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# Management of opioid-induced constipation in palliative patients with disseminated cancer

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## Abstract

Stool constipation is one of the most common afflictions affecting palliative patients with advanced cancer. The widespread use of opioids in the analgetic treatment of this group of patients exacerbates the already existing problem of constipation or is the underlying cause of its occurrence. Often, however, the etiology of the condition appears to be multifactorial. This article discusses the effects of opioids on the gastrointestinal tract as a cause of constipation, other possible causes of constipation in palliative patients, helpful definitions and how to diagnose constipation in this group of patients. Another important topic highlighted is the possibility of gastrointestinal obstruction and the possible management of its presence. Finally, the management of constipation is discussed, taking into account both non-pharmacological

and pharmacological treatment with traditional laxatives and peripheral opioid receptor antagonists (naldemedine, naloxegol, methylnaltrexone). The article is based on an analysis of the available scientific literature and cited sources.

**Keywords:** palliative patients, constipation, cancer, opioid, laxatives, defecation, obstruction, PAMORA, naldemedine

## Introduction

Constipation is one of the most common problems affecting cancer patients using opioids, and its frequency increases as the disease progresses. It causes discomfort and reduces the patient's quality of life. It may be considered a low priority in the general treatment of such a patient. There are various possible causes of constipation in cancer patients – malignant infiltration in the gastrointestinal tract, cachexia and the associated decrease in physical activity, reduced fluid and food intake, metabolic disorders, lack of intimacy during defecation (fear of soiling the bedding, unpleasant odor), or side effects of certain medicines (chemotherapeutic agents, opioid analgetics) [1]. Constipation treatment should be multifaceted and based not only on pharmacological methods, but also on improving lifestyle, physiotherapy, and ensuring intimacy during defecation [2].

## Epidemiology

Pain is one of the most common co-occurring symptoms in cancer patients. Its incidence ranges from 33% to as much as 64% in patients with advanced and disseminated cancer. The basis of pain treatment in such cases are primarily opioids. However, their use is associated with numerous side effects, one of which is opioid-induced constipation. Their incidence is 60-90% in palliative oncological patients (in some of them, opioids are the cause of exacerbation of previously existing constipation) [3]. The frequency of constipation also increases with the progression of cancer and with age, especially in patients over 60 years of age [4].

## Etiology

The causes of constipation in palliative cancer patients can be divided into organic and functional. Functional causes include age, lack of privacy when using the toilet, lack of activity, insufficient fluid and food intake. Organic causes include drugs with constipating potential (especially opioids, antiemetics that are 5-HT3 receptor antagonists, antidepressants, iron), metabolic disorders (dehydration, potassium deficiency, excess calcium, uremia in renal failure), abnormalities in the functioning of the neuromuscular system in the gastrointestinal tract (neuropathies, myopathies), abdominal and pelvic tumors, post-radiation fibrosis [5]. Opioid-induced constipations are caused by the direct action of these exogenous substances on opioid receptors (μ, κ, σ) located in the nerve plexuses of the digestive tract wall and in the central nervous system. Constipation occurs mainly as a result of stimulation of μ receptors. The action of opioids is multidirectional and its consequence is a decrease in the excitability of neurons in the intestines, impairing their motor activity, inhibition of the release of acetylcholine and vasoactive intestinal peptide (VIP), which is associated with reduced secretion of water and chlorides into the intestinal lumen, resulting in increased stool hardness. Opioids are also believed to increase the threshold of sensory sensitivity of the rectum and the tension of the anal sphincter. The effect of opioids on the digestive system is presented in Table 1 [6].

| Site of action | Pharmacological action of opioids |
|---|---|
| Oesophagus | Dysmotilities, 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 | Redused 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 |

Tabel 1. Effects of opioids on different levels of the digestive system.

