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Review

Opioid-induced Constipation: Old and New Concepts in Diagnosis and Treatment

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Daily use of opioid analgesics has significantly increased in recent years due to an increasing prevalence of conditions associated with chronic pain. Opioid-induced constipation (OIC) is one of the most common, under-recognized, and under-treated side effects of opioid analgesics. OIC significantly reduces the quality of life by causing psychological distress, lowering work productivity, and increasing access to healthcare facilities. The economic and social burden of OIC led to the development of precise strategies for daily clinical practice. Key aspects are the prevention of constipation through adequate water intake and fiber support, avoidance of sedentariness, and early recognition and treatment of cofactors that could worsen constipation. Recommended first-line therapy includes osmotic (preferably polyethylene glycol) and stimulant laxatives. Peripherally acting μ-opioid receptor antagonists, such as methylnaltrexone, naloxegol, or naldemedine, should be used in patients that have not responded to the first-line treatments. The bowel functional index is the main tool for assessing the severity of OIC and for monitoring the response. The paper discusses the recent literature on the pathophysiology, clinical evaluation, and management of OIC and provides a pragmatic approach for its assessment and treatment.

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Key Words
Constipation; Laxatives; Methylnaltrexone; Naldemedine; Naloxegol

Introduction

Longstanding pain is a cause of severe distress in patients suffering from chronic diseases because it significantly reduces the quality of life (QOL) and causes an increase in health costs. Ensuring adequate pain control is a primary therapeutic goal in patients with chronic pain and/or short life expectancy.

Opioids are a class of powerful analgesics used to treat pain.[1] Their use has been considerably increasing in recent years due to various factors. The progressive aging of the population has led to an increase in the prevalence of chronic and oncologic diseases, for which pain control strategies are necessary. As a result, a significant increase in the prescription of opioids occurred in the last 20 years in Europe.[2] The pharmaceutical industry has made available a wide variety of opioids, of which use, properly monitored by experienced physicians, can be considered safe and effective.[3]

Greater use of opioids is undoubtedly associated with increased

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side effects. Opioid-induced constipation (OIC) is one of the most common events.[4] Physicians prescribing therapy with opioids should adequately inform the patient about the side effects of long-term use of these drugs. For this reason, the prescription of opioids for the treatment of chronic pain must be well thought out. Adverse effects on the digestive system caused by opioid drugs can be multiple and so debilitating to cause, in severe cases, opioid withdrawal. This modification in the treatment can cause inadequate pain control, which, in turn, may bring severe physical and psychological distress for the patient and increased access to healthcare facilities.

This review discusses OIC, its pathophysiology, its impact on the QOL of patients taking opioids, and its treatment.

Definitions

Since opioid receptors are distributed throughout the digestive tract and central nervous system,[5] patients may experience a wide variety of digestive symptoms, collectively known as opioid-induced bowel dysfunction (OIBD).[6,7] OIBD includes nausea, vomiting, abdominal discomfort, and dry mouth; these symptoms generally tend to improve spontaneously over time, unlike symptoms of the lower digestive tract.[8] To distinguish OIBD from self-limiting conditions (for example, infections), recently, a multidisciplinary panel of Italian experts proposed a standardized definition of OIBD, defining it as a set of digestive signs and symptoms with onset or worsening lasting for at least 2 weeks from the start of opioid treatment or dose increase.[9]

OIC is the most prevalent form of OIBD. According to the Rome IV criteria, OIC is defined as new, or escalating, symptoms of constipation occurring when starting, changing or increasing opioid therapy with several clinical features including less than 3 spontaneous bowel movements per week, a sensation of incomplete evacuation, and/or anorectal blockage or obstruction (Table 1).[10-12]

Epidemiology

Currently, no data allow the exact prevalence and frequency of OIC.[13] Prevalence data vary among studies due to differences in definitions of OIC, study types, settings, data reporting, scale used for assessment and monitoring, patient inclusion criteria, and types of used opioids.[14]

Globally, in international studies, the prevalence of OIC ranges from 8.9% to 81.0%.[9] The prevalence of OIC increases with the prolonged duration of opioid use.[15] In an American cohort, the prevalence was the 6.0% over more than 80 000 patients, but it was shown that constipation symptoms were more severe than in chronic idiopathic constipation.[16] In another cohort study, the prevalence was 4.6%, but the multivariate analysis did not find any significative difference according to different opioid molecules.[17] In children with acute lymphoblastic leukemia, OIC was much more relevant, with a prevalence of 33.9%, but it was more common in case of prior diagnosis of constipation or if hospital stay was longer.[18]

