, 31]. Within the gastrointestinal tract itself, tolerance also develops to varying degrees [5]. For example, a down-regulation mechanism leads to the development of tolerance in the ileum. In contrast, opioid tolerance does not develop in the colon. This has to do with the preserved production of β arrestin-2 in the colon, which results in the unblocking of the opioid receptor and its return to the cell membrane [3, 5, 30]. The lack of, or weaker development of opioid tolerance occurring in parts of the gastrointestinal tract means that adverse effects in the form of constipation do not tend to subside and can increase as the dose of drug necessary to achieve an analgesic effect increases, even leading to small bowel obstruction [1, 32].

Epidemiology

Opioid-induced bowel dysfunction is a very common complication of chronic opioid therapy and occurs in 40–80% of patients taking opioids. The most common subtype of OIBD, which is OIC, depending on the study occurs with varying but high frequency [12, 22, 33, 34]. In one study, it reached 60–90% of cancer patients taking opioids [23]. In another study, OIC was reported to occur in between 51 and 87% of patients taking opioids during cancer and 41–57% of patients taking opioids for chronic non-cancer pain [7, 17]. The true incidence and complication numbers associated with OIC are likely higher due to underdiagnosis and undertreatment [35]. Opioid-induced bowel dysfunction caused a decrease in work capacity and productivity, reduced patients' ability to cope with activities of daily living, driving a vehicle and significantly affected their overall quality of life [1, 33, 36]. With this in mind, any constipation developed during the use of opioid drugs should raise suspicion of OIC. Despite this, OIC often remains undiagnosed and can lead to additional complications [7]. Fear of addiction and adverse effects is a strong factor in a patient's attitude toward opioid medications [1]. Complications related to constipation can be so significant and distressing to the patient that they often modify treatment on their own. In one study, a third of patients reported reducing drug doses, increasing dosing intervals, or finally forgoing analgesic treatment with opioids to avoid OIBD symptoms [22, 35].

Diagnostics

Current diagnostic methods for OIC include both objective criteria and subjective feelings of the patient [18, 37]. An important aspect of the diagnostic process of OIC appears to be the need for a uniform definition of OIC, which was only proposed in 2016 by the Rome Foundation based on previous proposals [5]. The most commonly used diagnostic criteria include a positive history of opioid use, fewer than three spontaneous defecations per week, and at least two of the following symptoms if they occurred for at least 25% of the time in a recent week: incomplete bowel evacuation, straining during defecation, infrequent and hard or lumpy stools [5, 7, 12, 18]. The above criteria are included in the Rome IV criteria shown in detail in Table 2 [35]. A slightly different

Table 2. Rome IV diagnostic criteria for opioid-induced constipation

1. New, or worsening, symptoms of constipation when initiating, changing, or increasing opioid therapy, that must include two or more of the following: • Straining during more than ¼ (25%) of defecations • Lumpy or hard stools (Bristol Stool Form Scale 1–2) in more than ¼ (25%) of defecations • A sensation of incomplete evacuation in more than ¼ (25%) of defecations • A sensation of anorectal obstruction/blockage in more than ¼ (25%) of defecations • Manual manoeuvres to facilitate more than ¼ (25%) of defecations (e.g., digital evacuation, support of the pelvic floor) • Fewer than three spontaneous bowel movements (SBMs) per week
2. Loose stools are rarely present without the use of laxatives

definition of constipation in palliative patients was proposed by Dzierżanowski and Larkin, defining it as "a decreased frequency of bowel movements (BM) or laxatives necessary to induce BM or patient-reported symptoms such as difficulty of defecation, too hard stools, too small stools, or sensation of incomplete defecation". To reduce the misdiagnosis of constipation in patients with minor bowel dysfunction, the authors distinguished three additional criteria, at least one of which must be met. These criteria relate to 1) Ease of defecation assessed as moderate to extreme difficulty (≥ 2 on a 0–4 scale); 2) Last bowel movements present ≥ 2 days before; 3) Frequency of bowel movements reported as ≤ 3 days with defecation per week [38]. However, the use of a rigid definition is not a perfect solution, as it often leads to misdiagnosis in many patients, especially those receiving palliative care [1, 18, 37]. Indeed, constipation is a common problem in hospice patients and is not always related to opioid use. For example, the treatment rate for constipation in hospice patients was 63% in those not taking opioids and 87% with opioid treatment included [1]. A thorough patient interview is crucial in this case, as patients often provide an individual subjective definition of constipation based on personal experiences and based on bowel habits such as frequency, difficulty with defecation, or stool consistency. With this in mind, patients taking opioids should undergo careful clinical observation and a thorough interview for changes in bowel habits during the course of opioid drug therapy [18, 37].