However, in palliative patients, the etiology of constipation is often multifactorial, which causes many difficulties in treating such a patient. It is necessary to analyze all possible causes of constipation, prioritize treatment, and exclude conditions that are dangerous to the patient, such as gastrointestinal obstruction [7, 8]. It is also necessary to take into account the phenomenon that masks the presence of constipation, the so-called false diarrhea. In its pathophysiology, the main role is played by long- lasting constipation, which can lead to the formation of callus stones and bunging of the rectal area. Loose stool above the fecal blockage begins to flow downwards, similarly to diarrhea. In this case, the medical history is characterized by increased frequency of passing small amounts of liquid brown stool, discomfort in the abdominal cavity and sometimes an urinary urgency. Palpation of the abdomen and digital rectal examination are useful to detect residual fecal masses. The basis of treatment are laxatives, in particular clyster (enema), manual extraction of residual stool or, in more severe cases, surgical emptying of the rectal ampulla [9, 10].

**Diagnosis**

The definition of constipation in the group of palliative patients was presented in the work by Dzierżanowski and Larkin, formulating it as a decrease in the frequency of defecation or the need to use laxatives to initiate defecation, or the patient reporting such symptoms as: too hard/too small stools/difficulty in defecation/feeling of incomplete defecation. In order to reduce the risk of incorrect diagnosis, the authors proposed three additional criteria for the diagnosis of constipation in palliative patients (at least 1 of the following in the last 7 days):

1) Frequency of defecation ≤ 3 per week
2) Last defecation ≥ 2 days ago
3) Difficulty in defecation ≥ 2 on a scale of 0 to 4

The ease of defecation is defined as:

0 - normal

1 - mild

2 - moderate

3 - severe

4 - extreme difficulty [11]

Opioid-induced constipation according to the Rome IV Criteria is defined as new or worsening constipation symptoms occurring after initiation, change, or increase in opioid use and ≥ 2 of the following criteria are present:

1) < 3 idiopathic defecation per week

2) need for manual assistance of defecation (manual extraction of stool, abdominal pressure) in > 25% of defecation

3) feeling of incomplete defecation in > 25% of defecation

4) lumpy or hard stool in > 25% of defecation

5) increased urge in > 25% of defecation

6) feeling of blockage of the anus/rectum in > 25% of defecation

Considering the multifactorial etiology of constipation, it is essential to thoroughly examine the patient and analyze the history and symptoms. It is necessary to exclude dangerous causes of constipation such as intestinal obstruction and acute conditions in the abdominal cavity [12].

| | | |
|---|---|---|
| Type 1 |  | Separate hard lumps, like nuts (hard to pass) |
| Type 2 |  | Sausage-shaped but lumpy |
| Type 3 |  | Like a sausage, but with cracks on the surface |
| Type 4 |  | Like a sausage or snake, smooth and soft |
| Type 5 |  | Soft blobs with clear-cut edges (passed easily) |
| Type 6 |  | Fluffy pieces with ragged edges, a mushy stool |
| Type 7 |  | Watery, no solid pieces (entirely liquid) |

Figure 1. The Bristol Stool Form Scale [13]

In the medical history, attention should be paid to the frequency and change of defecation, the date of the last stool, the consistency and presence of pathological content in the stool, symptoms accompanying constipation and stool, the amount of fluids consumed, diet, physical activity adapted to the patient's age, medications used (including laxatives), comorbidities (especially those related to the digestive system) and other possible somatic, psychological and social symptoms. Additionally, the stool should be assessed using the Bristol Stool Form Scale (Figure 1). In order to assess the severity of constipation in palliative patients, The Patient Assessment of Constipation-Symptoms (PAC-SYM) questionnaire is helpful, in which the patient subjectively rates the severity of symptoms experienced during the last 2 weeks. Symptoms are scored on a scale of 0-4 and assigned to three symptom groups - abdominal, rectal and stool - related.

In the physical examination, it is necessary to palpate the abdominal cavity in order to look for pathological resistance, pain, peritoneal symptoms and auscultation of the abdominal cavity (assessment of peristalsis). An extremely important examination is the digital rectal examination (digital examination of the anus and rectum) aimed at assessing the anatomical structures of this area, assessing the presence of stool and its consistency. In palliative patients with a stoma, the stoma bag and the area around the bag outlet should be carefully checked. In some cases, when looking for the etiology of constipation, it is necessary to extend the diagnostics with laboratory tests, imaging tests and gastroscopy or colonoscopy. It is extremely important to exclude possible gastrointestinal obstruction in the patient [7,14].