Economic and Psycho-social Aspects

Economic Burden of Opioid-induced Constipation

OIC has been associated with economic and clinical burdens and can significantly reduce the QOL of cancer and non-cancer patients.[19]

In the United States of America, a study assessed the economic impact of OIC in a group of non-oncological patients who have been using opioid drugs for at least 90 days.[20] A sample of 16 766 long-term opioid users was divided into 3 cohorts: nonelderly patients (aged 18-64 years), elderly patients (aged > 64 years), and patients receiving opioid drugs in long-term care facilities. Finally,

Table 1. The Rome IV Diagnostic Criteria for Opioid-induced Constipation (Adapted From Webster et al[12])

Diagnostic criteria
A) New, or worsening, symptoms of constipation when initiating, changing, or increasing opioid therapy, that must include "two or more" of the following:
1. Straining during more than ¼ (25%) of defecations
2. Lumpy or hard stools (Bristol stool form scale 1-2) more than ¼ (25%) of defecations
3. Sensation of incomplete evacuation more than ¼ (25%) of defecations
4. Sensation of anorectal obstruction/blockage more than ¼ (25%) of defecations
5. Manual maneuvers to facilitate more than ¼ (25%) of defecations (eg, digital evacuation and support of the pelvic floor)
6. Fewer than three spontaneous bowel movements per week
B) Loose stools are rarely present without the use of laxatives.

each cohort of opioid patients was divided into a constipation group and a group that did not develop constipation. Among the elderly patients, the group with OIC had a higher mean annual number of emergency department visits than the patients without OIC (1.6 vs 0.8, respectively, $P < 0.01$).[20] Nonelderly and elderly patients with OIC had a higher number of hospital admissions (131 vs 78, $P < 0.01$ and 96 vs 58, $P < 0.01$, respectively) and a longer inpatient length of stay than the patients without OIC (3 days vs 1 day, $P < 0.01$ and 5.2 days vs 2.1 days, $P < 0.01$, respectively). Nonelderly patients with OIC had more annual office visits than those without OIC (20.7 vs 15.9, $P < 0.01$). In the long-term care cohort, there was no significant difference in healthcare resource utilization between the groups with and without OIC.[20] Patients with OIC had significantly higher total healthcare costs than patients without OIC in all 3 cohorts, including the nonelderly population ($23 631 ± $67 209 vs $12 652 ± $19 717, $P < 0.001$), the elderly population ($16 923 ± $38 191 vs $11 117 ± $19 525, $P = 0.009$), and the long-term care population ($16 000 ± $22 897 vs $14 437 ± $25 690, $P = 0.049$).

In Europe, a few published studies assessed the economic burden of OIC. A Swedish study examined the indirect (eg, production loss) and direct medical costs (eg, healthcare visits and telephone consultations) associated with OIC using survey data.[21] The sample of OIC patients was divided into 3 cohorts based on the severity of the OIC. It was assessed by asking patients to vote from 0 to 10 to define the severity of their constipation. Patients with severe constipation had the highest total monthly costs of €1525, whereas patients with mild and moderate problems had €1196 and €1088 loss, respectively. The largest cost item in all 3 groups with constipation was due to indirect costs.[21]

A further factor aggravating the economic burden of OIC is the lack of awareness among clinicians about OIC in patients on opioid therapy.[10] OIC is often underdiagnosed and, as a result, under-treated, despite effective treatments.[22] Persistent constipation during long-term opioid treatment negatively impacts the patient's QOL, and symptoms may be so debilitating that they reduce adherence to pain therapy.[23] A multinational internet-based survey found that over 33.0% of the population using opioids had to miss, decrease, or stop opioids to reduce constipation.[24] Consequently, inadequate pain control increases the number of outpatient visits, hospitalizations and surgery.

Psycho-social Aspects and Quality of Life

For many patients, OIC significantly impairs health-related QOL (HRQOL),[25] work productivity,[26] and sexual activity,[27] resulting in significant distress.[27,28]

As mentioned above, distress can be so severe that patients could sacrifice effective pain control to relieve constipation. Even without modifications in opioid therapy, OIC has been shown to have a negative impact on HRQOL. In a multinational, internet-based survey designed to assess the impact of OIBD in patients receiving opioid therapy for chronic pain and taking laxatives (PROBE-1), most patients reported that their OIBD symptoms had at least a moderate negative impact on their HRQOL. A third of patients missed, reduced or stopped opioid use to improve constipation.[24] A prospective cohort study assessing HRQOL in patients taking opioids for chronic non-cancer pain showed similar results: at the baseline, OIC patients presented higher disability, pain interference and severity scores than patients without OIC. These scores significantly worsened at 6 months within the group of patients with OIC.[29]