The Bowel Function Index (BFI) is another support tool for the clinical condition and progress assessment of patients with OIC [5]. It consists of the patient's assessment of ease of defecation, the feeling of incomplete bowel emptying and a subjective evaluation of constipation. Each variable is rated on a scale of 0 to 100 based on the past 7 days. The sum of each variable is then divided by three, so the maximum possible score is 100 [7, 25]. The use of the BFI in patients chronically taking opioids can help evaluate non-pharmacological management of OIC and differentiate those patients in whom consideration of specific pharmacological treatment is indicated [25]. A BFI value of more than 30 is considered to be the differentiating point between patients without constipation and those with constipation, and this value is also considered an indicator that supports the need to implement specific pharmacological treatment in patients using laxatives [23]. A change in the value of the BFI index by ≥ 12 points constitutes a significant clinical change [7]. An important aspect of the diagnosis of OIC is the identification of barriers that impede it. The primary difficulty is the lack of awareness among medical personnel about the possible serious consequences of OIC [18]. Although one study found that almost all clinicians surveyed listed constipation among the possible potential complications of opioid therapy, a conversation with the patient about his or her complaints of defecation may not be held [18, 22]. Patients themselves also may not report the onset of constipation symptoms when it is an embarrassing issue for them. A gentle approach to the patient with respect for their intimacy and an understanding of the limitations caused by chronic illness is crucial in this case [18]. Another important aspect is that patients often do not receive enough information about OIC and may not identify constipation as an adverse effect of opioid use [22]. It is therefore extremely important for patients to understand and be aware of the potential adverse effects of taking opioids [12]. Since the diagnosis of OIC is based on symptoms much more than objective diagnostic markers an extremely important aspect is a differential diagnosis based on the exclusion of other causes of constipation such as neurological disease, metabolic disorders, or a tumour compressing the colon causing mechanical obstruction [12, 18, 37]. Other ancillary tools for assessing the condition of a patient with OIC are the patient assessment of constipation quality of life (PAC-QOL) patient assessment of constipation symptoms (PAC-SYM), and the Knowles Eccersley Scott Symptom Score, but these are difficult to use in daily clinical practice [7].

Treatment

An extremely important aspect is to make sure that opioid treatment is implemented only in cases that require it, and that patients take the minimum effective dose [12]. Among the primary forms of OIC prevention are analysis and, if possible, changes in the patient's lifestyle including aspects such as changing eating habits, increasing the amount of fibre in the diet and the amount of fluid intake [6, 7, 36, 39, 40]. It may also be helpful to change the opioid agent used, reducing the dose or route of administration. In the next stage, non-specific laxatives should be considered along with lifestyle changes [24, 40]. For patients who do not achieve a satisfactory effect, or if OIC symptoms are exacerbated, there is the possibility of using specific pharmacological treatment to reduce the effects of opioids on the gastrointestinal tract [1, 6, 18, 24].

The starting point of drug therapy with opioid receptor antagonists is the use of peripherally acting drugs that do not cross the blood–brain barrier. They then do not inhibit the analgesic effect of opioids, which still affect receptors within the central nervous

system. Instead, they inhibit the effects of the opioid on peripheral receptors, leading to a reduction in adverse effects [14, 17, 40]. Such agents include non-specific opioid receptor antagonists and peripherally acting opioid receptor antagonists (PAMORA) [14, 40, 41]. The most commonly used PAMORA agents in second-line treatment include methylnaltrexone, haloenol and naldemedine [14]. However, the use of μ receptor antagonist-based drug therapy is associated with a higher risk of adverse effects such as nausea, diarrhoea, abdominal pain and vomiting than in the placebo-controlled group [35].

Laxatives

Laxatives are among the non-specific therapeutic forms of OIC. They are the primary first-line agents used in the prevention and treatment of OIC [13, 18, 20, 27, 35]. They increase the hydration of the stool, making it move more easily through the digestive tract and easier to excrete. The most commonly used laxatives include osmotic agents and stimulants [18, 27]. However, their effectiveness is severely limited and they do not always have the intended therapeutic effect. Studies have shown that only 50% of patients experience satisfactory relief from OIC after using laxatives alone [6, 20, 24, 31]. Another study presented that up to 81–94% of patients using laxatives for OIC do not achieve satisfactory improvement [41].