**Obstruction of the digestive tract**

In the differential diagnosis, attention should also be paid to the possible occurrence of large intestine obstruction. In palliative patients, a thorough medical interview and physical examination are sufficient to diagnose and start treatment [15]. Possible radiological tests, which could be performed in a terminally ill patients with symptoms suggesting gastrointestinal obstruction in the form of contrast studies of the lower gastrointestinal tract or abdominal computed tomography, should be considered only in patients in good general condition who would benefit from surgical treatment [16]. In cancer patients, symptoms of large bowel obstruction remain invisible for a long time and have the character of partial obstruction. In the medical interview, there may be recurrent colic pain - the lower the obstacle, the longer the intervals between pains, significant bloating covering the entire

abdomen and constipation. In case of partial obstruction, it is possible to pass gases and stool. Nausea and foul-smelling vomiting of a faecal nature appear relatively late due to the efficient ileocaecal valve preventing the retrograde passage of the contents of the ascending colon into the small intestine [17]. The gradual accumulation of fluids, food, gases and increased activity and changes in the composition of bacterial flora lead to damage of the intestinal epithelium, development of an inflammatory response, swelling of the mucosa and increased permeability of the intestinal wall. The accumulating fluids together with bacterially liquefied faeces are excreted to the outside in the form of abundant diarrhea, this is the so-called overflow diarrhea consisting of secretions formed over the blocked stool [15,17,18]. In the physical examination, it is necessary to perform a digital rectal examination, which may reveal a rectal tumor causing obstruction or the presence of a neoplastic infiltration, perform abdominal palpation and in slim people, intestinal distension may be noticeable [17]. In a terminally ill patients, the priority in the choice of treatment for obstruction should be: improving the quality of life and relieving troublesome clinical symptoms. Palliative surgical interventions are associated with a high risk of perioperative mortality, which is why less invasive methods of treatment are sought. A safer alternative for palliative patients may be self-expandable metallic stents (SEMS) [18]. Retrospective non-randomized comparative studies in patients with colorectal cancer comparing the use of self-expandable metallic stents (SEMS) and urgent palliative surgery for the relief of gastrointestinal obstruction showed shorter hospital stay, fewer early complications, and lower hospital mortality in the group of patients with self-expandable metallic stents (SEMS). However, there was no difference in long-term survival between the two groups [19,20]. These studies are limited by the lack of randomization and the possibility of selection bias—healthier patients with obstruction may have undergone surgery, whereas patients considered to be at high surgical risk may have been rejected and referred for endoscopic stent placement. These observations seem to be supported by a retrospective randomized, controlled trial of 22 patients that showed shorter hospital stays in patients with self-expandable metallic stents (SEMS) and no difference in survival between the two groups. An additional observation was a reduced frequency of stoma use in patients with SEMS, which allows for maintaining a better quality of life in palliative patients [21]. Further randomized clinical trials conducted in larger studies groups are necessary to confirm the above results. In patients who will not benefit from surgical intervention and in patients with poor general health, treatment of obstruction is limited to symptomatic treatment. It involves the use of painkillers, corticosteroids, antiemetics, and antisecretory drugs [18].