Patients with OIC often experience increased anxiety and depression, impairments in activities of daily living, low self-esteem, and feelings of embarrassment.[27] According to a survey conducted by Rauck et al,[27] 40.0% of patients with OIC have work difficulties, and constipation interferes with daily activities and sexual life in 45.0% of patients. Similar results were found in a European survey: patients with OIC have a higher percentage of nonattendances from work and more time spent in the bathroom than patients without OIC; they also present difficulties in carrying out daily activities, having hobbies and social interactions.[30]

Physician-Patient Communication

A prospective, longitudinal, observational cohort study showed a different perception of OIC between healthcare providers and patients.[31] This study showed that 35.0% of opioid prescribers were unaware that the patients met the criteria for OIC. Only 58.0% reported that patients complained of having a small number of bowel movements per week. The proportion of agreement between physicians and patients on the presence of constipation at baseline was 61.0%. It was reported that many doctors were unaware of the severity of their patient's OIC symptoms. The reasons for lack of discussion of OIC symptoms may be related to the fact that the patients may not mention OIC symptoms for fear of losing the opioid medication, or they believe that OIC is a condition that should be self-managed and not shared with a physician, or simply for embarrassment.[31] However, the patient frequently complains about inadequate information about OIC by his doctor. In a survey by Andersen et al,[30] half of the patients asserted they would prefer to receive more information about OIC from their healthcare providers. In

addition, about 36.0% of patients reported that they had acquired most information about OIC from sources other than their doctor, including the internet, television, and experiences of friends or relatives.[30]

Better communication between physicians and patients could avoid delays in diagnosis and remove obstacles that do not allow proper treatment of the OIC.[27] At every follow-up visit, physicians should investigate any side effects of opioid drugs (including constipation) and their impact on their daily lives, trying gently to overcome the reluctance and embarrassment shown by patients.[31]

Pathophysiology

Opioid molecules have a deep influence on digestive physiology: they may influence the processes of motility, fluid absorption and sphincter contraction. Opioid receptors include μ-, δ-, and κ-receptors; they are widely distributed throughout the digestive system, with a density that changes depending on the tract and wall layer.[32] Mu-receptors are thought to play a central role in the OIC. They are mainly found in the stomach and proximal colon, on the membranes of intestinal muscle cells, myenteric and submucosal neurons and mononucleate cells of the lamina propria.[33] μ-receptors are not expressed in epithelial cells.

These receptors can be bound by endogenous (encephalins and endorphins) or exogenous (opioids) ligands, causing their internalization and binding to Gi/Go inhibitory proteins that activate or inhibit intracellular signal transduction pathways.[10,32] The result is a reduction in neuro-excitability and neurotransmission, which is responsible for the overall inhibition of gastrointestinal secretion and motility.[32]

Gastrointestinal motility strictly depends on a fine balance between excitatory and inhibitory pathways primarily mediated by submucosal and myenteric neurons.[34] Encephalins and endorphins play an important role in regulating peristalsis. On the other hand, exogenous opioids can disrupt intestinal motility, increasing wall musculature tone, slowing propulsive movements[35] and triggering tonic spasms in the colon and small intestine.[3]

Opioid receptors also affect the secretion and absorption of water in the gastrointestinal tract.[10,35] In the small bowel, the endoluminal secretion of fluids is mainly stimulated by molecules such as vasoactive intestinal peptideand acetylcholine produced by neurons of the submucosa.[33] These neurotransmitters activate a series of intracellular pathways that culminate in the intraluminal secretion of chloride and, consequently, of water by osmotic gradient.[36] The process so far described is blocked by the activation of μ-receptors on secretory neurons of the submucosa.[37] Moreover, a further reduction in the intestinal fluid content is facilitated by prolonged fecal stasis due to altered intestinal motility. The overall reduction in fecal mass leads to a reduction in colic motility which depends on intrinsic neuronal reflexes resulting from the activation of mechanoreceptors.[38]

For this reason, patients taking opioids frequently complain of dry and hard stools.[10] Opioids also inhibit saliva production, causing dry mouth,[9] and reduce biliary and pancreatic secretions, impairing digestion along with nutrients and drug absorption.[38] Finally, stimulation of opioid receptors increases the resting tone of all sphincters in the digestive tract.[10] The increased tone of the internal anal sphincter produces straining, anal blockage, hemorrhoids, and, in severe cases, colon perforation.[39]

Clinical Assessment

When OIC is suspected, the first diagnostic step is to make an accurate anamnesis. The relationship between the onset or worsening of intestinal symptoms and the starting of opioid therapy should be assessed. For this purpose, it is important to define baseline bowel habits and any changes after introducing opioid drugs.[10] If the onset of symptoms precedes the start of opioid therapy, it is important to understand how constipation has been treated and with what results.