A major problem with the use of laxatives to treat OIC is the lack of placebo-controlled clinical trials confirming their efficacy [18, 39]. Macrogols are currently the preferred laxatives for the treatment of OIC due to their high safety profile and relatively low risk of adverse effects [14]. Among other commonly used preparations among patients with constipation are agents based on senna, docusate sodium, bisacodyl and lactulose [24]. However, these preparations show negligible efficacy with long-term use. In addition, lactulose, unlike macrogol, undergoes intestinal fermentation leading to adverse effects such as bloating, abdominal discomfort and abdominal pain [14, 28]. Although laxatives are among the agents recommended for the treatment of OIC in patients receiving palliative care, due to their cachexia and the aetiology of OIC, the options for their use are often limited [37]. Laxatives also lead to many adverse effects such as flatulence, vomiting and nausea and may be associated with alternating episodes of constipation and diarrhoea [17].

Prucalopride

In cases of limited efficacy of laxatives for chronic constipation, there is the option of using a prokinetic agent based on prucalopride. Prucalopride is a highly selective 5-HT_4 receptor agonist. Its action stimulates gut motility by interacting with 5-HT_4 receptors in the gastrointestinal tract, which results in acetylcholine release from cholinergic neurons. Studies to date indicate a high safety profile for prucalopride, which can be effective in chronic constipation despite the lack of clear guidelines for its application [42, 43].

Lubiprostone

Lubiprostone is among the agents approved for the treatment of OIC in patients treated with opioids for non-cancer pain by the U.S. Food and Drug Administration (FDA). It works by activating C1C-2 chloride channels in the intestine [7, 31, 39, 44, 45]. Activation of chloride channels increases the degree of hydration of the digestive contents found in the intestine, facilitating intestinal transit [7, 18, 24, 46]. Analyses showed an advantage for lubiprostone over placebo, but no advantage for prescription agents over over-the-counter laxatives [35]. A randomized, double-blind, placebo-controlled phase three study evaluated the effect of lubiprostone in the treatment of OIC at a dose of 25 μg twice daily. It showed a significant increase in the number of spontaneous bowel movements after lubiprostone compared to placebo (3.3 *vs.* 2.4 SBMs/week, $p = 0.005$). Moreover, the percentage of patients who experienced spontaneous bowel movements after the first dose of lubiprostone was also higher than in the placebo-controlled trial [45]. Three randomized, double-blind, placebo-controlled studies of chronic non–cancer pain patients treated with opioids with confirmed OIC showed no effect of lubiprostone used at a dose of 24 μg twice daily on opioid analgesia [46]. Analysis of the frequency of adverse effects of lubiprostone showed that they occurred at a similar frequency as in the placebo-controlled group ($p < 0.125$). The most common adverse effects with a higher frequency of lubiprostone use included gastrointestinal complaints in the form of nausea, diarrhoea and abdominal pain. Studies have shown that lubiprostone does not affect the analgesic effect of opioids used [7, 44].

Naloxegol

Naloxegol 12.5 mg and 25 mg is an FDA-approved drug for the treatment of OIC [35]. It is a targeted formulation that acts as an antagonist to the opioid receptor. It is a conjugate of naloxone with a polymer part consisting of a polyethylene glycol residue, which is responsible for limiting the penetration of the blood–brain barrier by the drug. This limits the abolition of the analgesic effect while limiting the adverse effects associated with action on peripheral opioid receptors [14, 24, 26, 27, 39, 40]. Naloxegol

has been shown to significantly reduce increased sphincter muscle tone while taking opioid drugs [14].

In two identical 12-week placebo-controlled, double-blind phase III clinical trials KODIAC-04 (n = 652) and KODIAC-05 (n = 700), patients treated with opioids for chronic non–cancer pain were observed for the efficacy of naloxegol in treating OIC [41, 47, 48]. The drug's efficacy was assessed by the number of SBM per week. The primary response endpoint was the criterion of at least three SBM per week with an increase of at least one SBM from baseline for at least 9 of the 12 weeks of treatment with an emphasis on efficacy during 3 of the last 4 weeks of the study. The secondary endpoint was defined as the response in the subpopulation of patients who did not achieve the expected response after laxatives prior to the inclusion of naloxegol therapy. The study evaluated parameters such as the time to the first SBM after the first naloxegol dose and the average number of days per week with an SBM. In the above study, patients were randomly divided into three groups receiving oral naloxegol 25 mg or naloxegol 12.5 mg or placebo [48].