## Treatment

In the treatment of constipation, it is necessary to implement both pharmacological and non-pharmacological methods of treatment. All patients taking opioid painkillers, unless there are contraindications (e.g. diarrhea), should be given prophylaxis in the form of laxatives. The first choice is osmotic drugs and those that stimulate the nerve plexuses in the intestinal wall. In the case of constipation despite prophylaxis, drugs that are peripherally acting mu-opioid receptor antagonists (PAMORA) are used next [14]. Benefits may also be obtained by changing the oral opioid, which may have been responsible for the increased incidence of constipation, to transdermal fentanyl or buprenorphine, because of their lower constipating effect. In a randomized, controlled, multicenter study conducted in Italy, the efficacy of four opioids (e.g. oral morphine and oxycodone and transdermal buprenorphine and fentanyl) was compared in terms of safety and analgesic profile. The study included 520 cancer patients from 44 centers. The analgesic effects of the drugs were similar. Side effects were mostly very similar for all of these drugs. It should be noted, however, that fentanyl use caused slightly less constipation in the studied patients, but this was not a statistically significant difference. The only significant differences were observed in the case of the effects on the nervous system, where confusion, hallucinations and myoclonus occurred more often in people using morphine [22]. The limitation of this study was that it lasted 28 days, the same study, but in a longer period of time could have yielded completely different results, if only because of the long half-life and time to reach equilibrium of buprenorphine [23]. In addition, the drug doses were incorrectly calculated, the conversion ratio from oral morphine to transdermal buprenorphine was 85:1, which led to too much of the drug being used, hence the adverse side effects. The doses of buprenorphine patches needed to achieve the same analgesic effect as oral morphine should be lower and converted using a conversion factor of 1:70 (morphine: TD buprenorphine) [24]. Similar conclusions were drawn in another randomized clinical trial conducted by Nosek K et al. with a smaller control group. In contrast to the previous study, anti-constipation prophylaxis was administered in the form of lactulose, 10 ml twice daily, which could have biased the study results regarding this side effect [25]. One of the studies conducted over a longer period of time is a retrospective cohort study, which analyzed a large group of patients over a 3-month period. It found a lower incidence of constipation in patients receiving fentanyl patches compared to patients receiving oxycodone or oral morphine [26].

However, there are no studies that would directly compare the effectiveness and effects of buprenorphine and fentanyl patches.

## 1. Non-pharmacological methods

As for non-pharmacological methods, they have limited application in palliative patients. If the patient's condition allows it, a positive effect may be brought about by, among others, an appropriate diet, high fluid intake, physical activity depending on the patient's clinical condition, and appropriate privacy during defecation. The credibility of the above recommendations may be confirmed by a short-term, randomized, retrospective study conducted on a group of 237 cancer patients receiving palliative care. It assessed the relationship between the frequency of defecation and factors such as: insufficient physical activity, the patient's level of fitness, insufficient food and fluid intake, and insufficient privacy. Each of the assessed factors was associated with a decrease in the frequency of stools, which was particularly pronounced in the case of insufficient food and fluid intake [27]. An interesting alternative for palliative patients with significantly limited physical activity may be abdominal massage, which does not cause any side effects. This method has been evaluated in randomized clinical trials on small groups of patients with conflicting results. The first, on a group of 30 patients with multiple sclerosis, showed a slight improvement in defecation in the control group using abdominal massage [28]. The second, on 32 patients with Parkinson's disease, showed no significant differences between the two groups [29]. Unfortunately, these studies are limited by the small study group and lack of blinding, so the placebo effect cannot be ruled out.

## 2. Pharmacological methods

### Laxatives

Laxatives are drugs with different mechanisms of action, used as a first-line medications in the treatment of opioid-induced constipation and also in its prevention. They are safe and affordable. Their use has been proven to be more effective than placebo, although there are no specific and conclusive clinical trials to determine the optimal treatment with these drugs in the population of palliative care patients using opioids [30]. Among laxatives, macrogol are the preferred preparations due to their low risk of side effects and high safety [31]. These

drugs should be used regularly rather than on an ad hoc basis [30]. If the response to laxatives is insufficient, the dose of the agent used should be increased or another agent with a different mechanism of action should be added (e.g. a combination of a stimulant and osmotically active drug) [31]. It is important to remember that laxatives also have numerous side effects: bloating, alternating episodes of diarrhea and constipation, nausea, vomiting, abdominal pain and bisacodyl suppositories cause rectal inflammation [32].

**a) Osmotic laxatives**

Their action is to increase the amount of water passing into the lumen of the intestine, this leads to an increase in the softness and volume of the stool. These include lactulose or polyethylene glycol (macrogol). Unlike macrogol, lactulose is fermented by intestinal bacteria with the production of carbon dioxide and hydrogen gas, leading to gas, bloating, and abdominal pain [32].