The patient's pharmacological record should be carefully addressed to verify the presence of drugs that may contribute to constipation (Table 2).

Table 2. Drugs That May Cause Constipation

Calcium or aluminium antacids
Anticonvulsants
Tricyclics antidepressants and anticholinergics
5-HT_3 receptor antagonists
Antiparkinsonian drugs
Bile acid sequestrants
Iron
Aspirin
Calcium antagonists and calcium-based drugs
Diuretics (furosemide, hydrichlorotiazide)
Muscle relaxants
Phenobarbital
Vinca alkaloids
NSAIDS
Opioids
Paracetamol

5-HT_3, 5-hydroxytryptamine receptor 3.

In all patients with suspicion of OIC, an accurate physical evaluation should be performed, including an examination of the perineum and a digital rectal examination to rule out anorectal malignancy or any other condition that may worsen constipation.[40] Functional disorders of defecation should be suspected in patients not responding to treatment for OIC.[41] Generally, blood tests are not useful except in suspicion of cofactors that worsen constipation (eg, hypothyroidism and electrolyte disorders).[42] Colonoscopy should be performed in all patients with symptoms suggestive of colorectal cancer or in patients who should be screened for this condition.[43] The acquisition of abdominal radiological images should not be performed routinely but only when intestinal occlusion, perforation, fecaloma or anatomical abnormalities (eg, dolichocolon or megacolon) are suspected.[39]

In challenging clinical settings (eg, cancer patients), it is often difficult to diagnose OIC based solely on the patient clinical and pharmacological history. The Rome IV criteria (Table 1) offer a standardized definition of OIC, useful in both clinical and research contexts. Therefore, the diagnosis of OIC must always be performed in accordance with the Rome IV criteria.[44] OIC management is multidisciplinary and includes specialists such as gastroenterologists, general practitioners, oncologists, geriatricians, and pain therapists. Using universally established diagnostic criteria would allow more precise epidemiological data and avoid diagnostic delays or overtreatment.[9]

Patient-reported Opioid-induced Constipation Outcome Measures

Different scales are available in clinical practice for diagnosis and evaluation of the severity of OIC.[10] Here we report the most appropriate ones for a first evaluation of the OIC and for monitoring the therapeutic response.

The bowel function index (BFI) is a simple questionnaire provided to the patient. It allows not only to facilitate the diagnosis of OIC but also to evaluate the response to therapy. It consists of 3 questions to investigate the ease of defecation, the sense of incomplete defecation and the patient's judgment on constipation. Based on the experience in the last 7 days, the patient gives each question a score between 0 and 100.[10] Zero means no symptoms, while 100 means severe symptoms. The average of the 3 scores gives the final score. A score higher than 30 is compatible with OIC and requires therapeutic intervention.[45] A reduction of the score of at least 12 points after a therapeutic intervention indicates its effectiveness.[45] The BFI is a reliable score, easy to use and, above all, representative of the severity of the OIC (Table 3).[45]

Bristol stool chart (BSC), displayed in Figure 1, is a medical

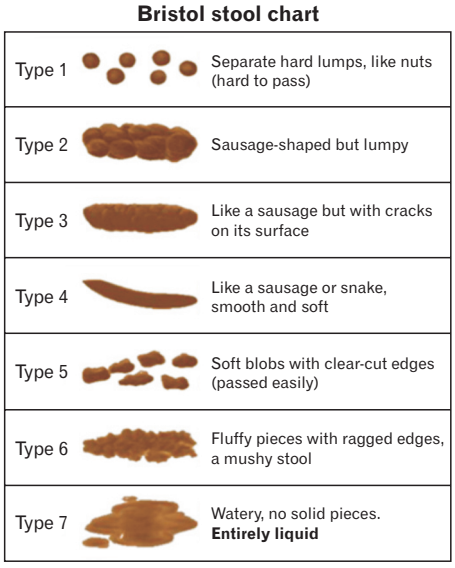

Figure 1. Bristol stool chart.