The response to treatment with the 25 mg dose was significantly higher than in the placebo-controlled trial, being in study KODIAC 04, 44.4% *vs.* 29.4%, p = 0.001, and in study KODIAC 05, 39.7% *vs.* 29.3%, p = 0.02. For patients in whom treatment with laxatives did not have the intended effect, the results were as follows: study KODIAC 04, 48.7% *vs.* 28.8%, p = 0.002; study KODIAC 05, 46.8% *vs.* 31.4%, p = 0.01. The 12.5 mg dose of naloxegol also showed a significant advantage over placebo in the study KODIAC 04 40.8% *vs.* 29.4%, p = 0.02 and for patients with an unsatisfactory response to laxatives 42.6% *vs.* 28.8%, p = 0.03. A reduction in the time to first SBM and an increase in the average number of spontaneous defecations per week were observed in both studies with the 25 mg dose ($p < 0.001$) and in the KODIAC 04 study with the 12.5 mg dose ($p < 0.001$). Adverse effects among which gastrointestinal complaints predominated were observed more frequently in the group using 25 mg of naloxegol [48]. Thus, the study demonstrated the efficacy of naloxegol in the treatment of OIC.

The KODIAC 08 study dedicated to the safety and tolerability of naloxegol showed that naloxegol used for up to 52 weeks at a dose of 25 mg per day was generally safe and well tolerated by patients. The study assessed the incidence of adverse effects relative to standard care which was 81.8% with naloxegol and 72.2% with usual care. Adverse effects that occurred more frequently after naloxegol than in the group receiving standard care were abdominal pain (17.8% *vs.* 3.3%), diarrhoea (12.9% *vs.* 5.9%), nausea (9.4% *vs.* 4.1%), headache (9.0% *vs.* 4.8%), flatulence (6.9% *vs.* 1.1%) and upper abdominal pain (5.1% *vs.* 1.1%) [39]. Although all of the above studies refer to patients with chronic non-cancer pain, the European Medicines Agency (EMA) recognizes that their results can also be related to and applied to patients with cancer-related pain, including patients receiving palliative care [14]. In a 52-week randomized open-label, multicentre study, naloxegol at a dose of 25 mg was found to be safe and well tolerated [7].

Methylnaltrexone

Methylnaltrexone is the first drug registered for the treatment of PAMORA. It is registered and indicated for the treatment of OIC in patients with long-term use of opioids, including palliative care patients [18, 24, 31, 40]. Methylnaltrexone is a peripherally acting drug [49]. It is a derivative of naltrexone containing a methyl group, which increases its polarity and reduces its solubility in lipids, limiting its ability to penetrate the blood–brain barrier [7, 25, 26]. The lack of blood–brain barrier penetration means that methylnaltrexone does not abolish the analgesic effect of the opioids used [7, 37]. It is available as a formulation for subcutaneous injection and oral tablets.

Phase III placebo-controlled studies have demonstrated the efficacy of subcutaneously applied methylnaltrexone in inducing rescue bowel movement and relief of constipation [24]. After the injection of methylnaltrexone, 48–61% of patients achieved SBM within 4 hours after receiving the drug [49]. Orally administered methylnaltrexone at a dose of 450 mg had an efficacy of 28% in inducing rescue-free bowel movement compared to 18.8% after placebo [7]. In another study, patients undergoing 24-hour evaluation after methylnaltrexone injection achieved rescue SBM in 59.1% of cases compared to 19.1% of subjects in the placebo group [26]. A meta-analysis of the data showed the superiority of subcutaneously applied methylnaltrexone over placebo in improving bowel movements and reducing gastrointestinal discomfort in a group of patients with cancer pain [7].