**b) Laxatives that act by stimulating the nerve plexuses of the large intestine**

Their action is based on direct stimulation of the nerve plexus in the submucosal layer (Meissner's plexus) and in the muscular layer (Auerbach's plexus) resulting in stimulation of peristalsis and secretory activity of the intestines. These include bisacodyl, anthranoids (e.g. senna), and glycerol. Bisacodyl and glycerol are most commonly administered in the form of rectal suppositories while anthranoids are administered orally [33]. The effectiveness of anthranoids decreases with long-term use due to the emergence of tolerance, which is why they are only recommended for short-term use [31].

**c) Other laxatives**

Laxatives that increase stool volume in intestinal obstruction are not recommended because they worsen the course of the obstruction by increasing the amount of stool. Sodium docusinate, which belongs to the stool softeners, increases the surface tension of the stool which allows water and fats to enter the stool and inhibits the absorption of water in the small and large intestine, for this reason it can be used in addition to soften fecal masses. Emolient laxatives are not recommended for the treatment of opioid-induced constipation [14].

**Drugs from the PAMORA group**

They are a group of drugs that are peripheral opioid receptor antagonists, whose mechanism of action is to selectively block μ receptors in the gastrointestinal tract thereby antagonizing the side effects of opioids [30]. They are second-line drugs used to treat opioid-induced constipation; the most commonly used PAMORAs include naldemedine, naloxegol and methylnaltrexone. They do not affect the effects of opioids used to treat pain because they do not penetrate the blood-brain barrier [35].

**a) Naldemedine**

It is a derivative of naltrexone with an additionally attached side chain, which results in reduced penetration of the substance through the blood-brain barrier. Those molecules that do cross the barrier are very quickly eliminated from the central nervous system using P-glycoprotein. Due to this structure of the drug, it acts mainly on opioid receptors located peripherally. It is well absorbed from the digestive system, reaching maximum concentration less than an hour after consumption. Food has no significant effect on its absorption. Naldemedine is metabolized by cytochromes P450 3A4 located in the liver. It is mostly excreted in urine and feces as metabolites. It is safe for use in patients with renal failure as well as in mild or slightly severe liver damage (Child-Pugh grade A/B). It is registered for the treatment of opioid-induced constipation in patients with or without cancer. It can be used concomitantly with an opioid analgetic (does not affect their effect) and in combination with laxatives. Its maximum daily dose is 200 μg (usually 1 tablet is used daily at a fixed time, regardless of meal). In 50% of patients, stool is passed within 4 hours. Its long-term use is safe. In case of hypersensitivity to the drug or gastrointestinal obstruction, naldemycin is contraindicated [35,12].

**b) Naloksegol**

It is a PEGylated derivative of naloxone, which means it does not cross the blood-brain barrier. It is metabolized in the liver with the participation of cytochrome CYP3A and excreted mainly in the feces, only in small amounts in the urine. Naloxegol is used in the form of

tablets (25 mg or 12.5 mg), one hour before or 2 hours after a meal once a day. The tablet can also be crushed and the drug administered through a tube. Contraindications to use are the same as in the case of naldemycin. It is registered for the treatment of opioid-induced constipation [12].

**c) Methylnaltrexone**

Is a methylated derivative of naltrexone so it does not penetrate the blood-brain barrier. It can be used by subcutaneous injection and orally. In a 4-week study using placebo and methylnaltrexone administered subcutaneously, its superiority in the treatment of constipation compared to placebo was demonstrated [35]. The drug is used in weight-dependent doses. It is excreted mainly through the kidneys. It is used as a PAMORA drug of choice in palliative patients [14, 36].

## 3. Other possible treatments

If laxatives and PAMORA drugs are ineffective, supportive measures can be considered in the form of: TENS - transcutaneous nerve stimulation, acupuncture, aromatic massage, abdominal massage, herbal preparations, rectal infusions or manual stool extraction [14].

## Conclusions

Despite the common problem of constipation in palliative patients, there is still insufficient research to allow for the construction of specific recommendations regarding the treatment of such patients. Their multifactorial etiology can also cause many diagnostic difficulties. It must be remembered that a terminally ill patient cannot be treated causally, only persistent symptoms can be alleviated in order to ensure maximum comfort of life. Therefore additional intensive diagnostics and severe surgical interventions can only burden the patient unnecessarily.

## Disclosure:

## Author's contribution

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