Table 3. Bowel Functional Index

Item	Question	Rate
1	During the last 7 days, how would you rate your ease of defaecation on a scale from 0-100, when 0 = easy and 100 = severe difficulty?	0-100
2	During the last 7 days, how would you rate any feeling of incomplete bowel evacuation on a scale from 0-100, when 0 = no feeling and 100 = very strong feeling?	0-100
3	During the last 7 days, how would you rate your constipation on a scale from 0-100, when 0 = not at all and 100 = very strong?	0-100
Total score		Mean of 3 scores
	Mean score ≥ 30 suggests OIC	
	Mean score reduction ≥ 12 represents a clinically significant change	

OIC, opioid-induced constipation.

tool that classifies stools into 7 groups based on their shape and appearance. It is used to diagnose constipation and diarrhea and assess treatment effectiveness. The type of stool or feces depends on the time it spends in the colon. Type 1-2 indicate constipation and are therefore compatible with OIC.[46]

The Patient Assessment of Constipation QOL (PAC-QOL) questionnaire is a reliable tool for measuring this parameter in patients with constipation.[47] This questionnaire includes 28 self-reported elements that examine the effects of constipation on the patient's QOL in the past 2 weeks. Each item investigates physical discomfort, psycho-social discomfort, treatment satisfaction, and concerns. Each item is rated on a 5-point scale, where zero indicates the absence of effects on QOL, while 5 indicates a serious impairment on QOL.[45-47]

The Patient Assessment of Constipation Symptoms (PAC-SYM) assesses bowel symptoms using 3 subscales[48]: abdominal symptoms (discomfort, pain, bloating, cramps), rectal symptoms (pain, burning, bleeding/tearing), stool symptoms (incomplete bowel movements, too hard stools, too small stools, straining/squeezing; inability to have a bowel movement despite feeling like you had to). Each item is rated on a 5-point scale, where zero indicates the absence of symptoms, while 5 indicates severe symptoms.[45]

Treatment

General Measures

Before starting any treatment for constipation, it is mandatory to ensure that the indication of opioid use is appropriate and that the patient takes the minimum effective dose for pain control.[49] The patient should be adequately informed about the risks of long-term opioid drug therapy and its incorrect use. Bowel function should be assessed before opioid therapy (baseline) and at regular intervals using a validated measurement scale (eg, BFI and BSC).[9,10] The purpose of these precautions is to correct bowel function before it worsens as a result of opioid long-term therapy: this should help to avoid discontinuations in taking opioid drugs that could lead to inadequate pain control.[9]

The first approach to the treatment of constipation is to encourage lifestyle changes, suggesting patient adequate daily intake of water and fiber (25-30 g of soluble fiber daily), avoiding heavy meals and foods rich in fats, performing physical exercise if tolerated, evacuating as soon as the urge of defecation occurs.[49]

Oral fiber supplementation is recommended only if the daily fiber intake is inadequate. As opioid drugs inhibit intestinal motility, excess fiber could lead to bloating, flatulence and fecalomas.[9] Water-soluble fibers should be preferred among many available fiber types (eg, psyllium). Daily intake of fiber should not be higher than 20 g.

Most patients using opioid drugs may have additional factors contributing to constipation (Table 4). If possible, anything that could worsen constipation should be prevented or treated. In bedridden patients and those who have already experienced fecal impaction, alternative pain control strategies must be considered before opioid drug administration.[9]

If possible, medications that may cause constipation should not be used or administered at the minimum effective dosage.

Not all opioid drugs cause constipation in the same way. Patients with constipation could benefit from a change in the type of opioid or mode of administration. For example, transdermal buprenorphine is associated with a lower risk of OIC as it bypasses the gastrointestinal tract and first-pass metabolism. It can be administered through transdermal patches that have a duration of 7 days.[50]

Table 4. Comorbidities Predisposing to Constipation

Prolonged immobility, decubitus ulcers, living in nursing homes or long-term care
Endocrine disorders (long-term diabetes, hypothyroidism, hyperparathyroidism, and panhypopituitarism)
Cancer
Amyloidosis
Electrolyte disorders (dehydration, hypokalaemia, hyponatraemia, hypercalcemia, and hypermagnesemia)
Idiopathic constipation, functional constipation, and functional defecation disorders
Neurological disorders (Parkinson's disease, dementia, multiple sclerosis, neuropathies, and spinal cord injury)
Psychiatric disorders (depression, anorexia, and schizophrenia)
Colorectal disease (congenital megacolon, actinic colitis, previous surgery, Crohn's disease, anal stenosis, hemorrhoids, anal fissures, and perianal abscess)
Chronic renal failure
General disability
Rectocele and strictures

Similarly, fentanyl transdermal preparations are less frequently associated with constipation than morphine orally administered at an equipotent dosage.[49] Tapentadol is less frequently associated with constipation than oxycodone.[10]