In a 4-week placebo-controlled study, the efficacy of a subcutaneous injection of methylnaltrexone at a dose of 12 mg daily or every other day was evaluated. The study showed the superiority of methylnaltrexone over placebo in reducing the time to rescue free bowel movement, increasing the average number of SBM per week, reducing effort during defecation, and decreasing the sensation of incomplete defecation. The most common adverse effects of methylnaltrexone use included abdominal pain and nausea [25]. Based on the study, methylnaltrexone

is unlikely to significantly increase the frequency of serious adverse effects, and the study supports its effectiveness in improving bowel function in palliative care patients [26]. The recommended doses are 8 mg for patients weighing up to 62 kg and 12 mg for patients weighing up to 114 kg. The adverse effects of the treatment used in the studies were mainly mild and related to gastrointestinal complaints [7, 37]. Methylnaltrexone is not extensively metabolized in the human body. After intravenous and subcutaneous administration, its demethylation does not occur. It is excreted mainly through the kidneys [24]. Unfortunately, the Polish health system does not reimburse methylnaltrexone, which significantly limits its use in everyday clinical practice.

Alvimopan

Alvimopan has a high affinity for the peripheral opioid receptor, but its use is associated with an increased risk of myocardial events [26]. For this reason, alvimopan is a drug intended for short-term use and is not suitable for treating patients with chronic constipation caused by the use of opioid drugs in palliative care. It can be used after surgery for 7 days but is not recommended for patients going home [27, 37].

Oxycodone combined with naloxone

Changing the treatment strategy for chronic pain with opioid agents may result in a reduction in the severity of OIC symptoms. One possible therapeutic option to consider includes a form of combined therapy with an extended-release formulation containing oxycodone in combination with naloxone [32]. Oxycodone is a semisynthetic opioid that binds to μ and κ opioid receptors. Naloxone, on the other hand, is a semisynthetic morphine derivative and an opioid antagonist that interacts with μ, κ and δ opioid receptors [32, 50]. Naloxone has a very high affinity for opioid receptors and consequently displaces opioids from their receptors. Naloxone injection is used in cases of opioid intoxication and results in the abolition of their effects [32, 51]. However, the use of an oral formulation based on oxycodone and naloxone allows the maintenance of analgesia associated with the use of opioid agents, while reducing OIC symptoms. This effect is due to the specific pharmacological properties of the preparation.

The systemic bioavailability of orally administered naloxone is very low due to intensive first-pass metabolism in the liver and ranges from 0.9–2% at doses of 5–120 mg. On the other hand, systemic bioavailability of orally administered oxycodone is up to 87% in patients with a healthy liver. Thanks to this combination of bioavailability of the individual components of the orally administrated medical preparation, naloxone does not abolish the systemic bioavailability of oxycodone. However, acting in the gastrointestinal tract naloxone reduces the binding of oxycodone to the opioid receptor located in the intestinal wall, which contributes to a reduction in the severity of OIC [32, 34, 52]. The use of oxycodone in combination with naloxone shows analgesic effects similar to those of other opioids. A 2:1 ratio of oxycodone to naloxone is most beneficial to patients [34]. Previous publications support the high safety profile of naloxone in OIC. The use of oxycodone naloxone in clinical trials was also well tolerated and resulted in improved bowel function in patients [34, 52].

Naldemedine

Naldemedine is the latest PAMORA [7, 17]. The chemical structure of naldemedine is similar to naltrexone, but the presence of large hydrophilic side chains increases the drug's molecular weight and polarity. This limits the penetration of naldemedine into the CNS by penetrating the blood–brain barrier, so the drug does not abolish the analgesic effect of the opioids used [13, 17, 37]. The drug, when used in oral form, is rapidly absorbed and reaches maximum plasma concentration in 45 minutes [13, 17]. The drug is excreted 57% in urine and 35% in faeces [37].

Two randomized double-blind, placebo-controlled phase III studies COMPOSE-1 and COMPOSE-2 evaluated the effects of naldemedine on a group of 1,095 patients. The study included patients aged 18–80 with opioid-related constipation with chronic non-cancer pain who had been taking opioid treatment for the past three months, including a stable dose equivalent to at least 30 mg of morphine sulphate for the past month [53]. In the above studies, patients were divided 1:1 into a group taking oral naldemedine 0.2 mg once daily and a group taking a placebo. The primary efficacy endpoint was defined as drug efficacy defined as at least three SBM per week with an increase of at least one SBM from baseline for at least 9 of the 12 weeks of the study including efficacy for at least 3 of the last 4 weeks of the study [53]. In both studies, the naldemedine groups had a higher rate of patients achieving improvement after treatment. In the COMPOSE-1 study, this was 47.6% *vs.* 34.6% in the placebo group ($p = 0.002$). In the COMPOSE-2 study, this was 52.5% in the naldemedine group and 33.6% in the placebo group ($p < 0.0001$). The percentage of adverse effects in COMPOSE-1 and COMSPOSE-2 studies was similar in the naldemedine and placebo groups. The most common adverse effects included gastrointestinal discomfort in 15% of patients using naldemedine in the COMPOSE-1 study

(*vs.* 7% in the placebo group) and 16% of patients taking naldemedine in the COMPOSE-2 study (*vs.* 7% in the placebo group) [53].