Laxatives

Standard laxatives are a class of drugs that can cause laxation according to different mechanisms of action.[49] They are safe and low-cost drugs. They are now considered the first line in treating OIC.[9,10,49] Osmotic laxatives such as polyethylene glycol (also known as Macrogol) and lactulose are effective compared to placebo in treating OIC in clinical trials.[51] However, the use of polyethylene glycol should be preferred as lactulose may be fermented by the gut microbiota, causing bloating and flatulence.[10] Although widely used in clinical practice, no clinical trials have defined the efficacy and safety of stimulant laxatives in treating OIC. Saline osmotic laxatives can cause electrolyte balance disorders, so they should be used cautiously in cancer patients and those with chronic heart and kidney failure.[9] Anthraquinones, such as senna and bisacodyl, are quickly effective in treating idiopathic chronic constipation. However, their therapeutic efficacy tends to decrease over time.[52] They can also cause evacuative urgency, fecal incontinence, and abdominal pain. Their use in the OIC, therefore, needs to be limited.

The use of osmotic laxatives is recommended as a first line of treatment in OIC.[49] When the therapeutic response is inadequate or absent, increasing the dose or adding a second laxative with a different mechanism of action (for example, a stimulant laxative) is suggested before moving on to second-line treatment.[49] Laxatives should be taken regularly and not as needed. Almost 75.0% of OIC patients benefit from laxatives.[53] Recent European recommendations for OIC management suggest using laxatives for prophylactic purposes when starting opioid therapy.[10] Harada et al,[54] in a recent study, showed that the prophylactic use of laxatives reduces the incidence of OIC in patients with gastrointestinal cancer.

Peripherally Acting μ-opioid Receptor Antagonists

Peripherally acting μ-opioid receptor antagonists (PAMORAs) selectively block μ-receptors in the gastrointestinal tract, antagonizing the side effects of opioid drugs.[14] PAMORAs do not cross the blood-brain barrier and therefore do not block the effects of opioid drugs on μ-receptors in the central nervous system, preserving analgesia.[55] Therefore, the use of these drugs is contraindicated in patients with impaired blood-brain barrier integrity.[56]

Three PAMORAs have been specifically approved in Europe for treating OIC: naloxegol, methylnatrexone, and naldemedine.

Naloxegol is a pegylated derivative of naloxone. Pegylation allows naloxegol to selectively block μ-intestinal receptors, crossing the blood-brain barrier in a limited way. Naloxegol was the first orally-administered PAMORA approved for OIC in oncological and non-oncological patients. Data supporting naloxegol use are derived from 2 phase 3, randomized double-blind, placebo-controlled trials (KODIAC-04 and KODIAC-05).[57] In both clinical studies, the primary endpoint was represented by at least 3 spontaneous bowel movements (SBM) per week, with a baseline increase of at least 1 SBM for at least 3 of the final 4 weeks of a 12-week treatment period. From these trials, it emerged that patients treated with naloxegol at a dosage of 25 mg/day have a higher response rate than patients treated with placebo (44.4% vs 29.4% respectively in KODIAC-04, $P = 0.001$ and 39.7% vs 29.3% respectively in KODIAC-05, $P = 0.020$).[57] The recommended dose is 25 mg/day, but it can be tapered to 12.5 mg/day if not well-tolerated or in patients with moderate or severe renal failure.[58] Safety studies have shown that the most commonly observed side effects were generalized abdominal pain, diarrhea, nausea, vomiting, and headache.[57,59,60] These side effects were generally mild or moderate, transient, and disappeared after naloxegol withdrawal. The use of naloxegol did not interfere in any way with analgesia. Recently, Dols MC et al[61] have shown that naloxegol, after 3 weeks of treatment, increases the number of SBM/week and improves the QOL.

Methylnaltrexone is a derivative of naltrexone with an N-methyl group that gives it a low solubility in lipids and, therefore, a poor ability to cross the blood-brain barrier.[10] It is available in oral and subcutaneous formulations. The recommended dose for the subcutaneous formulation is 8 mg/day for patients up to 62 kg and 12 mg/day for patients up to 114 kg.[62] The recommended dose for the oral formulation is 450 mg/day in a single administration, to be taken about 30 minutes before the first meal of the day.[58] Several placebo-controlled clinical trials have demonstrated the efficacy of methylnaltrexone in oncological and non-oncological patients.[63-65] Meta-analysis of the available clinical trials showed that subcutaneous methylnaltrexone in cancer patients improves spontaneous bowel movements, reduces abdominal cramps and flatulence, improves the QOL, and reduces access to health care without compromising pain control.[66] Patients treated with methylnaltrexone have spontaneous bowel movements within 4 hours from the first administration.[25] However, some cases of gastrointestinal perforation have been reported in the literature following the use of methylnaltrexone.[67] Therefore, methylnaltrexone should be used cautiously in patients with predisposing conditions (eg, abdominal neoplasms and strictures).

Naldemedine, a molecule whose structure is similar to naltrexone but more unable to cross the blood-brain barrier, is the last PAMORA approved by the European Medicines Agency (EMA) for treating OIC. Data supporting the use of naldemedine come from four placebo-controlled double-blind, randomized clinical trials, including a phase 2b trial[68] and 3 phase 3 trials (COMPOSE-1, COMPOSE-2, and COMPOSE-3).[69,70] In COMPOSE-1 and COMPOSE-2, the effectiveness and safety of naldemedine 0.2 mg/day versus placebo were evaluated for 12 weeks. The primary endpoint in both trials was the ability to achieve at least 3 SBM per week. In both trials, subjects treated with naldemedine achieved a statistically significant increase in SBM per week compared to the control group (47.6% vs 34.6% respectively in COMPOSE-1, $P = 0.002$ and 52.5% vs 33.6% respectively in COMPOSE-2, $P < 0.0001$).[9,67] In the COMPOSE-3 trial, which included 52 weeks of follow-up, the treatment group was associated with an increased frequency of weekly SBM and improved QOL compared with the placebo.[71] The most frequent adverse effects related to the use of naldemedine are abdominal pain and diarrhea[69]: both are found more frequently in treated subjects than those who received the placebo (COMPOSE-1: 22.0% vs 17.0%; COMPOSE-2 20.0% vs 17.0%). None of these symptoms have been so severe as to cause opioid withdrawal.[9,69]

The use of naldemedine, naloxegol, and methylenexone is approved by the EMA for treating OIC in patients who have not had a satisfactory clinical response to standard laxatives. PAMORAs should be avoided in patients with sub-occlusion or intestinal occlusion and abdominal tumors.[72]

Intestinal Secretagogues

The intestinal secretagogues act by stimulating the secretion of chloride ions and water in the intestinal lumen through the binding with the guanylate cyclase C receptors. Through this mechanism of action, these drugs hydrate the stool facilitating its elimination without impacting colonic mobility.

Lubiprostone is a derivative of prostaglandin E1 and is approved in the USA for treating OIC in adult patients with chronic non-cancer pain.[73] In Europe, it is approved only for treating functional constipation and irritable bowel syndrome.[9] A randomized placebo-controlled 12-week clinical trial demonstrated the effectiveness of lubiprostone in increasing SBM compared to baseline (treatment group 3.3 vs placebo group 2.4, $P = 0.005$) after 8 weeks of treatment.[73] Adverse effects occurred more frequently in treated patients compared with placebo and included nausea (16.8% vs 5.8%, $P < 0.001$), diarrhea (9.6% vs 2.9%, $P = 0.007$) and abdominal pain (8.2% vs 2.4%, $P = 0.0014$).[73]

Linaclotide is a guanylate cyclase C agonist whose use is approved in Europe for the treatment of constipation associated with irritable bowel syndrome, but not OIC.[9] However, a phase IIb study in which 254 patients with OIC were randomized to receive 145 μg or 290 μg daily lubiprostone for 8 weeks showed a significant increase in SBM.[74] The most frequent adverse effect reported was diarrhea.

At present, in Europe, the use of lubiprostone and linaclotide is off-label. Intestinal secretagogues should be used in research settings and, in the clinical setting, in patients with chronic non-oncological pain in therapy with OIC who have not responded to treatment with PAMORAs. Their use should be considered after careful multidisciplinary and expert evaluation.[9]

Prucalopride

Prucalopride is a selective agonist of the 5-hydroxytryptamine receptor 4 (5-HT_4). These receptors are expressed by myenteric neurons, smooth muscle and epithelial cells. Therefore, the 5-HT pathway exerts an enterokinetic action by acting on different cellular targets, modulating gastrointestinal motility and transmission of visceral pain.[49] These receptors are the target of several drugs used for the treatment of gastroparesis, idiopathic chronic constipation and constipation associated with irritable bowel syndrome. There is currently insufficient evidence to support the use of prucalopride in patients with OIC. Therefore, in Europe the use of this drug in the treatment of OIC is off-label.[9]

Treatment Algorithm

A treatment algorithm based on the current published guidelines is proposed in Figure 2.[10,48,74,75]

Conclusions

Opioid therapy has several side effects on digestive functions that can alter bowel habits and defecator patterns. Patients who take opioid drugs and who have experience with OIBD and OIC may have a low QOL and psycho-social problems. Reducing the dosage of opioids or their complete suspension to reduce constipation is an additional cause of physical and emotional discomfort for patients and increases the risk of hospitalization due to lack of pain control.