The 2-week randomized, double-blind, placebo-controlled phase III COMPOSE-4 study analyzed the efficacy of naldemedine 0.2 mg once daily orally among 193 patients with OIC and cancer. The results showed an advantage of naldemedine (71.1% of responders with 0.2 mg naldemedine treatment) over placebo with 34.4% of responders ($p < 0.0001$) [54]. The 12-week extension study COMPOSE-5 analysed the safety of naldemedine in a group of 131 patients with OIC and cancer. In the study, 80.2% of patients had treatment-related adverse effects, the most common of which was gastrointestinal complaints occurring in 43.5% of subjects. In the COMPOSE-4 study, the percentage of gastrointestinal complaints was 23.7%. Such a significant difference in results is likely related to the length of treatment in both studies (COMPOSE-4 two weeks *vs.* COMPOSE-5 twelve weeks). In both studies, the most common gastrointestinal complaint was diarrhoea. In conclusion, naldemedine used at a dose of 0.2 mg orally once daily was well tolerated among cancer patients with OIC [37, 54].

Conclusions

In an era of continuous medical progress, the survival time of patients affected by many serious diseases has increased significantly. Longer survival times inevitably entail an increase in the duration of treatment itself, an indispensable aspect of which is the management of severe pain in patients receiving palliative care. Opioid agents are among the most effective analgesics, the use of which has increased significantly in recent years. In addition to their high efficacy, their use is unfortunately associated with a high risk of adverse effects, the most common of which is OIC.

The key to proper treatment of OIC is a good understanding of the causes of the disease, which enables the use of targeted treatment. The pathophysiology of the development of OIC, presented in the article, allows to understand the mechanisms of opioids' effects on the gastrointestinal tract, which, in the authors' opinion, is crucial for the proper diagnosis and effective treatment of affected patients. Numerous diagnostic tools serve only an auxiliary function, as the diagnosis of OIC is based largely on the patient's subjective feelings rather than objective diagnostic parameters. For this reason, careful observation, a conversation with the patient combined with an analysis of the bowel rhythm before and after the inclusion of opioid therapy, seems crucial. It should be kept in mind that unrecognized and untreated OIC can carry serious clinical implications including serious complications such as gastrointestinal perforation.

Current recommendations in the treatment of OIC assume a gradation of therapeutic approaches. First consideration should always be given to modifying the patient's lifestyle, including eating habits, the amount of dietary fibre consumed, the amount of fluid intake, or the amount of daily exercise. Non-specific laxatives can be considered on par with lifestyle modification recommendations. Although they have limited efficacy and there are not enough placebo-controlled clinical trials to confirm their effectiveness they have many advantages. They are inexpensive, readily available mostly well tolerated by patients and often provide relief from constipation. For this reason, most recommendations assume the use of laxatives in the first stage of OIC treatment.

If first-line management is insufficiently effective, there is ample opportunity to use agents that target the cause of OIC strictly. Such agents include drugs from the group of peripherally acting opioid receptor antagonists (PAMORA). For the treatment of OIC, naloxegol, methylnaltrexone and naldemedine are the most widely used. Numerous randomized, placebo-controlled clinical trials have confirmed the efficacy of these drugs in the treatment of OIC without affecting the analgesic effect of the opioids used. PAMORAs are mostly well tolerated by patients, and adverse effects are mainly related to gastrointestinal complaints and are mainly mild. PAMORAs show high efficacy in increasing the average number of bowel movements per week and accelerating the time to first rescue bowel movement after the first dose of the drug. For this reason, they are recommended for the treatment of patients with OIC in whom first-line therapeutic approaches have failed. However, when selecting treatment, it should be borne in mind that patients receiving palliative care often suffer from significant cachexia and may have certain limitations that limit the use of specific therapies. Also, it is important not to forget to carry out a thorough differential diagnosis to not overlook other serious diagnoses such as electrolyte disorders or gastrointestinal obstruction. Thus, in the treatment and prevention of OIC in palliative care, the most important thing seems to be a holistic approach to the patient and an individualized selection of therapeutic methods.

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Author contributions

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Supplementary material

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