Osmotic laxatives are the first line of treatment in patients with OIC, and are the first line mainstay for improving symptoms. In recent years, new treatments for OIC have been approved. The

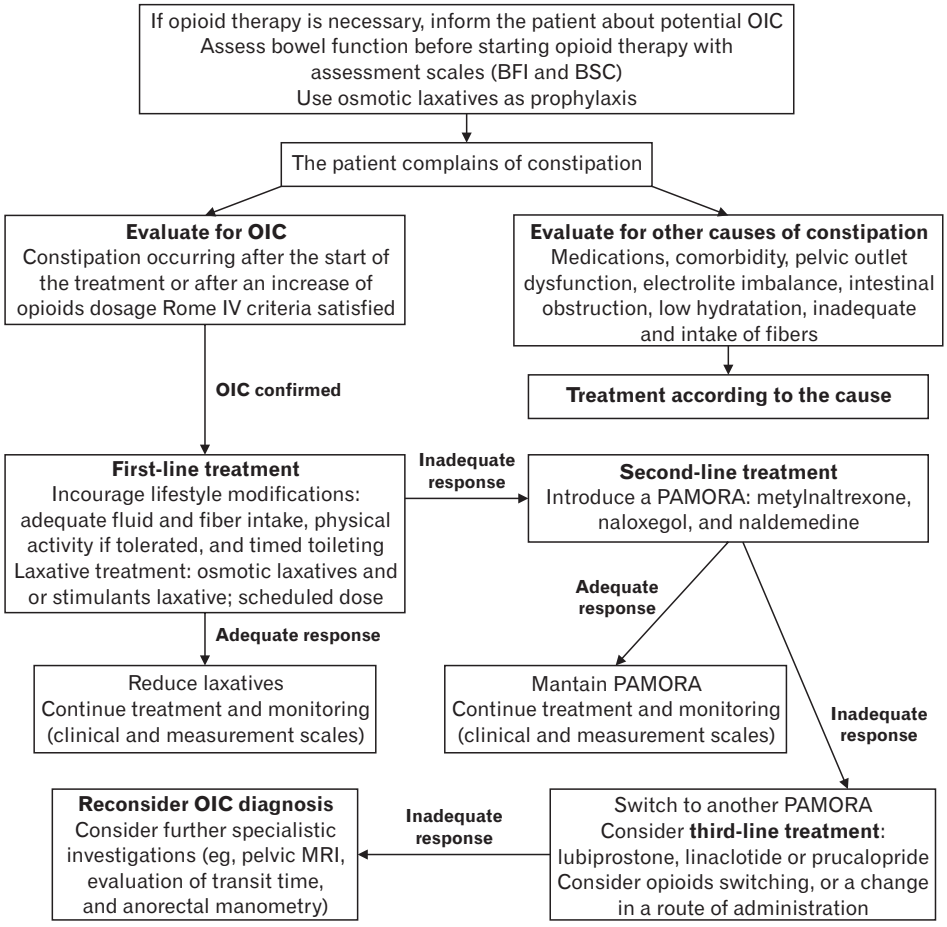

Figure 2. Management of opioid-induced constipation (OIC). BFI, bowel function index; BSC, Bristol stool chart; MRI, magnetic resonance imaging; PAMORA, peripherally acting μ-opioid receptor antagonist.

PAMORAs (methylenexone, naloxegol, and naldemedine) have been approved for the treatment of OIC not responding to osmotic laxatives or the combination of osmotic laxatives and stimulants, and these could be the "now kids on the block" for OIC treatment. However, further studies are needed to state the long-term safety and efficacy of PAMORAs, especially in more complex populations such as children and adolescents, fragile elderly with cognitive decay and terminal patients.

In practice, a stepwise approach is highly recommended, starting with lifestyle changes, then osmotic laxatives as first-line therapy, and adding a second laxative if a single one is insufficient. Second-line therapy includes PAMORAs. There are no recommendations for which specific PAMORA to choose. Prokinetics ad intestinal secretagogues are off-label, and they should be considered potential alternatives in case of failure of the PAMORAs.

Finally, further efforts by pharmacological research are needed to identify new molecules that can expand the spectrum of drugs available for treating digestive complications related to the use of opioid drugs. It is crucial to raise health professional awareness of the impact of OIC on patients and their caregivers. Management of patients using opioid drugs should be multidisciplinary, and the assessment of intestinal function and the prevention of constipation should be systematic and part of the pain management program.

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